Ortho-Chlorination of phenoxy 1,2-dioxetane yields superior chemiluminescence probes for *in vitro* and *in vivo* imaging

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Supporting Information

Supplementary Figures

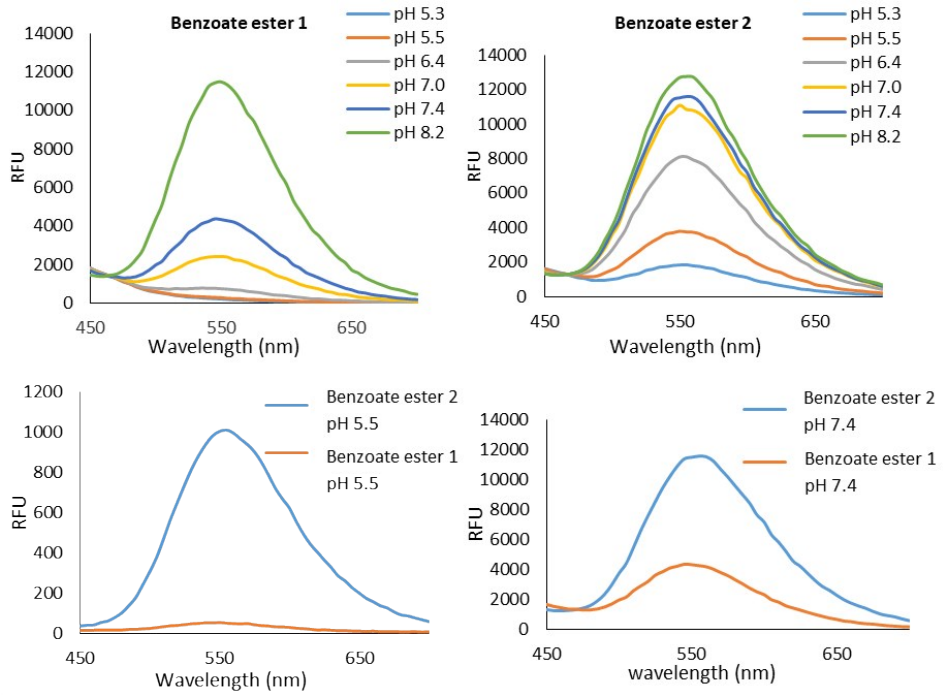


Figure S1. Fluorescence emission spectra of benzoate esters **1** and **2** [50 µM] in PBS, different pH and 5% DMSO, Ex: 400 nm.

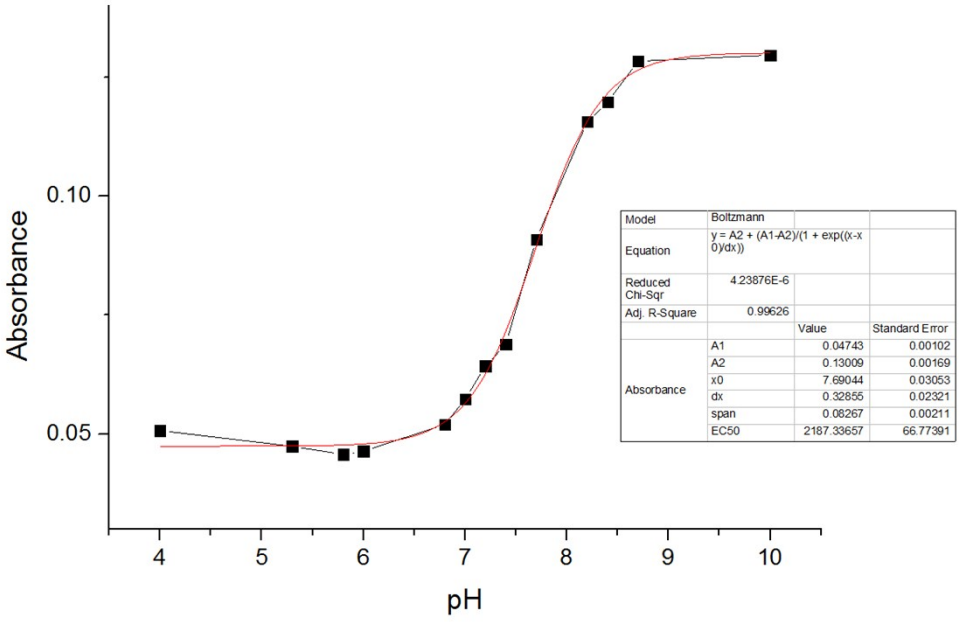


Figure S2. Single pKa calculation of **benzoate 1b** via Boltzmann fit in Origin software. The absorbance measurements were done in triplicates and the pKa calculated was averaged and taken as the pKa value.

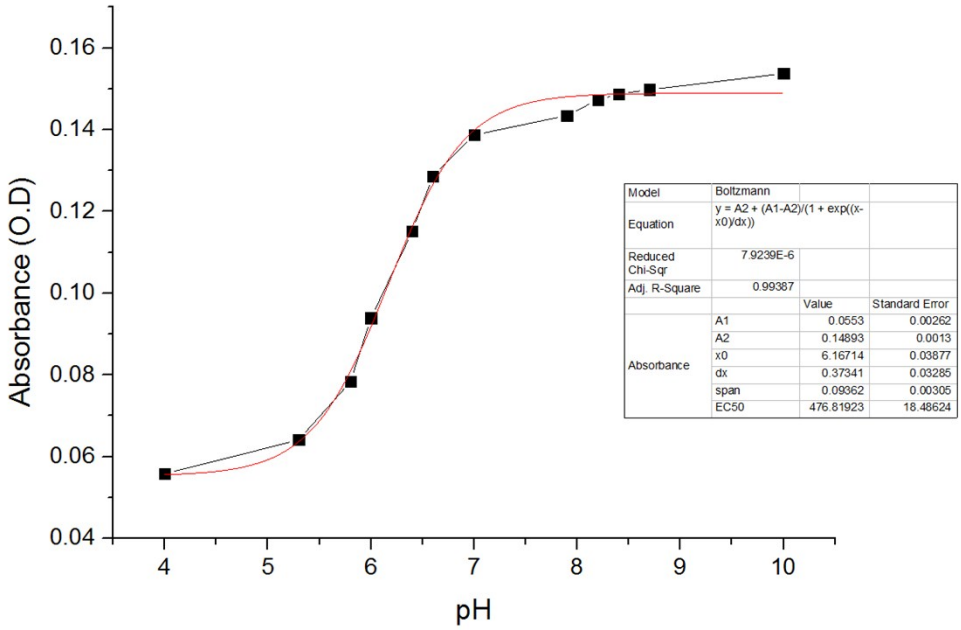


Figure S3. Single pKa calculation of **benzoate 2b** via Boltzmann fit in Origin software. The absorbance measurements were done in triplicates and the pKa calculated was averaged and taken as the pKa value.

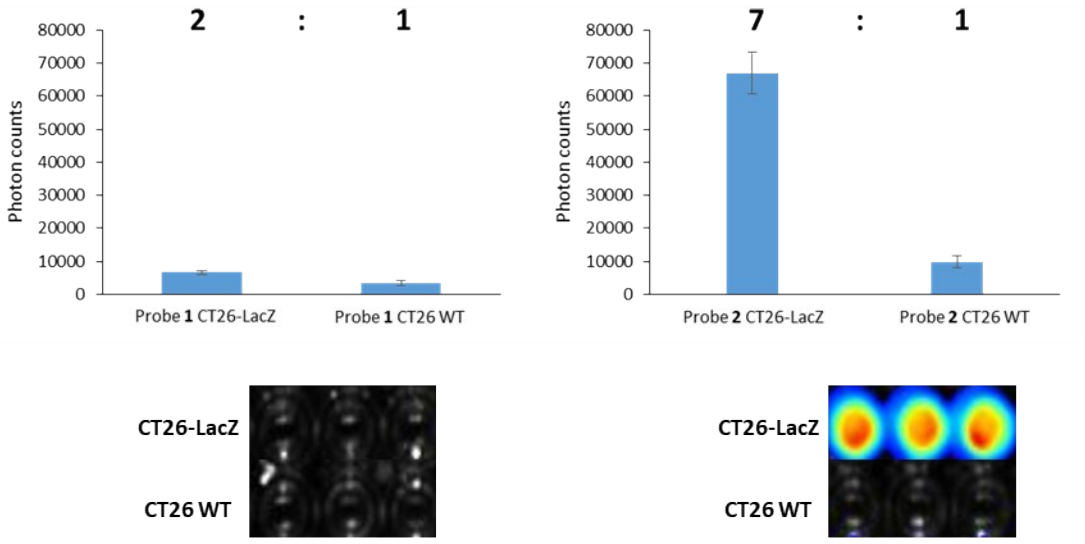


Figure S4. Chemiluminescent imaging and signal quantification of probes **1** and **2** [5 µM] in murine CT26 colon carcinoma cells.

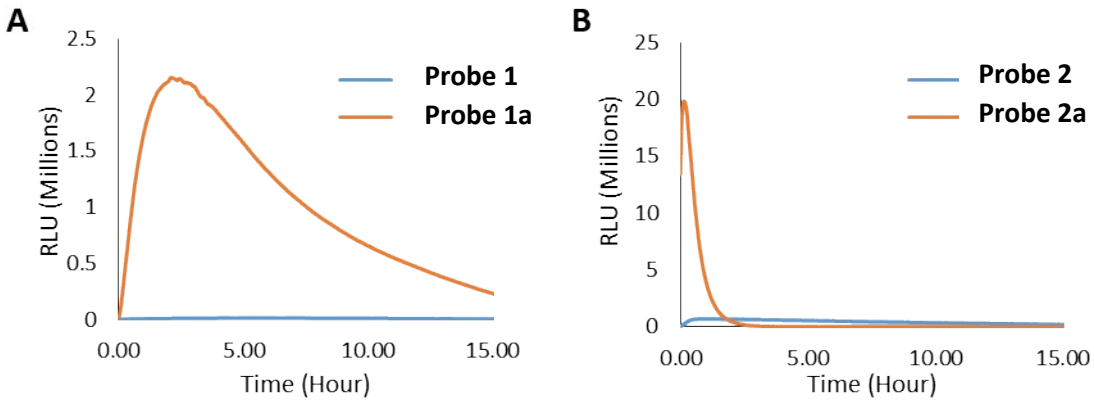


Figure S5. . (A) Chemiluminescent kinetic profile for probes **1** and **1a** [100 µM] upon activation with 1.5 units/mL β-galactosidase in PB pH 5.5, 1% DMSO at 37°C. (B) Chemiluminescent kinetic profile for probes **2** and **2a** [100 µM] upon activation with 1.5 units/mL β-galactosidase in PB pH 5.5, 1% DMSO at 37°C.

