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Caging the Uncageable: Using Metal Complex Release for Photochemical Control over Irreversible Inhibition

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Supporting Information

(66 Pages)

Part A. General considerations

All reagents were purchased from commercial suppliers and used as received. NMR spectra were recorded on a Varian FT-NMR Mercury 400 MHz Spectrometer. HRMS data was acquired on an electrospray time-of-flight (TOF) mass spectrometer. All reactions were performed under ambient atmosphere unless otherwise noted. Compounds **S1**,[1] H-Phe-NMe_2·TFA,[2],[3] N-[4-(2-Aminoethyl)phenyl] acetamide[4] and $[Ru(tpy)(Me_2bpy)Cl](Cl)_2$[5] used in this report were synthesized according to previously reported literature procedures. Anaerobic reactions were performed in Schlenk tubes by purging the solutions with Ar or N_2.

Compound abbreviations are as follows:

tpy: 2,2′:6′,2′′-Terpyridine

Me_2bpy: 6,6′-Dimethyl-2,2′-bipyridine

HBTU: 2-(1H-Benzotriazole-1- yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

TFA: Trifluoroacetic acid

EtOH: Ethanol

KOH: Potassium hydroxide

EtOAc: Ethyl acetate

Na_2SO_4: Sodium sulfate

DIPEA: *N,N*-Diisopropylethylamine

MeOH: Methanol

IPA: Isopropanol

TLC: Thin layer chromatography

DCC: Dicyclohexylcarbodiimide

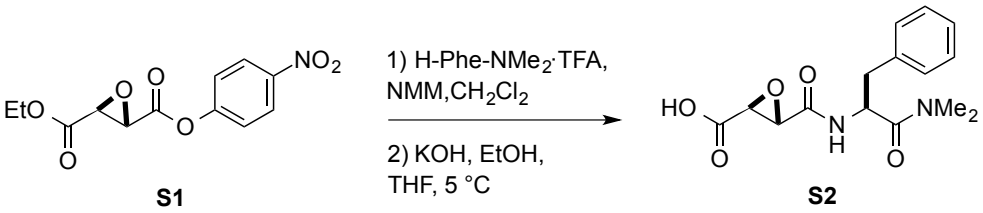
PNP: *p*-Nitrophenol

NMM: *N*-Methylmorpholine

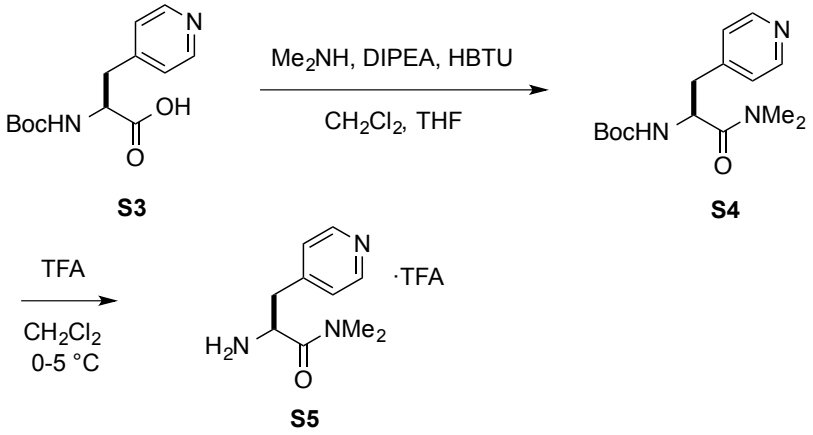
EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

HOBT: 1-Hydroxybenzotriazole

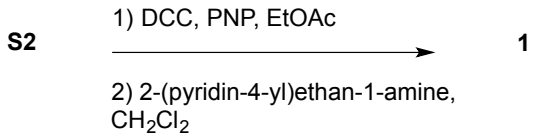
Part B. Synthetic schemes for preparation of epoxysuccinyl inhibitors



