Supporting Information for

Fluorogenic, Two-Photon Triggered Photoclick Chemistry in Live Mammalian Cells

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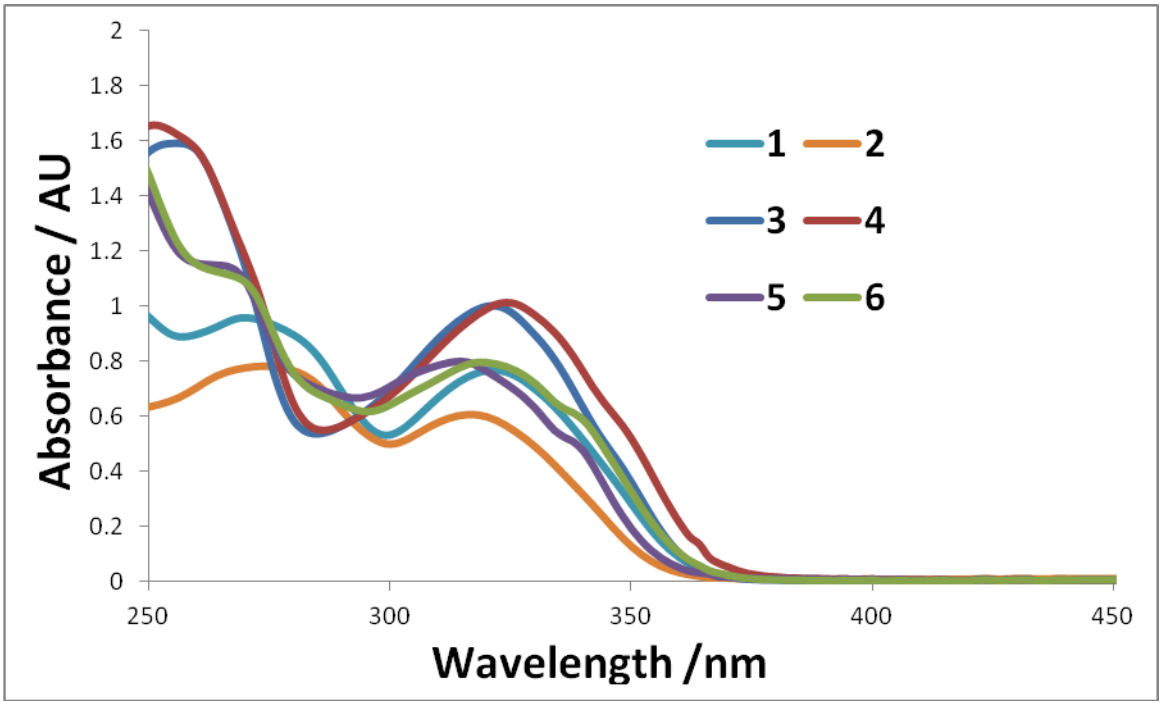
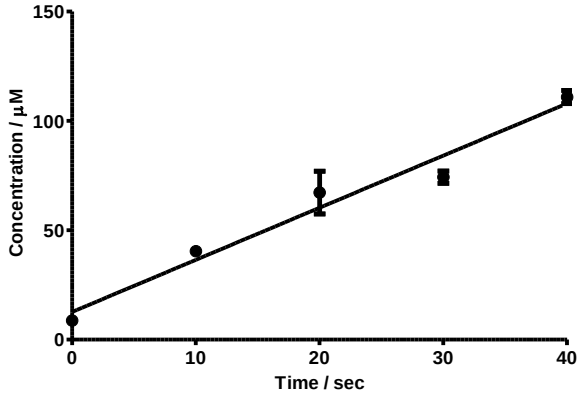


Tetrazole	1	2	3	4	5	6
ε_{350} (M^{-1} cm^{-1})	11,200	5;100	14,400	20,700	7,700	13,000
ε_{365} (M^{-1} cm^{-1})	1,700	700	1,900	4,500	1,300	2,000

Figure S1. UV-Vis spectra of tetrazoles **1-6** dissolved in acetonitrile/PBS (1:1) at 25 µM concentrations.

a)



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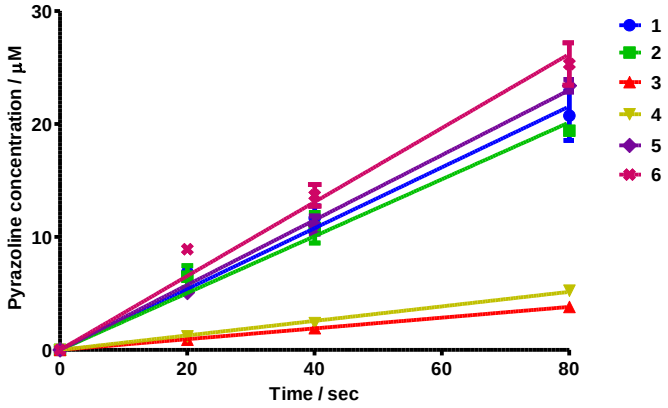
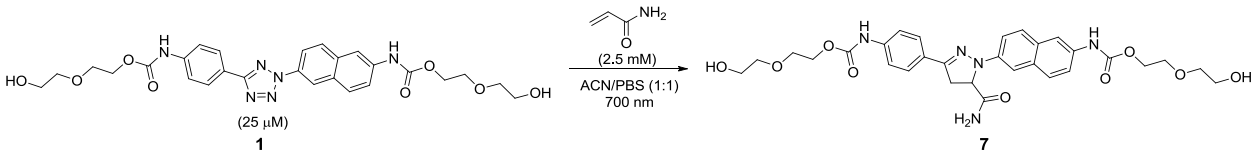
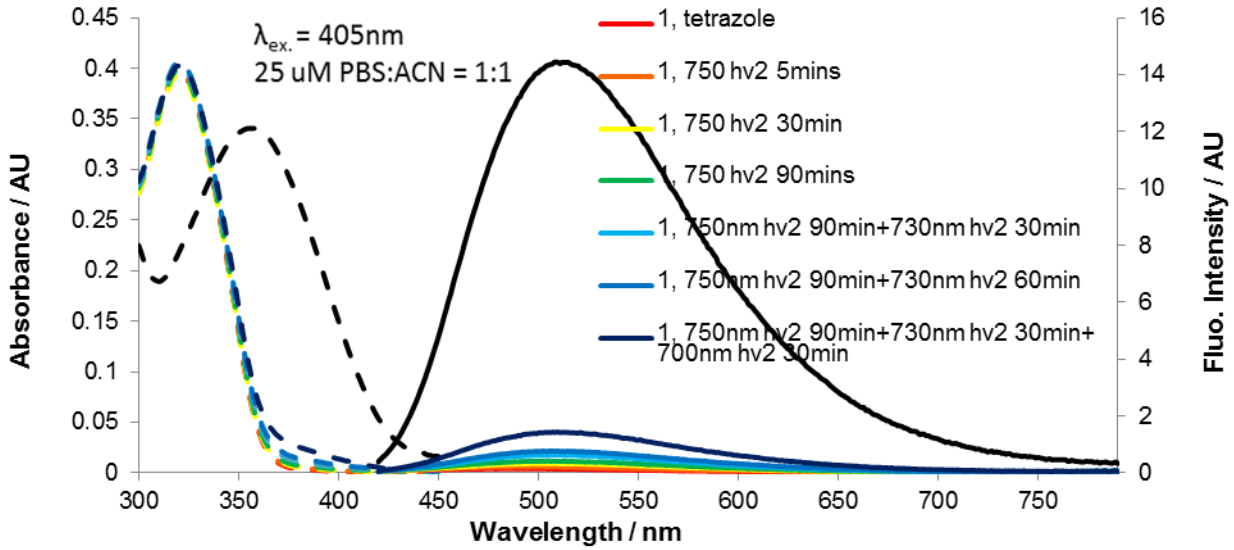


c)

Tetrazole	**1**	**2**	**3**	**4**	**5**	**6**
ε_{365} (M^{-1} cm^{-1})	1,700	700	1,900	4,500	1,300	2,000
k_0 (µM/s)	0.27	0.25	0.048	0.064	0.29	0.33
Φ_t	0.33	0.75	0.053	0.029	0.47	0.33

Figure S2. Determining photoinduced tetrazole ring rupture quantum yields using a ferrioxalate-polyoxometalate-based chemical actinometer.[1] (a) Photoinduced formation of POM^- over a period of 80 sec. (b) Time course of the single-photon induced photoclick reactions for the various tetrazoles as monitored by HPLC. (c) Summary of single-photon induced tetrazole ring rupture kinetics. A_s is absorbance of ferrioxalate-polyoxometalate at 365 nm, which was 2.705, determined by UV-Vis spectrophotometer, $[oxalate]_0$ = 60 mM, $[Fe^{3+}]_0$ = 5 mM, $[SiW_{12}O_{40}^{4-}]_0$ = 1 mM, *p*H = 4.5.

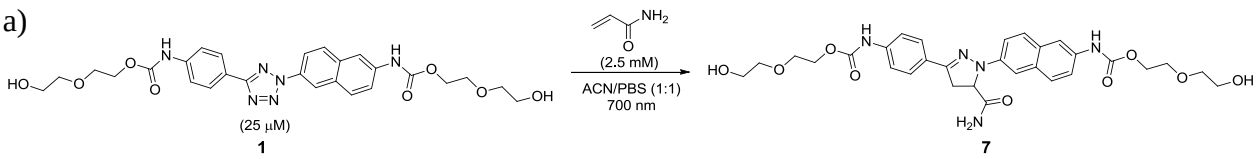


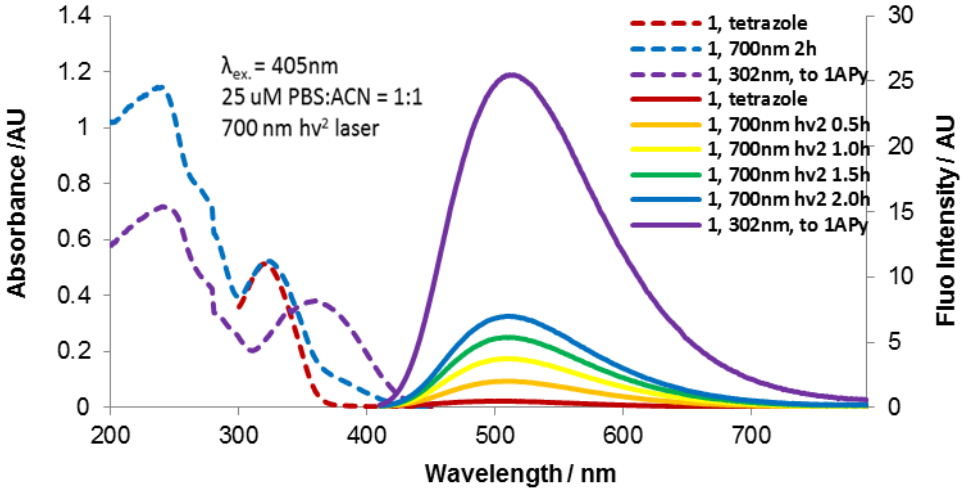


Focused laser irradiation	750 nm (5 min)	750 nm (30 min)	750 nm (90 min)	750 nm (90 min) followed by 730 nm (30 min)	750 nm (90 min) followed by 730 nm (60 min)	750 nm (90 min) followed by 730 nm (30 min) followed by 700 nm (30 min)
Yield (%)	1.6	2.4	3.0	4.4	5.4	9.9

Figure S3. Examining two-photon reaction conditions by fluorescence spectroscopy. Dash lines, UV-Vis spectra of tetrazole **1** and the corresponding pyrazoline; solid lines, fluorescence spectra of the pyrazoline, λ_{ex} = 405 nm. A solution of 25 μM tetrazole **1** and 2.5 mM acrylamide in 400 μL ACN/PBS mixed solvent in a quartz cuvette was subjected to focused femtosecond pulsed laser irradiation. The reaction yield was determined by comparing the integration area of the pyrazoline fluorescence spectrum between 420 nm and 790 nm to that of a fully converted pyrazoline (black line).

a)





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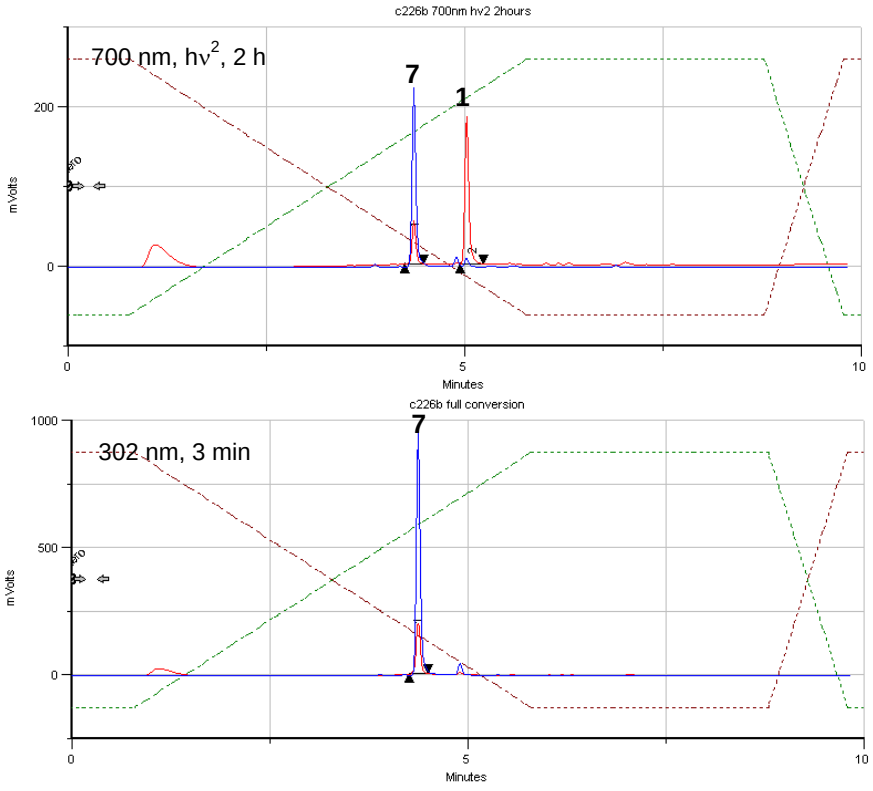
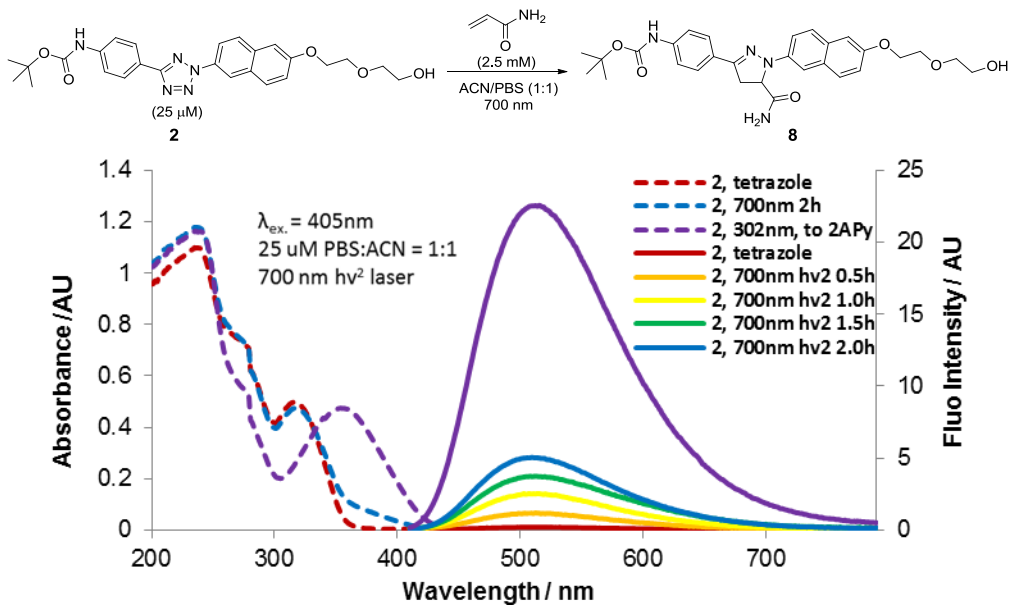


Figure S4. Studies of the two-photon induced cycloaddition reaction between tetrazole **1** (25 µM) and acrylamide (2.5 mM) in ACN/PBS (1:1). (a) UV-Vis absorption and fluorescence spectra of tetrazole and the corresponding pyrazoline. (b) HPLC trace of the cycloaddition reaction mixture after femtosecond pulsed laser (700 nm, top) or UV (302 nm, bottom) irradiation.

a)



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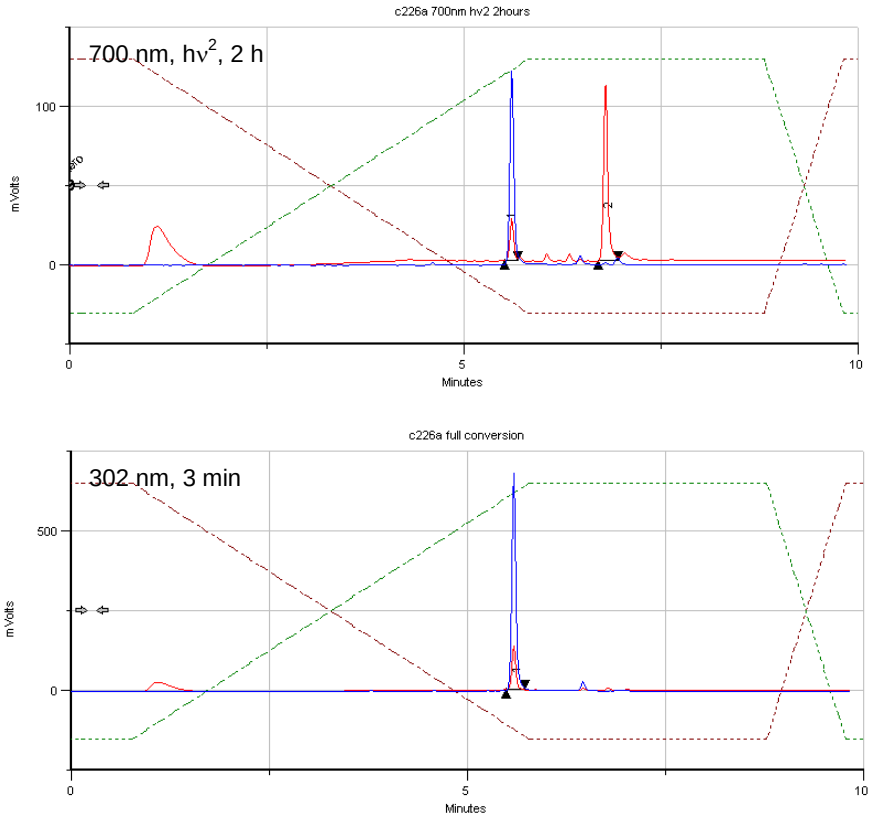
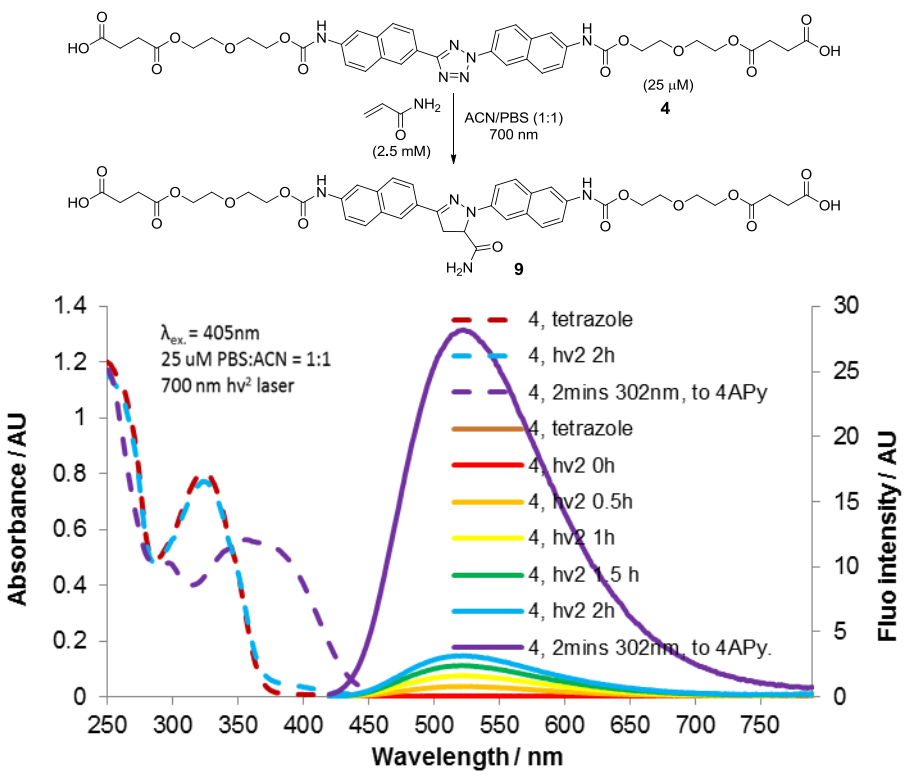


Figure S5. Two-photon induced cycloaddition reaction of tetrazole **2** (25 μM) with acrylamide (2.5 mM) in ACN/PBS (1:1). (a) UV-Vis absorption and fluorescence spectra of tetrazoles and pyrazolines. (b) HPLC trace of the cycloaddition reaction mixture after femtosecond pulsed laser (700 nm, top) or UV (302 nm, bottom) irradiation.

a)



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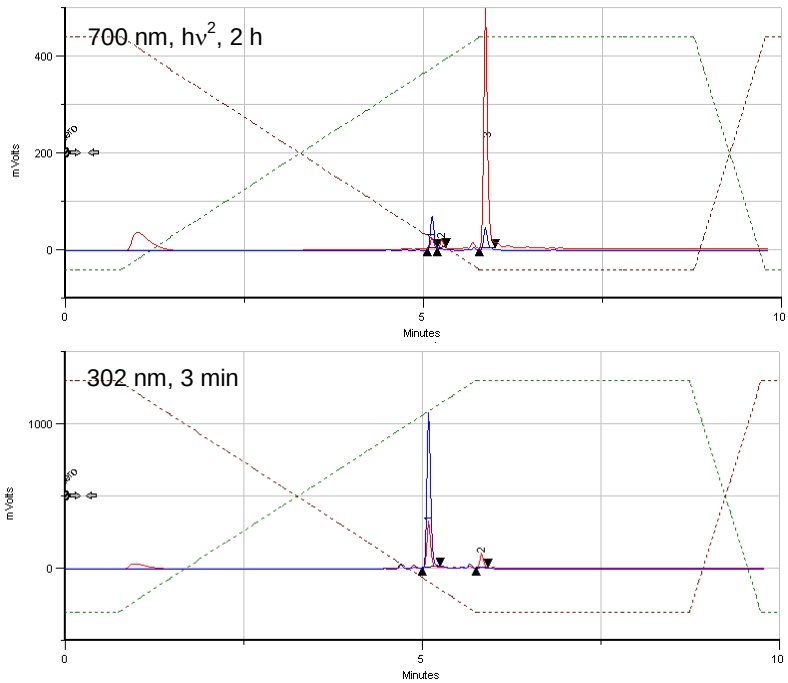
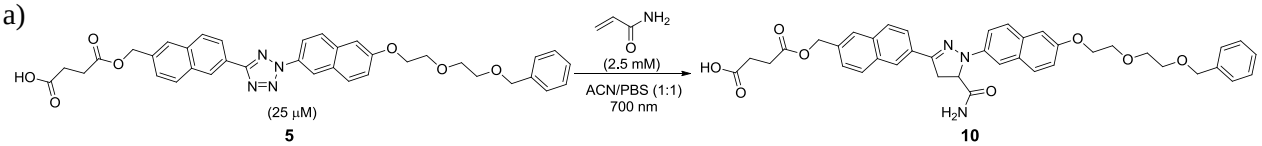
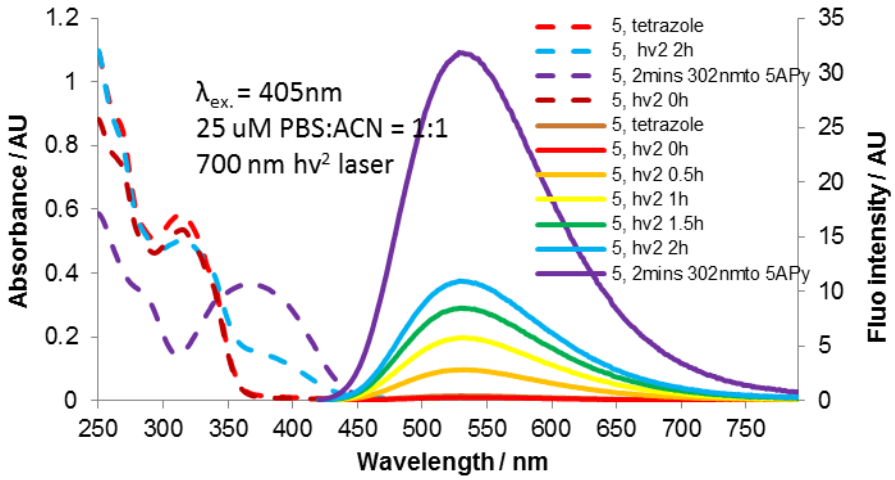


Figure S6. Two-photon induced cycloaddition reaction of tetrazole **4** (25 μM) with acrylamide (2.5 mM) in ACN/PBS (1:1). (a) UV-Vis absorption and fluorescence spectra of tetrazoles and pyrazolines. (b) HPLC trace of the cycloaddition reaction mixture after femtosecond pulsed laser (700 nm, top) or UV (302 nm, bottom) irradiation.

a)





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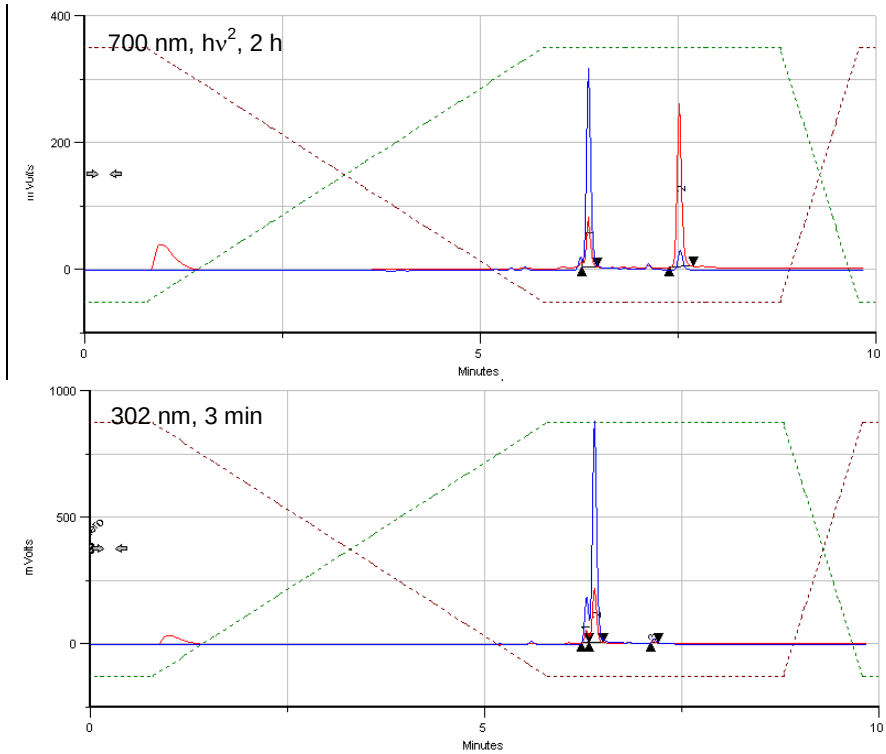
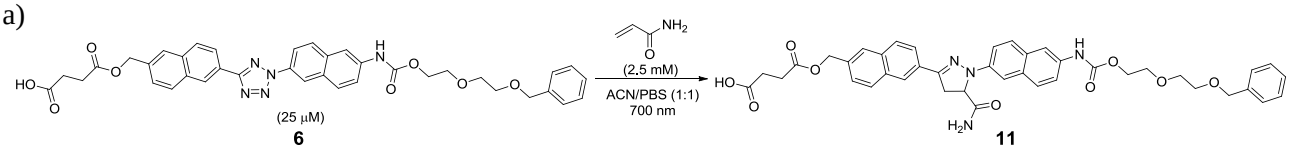
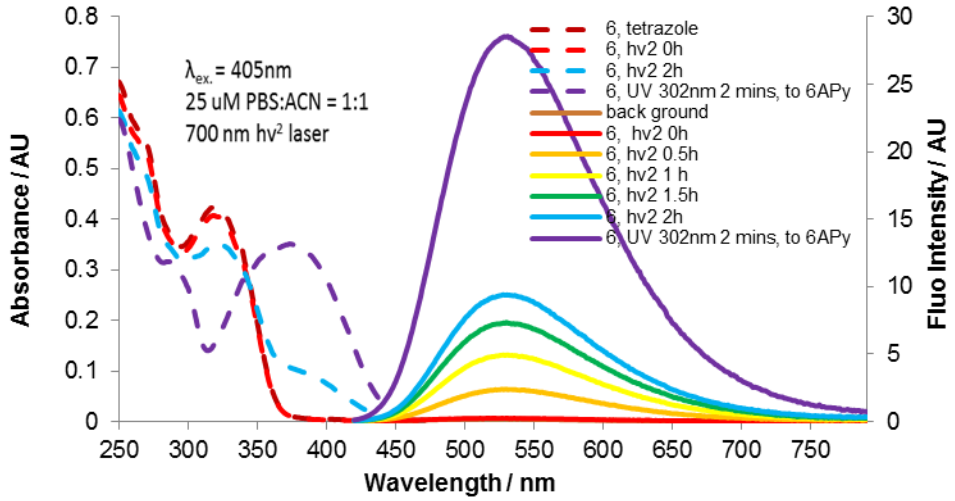


Figure S7. Two-photon induced cycloaddition reaction of tetrazole **5** (25 µM) with acrylamide (2.5 mM) in ACN/PBS (1:1). (a) Absorption and fluorescence spectra of tetrazole **5** and the corresponding pyrazoline. (b) HPLC trace of the cycloaddition reaction mixture after femtosecond pulsed laser (700 nm, top) or UV (302 nm, bottom) irradiation.

a)





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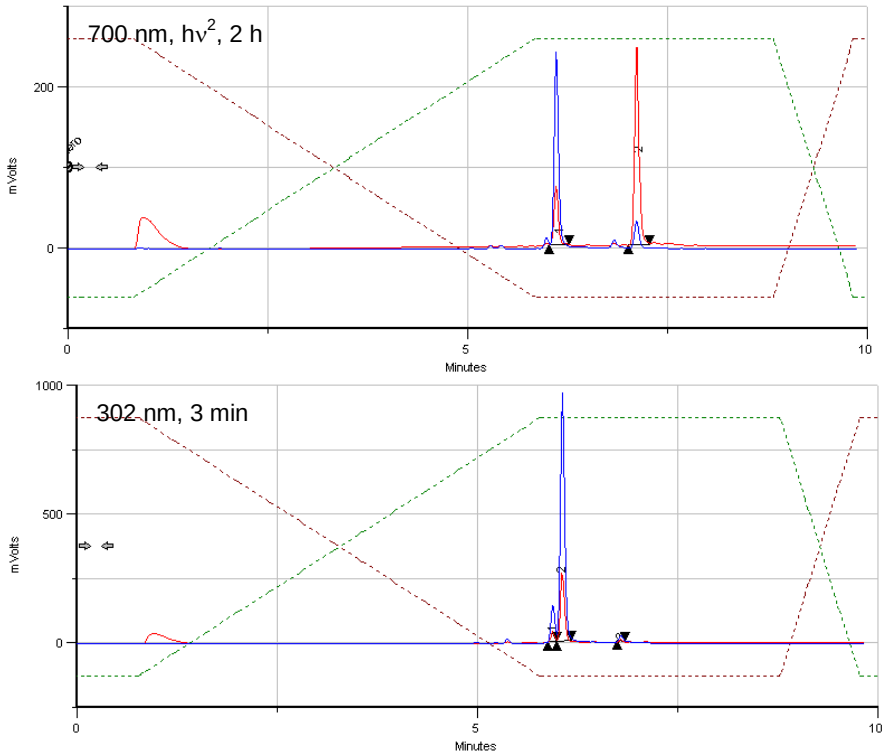


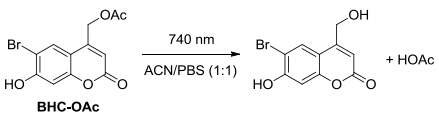
Figure S8. Two-photon induced cycloaddition reaction of tetrazole **6** (25 µM) with acrylamide (2.5 mM) in ACN/PBS (1:1). (a) Absorption and fluorescence spectra of tetrazole **6** and the corresponding pyrazoline. (b) HPLC trace of the cycloaddition reaction mixture after femtosecond pulsed laser (700 nm, top) or UV (302 nm, bottom) irradiation.

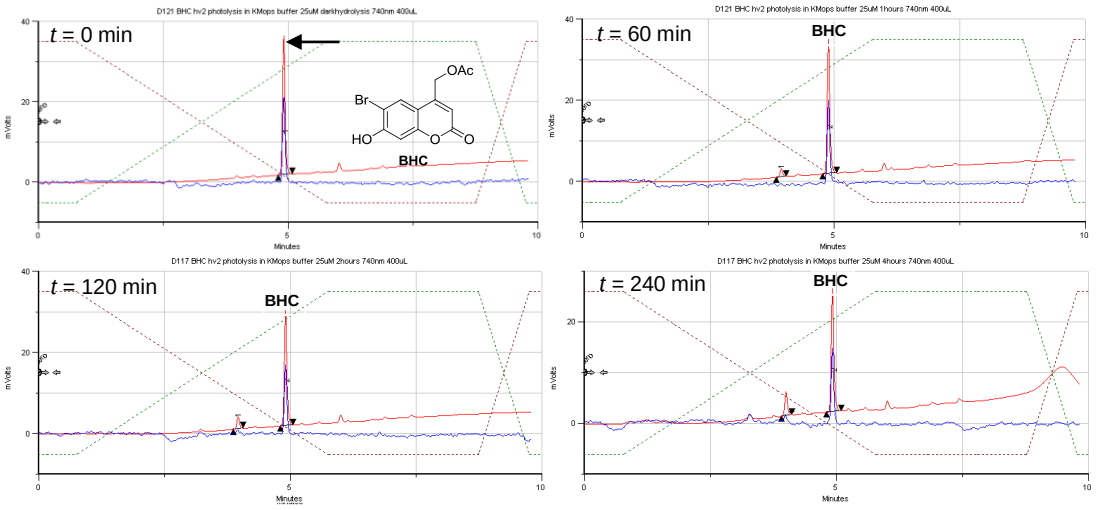
Table S1. Photophysical properties of the pyrazolines and fluorescence "turn-on" at 405 nm excitation. [a]

Pyrazoline	λ_{max} [b] (nm)	ε_{405} [c] (nm)	λ_{em} (nm)	Φ_f [d]	Fluorescence "turn-on" fold change [e]	Brightness [f]
7	359	6,200	507	0.16	13	1,000
8	354	5,800	506	0.15	23	880
9	357	14,000	521	0.074	29	1,100
10	369	10,000	529	0.12	38	1,200
11	374	10,000	530	0.11	33	1,100

[a] The pyrazoline was obtained by irradiating the solution of 25 μM tetrazole and 2.5 mM acrylamide (100 equiv) in ACN/PBS (1:1) with 365 nm handheld UV light. [b] λ_{max} in 300~500 nm region. [c] Extinction coefficient at 405 nm. [d] Fluorescence quantum yield measured using DAPI as a standard; λ_{ex} = 405 nm.[S1] [e] Fluorescence intensity increase after 2 hours of 700 nm focused femtosecond laser irradiation. [f] Brightness = $\varepsilon_{405} \times \Phi_f$.

a)





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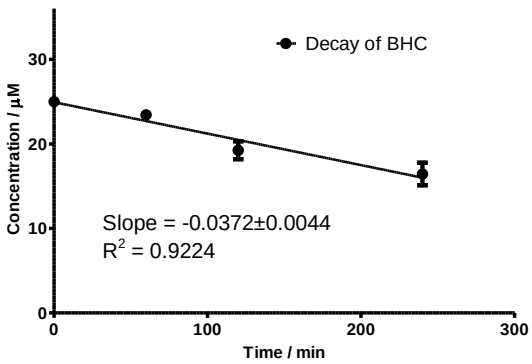
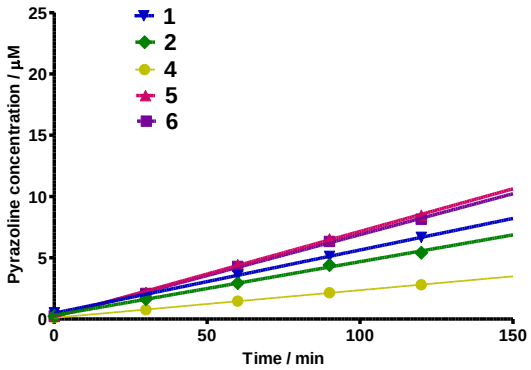


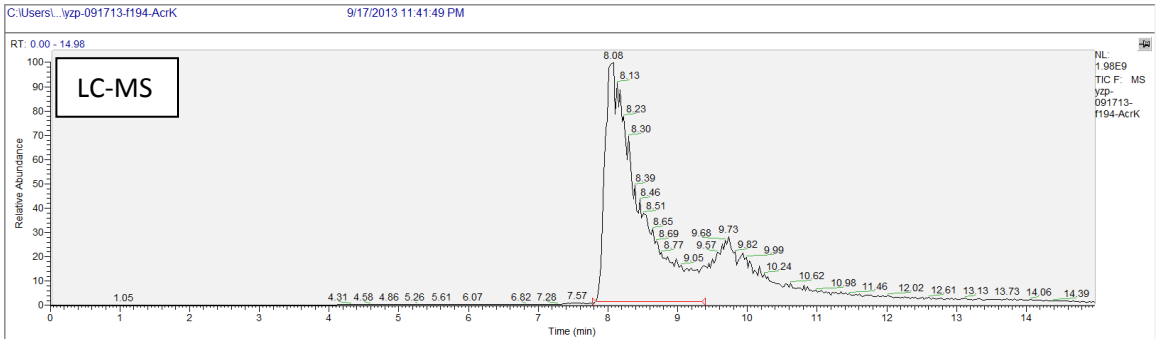
c)



d)

	1	**2**	**4**	**5**	**6**
k_0 (µM/min)	0.0520 ± 0.0005	0.044 ± 0.001	0.0230 ± 0.0002	0.070 ±0.001	0.067 ± 0.001
Φ_T	0.33	0.75	0.029	0.47	0.33
δ_{cT} (GM)	3.0	2.5	1.3	4.0	3.8
δ_{aT} (GM)	9.1	3.3	45	8.5	12

Figure S9. Determination of reaction cross sections of the tetrazoles: (a) HPLC analyses of the two-photon induced hydrolysis of bromohydroxycoumarin acetate (BHC-OAc; 25 µM in KMops buffer) upon 740 nm photoirradiation. The laser power was set at 470 mW and the laser was focused on the middle section of the reaction cuvette. Red traces = absorption at 254 nm; blue traces = absorption at 370 nm. (b) Plot of BHC-OAc photolysis with the data fitted to a linear equation. (c) Time courses of the pyrazoline cycloadduct formation for the various tetrazoles. (d) Tabulated reaction rate (k_0), two-photon absorbance cross-section (δ_{aT}), ring rupture quantum yield (Φ_T), and two-photon reaction cross-section (δ_{cT}).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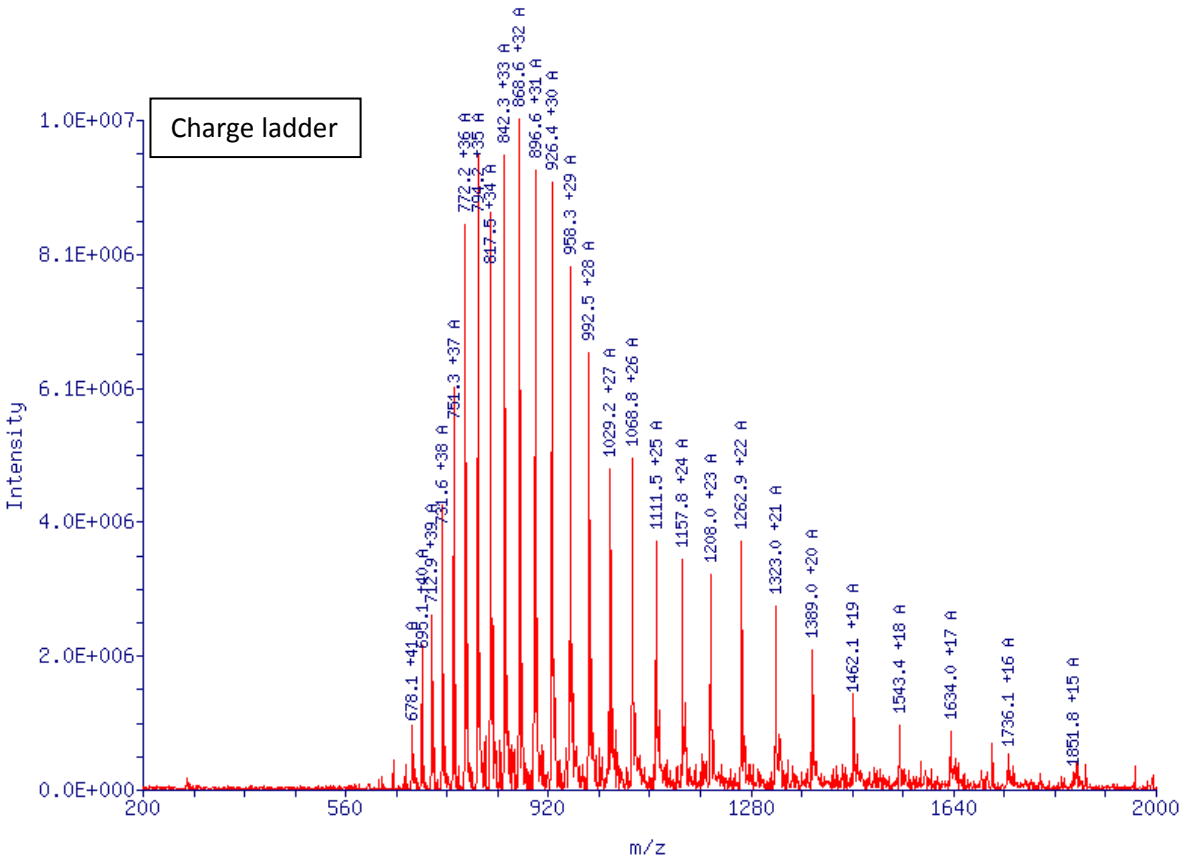
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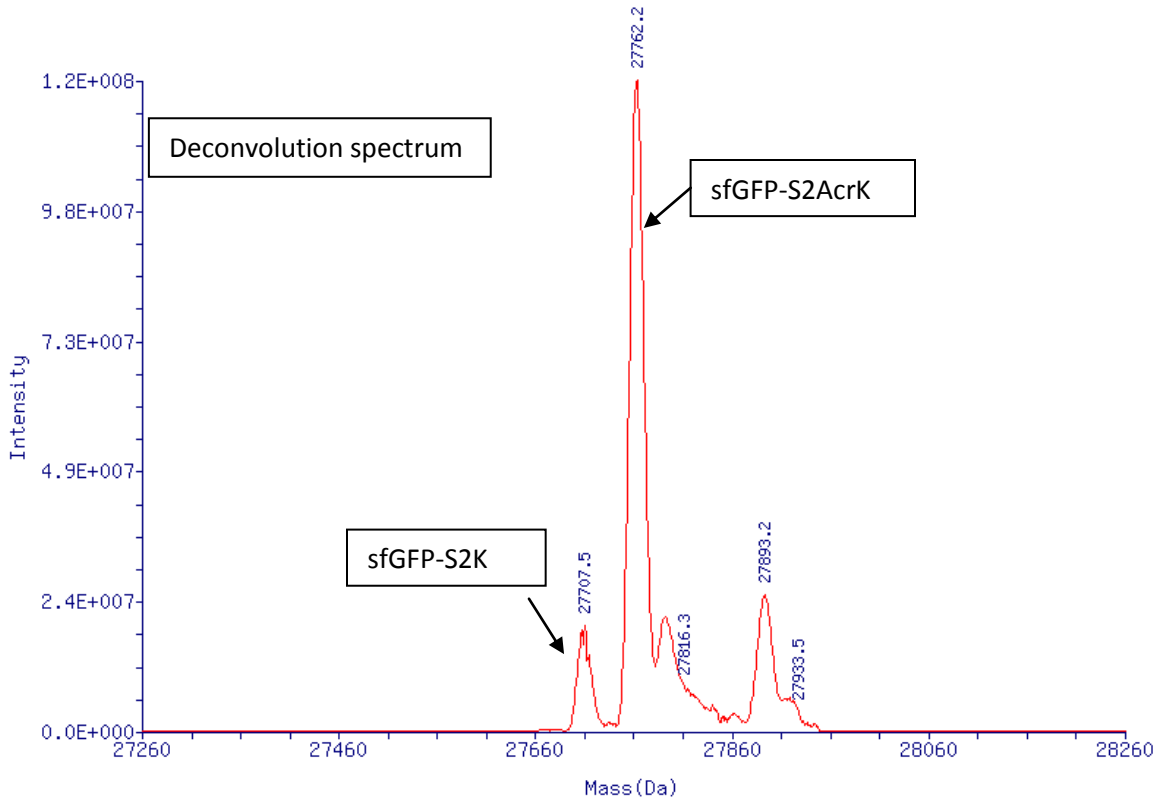
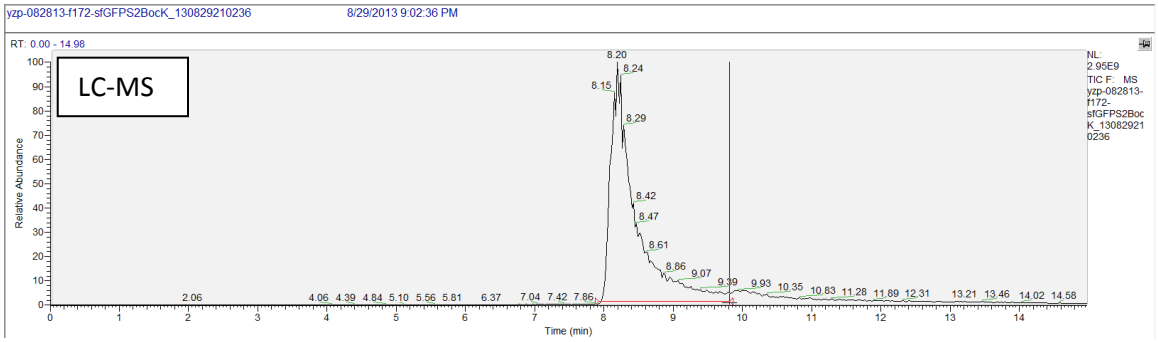


Mass (Da)	+- Std. Dev.	Intensity	Score	Delta Mass	%Relative	%Total
27762.2	0.6	1.22E+008	41.47	0.0	100.00	66.44
27893.2	2.0	2.55E+007	24.91	131.0	20.84	13.85
27707.5	1.7	1.97E+007	20.10	-54.7	16.13	10.72
27816.3	2.7	8.28E+006	16.06	54.1	6.77	4.50