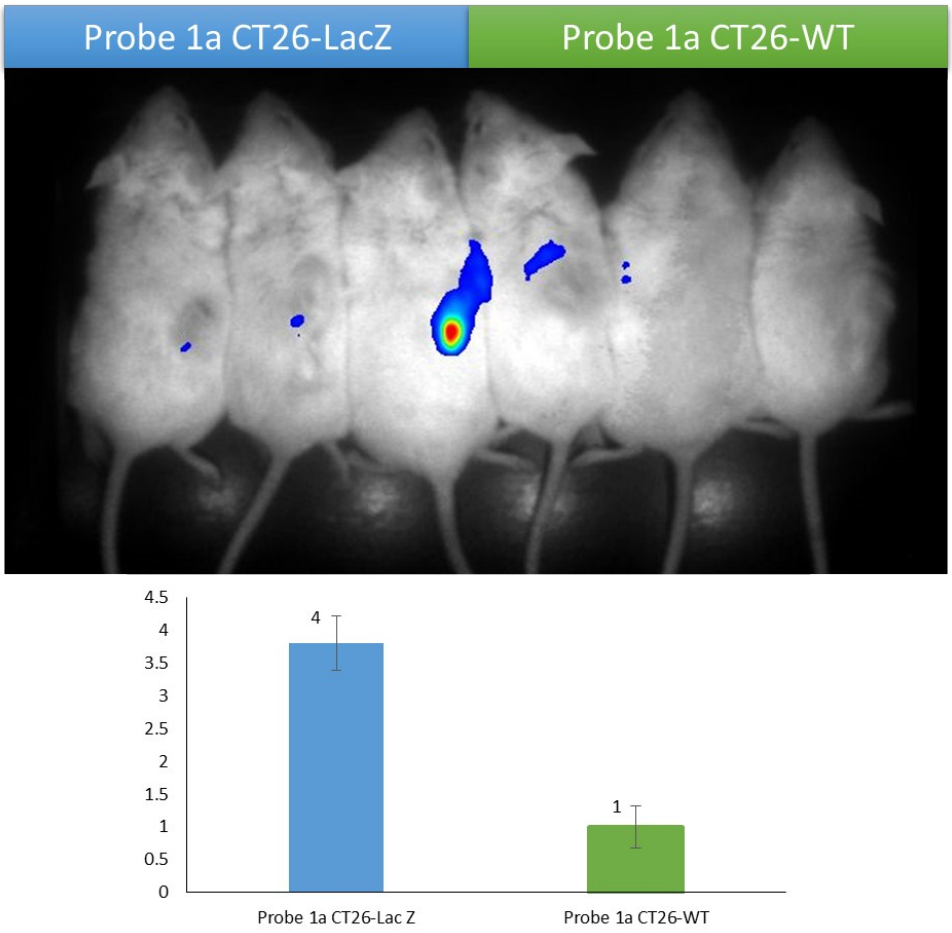


Figure S6. (Top) *in vivo* imaging triplicates of endogenous β-galactosidase in murine CT26 colon carcinoma tumors. Probe **1a**, 100 µL of 100 µM was injected intratumorally (IT). (Bottom) Normalized values of signal intensities measured for probe **1a** with CT26-LacZ and CT26-WT.

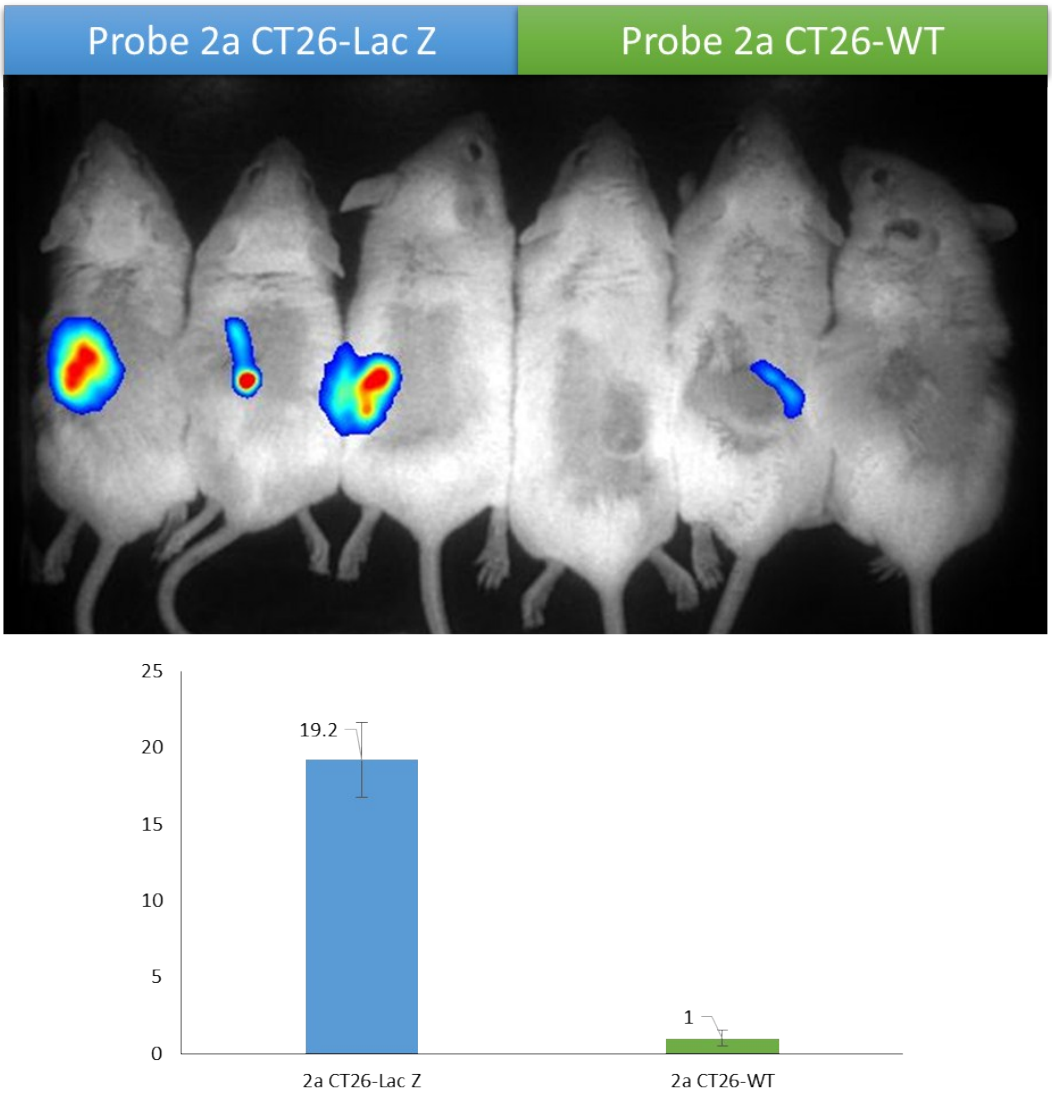


Figure S7. (Top) *in vivo* imaging triplicates of endogenous β-galactosidase in murine CT26 colon carcinoma tumors. Probe **2a**, 100 µL of 100 µM was injected intratumorally (IT). (Bottom) Normalized values of signal intensities measured for probe **2a** with CT26-LacZ and CT26-WT.

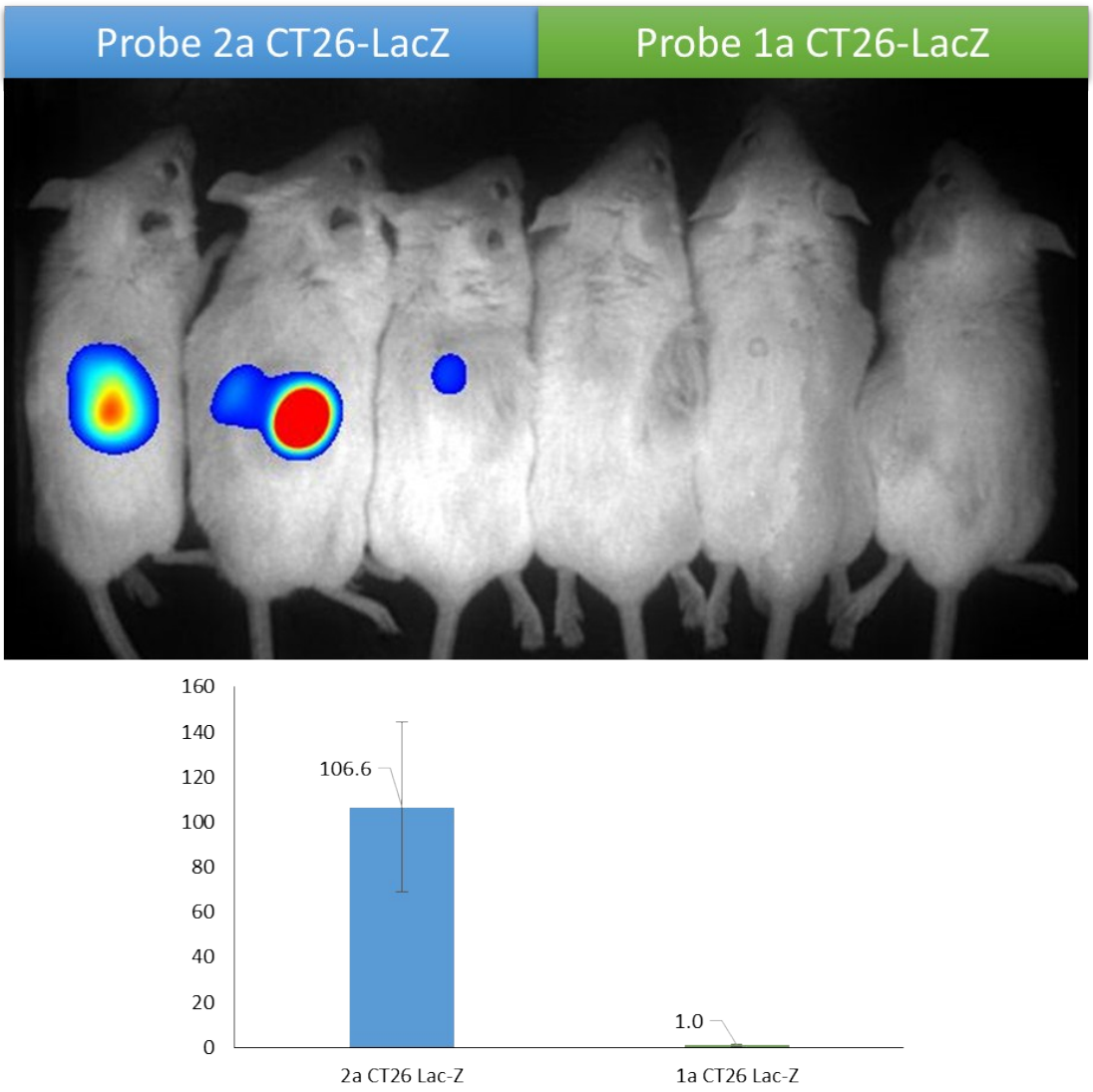
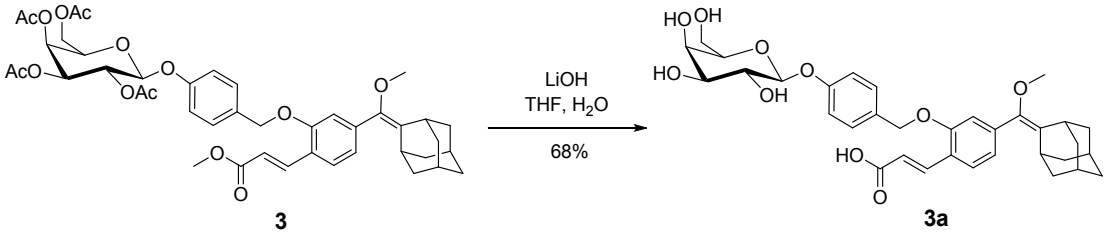


Figure S8. (Top) *in vivo* imaging triplicates of endogenous β-galactosidase in CT26 tumors. Probes **1a** and **2a**, 100 µL of 100 µM were injected intratumorally (IT). (Bottom) Normalized values of signal intensities measured for probe **2a** with CT26-LacZ compared to probe **1a** with CT26-LacZ.