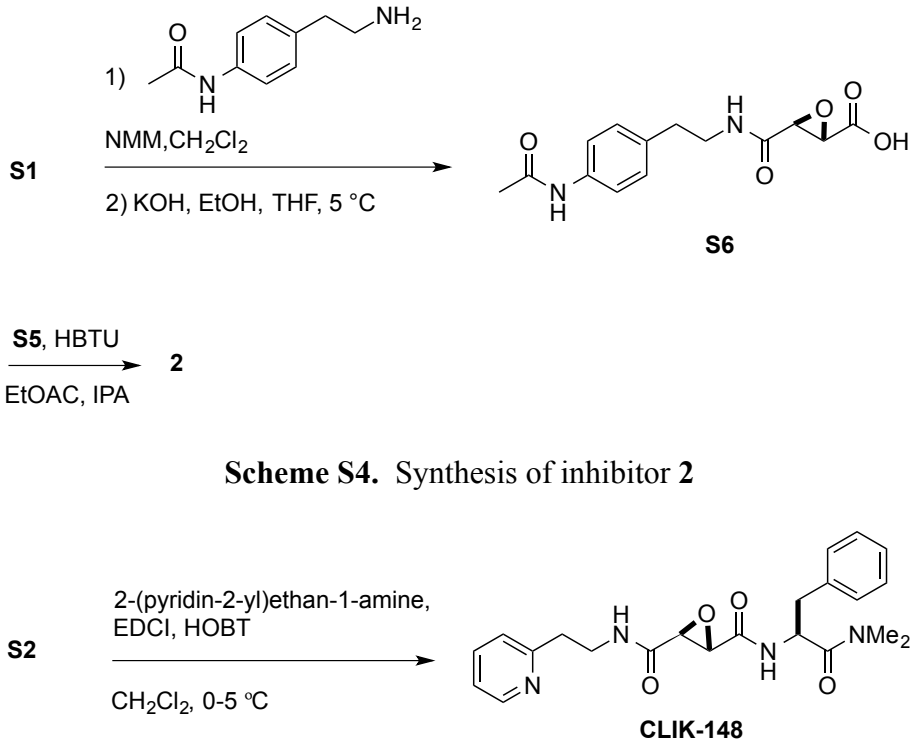
Scheme S1. Synthesis of acid **S2**



Scheme S2. Synthesis of amine TFA salt **S5**

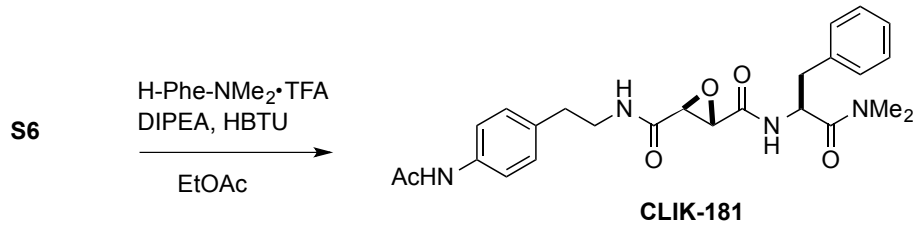


Scheme S3. Synthesis of inhibitor **1**



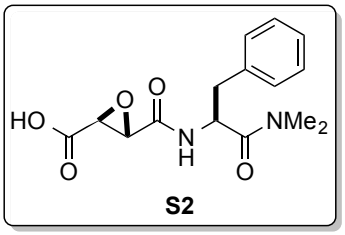
Scheme S4. Synthesis of inhibitor **2**

Scheme S5. Synthesis of **CLIK-148**



Scheme S6. Synthesis of **CLIK-181**

Part C. Experimental procedures and tabulated data for new compounds

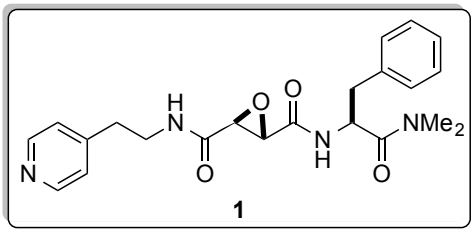


S2

(2*S*,3*S*)-3-((1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)oxirane-2-carboxylic acid (S2). A solution of **S1**[1] (Scheme S1, 6.06 g, 21.5 mmol) and CH_2Cl_2 (75 mL) was maintained at rt for 5 min under nitrogen atmosphere. A solution of H-Phe-NMe_2·TFA[2,3] (5.50 g, 18.0 mmol) and NMM (4.00 mL, 35.9 mmol) in CH_2Cl_2 (75 mL) was added dropwise over a period of 20 min. The reaction mixture was stirred at rt for 4 h. After consumption of starting material, as judged by TLC analysis, the solvent was evaporated *in vacuo*. The crude product was purified by silica gel chromatography (50% to 100% EtOAc:Hexanes) to give the ethyl ester as a clear viscous oil (3.27 g, 56%). The product was analyzed by ^{1}H NMR (> 95% purity, 934 mg, 2.79 mmol) and was used without further purification. R_f = 0.5, silica, EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 3H), 7.15 (d, *J* = 6.5 Hz, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 5.14 (dd, *J* = 8.1, 6.5 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 1H), 3.60 (d, *J* = 2.0 Hz, 1H), 3.28 (d, *J* = 2.0 Hz, 1H), 3.03–2.92 (m, 2H), 2.90 (s, 3H), 2.71 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H).

A solution of the ethyl ester (934 mg, 2.79 mmol), dry THF (28 mL) and EtOH (28 mL) was maintained at 0 °C for 10 min under nitrogen atmosphere. KOH (157 mg, 2.79 mmol) in dry EtOH (2.8 mL) was added dropwise over a period of 20 min while maintaining the temperature below 5 °C. The reaction mixture was maintained below 5 °C for 30 min. After consumption of