Figure S10. LC/ESI-MS analysis of sfGFP-S2AcrK. Calcd mass 27764.1 Da (amino acid sequence losing first methionine, adding two water molecule and oxidation with oxygen atom), found 27762.2 ± 0.6 Da. Yield = 1.4 mg/L. Sequence is M # K G E E L F T G V V P I L V E L D G D V N G H K F S V R G E G E G D A T N G K L T L K F I C T T G K L P V P W P T L V T T L T Y G V Q C F S R Y P D H M K R H D F F K S A M P E G Y V Q E R T I S F K D D G T Y K T R A E V K F E G D T L V N R I E L K G I D F K E D G N I L G H K L E Y N F N S H N V Y I T A D K Q K N G I K A N F K I R H N V E D G S V Q L A D H Y Q Q N T P I G D G P V L L P D N H Y L S T Q S V L S K D P N E K R D H M V L L E F V T A A G I T H G M D E L Y K G S H H H H H H, where # is AcrK.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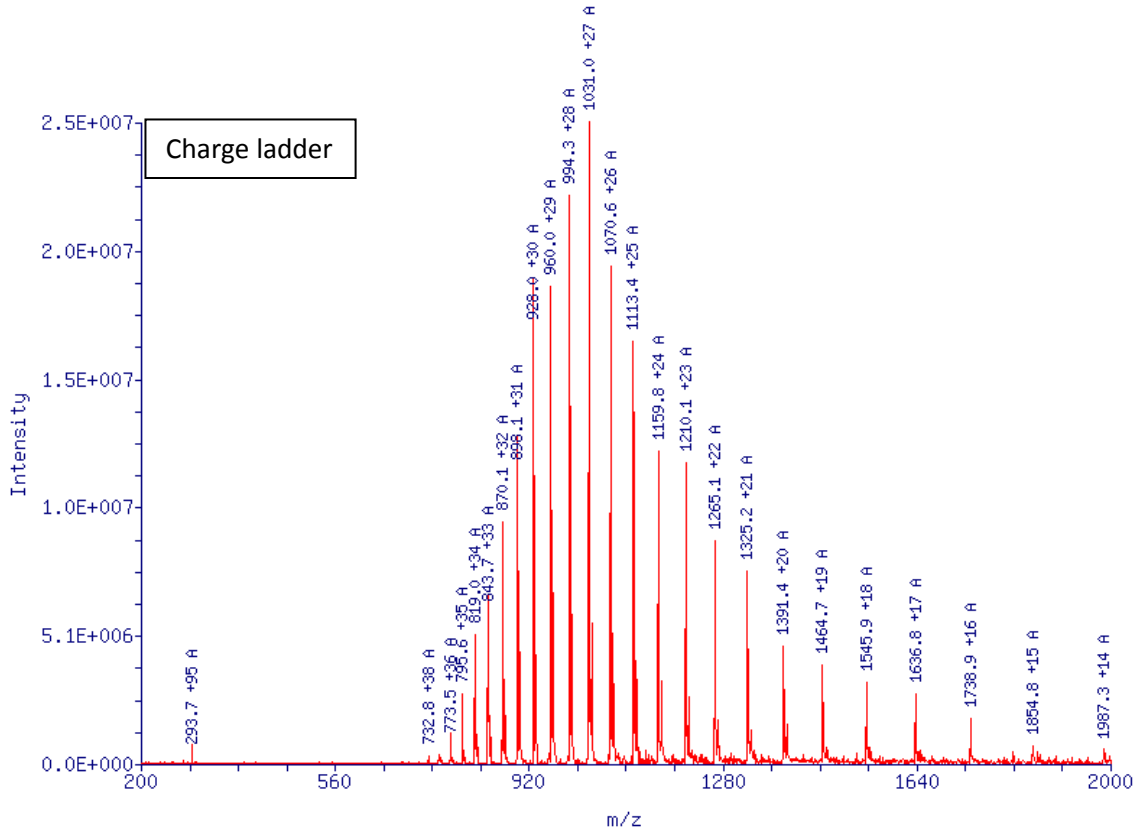
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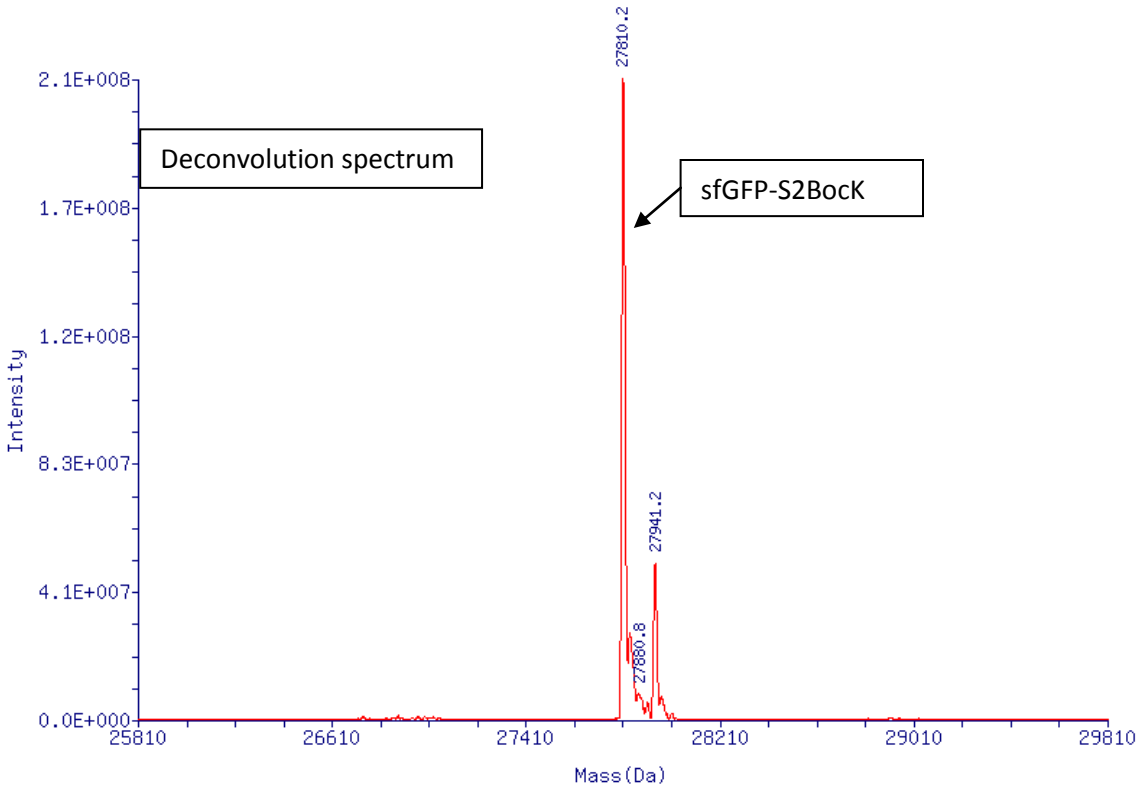

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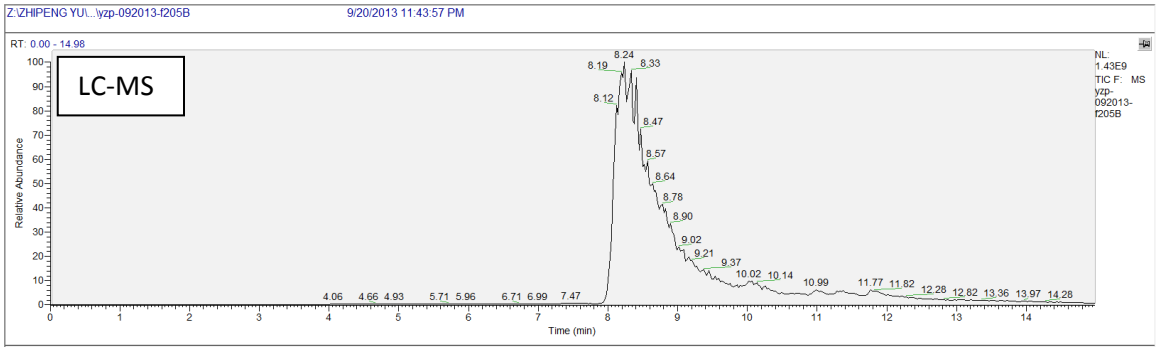
27851.0	2.9	2.17E+007	23.36	40.8	10.51	7.47
27880.8	2.9	8.00E+006	12.37	70.6	3.87	2.75

Figure S11. LC/ESI-MS analysis of sfGFP-S2BocK. Calcd mass 27810.2 Da (the amino acid sequence losing first methionine, adding two water molecules and one oxygen atom), found 27810.2 ± 1.4 Da. Yield = 8.6 mg/L. Sequence is M # K G E E L F T G V V P I L V E L D G D V N G H K F S V R G E G E G D A T N G K L T L K F I C T T G K L P V P W P T L V T T L T Y G V Q C F S R Y P D H M K R H D F F K S A M P E G Y V Q E R T I S F K D D G T Y K T R A E V K F E G D T L V N R I E L K G I D F K E D G N I L G H K L E Y N F N S H N V Y I T A D K Q K N G I K A N F K I R H N V E D G S V Q L A D H Y Q Q N T P I G D G P V L L P D N H Y L S T Q S V L S K D P N E K R D H M V L L E F V T A A G I T H G M D E L Y K G S H H H H H H, where # is BocK.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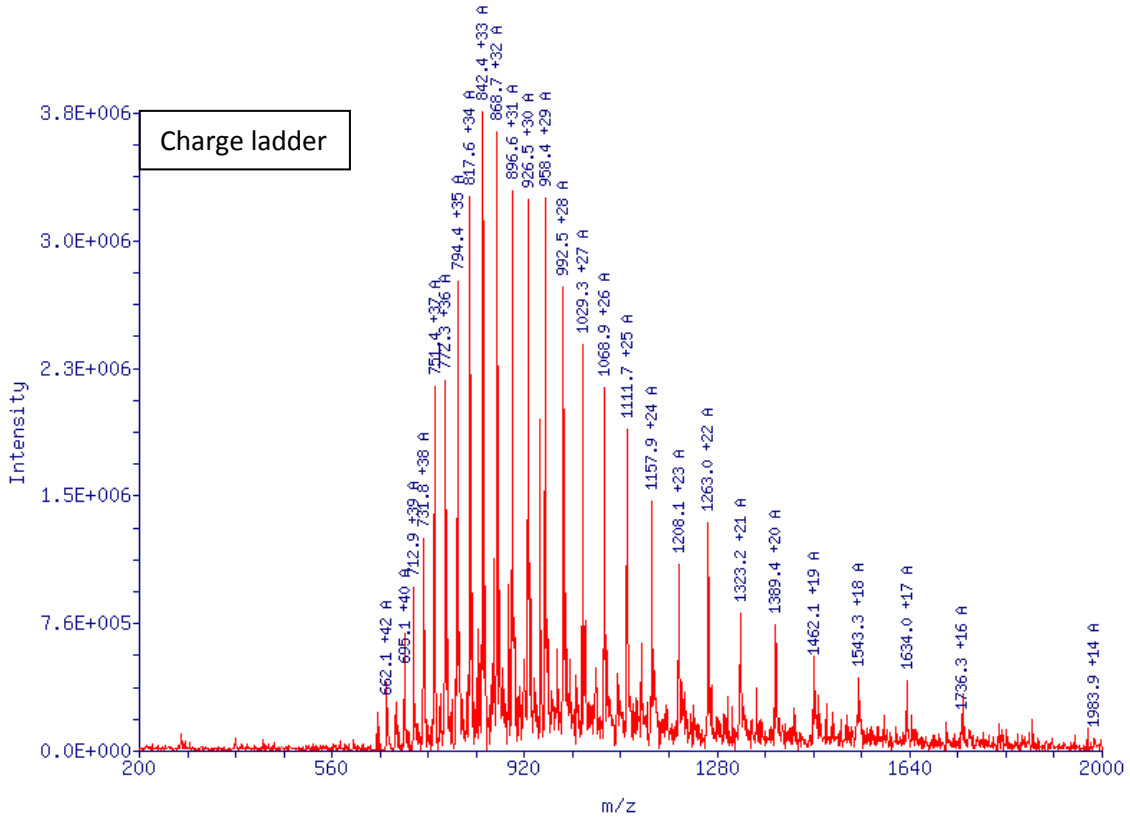
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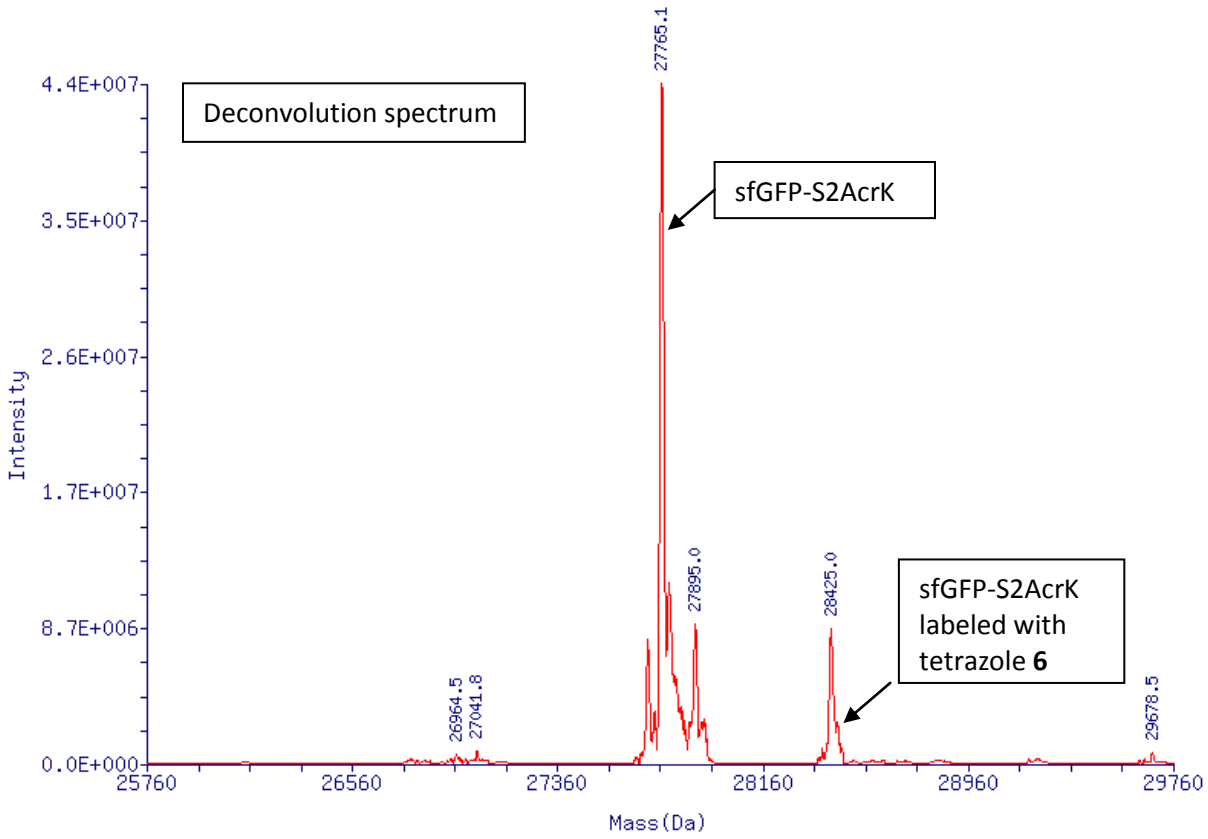
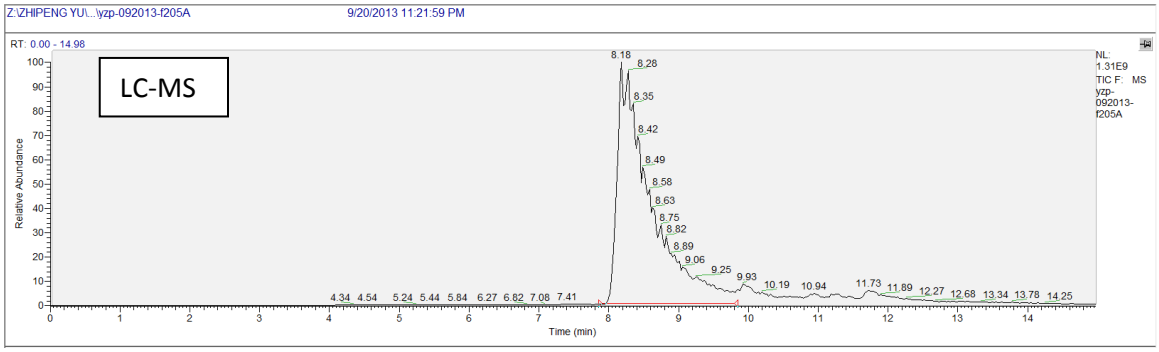
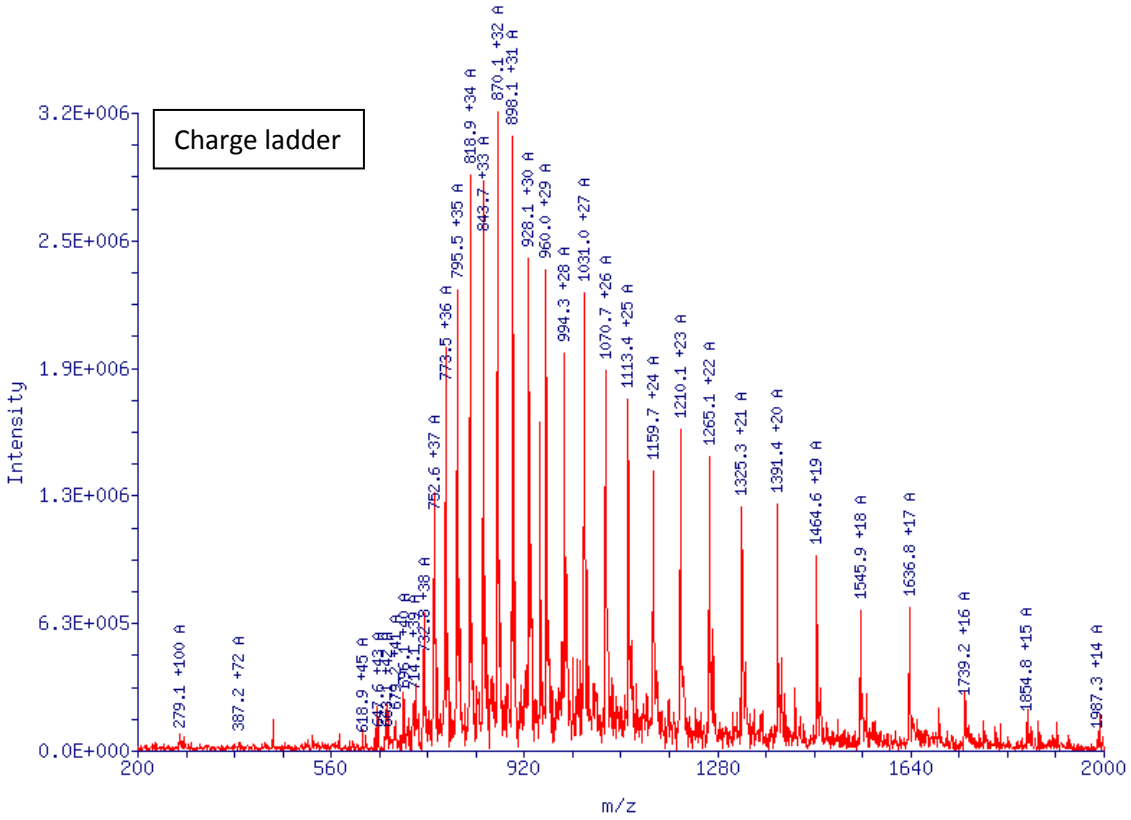
0.0E+000
200
560
920
1280
1640
2000

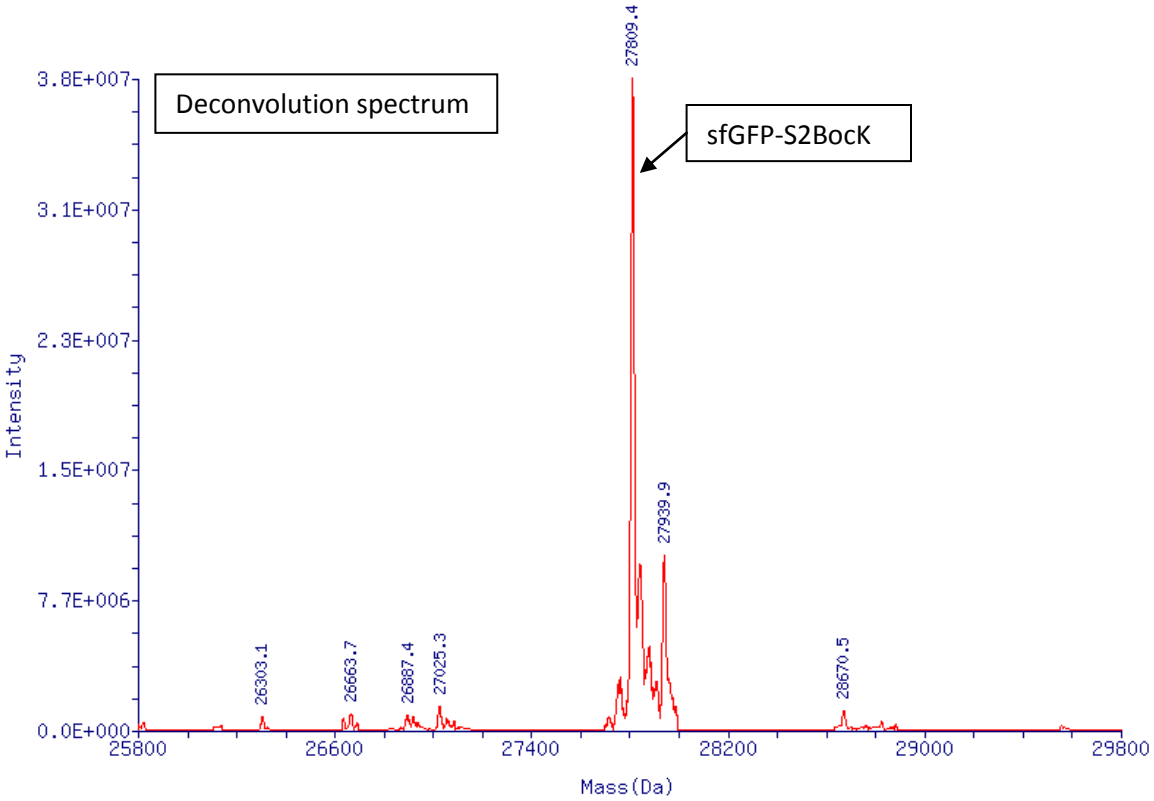


Mass(Da)	+- Std. Dev.	Intensity	Score	Delta Mass	%Relative	%Total
27765.1 (SM)	1.9	4.37E+007	31.38	0.0	100.00	48.06
27804.5	2.9	9.38E+006	16.82	39.4	21.46	10.31
27895.0	2.7	9.00E+006	15.15	129.9	20.60	9.90
28425.0 (product)	3.2	8.63E+006	16.40	659.9	19.75	9.49
27709.7	3.1	7.97E+006	12.91	-55.4	18.24	8.77

Figure S12. LC/ESI-MS analysis of sfGFP-S2AcrK after the femtosecond laser triggered photo-click reaction with tetrazole **6**. Calcd mass 28425.3 Da (starting material sfGFP-S2AcrK adding the nitrile imine derived from tetrazole **6**), found 28425.0 ± 3.2 Da. Yield = 16.5% (calculated by comparing the ion count of the product to that of the starting material plus product).


Z:\ZHIPENG YU\...\yzp-092013-f205A
9/20/2013 11:21:59 PM
RT: 0.00 - 14.98
LC-MS
Relative Abundance
Time (min)
NL:
1.31E9
TIC F: MS
YZP-092013-f205A


Charge ladder
Intensity
m/z
3.2E+006
2.5E+006
1.9E+006
1.3E+006
6.3E+005
0.0E+000
200
560
920
1280
1640
2000
279.1 +100 A
387.2 +72 A
618.9 +45 A
752.6 +37 A
773.5 +36 A
795.5 +35 A
818.9 +34 A
843.7 +33 A
870.1 +32 A
898.1 +31 A
928.1 +30 A
960.0 +29 A
994.3 +28 A
1031.0 +27 A
1070.7 +26 A
1113.4 +25 A
1159.7 +24 A
1210.1 +23 A
1265.1 +22 A
1325.3 +21 A
1391.4 +20 A
1464.6 +19 A
1545.9 +18 A
1636.8 +17 A
1739.2 +16 A
1854.8 +15 A
1987.3 +14 A



Mass(Da)	+- Std. Dev.	Intensity	Score	Delta Mass	%Relative	%Total
27809.4	1.5	3.83E+007	32.30	0.0	100.00	54.79
27939.9	2.7	1.02E+007	17.37	130.5	26.78	14.67
27852.0	2.8	8.42E+006	16.03	42.6	22.01	12.06
27752.6	4.0	3.13E+006	5.80	-56.8	8.18	4.48
27025.3	4.0	1.36E+006	6.45	-784.1	3.54	1.94
28670.5	5.2	1.15E+006	4.62	861.1	2.99	1.64

Figure S13. LC/ESI-MS analysis of sfGFP-S2BocK after the femtosecond laser triggered photo-click reaction with tetrazole **6**.

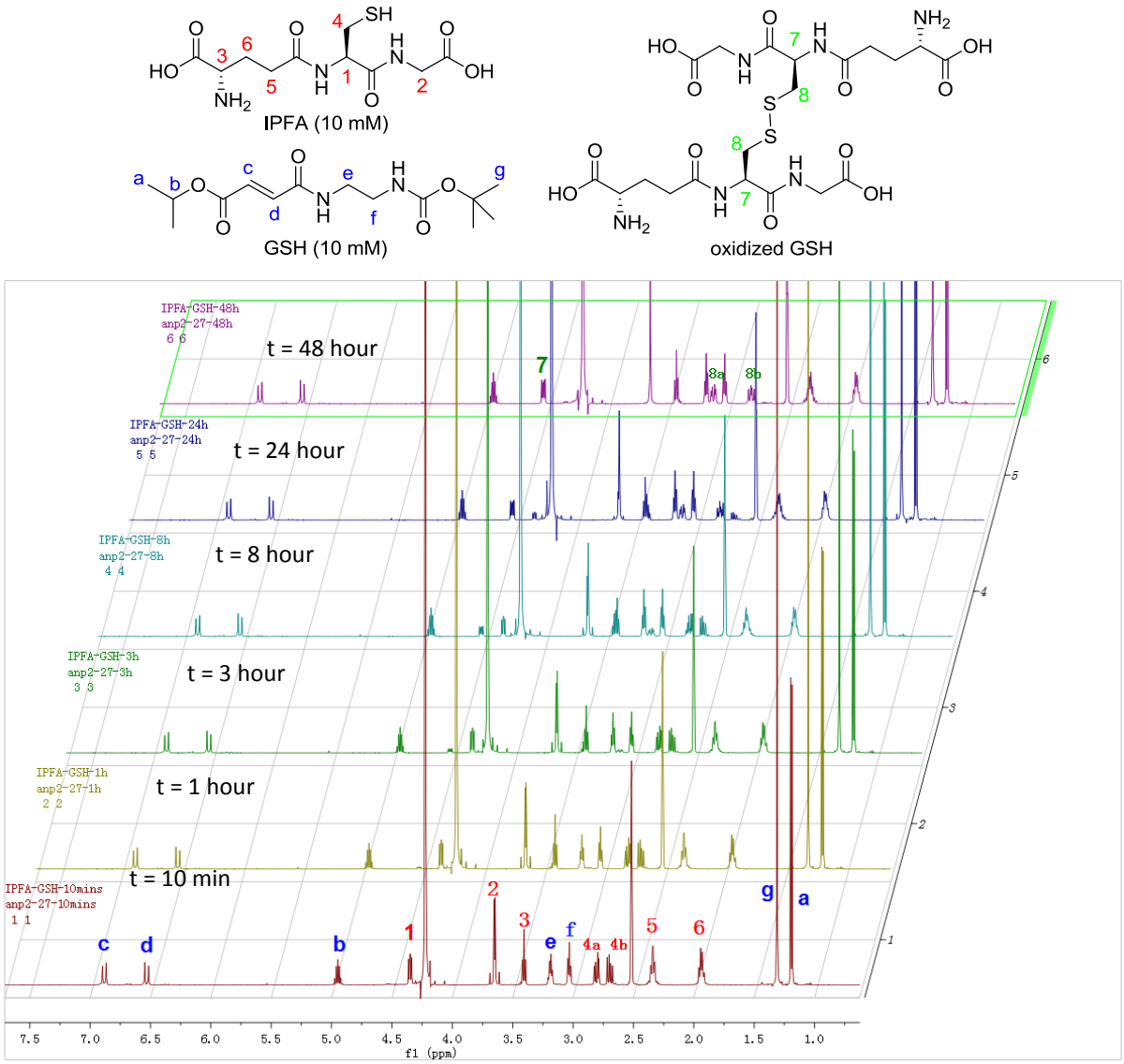
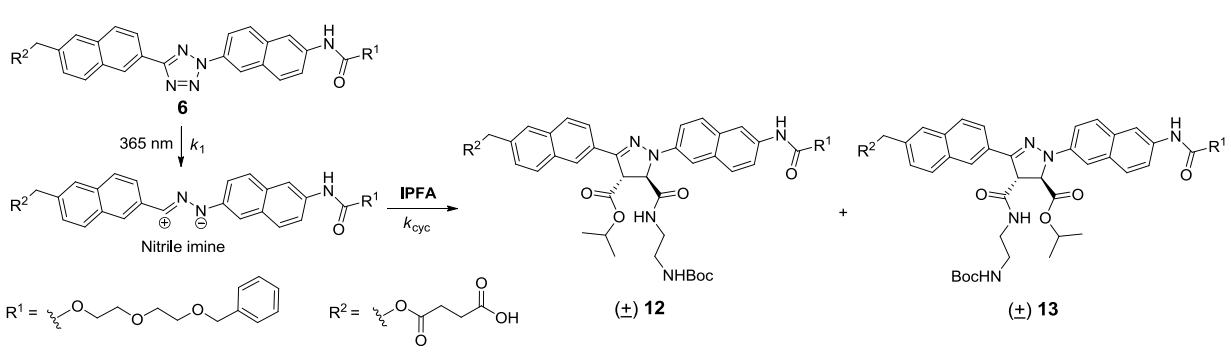
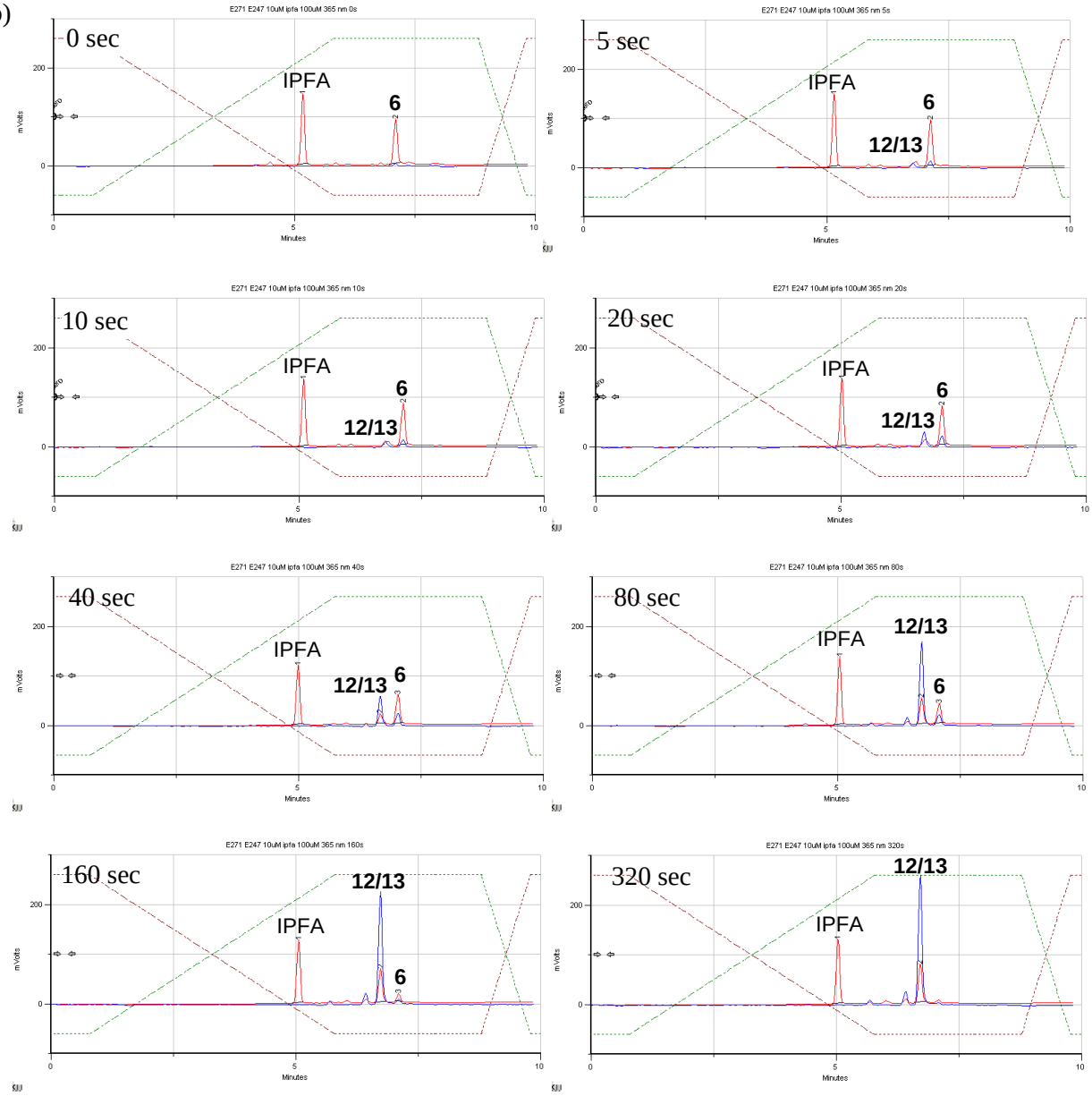


Figure S14. Stability of *mono*-isopropyl fumarate amide (IPFA) towards glutathione at 23°C in mixed DMSO-d_6/deuterated PBS buffer (7:3) as monitored by ^{1}H NMR. Condition: 10 mM IPFA was mixed with 10 mM GSH (reduced form) in deuterated solvent. The formation of oxidized GSH dimer was confirmed by observation of the intact mass ion [M+H$^+$] of 613.0 in LC-MS analysis.

a)


6
365 nm
k_1
Nitrile imine
IPFA
k_{cyc}
NHBoc
BocHN
(±) 12
(±) 13
R^1 =
R^2 =
OH

b)


0 sec
IPFA
6
5 sec
12/13
10 sec
20 sec
40 sec
80 sec
160 sec
320 sec
Minutes
mVolts

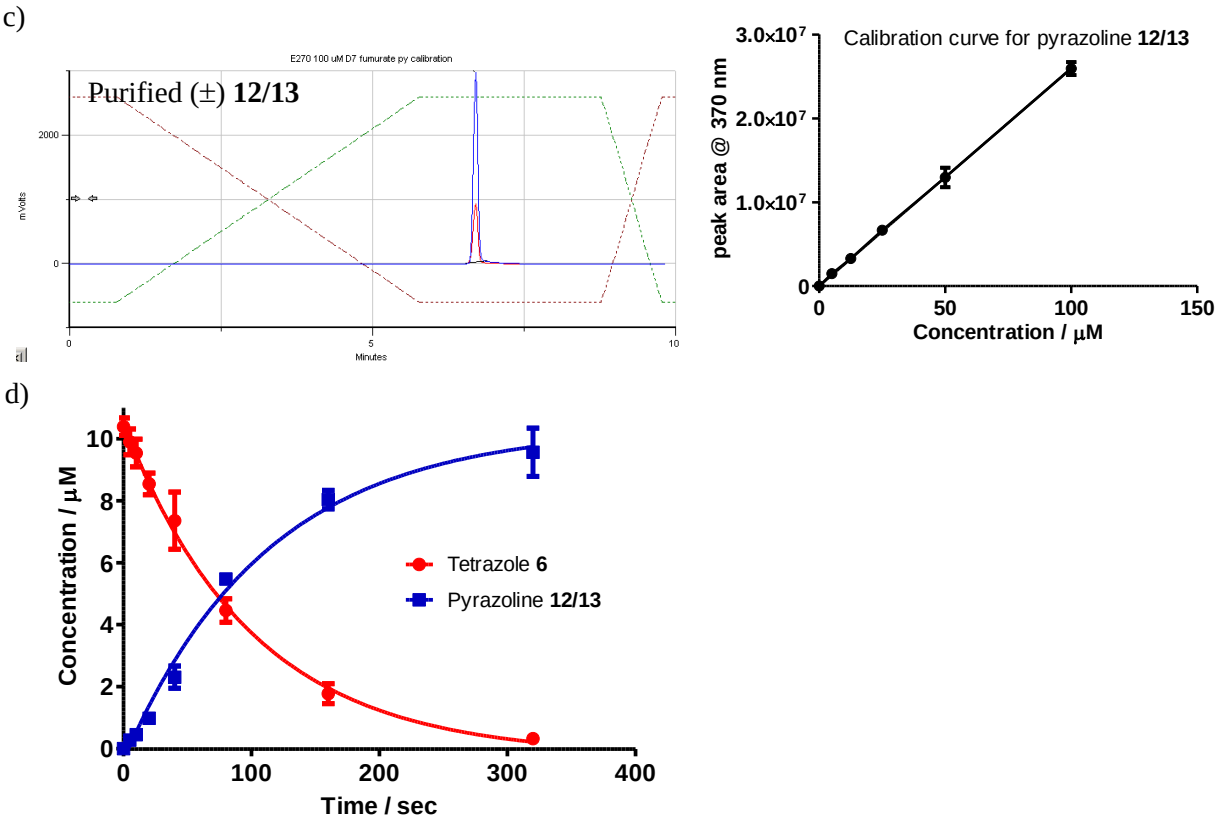


Figure S15. Kinetic studies of the photoinduced cycloaddition reaction between tetrazole **6** (10 µM) and IPFA (100 µM) in acetonitrile/PBS (1:1) under 365 nm photoirradiation. (a) Reaction scheme. (b) Time course of the cycloaddition reactions at 0, 5, 10, 20, 40, 80, 160 and 320 sec intervals monitored by reverse-phase HPLC. Red traces = absorbance at 254 nm; blue traces = absorbance at 370 nm; (c) HPLC trace of the purified pyrazoline cycloadduct, and the calibration curve of the pyrazoline cycloadducts **12/13** over the concentration range of 0 ~ 100 µM. (d) Plot of the changes in concentration for tetrazole **6** and the pyrazoline cycloadducts **12/13** over the course of the reaction. The photoinduced disappearance of tetrazole **6** (red curve) was fitted to an exponential decay equation: $y = (y_0\text{-a})e^{-kt} + a$, whereas the formation of the pyrazoline cycloadduct (blue curve) was fitted to an exponential rise to maximum equation: $y = (y_0\text{-a})\, e^{k_{obs}t} + a$. to give $k_{obs} = 0.0089 \pm 0.00085\ s^{-1}$. The second-order rate constant of the cycloaddition, k_2, was calculated to be $89 \pm 8.5\ M^{-1}\ s^{-1}$ based on the equation: $k_2 = k_{obs}/[IPFA]$.

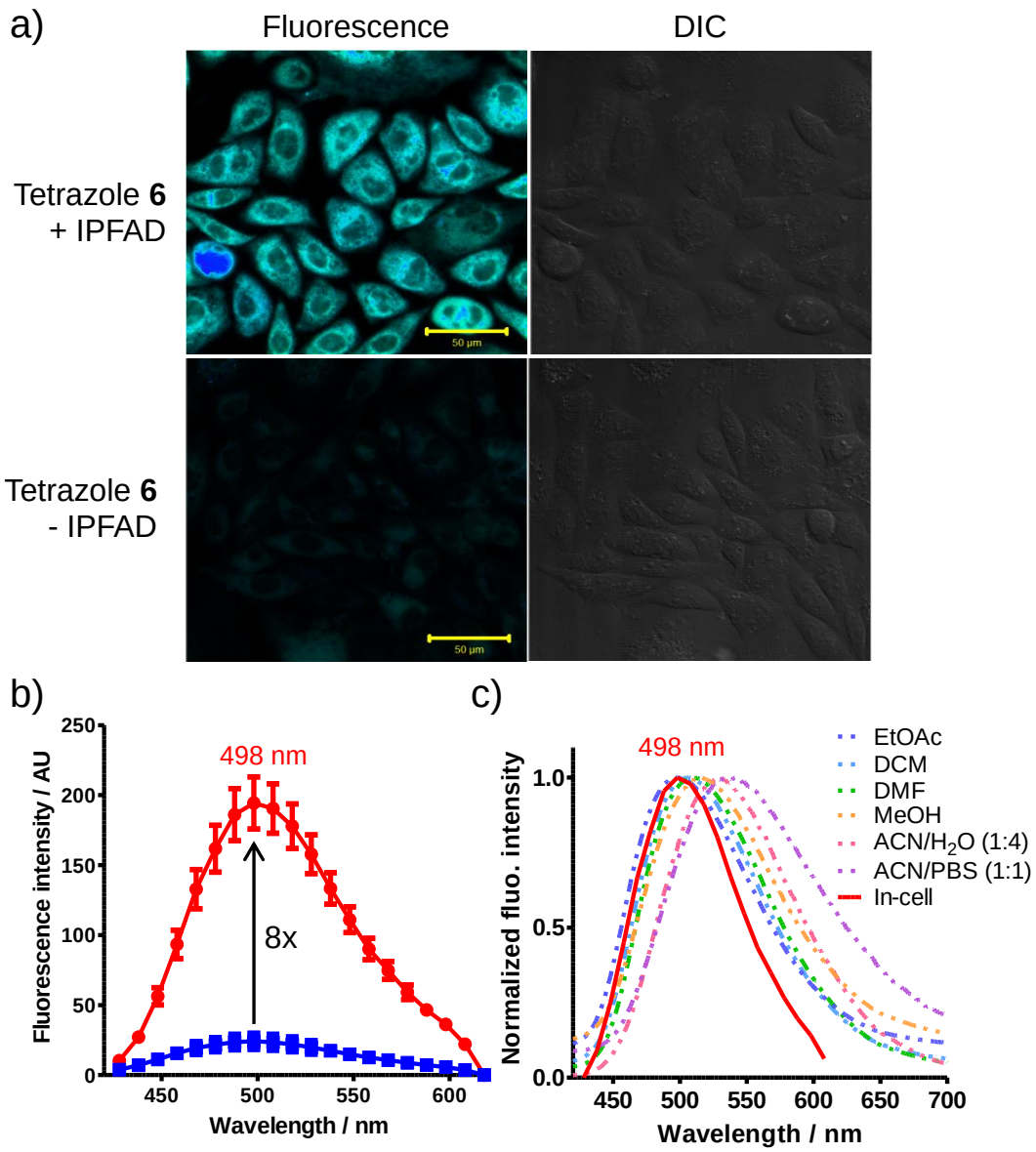


Figure S16. Fluorescence microscopy of the single-photon induced, naphthalene-tetrazole-based photoclick chemistry in CHO-K1 cells. (a) Fluorescence and DIC images of CHO-K1 cells after the photoclick reaction. CHO-K1 cells were incubated with tetrazole 6 overnight. The cells were then washed with DMEM medium prior to the IPFAD treatment for 30 min in OPTI-MEM. Without any further washing, cells were exposed to 3-min 365 nm photoirradiation before confocal microscopy. The fluorescence images are λ-coded; λ_{ex} = 405 nm; scale bar = 50 µm. (b) Spectrum of the cytosolic fluorescence for CHO-K1 cells treated with (red circle) or without (blue square) 30 µM IPFAD. The intensities of ten unsaturated cytosolic fluorescent spots were quantified using ImageJ program and used in plotting. (c) Overlay of in-cell fluorescence spectrum with those measured in organic solvents.

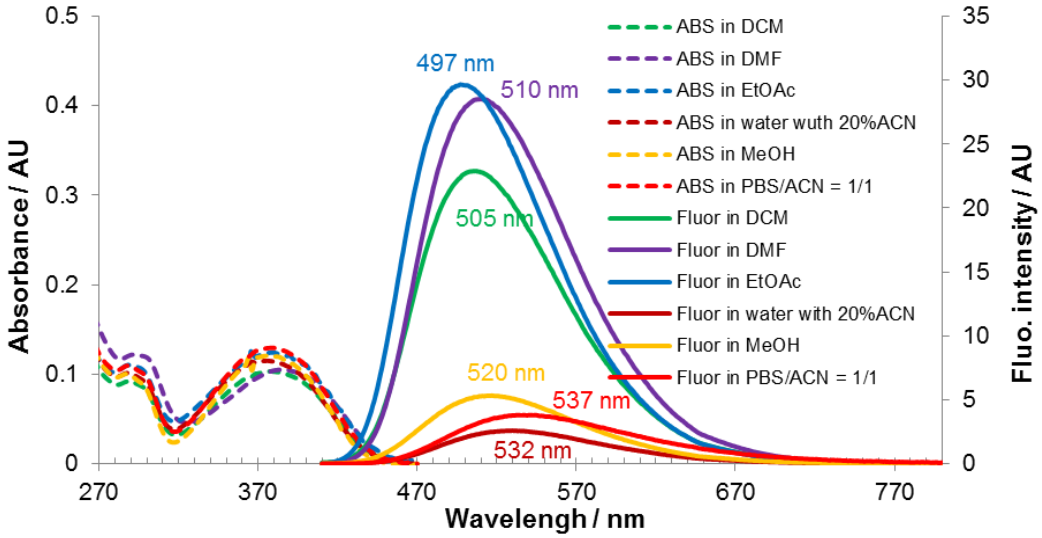


Figure S17. Solvent dependency of UV-Vis (dash lines) and fluorescence spectra (solid lines) of pyrazolines **12/13**. Compounds were dissolved in the indicated solvent at 5 μM concentration. For fluorescence measurement, λ_{ex} = 405 nm. The maximum emission wavelengths were marked on top of the spectra.

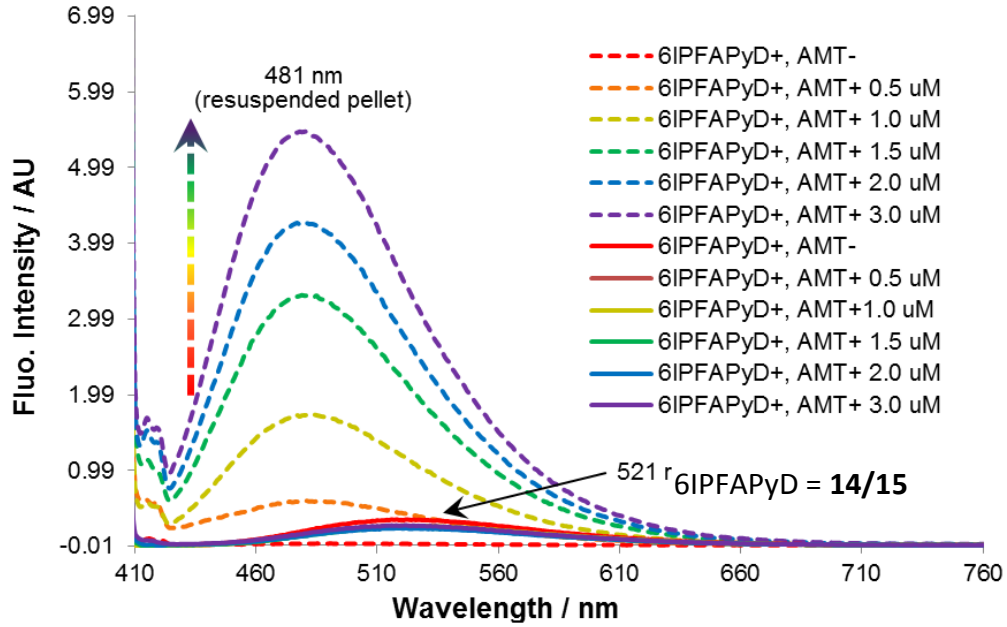


Figure S18. Microtubule binding induced fluorescence change for pyrazoline-docetaxel **14/15**. Solid lines, fluorescence spectra of the supernatants; dash lines, fluorescence spectra of the resuspended pellets. To a solution of 2.5 μM docetaxel-pyrazolines **14/15** in GAB was added various amounts of suspended assembled microtubules (AMT), and after a brief centrifugation the fluorescence spectra of both the supernatants and the re-suspended pellets were acquired, λ_{ex} = 405 nm.

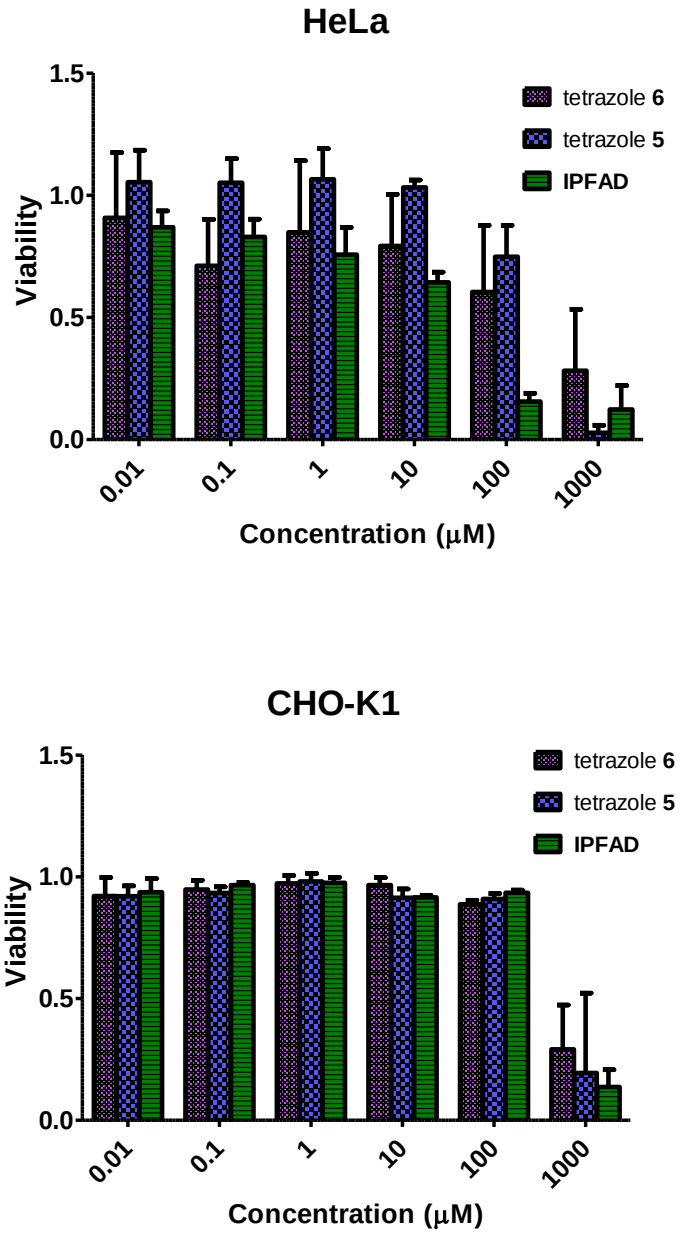


Figure S19. MTS-based cytotoxicity assay for tetrazoles **5** and **6** and IPFAD toward HeLa cells (top) and CHO cells.