General methods

All reactions requiring anhydrous conditions were performed under an Argon atmosphere. All reactions were carried out at room temperature unless stated otherwise. Chemicals and solvents were either A.R. grade or purified by standard techniques. Thin layer chromatography (TLC): silica gel plates Merck 60 F_{254}: compounds were visualized by irradiation with UV light. Column chromatography (FC): silica gel Merck 60 (particle size 0.040-0.063 mm), eluent given in parentheses. Reverse-phase high pressure liquid chromatography (RP-HPLC): C18 5u, 250x4.6 mm, eluent given in parentheses. Preparative RP-HPLC: C18 5u, 250x21mm, eluent given in parentheses. ^{1}H-NMR spectra were measured using Bruker Avance operated at 400MHz. ^{13}C-NMR spectra were measured using Bruker Avance operated at 100 MHz. Chemical shifts were reported in ppm on the δ scale relative to a residual solvent (CDCl3: δ = 7.26 for 1H-NMR and 77.16 for 13C-NMR, DMSO-d6: δ = 2.50 for 1H-NMR and 39.52 for 13C-NMR). Mass spectra were measured on Waters Xevo TQD. Chemiluminescence was recorded on Molecular Devices Spectramax i3x. All general reagents, including salts and solvents, were purchased from Sigma-Aldrich. Light irradiation for photochemical reactions: LED PAR38 lamp (19W, 3000K).

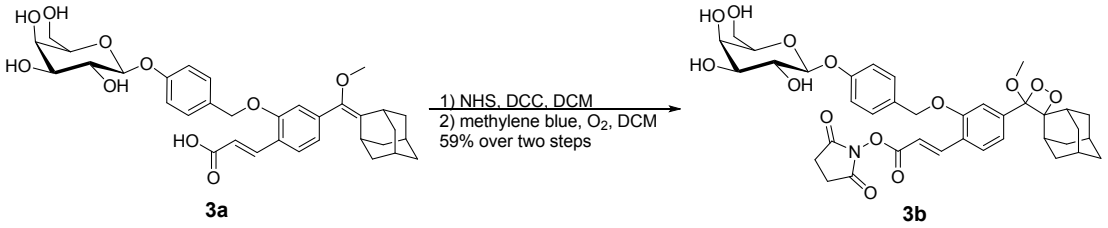
Abbreviations. **ACN**- Acetonitrile, **DCM**- Dichlorometane, **DIPEA**- diisopropylethylamine, **DMF**- N,N'-Dimethylformamide, **Et_2O**- diethylether, **Et_3N**- Triethylamine, **EtOAc**- Ethylacetate, **HBTU**- 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, **K_2CO_3**- potassium carbonate, **MeOH**- Methyl alcohol, **NH_4Cl-** ammonium chloride, **$Na_2S_2O_3$-** Sodium Thiosulfate, **Na_2SO_4**- Sodium Sulfate, **TMS-Cl** - Trimethylsilyl chloride, **TFA**- Trifluoroacetic acid, **TIPS**- Triisopropylsilane



3 3a

Compound 3a

Enol ether **3**[1] (120 mg, 0.147 mmol, 1 eq), LiOH (21.3 mg, 0.887 mmol, 6 eq) were dissolved in 2 ml of of 4:1 solution THF:H_2O. Reaction mixture was stirred at room temperature and monitored via RP-HPLC. Upon completion, reaction mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl solution followed by brine. Organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford 64 mg (68% yield) of off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ 7.95 – 7.84 (m, J = 16.1 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 6.89 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 16.1 Hz, 1H), 4.91 (s, 2H), 4.84 (d, J = 7.6 Hz, 1H), 3.99 (d, J = 6.4 Hz, 2H), 3.90 – 3.82 (m, 1H), 3.81 – 3.68 (m, J = 9.7, 5.0 Hz, 3H), 3.69 – 3.58 (m, J = 16.1, 7.9 Hz, 2H), 3.21 (s, 3H), 3.16 (s, 1H), 2.61 (s, 1H), 1.93 – 1.68 (m, 12H). ^{13}C NMR (101 MHz, CDCl3) δ 229.19, 190.05, 174.44, 170.37, 157.42, 157.17, 142.84, 140.80, 139.15, 133.77, 130.46, 129.34, 128.53, 122.66, 122.30, 118.13, 116.86, 113.12, 101.15, 74.85, 73.28, 70.98, 70.25, 68.81, 61.19, 58.00, 39.20, 39.04, 37.07, 32.42, 30.44, 29.71, 28.22, 20.75. MS (ES-): *m/z* calc. for $C_{34}H_{40}O_{10}$: 608.26 ; found: 607.4 $[M-H]^-$.

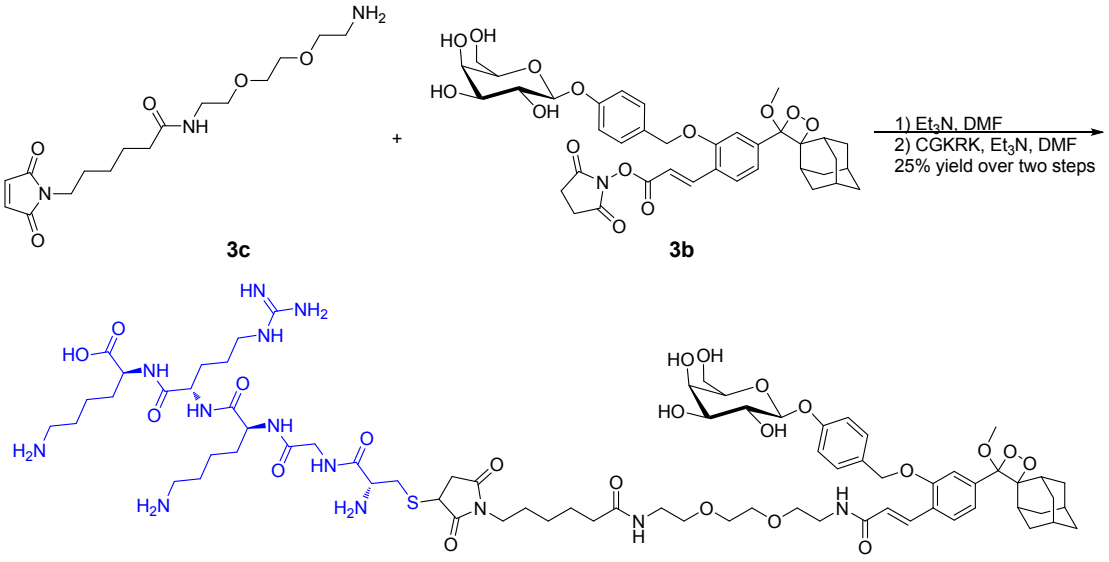


3a 3b

Compound 3b

Compound **3a** (150 mg, 0.246 mmol, 1 eq) was dissolved in 1.5 ml of DCM and cooled to 0°C. N-hydroxysuccinimide (57 mg, 0.49 mmol, 2 eq) was added followed by N,N'-Dicyclohexylcarbodiimide (76 mg, 0.37 mmol, 1.5eq). The reaction was allowed to warm up to room temperature and monitored by RP-HPLC. Upon completion, 5 ml of DCM were added, followed by catalytic amount of methylene

blue. Oxygen was bubbled through the solution, while irradiating with yellow light. The reaction was monitored by RP-HPLC (50-100% ACN in water, 20 min). Upon completion, the reaction mixture was concentrated by evaporation under reduced pressure and the crude product was purified by preparative RP-HPLC (50-100% ACN in water, 20 min) to afford compound **3b** (61 mg, 34% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 8.10 (d, *J* = 16.2, 1H), 7.49 (d, *J* = 18.9 Hz, 1H), 7.45 – 7.14 (m, 3H), 7.15 – 6.81 (m, 3H), 6.67 (d, *J* = 16.2 Hz, 1H), 5.07 (m, 2H), 4.79 (d, *J* = 7.6 Hz, 1H), 3.99 – 3.75 (m, 6H), 3.75 – 3.65 (m, 2H), 3.58 (d, *J* = 6.4 Hz, 2H), 3.11 (s, 3H), 2.91 (s, 1H), 2.75 (s, 3H), 1.98 (s, 1H), 1.92 (s, 1H), 1.66 (m, 9H), 1.38 (d, *J* = 11.6 Hz, 1H), 1.28 – 1.18 (m, 1H), 1.14 (d, *J* = 12.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 170.17, 162.69, 157.78, 157.33, 144.77, 139.64, 129.94, 129.79, 129.20, 123.59, 116.86, 113.04, 111.72, 101.19, 95.81, 74.83, 73.40, 70.91, 70.41, 68.66, 61.13, 50.01, 36.22, 34.72, 33.56, 33.18, 33.09, 32.22, 31.67, 31.48, 25.94, 25.76, 25.62, 25.49, 24.85. MS (ES+): *m/z* calc. for $C_{38}H_{43}NO_{14}$: 737.75; found: 760.6 $[M+Na]^+$.

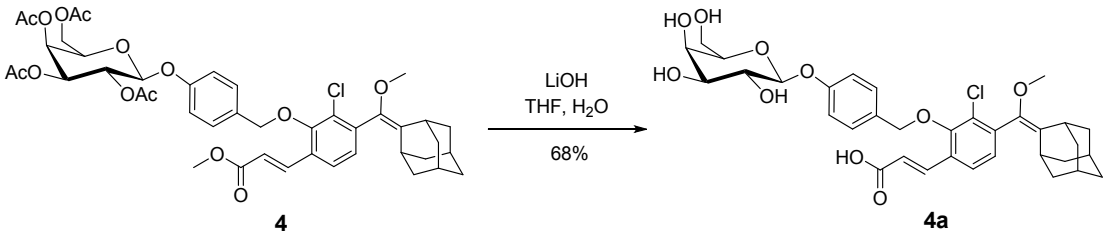


3c + **3b** → **probe 1a**

Probe 1a

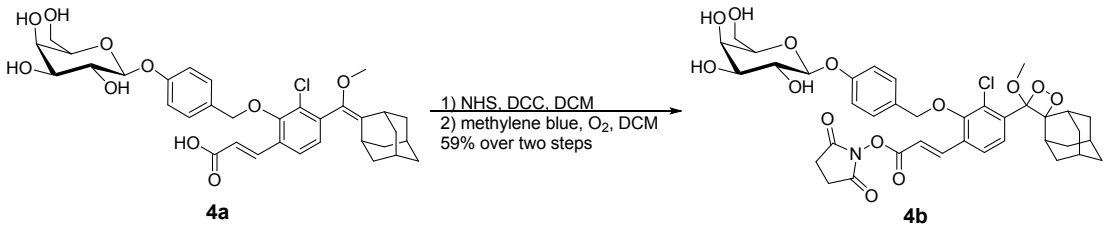
Compound **3c**[2] (54 mg, 0.073 mmol, 1 eq) and compound **3b** (27 mg, 0.08 mmol, 1 eq) were dissolved in DMF (0.5 ml) and a few drops of Et_3N were added. The Reaction was monitored by RP-HPLC (30-100% ACN in water, 20 min). Upon completion, **CGKRK**[3] (92 mg, 0.088 mmol, 1.2 eq) was added. The Reaction was monitored by RP-HPLC (30-100% ACN in water, 20 min). Upon completion, the

reaction mixture was concentrated by evaporation under reduced pressure. The crude product was purified by preparative RP-HPLC (30-100% ACN in water, 20 min) to afford compound **probe 1a** (36 mg, 25% yield) as a white solid. HRMS (ES-): *m/z* calc. for $C_{73}H_{111}N_{13}O_{22}S$: 1553.73; found: MH^+ 1554.7772.