the starting material, as judged by TLC analysis, the solvent was evaporated *in vacuo* and the residue was dissolved in cold water (30 mL) and acidified to pH 2 using 10% $KHSO_4$ (aq) over a period of 15 min. The aqueous layer was extracted with EtOAc (3 × 30 mL), washed with brine (1 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to obtain **S2** as a white solid (815 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.3 Hz, 1H), 7.31–7.29 (m, 3H), 7.19–7.17 (m, 2H), 5.16 (dd, *J* = 15.7, 8.3 Hz, 1H), 3.55 (d, *J* = 1.6 Hz, 1H), 3.51 (d, *J* = 1.6 Hz, 1H), 3.06–2.97 (m, 2H), 2.89 (s, 3H), 2.76 (s, 3H); $[\alpha]_D^{25}$ + 81 (c = 1.0, $CHCl_3$) ^{13}C NMR (100 MHz $CDCl_3$) δ 172.3, 171.1, 165.5, 135.3, 129.2, 128.7, 127.5, 53.4, 51.4, 50.5, 38.8, 37.3, 36.2; IR (thin film): 3273, 3063, 3028, 2934, 2340, 1738, 1732, 1682, 1622, 1537, 1497, 1454, 1404, 1337, 1250, 1206, 1111, 1082, 1029, 895, 860, 748, 700, 648, 525, 480; HRMS (ESMS) calcd for $C_{15}H_{18}N_2O_5$ 307.1216 $[M+H]^+$, found: 307.1302.

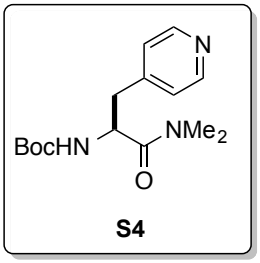


1

(2*S*,3*S*)-3-((1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)oxirane-2-carboxylate (**1**). A solution of **S2** (815 mg, 2.66 mmol) and *p*-nitrophenol (370 mg, 2.66 mmol) in EtOAc (8 mL) was maintained at 0 °C for 5 min under nitrogen atmosphere. A solution of DCC (565 mg, 2.74 mmol) in EtOAc (8 mL) was added in a dropwise fashion over a period of 30 min. The reaction mixture was allowed to warm to rt and was maintained overnight for 18 h. After consumption of the starting material, as judged by TLC analysis, the reaction mixture was filtered through celite. The solvent was evaporated *in vacuo* to obtain the *p*-nitrophenol ester as a crude yellow solid (1.14 g). The *p*-nitrophenol ester was analyzed by ^{1}H NMR and TLC, showing only *p*-nitrophenol as a minor impurity, and was used without further purification. R_f = 0.4, silica, 1:1 Hexane:EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.9 Hz, 2H), 7.35–7.29 (m, 5H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.16 (dd, *J* = 14.6, 8.1 Hz, 1H) 3.78 (d, *J* = 2.0 Hz, 1H), 3.50 (d, *J* = 2.0 Hz, 1H), 3.08–3.02 (m, 1H), 2.99-2.96 (m, 1H), 2.93 (s, 3H), 2.76 (s, 3H).