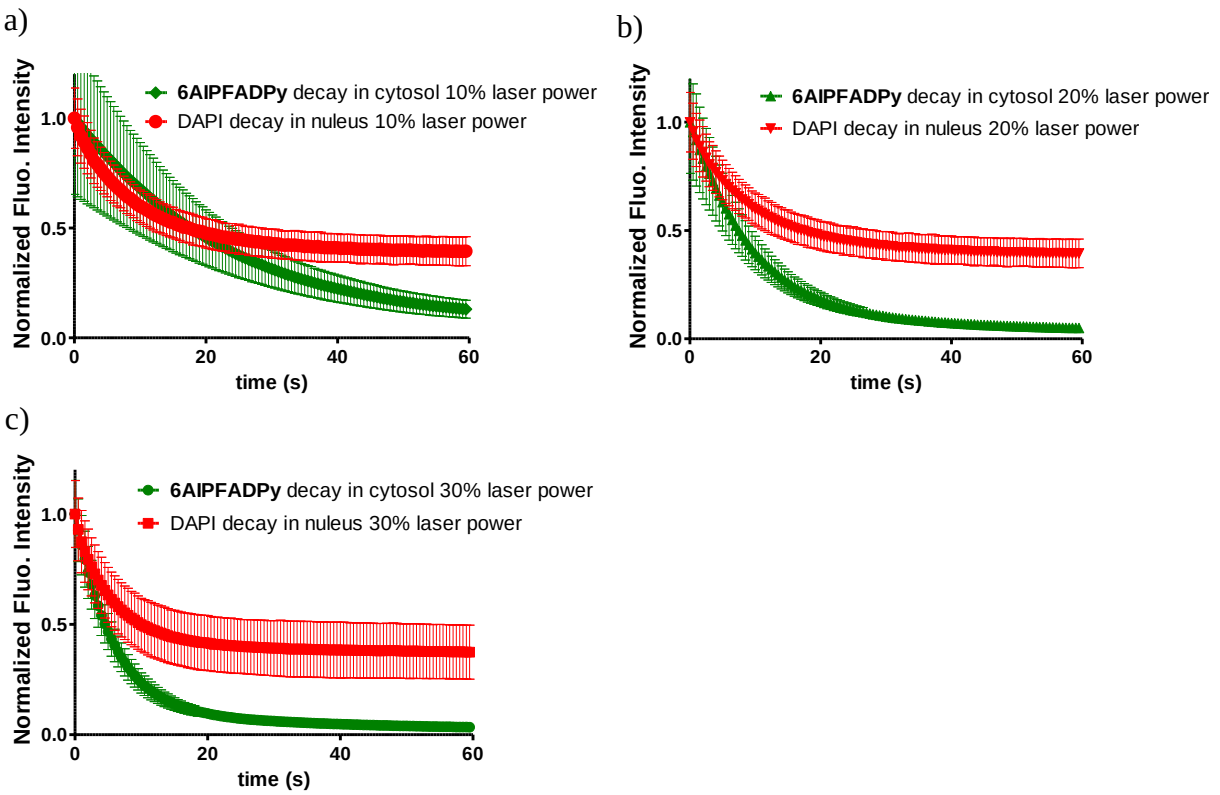
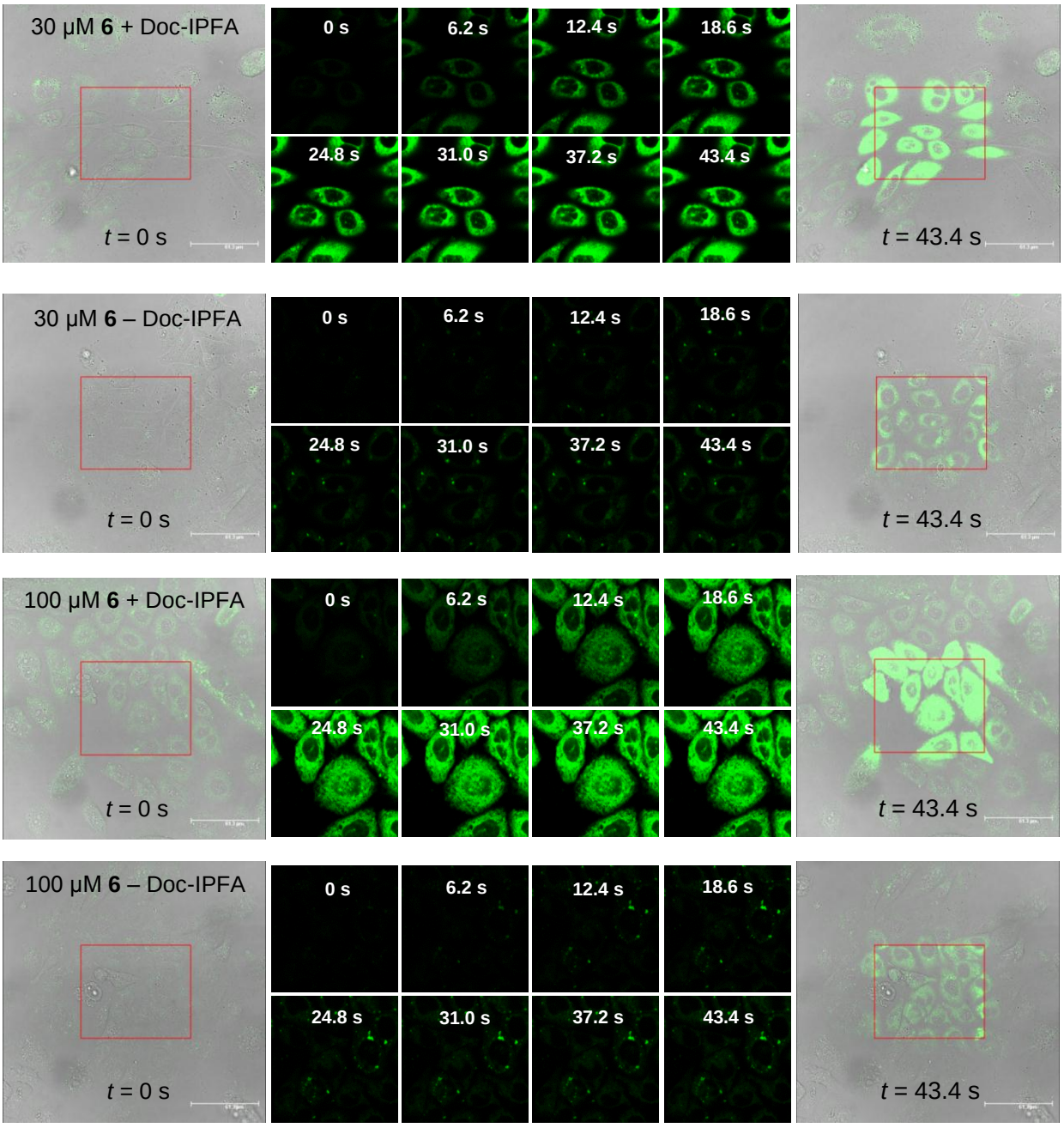


Figure S20. Photostability of pyrazoline-docetaxel **14/15** generated in situ in CHO-K1 cells in comparison with DAPI dye using (a) 10%, (b) 20% and (c) 30% laser power. The normalized fluorescence intensities and standard deviations were derived from quantification of 10 cells using ImageJ program. The full field in the imaging area (256 × 256 pixel, 211.7 × 211.7 μm) was exposed to 405 nm laser irradiation (15 mW) at 2.55 μs per pixel illumination dwell while imaging; the scanning sequence was repeated for 60 s. The acquisition window was set at 441~476 nm for DAPI and 495~617 nm for pyrazoline-docetaxel **14/15**.

a)


30 μM **6** + Doc-IPFA
0 s
6.2 s
12.4 s
18.6 s
24.8 s
31.0 s
37.2 s
43.4 s
t = 0 s
t = 43.4 s
30 μM **6** – Doc-IPFA
0 s
6.2 s
12.4 s
18.6 s
24.8 s
31.0 s
37.2 s
43.4 s
t = 0 s
t = 43.4 s
100 μM **6** + Doc-IPFA
0 s
6.2 s
12.4 s
18.6 s
24.8 s
31.0 s
37.2 s
43.4 s
t = 0 s
t = 43.4 s
100 μM **6** – Doc-IPFA
0 s
6.2 s
12.4 s
18.6 s
24.8 s
31.0 s
37.2 s
43.4 s
t = 0 s
t = 43.4 s

b)

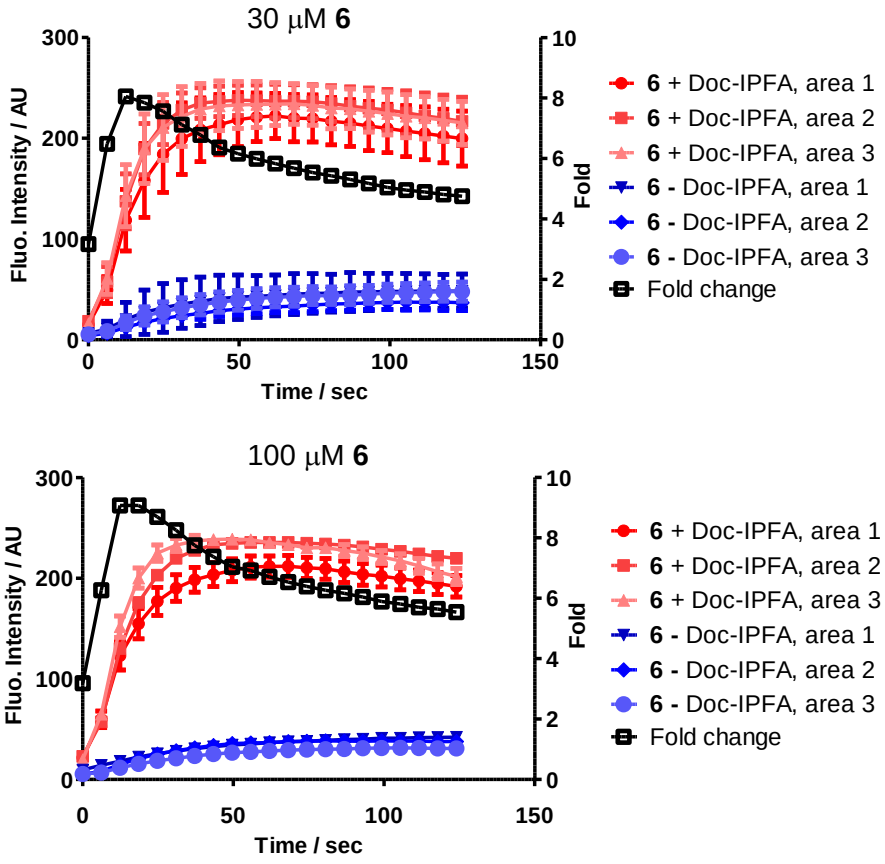


Figure S21. Spatiotemporally controlled imaging of microtubules in real time via two-photon induced fluorogenic cycloaddition reaction in CHO cells. (a) DIC/fluorescence overlay image before photoirradiation (first panel), time-lapsed fluorescence images (middle panels), and DIC/fluorescence overlay image (last panel) of CHO cells under the various treatment conditions. The red rectangle area in each panel was exposed to a focused 700 nm fs-pulsed laser light. Scale bar = 61.3 μm. (b) Plots of average fluorescence intensities in 10 cytosolic regions in the selected CHO-K1 cells (repeated three times). The fold change is the ratio of average cytosolic fluorescence intensity with IPFAD versus without IPFAD treatment at each time point during the irradiation process.

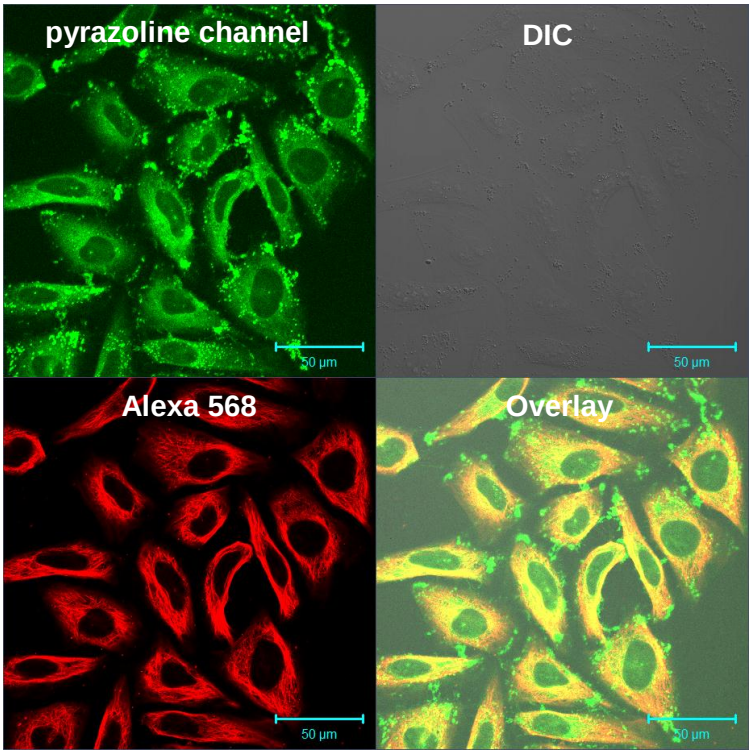
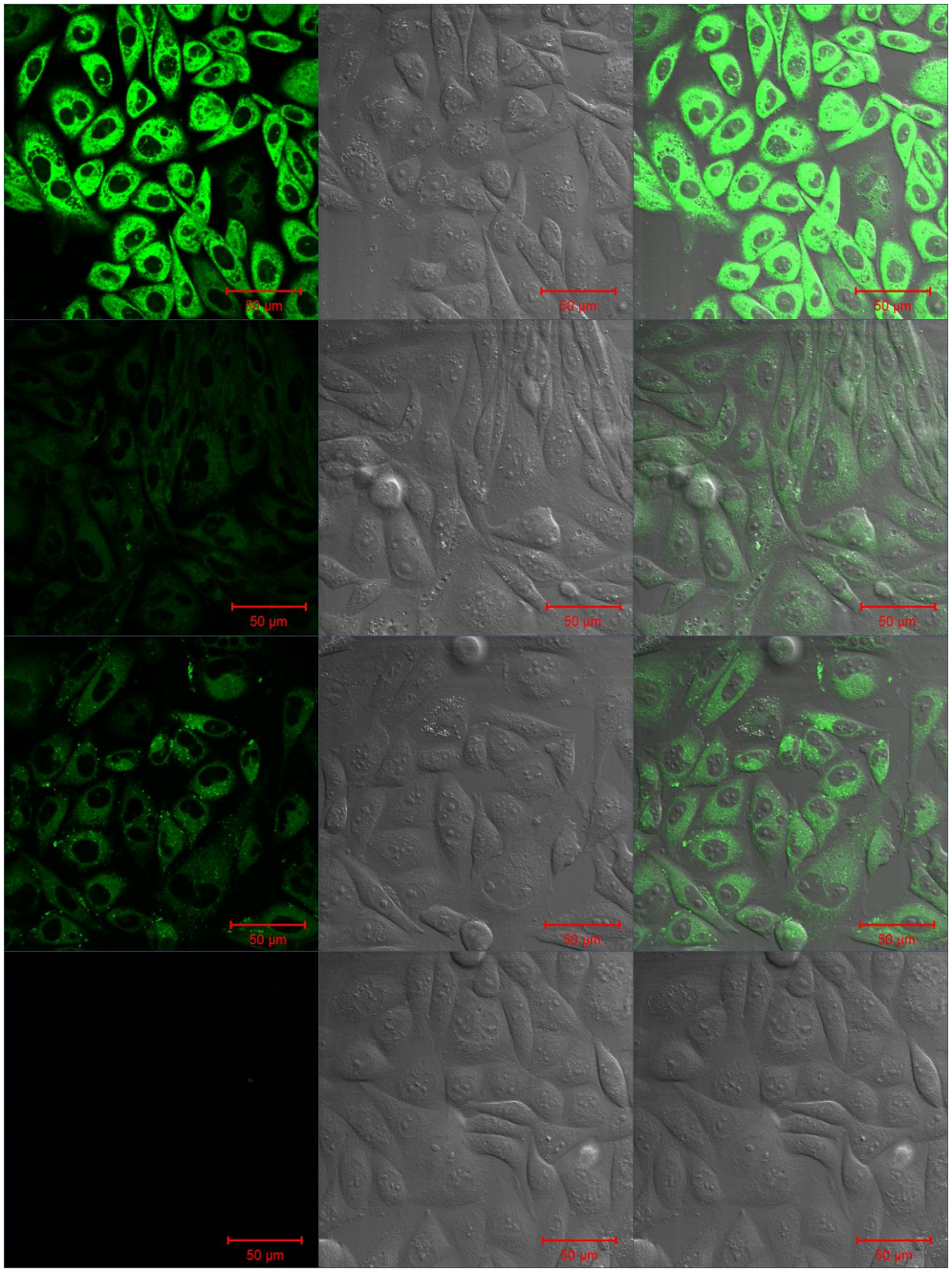


Figure S22. Confocal micrographs confirm labeling specificity of docetaxel-pyrazolines **14/15** towards microtubules. HeLa cells were treated with 10 µM tetrazole **6** for 120 min and 10 µM docetaxel-IPFA for 30 min before photoirradiation by a 365 nm UV light for 3 min. The cells were then permeabilized and fixed with paraformaldehyde before staining with anti-*α*-tubulin antibody followed by fluorescent detection with Alexa Fluor 568-conjugated antimouse IgG antibody. All images were acquired with a Zeiss LSM 710 laser scanning confocal microscope and processed using Zeiss ZEN 2011 Light edition program. For pyrazoline channel, ex = 405 nm; em = 462-580 nm; beam splitter, f-MBS 405/610c. For Alexa 568 channel, ex = 580 nm; em = 585-645 nm; beam splitter, f-MBS 405/580c. The Pearson's correlation coefficient between the pyrazoine channel and the Alexa 568 channel was determined to be 0.66 (Pearson's correlation coefficient is a method of quantifying correlation in many fields of research. In many forms of correlation analysis the values for Pearson's will range from 1 to -1. A value of 1 represents a perfect correlation; -1 represents perfect exclusion and zero represents random localization).[S2]

a)


Pyrazoline Channel
DIC Channel
Overlay
30 µM 6 (14 h)
30 µM Docetaxel-IPFA (30 min)
30 µM 6 (14 h)
–Docetaxel-IPFA
30 µM docetaxel-14/15 (14 h)
No treatment
50 µm

b)

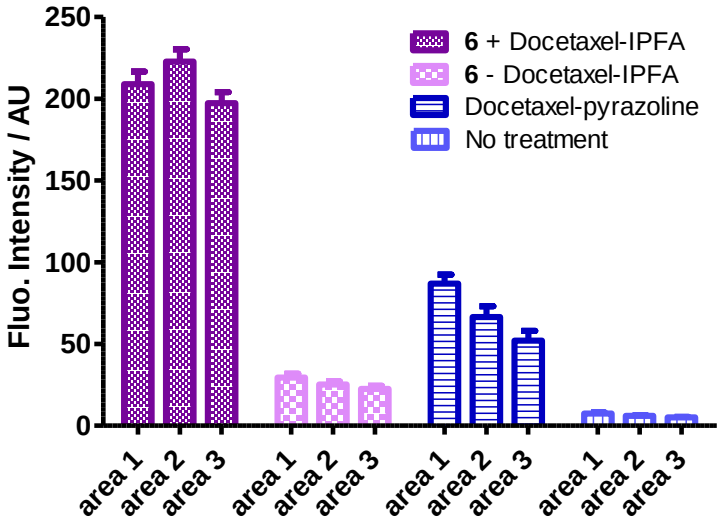


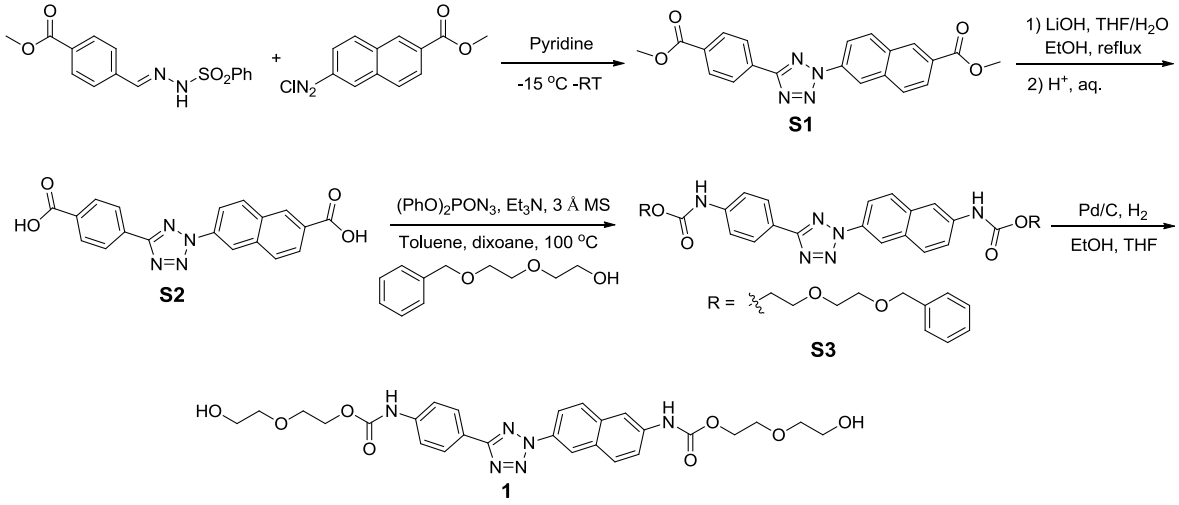
Figure S23. Comparison of the *in situ* generated pyrazoline fluorophore **14/15** *vs*. the preformed pyrazoline fluorophore **14/15** for microtubule labeling in live CHO cells. (a) Confocal micrographs of CHO cells under the various treatment conditions. Scale bar = 50 μm. The images were acquired with a Zeiss LSM 710 laser scanning confocal microscope (ex, 405 nm; em, 462-580 nm; beam splitter, f-MBS 405/610c). (b) Fluorescence intensity of the cytosolic regions inside selected CHO-K1 cells. The cytosolic fluorescence intensity was quantified using ImageJ program.

General Information

Solvents and chemicals were purchased from commercial sources and used directly without further purification. Flash chromatography was performed with SiliCycle P60 silica gel (40-63 μm, 60Å). ^{1}H NMR spectra were recorded with Inova-300, -400 or -500 MHz spectrometers and chemical shifts were reported in ppm using either TMS or deuterated solvents as internal standards (TMS, 0.00; $CDCl_3$, 7.26; CD_3OD, 3.31; DMSO-d_6, 2.50). Multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded at 75.4 MHz, and chemical shifts were reported in ppm using deuterated solvents as internal standards ($CDCl_3$, 77.0; DMSO-d_6, 39.5; CD_3OD, 49.05). UV-Vis absorption spectra were recorded using 1-cm quartz cuvettes on a HP-8452 Diode Array Spectrophotometer. Fluorescence spectra were recorded using 1-cm plastic cuvettes on a JY Fluorolog Spectrofluorometer at 20 ºC. The single-photon activated fluorescence images were acquired with a Zeiss LSM-710 confocal microscope equipped with a continuous laser and fluorescence lifetime (FLIM) detector.

Experimental Procedures and Characterization Data

Scheme S1. Synthesis of tetrazole **1**

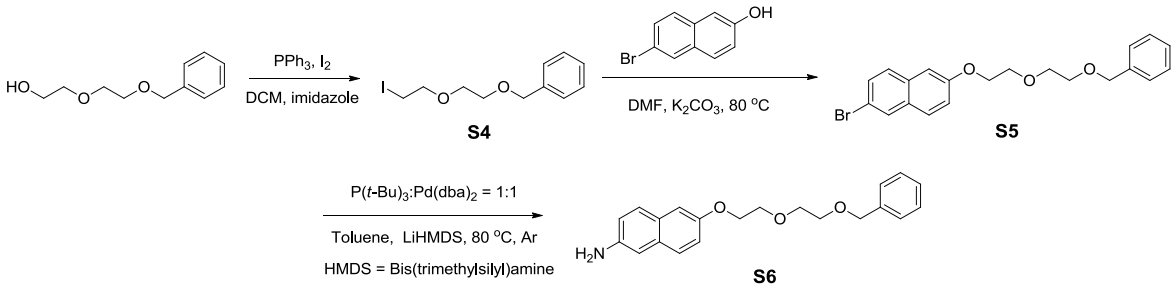


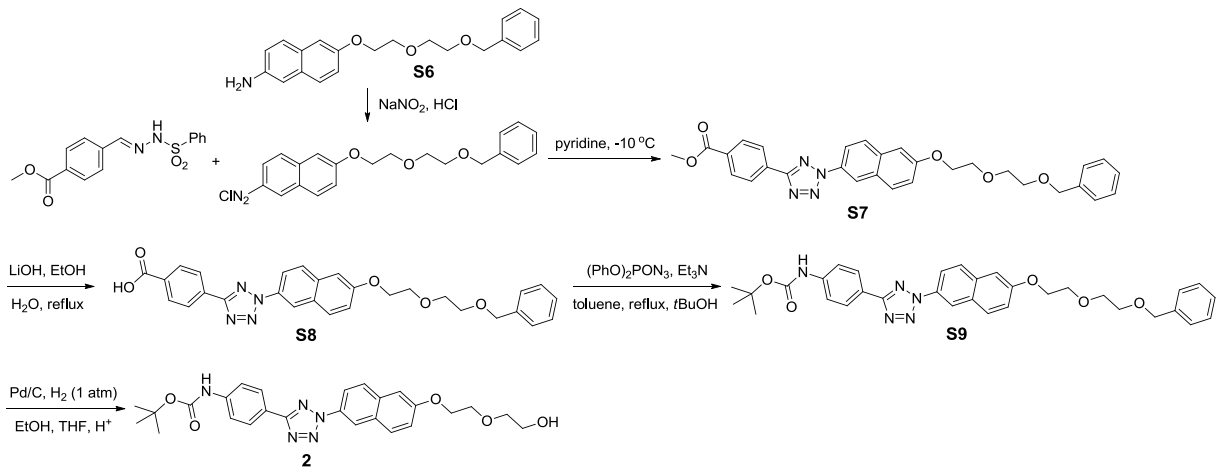
6-(5-(4-Carboxyphenyl)-2*H*-tetrazol-2-yl)-2-naphthoic acid (S2): Tetrazole **S1** was obtained as a red solid according to the literature procedure[S3] from (*E*)-methyl 4-((2-(phenylsulfonyl)-hydrazono)methyl)benzoate and 6-(methoxycarbonyl)-naphthalene-2-diazonium chloride (71% yield). Tetrazole **S1** was treated with 20 equiv LiOH in EtOH/THF/H_2O (3:1:1) mixed solvent to afford the desired naphthalene-tetrazole dicarboxylic acid **S2** as a pink powder (90% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.3 (s, 2H), 8.87 (d, J = 2.0 Hz, 1H), 8.75 (s, 1H), 8.47-8.45 (m, 1H), 8.40-8.38 (dd, J = 9.0, 2.0 Hz, 1H), 8.36-8.31 (m, 3H), 8.20-8.17 (m, 2H), 8.12 (dd, J = 8.5, 1.5 Hz, 1H); HRMS (ESI-FT-ICR) calcd for $C_{19}H_{13}N_4O_4$ 361.0931 [M+H$^+$], found 361.0932.

(6-(5-(4-(((2-(2-(Benzyloxy)ethoxy)ethoxy)carbonyl)amino)phenyl)-2*H*-tetrazol-2-yl)naphthalen-2-yl)carbamic acid 2-(2-(benzyloxy)ethoxy)ethyl ester (S3): A solution of naphthalene-tetrazole dicarboxylic acid **S2** (88.5 mg, 0.246 mmol), triethylamine (83.5 μL, 0.6 mmol) and 3 Å molecular sieves (0.1 g) in a mixed solvent of 2-(2-(benzyloxy)ethoxy)ethanol (0.3 mL), toluene (2.7 mL), dioxane (3.0 mL) was treated with diphenylphosphoryl azide (130 μL, 0.6 mmol) under argon, and the mixture was refluxed at 100°C with vigorous stirring. Once the reaction was complete based on TLC monitoring, molecular sieves were removed by filtration through a thin layer of Celite. The solvent was evaporated and the residue was applied to silica gel flash chromatography (EtOAc/hexanes = 1:2) to give the desired product as a pink solid (85 mg, 51% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.53 (d, J = 2.5 Hz, 1H), 8.25 (dd, J = 8.5, 1.5 Hz, 1H), 8.20-8.18 (m, 2H), 8.06 (brs, 1H), 7.92-7.88 (m, 2H), 7.53-7.52 (m, 2H), 7.43 (dd, J = 9.0, 2.0 Hz, 1H), 7.36-7.26 (m, 10H), 7.00 (brs, 1H), 6.95 (brs, 1H), 4.59 (s, 4H), 4.42-4.37 (m, 4H), 3.82-3.78 (m, 4H), 3.75-3.71 (m ,4H), 3.69-3.66 (m ,4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.74, 153.27, 153.10, 139.89, 138.09, 136.66, 133.99, 133.29, 129.55, 129.52, 129.20, 128.37, 127.95, 127.72, 127.65, 122.15, 120.53, 118.55, 118.50, 117.84, 114.60, 73.31, 70.65, 69.39, 64.51, 64.45; MS (ESI) calcd for $C_{41}H_{42}N_6NaO_8$ 769.8 [M+Na^+], found 769.1.

Tetrazole 1: A solution of tetrazole **S3** (75 mg, 0.1 mmol) in 2 mL EtOH/THF (1:1) containing 20 μL 2 N HCl was treated with 10% palladium on carbon (7.5 mg, 10 wt%) under argon at room temperature, and the mixture was stirred in the atmosphere of hydrogen balloon. After 12 hours, the mixture was filtered through a thin layer of Celite and the filtrate was evaporated to dryness in vacuum. The residue was then purified through recrystallization in EtOH to give the titled compound as white crystals (47 mg, 83% yield): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.19 (brs, 1H), 10.14 (brs, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.24 (brs, 1H), 8.21 (dd, J = 9.0, 2.5 Hz, 1H), 8.14-8.12 (m, 3H), 8.10-8.09 (m, 1H), 7.73-7.71 (m, 2H), 7.69 (dd, J = 8.5, 2.0 Hz, 1H), 4.64 (t, J = 5.5 Hz, 2H), 4.29-4.24 (m, 4H), 3.71-3.67 (m, 4H), 3.65-3.51 (m ,4H), 3.50-3.46 (m ,4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.81, 154.00, 153.84, 142.08, 138.90, 134.19, 132.72, 129.92, 129.79, 129.13, 127.90, 121.42, 120.77, 118.85, 118.72, 118.45, 113.85, 72.72, 69.01, 64.33, 60.63; HRMS (ESI) calcd for $C_{27}H_{31}N_6O_8$ 567.2198 [M+H^+], found 567.2198.

Scheme S2. Synthesis of tetrazole **2**





((2-(2-Iodoethoxy)ethoxy)methyl)benzene (S4): To a solution of PPh_3 (8.42 g, 32.1 mmol) and imidazole (5.20 g, 76.5 mmol) in 80 mL anhydrous DCM at -10°C was added iodine (8.15 g, 32.1 mmol) in small portions, and the mixture was stirred for 15 min. A solution of 2-(2-(benzyloxy)ethoxy)ethanol (6.00 g, 30.6 mmol) in anhydrous DCM was then added dropwise, and the mixture was slowly warmed up to room temperature with stirring. Once reaching completion based on TLC monitoring, the reaction was quenched by adding 10 mL water and the mixture was extracted with 3 × 10 mL DCM. The organic layer was separated, washed once with brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:6) to give the titled compound as a light pink oil (8.03 g, 86% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 4H), 7.30-7.25 (m, 1H), 4.58 (s, 2H), 3.76 (t, J = 7.0 Hz, 2H), 3.70-3.68 (m, 2H), 3.65-3.63 (m, 2H), 3.27 (d, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 128.3, 127.7, 127.6, 73.2, 71.9, 70.2, 69.3, 2.8; MS (ESI) calcd for $C_{11}H_{15}INaO_2$ 329.1 [M+Na^+], found 329.2.

2-(2-(2-(Benzyloxy)ethoxy)ethoxy)-6-bromonaphthalene (S5): To a suspension of 6-bromo-naphthalen-2-ol (4.00 g, 17.9 mmol) and K_2CO_3 (4.95 g, 35.86 mmol) and in 30 mL anhydrous DMF, was added a solution of **S4** (5.66 g, 18.5 mmol) in 5 mL DMF, and the mixture was stirred at 80°C. After the reaction reached completion based on TLC monitoring, the solvent was removed under reduced pressure. The resulting residue was dissolved in 20 mL water and extracted with 3×20 mL EtOAc. The organic layer was separated, washed three times with 20 mL water and once with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:6) to give the desired product as a light yellow oil (5.97 g, 83% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 9.0 Hz, 1H), 7.47 (dd, J = 9.0, 2.5 Hz, 1H), 7.36-7.31 (m, 4H), 7.29-7.25 (m, 1H), 7.19 (dd, J = 9.0, 2.5 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 4.58 (s, 2H), 4.24 (t, J = 5.0 Hz, 2H), 3.94-3.92 (m, 2H), 3.79-3.77 (m, 2H), 3.69-3.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 138.1, 132.9, 130.0, 129.5, 128.4, 128.3, 127.7, 127.6,

120.0, 117.0, 106.7, 73.3, 70.9, 69.6, 69.4, 67.5; MS (ESI) calcd for $C_{21}H_{22}BrO_3$ 401.1 [M+H$^+$], found 401.1.

6-(2-(2-(Benzyloxy)ethoxy)ethoxy)naphthalen-2-amine (S6): In a round-bottom flask were placed bromonaphthalene **S5** (4.08 g, 10.2 mmol), P^{t}Bu$_3$ (124 μL, 0.509 mmol), Pd(dba)$_2$ (292 mg, 0.509 mmol), LiHMDS (1.0 M in THF, 20.2 mL, 20.2 mmol) and 30 mL anhydrous toluene.[S4] The flask was capped with a PTFE septum and purged with argon. The mixture was stirred at 80 °C while the reaction progress was monitored by TLC. Upon disappearance of **S5**, the crude mixture was diluted with Et_2O (30 mL) and quenched by adding 15 mL of 3 N HCl at 0°C. The mixture was transferred to a separation funnel and added 20 mL DCM. The *p*H of the solution was adjusted to 10 by adding suitable amount of 1 N NaOH, and the mixture was extracted with 3×20 mL DCM. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes = 1:2) to give the desired product as a light yellow powder (2.87 g, 84% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 9.0 Hz, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.36-7.31 (m, 4H), 7.29-7.25 (m, 1H), 7.09 (dd, J = 9.0, 2.5 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 8.0, 2.5 Hz, 1H), 4.58 (s, 2H), 4.20 (t, J = 5.0 Hz, 2H), 3.90 (t, J = 5.0 Hz, 2H), 3.78-3.76 (m, 2H), 3.71 (brs, 2H), 3.68-3.66 (m, 2H); MS (ESI) calcd for $C_{21}H_{24}NO_3$ 338.2 [M+H$^+$], found 338.2.

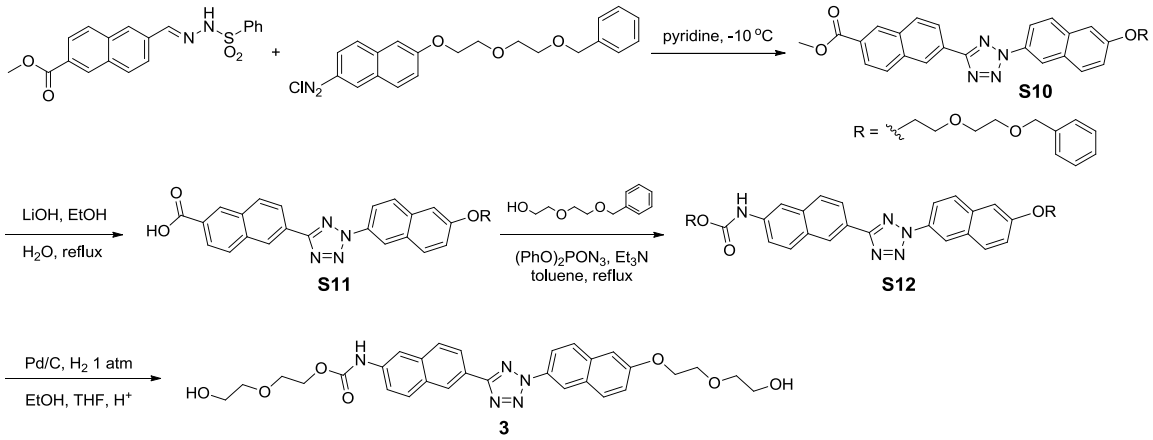
Methyl 6-(2-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)-2-naphthoate (S7): A cooled solution of sodium nitrite (62 mg, 0.9 mmol) in 2 mL water was added to a solution of naphthalenamine (**S6,** 337 mg, 1.0 mmol) in 1 mL of concentrated HCl and 7 mL of 50% ethanol in water kept at a temperature below 5 °C. The resulting diazonium chloride solution was added dropwise to a stirred solution of (*E*)-methyl 4-((2-(phenylsulfonyl)hydrazono)methyl) benzoate (286 mg, 0.9 mmol) in 10 mL pyridine at -10 °C over 30 min.[S5] The reaction mixture was allowed to warm up to room temperature over 12 hours with stirring. The organic solvents were then removed under reduced pressure, and the solution was diluted by adding 30 mL DCM. The precipitate was then collected on a filtration funnel and washed successively with water, ethanol and DCM. The crude was recrystallized in hot ethanol to give a pink crystalline solid as the desired product (189 mg, 40% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 1.5 Hz, 1H), 8.39-8.36 (m, 2H), 8.27 (dd, J = 9.0, 2.0 Hz, 1H), 8.22-8.21 (m, 2H), 7.90 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.37-7.32 (m, 4H), 7.31-7.27 (m, 2H), 7.23 (d, J = 2.5 Hz, 1H), 4.60 (s, 2H), 4.31 (t, J = 4.5 Hz, 2H), 3.98 (s, 3H), 3.98-3.96 (m, 2H), 3.81-3.79 (m, 2H), 3.71-3.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 164.2, 158.1, 138.1, 134.8, 132.4, 131.7, 131.3, 130.2, 130.1, 128.5, 128.3, 127.7, 127.6, 126.9, 120.8, 118.3, 106.8, 73.3, 70.9, 69.6, 69.4, 67.6, 52.3; MS (ESI) calcd for $C_{30}H_{29}N_4O_5$ 525.2 [M+H$^+$], found 525.3.

4-(2-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)benzoic acid (S8): A solution of **S7** (128 mg, 0.244 mmol) in 5 mL MeOH/THF/H_2O (1:2:1) was treated with LiOH monohydrate (120 mg, 2.44 mmol), and the mixture was heated to 50°C under vigorous stirring. After the reaction was complete based on TLC monitoring, the reaction mixture was adjusted to pH = 1 with 2 N HCl. The precipitate was collected, washed successively with water and EtOH, and dried to give the titled product as a light pink solid (99 mg, 80% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (d, J = 2.0 Hz, 1H), 8.30-8.29 (m, 2H), 8.25 (dd, J = 9.0, 2.0 Hz, 1H), 8.17-8.13 (m, 3H), 8.10 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.34 (dd, J = 9.0, 2.5 Hz, 1H), 7.33-7.32 (m, 4H), 7.29-7.26 (m, 1H), 4.51 (s, 2H), 4.29 (t, J = 4.0 Hz, 2H), 3.86 (t, J = 4.0 Hz, 2H), 3.70-3.68 (m, 2H), 3.62-3.60 (m, 2H); MS (ESI) calcd for $C_{29}H_{26}N_4NaO_5$ 533.2 [M+Na$^+$], found 533.3.

***tert*-Butyl (4-(2-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)phenyl) carbamate (S9):** To a suspension of **S8** (122 mg, 0.24 mmol), NEt_3 (139 µL, 1 mmol), and 3Å molecular sieve (0.1 g) in 3 mL ^{t}BuOH/toluene (1:1) was added diphenylphosphoryl azide (104 µL, 0.48 mmol), and the mixture was refluxed with stirring under argon for 3 hours. After the reaction was complete based on TLC monitoring, the molecular sieve was removed via filtration, and the filtrate was concentrated under reduced pressure The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:2 to 2:1) followed by recrystallization in EtOH to give the titled compound as a white crystalline solid (66 mg, 48% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 2.0 Hz, 1H), 8.26 (dd, J = 8.5, 2.0 Hz, 1H), 8.22-8.20 (m, 2H), 7.87 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.37-7.33 (m, 3H), 7.32-7.27 (m, 3H), 7.21 (d, J = 2.0 Hz, 1H), 6.66 (s, 1H), 4.60 (s, 2H), 4.30 (t, J = 4.0 Hz, 2H), 3.97 (t, J = 4.0 Hz, 2H), 3.81-3.79 (m, 2H), 3.70-3.68 (m, 2H), 1.55 (s, 9H); MS (ESI) calcd for $C_{33}H_{36}N_5O_5$ 582.3 [M+H$^+$], found 582.2.

***tert*-Butyl (4-(2-(6-(2-(2-hydroxyethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)-phenyl) carbamate (2):** To a solution of tetrazole **S9** (66 mg, 0.11 mmol) in EtOH/THF (1:1; 2 mL) and 20 µL 2 N HCl was added 10% palladium on carbon (7 mg, 10 wt %) at room temperature, and the mixture was stirred under 1 atm hydrogen gas atmosphere. After 24 hours, the mixture was filtered through a layer of Celite to remove the catalyst and the filtrate was evaporated to dryness in vacuum. The white residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:2 to 2:1) followed by recrystallization in EtOH to give the titled compound as a white solid (55 mg, 82% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 2.0 Hz, 1H), 8.27 (dd, J = 8.5, 2.0 Hz, 1H), 8.23-8.20 (m, 2H), 7.90 (dd, J = 9.0, 2.0 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.30 (dd, J = 9.0, 2.5 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 6.67 (s, 1H), 4.30 (t, J = 4.0 Hz, 2H), 3.97 (t, J = 4.0 Hz, 2H), 3.82-3.80 (m, 2H), 3.74-3.72 (m, 2H), 2.14 (brs, 1H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 157.7, 152.4, 140.4, 134.6, 132.6, 130.1, 128.4, 127.9, 121.7, 120.5, 118.4, 118.3, 118.1, 106.8, 81.0, 72.6, 69.5, 67.5, 61.7, 28.3; HRMS (ESI) calcd for $C_{26}H_{30}N_5O_5$ 492.2241 [M+H$^+$], found 492.2228.

Scheme S3. Synthesis of tetrazole **3**



Methyl 6-(2-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)-2-naphthoate (S10): A solution of sodium nitrite (117 mg, 1.69 mmol) in 3 mL water was added to a solution of naphthalenamine **S6** (547 mg, 1.69 mmol) in 2 mL of concentrated HCl and 15 mL of 50% EtOH/H_2O kept at a temperature below 5°C. The resulting naphalendiazonium chloride salt solution was added dropwise to a stirred solution of (*E*)-methyl 6-((2-(phenylsulfonyl)hydrazono) methyl)-2- naphthoate (645 mg, 1.75 mmol) in 15 mL pyridine at -10°C over 30 min. The reaction mixture was allowed to slowly warm up to room temperature over 12 hours with stirring. The solvent was then removed under reduced pressure, and the crude mixture was diluted with 30 mL DCM. The precipitate was collected with a filtration funnel and washed successively with water, ethanol and DCM. After recrystallization in hot ethanol, the titled compound was obtained as a pink crystalline solid (502 mg, 52% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.73 (d, J = 1.5 Hz, 2H), 8.40-8.36 (m, 2H), 8.30 (d, J = 8.5 Hz, 1H), 8.27 (dd, J = 9.0, 2.5 Hz, 1H), 8.14 (d, J = 9.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.08 (dd, J = 8.5, 1.5 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.36 (dd, J = 8.5, 2.5 Hz, 1H), 7.37-7.32 (m, 4H), 7.29-7.26 (m, 1H), 4.51 (s, 2H), 4.29 (t, J = 4.5 Hz, 2H), 3.95 (s, 3H), 3.86 (t, J = 4.5 Hz, 2H), 3.70-3.68 (m, 2H), 3.62-3.60 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 164.6, 158.2, 138.9, 135.3, 135.2, 133.5, 132.2, 131.2, 130.9, 130.8, 129.8, 129.3, 128.6, 128.3, 127.9, 127.8, 126.7, 126.6, 126.2, 124.9, 121.0, 118.9, 118.8, 110.0, 107.5, 72.5, 70.4, 69.6, 69.3, 67.9, 52.8; MS (ESI) calcd for $C_{68}H_{60}N_8NaO_{10}$ 1171.4 [2M+Na^+], found 1171.1.

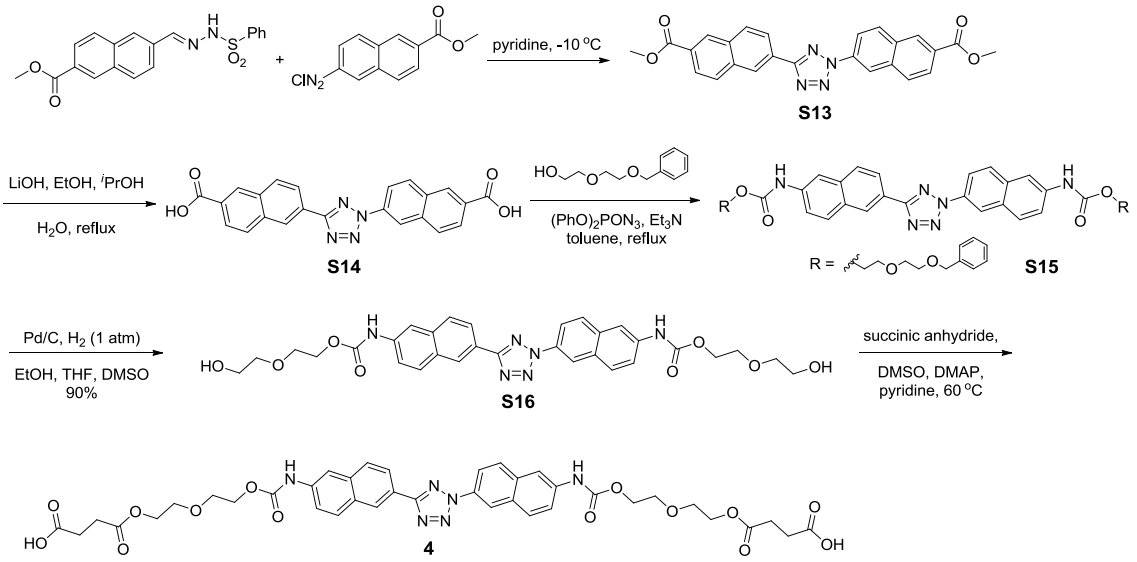
6-(2-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)-2-naphthoic acid (S11): To a solution of **S10** (150 mg, 0.261 mmol) in 5 mL EtOH/H_2O (3:1) was added LiOH monohydrate (110 mg, 2.61 mmol), and the mixture was heated to 65°C under vigorous stirring. After the reaction reached completion based on TLC monitoring, the mixture was adjusted to *p*H = 1 with 2 N HCl. The precipitate was collected, washed successively with water and EtOH, and dried to give the titled compound as a light yellow solid (122 mg, 82% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.22 (brs, 1H), 8.89 (s, 1H), 8.72 (s, 1H), 8.70 (s, 1H), 8.35 (s, 2H), 8.28-

8.25 (m, 2H), 8.13 (d, J = 9.5 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 8.06 (dd, J = 9.0, 2.5 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.38-7.32 (m, 5H), 7.29-7.26 (m, 1H), 4.51 (s, 2H), 4.28 (t, J = 4.0 Hz, 2H), 3.85 (t, J = 4.0 Hz, 2H), 3.70-3.68 (m, 2H), 3.62-3.60 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 164.6, 158.2, 138.8, 135.2, 135.1, 133.5, 132.2, 131.0, 130.8, 130.7, 129.8, 129.5, 129.3, 128.6, 128.3, 127.9, 127.8, 126.6, 126.4, 124.7, 121.0, 118.8, 118.7, 107.5, 72.5, 70.4, 69.6, 69.3, 67.8; MS (ESI) calcd for $C_{33}H_{28}N_4NaO_5$ 583.2 [M+Na$^+$], found 583.2.

2-(2-(Benzyloxy)ethoxy)ethyl (6-(2-(6-(2-(2-(benzyloxy)ethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)naphthalen-2-yl)carbamate (S12): To a suspension of **S11** (172 mg, 0.306 mmol), NEt_3 (139 μL, 1 mmol) and 3 Å molecular sieve (0.1 g) in 6 mL 2-(2-(benzyloxy)ethoxy)ethanol/ toluene (1:10) was added diphenylphosphoryl azide (100 μL, 0.46 mmol) under argon with vigorous stirring, and the mixture was refluxed for 3 hours. After reaction reached completion based on TLC monitoring, the molecular sieve was removed via filtration and the filtrate was concentrated. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:2 to 2:1) followed by recrystallization in EtOH to give the titled compound as a white solid (209 mg, 91% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.31 (t, J = 9.0 Hz, 1H), 8.30 (t, J = 9.0 Hz, 1H), 8.05 (s, 1H), 7.92-7.89 (m, 4H), 7.42 (dd, J = 8.5, 2.5 Hz, 1H), 7.37-7.26 (m, 10H), 7.24-7.21 (m, 2H), 6.98 (s, 1H), 4.60 (s, 2H), 4.59 (s, 2H), 4.41 (m, 2H), 4.30 (t, J = 4.0 Hz, 2H), 3.97 (t, J = 4.0 Hz, 2H), 3.81-3.80 (m, 4H), 3.75-3.73 (m, 2H), 3.71-3.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 157.9, 153.2, 138.1, 138.1, 136.5, 134.9, 134.7, 132.6, 130.0, 129.8, 129.7, 128.4, 128.3, 128.2, 127.7, 127.7, 127.6, 126.6, 125.3, 124.7, 123.3, 120.7, 120.1, 120.0, 119.7, 118.3, 118.1, 114.6, 106.8, 73.3, 70.9, 70.6, 69.6, 69.5, 69.4, 69.4, 67.6, 64.4; MS (ESI) calcd for $C_{44}H_{43}N_5NaO_7$ 776.3 [M+Na$^+$], found 776.2.