Compound 4a

Enol ether **4**[1] (120 mg, 0.147 mmol, 1 eq), LiOH (21.3 mg, 0.887 mmol, 6 eq) were dissolved in 2 ml of of 4:1 solution THF:H_2O. Reaction mixture was stirred at room temperature and monitored via RP-HPLC. Upon completion, reaction mixture was diluted with EtOAc and washed with saturated aqueous solution NH_4Cl followed by brine. Organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford 64 mg (68% yield) of yellow solid. ^{1}H NMR (400 MHz, CDCl3) δ 7.95 – 7.84 (m, J = 16.1 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 6.89 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 16.1 Hz, 1H), 4.91 (s, 2H), 4.84 (d, J = 7.6 Hz, 1H), 3.99 (d, J = 6.4 Hz, 2H), 3.90 – 3.82 (m, 1H), 3.81 – 3.68 (m, J = 9.7, 5.0 Hz, 3H), 3.69 – 3.58 (m, J = 16.1, 7.9 Hz, 2H), 3.21 (s, 3H), 3.16 (s, 1H), 2.61 (s, 1H), 1.93 – 1.68 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.83, 157.47, 153.79, 140.13, 139.46, 138.22, 132.53, 130.98, 130.08, 129.82, 129.62, 127.79, 124.88, 119.21, 116.93, 100.95, 74.74, 73.92, 73.27, 72.36, 71.18, 70.01, 69.18, 64.50, 61.42, 39.14, 38.70, 37.70, 37.07, 35.61, 33.91, 30.26, 29.76, 29.03, 28.26. MS (ES-): *m/z* calc. for $C_{34}H_{39}ClO_{10}$: 642.22 ; found: 641.5 $[M-H]^-$.

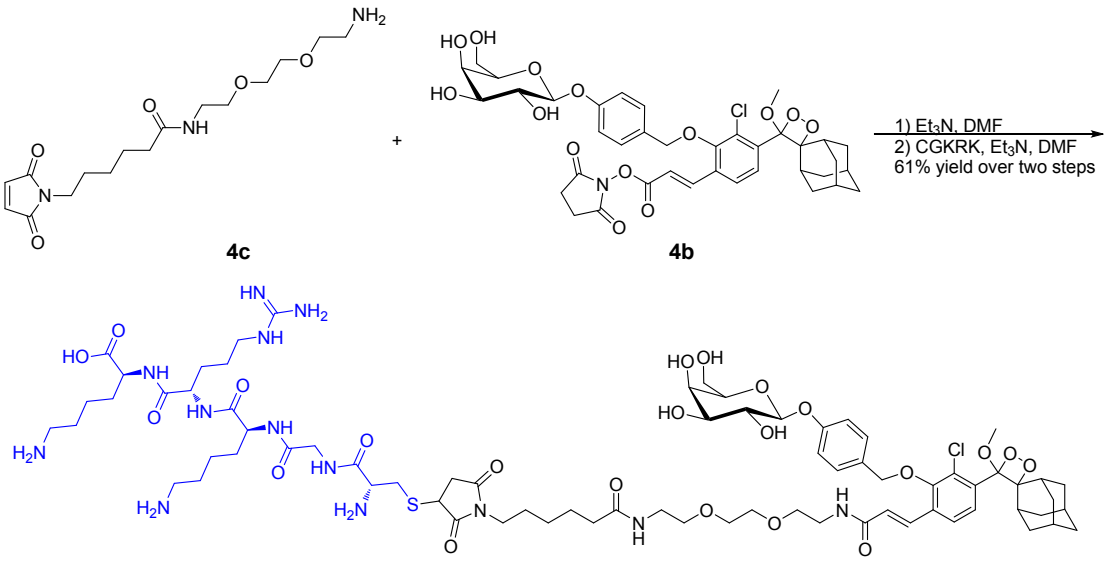


4a **4b**

Compound 4b

Compound **4a** (209 mg, 0.323 mmol, 1 eq) was dissolved in 1.5 ml of DCM and cooled to 0°C. N-hydroxysuccinimide (75 mg, 0.634 mmol, 2 eq) was added followed by N,N'-Dicyclohexylcarbodiimide (100 mg, 0.488 mmol, 1.5eq). The reaction was allowed to warm up to room temperature and monitored by RP-hplc. Upon completion, 5 ml of DCM were added, followed by catalytic amount of methylene blue. Oxygen was bubbled through the solution, while irradiating with yellow light. The reaction was monitored by RP-HPLC (50-100% ACN in water, 20 min). Upon completion, the reaction mixture was concentrated by evaporation under reduced pressure and the crude product was purified by preparative RP-HPLC (50-100% ACN in water, 20 min) to afford compound **4b** (138 mg, 59% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.93 – 7.83 (m, 2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.47 (d, *J* = 16.3 Hz, 1H), 4.94 – 4.78 (m, 2H), 3.94 (s, 1H), 3.82 – 3.49 (m, 8H), 3.16 (s, 3H), 2.95 (s, 1H), 2.81 (s, 4H), 2.25 (d, *J* = 11.5 Hz, 1H), 1.92 (s, 1H), 1.80 – 1.49 (m, 8H), 1.41 (d, *J* = 12.4 Hz, 1H), 1.24 (dd, *J* = 24.2, 12.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 170.10, 161.77, 157.85, 154.61, 143.63, 136.49, 130.89, 129.42, 129.01, 127.92, 125.51, 116.79, 114.34, 111.73, 101.14, 96.55, 76.34, 74.88, 73.29, 70.98, 68.88, 61.40, 36.48, 33.87, 33.58, 32.59, 32.15, 31.52, 26.11, 25.78, 25.63. MS (ES+): *m/z* calc. for $C_{38}H_{42}ClNO_{14}$: 771.23; found: 772.6 $[M+H]^+$.