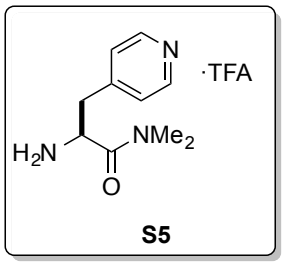
The crude *p*-nitrophenol ester in dry CH_2Cl_2 (20 mL) was maintained at rt for 5 min under nitrogen atmosphere. 2-(pyridin-4-yl)ethan-1-amine (325 mg, 2.66 mmol) in CH_2Cl_2 (20 mL) was added dropwise over a period of 20 min. The reaction mixture was maintained under nitrogen atmosphere for 16 h at rt. After consumption of the starting material, as judged by TLC

analysis, the organic layer was evaporated *in vacuo* to give a crude mixture which was purified by silica gel chromatography (0% to 20% MeOH:EtOAc) to afford the product **1** as a white solid (619 mg, 57% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 7.3 Hz, 2H), 7.32–7.22 (m 3H), 7.15–7.09 (m, 4H), 7.04 (d, J = 8.0 Hz, 1H), 6.24 (t, J = 6.9 Hz, 1H), 5.10 (dd, J = 14.7, 8.0 Hz, 1H), 3.53 (q, J = 6.9 Hz, 2H), 3.31 (s, 2H), 3.01–2.91 (m, 2H), 2.89 (s, 3H), 2.82 (t, J = 6.9 2H), 2.70 (s, 3H); $[\alpha]_D^{25}$ + 34 (c = 1.0, $CHCl_3$) ^{13}C NMR (100 MHz $CDCl_3$) δ 170.4, 165.9, 164.8, 150.1, 147.3, 135.6, 129.3, 128.6, 127.3, 124.0, 54.8, 54.6, 49.6, 39.2, 39.1, 36.9, 35.7, 34.8; IR (thin film): 3275, 3063, 3028, 2934, 1630, 1605, 1530, 1497, 1418, 1402, 1341, 1244, 1146, 1098, 1082, 1001, 895, 810, 748, 700, 664, 519, 496; HRMS (ESMS) calcd for $C_{22}H_{26}N_4O_4$ 411.1954 $[M+H]^+$, found: 411.2029.