2-(2-Hydroxyethoxy)ethyl (6-(2-(6-(2-(2-hydroxyethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazole-5-yl)naphthalen-2-yl)carbamate (3): A solution of **S12** (150 mg, 0.2 mmol) in EtOH/THF (1:1; 2 mL) and 20 μL 2 N HCl was treated with 10 % palladium on carbon (15 mg, 10 wt %) under argon at room temperature, and the mixture was stirred under 1 atm hydrogen atmosphere. After 24 hours, the mixture was filtered through a layer of Celite to remove the catalyst and the filtrate was evaporated to dryness in vacuum. The white residue was recrystallized in EtOH to give the titled compound as a white crystal (85 mg, 74% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.73-8.72 (m, 2H), 8.27 (dd, J = 8.5, 2.5 Hz, 1H), 8.22 (dd, J = 9.0, 1.5 Hz, 1H), 8.20 (s, 1H), 8.14 (d, J = 9.5 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.66 (dd, J = 9.0, 2.0 Hz, 1H), 7.52 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 9.0, 2.5 Hz, 1H), 4.67-4.63 (m, 2H), 4.29-4.27 (m, 4H), 3.84 (t, J = 4.5 Hz, 2H), 3.71-3.69 (m, 2H), 3.56-3.52 (m ,6H), 3.50-3.48 (m ,2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.1, 158.1, 154.0, 138.8, 135.0, 132.3, 130.7, 129.9, 129.4, 129.3, 128.7, 128.3, 126.6, 124.4, 122.5, 120.9, 120.7, 118.7, 113.8, 107.4, 72.9, 72.7, 69.2, 69.0, 67.9, 64.3, 60.7, 60.6; HRMS (ESI) calcd for $C_{30}H_{32}N_5O_7$ 574.2296 [M+H$^+$], found 574.2292.

Scheme S4. Synthesis of tetrazole **4**



Dimethyl 6,6'-(2*H*-tetrazole-2,5-diyl)bis(2-naphthoate) (S13): A cooled solution of sodium nitrite (54 mg, 0.77 mmol) in 1 mL water was added to a solution of naphthalenamine (155 mg, 0.77 mmol) in 1 mL of concentrated HCl and 5 mL EtOH/H_2O (1:1) kept at a temperature below 5°C. The resulting naphalendiazonium chloride solution was then added dropwise to a stirred solution of (*E*)-methyl 6-((2-(phenylsulfonyl)hydrazono)methyl)-2-naphthoate (300 mg, 0.80 mmol) in 7.5 mL pyridine at -10°C over 30 min. The reaction mixture was allowed to slowly warm up to room temperature with stirring over a period of 12 hours. The solvent was then removed under reduced pressure, and the crude mixture was diluted by adding 30 mL DCM. The precipitate was collected on a filtration funnel and washed successively with water, EtOH, and DCM. The crude as recrystallized in hot DMSO to give the titled compound as a pink crystalline solid (270 mg, 80% yield). Since the compound was not soluble in DMSO-d_6 at room temperature, it was used directly in the next step reaction without further characterization.

6,6'-(2*H*-tetrazole-2,5-diyl)bis(2-naphthoic acid) (S14): A solution of **S13** (163 mg, 0.372 mmol) in 5 mL EtOH/^{i}PrOH/H_2O (10:10:1) was treated with LiOH monohydrate (312 mg, 7.44 mmol), and the mixture was heated to 70°C under vigorous stirring. After the reaction reached completion based on TLC monitoring, the reaction mixture was adjusted to *p*H = 1 with 2 N HCl. The precipitate was collected, washed successively with water and EtOH, and dried in vacuum to give the titled compound as a gray powder (137 mg, 90% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.86 (s, 1H), 8.67 (s, 1H), 8.63 (s, 1H), 8.41-8.36 (m, 2H), 8.36-8.30 (m, 2H), 8.23 (d, J = 8.0 Hz, 1H), 8.18 (t, J = 9.0 Hz, 2H), 8.12 (d, J = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.1, 168.0, 165.1, 134.6, 134.6, 134.3, 134.0, 133.8, 133.0, 131.7, 130.7, 129.5, 129.4, 128.5, 128.5, 128.5, 127.8, 126.6, 125.1, 125.0, 124.1, 118.5, 118.3; MS (ESI) calcd for $C_{23}H_{14}N_4NaO_4$ 433.1 [M+Na^+], found 433.2.

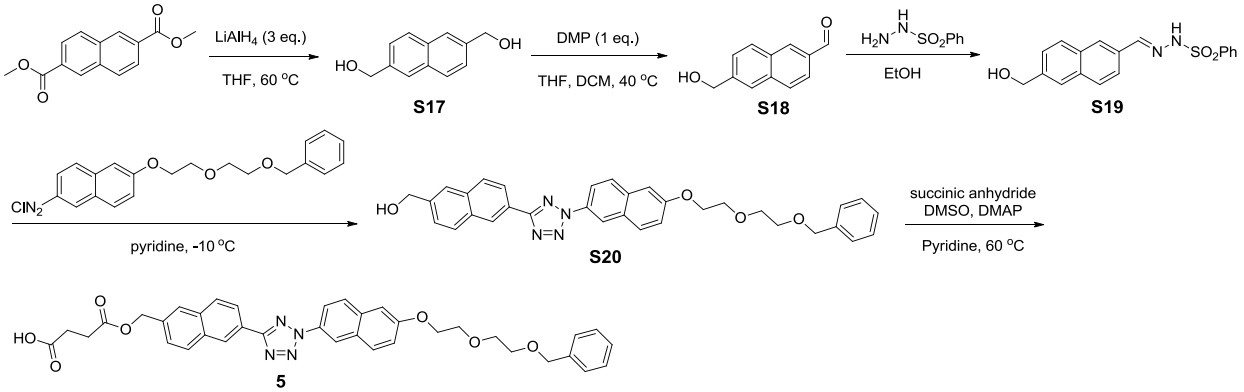
6,6'-(2*H*-tetrazole-2,5-diyl)bis(2-(2-benzyloxyethoxy)ethyl(naphthalen-2-yl)carbamate) (S15): To a stirred suspension of **S14** (115 mg, 0.28 mmol), triethylamine (235 μL, 1.69 mmol) and 3 Å molecular sieve (0.2 g) in 20 mL 2-(2-(benzyloxy)ethoxy)ethanol/toluene (1:1) under argon was added diphenylphosphoryl azide (183 μL, 0.84 mmol), and the mixture was refluxed for 3 hours. After reaction reached completion based on TLC monitoring, the molecular sieve was removed via filtration and the filtrate was concentrated. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:2 to 2:1) followed by recrystallization in EtOH to give the titled compound as a white solid (153 mg, 68% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.29 (dd, J = 6.0, 2.5 Hz, 1H), 8.28 (dd, J = 6.0, 2.5 Hz, 1H), 8.08 (s, 1H), 8.02 (s, 1H),7.94-7.89 (m, 4H), 7.44 (dd, J = 9.0, 2.2 Hz, 1H), 7.40 (dd, J = 9.0, 2.2 Hz, 1H), 7.37-7.26 (m, 10H), 7.02 (s, 1H), 6.98 (s, 1H), 4.59 (s, 4H), 4.42-4.40 (m, 4H), 3.82-3.80 (m, 4H), 3.75-3.73 (m, 4H), 3.70-3.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 153.4, 138.0, 136.6, 136.5, 134.8, 133.8, 133.1, 129.7, 129.5, 129.4, 129.1, 128.3, 128.1, 127.7, 127.6, 126.4, 124.4, 123.1, 120.6, 119.8, 118.2, 117.6, 114.6, 73.3, 70.6, 69.4, 64.4, 64.4; MS (ESI) calcd for $C_{45}H_{45}N_6O_8$ 797.3 [M+H$^+$], found 797.2.

6,6'-(2*H*-tetrazole-2,5-diyl)bis(2-(2-hydroxyethoxy)ethyl(naphthalen-2-yl)carbamate) (S16): A solution of tetrazole **S15** (54 mg, 0.072 mmol) in 3 mL EtOH/THF/DMF (1:1:1) and 50 μL 3 N HCl was treated with 10% palladium on carbon (6 mg, 10 wt%) under argon at room temperature, and the reaction mixture was stirred under 1 atm hydrogen atmosphere. After 24 hours, the mixture was filtered through a layer of Celite and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:2 to 2:1) followed by recrystallization in EtOH to give the titled compound as a white powder (36 mg, 81% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (s, 1H), 10.15 (s, 1H), 8.73 (s, 1H), 8.70 (d, J = 2.0 Hz, 1H), 8.27-8.22 (m, 3H), 8.20 (s, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 9.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.70 (dd, J = 9.5, 2.0 Hz, 1H), 7.66 (dd, J = 9.5, 2.0 Hz, 1H), 4.64 (t, J = 5.5 Hz, 2H), 4.28-4.27 (m, 4H), 3.70 (t, J = 5.0 Hz, 4H), 3.55-3.52 (m, 4H), 3.50-3.48 (m, 4H); MS (ESI) calcd for $C_{62}H_{64}N_{12}NaO_{16}$ 1255.4 [M+Na$^+$], found 1255.1.

6,6'-(2*H*-tetrazole-2,5-diyl)bis(4-(2-(2-(((naphthalen-2-yl)carbamoyl)oxy)ethoxy)ethoxy)-4-oxobutanoic acid) (4): To a solution of tetrazole **S16** (36 mg, 0.058 mmol), DMAP (7 mg, 0.058 mmol), and pyridine (20 μL, 0.24 mmol) in 2 mL DMSO was added succinic anhydride (24 mg, 0.24 mmol) under argon at room temperature, and the mixture was heated to 60°C. The reaction progress was monitored by HPLC. After 24 hours, the mixture was quenched by adding 10 mL of water and 1 mL of 3 N HCl, and the solution was extracted with 3×10 mL EtOAc. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was recrystallized in EtOH/H_2O (2:1) twice to give the titled compound as a light yellow powder (39 mg, 83% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.21 (brs, 2H), 10.18 (s, 1H), 10.14 (s, 1H), 8.73 (s, 1H), 8.70 (d, J = 1.5 Hz, 1H), 8.27-8.22 (m, 3H), 8.20 (s,

1H), 8.14 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 9.5 Hz, 1H), 8.09 (d, *J* = 9.5 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.70 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.0 Hz, 1H), 4.29-4.28 (m, 4H), 4.17 (t, *J* = 4.5 Hz, 4H), 3.72 (t, *J* = 4.5 Hz, 4H), 3.67 (t, *J* = 4.5 Hz, 4H), 2.54-2.50 (m, 4H), 2.50-2.45 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.7, 172.6, 165.1, 153.9, 138.9, 138.8, 135.0, 134.2, 132.7, 130.0, 129.9, 129.8, 129.4, 129.1, 128.7, 126.6, 124.4, 122.5, 121.4, 120.7, 118.6, 118.5, 113.9, 69.0, 68.6, 64.1, 63.8, 29.0; HRMS (ESI) calcd for $C_{39}H_{41}N_6O_{14}$ 817.2675 [M+H$^+$], found 817.2672.

Scheme S5. Synthesis of tetrazole **5**



Naphthalene-2,6-diyldimethanol (S17)[S6]**:** A solution of dimethyl naphthalene-2,6-dicarboxylate (2.44 g, 10 mmol) in 150 mL anhydrous THF was warmed to 60°C under argon protection with vigorous stirring. Lithium aluminum hydride powder (1.14 g, 30 mmol) was added carefully in small portions to the above solution. The reaction was monitored by withdrawing a small amount of the reaction mixture, quenching the mixture with 1 N HCl, and analyzing the quenched product by TLC. After complete disappearance of the starting materials, the reaction was quenched by adding EtOH dropwise at 0°C until there was no gas being released. The solution was adjusted to *p*H 2 by adding 3 N HCl, and the mixture was extracted with 3×30 mL EtOAc. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was recrystallized in EtOH/EtOAc (2:1) twice to give the titled compound as a white powder (1.72 g, 91% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.89 (s, 2H), 7.44 (dd, *J* = 8.0, 1.0 Hz, 2H), 5.30 (t, *J* = 6.0 Hz, 2H), 4.65 (t, *J* = 6.0 Hz, 4H); MS (ESI) calcd for $C_{12}H_{13}O_2$ 189.1 [M+H$^+$], found 189.2.

6-(Hydroxymethyl)-2-naphthaldehyde (S18): A solution of naphthalene-2,6-diyldimethanol (759 mg, 4.04 mmol) in 50 mL anhydrous THF/DCM (1:1) was warmed to 40°C under argon protection with vigorous stirring. Dess–Martin periodinane powder (1.71 g, 4.0 mmol) was added carefully in small portions to above solution. The reaction was monitored by TLC. After complete consumption of the starting materials, the reaction was quenched by adding saturated $NaHCO_3$ at 0°C. The mixture was filtered and the filtrate was extracted with 3×30 mL EtOAc. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated at

reduced pressure. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:2 to 2:3) to give the titled compound as a white solid (445 mg, 59% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.32 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.95 (dd, J = 9.0, 1.5 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.89 (s, 1H), 7.58 (dd, J = 8.0, 1.5 Hz, 1H), 4.92 (s, 2H), 2.04 (brs, 1H); MS (ESI) calcd for $C_{12}H_{11}O_2$ 187.1 [M+H$^+$], found 187.2.

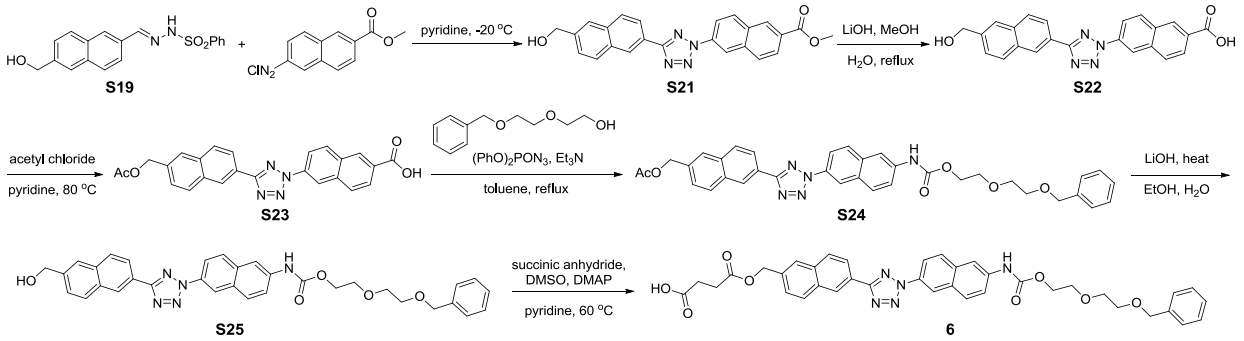
(*E*)-*N'*-((6-(hydroxymethyl)naphthalen-2-yl)methylene)benzenesulfonohydrazide (S19): A solution of benzenesulfonohydrazide (397 mg, 2.31 mmol) in 5 mL anhydrous EtOH was warmed to 40°C with vigorous stirring. A solution of **S18** (429 mg, 2.31 mmol) in 3 mL EtOH was then added carefully in small portions. The reaction mixture was stirred at 0°C, and the precipitate was collected and washed with EtOH. The crystalline solid was dried under vacuum to give the titled compound as a yellow solid (720 mg, 92% yield). The product was used directly in the next step reaction.

(6-(2-(6-(2-(2-(Benzyloxy)ethoxy)ethoxy)naphthalen-2-yl)-2*H*-tetrazol-5-yl)naphthalen-2-yl)methanol (S20): To a cooled solution of sodium nitrite (13 mg, 0.21 mmol) in 0.5 mL water was added a solution of naphthalenamine (70 mg, 0.21 mmol) in 0.3 mL concentrated HCl and 1 mL EtOH/H_2O (1:1) at a temperature below 5°C. The resulting naphalendiazonium chloride solution was added dropwise to a stirred solution of **S19** (64 mg, 0.19 mmol) in 2.5 mL pyridine over 30 min while the temperature was maintained at -10°C. The reaction mixture was allowed to warm up slowly to room temperature with stirring for 12 hours. The solvent was then removed under reduced pressure, and the crude mixture was diluted with 30 mL DCM. The precipitate was collected with a filtration funnel and washed successively with water, EtOH and DCM. The crude product was recrystallized in hot EtOH to give the titled compound as a pink crystalline solid (30 mg, 29% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.74 (d, J = 2.0 Hz, 1H), 8.28 (dd, J = 8.5, 2.0 Hz, 1H), 8.27 (dd, J = 8.0, 1.5 Hz, 1H), 8.16-8.11 (m, 4H), 7.95 (s, 1H), 7.58 (dd, J = 8.5, 1.5 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.58 (dd, J = 9.0, 2.5 Hz, 1H), 7.33-7.31 (m, 4H), 7.29-7.26 (m, 1H), 5.43 (t, J = 6.0 Hz, 1H), 4.72 (d, J = 5.5 Hz, 2H), 4.51 (s, 2H), 4.29 (t, J = 4.5 Hz, 2H), 3.86 (d, J = 4.0 Hz, 2H), 3.70-3.68 (m, 2H), 3.62-3.60 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.0, 158.1, 142.5, 138.9, 135.1, 134.3, 132.3, 132.3, 130.7, 129.3, 129.3, 128.9, 128.6, 128.3, 127.9, 127.8, 126.7, 124.7, 124.0, 123.8, 120.9, 118.7, 107.5, 72.5, 70.4, 69.6, 69.3, 67.9, 63.3; MS (ESI) calcd for $C_{33}H_{30}N_4NaO_4$ 569.2 [M+Na$^+$], found 569.3.

4-((6-(2-(6-(((2-(2-(Benzyloxy)ethoxy)ethoxy)carbonyl)amino)naphthalen-2-yl)-*2H*-tetrazol-5-yl)naphthalen-2-yl)methoxy)-4-oxobutanoic acid (5): To a solution of tetrazole **S20** (30 mg, 0.055 mmol), DMAP (7 mg, 0.055 mmol), and pyridine (13 μL, 0.17 mmol) in 0.5 mL DMSO was added succinic anhydride (17 mg, 0.17 mmol) under argon at room temperature, and the mixture was heated to 60°C for 24 hours. The reaction was quenched by adding 10 mL water and 1 mL of 3 N HCl, and the resulting mixture was extracted with 3×10 mL DCM. The organic

layer was separated, washed successively with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was recrystallized in EtOH/H_2O (2:1) twice to give the titled compound as a pink powder (19 mg, 49% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.30 (brs, 1H), 8.83 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.30 (dd, J = 8.5, 1.5 Hz, 1H), 8.27 (dd, J = 8.5, 2.0 Hz, 1H), 8.19-8.10 (m, 4H), 8.01 (s, 1H), 7.60 (dd, J = 9.0, 1.5 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 9.0, 2.0 Hz, 1H), 7.33-7.31 (m, 4H), 7.29-7.26 (m, 1H), 5.32 (s, 2H), 4.52 (s, 2H), 4.29 (t, J = 4.0 Hz, 2H), 3.86 (t, J = 4.0 Hz, 2H), 3.70-3.68 (m, 2H), 3.62-3.60 (m, 2H), 2.66-2.64 (m, 2H), 2.56-2.53 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.8, 172.5, 164.9, 158.2, 138.9, 136.0, 135.1, 134.1, 132.7, 132.3, 130.7, 129.5, 129.4, 129.3, 128.6, 128.3, 127.9, 127.8, 127.1, 126.7, 124.5, 124.3, 121.0, 118.7, 118.7, 107.5, 72.5, 70.4, 69.6, 69.3, 67.9, 65.8, 29.2, 29.2; MS (ESI) calcd for $C_{37}H_{34}N_4NaO_7$ 669.2 [M+Na$^+$], found 669.1.

Scheme S6. Synthesis of tetrazole **6**



Methyl 6-(5-(6-(hydroxymethyl)naphthalen-2-yl)-2*H*-tetrazol-2-yl)-2-naphthoate (S21): To a cooled solution of sodium nitrite (104 mg, 1.5 mmol) in 2 mL water was added a solution of naphthalenamine (315 mg, 1.5 mmol) in 2 mL concentrated HCl and 10 mL EtOH/H_2O (1:1) at a temperature below 5°C. The resulting naphalendiazonium chloride solution was added dropwise to the stirred solution of **S19** (510 mg, 1.5 mmol) in 20 mL pyridine over 30 min while the temperature was maintained at -20°C. The reaction mixture was allowed to warm up to room temperature with stirring for 12 hours. The solvent was then removed under reduced pressure, and the crude mixture was diluted with 30 mL DCM. The precipitate formed was collected with a filtration funnel, washed successively with water, EtOH and DCM. The crude product was recrystallized in hot EtOH to give the titled compound as a gray powder (321 mg, 52% yield): ^{1}H NMR (500 MHz, 70°C DMSO-d_6) δ 8.86 (s, 1H), 8.79 (s, 1H), 8.76 (s, 1H), 8.45 (s, 1H), 8.42 (s, 1H), 8.32 (d, J = 7.0 Hz, 1H), 8.26 (s, 1H), 8.13-8.11 (m, 3H), 7.94 (s, 1H), 7.60 (s, 1H), 5.2 (brs, 1H), 4.73 (s, 2H), 3.96 (s, 3H).

6-(5-(6-(Hydroxymethyl)naphthalen-2-yl)-2*H*-tetrazol-2-yl)-2-naphthoic acid (S22): To a solution of **S21** (321 mg, 0.78 mmol) in 5 mL EtOH/H_2O (3:1) was added LiOH monohydrate (319 mg, 7.8 mmol), and the mixture was heated to 70°C under vigorous stirring. After the

reaction was complete based on TLC monitoring, the mixture was cooled down and the *p*H was adjusted to 1 with 2 N HCl. The precipitate was collected, washed successively with water and EtOH, and dried in vacuum to give the titled compound as a pink powder (299 mg, 95% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.27 (brs, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.81 (s, 1H), 8.76 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.42 (dd, J = 9.0, 2.0 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.42 (dd, J = 8.0, 1.5 Hz, 1H), 8.14-8.12 (m, 3H), 7.94 (s, 1H), 7.58 (dd, J = 8.5, 1.5 Hz, 1H), 5.41 (t, J = 5.0 Hz, 1H), 4.71 (d, J = 4.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.5, 165.3, 142.6, 135.5, 135.2, 134.4, 132.7, 132.3, 132.3, 130.9, 130.0, 129.6, 129.4, 128.9, 127.2, 126.8, 126.7, 124.7, 124.1, 123.6, 119.0, 118.4, 63.3; MS (ESI) calcd for $C_{23}H_{15}N_4O_3$ 395.1 [M-H$^-$], found 395.2.

6-(5-(6-(Acetoxymethyl)naphthalen-2-yl)-2*H*-tetrazol-2-yl)-2-naphthoic acid (S23): To a solution of **S22** (260 mg, 0.66 mmol) in 6 mL pyridine was added acetyl chloride (186 μL, 1.97 mmol) under argon at room temperature, and the mixture was heated to 80°C. After 12 hours, the reaction was quenched by adding 10 mL water and 5 mL 3 N HCl. The precipitate was collected, washed with water and EtOH, dried in vacuum to give the titled compound as a white powder (254 mg, 88% yield): ^{1} H NMR (500 MHz, DMSO-d_6) δ13.28 (brs, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.85 (s, 1H), 8.76 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.42 (dd, J = 9.0, 2.0 Hz, 1H), 8.32 (dd, J = 8.0, 2.0 Hz, 2H), 8.19-8.17 (m, 2H), 8.12 (d, J = 8.5 Hz, 1H), 8.01 (s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 5.29 (s, 2H), 2.14 (s, 3H); MS (ESI) calcd for $C_{25}H_{17}N_4O_4$ 437.1 [M-H$^-$], found 437.2.

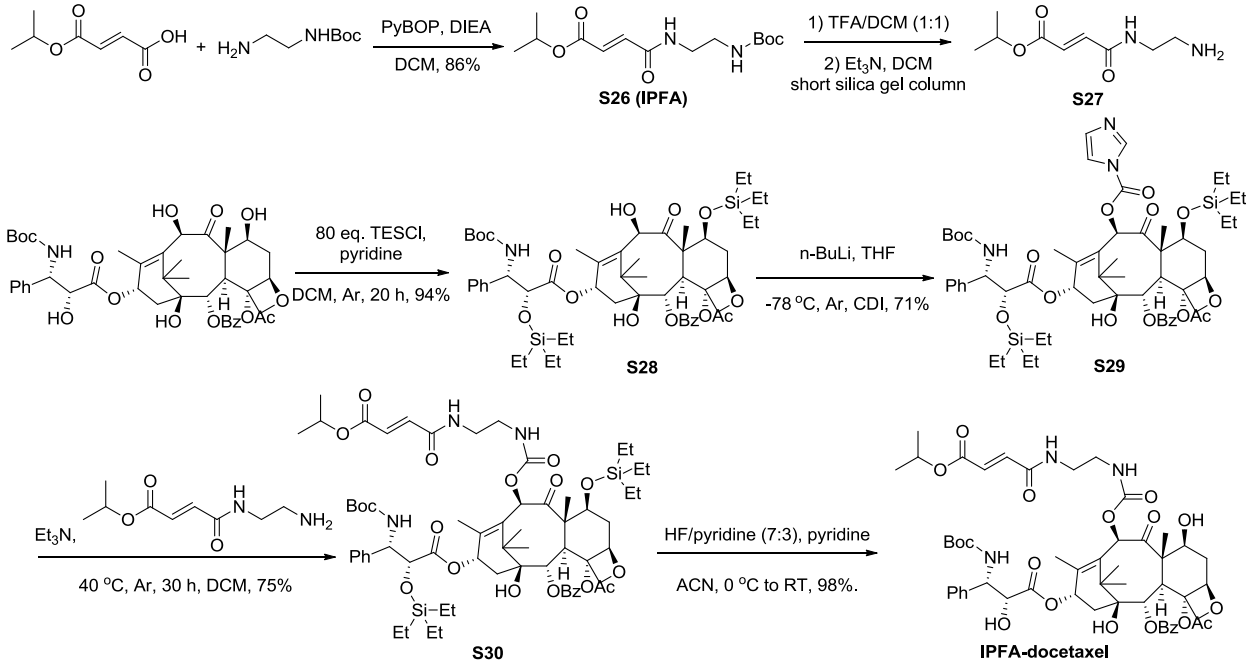
(6-(2-(6-(((2-(2-(Benzyloxy)ethoxy)ethoxy)carbonyl)amino)naphthalen-2-yl)-2*H*-tetrazol-5-yl)naphthalen-2-yl)methyl acetate (S24): To a suspension of **S23** (160 mg, 0.37 mmol), NEt_3 (203 μL, 1.46 mmol) and 3 Å molecular sieves (0.5 g) in 25 mL 2-(2-(benzyloxy)ethoxy)ethanol/ toluene (1:4) was added diphenylphosphoryl azide (103 μL, 0.48 mmol) with vigorous stirring, and the mixture was refluxed under argon for three hours. After the reaction was complete based on TLC monitoring, the molecular sieves were removed via filtration and the filtrate was concentrated. The residue was then purified by silica gel flash chromatography (EtOAc/hexanes = 1:2 to 2:1) twice to give the titled compound as a white solid after recrystallization in EtOH (101 mg, 47% yield): ^{1} H NMR (500 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.84 (s, 1H), 8.70 (d, J = 2.0 Hz, 1H), 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 8.26 (dd, J = 9.0, 2.0 Hz, 2H), 8.18 (t, J = 7.5 Hz, 2H), 8.14 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.02 (s, 1H), 7.70 (dd, J = 9.5, 2.0 Hz, 1H), 7.62 (dd, J = 9.0, 1.5 Hz, 1H), 7.36-7.30 (m, 4H), 7.28-7.25 (m, 1H), 5.29 (s, 2H), 4.50 (s, 2H),4.30-4.28 (m, 2H), 3.72-3.71 (m, 2H), 3.64-3.62 (m, 2H), 3.60-3.58 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.7, 164.9, 154.0, 139.0, 138.8, 136.0, 134.3, 134.1, 132.8, 132.7, 129.9, 129.8, 129.6, 129.4, 129.1, 128.6, 127.9, 127.8, 127.4, 127.0, 126.7, 124.5, 124.4, 121.4, 118.7, 118.6, 72.5, 70.2, 69.6, 69.1, 65.8, 64.3, 21.2; MS (ESI) calcd for $C_{36}H_{33}N_5NaO_6$ 654.2 [M+Na$^+$], found 654.1.

2-(2-(Benzyloxy)ethoxy)ethyl (6-(5-(6-(hydroxymethyl)naphthalen-2-yl)-2*H*-tetrazol-2-yl) naphthalene-2-yl)carbamate (S25): A solution of **S24** (90 mg, 0.14 mmol) in 3 mL EtOH/H_2O

(5:1) was treated with LiOH monohydrate (30 mg, 0.71 mmol), and the mixture was heated to 50 °C under vigorous stirring. After the reaction was complete based on TLC monitoring, the reaction mixture was cooled to room temperature and the pH of the solution was adjusted 5 using 2 N HCl. The precipitate was collected in a filtration funnel, washed successively with water and EtOH, dried in vacuum to give the titled compound as a white powder (66 mg, 78% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.62 (d, J = 2.5 Hz, 1H), 8.35 (dd, J = 8.5, 1.5 Hz, 1H), 8.32 (dd, J = 9.0, 2.0 Hz, 1H), 8.10 (s, 1H), 8.00-7.92 (m, 4H), 7.88 (s, 1H), 7.56 (dd, J = 8.5, 1.5 Hz, 1H), 7.46 (dd, J = 8.5, 2.5 Hz, 1H), 7.35-7.32 (m, 4H), 7.30-7.26 (m, 1H), 7.00 (s, 1H), 4.91 (d, J = 8.0 Hz, 2H), 4.60 (s, 2H), 4.42-4.41 (m, 2H), 3.82-3.80 (m, 2H), 3.75-3.73 (m, 2H), 3.69-3.68 (m, 2H), 1.89 (t, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.1, 153.9, 142.5, 138.9, 138.8, 134.3, 134.2, 132.7, 132.3, 129.9, 129.8, 129.3, 129.1, 128.9, 128.6, 127.9, 127.8, 126.7, 124.7, 124.1, 123.8, 121.4, 118.7, 118.5, 113.9, 72.5, 70.2, 69.5, 69.1, 64.2, 63.3; MS (ESI) calcd for $C_{34}H_{31}N_5NaO_5$ 612.2 [M+Na^+], found 612.1.

4-((6-(2-(6-(((2-(2-(Benzyloxy)ethoxy)ethoxy)carbonyl)amino)naphthalen-2-yl)-2*H*-tetrazol-5-yl)naphthalen-2-yl)methoxy)-4-oxobutanoic acid (6): To a solution of tetrazole alcohol **S24** (64 mg, 0.11 mmol), DMAP (1.0 mg, 0.0055 mmol), pyridine (0.5 mL) in 2 mL dioxane was added succinic anhydride (33 mg, 0.33 mmol) at room temperature and heated to 70°C under argon. The reaction progress was monitored by HPLC. After 24 hours, the mixture was quenched by adding 10 mL water and 1 mL of 2 N HCl. The resulting mixture was extracted with 3×10 mL DCM/EtOH (5:1). The organic layer was separated, washed successively with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was recrystallized in EtOH/EtOAc/H_2O (7:2:1) twice to give the titled product as a pink powder (67 mg, 88% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (brs, 1H), 10.19 (brs, 1H), 8.84 (s, 1H), 8.70 (d, J = 2.0 Hz, 1H), 8.31 (dd, J = 8.5, 1.5 Hz, 1H), 8.26 (dd, J = 8.5, 2.0 Hz, 1H), 8.25 (d, J = 2.5 Hz, 1H), 8.19-8.11 (m, 4H), 8.01 (s, 1H), 7.70 (dd, J = 9.5, 2.0 Hz, 1H), 7.61 (dd, J = 8.0, 1.5 Hz, 1H), 7.33-7.27 (m, 4H), 7.27-7.25 (m, 1H), 5.33 (s, 2H), 4.50 (s, 2H), 4.30-4.28 (m, 2H), 3.73-3.71 (m, 2H), 3.65-3.63 (m, 2H), 3.61-3.58 (m, 2H), 2.67-2.64 (m, 2H), 2.56-2.53 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.8, 172.5, 164.9, 158.2, 138.9, 136.0, 135.1, 134.1, 132.7, 132.3, 130.7, 129.5, 129.4, 129.3, 128.6, 128.3, 127.9, 127.8, 127.1, 126.7, 124.5, 124.3, 121.0, 118.7, 118.7, 107.5, 72.5, 70.4, 69.6, 69.3, 67.9, 65.8, 29.2; MS (ESI) calcd for $C_{38}H_{35}N_5NaO_8$ 712.2 [M+Na^+], found 712.1.

Scheme S7. Synthesis of IPFA-docetaxel (IPFAD)



(*E*)-Isopropyl 4-((2-((*tert*-butoxycarbonyl)amino)ethyl)amino)-4-oxobut-2-enoate (S26): To a suspended solution of (*E*)-4-isopropoxy-4-oxobut-2-enoic acid (316 mg, 2.0 mmol) in 20 mL DCM was added DIEA (1066 µL, 6.0 mmol), then the acid was dissolved. PyBOP (1144 mg, 1.1 mmol) was added to the above solution followed by *N*-Boc-ethylenediamine (160 mg, 2.2 mmol). The reaction was stirred at room temperature for 1 h. Additional 10 mL DCM was added and the organic layer was separated and washed successively by 5% citric acid in water and saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexanes = 1:1) to give the titled compound as a white solid (519 mg, 86% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (br, 1H), 6.91 (d, J = 15 Hz, 1H), 6.72 (d, J = 16 Hz, 1H), 5.38 (t, J = 6.0 Hz, 1H), 5.04 (m, 1H), 3.45-3.39 (m, 2H), 3.30-3.24 (m, 2H), 1.38 (s, 9H), 1.23 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.1, 164.5, 156.9, 136.2, 130.5, 79.6, 68.7, 40.7, 39.9, 28.3, 21.6; ESI-MS calcd for $C_{14}H_{24}N_2NaO_5$ 323.2 [M+Na^+], found 323.1.

(*E*)-Isopropyl 4-((2-aminoethyl)amino)-4-oxobut-2-enoate (S27): To a solution of **S26** (30 mg, 0.10 mmol) in 10 mL DCM at 0°C was added trifluoroacetic acid (0.5 mL). The mixture was stirred under argon at 0°C under the starting materials disappeared. The solvent was removed and 1 mL saturated $NaHCO_3$ solution was added to neutralize the solution. The water was removed through air-drying, and the residue was purified by silica gel flash chromatography (10-30% methanol in DCM) to give the titled compound as a light-yellow solid (15 mg, 75% yield): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.01 (d, J = 15.9 Hz, 1H), 6.69 (d, J = 15.3 Hz, 1H), 5.07 (m,

1H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.11 (t, *J* = 6.0 Hz, 2H), 1.29 (s, 3H), 1.27 (s, 3H); ESI-MS calcd for $C_9H_{17}N_2O_3$ 201.2 [M+H$^+$], found 201.1.

2'-TESO-7-TESO-docetaxel (S28): A solution of docetaxel (10-deacetylbaccatin III, 10-DAB) (200 mg, 0.248 mmol) and pyridine (4 mL) in 4 mL DCM at room temperature was treated with chlorotriethylsilane in 8 portions (416 μL each time for 10 min, 2.48 mmol; 80 equiv total) under argon. When thin layer chromatography (TLC) (silica, 30% EtOAc/hexanes) showed the disappearance of the starting materials, the reaction was quenched with aqueous NH_4Cl (15 mL). After dilution with EtOAc (10 mL), the reaction mixture was extracted with DCM (10 mL × 4). The organic layer was separated, washed with ammonium chloride (5 mL × 2) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (20-50% EtOAc/hexanes) to give 2'-TESO-7-TESO-docetaxel as a white powder (242 mg, 94% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30-7.26 (m, 3H), 6.33 (t, *J* = 9.5 Hz, 1H), 5.67 (d, *J* = 7.5 Hz, 1H), 5.47 (broad, d, *J* = 8.0 Hz, 1H), 5.28 (broad, d, *J* = 8.0 Hz, 1H), 5.13 (s, 1H), 4.95 (d, *J* = 9.5 Hz, 1H), 4.55 (s, 1H), 4.40 (dd, *J* = 11.0, 7.0 Hz, 1H), 4.31 (d, *J* = 8.5 Hz, 1H), 4.27 (s, 1H), 4.20 (d, *J* = 9.0 Hz, 1H), 3.90 (d, *J* = 7.0 Hz, 1H), 2.53 (s, 3H), 2.48 (ddd, *J* = 15.5, 9.0, 6.5 Hz, 1H), 2.35 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.18-2.13 (m, 1H), 1.96-1.91 (m, 1H), 1.93 (s, 3H), 1.75 (s, 3H), 1.61 (s, 1H), 1.31 (s, 9H), 1.27 (s, 3H), 1.16 (s, 3H), 0.95 (t, *J* = 7.5 Hz, 9H), 0.78 (t, *J* = 8.0 Hz, 9H), 0.62-0.50 (m, 6H), 0.47-0.31 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.8, 171.5, 170.1, 167.0, 155.1, 139.0, 138.5, 135.7, 133.5, 130.1, 129.2, 128.6, 128.4, 127.6, 126.3, 125.4, 84.2, 80.9, 79.8, 79.0, 75.2, 75.0, 74.0, 72.7, 71.3, 57.7, 46.4, 43.2, 37.2, 35.7, 30.3, 28.1, 26.6, 22.9, 21.0, 14.1, 10.1, 6.7, 6.4, 5.1, 4.2; ESI-MS calcd for $C_{55}H_{82}NO_{14}Si_2$ 1036.5 [M+H$^+$], found 1036.1.

2'-TESO-7-TESO-10-1*H*-imidazole-1-carboxyoxyl-docetaxel (S29): A solution of DiTES-docetaxel **S28** (220 mg, 0.212 mmol) in 3 mL anhydrous THF was cooled to -78 °C under argon for 10 min and then treated with n-butyl lithium (2.5 M in hexanes, 125 μL, 0.298 mmol) with stirring for 20 min. A solution of 1,1'-carbonyldiimidazole (CDI, 241 mg, 1.48 mmol) in 3 mL anhydrous THF was added dropwise at -78 °C, and the mixture was allowed to warm to room temperature slowly. When thin layer chromatography (TLC) (silica, 50 % EtOAc/hexanes) showed the disappearance of the starting materials (~1 h), the reaction was quenched by adding aqueous NH_4Cl (15 mL). After dilution with EtOAc (10 mL), the reaction mixture was extracted with DCM (10 mL× 4). The organic layer was separated, washed with ammonium chloride (5 mL × 2) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel flash chromatography (20-50% EtOAc/hexanes) to give the titled compound as a white powder (170 mg, 71% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.41-7.36 (m, 2H), 7.32-7.28 (m, 3H), 7.11 (s, 1H), 6.57 (s, 1H), 6.31 (t, *J* = 9.0 Hz, 1H), 5.74 (d, *J* = 7.0 Hz, 1H), 5.51 (broad, d, *J* = 9.0 Hz, 1H), 5.28 (broad, d, *J* = 8.5 Hz, 1H), 4.97 (d, *J* = 9.0 Hz, 1H), 4.58 (s,

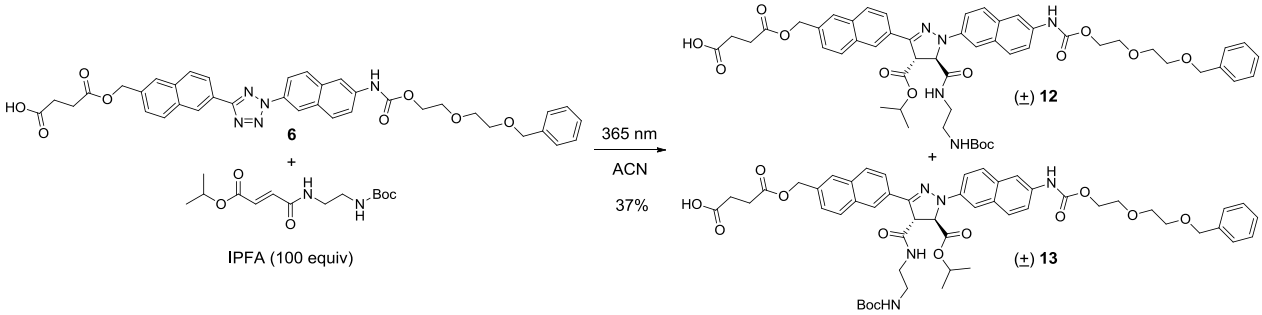
1H), 4.53 (dd, *J* = 10.5, 6.5 Hz, 1H), 4.41 (t, *J* = 6.5 Hz, 1H), 4.33 (d, *J* = 8.5 Hz, 1H), 4.20 (d, *J* = 8.5 Hz, 1H), 3.84 (d, *J* = 7.0 Hz, 1H), 2.60-2.53 (m, 1H), 2.56 (s, 3H), 2.42 (dd, *J* = 15.5, 10.0 Hz 1H), 2.28-2.21 (m, 1H), 2.08 (s, 3H), 1.94 (t, *J* = 12.5 Hz, 1H), 1.79 (s, 3H), 1.31 (s, 9H), 1.29 (s, 3H), 1.27 (s, 3H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.78 (t, *J* = 8.0 Hz, 9H), 0.64-0.58 (m, 6H), 0.47-0.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.3, 171.5, 170.1, 166.9, 155.1, 147.5, 142.8, 138.8, 137.2, 133.5, 132.1, 130.8, 130.1, 129.1, 128.6, 128.5, 127.6, 126.3, 117.1, 84.1, 81.0, 79.8, 78.7, 78.4, 76.4, 75.1, 74.8, 72.2, 71.1, 58.4, 46.6, 43.2, 37.1, 35.3, 28.1, 26.6, 22.9, 21.9, 14.3, 10.0, 6.7, 6.4, 5.3, 4.2; ESI-MS calcd for $C_{59}H_{83}N_3NaO_{15}Si_2$ 1152.5 [M+Na^+], found 1152.5.

2'-TESO-7-TESO-10-IPFA-docetaxel (S30): A stirred solution of **S29** (113 mg, 0.10 mmol) in 2 mL anhydrous DCM was treated with triethylamine (139 μL, 1.00 mmol) at room temperature under argon for 20 min. A solution of (*E*)-isopropyl 4-((2-aminoethyl)amino)-4-oxobut-2-enoate (IPFAA, 400 mg, 2.0 mmol) in 1 mL anhydrous DCM was then added, and the mixture was heated to 50 °C in sealed tube overnight. When thin layer chromatography (TLC) (silica, 40% EtOAc/hexanes) showed the complete disappearance of the starting materials, the reaction was quenched by adding aqueous NH_4Cl (5 mL). After dilution with DCM (5 mL), the reaction mixture was extracted with DCM (10 mL × 3). The organic layer was separated and washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (20-50% EtOAc/hexanes) to give the titled compound as a white powder (95 mg, 75% yield): ^{1}H NMR (CD_3OD, 500 MHz) δ 8.53 (s, 1H), 8.06 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.30-7.33 (m, 4H), 7.21-7.23 (m, 1H), 6.92 (d, *J* = 15.5 Hz, 1H), 6.62 (d, *J* = 15.5 Hz, 1H), 6.29 (s, 1H) 6.03 (t, *J* = 8.5 Hz, 1H), 5.59 (d, *J* = 7.0 Hz, 1H), 5.11 (s, 1H), 5.00 (m, *J* = 6.5 Hz, 1H), 4.94 (d, *J* = 9.0 Hz, 1H), 4.52 (d, *J* = 4.5 Hz, 1H), 4.45(dd, *J* = 10.5, 6.5 Hz, 1H) 4.14 (d, *J* = 9.0 Hz,1H), 4.12 (d, *J* = 9.5 Hz, 1H), 3.77 (d, *J* = 7.5 Hz, 1H), 3.43 (brs, 1H), 3.33 (t, *J* = 5.5 Hz, 2H), 3.24-3.29 (m, 1H), 3.15-3.19 (m, 1H), 2.47-2.51 (m, 1H), 2.45 (s, 3H), 2.29 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.02 (dd, *J* = 14.5, 9.5 Hz, 1H), 1.90 (s, 3H), 1.75 (t, *J* = 12 Hz, 1H), 1.61 (s, 3H), 1.33 (s, 9H), 1.23 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.88 (t, *J* = 9.0 Hz, 9H), 0.80 (t, *J* = 9.0 Hz, 9H), 0.50-0.59 (m, 6H), 0.39-0.49 (m, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 204.3, 173.0, 172.1, 170.2, 166.2, 165.0, 156.2, 155.9, 140.1, 138.7, 136.7, 134.3, 133.2, 130.0, 129.9, 129.8, 128.3, 128.2, 127.6, 126.9, 84.2, 80.6, 79.4, 77.6, 75.8, 74.8, 74.0, 72.5, 71.5, 68.6, 58.2, 57.5, 46.6, 432, 40.1, 39.8, 39.3, 37.0, 35.2, 27.3, 25.5, 22.2, 21.8, 20.6, 13.7, 13.5, 9.5, 5.9, 4.9, 4.0, 3.5; ESI-MS calcd for $C_{65}H_{95}N_3NaO_{18}Si_2$ 1284.6 [M+Na^+], found 1284.4.

10-IPFA-docetaxel (IPFAD): To a stirred solution of **S30** (72 mg, 0.057 mmol) in pyridine (1.3 mL) and acetonitri1e (1.3 mL) at 0 °C was added dropwise a solution of HF/pyridine (70:30, 779 μL), and the mixture was allowed to warm to room temperature and stirred for additional 30 min. The reaction mixture was diluted with EtOAc, and the organic layer was separated and washed sequentially with saturated $NaHCO_3$ (25 mL), saturated $CuSO_4$ solution (10 mL × 4), water (10

mL × 3) and brine (10 mL). The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography (50% EtOAc in /hexanes to 100% EtOAc) to afford the titled compound as a white powder (58 mg, 98% yield): ^{1}H NMR (CD_3OD, 500 MHz) δ 8.10 (d, J = 7.5 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.38-7.39 (brs, 4H), 7.26 (m, 1H), 7.01 (d, J = 15.5 Hz, 1H), 6.68 (d, J = 15.5 Hz, 1H), 6.30 (s, 1H), 6.14 (t, J = 8.0 Hz, 1H), 5.64 (d, J = 7.0 Hz, 1H), 5.12 (brs, 1H), 5.08 (d, J = 6.0 Hz, 1H), 4.99 (dd, J = 9.0, 1.5 Hz, 1H), 4.51 (d, J = 3.0 Hz, 1H), 4.34 (dd, J = 11.0, 6.5 Hz, 1H), 4.19 (s, 2H), 3.81 (d, J = 6.5 Hz, 1H), 3.42 (t, J = 6.0 Hz, 2H), 3.33-3.37 (m, 1H), 3.25-3.30 (m, 1H), 2.47 (ddd, J = 14.5, 10.0, 6.5 Hz, 1H), 2.34 (s, 3H), 2.21-2.26 (m, 1H), 2.02-2.06 (m, 1H), 1.94 (s, 3H), 1.80 (t, J = 12.0 Hz, 1H), 1.65 (s, 3H), 1.40 (s, 9H), 1.30 (s, 3H), 1.29 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 205.5, 173.0, 170.4, 166.2, 165.1, 156.6, 156.4, 141.0, 139.1, 136.2, 133.8, 133.2, 130.0, 129.8, 128.3, 128.2, 127.4, 126.8, 84.5, 80.8, 79.3, 77.8, 76.1, 75.8, 74.9, 73.9, 71.2, 71.0, 68.7, 57.9, 57.2, 46.2, 43.1, 39.7, 39.3, 35.9, 35.3, 27.3, 25.6, 21.7, 21.1, 20.6, 13.5, 9.0; ESI-MS calcd for $C_{53}H_{67}N_3NaO_{18}$ 1256.4 [M+Na^+], found 1056.4.