4c **4b**

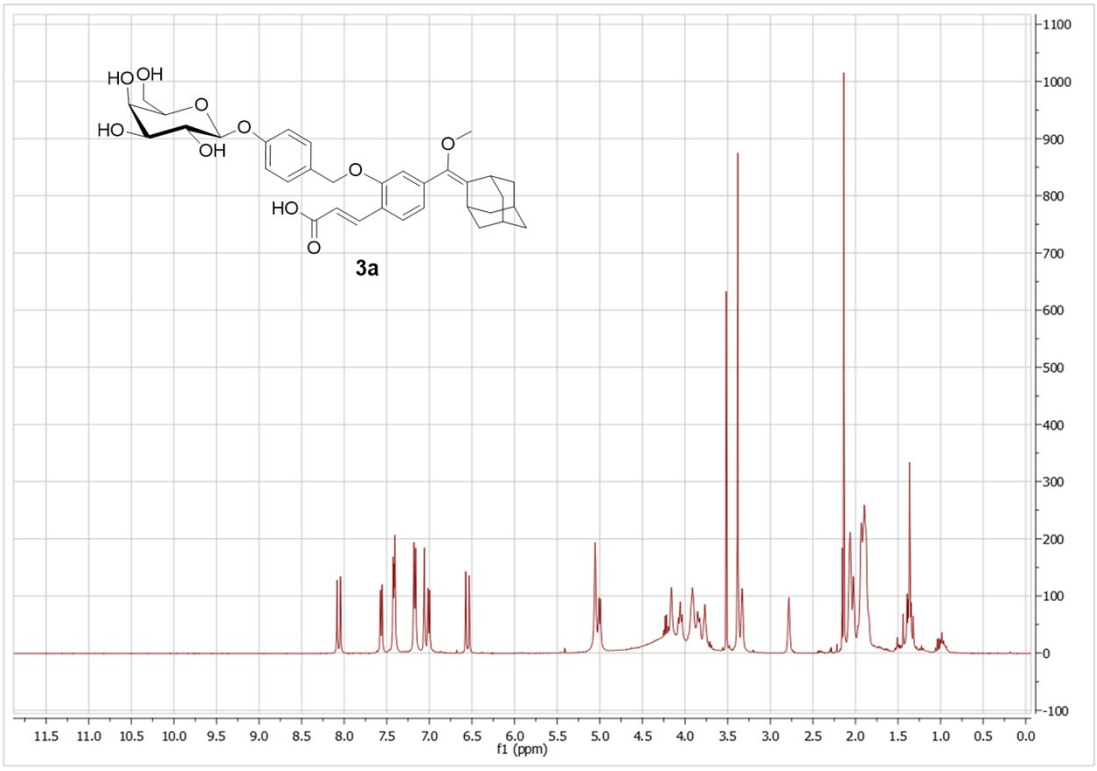
probe 2a

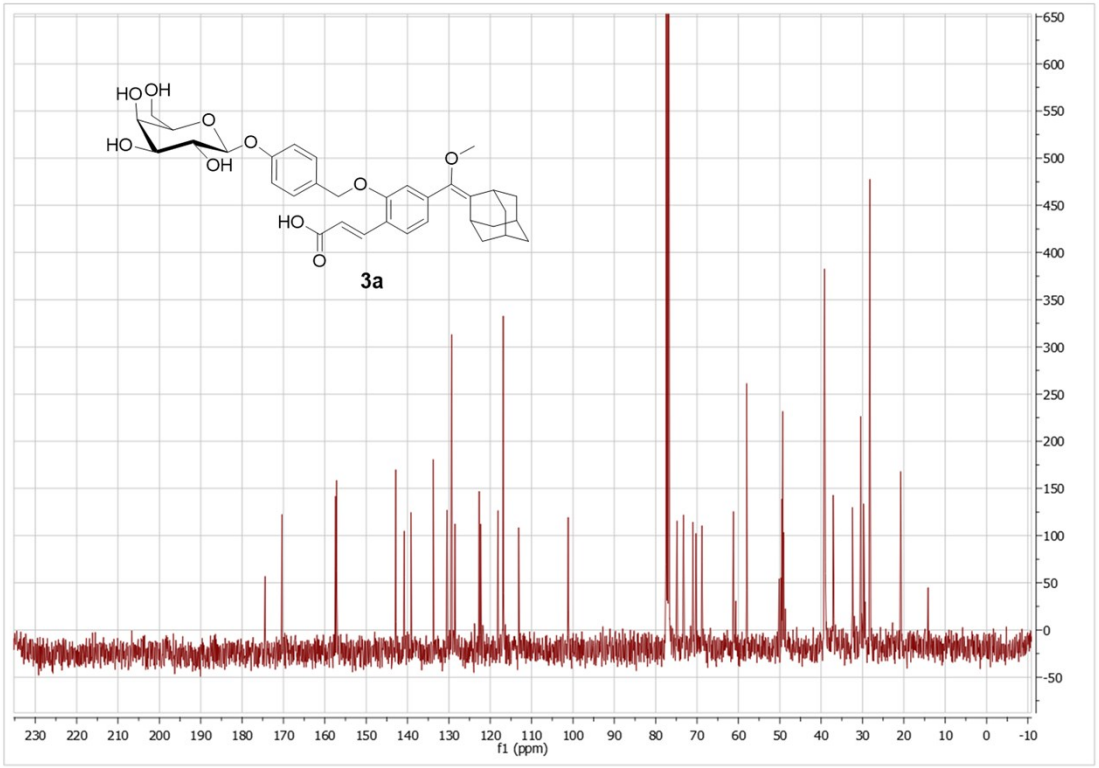
Probe 2a

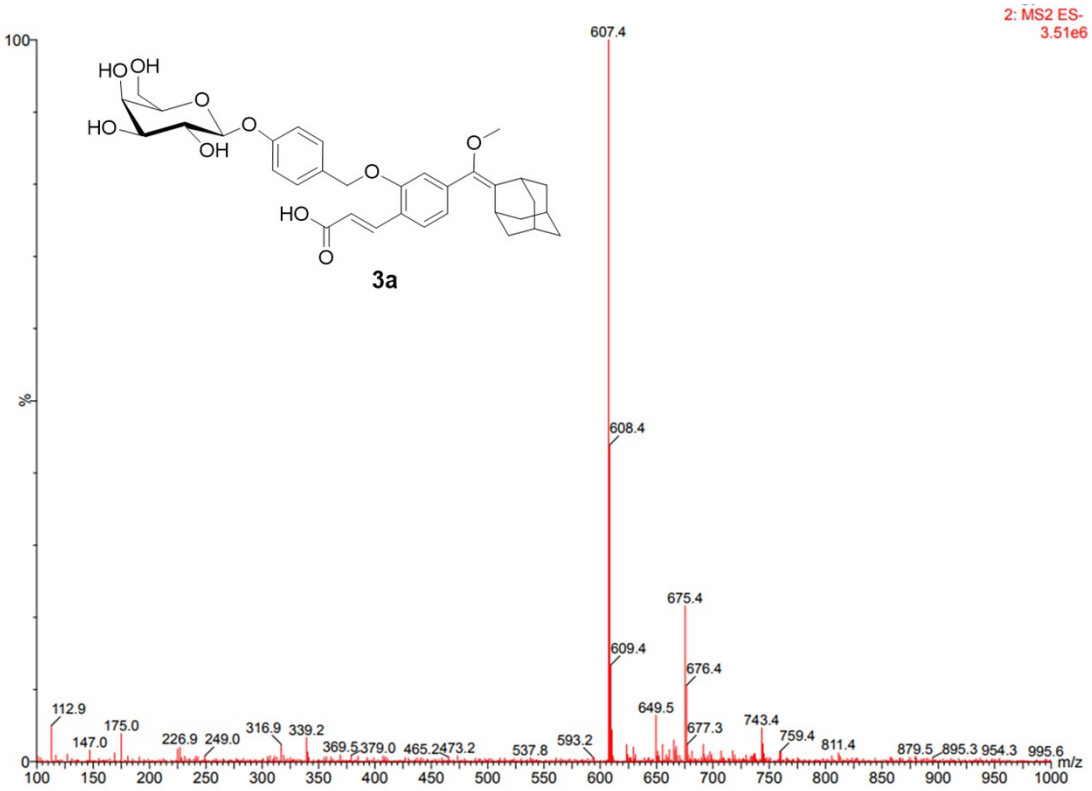
Compound **4c**[2] (5.3 mg, 0.015 mmol, 1 eq) and compound **4b** (10 mg, 0.013 mmol, 1 eq) were dissolved in DMF (0.5 ml) and a few drops of Et_3N were added. The Reaction was monitored by RP-HPLC (30-100% ACN in water, 20 min). Upon completion, **CGKRK**[3] (15 mg, 0.014 mmol, 1.1 eq) was added. The Reaction was monitored by RP-HPLC (30-100% ACN in water, 20 min). Upon completion, the reaction mixture was concentrated by evaporation under reduced pressure. The crude product was purified by preparative RP-HPLC (30-100% ACN in water, 20 min) to afford compound **probe 2a** (16.2 mg, 61% yield) as a white solid. HRMS (ES-): *m/z* calc. for $C_{73}H_{110}ClN_{13}O_{22}S$: 1587.73; found: MH^+ 1588.7365.

H-NMR, C-NMR, MS and/or HPLC Spectra of Key Compounds

Compound 3a



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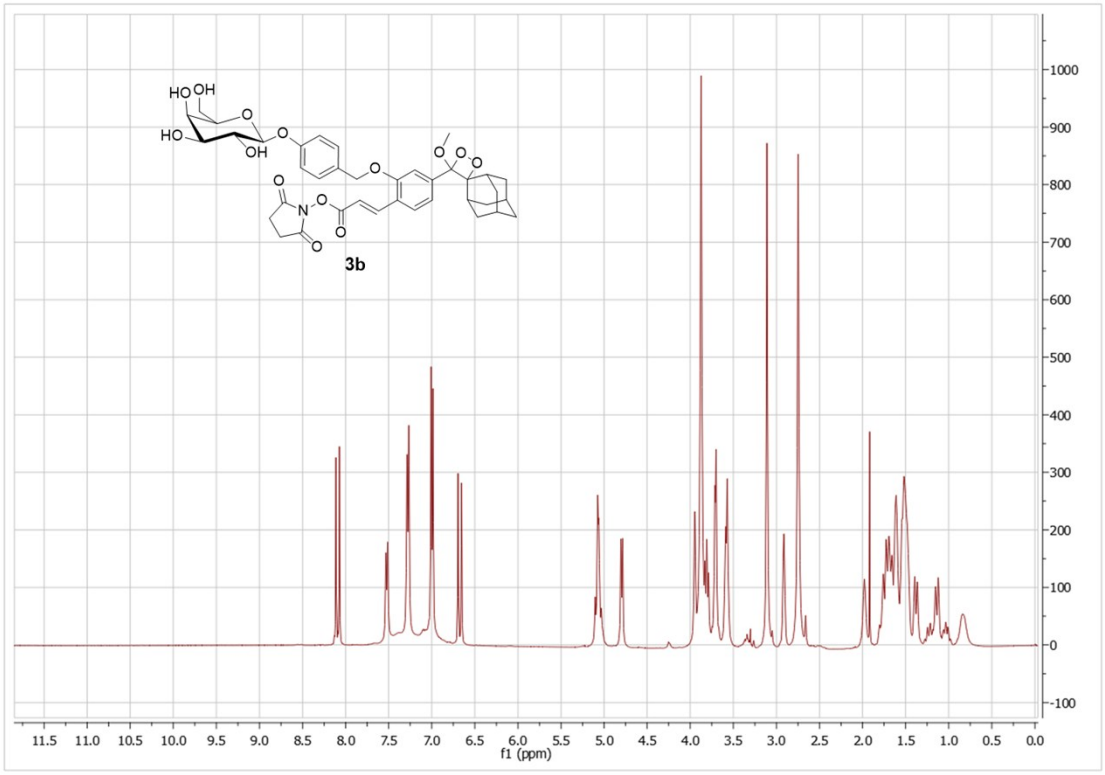
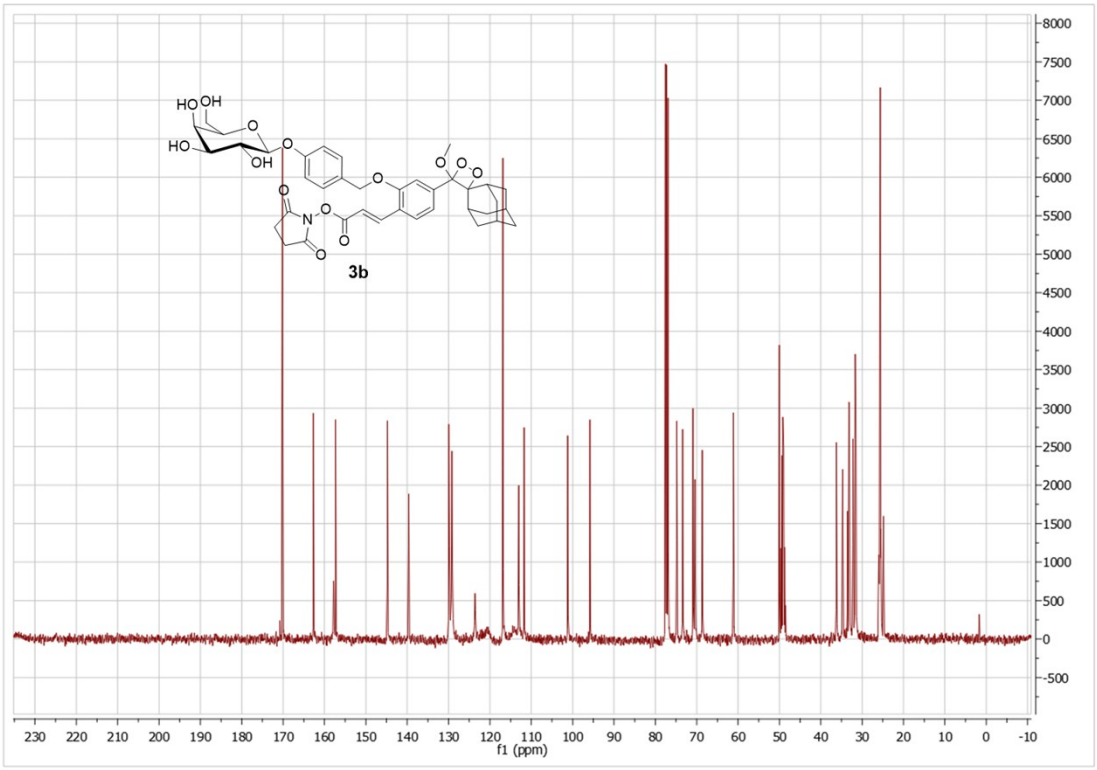
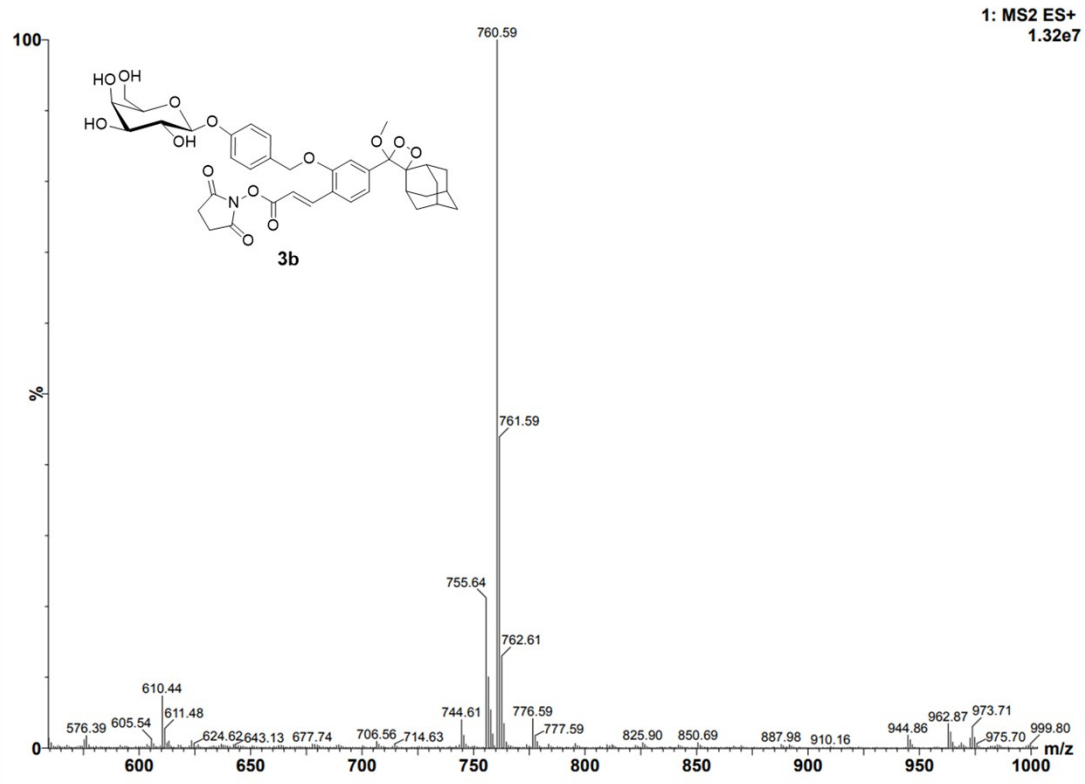
Compound 3b