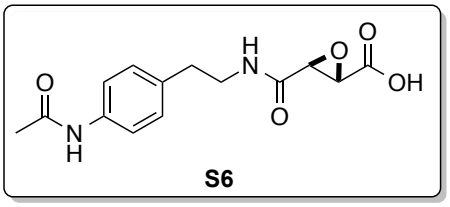
S4

***Tert*-butyl (*S*)-(1-(dimethylamino)-1-oxo-3-(pyridin-4-yl)propan-2-yl)carbamate (S4).** A suspension of Boc-*L*-4-pyridyl-alanine (500 mg, 1.88 mmol), HBTU (785 mg, 2.07 mmol), CH_2Cl_2 (10 mL) and DIPEA (654 μL, 3.76 mmol) was maintained at rt for 5 min under nitrogen atmosphere. Dimethylamine (2 M in THF, 1.25 mL, 2.50 mmol) was added dropwise over a period of 20 min. The reaction was maintained under nitrogen atmosphere for 4 h. After consumption of the starting material, as judged by TLC analysis, the reaction mixture was washed with 10 % $NaHCO_3$ solution (3 × 20 mL) and brine solution (1 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain crude product. The crude product was purified by silica gel chromatography (0% to 20% MeOH:EtOAc) to obtain the dimethyl amide **S4** as a clear oil (516 mg, 94 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.7 Hz, 2H), 7.10 (d, *J* = 4.7 Hz, 2H), 5.51 (d, *J* = 7.6 Hz, 1H), 4.86 (q, *J* = 7.6 Hz, 1H), 2.98–2.93 (m, 1H), 2.89–2.75 (m, 1H), 2.85 (s, 3H), 2.79 (s, 3H), 1.38 (s, 9H); $[\alpha]_D^{25}$ + 26.0 (c = 1.0, $CHCl_3$) ^{13}C NMR (100 MHz $CDCl_3$) δ 170.8, 155.0, 149.7, 145.6, 124.7, 79.8, 50.5, 39.1, 37.0, 35.6, 28.3; IR (thin film): 3296, 2976, 2932, 1703, 1639, 1603, 1495, 1414, 1366, 1319, 1273, 1250, 1165, 1047, 1020, 905, 868, 812, 731, 640, 573, 554, 511, 469; HRMS (ESMS) calculated for $C_{15}H_{23}N_3O_3$ $[M+H]^+$: 294.1739, found: 294.1820.



S5

Mono(1-(dimethylamino)-1-oxo-3-(pyridin-4-yl)propan-2-aminium) bis(2,2,2-trifluoroacetate) (S5). A solution of **S4** (516 mg, 1.76 mmol) in CH_2Cl_2 (1.5 mL) was cooled to 0 °C. TFA (1.5 mL, 14.4 mmol) was added dropwise over a period of 20 min while maintaining a temperature below 5 °C. The reaction mixture was maintained at 0-5 °C for 4 h. After consumption of the starting material, as judged by TLC analysis, TFA and CH_2Cl_2 was removed *in vacuo*. The reaction mixture was combined with CH_2Cl_2 and concentrated *in vacuo* (3 × 50 mL) to obtain product as a clear viscous oil that was used without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 8.85 (d, J = 6.5 Hz, 2H), 8.00 (d, J = 6.5 Hz, 2H), 4.92–4.89 (m, 1H), 3.55 (dd, J = 14.2, 6.1 Hz, 1H), 3.41 (dd, J = 14.2, 7.7 Hz, 1H), 3.05 (s, 3H), 2.98 (s, 3H).

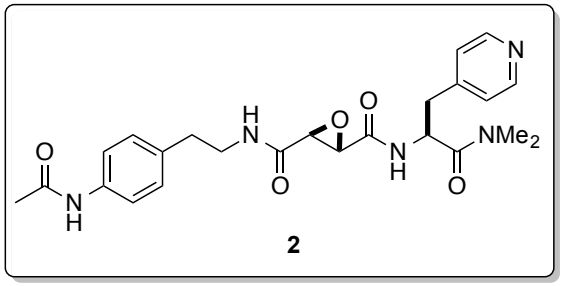


S6

(2*S*,3*S*)-3-((4-acetamidophenethyl)carbamoyl)oxirane-2-carboxylic acid (S6). A solution of *N*-(4-(2-aminoethyl)phenyl)acetamide (889 mg, 4.99 mmol) in CH_2Cl_2 (25 mL) was maintained at rt for 5 min under nitrogen atmosphere. A solution of 2-ethyl 3-(4-nitrophenyl) (2*S*,3*S*)-oxirane-2,3-dicarboxylate (**S1)** (1.40 g, 4.99 mmol) in CH_2Cl_2 (25 mL) was added dropwise over a period of 20 min. The reaction mixture was stirred at rt for 4 h. After consumption of the starting material, as judged by TLC analysis, the solvent was evaporated *in vacuo*. The crude