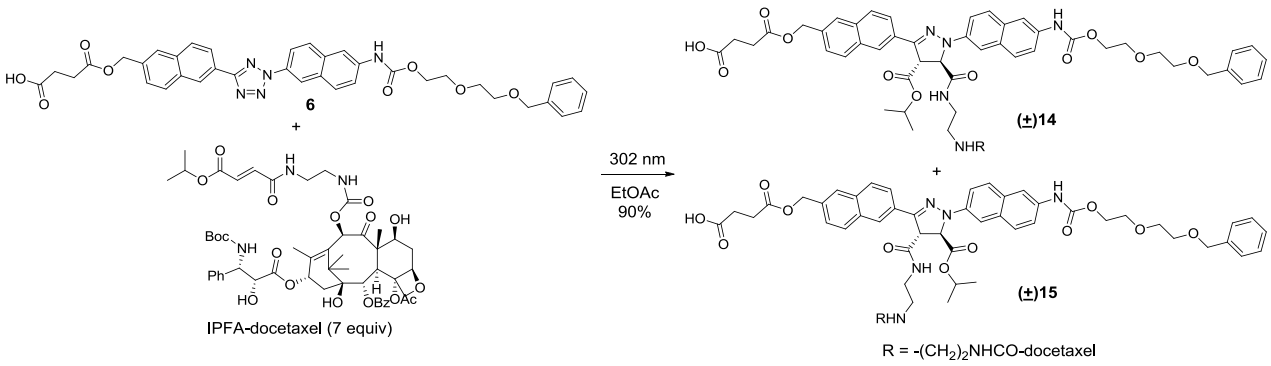
Scheme S8. Photoinduced cycloaddition of tetrazole **6** with IPFA



Pyrazolines (±)12/(±)13: To a solution of tetrazole **6** (20 mg, 0.029 mmol) in 20 mL ACN was added IPFA (87 mg, 0.29 mmol), and the stirred solution was irradiated with 365 nm UV lamp for 90 min at room temperature. The solvent was then evaporated and the residue was purified by silica gel flash chromatography to give a crude mixture of regioisomers **(±)12** and **(±)13** in roughly 1:1 ratio (15 mg). The mixture was further purified by preparative HPLC to give the desired the titled regioisomers as a yellow solid (10 mg, 37% yield): ^{1}H NMR (CD_3OD, 500 MHz) δ 8.26 (s, 1H), 8.08-8.03 (m, 1H), 8.07 and 7.92 (s, 1H), 7.84-7.76 (m, 4H), 7.65-7.53 (m, 3H), 7.43-7.40 (m, 1H), 7.36-7.32 (m, 1H), 7.24-7.18 (m, 3H), 7.15-7.12 (m, 2H), 6.40 (brs, 1H), 5.12 and 5.11 (s, 2H), 5.09 and 5.04 (d, J = 5.0 Hz and J = 6.0 Hz, 1H), 5.00-4.96 and 4.92-4.88 (m, 1H), 4.72 and 4.58 (d, J = 6.0 Hz and J = 5.5 Hz, 1H), 4.45 (s, 2H), 4.24-4.21 (m, 2H), 3.69-3.66 (m, 2H), 3.63-3.60 (m, 2H), 3.57-3.54 (m, 2H), 3.29-3.18 (m, 2H), 3.11-3.03 (m, 2H), 2.61-2.58 (m, 2H), 2.55-2.52 (m, 2H), 1.94 (s, 1H), 1.30 and 1.24 (s, 9H), 1.16-0.97 (d, J = 6.0 Hz, 6H); ^{13}C NMR (CD_3OD, 75 MHz) δ 174.8, 172.7, 170.8, 170.3, 169.7, 169.3, 157.1, 155.5, 154.6, 144.9, 141.0, 140.8, 138.1, 134.7, 134.6, 133.3 and 133.2, 132.8, 132.6, 130.9, 129.3, 129.2, 129.0, 128.2 and 128.1, 128.0, 127.9, 127.4, 127.2, 127.0, 126.8, 126.5, 126.1, 125.8,

124.4, 123.9, 120.0, 116.5 and 116.3, 109.9, 107.1, 78.7, 72.7, 70.1, 70.0, 69.2, 69.1, 68.1, 67.2, 65.8, 63.7, 57.0, 39.5, 28.8, 28.6, 27.3, 20.4, 20.2; MS (ESI) calcd for $C_{52}H_{59}N_5NaO_{13}$ 984.4 [M+Na^+], found 984.5.

Scheme S9. Photoinduced cycloaddition of tetrazole **6** with IPFAD



Pyrazolines (±)14/(±)15: A stirred solution of tetrazole **6** (1.5 mg, 0.002 mmol) and docetaxel-IPFA (15 mg, 0.015 mmol) in 10 mL EtOAc was irradiated with 302 nm UV lamp at room temperature for 5 min. The solvent was then evaporated and the residue was purified by silica gel flash chromatography to give a crude mixture of regioisomers (4.0 mg) in about 1:1 ratio. The crude product was further purified by preparative HPLC to give the titled pair of regioisomers as a yellow solid (3.1 mg, 91% yield): ^{1}H NMR (CD_3OD, 500 MHz) δ 8.48 (s, 2H), 8.19-8.16 (m, 2H), 8.10-8.01 (m, 3H), 8.07 and 7.92 (s, 1H), 7.95-7.82 (m, 4H), 7.78-7.63 (m, 4H), 7.57-7.51 (m, 3H), 7.44-7.43 (m, 1H), 7.39-7.36 (m, 2H), 7.34-7.21 (m, 5H), 6.31 (s, 1H), 6.21 and 6.18 (s, 1H), 6.13 and 6.08 (m, 2H), 5.64 and 5.59 (d, J = 7.0 Hz and J = 7.0 Hz, 2H), 5.30 (s, 2H), 5.22-5.20 and 4.99-4.96 (m, 1H), 5.13-5.05 (m, 2H), 5.01-4.97 (m, 1H), 4.84-4.81 and 4.70-4.68 (m, 1H), 5.00-4.96 and 4.92-4.88 (m, 1H), 4.55 and 4.54 (s, 2H), 4.49 (m, 1H), 4.38-4.30 (m, 3H), 4.17-4.15 (m, 2H), 3.80-3.75 (m, 3H), 3.72-3.70 (m, 2H), 3.67-3.64 (m, 2H), 3.46-3.44 (m, 1H), 3.41-3.38 (m, 1H), 3.6-3.17 (m, 1H), 2.70-2.67 (m, 2H), 2.62-2.58 (m, 2H), 2.51-2.43 (m, 1H), 2.33-2.31 (m, 3H), 2.27-2.20 (m, 1H), 2.08-2.00 (m, 1H), 1.96-1.95 (m, 1H), 1.79 and 1.75 (s, 3H), 1.66-1.57 (m, 4H), 1.38 (s, 9H), 1.31-1.22 (m, 3H), 1.16-1.15 and 1.09-1.07 (m, 6H); MS (ESI) calcd for $C_{91}H_{103}N_6O_{26}$ 1695.7 [M+H^+], found 1695.2.

Determination of tetrazole ring rupture quantum yield

The quantum yields for the photoinduced ring rupture of tetrazoles **1**-**6** were determined by measuring UV-vis absorption spectra of the pyrazoline products upon 365 nm photoirradiation followed by HPLC analysis. A ferrioxalate-polyoxometalate-based chemical actinometer[S7] was used as a reference (Φ_r = 0.18). The quantum yield for tetrazole ring rupture (Φ_T) was calculated using the following equation: $\Phi_T = (A_r/A_T)(k_T/k_r)\Phi_r = (\varepsilon_r c_r/\varepsilon_T c_T)(k_T/k_r)\Phi_r$, where ε_r and ε_T are the extinction coefficient of the reference and tetrazole compound, respectively; c_r and c_T are the concentration of the reference and tetrazole compound, respectively; k_r and k_T are kinetic constant of the reference and tetrazole compound in the photoinduced oxidation and

cycloaddition reaction, respectively. Because of the filtering effect, only initial stages of the photoinduced cycloaddition reactions (0 - 80 sec) were used in the curve-fitting to derive the zero-order rate constants, k_T, for the various tetrazoles.

Determination of two-photon cycloaddition cross section

For two-photon induced uncaging of the referenced compound BHC ester, the number of uncaged molecules per unit time (N_r) can be described as follows: $N_r = 0.5\delta_{ur}C_r[I_0^2(t)]\int S^2(r)dV$, where δ_{ur} and C_r are uncaging action cross section and concentration of BHC ester, respectively; $[I_0^2(t)]$ is mean squared light intensity; $S(r)$ is a unitless spatial distribution function, and its integral over the volume of a cuvette, $\int S^2(r)dV$, describes the extent of photo exposure on the compound. For photoinduced tetrazole ring rupture, the number of nitrile imine molecules generated per unit time (N_T) equals to the number of pyrazoline molecules formed per unit time (N_p) when excess acrylamide is used in the reaction: $N_T = N_p = 0.5\delta_{cT}C_T[I_0^2(t)]\int S^2(r)dV$, where N_p is derived by comparing the integration of pyrazoline fluorescence spectrum to that of the reference compound; C_T is the initial tetrazole concentration. Two-photon induced cycloaddition cross section was calculated by comparing the rate of cycloaddition to that of BHC ester uncaging under identical photoirradiation intensity using the following equation: $\delta_{cT} = \delta_{ur}C_rN_P/C_TN_r$. The literature value of the uncaging action cross section δ_{ur} was used in the calculation.[S8]

Kinetic study of photoinduced cycloaddition reaction between tetrazole 6 and IPFA under 365 nm photoirradiation

Aliquots of tetrazole **6** (1 mM in acetonitrile) and IPFA (20 mM in acetonitrile) were added into 0.5 mL acetonitrile/PBS (1:1 v/v) in quartz test tubes to obtain a final tetrazole **6** concentration of 10 μM and a final IPFA concentration of 100 μM. Under vigorous stirring, the solutions were irradiated with a handheld 365 nm UV lamp for a period of 0, 5, 10, 20, 40, 80, 160, and 320 sec, respectively. Then, 100 μL reaction mixtures were withdrawn and injected into a reverse phase HPLC, and the amount of the pyrazoline product formed in the mixtures were determined by comparing the integration area of the pyrazoline peak in HPLC chromatogram at 370 nm to a standard curve. The reactions were repeated three times to obtain the standard deviations.

Expression and purification of the sfGFP mutants

BL21(DE3) cells were transformed with the pEVOL-PylT-AcrKRS[S9] and pET-sfGFP-S2TAG plasmids. Cells were recovered in 1 mL SOC rich medium and incubated at 37 ºC for 1 h before plating on LB agar plate containing chloramphenicol (Cam) (34 μg/mL) and ampicillin (Amp) (100 μg/mL). A 5 mL overnight culture from a single colony was used to inoculate 50 mL LB medium supplemented with Cam and Amp. Cells were grown at 37 ºC in a shaker-incubator (250 rpm), and the protein expression was induced by adding 1 mM IPTG, 0.2% arabinose and 2 mM AcrK when OD_{600} reached 0.6. After 8 h induction, cells were harvested, resuspended in a lysis

buffer (50 mM NaH_2PO_4, 300 mM NaCl, 10 mM imidazole, *p*H 8.0), and sonicated in an ice/water bath four times (4 min each with 10 min interval). The lysate was centrifuged (45 min, 17,136 g, 4 ºC). The supernatant was incubated with 0.1 mL Ni-NTA resin (Thermo HisPur^{TM}) (2 h, 4 ºC). The slurry was then loaded to a column and the protein-bound resin was washed twice with 3 mL washing buffer (300 mM NaCl, 50 mM Na_2HPO_4, 50 mM imidazole, *p*H 8.0). The protein was finally eluted off the resin using the elution buffer (300 mM NaCl, 50 mM Na_2HPO_4, 250 mM imidazole, *p*H 8.0). The eluted fractions were collected, concentrated, and subjected to buffer-exchange to DPBS using an Amicon Ultra-15 Centrifugal Filter (10k MWCO, Millipore). The protein purity was analyzed by SDS-PAGE and LC/ESI-MS. The sfGFPS2BocK protein was expressed similarly except the growth medium was supplemented 1 mM BocK.

Two-photon photoclick reaction between sfGFP-S2AcrK and tetrazole 6

Aliquots of 20 µL of tetrazole **6** stock solution (1 mM in ACN) and sfGFP mutant protein stock solution (32 µL of 30.87 µM sfGFP-S2BocK and 59 µL of 16.44 µM sfGFP-S2AcrK in DPBS, *p*H 7.4) were added into an appropriate amount of CH_3CN/PBS (1:1 v/v) in a quartz micro fluorimeter cuvette fitted with PTFE stopper to obtain the final tetrazole concentration of 200 µM and the final sfGFP mutant protein concentration of 10 µM in 100 µL total volume. The reaction mixtures were photoirradiated with a Coherent Chameleon-Multiphoton Imaging Ti:Sapphire Laser (focused 700 nm fs-pulsed laser light, focusing at the center of the cuvette) for a period of 4 hours with periodic stirring. Then, aliquots of 10 µL reaction mixtures were withdrawn, diluted to 45 µL, and then injected into a Finnigan LCQ Advantage IonTrap mass spectrometry coupled with a Surveyor reverse phase HPLC system equipped with a Jupiter C4 column (5 µm, 300 Å, 2.00 × 50 mm) running a gradient of 5-95% ACN/H_2O containing 0.1% HCOOH with run time of 15 min, and flow rate of 200 µL. The intact protein masses were derived by de-convoluting the charge ladders using the ProMass software. Separately, SDS loading buffer was added to the eppendorf tubes containing 5 µL reaction mixtures, heated to 95 ºC, and loaded to a Tris-Glycine gel for SDS-PAGE analysis.

MTS cytotoxicity assay

One hundred µL of 5×10^4 HeLa or CHO cells suspended in DMEM medium supplemented with 10% FBS were added to the individual wells in a 96 well plate. After incubation at 37 ºC in a humidified CO2 incubator for 36 hours, the cells were treated with the compounds diluted with a concentration range from 10 nM to 1 mM for 24 hours. Afterwards, 20 µl MTS/PMS solution (CellTiter 96® Aqueous) was added to each well, and the plate was returned to the CO2 incubator for additional 4 hours incubation. The absorbance at 490 nm was then recorded using a plate reader. Each treatment conditions were repeated three times in order to obtain the average absorbance and the standard deviation. The data were plotted using the GraphPad Prism 5.0.

In-cell single-photon induced photoclick chemistry and confocal microscopy

CHO cells were allowed to grow to 80-90% confluency on 35-mm glass-bottom tissue culture dishes with in 2 mL DMEM medium supplemented with 10% FBS in a humidified 37°C, 5% CO_2 incubator. The cells were treated with tetrazole **6** for 14 hours, washed twice with pre-warmed fresh DMEM medium before switching to OPTI-MEM medium containing 30 μM IPFA-docetaxel. The incubation was continued for 30 min at 37°C. The cells were photoirradiated with a handheld UV lamp (365 nm) for 3 min and incubated for additional 2 min before confocal microscopy imaging. The control experiments were carried out under identical conditions except IPFA-docetaxel was not included in OPTI-MEM medium.

The imaging acquisitions were carried out using a Zeiss LSM-710 confocal microscope equipped with a continuous laser and fluorescence lifetime (FLIM) detector; InVis: f-MBS 405/505c Plate; DBS1: Mirror; FW1: rear with specific filter window (531-623 nm); and Plan-Apochromat 40x/1.3 oil objective. The data quantifications were carried out using the Zeiss ZEN 2009 light edition, LSM image browser, or NIH ImageJ program. For turn-on fluorescence quantification, at each time point the fluorescence intensities of the cytosols of 10 individual cells with unsaturated fluorescence inside the rectangular area were used to derive the average intensities along with standard deviations. For spectrum scan, the average intensities of the unsaturated fluorescence-labeled cytoskeleton areas in 10 selected cells were plotted to give the in-cell fluorescence spectrum along with standard deviations.

Microtubule-binding induced fluorescence enhancement in vitro

The chemically cross-linked, stabilized microtubules were prepared as described in literature.[S10] Briefly, lyophilized bovine brain tubulin (Cytoskeleton Inc.) was reconstituted by dissolving tubulin in glycerol assembly buffer (GAB: 3.4 M glycerol, 10 mM sodium phosphate, 1 mM EGTA, 6 mM $MgCl_2$, 0.1 mM GTP, pH = 6.5) to obtain a concentration of 50 μM. For microtubule assembly, 20 mM glutaraldehyde was added to the above solution and the mixture was kept at 37 °C for 30 min. The excess cross-linking agent was quenched by adding 60 mM $NaBH_4$, and the suspension was dialyzed overnight using Slide-A-Lyzer 10K dialysis cassettes (Pierce) against the GAB buffer and drop-frozen in liquid nitrogen to make the stock solution.

Aliquots of stabilized microtubules suspension stock solution (50 μM in GAB) and pyrazoline-docetaxel stock solution (10 mM in DMSO) were added into 0.5 mL GAB buffer with 20% ACN and 0.1 mM GTP in ultracentrifuge test tubes to obtain a final pyrazoline-docetaxel concentration of 2.5 μM and the assembled microtubule concentration of 0, 0.5, 1, 1.5, 2, 3 μM (based on molecular weight of monomeric tubulin), respectively. After vigorous vortex, the mixtures were kept at 37 °C for 5 min and cooled on ice for 5 min. Then, the samples were centrifuged at 13,500 rpm for 1 hour at 4 °C on a microcentrifuge. The supernatants were taken and their fluorescence spectra were measured using a fluorimeter with excitation at 405 nm. The pellets were suspended in tubulin glycerol buffer (TGB: 80 mM PIPES, 2 mM $MgCl_2$, 0.5 mM

EGTA, 60% glycerol, 0.1 mM GTP, pH = 6.9) and their fluorescence spectra were measured using a fluorimeter with excitation at 405 nm.

Spatiotemporally controlled imaging of microtubules *via* two-photon photoclick chemistry

CHO cells were allowed to grow to 80-90% confluency on 35-mm glass-bottom tissue culture plates in 2 mL DMEM medium supplemented with 10% FBS in a humidified 37 °C, 5% CO_2 incubator. The cells were treated with the indicated concentration of tetrazole **6** for 20 hours followed by DMEM washing (2×), and then the medium was switched to OPTI-MEM containing 40 μM IPFA-docetaxel. The treatment was continued at 37 °C for 30 min. The two-photon triggered photoclick reaction inside CHO cells was carried out using a Coherent Chameleon, modelocked Ti: Sapphire femtosecond pulsed laser (~140 fs pulses with 90 MHz repetition rate and tuned to 700 nm). A laser beam was introduced to the confocal/multi-photon fluorescence microscope (Leica TCS-SP2/AOBS) and focused on cells cultured in 35 mm, glass-bottom dishes using a 63x/NA1.4 oil immersion objective. The output laser power from the objective lens during the laser scanning, which initiated the two-photon reaction in cells in vivo, was measured to be ~25 mW. A 405 nm laser was used for exciting the newly formed pyrazoline fluorophore in a time-sequence mode (scanning speed of 6.2 s/frame) while simultaneous scanning the cells with the femtosecond 700 nm pulsed laser (Chameleon™ from Coherent, Modelocked Ti:Sapphire). Fluorescence images were acquired using a 530/30 bandpass filter. Images were acquired using Leica confocal software and processed using Leica LAS AF Lite. The cytosolic fluorescence intensity was analyzed using the ImageJ program.

Reference:

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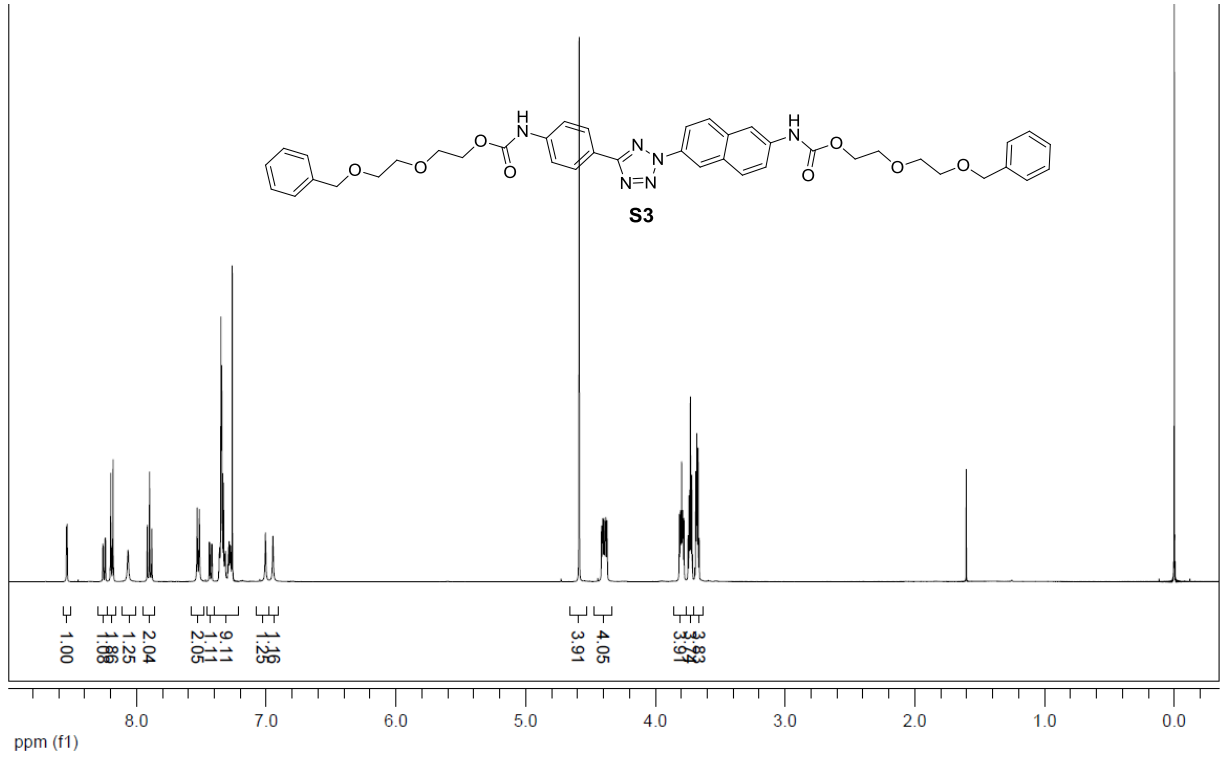
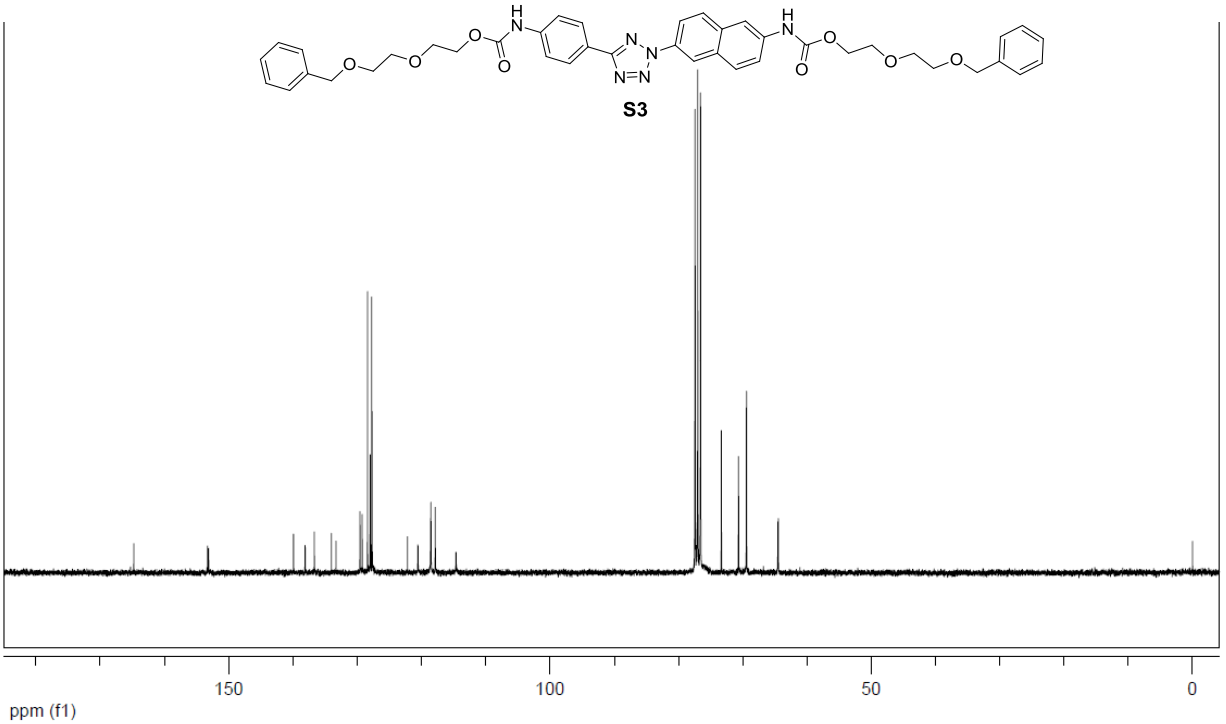
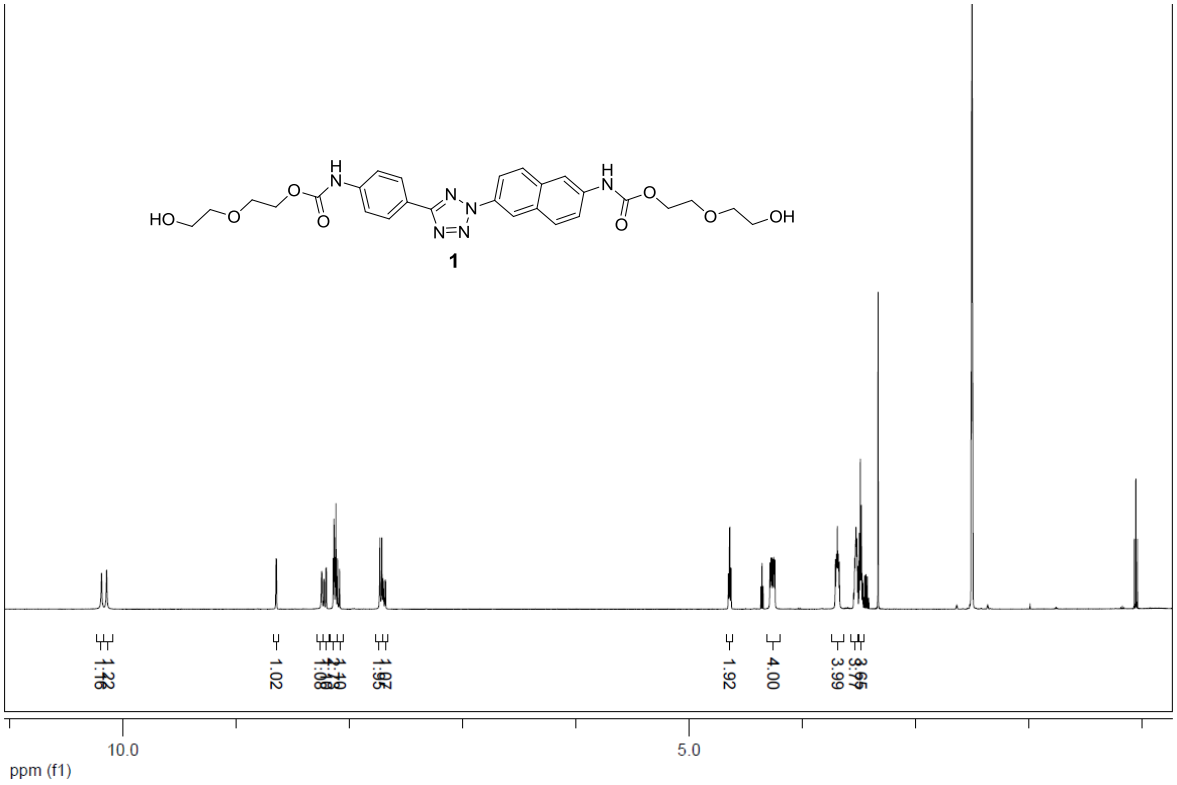
^{1}H and ^{13}C NMR Spectra