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962.87
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950
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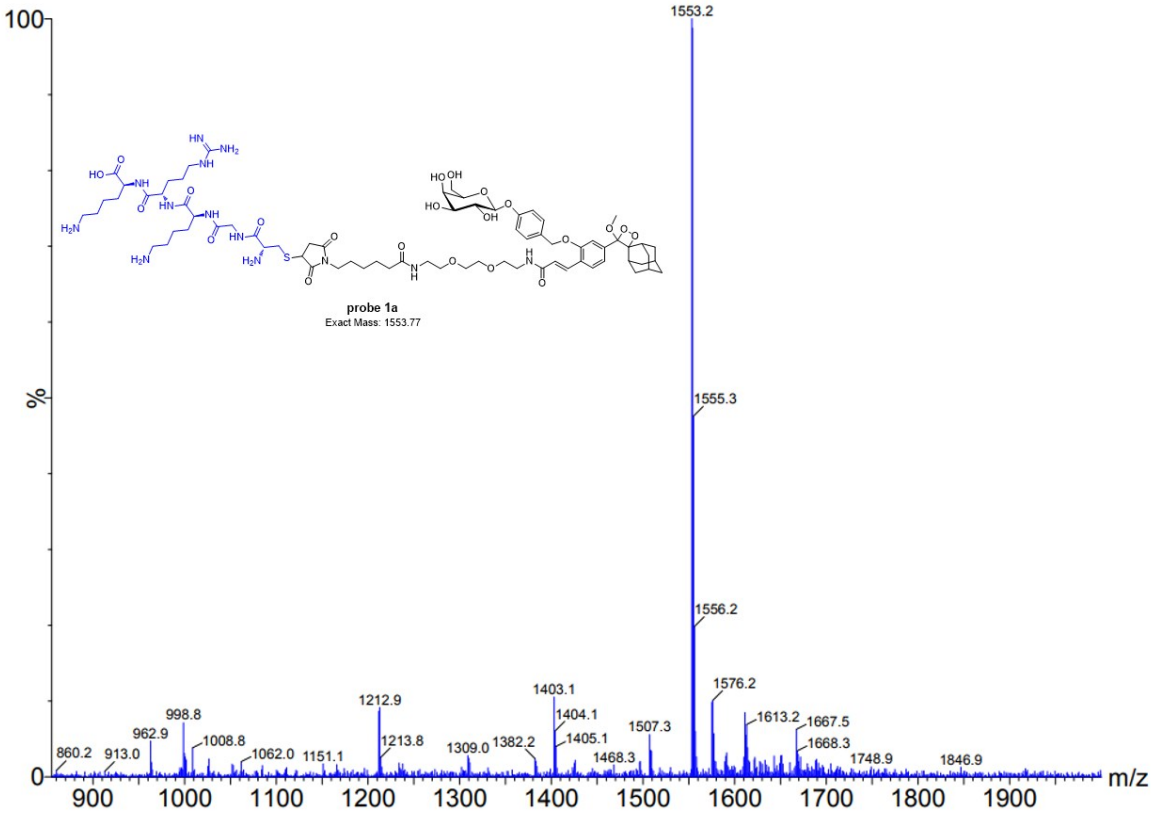
m/z
3b

Probe 1a



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 200.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
66 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 72-74 H: 105-115 N: 10-18 O: 18-25 S: 0-1 Cl: 0-1

3-168
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Ori Green
1: TOF MS ES+
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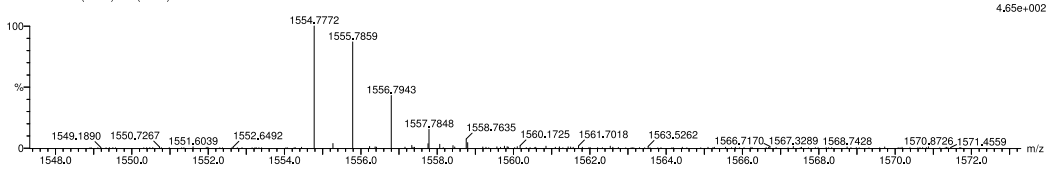

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Maximum:		5.0	2.0	200.0						
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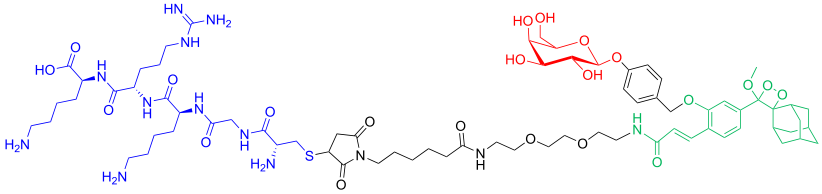
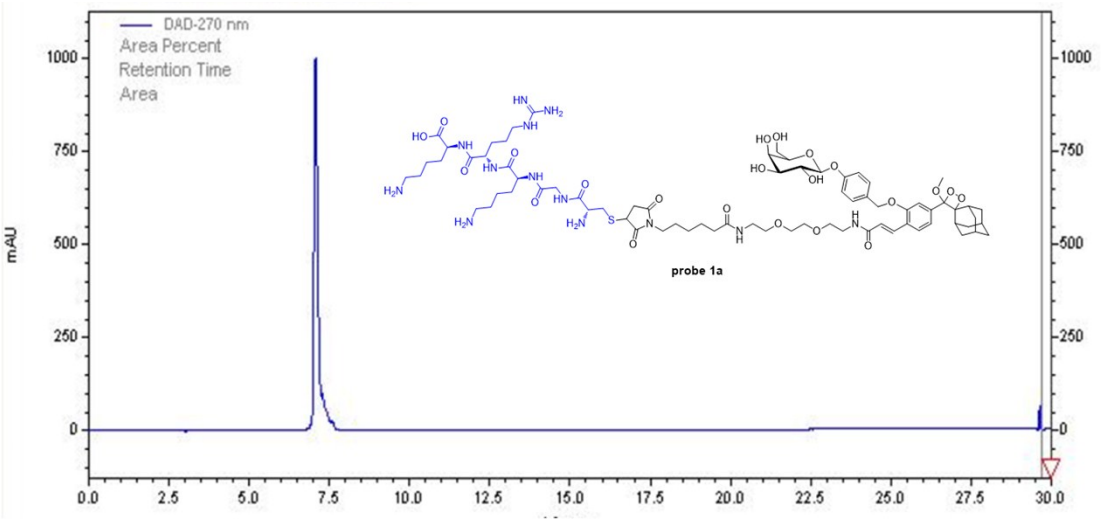
	1554.7779	-0.7	-0.5	29.5	32.2	0.6	C74	H108	N17	O18 S
	1554.7797	-2.5	-1.6	24.5	38.2	6.6	C73	H113	N15	O18 S Cl