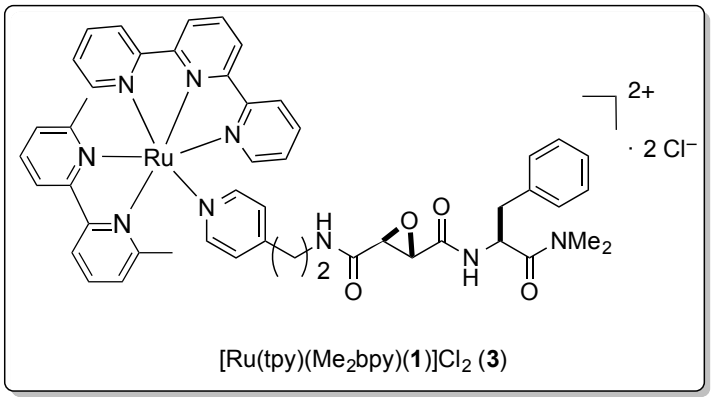
product was purified by silica gel chromatography (EtOAc) to afford the ethyl ester as clear oil (1.60 g, quant). R_f = 0.2, silica, 2:1 EtOAc:Hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.12 (t, *J* = 2.5 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 1H), 3.63 (d *J* = 2.0 Hz, 1H), 3.49 (q, *J* = 6.7 Hz, 2H), 3.35 (d, *J* = 2.0 Hz, 1H), 2.77 (dt, *J* = 6.7, 2.5 Hz, 2H), 2.16 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

A solution of the ethyl ester (1.60 g, 4.99 mmol), dry THF (50 mL) and EtOH (50 mL) was maintained at 0 °C for 10 min under nitrogen atmosphere. KOH (280 mg, 4.99 mmol) in EtOH (5 mL) was added dropwise over a period of 20 min while maintaining the temperature below 5 °C. The reaction mixture was maintained below 5 °C for 30 min. After consumption of the starting material, as judged by TLC analysis, the solvent was evaporated *in vacuo*, and the residue was dissolved in cold water (50 mL) and the solution was acidified to pH 2 using 10% $KHSO_4$ (aq) over a period of 15 min. The aqueous layer was extracted EtOAc (3 × 50 mL) and washed with brine (1 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain **S6** as a white solid (806 mg, 55% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 3.52 (d, *J* = 1.6 Hz, 1H), 3.45–3.39 (m, 3H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.10 (s, 3H); $[\alpha]_D^{25}$ + 51 (c = 1.1, MeOH) ^{13}C NMR (100 MHz CD_3OD) δ 170.2, 169.0, 167.1, 136.9, 134.5, 128.7, 120.0, 53.0, 51.7, 40.4, 34.2, 22.3; IR (thin film): 3289, 3111, 2928, 2490, 1728, 1713, 1659, 1601, 1537, 1514, 1452, 1412, 1371, 1319, 1250, 1113, 1086, 1042, 1020, 970, 895, 824, 652, 606, 556, 515; HRMS (ESMS) calculated for $C_{14}H_{16}N_2O_5Na$ $[M+Na]^+$: 315.0957, found: 315.0945.