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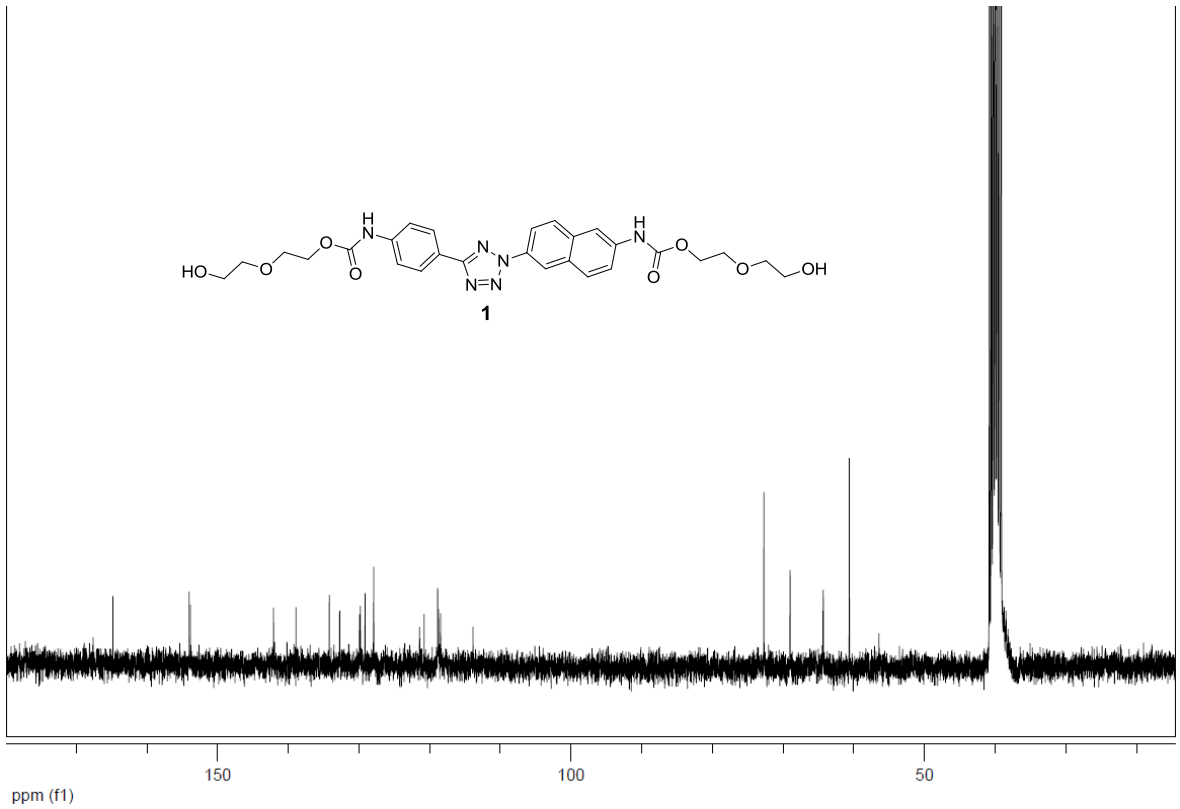
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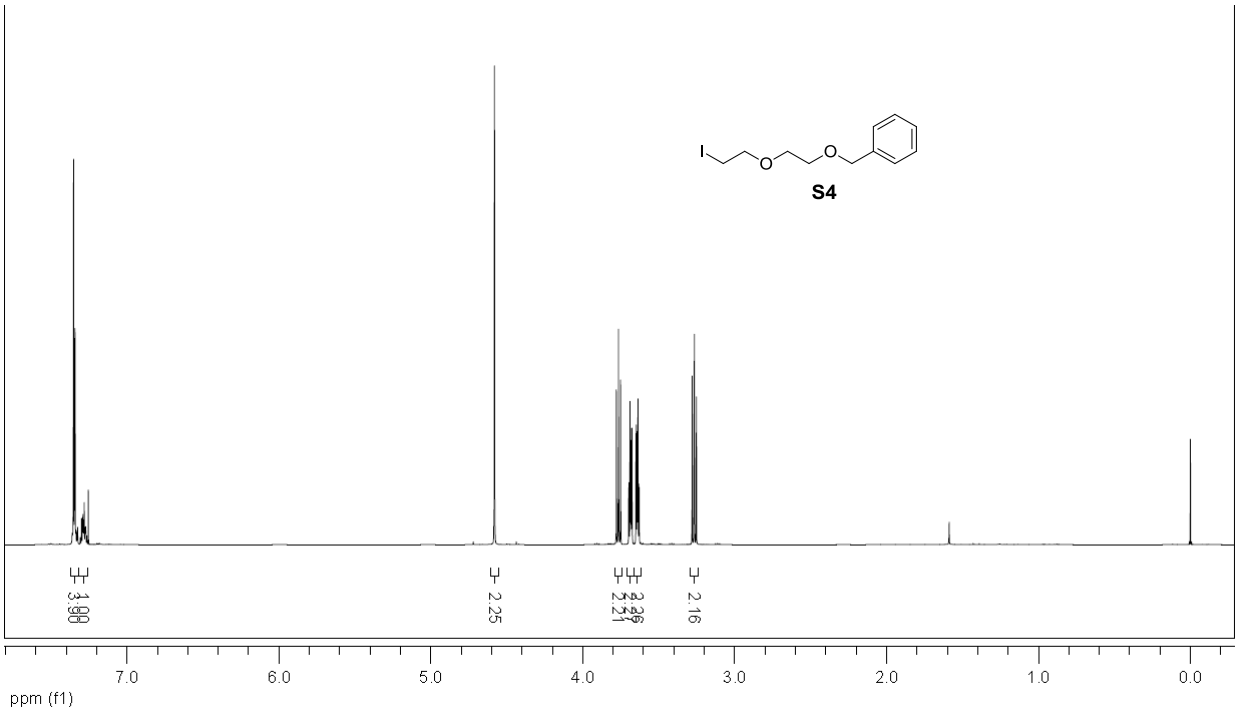
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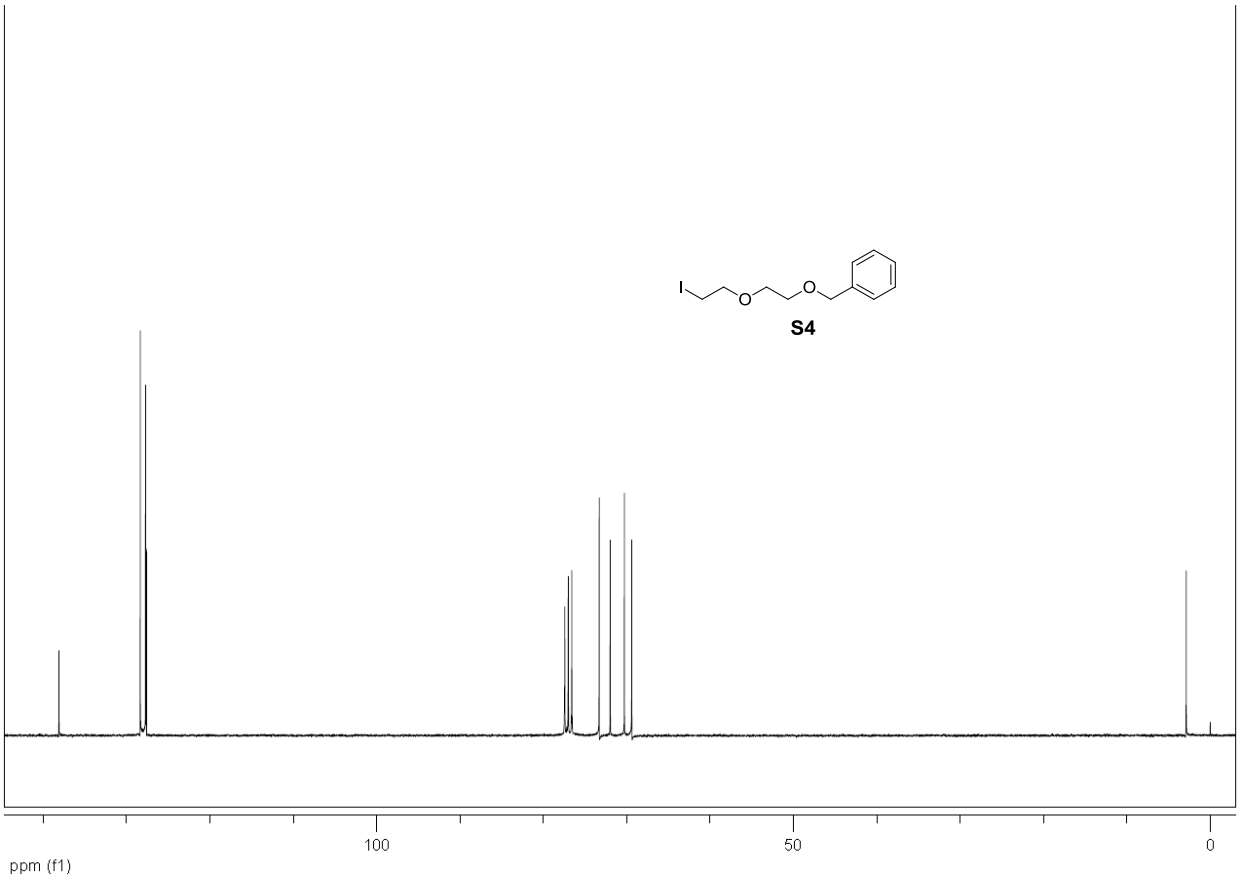
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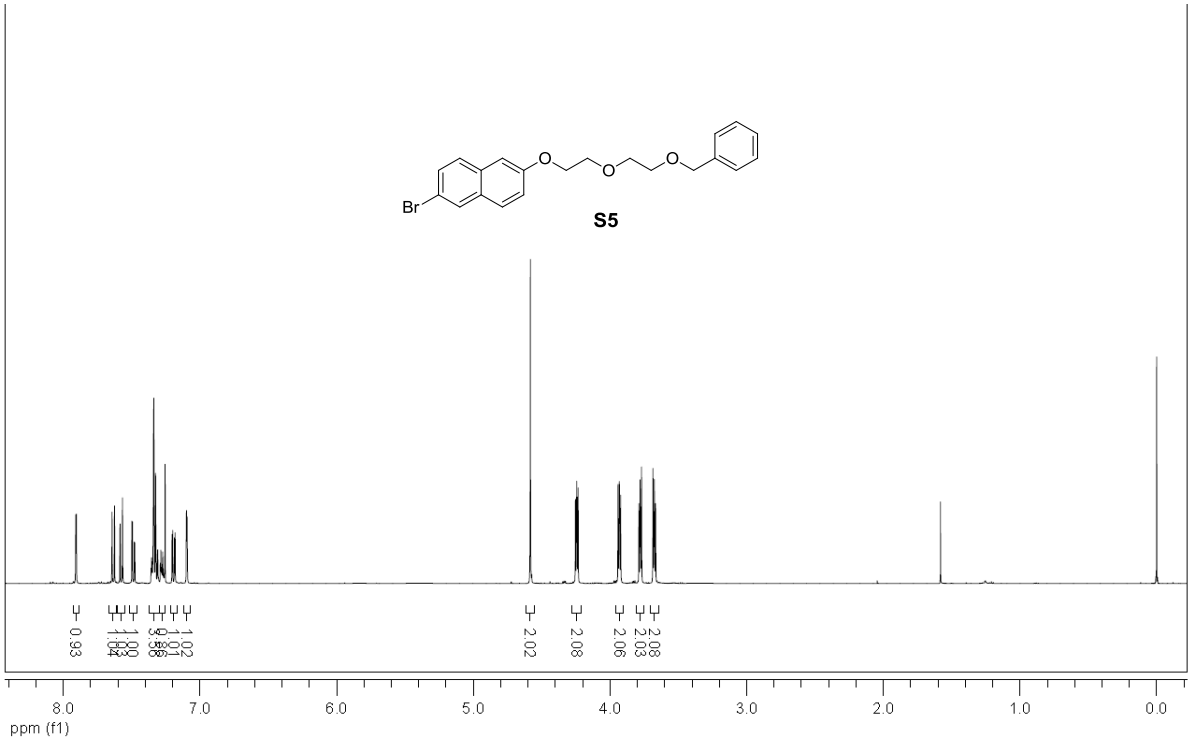
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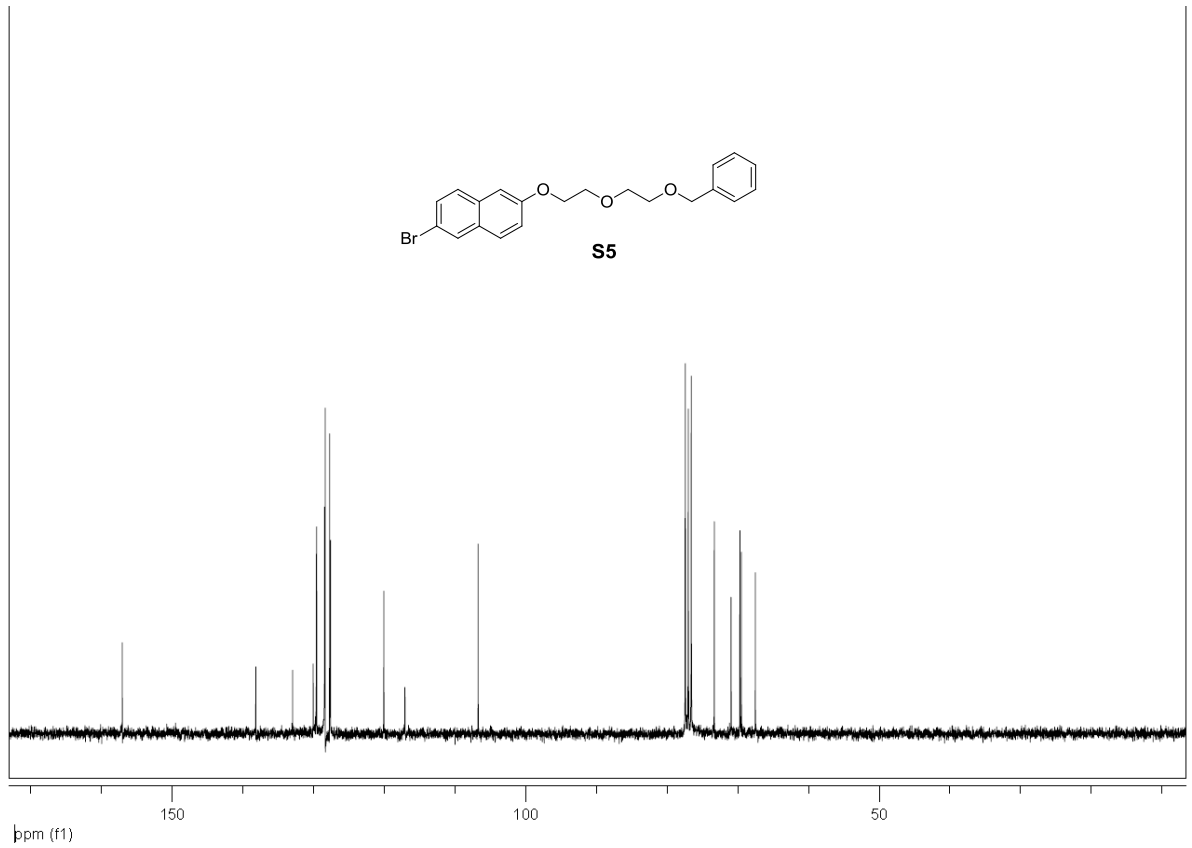
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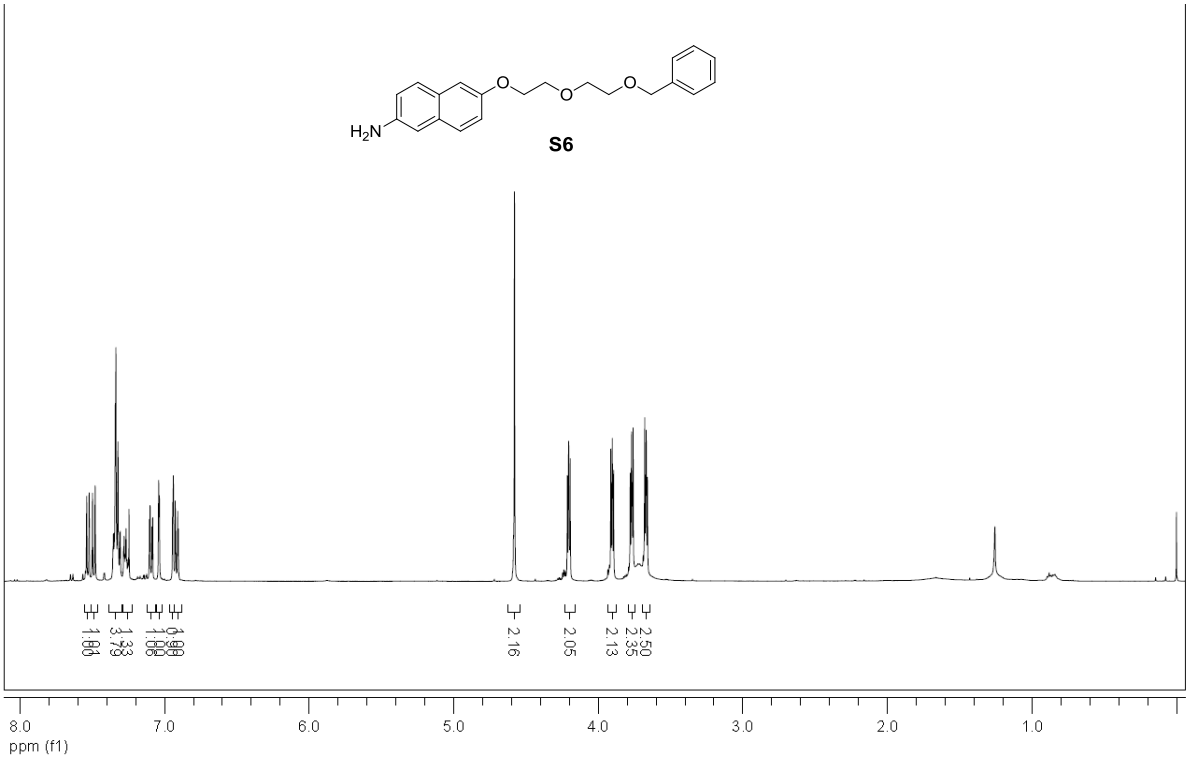
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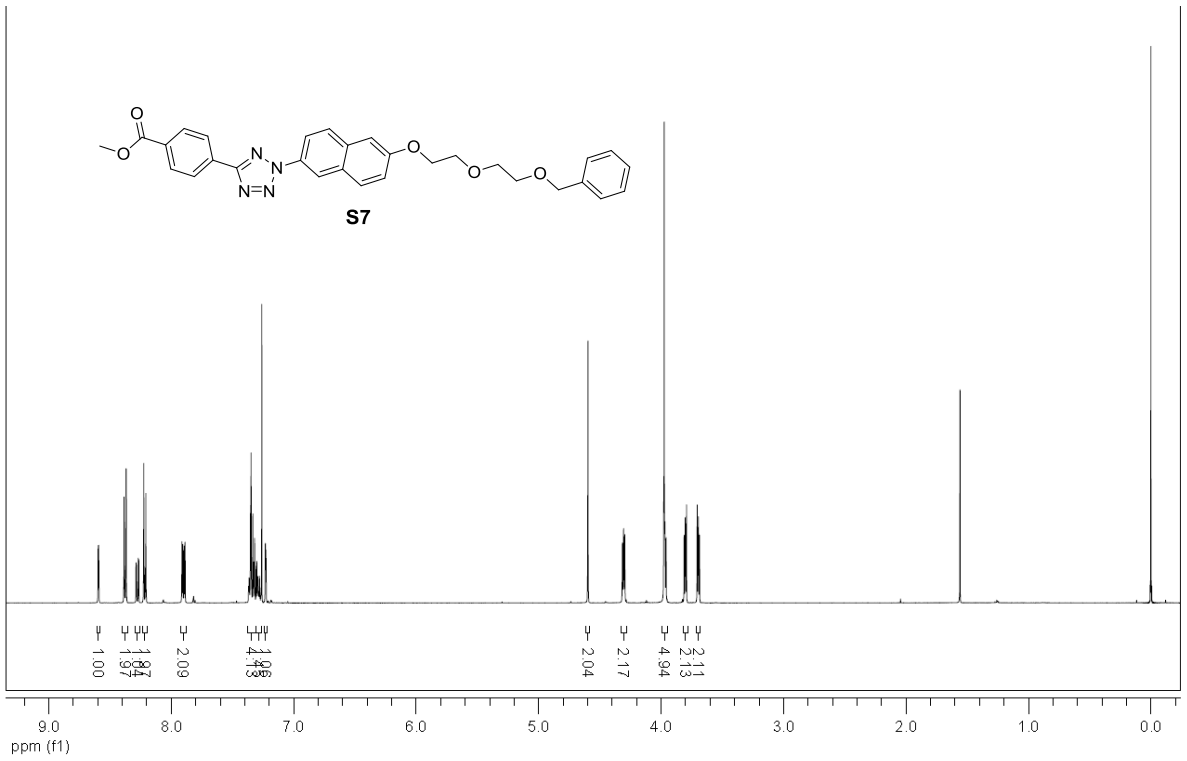
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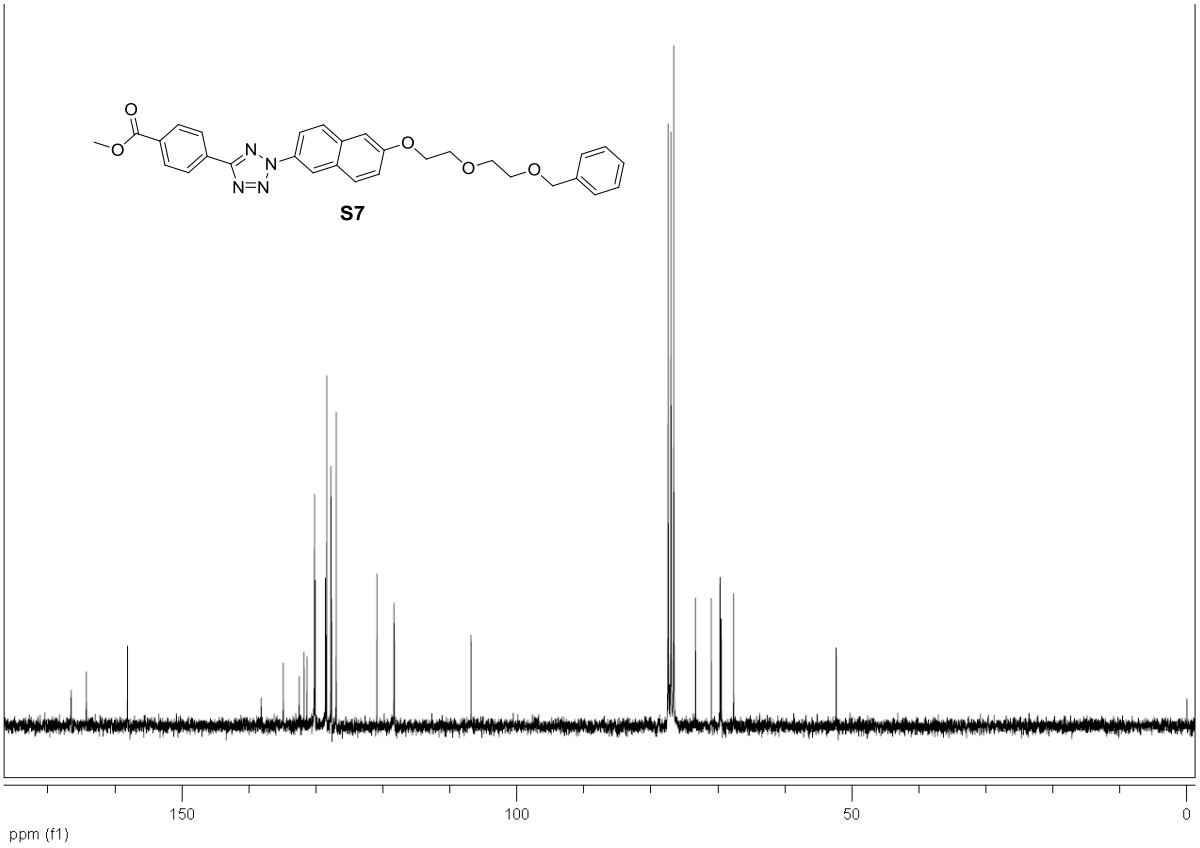
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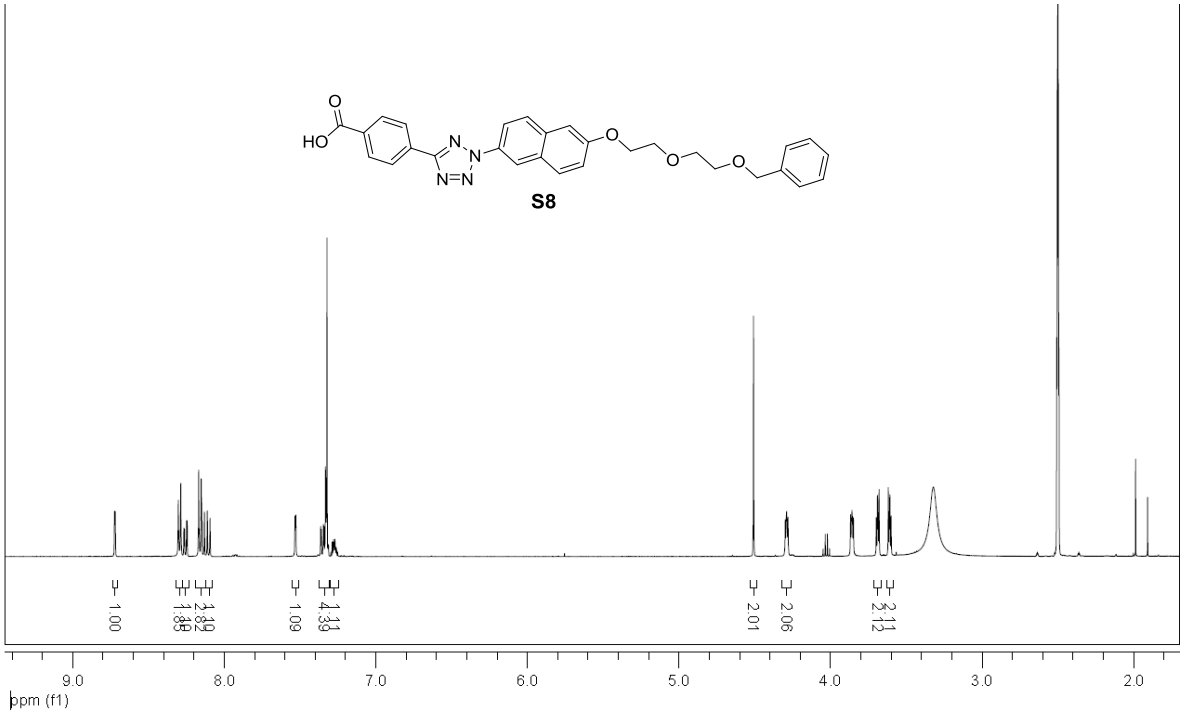
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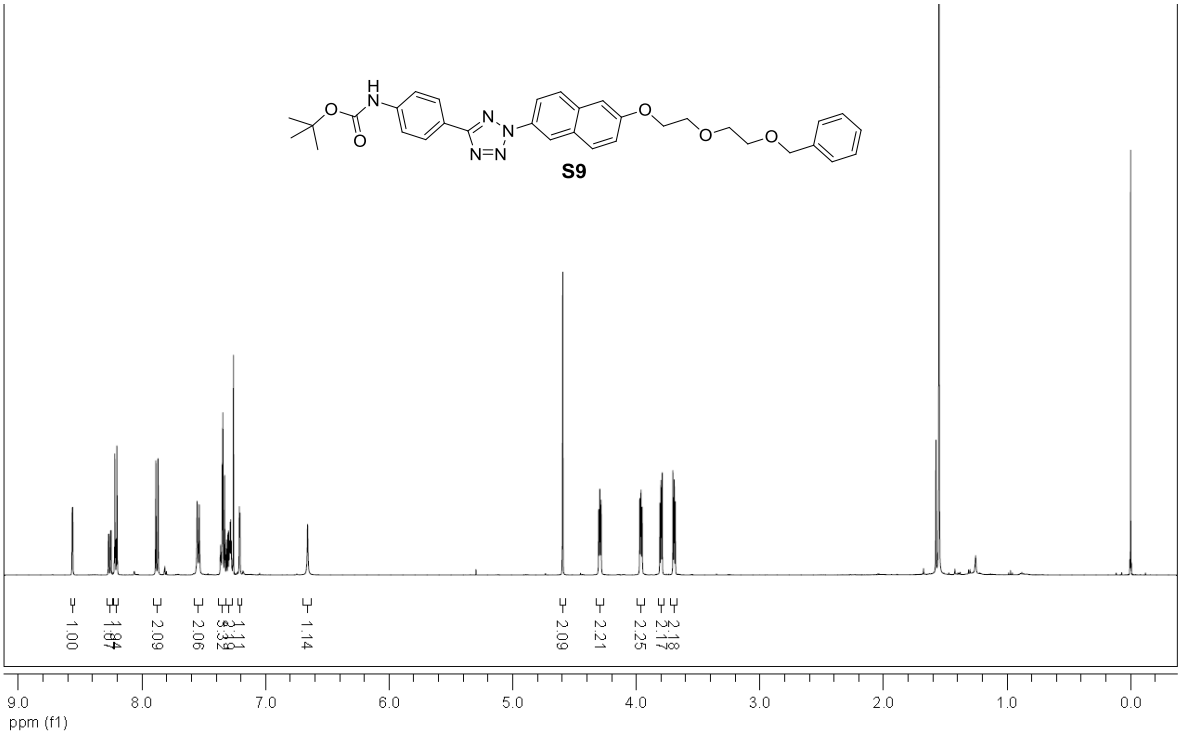
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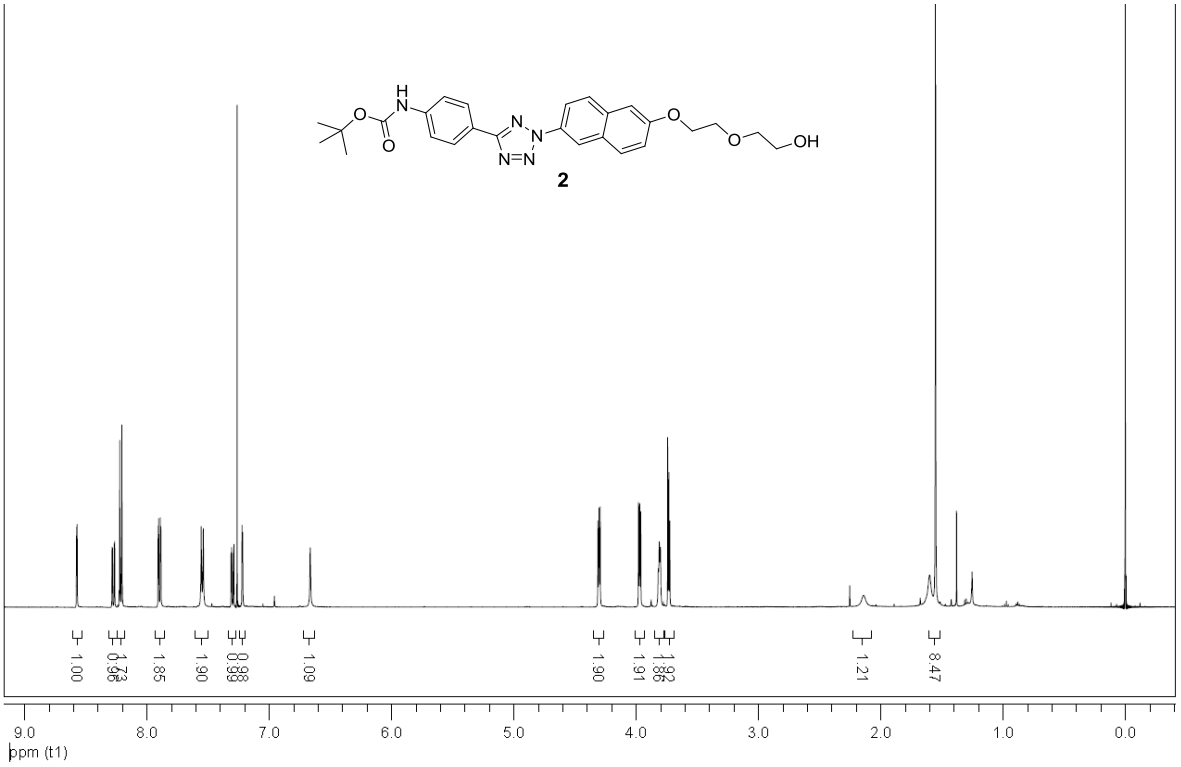
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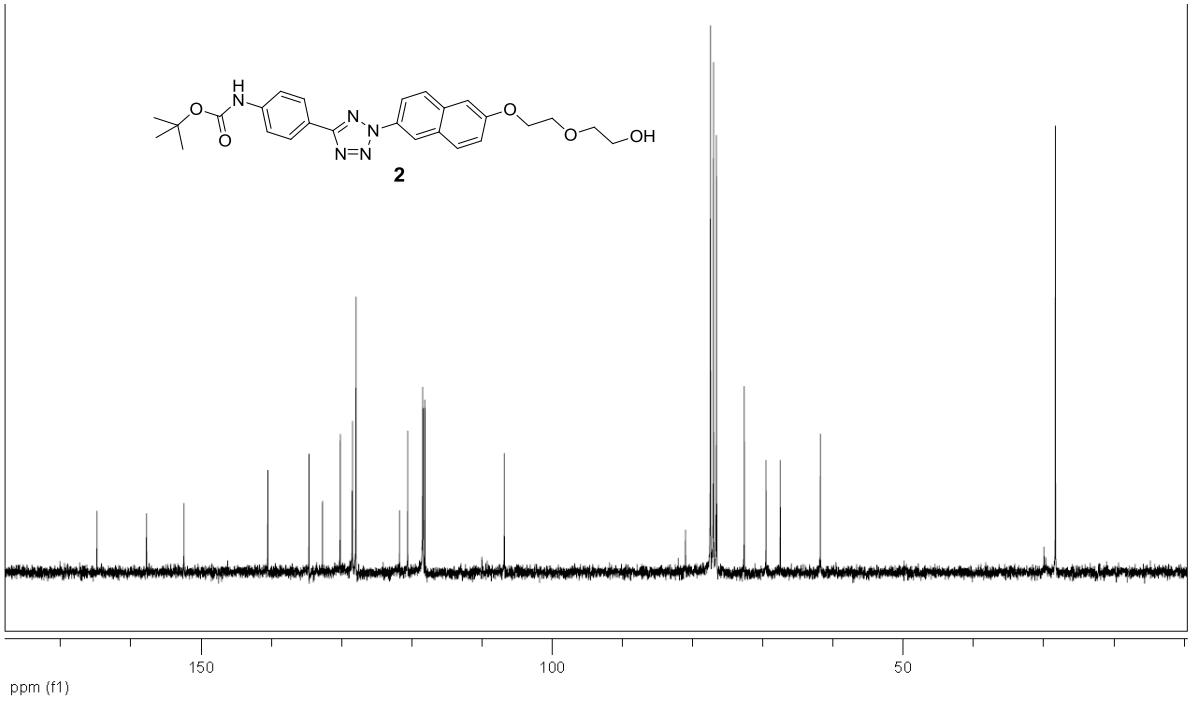
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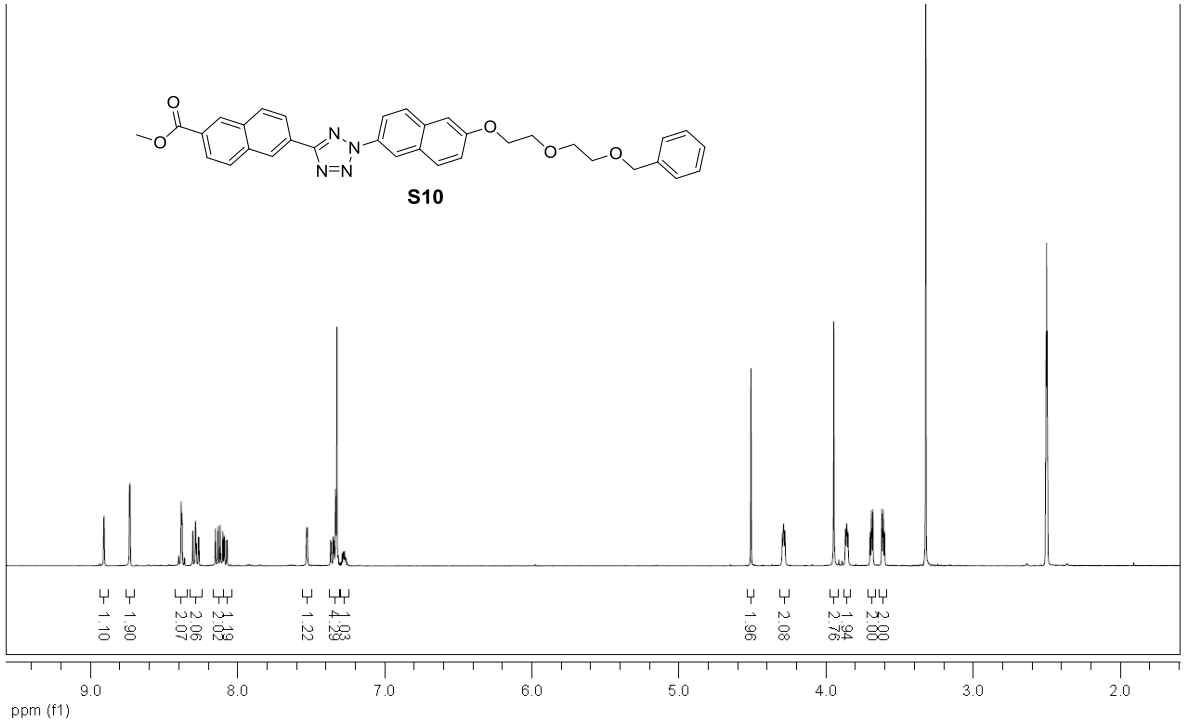
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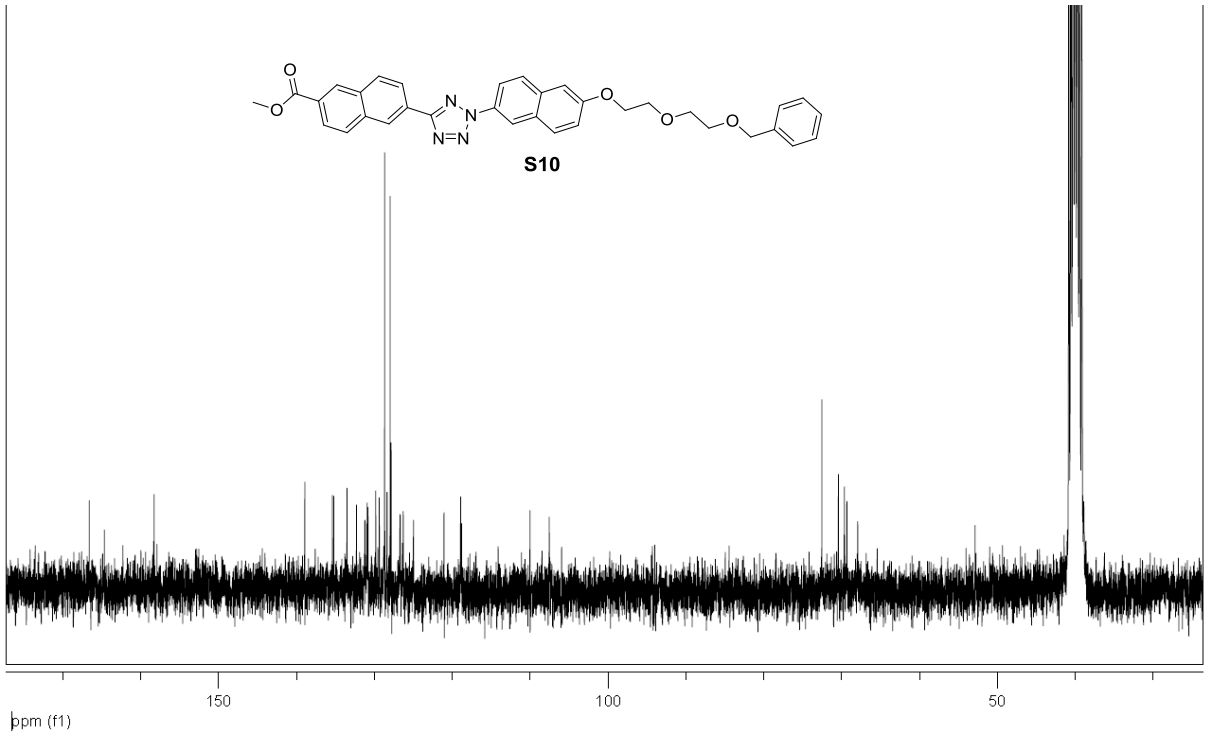
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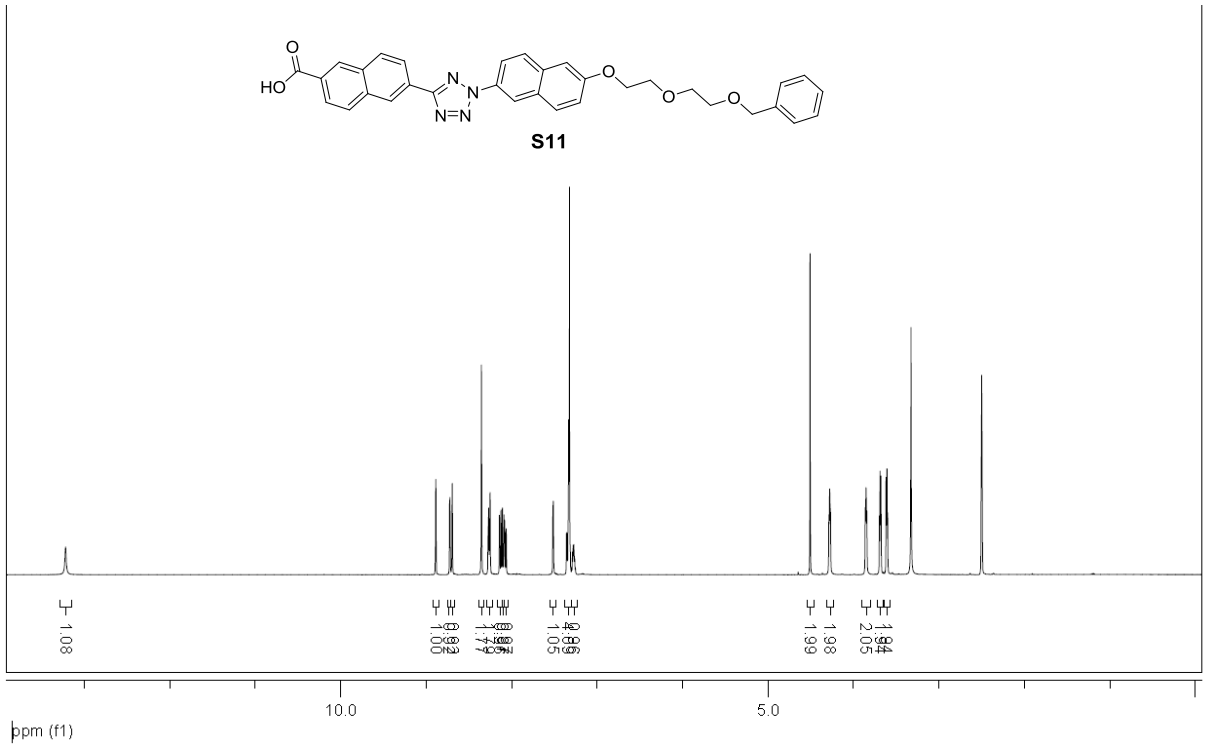
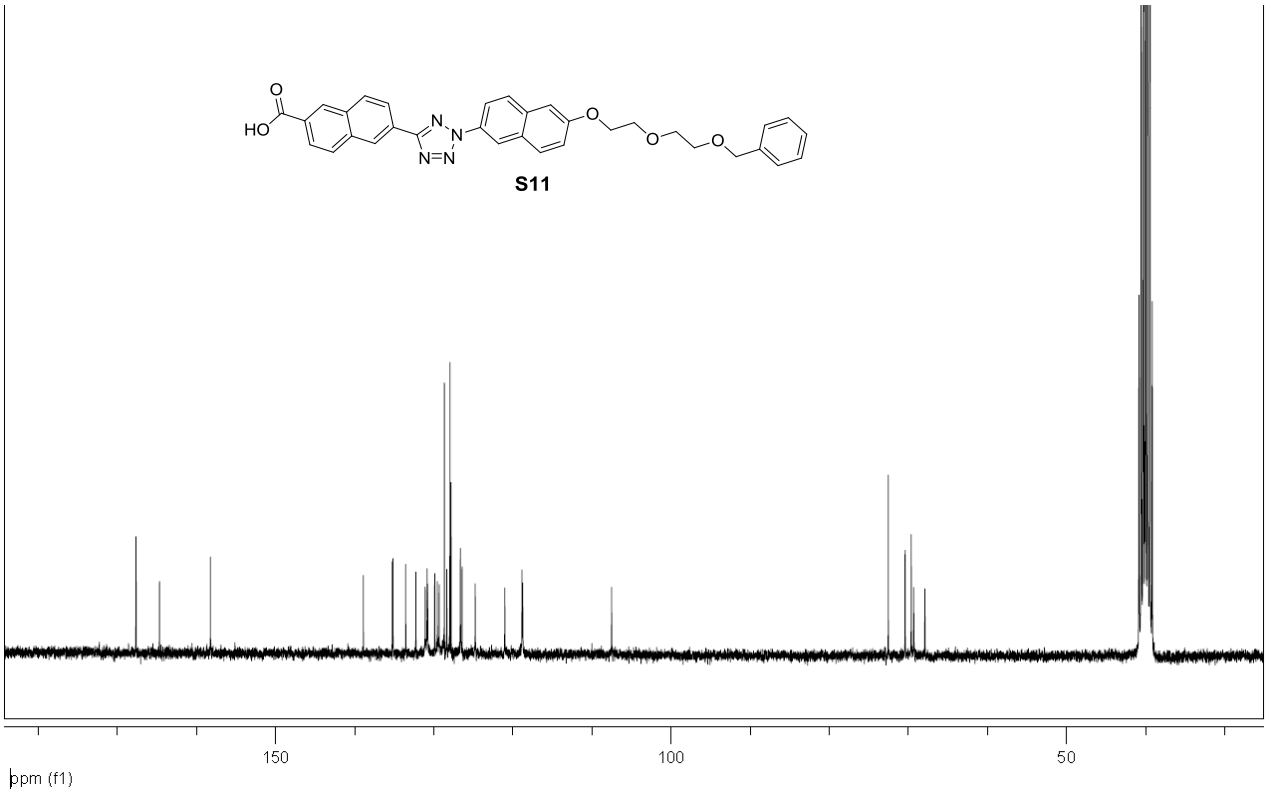
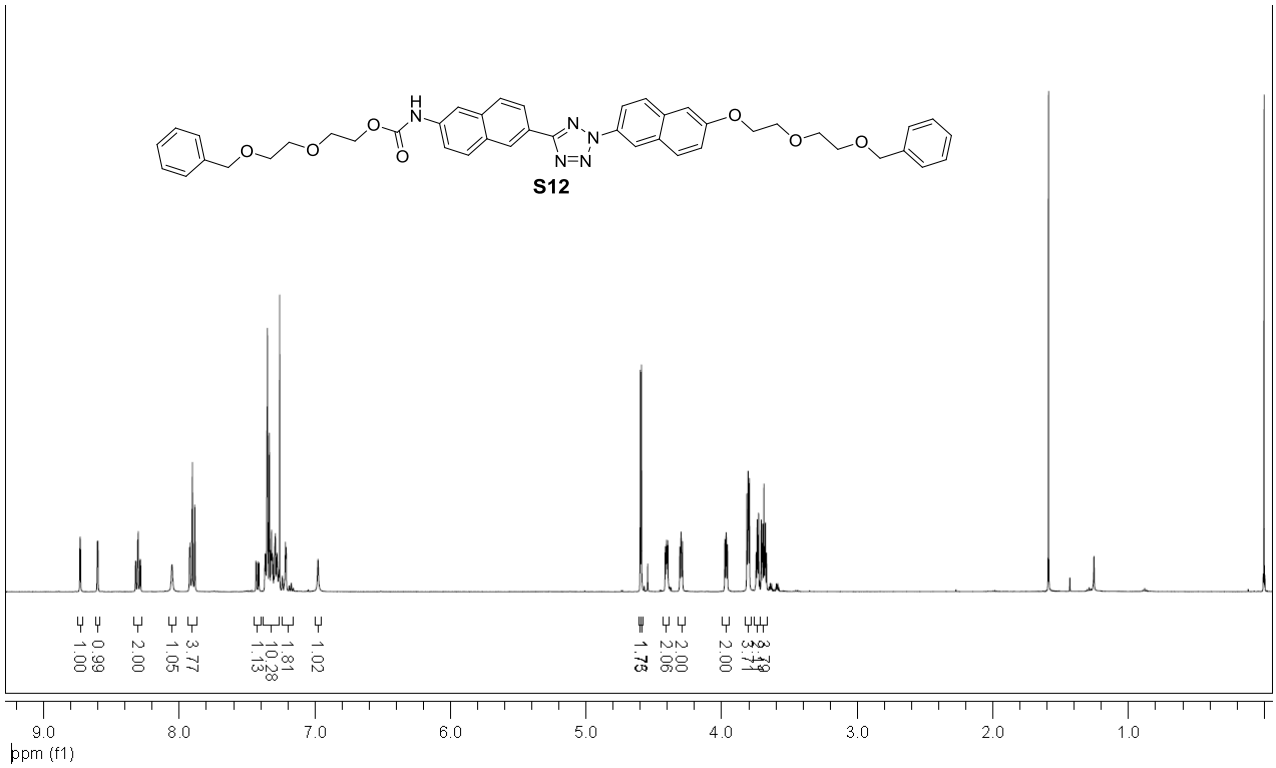
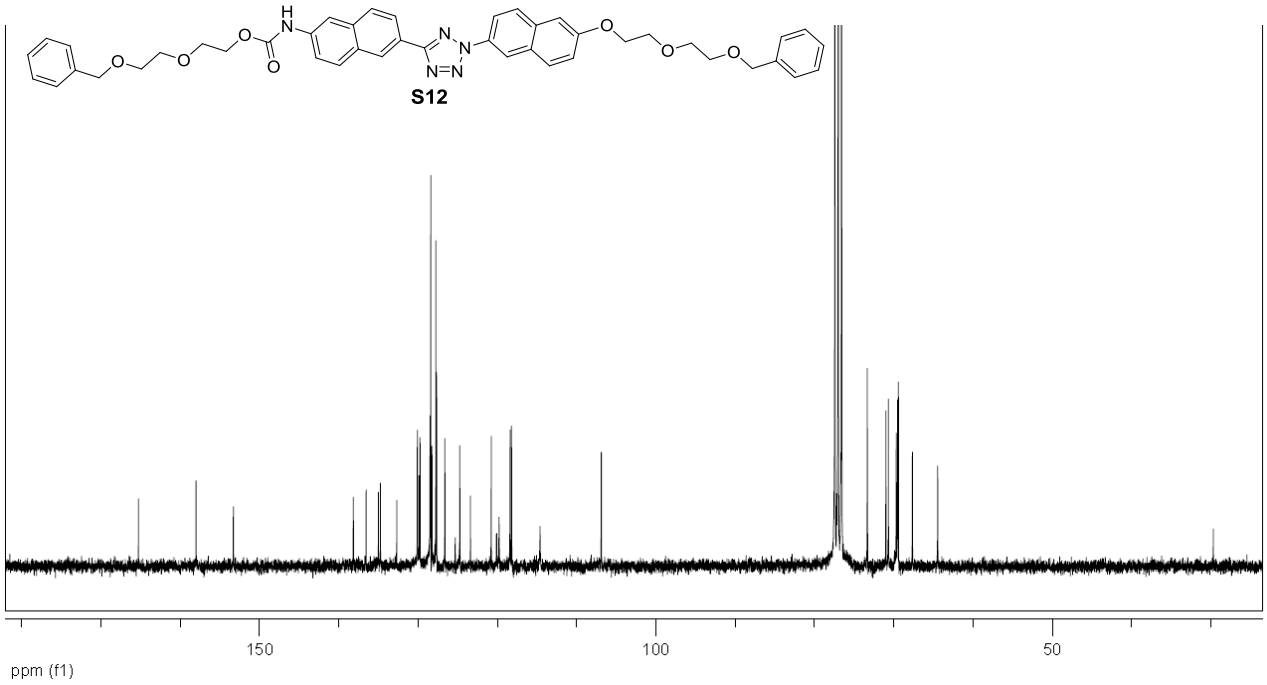
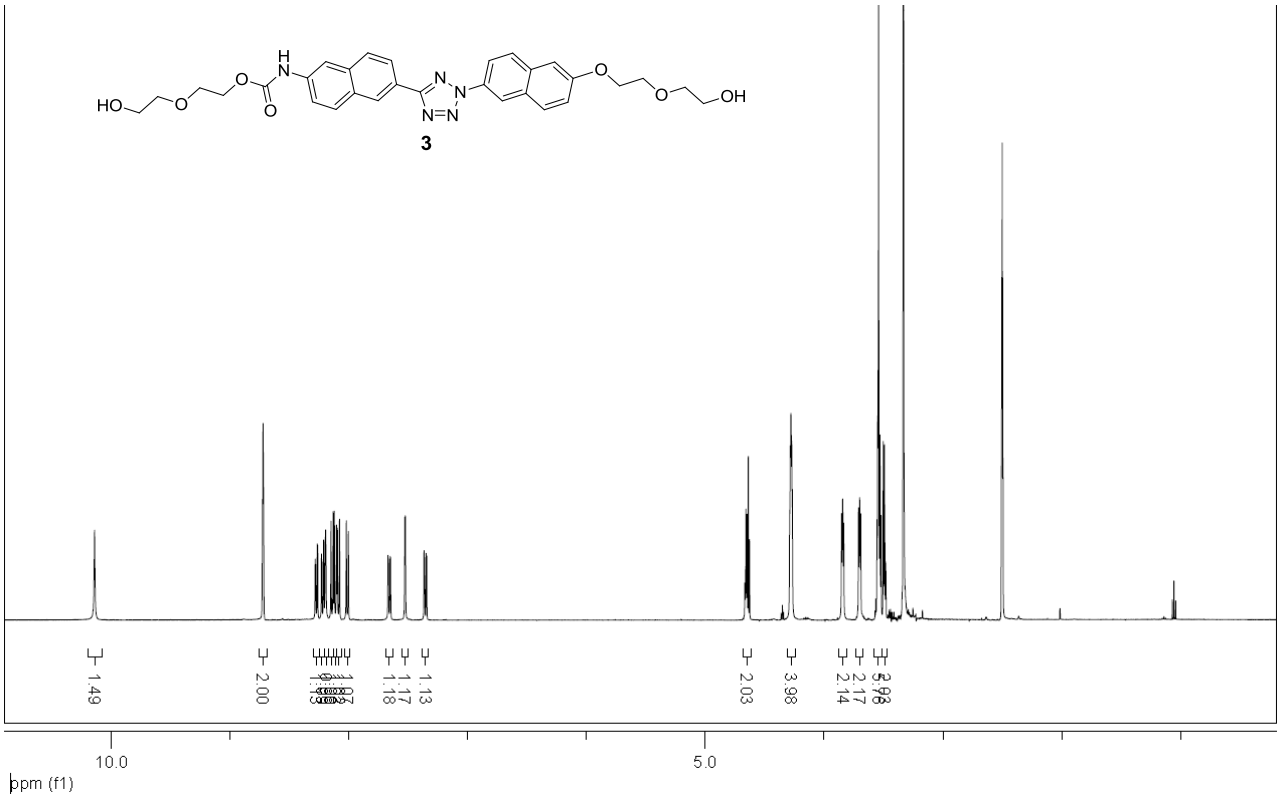
50
ppm (f1)

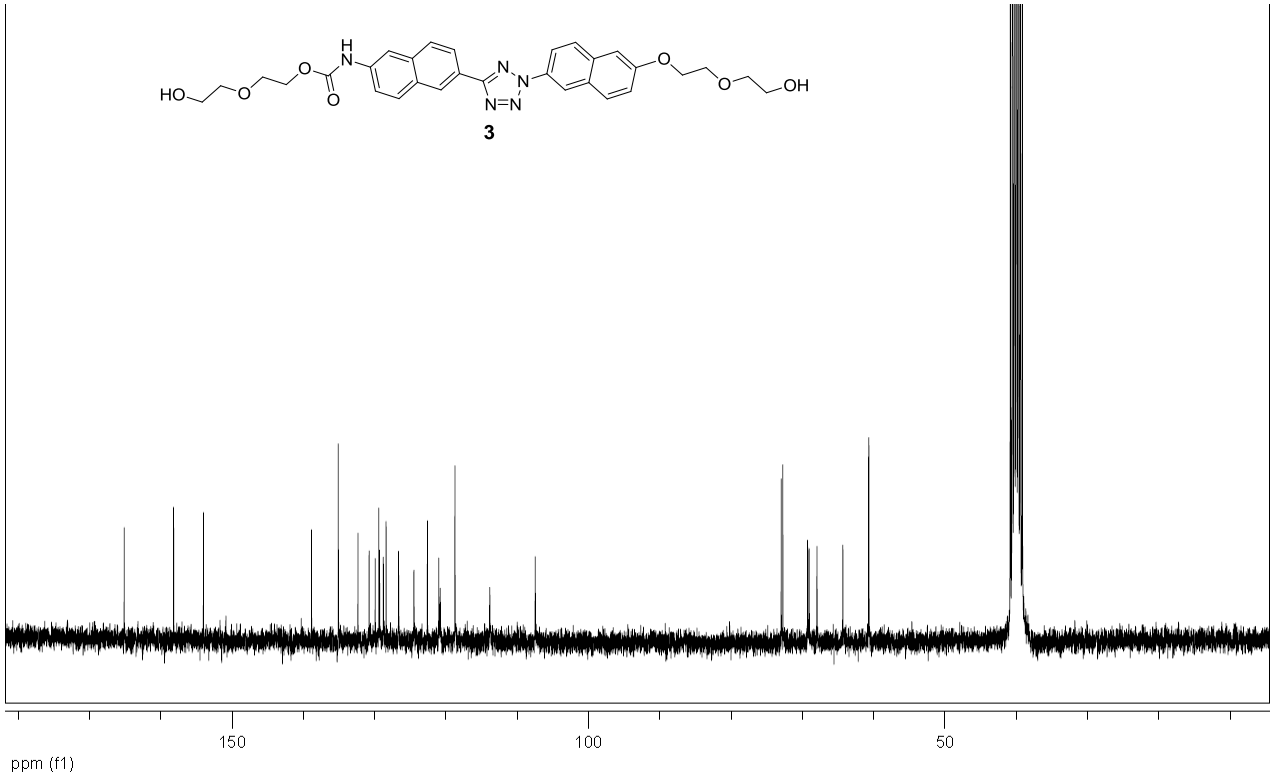

S11
1.08
1.00
0.82
1.74
0.89
0.86
1.05
1.99
1.98
2.05
1.84
10.0
5.0
ppm (f1)


HO
O
N
N
N=N
O
O
O
S11
150
100
50
ppm (f1)

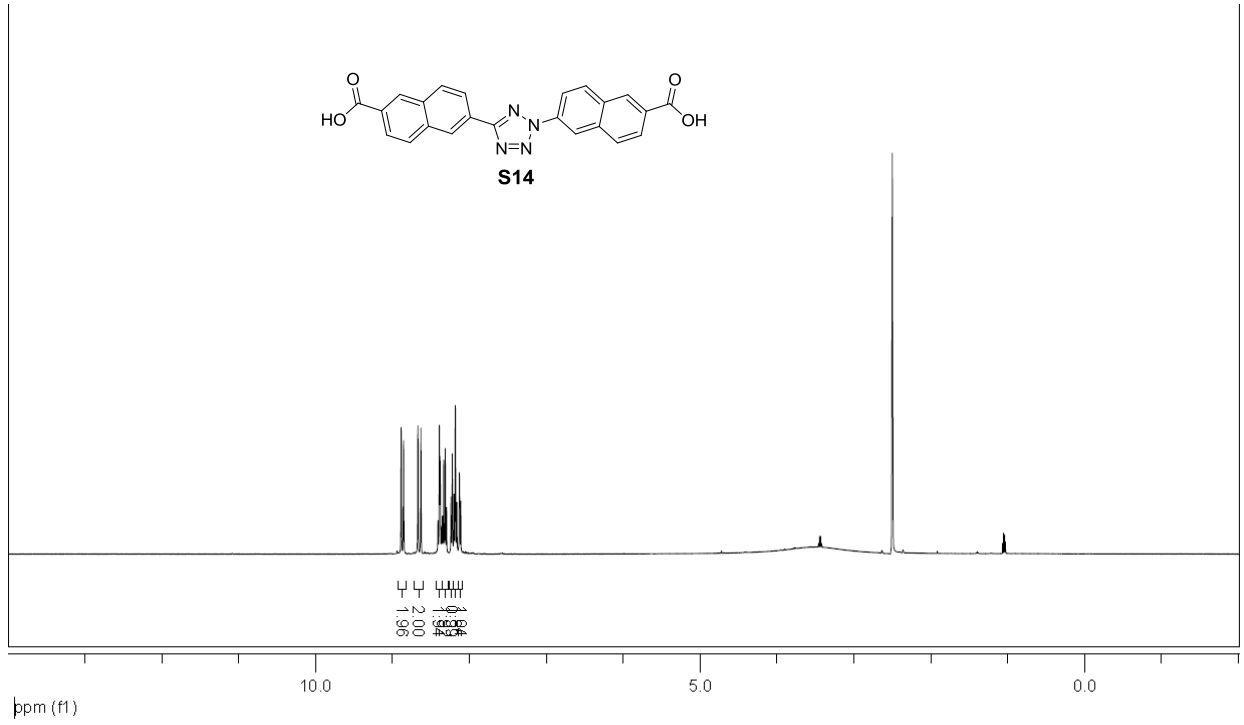

H
N
O
O
O
O
O
O
O
O
O
N
N
N=N
S12
1.00
0.99
2.00
1.05
3.77
1.13
10.28
1.81
1.02
1.73
2.06
2.00
2.00
3.71
3.79
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


S12
150
100
50
ppm (f1)

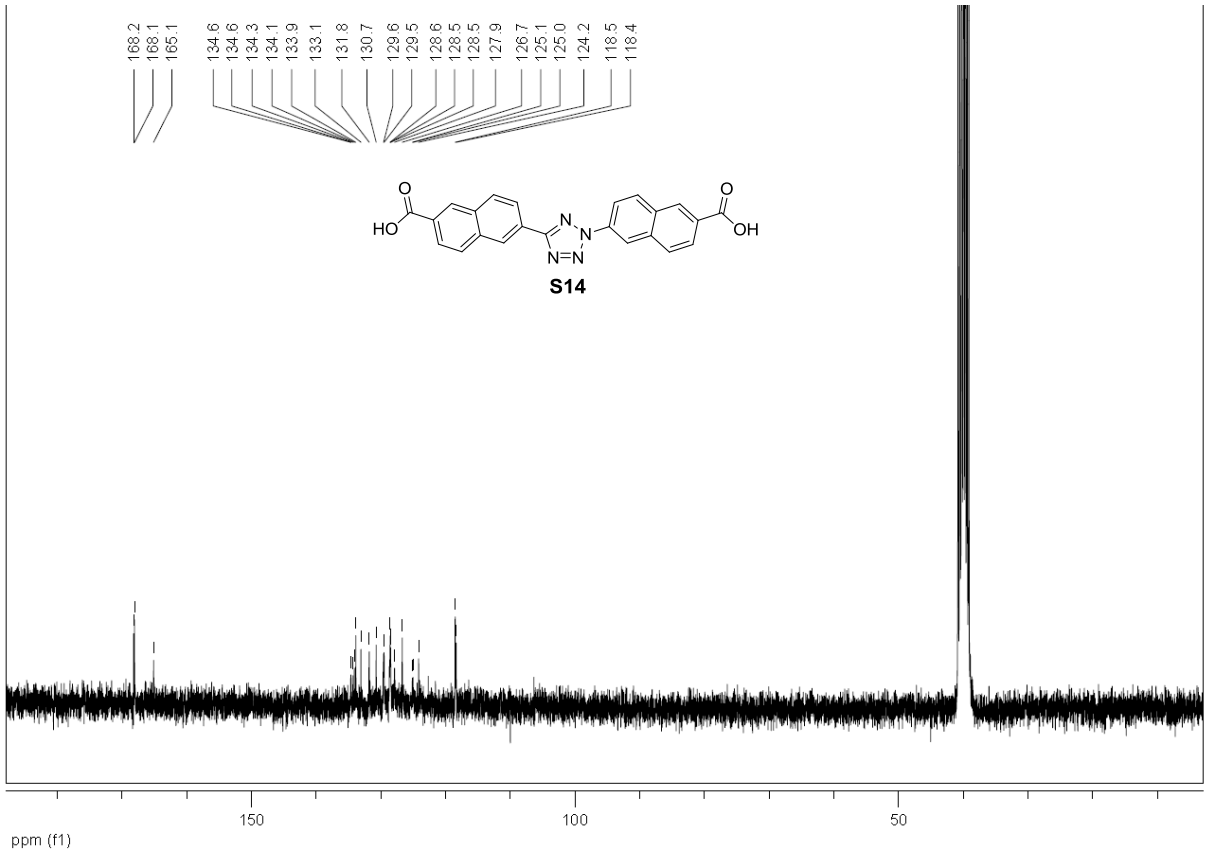

3
1.49
2.00
1.18
1.17
1.13
2.03
3.98
2.14
2.17
10.0
5.0
ppm (f1)

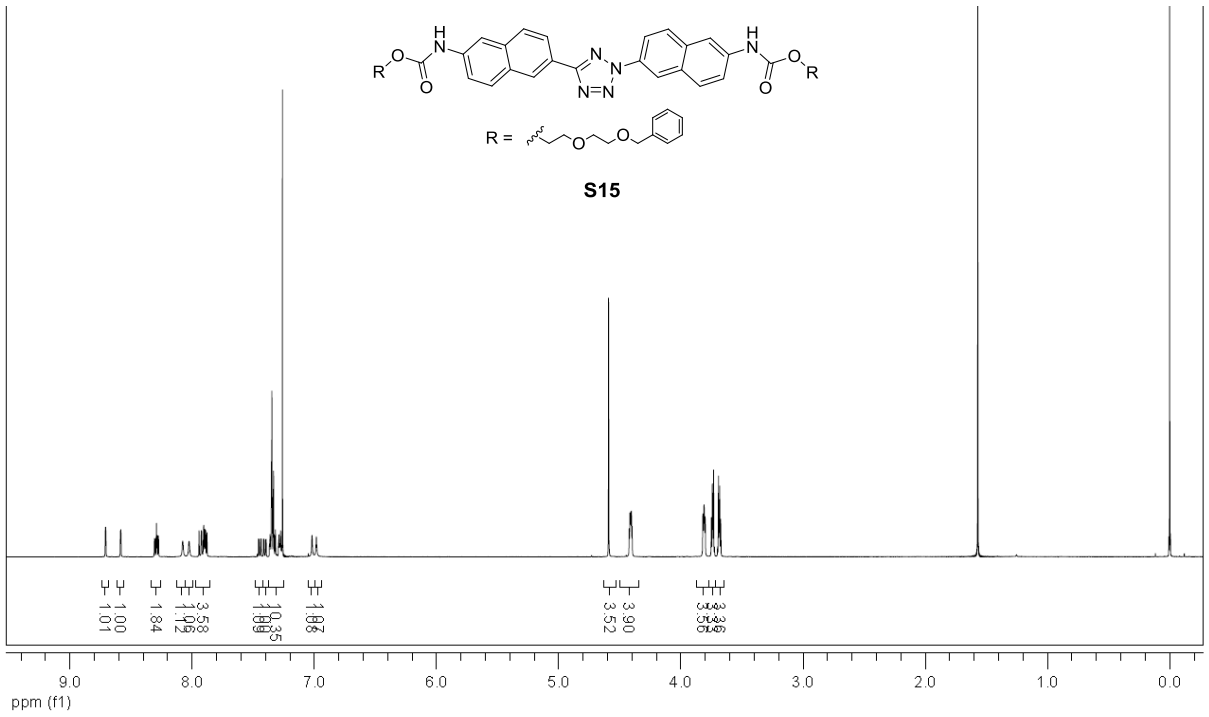

HO
O
O
O
H
N
O
N
N
N=N
O
O
OH
150
100
50
ppm (f1)

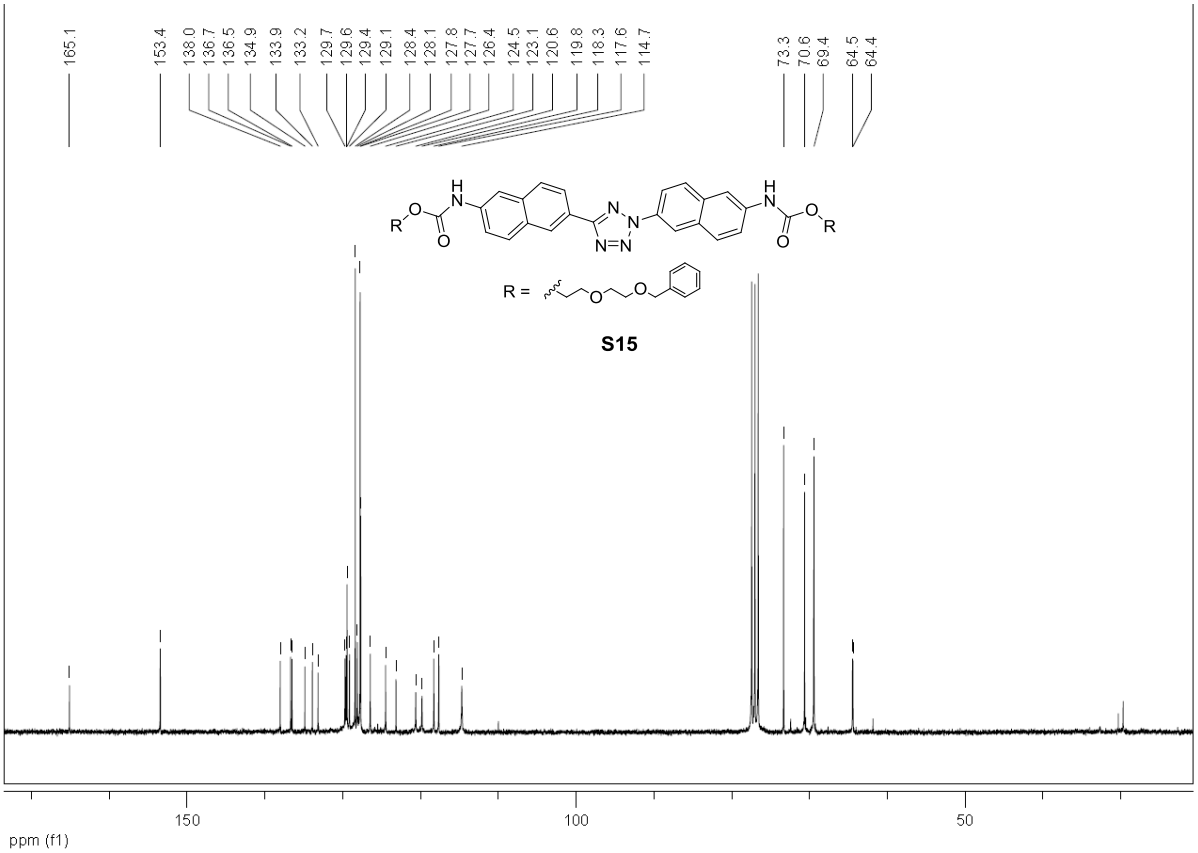
3


HO
O
O
N
N
N=N
O
OH
10.0
5.0
0.0
ppm (f1)