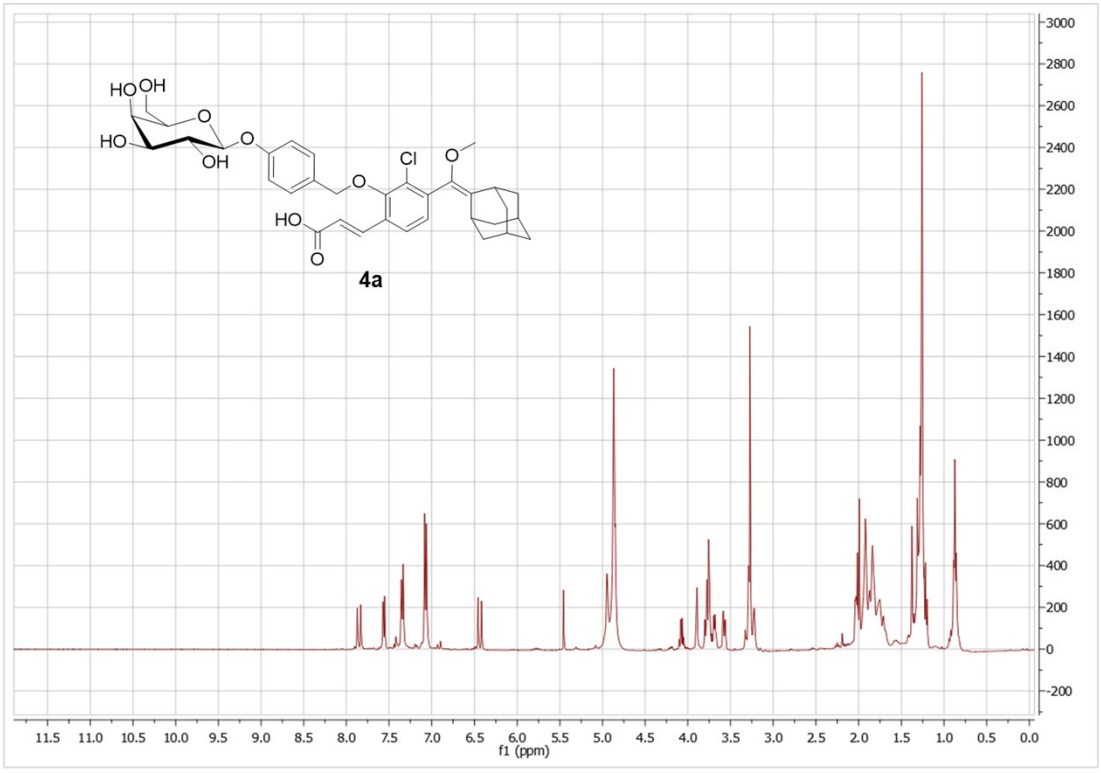


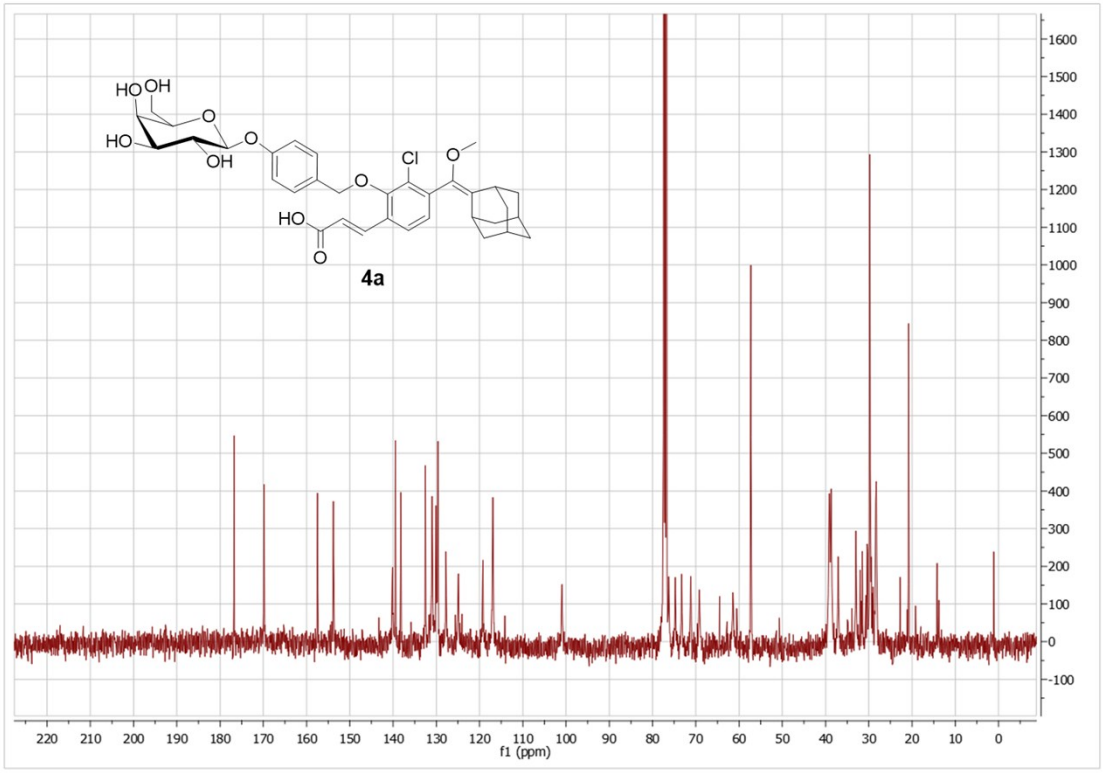
Chemical Formula: $C_{73}H_{111}N_{13}O_{22}S$
Exact Mass: 1553.77
Molecular Weight: 1554.82

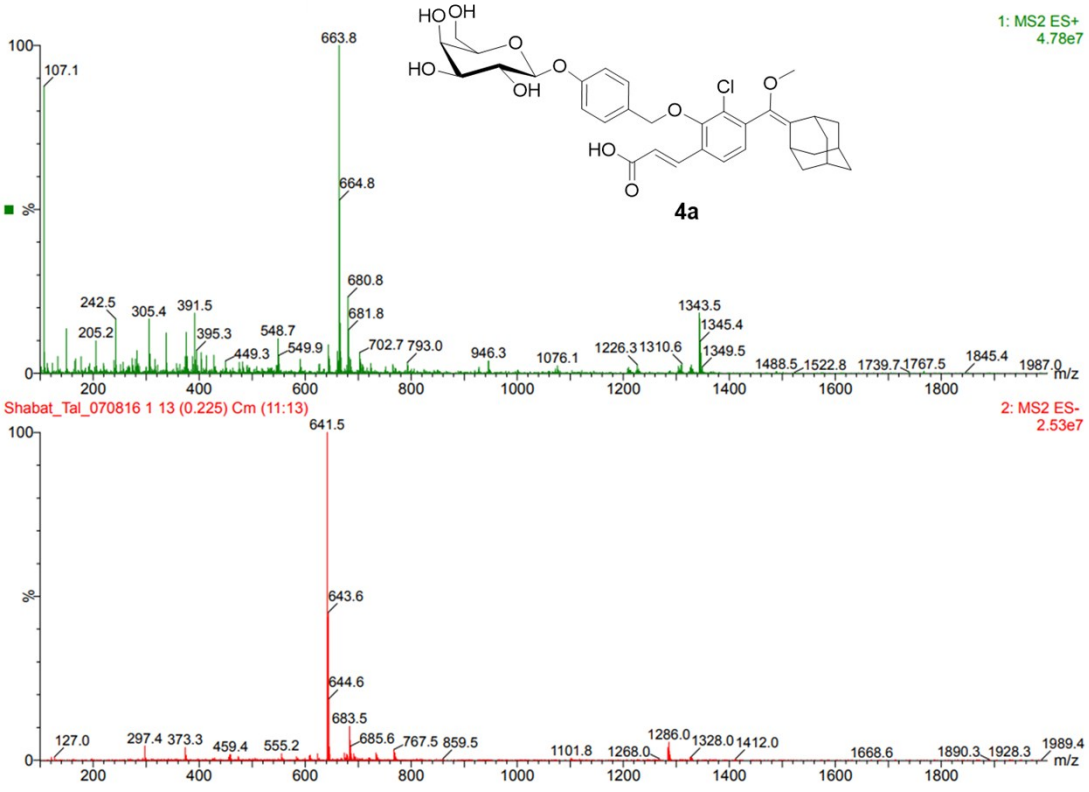


RP-HPLC chromatogram of probe **1a** (λ = 270 nm). C18 column. Eluent: 30%-90% ACN in H2O (0.1% TFA).

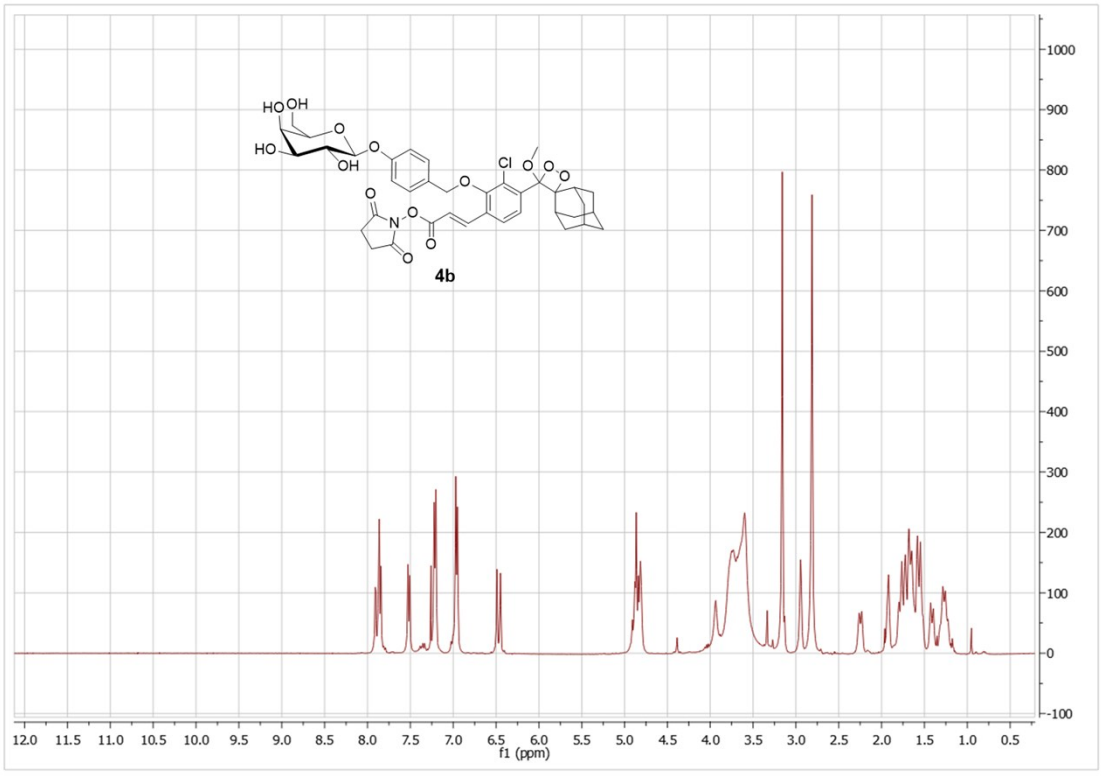
Compound 4a

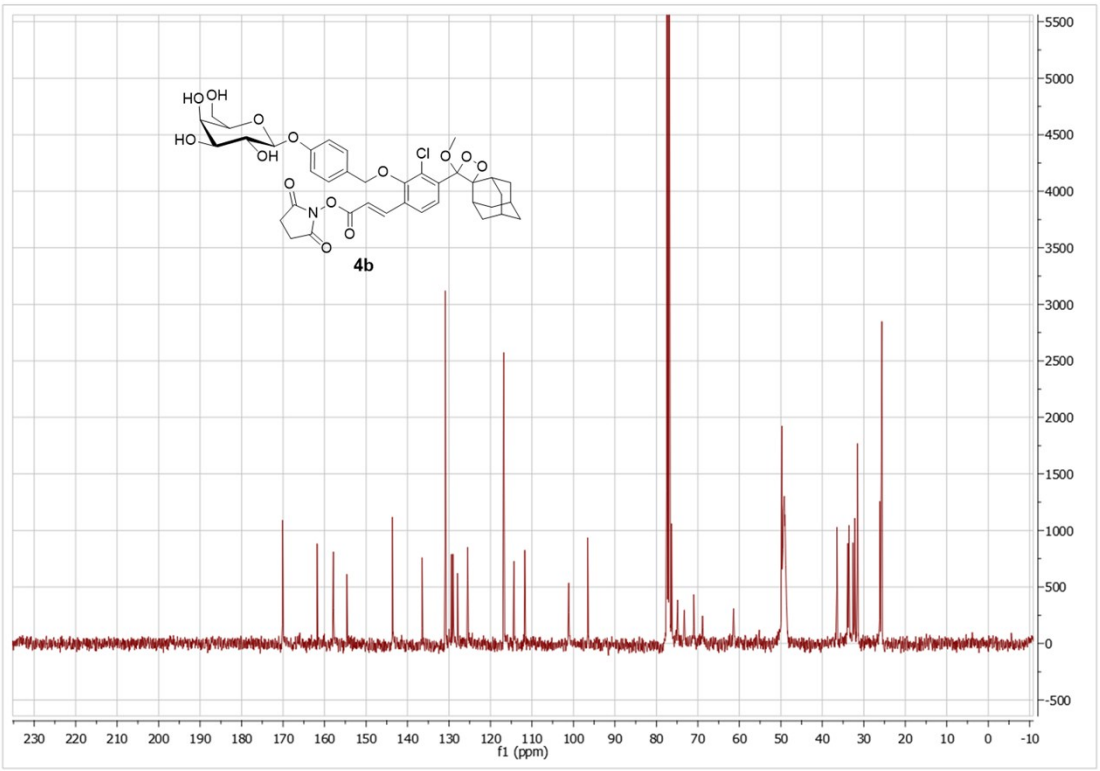



HO
OH
HO
OH
O
O
Cl
O
HO
O
4a
f1 (ppm)