2

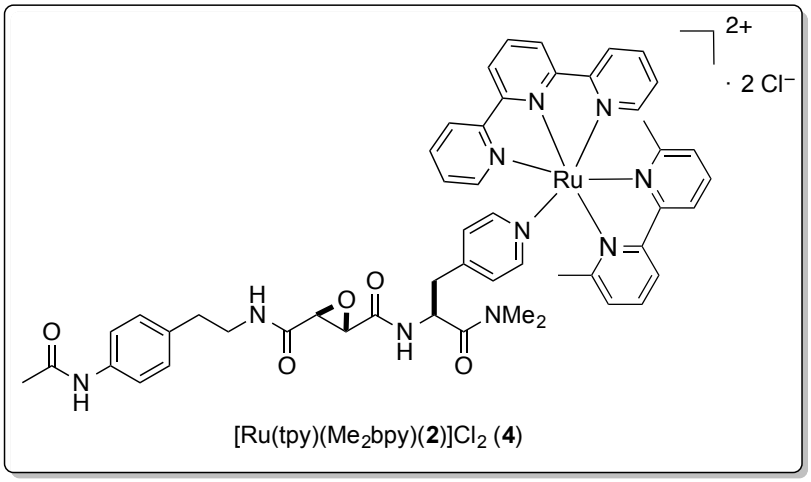
(2*S*,3*S*)-N^2-(4-acetamidophenethyl)-N^3-((*S*)-1-(dimethylamino)-1-oxo-3-(pyridin-4-yl)propan-2-yl)oxirane-2,3-dicarboxamide (2). A mixture of **S6** (257 mg, 0.879 mmol), **S5** (270 mg, 0.879 mmol), HBTU (367 mg, 0.967 mmol), EtOAc (30 mL) and IPA (20 mL) was maintained at rt for 5 min under nitrogen atmosphere. DIPEA (306 μL, 1.76 mmol) was added dropwise over a period of 20 min. The reaction mixture was stirred vigorously for 16 h. After consumption of the starting material, as judged by TLC analysis, solvent was evaporated *in vacuo* to obtain the crude product. The crude mixture was purified by silica gel chromatography (0% to 20% MeOH:EtOAc) to afford **2** as a white solid (340 mg, 83%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, *J* = 5.1 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 5.1 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.18 (dd, *J* = 7.8, 6.8 Hz, 1H), 3.46-3.39 (m, 4H), 3.16-3.13 (dd, *J* = 13.5, 6.8 Hz, 1H), 3.03–2.95 (m, 4H), 2.90 (s, 3H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.10 (s, 3H); $[\alpha]_D^{25}$ + 36.7 (c = 1.0, MeOH) ^{13}C NMR (100 MHz CD_3OD) δ 170.3, 170.2, 167.0, 166.7, 148.4, 147.7, 136.8, 134.6, 128.7, 125.2, 120.1, 120.0, 53.3, 53.0, 49.5, 40.4, 36.6, 36.2, 34.8, 34.3, 22.3; IR (thin film): 3258, 1653, 1634, 1601, 1537, 1514, 1412, 1315, 1261, 1192, 1144, 1099, 1030, 901, 818, 764, 723, 656, 646, 557, 503; HRMS (ESMS) calculated for $C_{24}H_{29}N_5O_5$ $[M-H]^+$: 468.2169, found: 468.2248.



[Ru(tpy)(Me$_2$bpy)(**1**)]Cl$_2$ (**3**)

[Ru(tpy)(Me$_2$bpy)(2)](Cl)$_2$ (3). In a sealable tube, a solution of **1** (263 mg, 0.640 mmol), $AgPF_6$ (89.0 mg, 0.352 mmol) in acetone:water (12:20 mL) was maintained at rt and argon was bubbled through the solution for 20 min. [Ru(tpy)(Me$_2$bpy)(Cl)](Cl) (100 mg, 0.160 mmol) was added and the mixture and sealed under an inert atmosphere, wrapped in aluminum foil and heated to 50 °C for 16 h, during which time it turned from dark violet to bright orange. After cooling to rt the crude mixture was filtered through celite to remove precipitated silver salts and the filter cake was washed with cold acetone. The solvent was removed *in vacuo* without external heating, resulting in an orange solid. The solid was dissolved in acetone (2 mL) and treated with a saturated solution of tetrabutylammonium chloride in acetone, added dropwise until precipitate formation completed. The red precipitate that was isolated by centrifugation, the acetone was decanted the solid was suspended in acetone, stirred vigorously for 16 h and centrifuged. The supernatant was decanted to provide a red precipitate. The resulting 173 mgs of solid was purified using neutral alumina gel chromatography (0% to 10% MeOH:CH_2Cl_2) to give a red solid after solvent removal, 102 mg R_f = 0.4, neutral alumina, 9:1 CH_2Cl_2:MeOH; The precipitate was dissolved in a small amount of MeOH (0.5 mL) and layered with Et_2O (10 mL). After storing this solution at –20 °C for 16 h, the complex precipitated as a red solid. The solution was decanted and layering was repeated two more times. The solid was isolated by