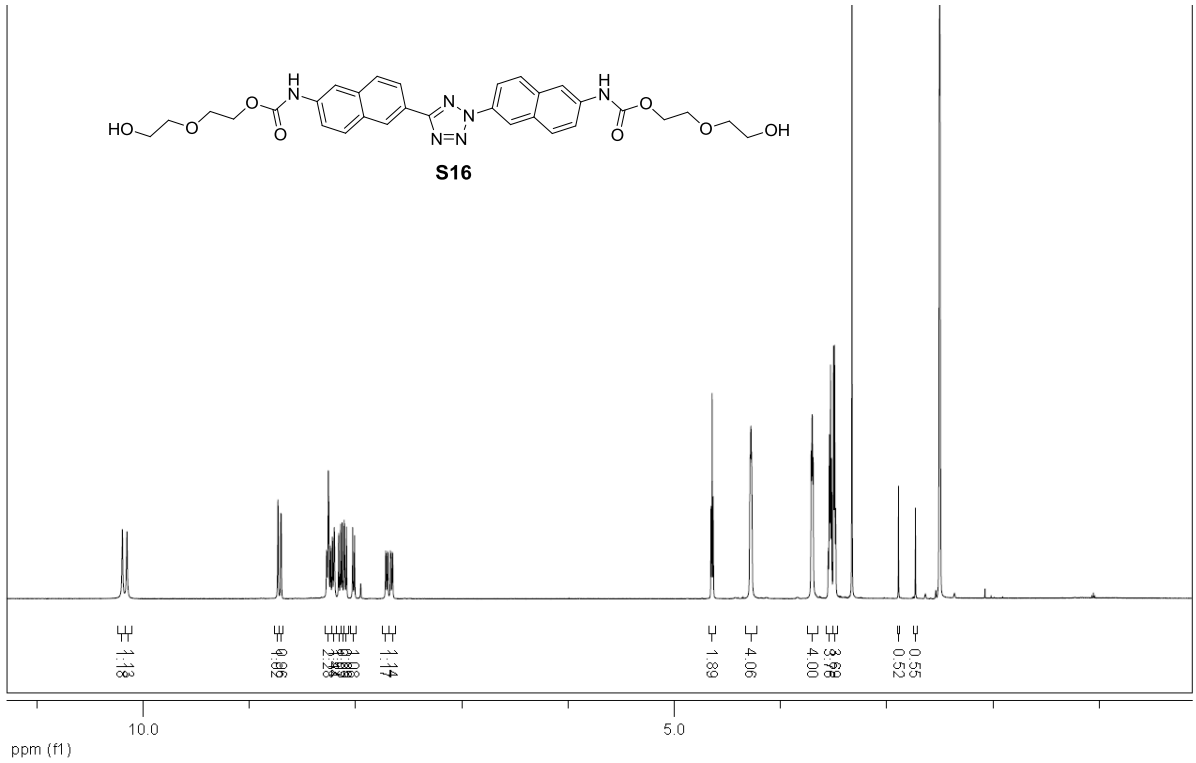
S14


168.2
168.1
165.1
134.6
134.6
134.3
134.1
133.9
133.1
131.8
130.7
129.6
129.5
128.6
128.5
128.5
127.9
126.7
125.1
125.0
124.2
118.5
118.4
HO
OH
N
N
N=N
S14
150
100
50
ppm (f1)

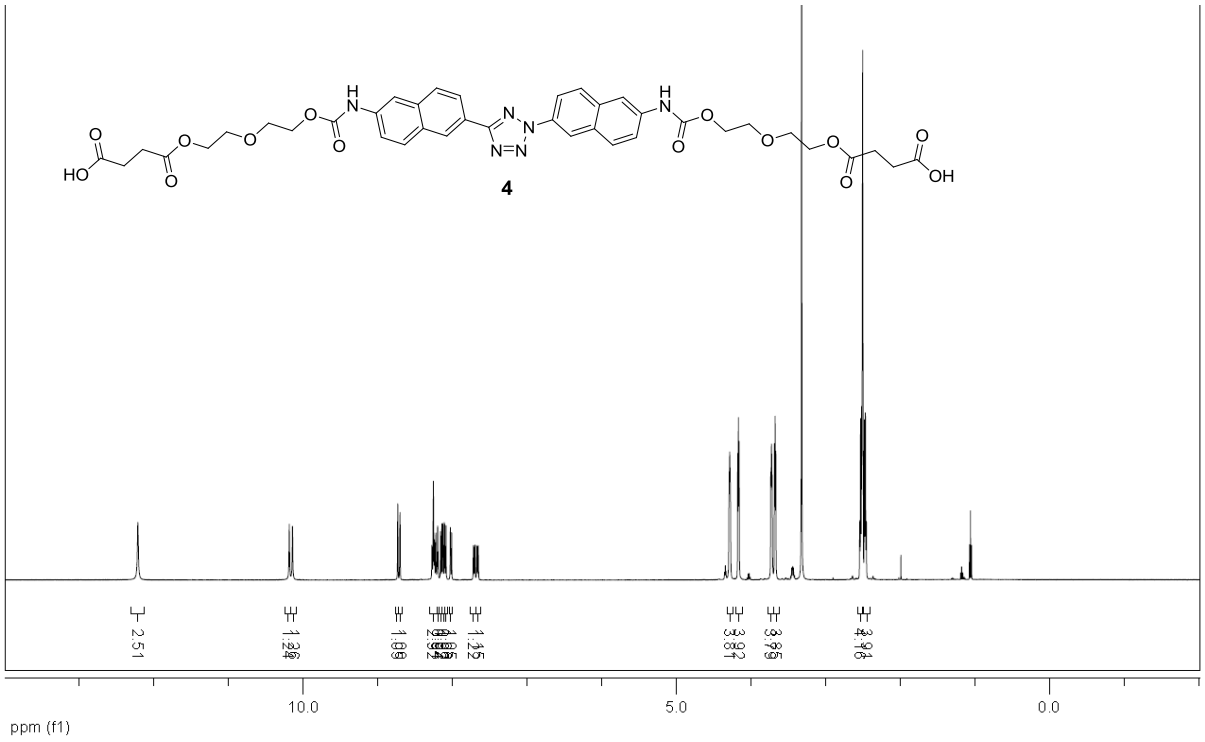

R =
S15
1.00
1.01
1.84
3.52
3.90
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

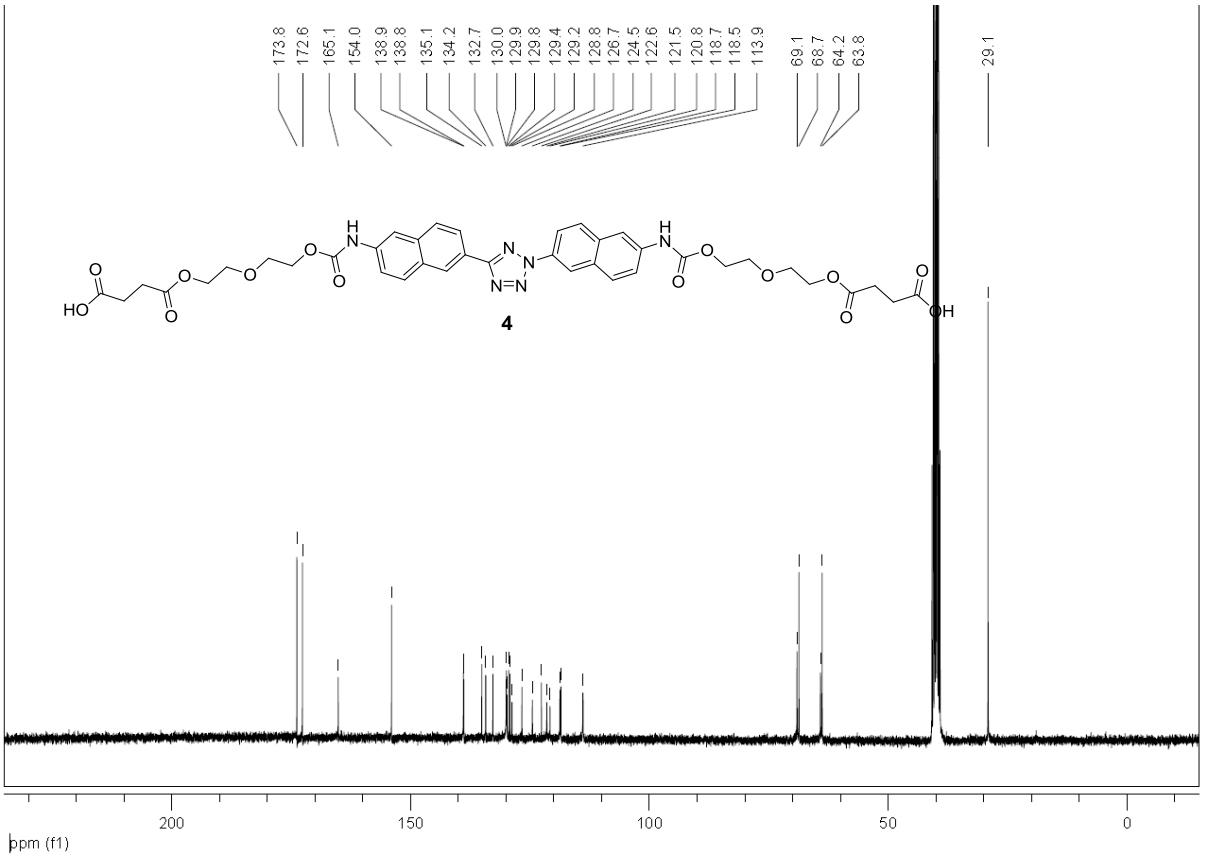

165.1
153.4
138.0
136.7
136.5
134.9
133.9
133.2
129.7
129.6
129.4
129.1
128.4
128.1
127.8
127.7
126.4
124.5
123.1
120.6
119.8
118.3
117.6
114.7
73.3
70.6
69.4
64.5
64.4
R =
150
100
50
ppm (f1)

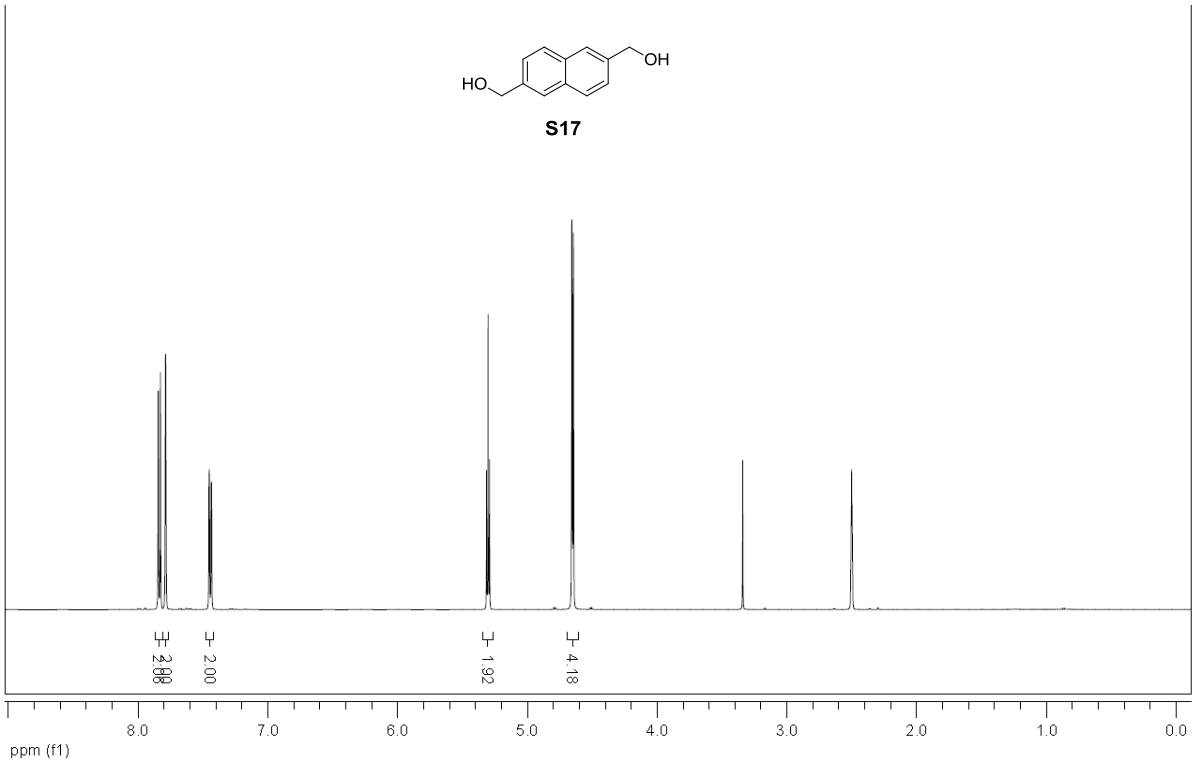
S15

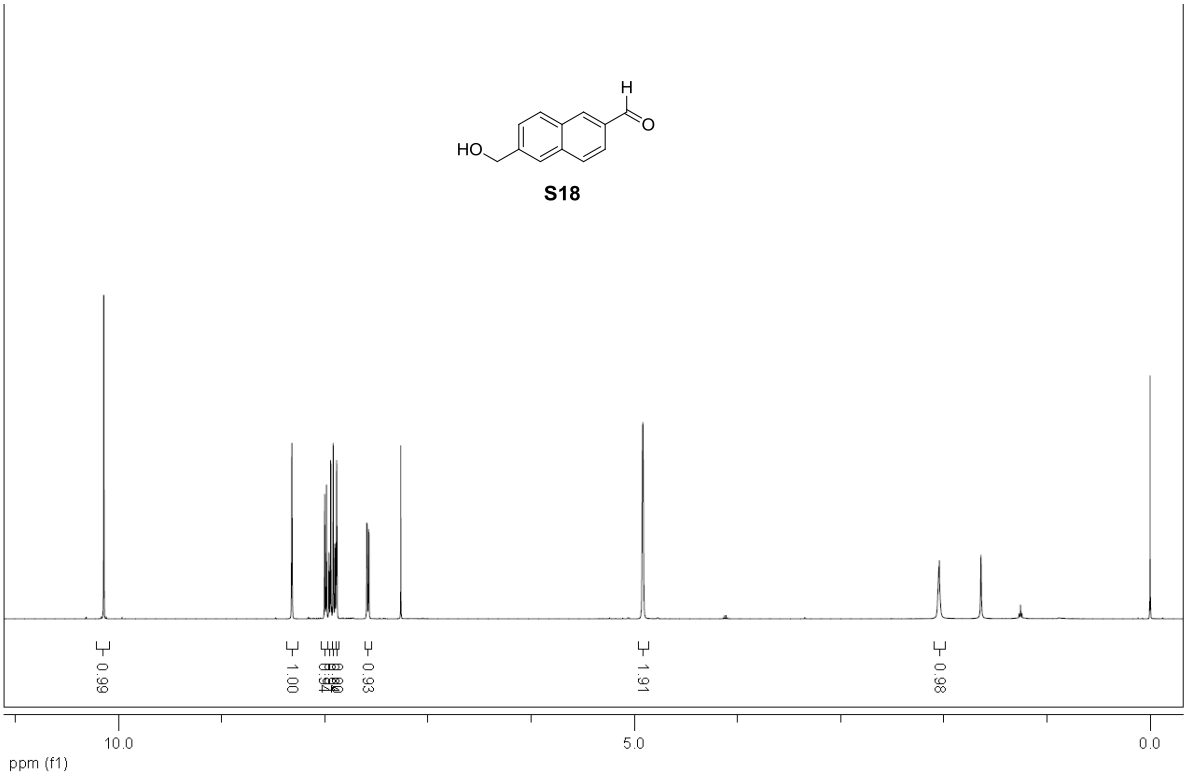

1.13
0.96
2.28
1.14
1.89
4.06
4.00
3.78
0.55
0.52
10.0
5.0
ppm (f1)

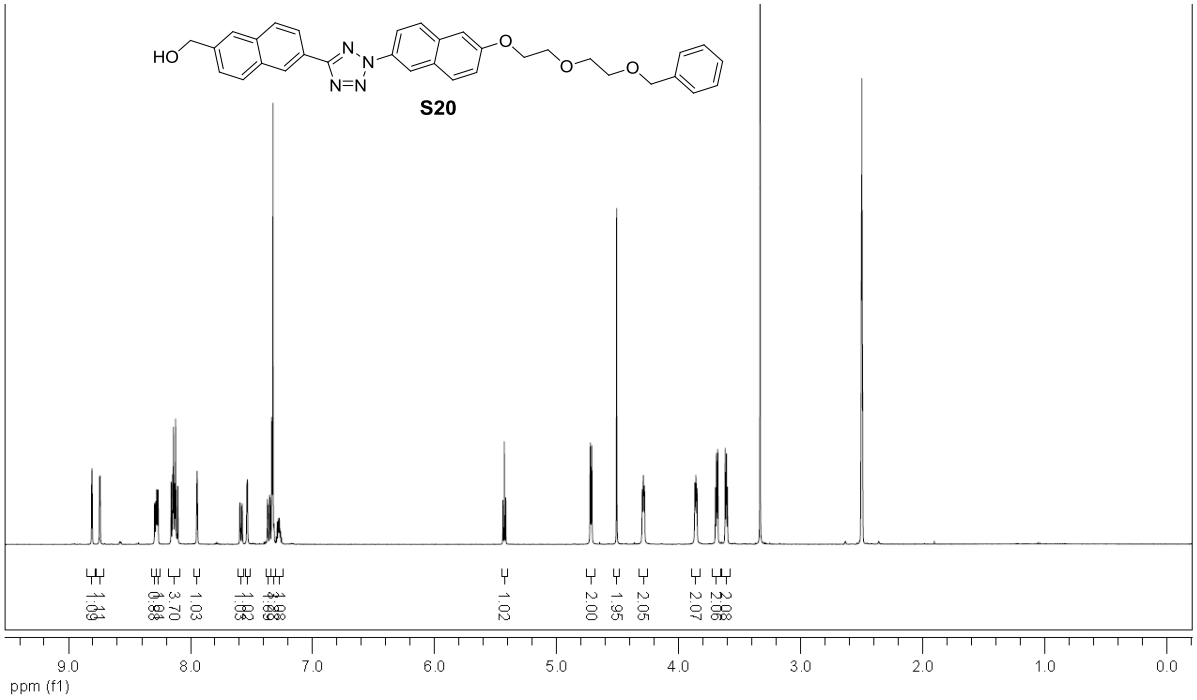
S16

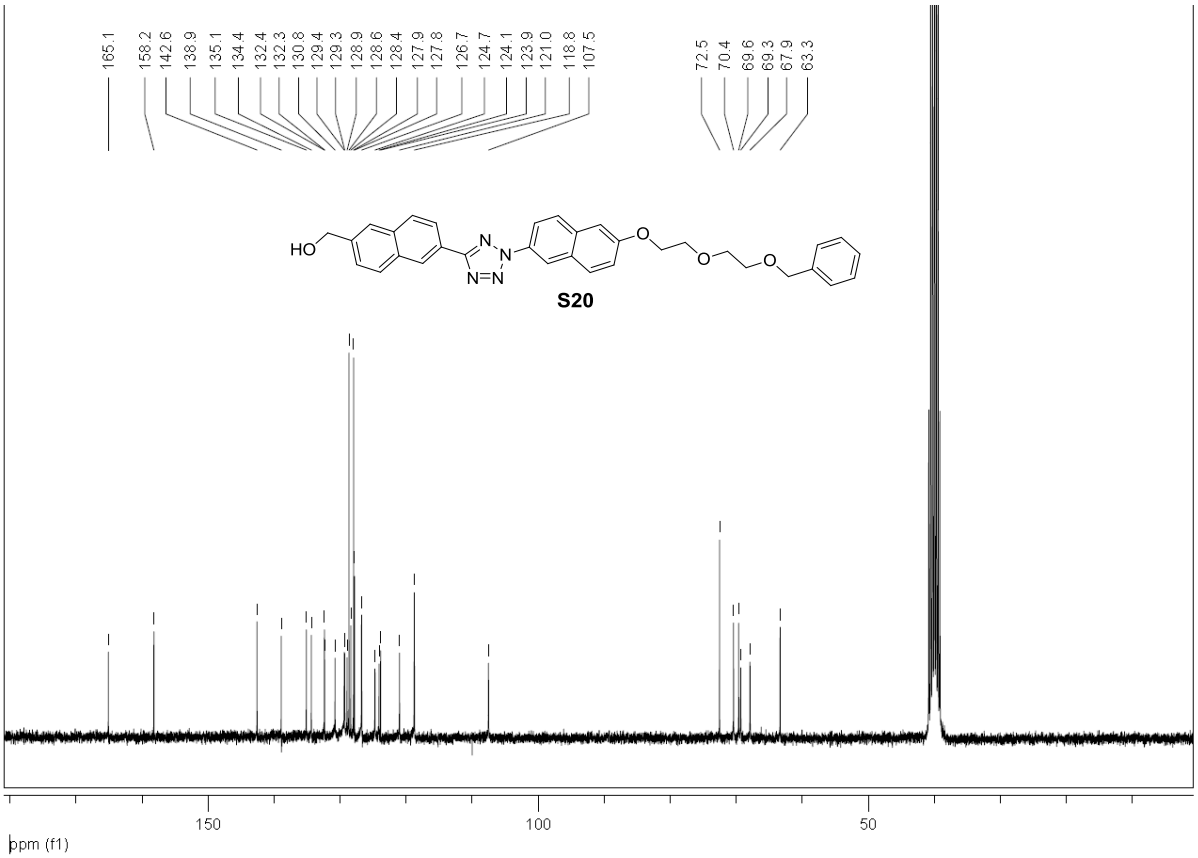

4
10.0
5.0
0.0
ppm (f1)

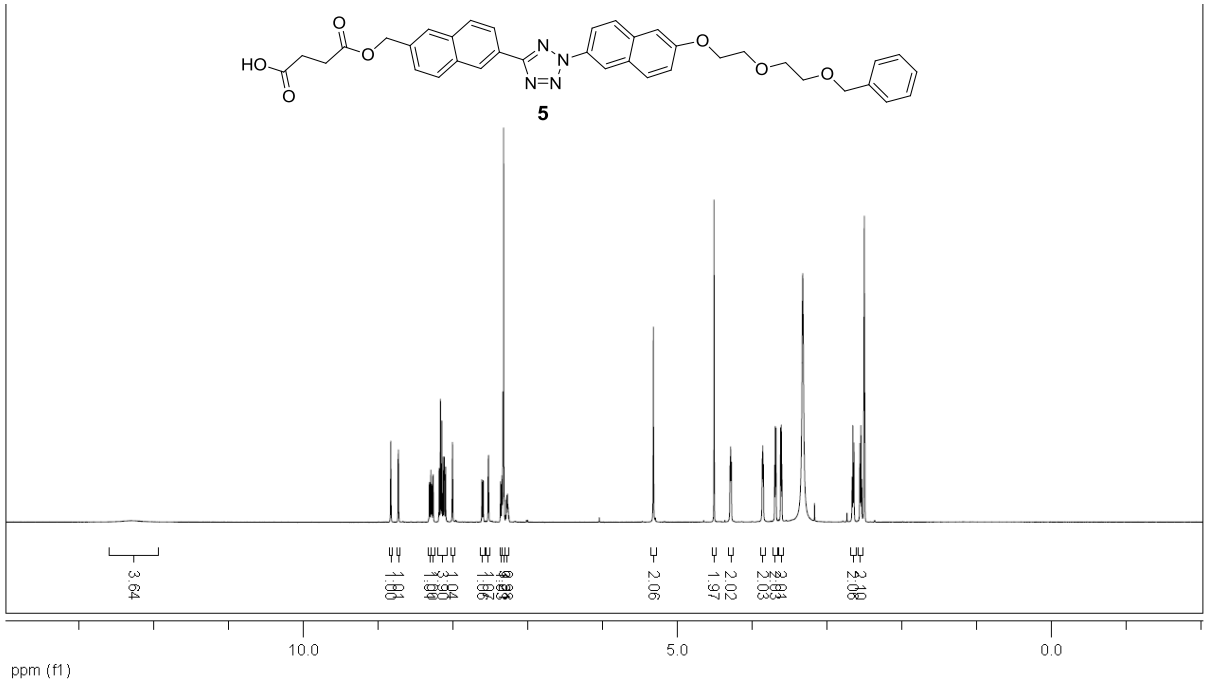

173.8
172.6
165.1
154.0
138.9
138.8
135.1
134.2
132.7
130.0
129.9
129.8
129.4
129.2
128.8
126.7
124.5
122.6
121.5
120.8
118.7
118.5
113.9
69.1
68.7
64.2
63.8
29.1
4
200
150
100
50
0
ppm (f1)

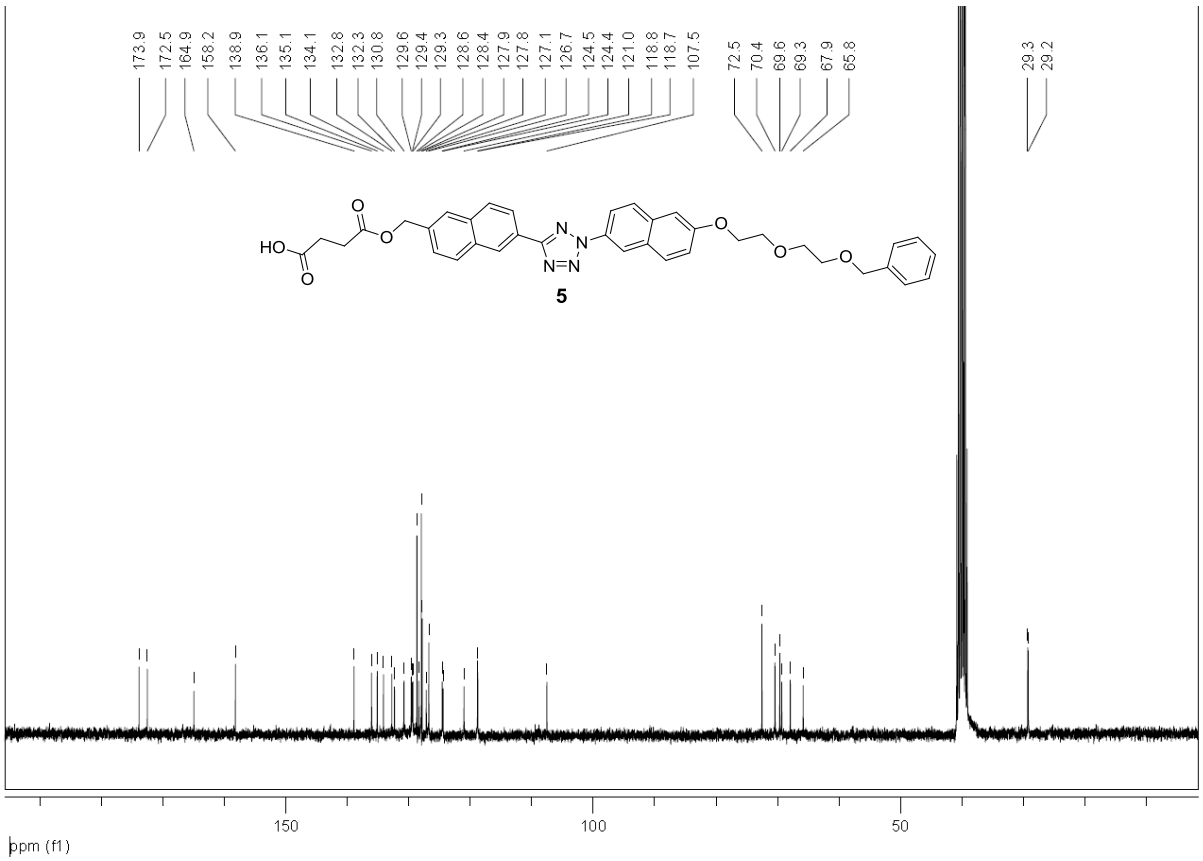

HO
OH
S17
2.00
2.00
1.92
4.18
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

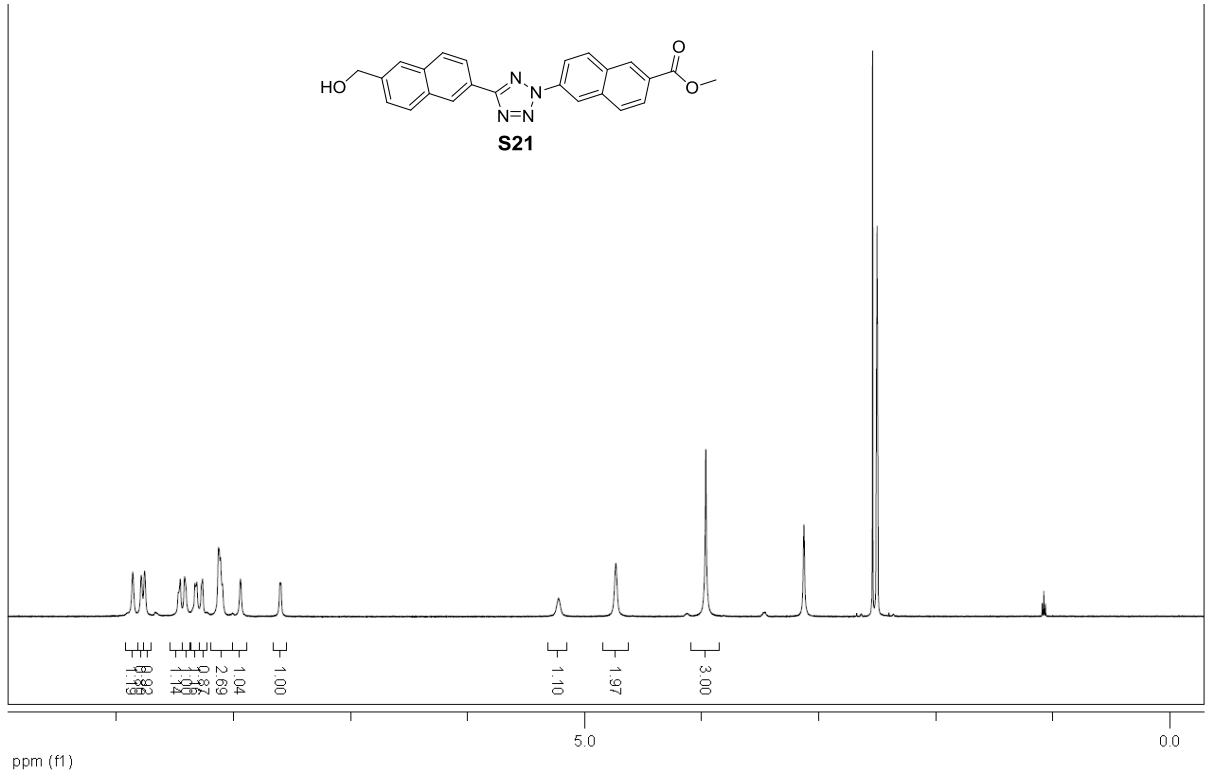

H
O
HO
S18
0.99
1.00
0.93
1.91
0.98
10.0
5.0
0.0
ppm (f1)

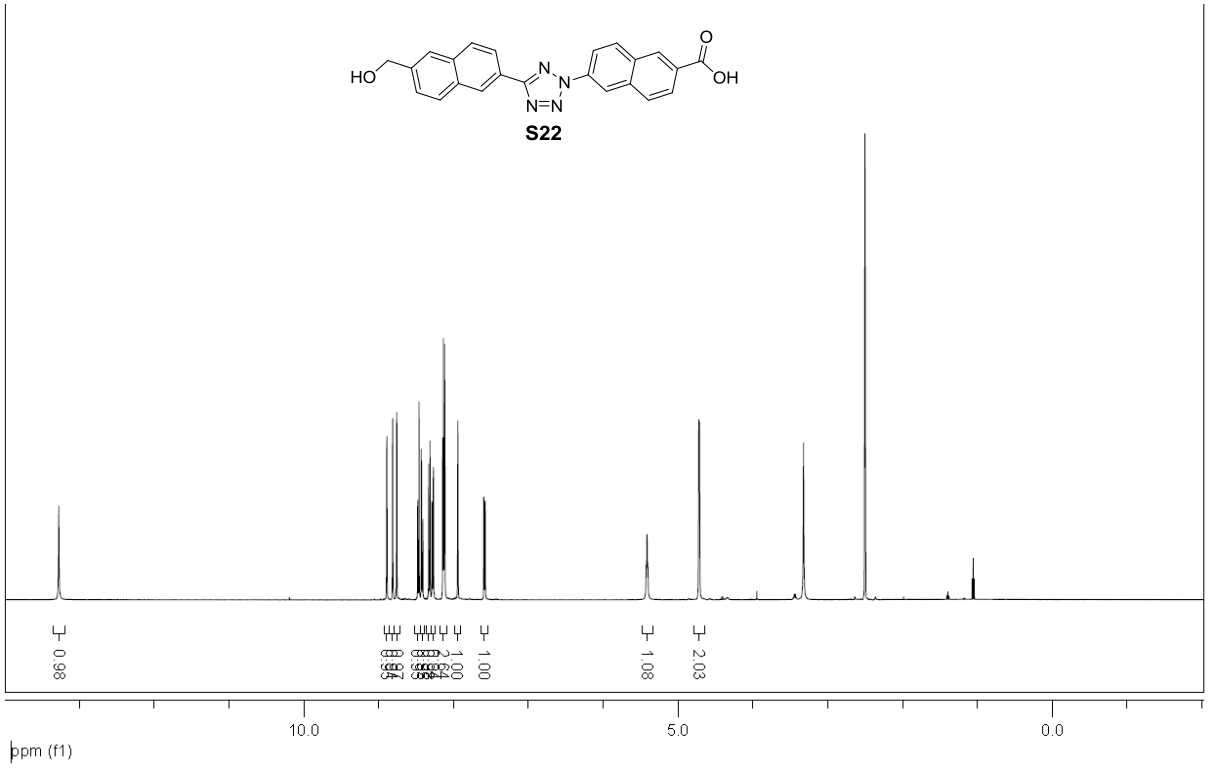

HO
N
N
N=N
O
O
O
S20
1.09
1.11
3.70
1.03
1.02
2.00
1.95
2.05
2.07
2.08
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

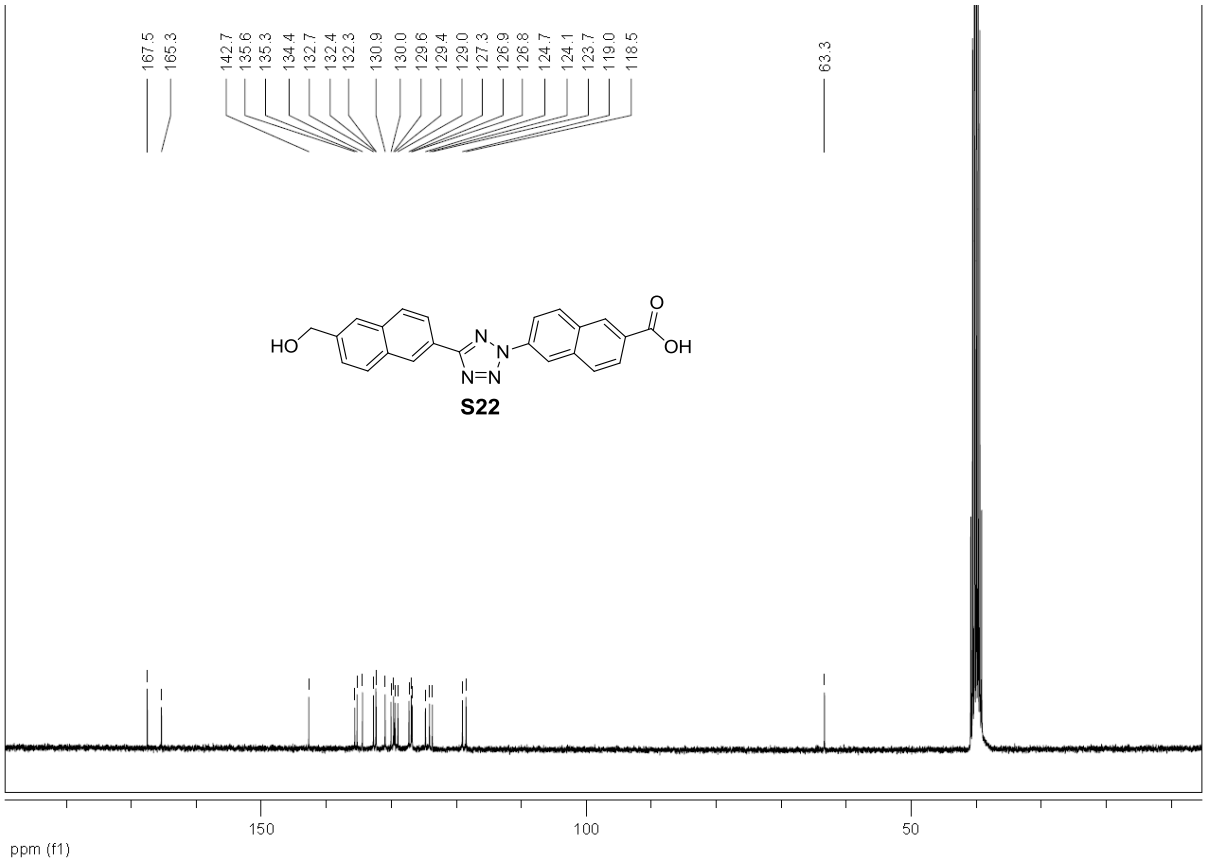

165.1
158.2
142.6
138.9
135.1
134.4
132.4
132.3
130.8
129.4
129.3
128.9
128.6
128.4
127.9
127.8
126.7
124.7
124.1
123.9
121.0
118.8
107.5
72.5
70.4
69.6
69.3
67.9
63.3
HO
N
N
N=N
O
O
O
S20
150
100
50
ppm (f1)


HO
O
O
O
N
N
N=N
O
O
O
O
5
3.64
1.00
1.80
1.96
2.06
1.97
2.02
2.03
2.08
10.0
5.0
0.0
ppm (f1)

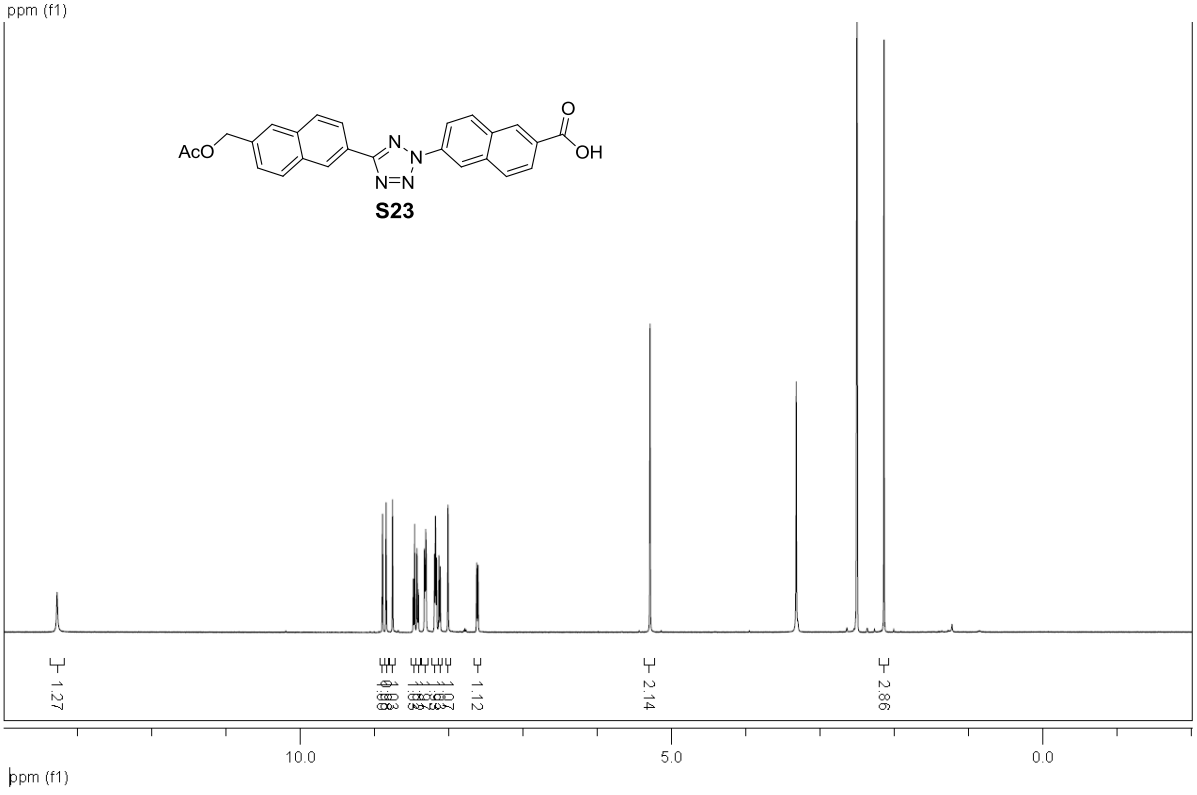

173.9
172.5
164.9
158.2
138.9
136.1
135.1
134.1
132.8
132.3
130.8
129.6
129.4
129.3
128.6
128.4
127.9
127.8
127.1
126.7
124.5
124.4
121.0
118.8
118.7
107.5
72.5
70.4
69.6
69.3
67.9
65.8
29.3
29.2
HO
O
O
O
N
N
N=N
O
O
O
O
5
150
100
50
ppm (f1)


HO
N
N
N=N
O
O
S21
1.00
1.04
2.69
1.10
1.97
3.00
5.0
0.0
ppm (f1)

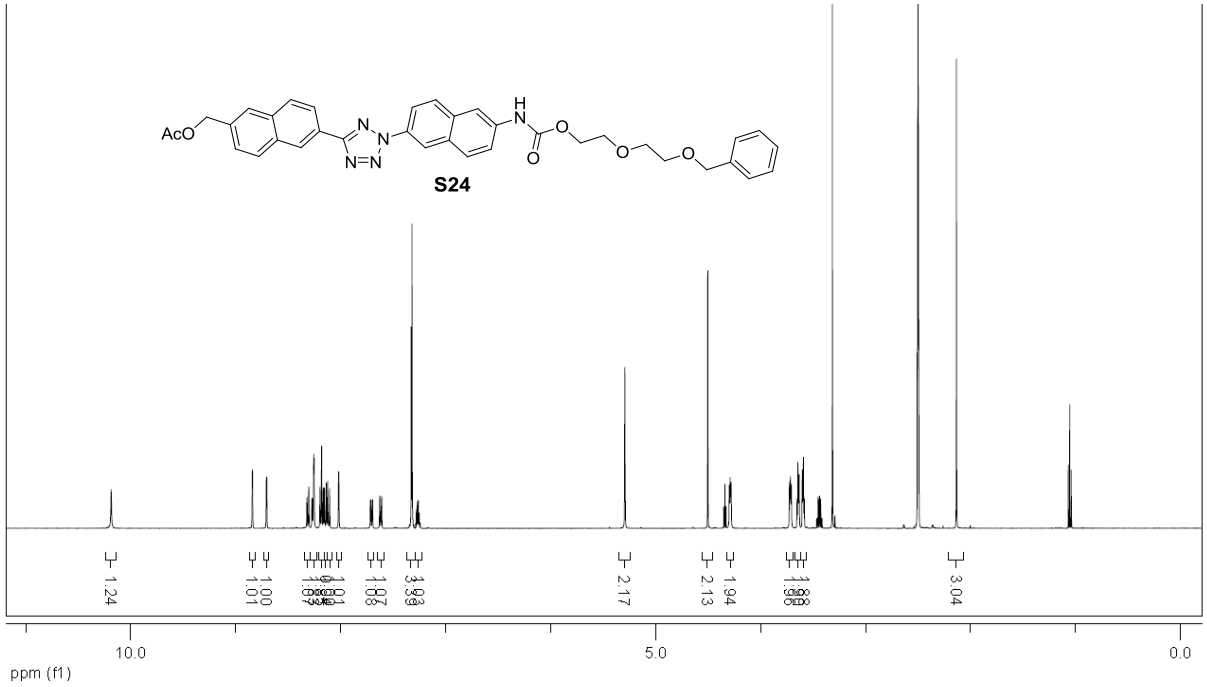

HO
N
N
N=N
O
OH
S22
0.98
1.00
1.00
1.08
2.03
10.0
5.0
0.0
ppm (f1)

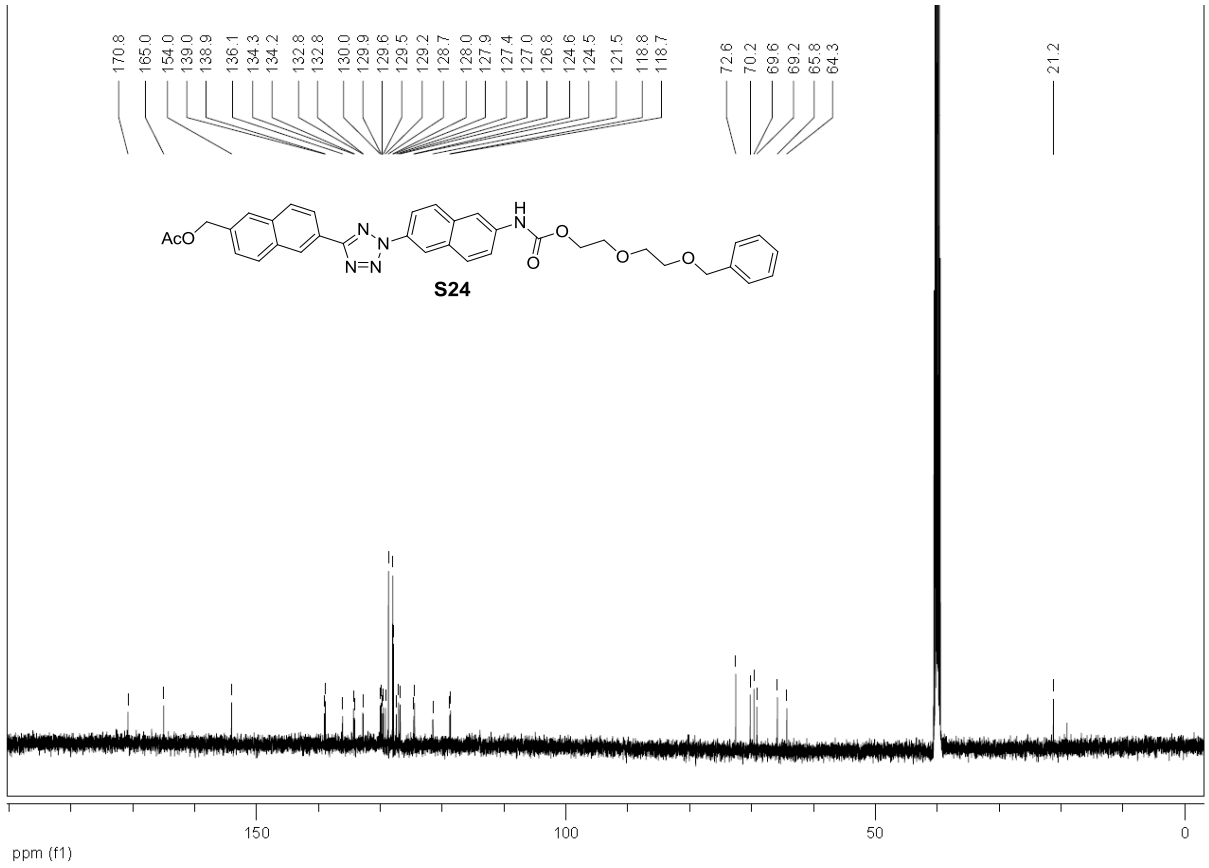

167.5
165.3
142.7
135.6
135.3
134.4
132.7
132.4
132.3
130.9
130.0
129.6
129.4
129.0
127.3
126.9
126.8
124.7
124.1
123.7
119.0
118.5
63.3
HO
N
N
N=N
O
OH
150
100
50
ppm (f1)