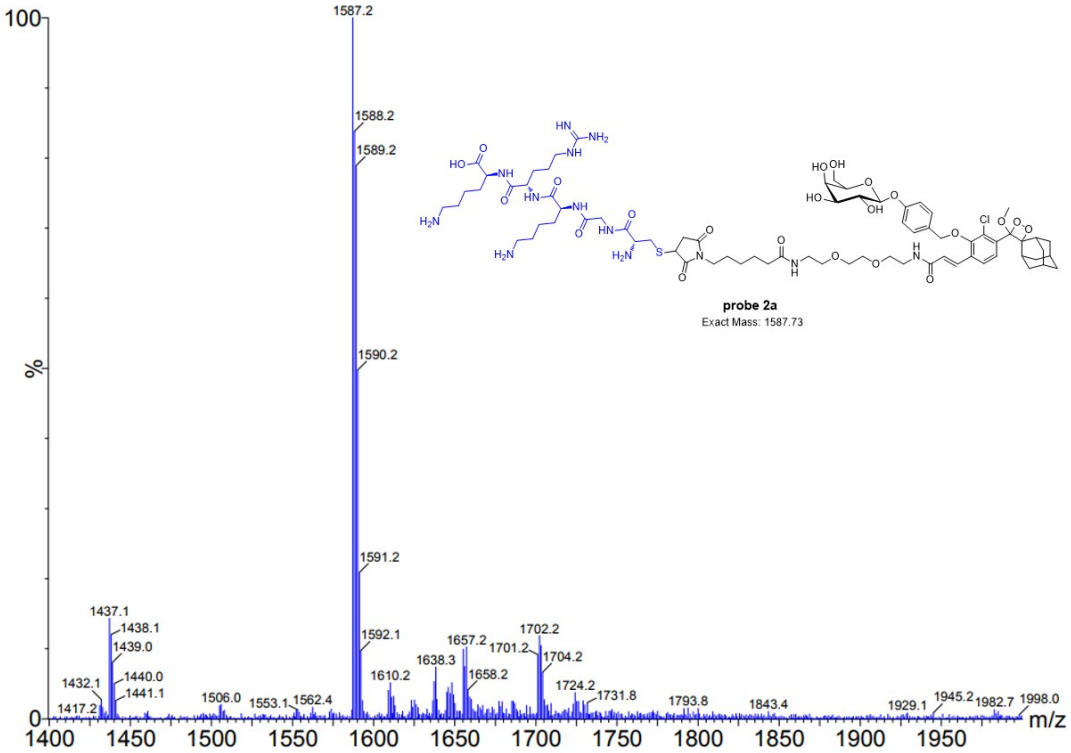

1: MS2 ES+
4.78e7
HO
OH
HO
OH
Cl
HO
4a
663.8
107.1
664.8
680.8
681.8
242.5
305.4
391.5
205.2
395.3
548.7
449.3
549.9
702.7
793.0
946.3
1076.1
1226.3
1310.6
1343.5
1345.4
1349.5
1488.5
1522.8
1739.7
1767.5
1845.4
1987.0
m/z
Shabat_Tal_070816 1 13 (0.225) Cm (11:13)
2: MS2 ES-
2.53e7
641.5
643.6
644.6
683.5
127.0
297.4
373.3
459.4
555.2
685.6
767.5
859.5
1101.8
1268.0
1286.0
1328.0
1412.0
1668.6
1890.3
1928.3
1989.4
m/z

Compound 4b





Probe 2a

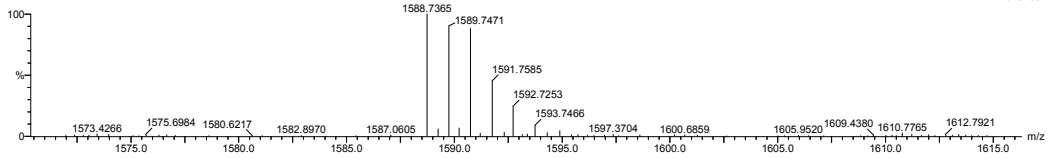


Elemental Composition Report **Page 1**

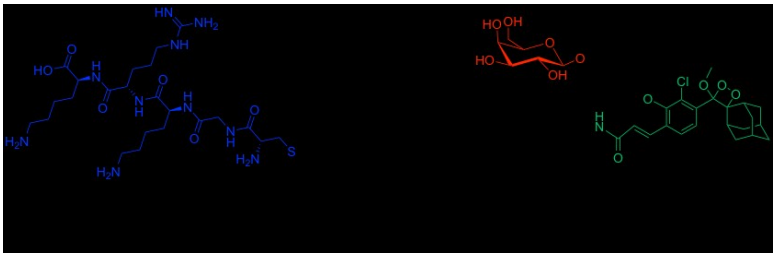
Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 200.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

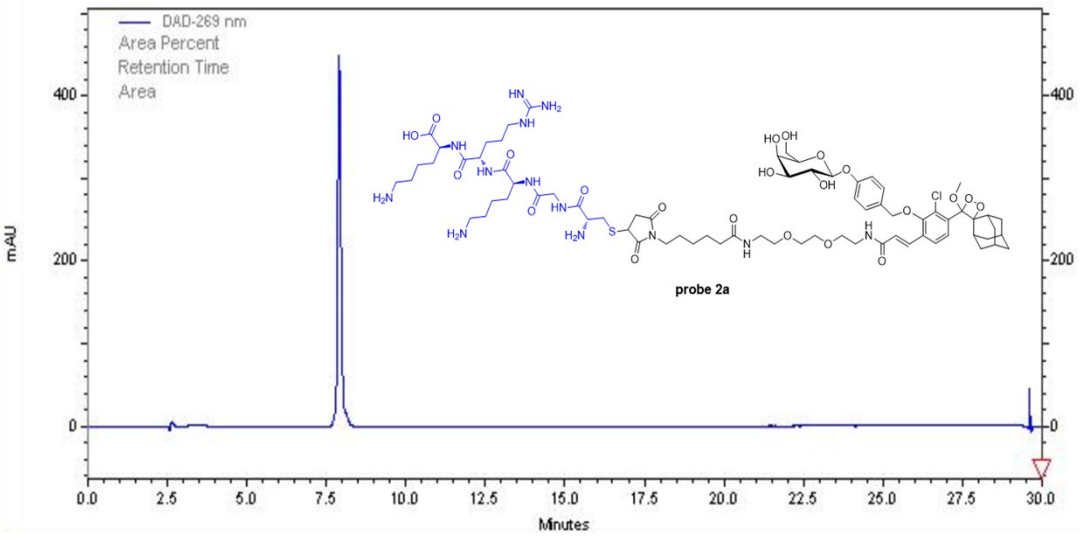
Monoisotopic Mass, Odd and Even Electron Ions
55 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 72-74 H: 105-115 N: 10-18 O: 18-25 S: 0-1 Cl: 0-1

3-125
SHABAT213b 14 (0.630) Cm (14)
Ori Green
1: TOF MS ES+
4.37e+002



Minimum:				-1.5				
Maximum:		5.0	2.0	200.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula	
1588.7365	1588.7358	0.7	0.4	29.5	37.1	6.5	C74 H106 N15 O22 S	
	1588.7376	-1.1	-0.7	24.5	31.6	0.9	C73 H111 N13 O22 S Cl	
	1588.7389	-2.4	-1.5	29.5	31.2	0.5	C74 H107 N17 O18 S Cl	





RP-HPLC chromatogram of probe **2a** (λ = 270 nm). C18 column. Eluent: 30%-90% ACN in H2O (0.1% TFA).

In vitro Experiments

Cell Culture

Murine colon carcinoma CT26.wt and CT26.CL5 cells were purchased from the American Type Culture Collection (ATCC Manassas, VA, USA). CT26.WT cell line was cultured in RPMI 1640 growing media supplemented with 10% FBS, 100 µg/mL streptomycin, 100 units/mL penicillin, 12.5 units/mL nystatin and 2 mM L-glutamine. CT26.CL25 cell line was cultured in RPMI 1640 growing media supplemented with 10% FBS, 100 µg/mL streptomycin, 100 units/mL penicillin, 12.5 units/mL nystatin, 2 mM L-glutamine, 4.5 g/L glucose, 10 mM HEPES and 1.0 mM sodium pyruvate and supplemented with 0.1 mM non-essential amino-acids and 0.4 mg/ml G418. Cells were grown at 37°C; 5% CO2.

Chemiluminescence imaging in living cells

CT26.wt and CT26.CL5 cells (40,000 cells/well) were seeded in 96 well corning clear bottom plates with their growth medium. Following 24 h, medium was replaced and to a fresh growth medium with materials **1**, **1a**, **2**, **2a** [5 µM]. Cells were immediately imaged using BioSpace Lab PhotonIMAGER^{TM} for 30 min. The experiment was repeated 3 times.

In vivo Experiments

Ethics Statement

All animal procedures were performed in compliance with Tel Aviv University, Sackler School of Medicine (Tel Aviv, Israel) guidelines, and protocols were approved by the Tel Aviv University Institutional Animal Care and Use Committee (IACUC).

Intravital non-invasive chemiluminescence imaging

Six 7-weeks old BALB/c female mice (Harlan Laboratories Israel Ltd., Jerusalem, Israel) were anesthetized using a mixture of ketamine (100 mg/kg) and xylazine (12 mg/kg) injected subcutaneously. Then, mice were injected subcutaneously with 50 µL of the materials **1**, **1a**, **2** or **2a**, previously incubated in PBS 7.4 (in the presence or absence of betagalactosidase) for 30 min. The mice were imaged and

chemiluminescence was monitored for up to 30 min by intravital non-invasive bioluminescence imaging system (Photon Imager; Biospace Lab, Paris, France). Images were obtained by Photo-Acquisition software (Biospace Lab) and analyzed by M3Vision Software (Biospace Lab). In addition, 30 6-weeks old BALB/c female mice (Harlan Laboratories Israel Ltd., Jerusalem, Israel) were inoculated subcutaneously with $1*10^6$ murine CT26 cells. 15 mice were inoculated with CT26-wt and 15 with CT26.Cl25. tumor growth was monitored q.o.d. until tumors were ~ 350 mm^3. Mice were anesthetized using a mixture of ketamine (100 mg/kg) and xylazine (12 mg/kg) injected subcutaneously. Then, mice were injected with 100 µL of the materials A, B, C or D, or saline control by intra-tumoral injection. The mice were imaged and chemiluminescence was monitored for up to 30 min by intravital non-invasive bioluminescence imaging system (Photon Imager; Biospace Lab, Paris, France). Images were obtained by Photo-Acquisition software (Biospace Lab) and analyzed by M3Vision Software (Biospace Lab).

Chemiluminescence signal was quantified as total signal of photons/exposure time (sec)/ tumor size (mm^3). Data is expressed as mean ± S.D.

References

[1] O. Green, T. Eilon, N. Hananya, S. Gutkin, C. R. Bauer, D. Shabat, *ACS Cent. Sci.* **2017**, *3*, 349–358.

[2] *Chem. Biol.* **2011**, *18*, 1261–1272.

[3] D. Shabat, M. Roth-Konforti, C. Bauer, *Angew. Chemie Int. Ed.* **2017**, DOI 10.1002/anie.201709347.