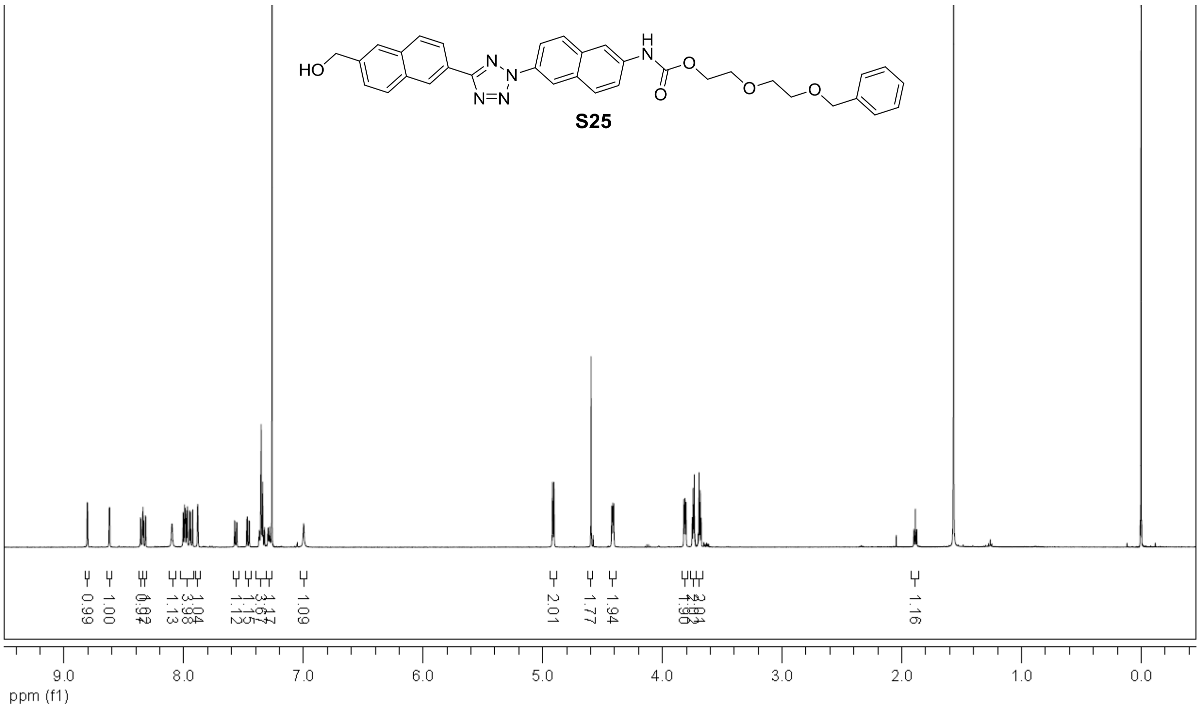
S22

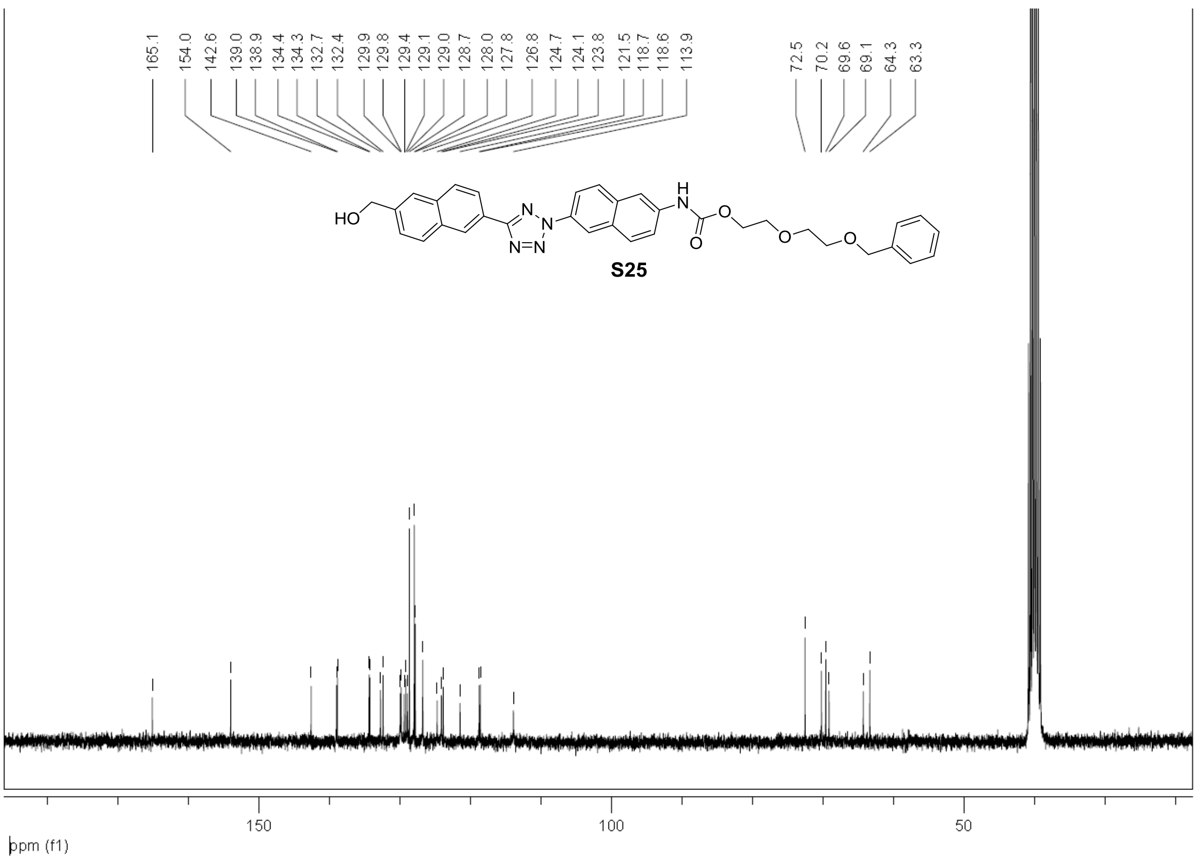

AcO
N
N
N=N
O
OH
1.27
1.12
2.14
2.86
10.0
5.0
0.0
ppm (f1)

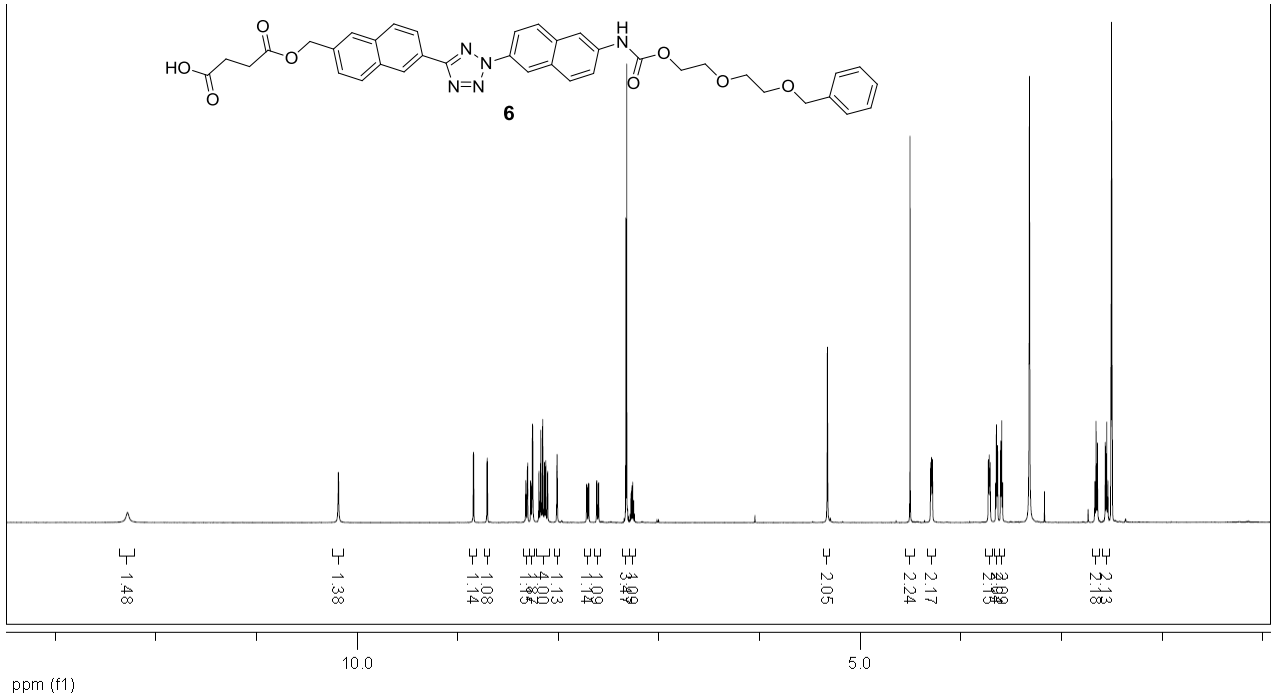
S23

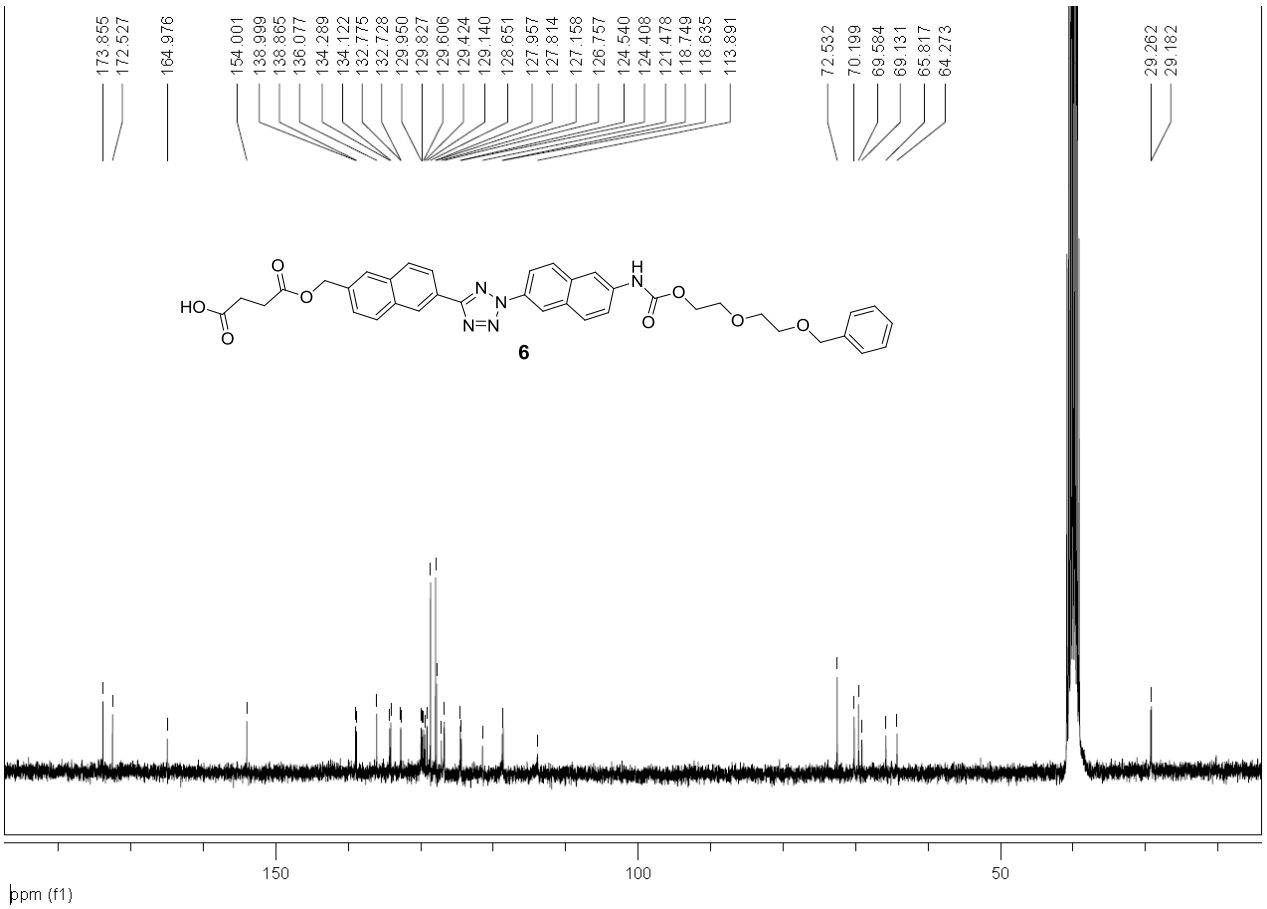

AcO
N
N
N=N
H
N
O
O
O
O
S24
1.24
1.00
1.01
1.07
1.08
3.03
2.17
2.13
1.94
3.04
10.0
5.0
0.0
ppm (f1)

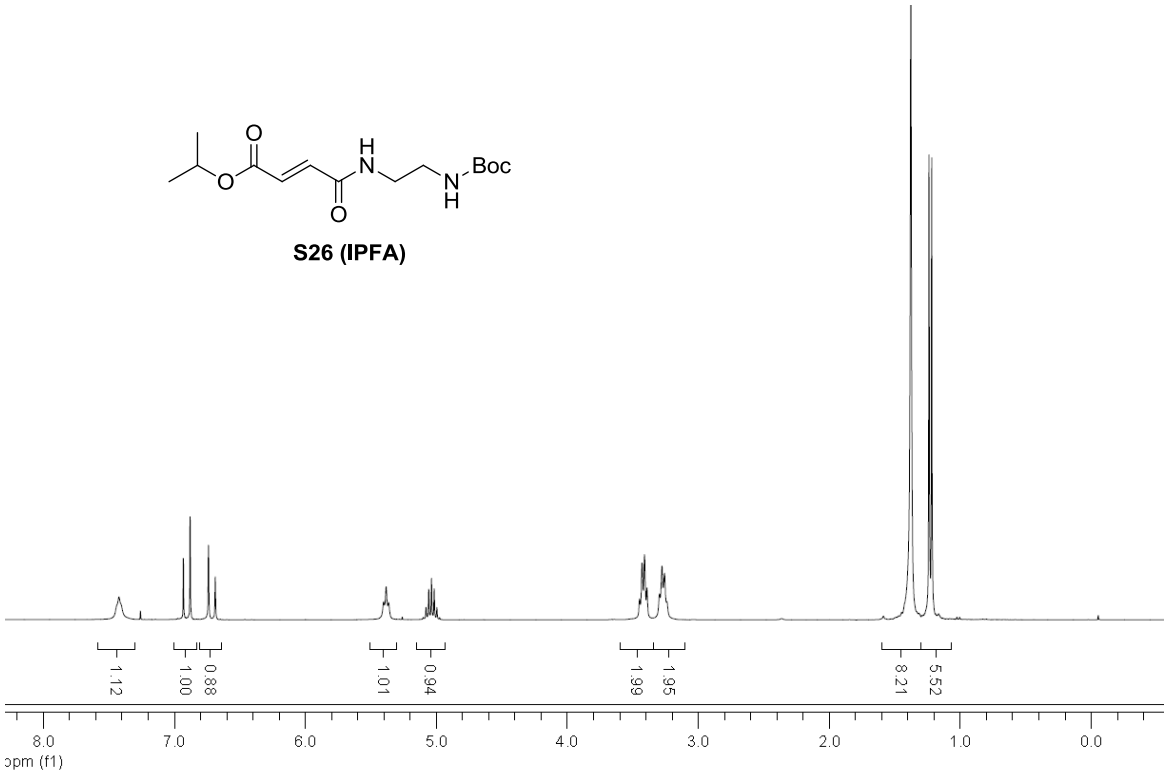

170.8
165.0
154.0
139.0
138.9
136.1
134.3
134.2
132.8
132.8
130.0
129.9
129.6
129.5
129.2
128.7
128.0
127.9
127.4
127.0
126.8
124.6
124.5
121.5
118.8
118.7
72.6
70.2
69.6
69.2
65.8
64.3
21.2
AcO
N
N
N=N
H
N
O
O
O
O
S24
150
100
50
0
ppm (f1)


HO
N
N
N
N
H
O
O
O
O
S25
0.99
1.00
1.13
1.12
1.09
2.01
1.77
1.94
1.16
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

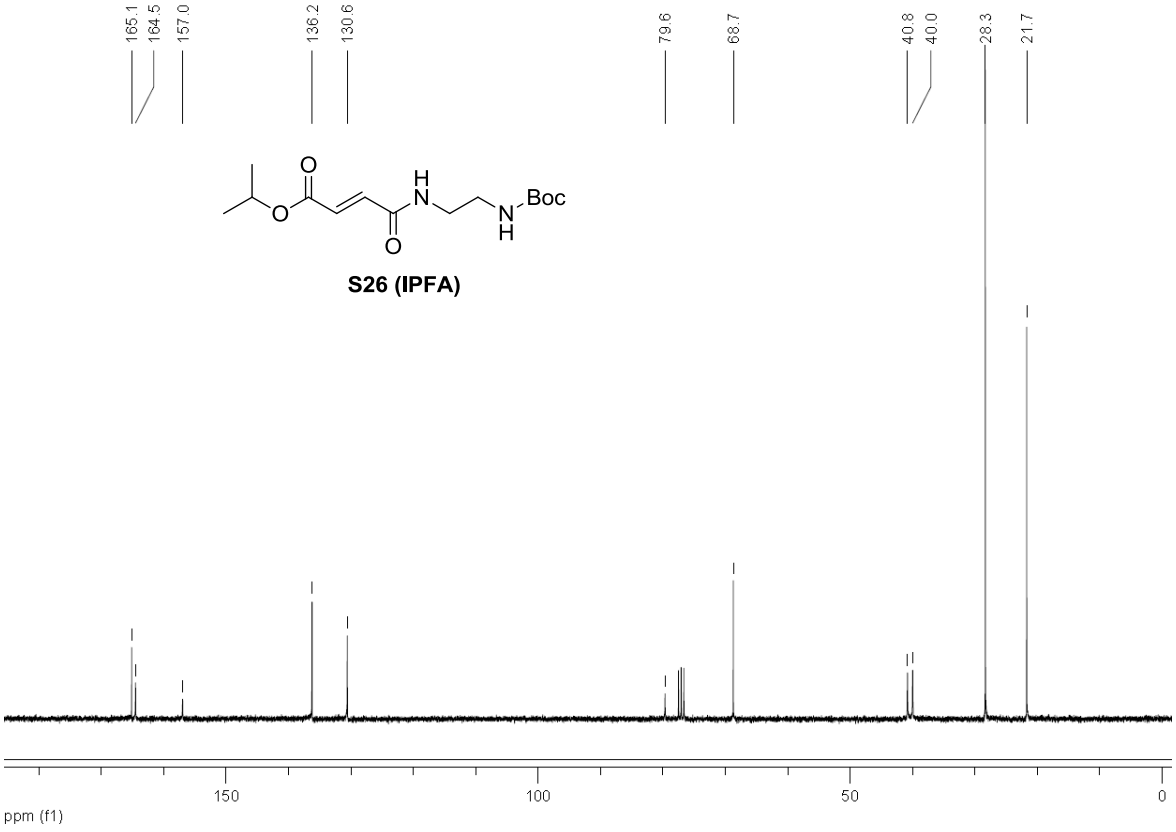

165.1
154.0
142.6
139.0
138.9
134.4
134.3
132.7
132.4
129.9
129.8
129.4
129.1
129.0
128.7
128.0
127.8
126.8
124.7
124.1
123.8
121.5
118.7
118.6
113.9
72.5
70.2
69.6
69.1
64.3
63.3
HO
N
N
N
N
H
O
O
O
O
S25
150
100
50
ppm (f1)


6
1.48
1.38
1.08
1.14
1.13
1.09
1.14
3.09
2.05
2.24
2.17
2.13
2.18
10.0
5.0
ppm (f1)

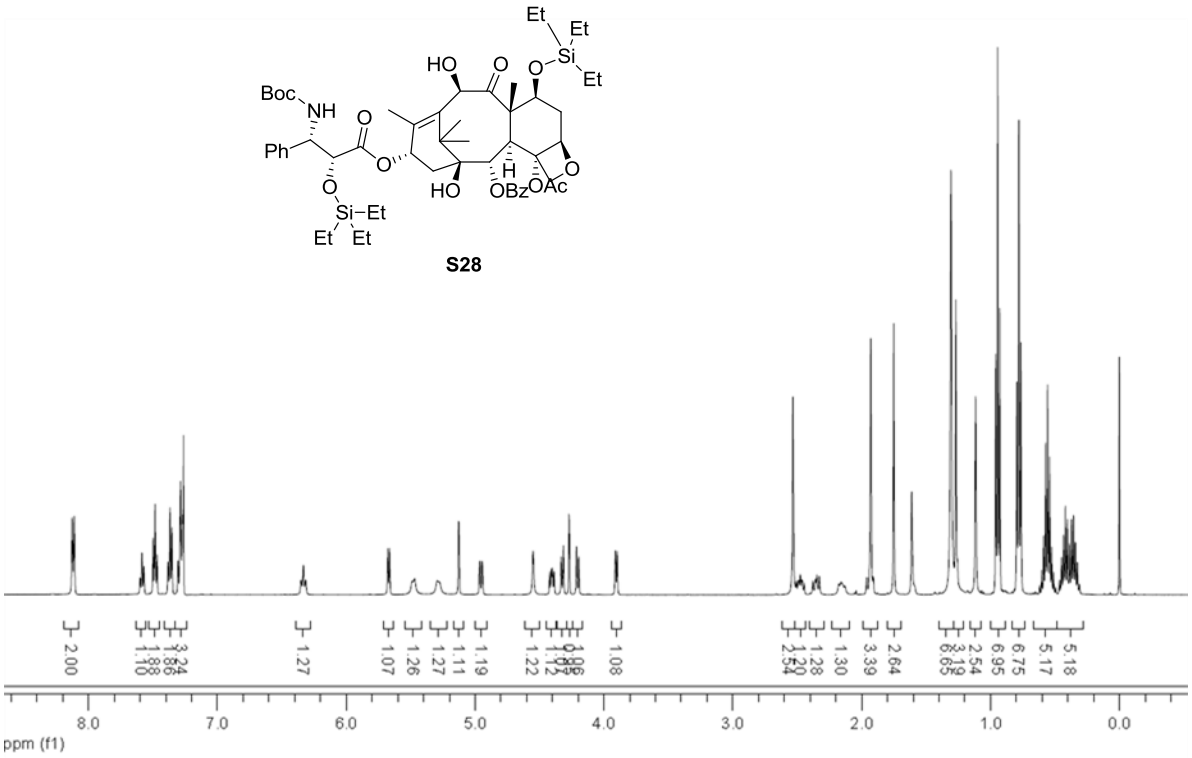

173.855
172.527
164.976
154.001
138.999
138.865
136.077
134.289
134.122
132.775
132.728
129.950
129.827
129.606
129.424
129.140
128.651
127.957
127.814
127.158
126.757
124.540
124.408
121.478
118.749
118.635
113.891
72.532
70.199
69.584
69.131
65.817
64.273
29.262
29.182
6
150
100
50
ppm (f1)



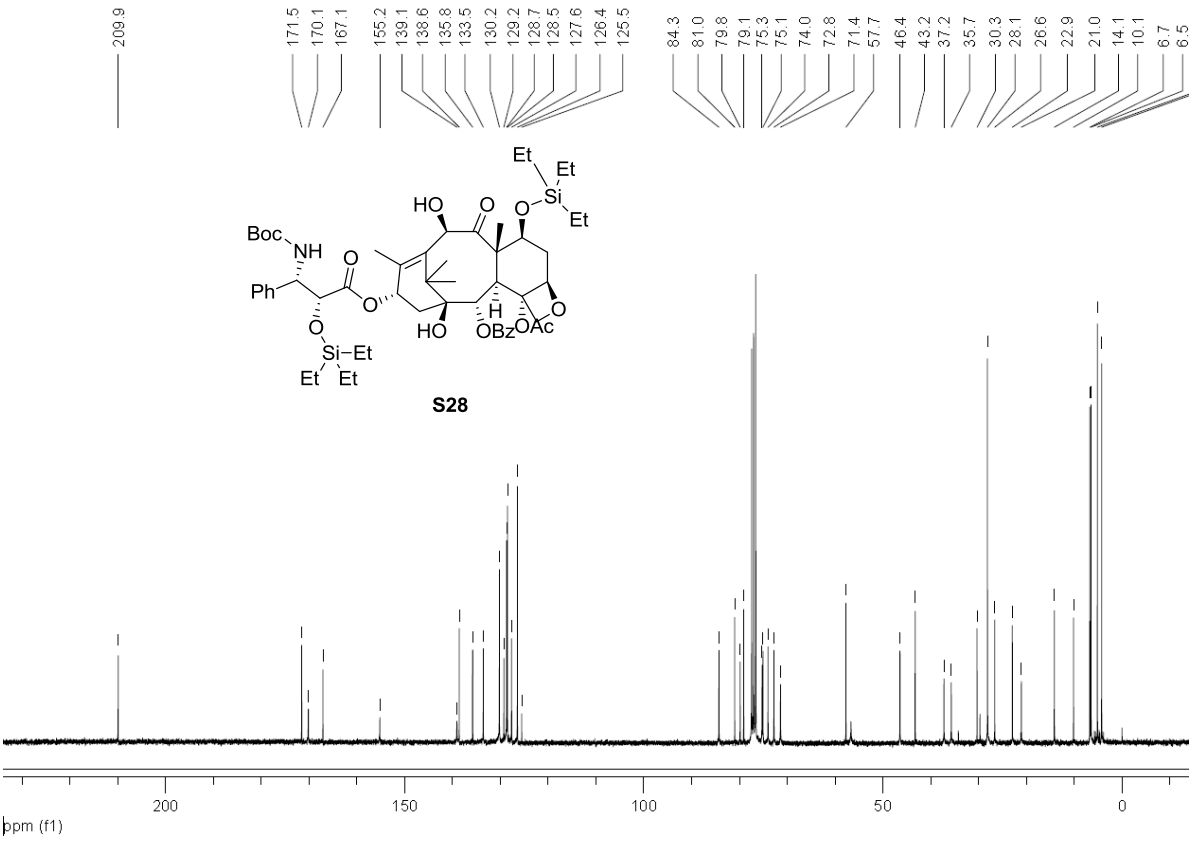
S26 (IPFA)



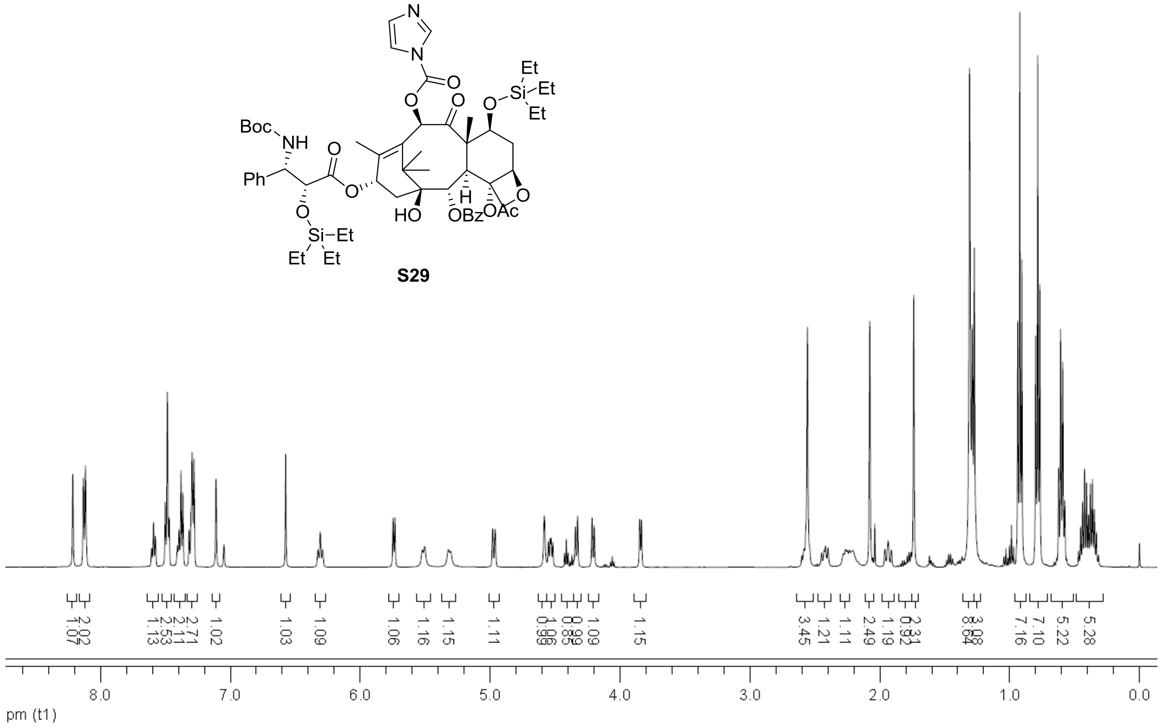
S26 (IPFA)

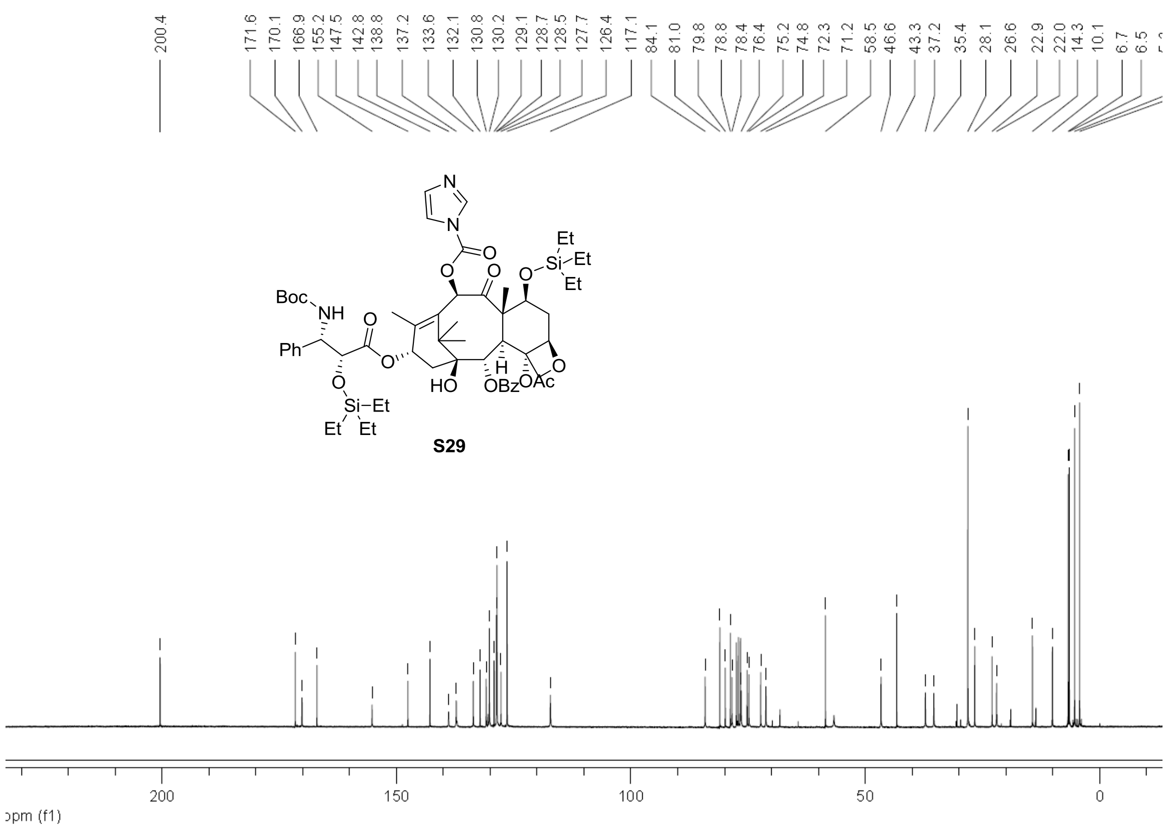

Et
Et
Si
Et
O
HO
O
Boc
NH
O
Ph
O
O
H
HO
OBz
OAc
O
O
Si–Et
Et
Et
2.00
1.27
1.07
1.26
1.27
1.11
1.19
1.22
1.08
1.30
3.39
2.64
2.54
6.95
6.75
5.17
5.18
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

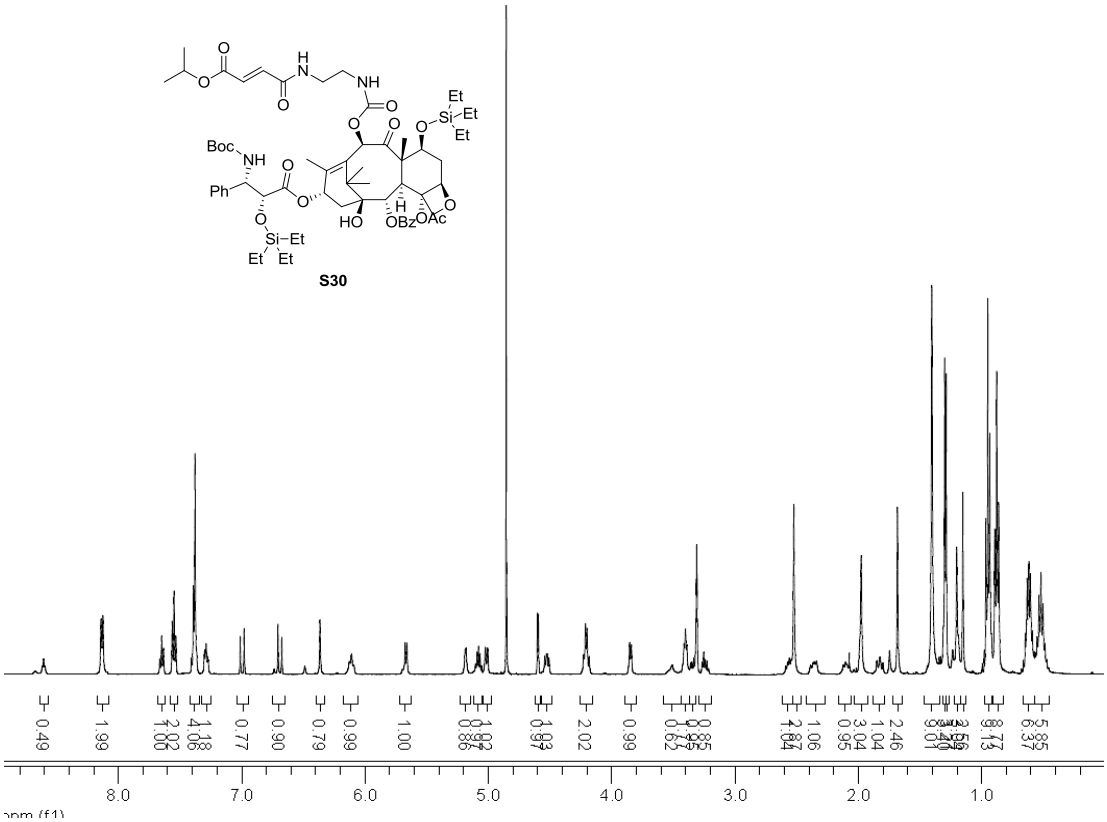
S28

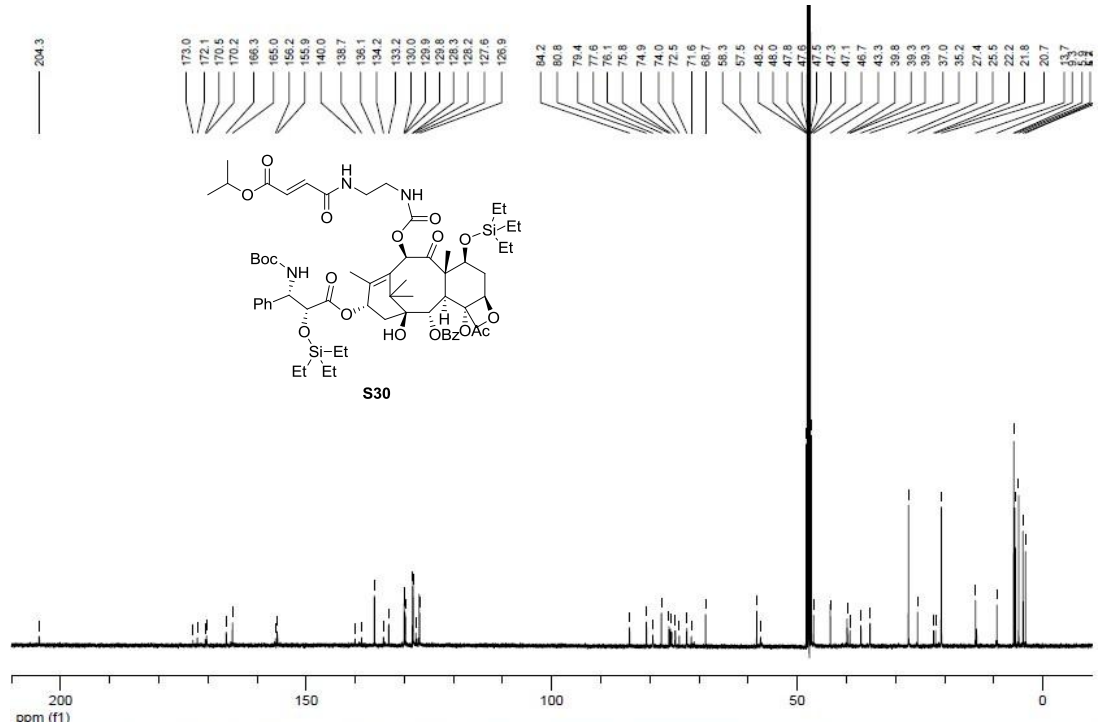

209.9
171.5
170.1
167.1
155.2
139.1
138.6
135.8
133.5
130.2
129.2
128.7
128.5
127.6
126.4
125.5
84.3
81.0
79.8
79.1
75.3
75.1
74.0
72.8
71.4
57.7
46.4
43.2
37.2
35.7
30.3
28.1
26.6
22.9
21.0
14.1
10.1
6.7
6.5
Et
Et
Si
Et
O
HO
O
Boc
NH
O
Ph
O
O
H
HO
OBz
OAc
O
O
Si–Et
Et
Et
200
150
100
50
0
ppm (f1)

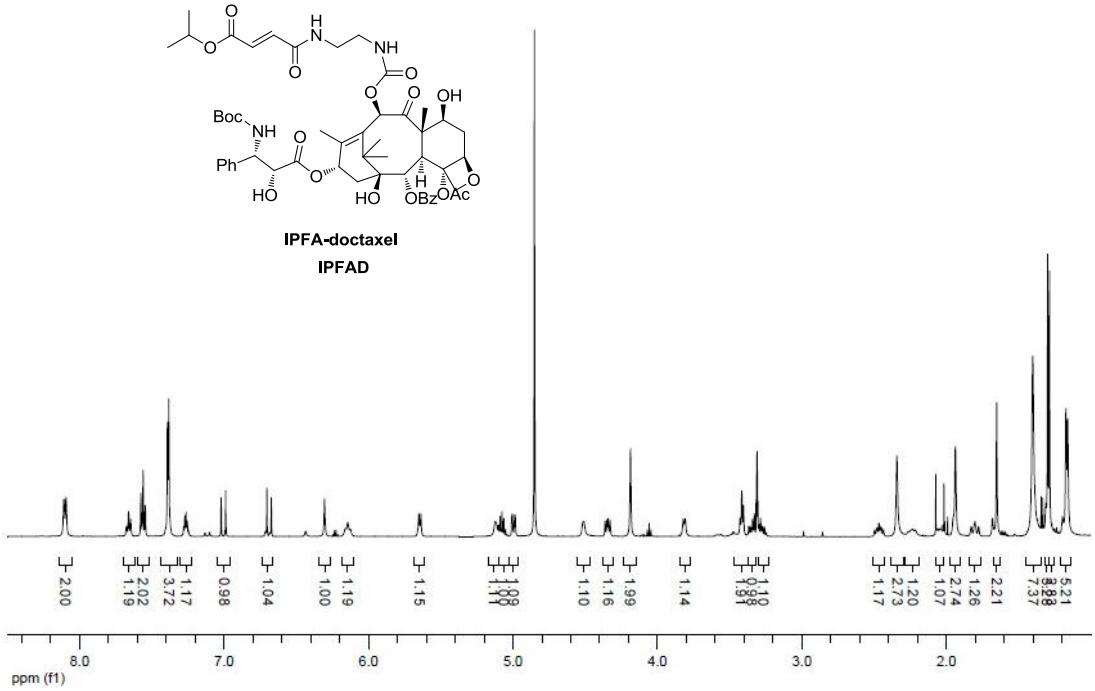
S28

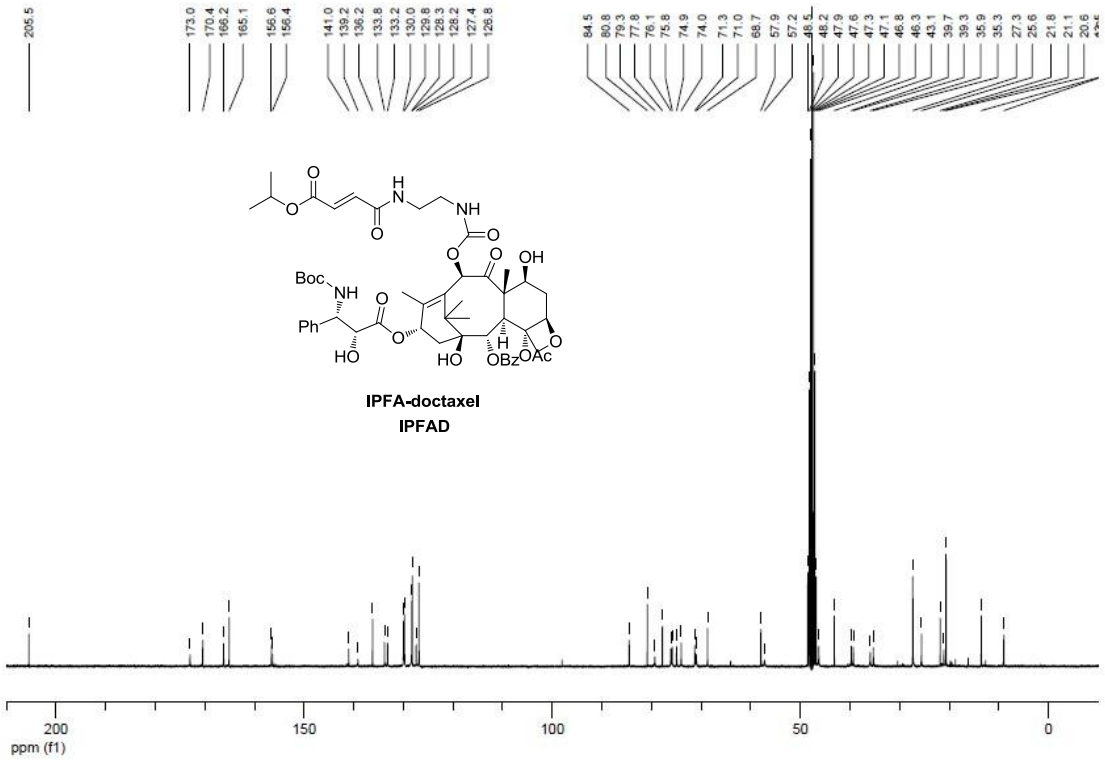

S29
Boc
NH
Ph
O
Si
Et
OBz
OAc
HO
H
N
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

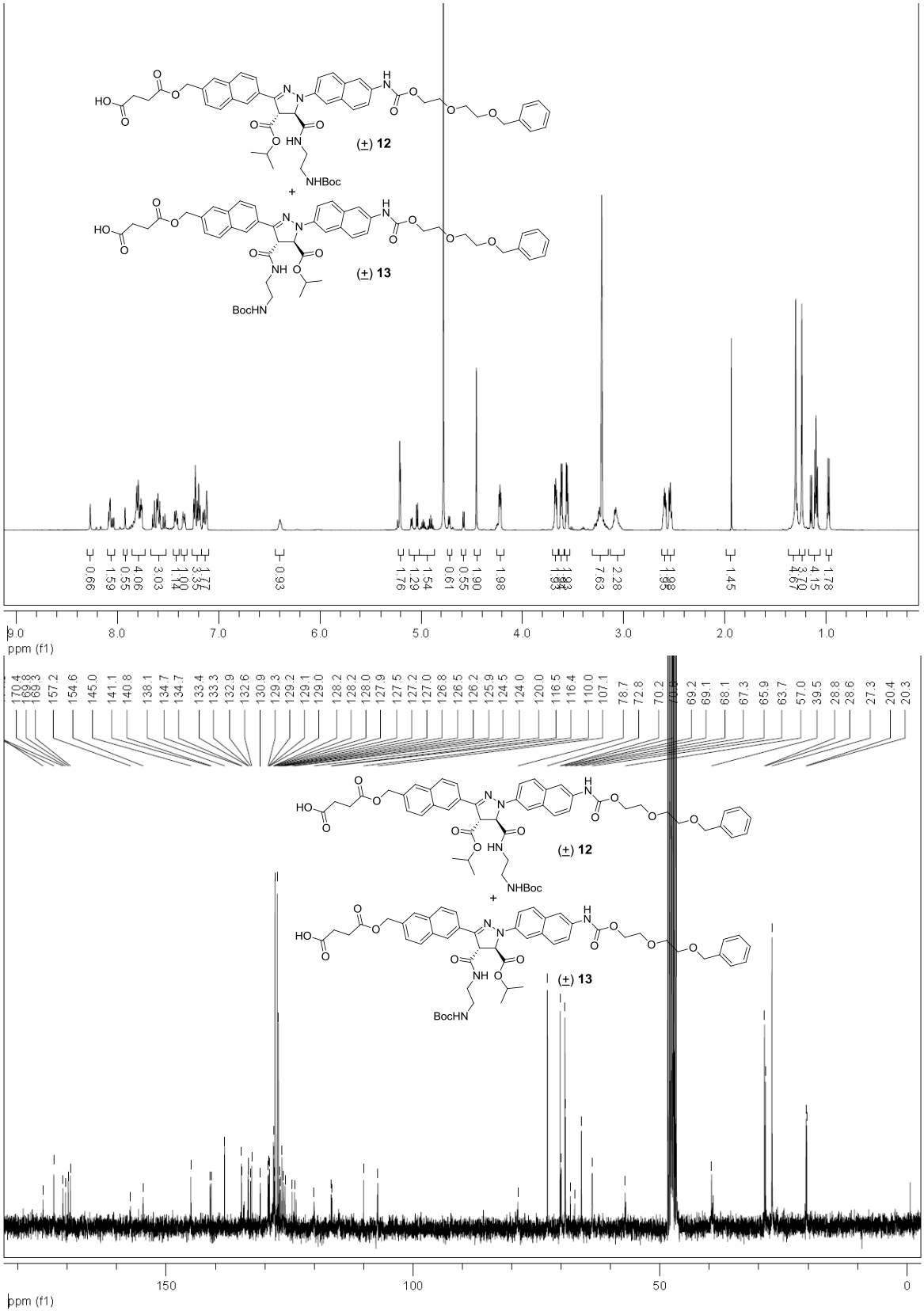

200.4
171.6
170.1
166.9
155.2
147.5
142.8
138.8
137.2
133.6
132.1
130.8
130.2
129.1
128.7
128.5
127.7
126.4
117.1
84.1
81.0
79.8
78.8
78.4
76.4
75.2
74.8
72.3
71.2
58.5
46.6
43.3
37.2
35.4
28.1
26.6
22.9
22.0
14.3
10.1
6.7
6.5
S29
200
150
100
50
0
ppm (f1)

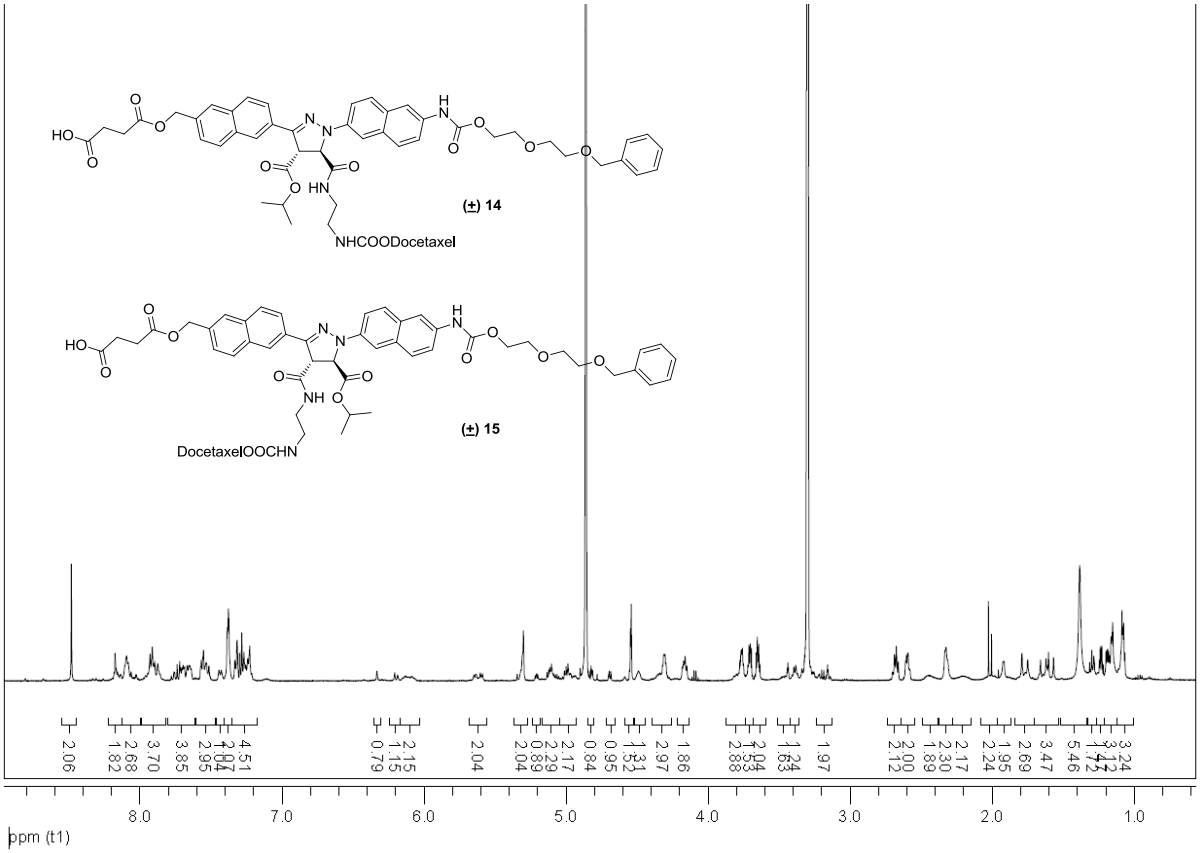

S30
0.49
1.99
2.02
4.00
4.18
4.06
0.77
0.90
0.79
0.99
1.00
0.86
0.97
2.02
0.99
0.85
0.92
1.06
2.84
0.95
3.04
1.04
2.46
8.01
8.13
6.37
5.85
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


S30
204.3
173.0
172.1
170.5
170.2
166.3
155.0
156.2
155.9
140.0
138.7
136.1
134.2
133.2
130.0
129.9
129.8
128.3
128.2
127.6
126.9
84.2
80.8
79.4
77.6
76.1
75.8
74.9
74.0
72.5
71.6
68.7
58.3
57.5
48.2
48.0
47.8
47.6
47.5
47.3
47.1
46.7
43.3
39.8
39.3
39.3
37.0
35.2
27.4
25.5
22.2
21.8
20.7
13.7
200
150
100
50
0
ppm (f1)


IPFA-doctaxel
IPFAD
ppm (f1)


IPFA-doctaxel
IPFAD
ppm (f1)


(±) 12
(±) 13
NHBoc
BocHN
ppm (f1)


(±) 14
NHCOODocetaxel
(±) 15
DocetaxelOOCHN
ppm (t1)