scraping and dried *in vacuo* to provide compound **3** as a microcrystalline red solid (62 mg, 39%): mp = 180 °C; ^{1}H NMR (400 MHz, D_2O) δ 8.44 (d, *J* = 8.3 Hz, 1H), 8.34–8.25 (m, 4H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.07 (m, 3H), 7.92–7.86 (m, 3H), 7.53–7.49 (m, 2H), 7.39–7.31 (m, 4H), 7.25–7.22 (m, 2H), 7.18–7.13 (m, 3H), 6.76–6.71 (m, 3H), 4.98 (t, *J* = 7.5 Hz, 1H), 3.27–3.12 (m, 2H), 3.03 (d, *J* = 2.0 Hz, 1H), 3.02 (d, *J* = 2.0 Hz, 1H), 3.00–2.94 (m, 1H), 2.89–2.85 (m, 1H), 2.83 (s, 3H), 2.78 (s, 3H), 2.52 (t, *J* = 5.9 Hz, 2H), 1.84 (s, 3H), 1.33 (s, 3H); IR (thin film): 3362, 3202, 3024, 2938, 2332, 1638, 1601, 1444, 1388, 1283, 1238, 1120, 893, 773, 703, 521, 482, 443; HRMS (ESMS) calcd for $C_{49}H_{49}N_9O_4Ru$ $[M]^{2+;}$ 464.6476 found: 464.6476; UV-vis λ_{max}= 474 (ε = 9,700 $M^{-1}cm^{-1}$); Anal. Calcd for $C_{49}H_{49}Cl_2N_9O_4Ru$ (**3**·5 H_2O) C, 53.99; H, 5.46; N, 11.57. Found: C, 53.91; H, 5.30; N, 11.71.



[Ru(tpy)(Me$_2$bpy)(**2**)]Cl$_2$ (**4**)

[Ru(tpy)(Me$_2$bpy)(4)](Cl)$_2$ (4). Compound **4** was prepared using the same procedure used to prepare **3**, starting from **2** (44 mg, 0.0941 mmol), $AgPF_6$ (26 mg, 0.103 mmol) [Ru(tpy)(Me$_2$bpy)(Cl)](Cl) (28 mg, 0.047 mmol) and acetone:water (4.2:7 mL). The complex was obtained as a microcrystalline red solid (18 mg, 36%): R_f = 0.4, neutral alumina, 9:1 CH_2Cl_2:MeOH; mp = 140 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (d, *J* = 8.3 Hz, 1H), 8.67–

8.64 (m, 2H), 8.60 (t, *J* = 8.3 Hz, 2H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.28 (t, *J* = 7.8 Hz, 1H), 8.24–8.20 (m, 2H), 8.17–8.11 (m, 3H), 7.79–7.72 (m, 2H), 7.62–7.59 (m, 2H), 7.56 (d, *J* = 5.9 Hz, 1H), 7.52 (d, *J* = 5.9 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.05–6.98 (m, 3H), 4.99 (dd, *J* =9.8, 4.9 Hz, 1H), 3.47 (td, *J* = 7.2, 3.2 Hz, 2H), 3.26 (d, *J* = 2.0 Hz, 1H), 3.24 (d, *J* = 2.0 Hz, 1H), 2.98–2.90 (m, 4H), 2.85 (s, 3H), 2.81–2.71 (m, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.51 (s, 3H); IR (thin film): 3372, 3242, 3053, 1638, 1603, 1535, 1514, 1445, 1412, 1317, 1250, 1121, 1055, 895, 775, 735, 642, 505, 465, 424; HRMS (ESMS) calcd for $C_{51}H_{52}N_{10}O_5Ru$ $[M]^{2+}$; 493.1583 found: 493.1599; UV-vis λ_{max}= 475 (ε = 10,400 $M^{-1}cm^{-1}$); Anal. Calcd for $C_{51}H_{52}Cl_2N_{10}O_5Ru$ (**4**·8 H_2O) C, 51.00; H, 5.71; N, 11.66. Found: C, 50.93; H, 5.37; N, 11.86.

(2*S*,3*S*)-*N*^{2}-((*R*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)-*N*^{3}-(2-(pyridin-2-yl)ethyl)oxirane-2,3-dicarboxamide (CLIK-148). A solution of **S2** (459 mg, 1.50 mmol), HOBT (223 mg, 1.65 mmol), EDCI (316 mg, 1.63 mmol) and CH_2Cl_2 (10 mL) was cooled to 0 °C under nitrogen atmosphere. A solution of 2-(pyridin-2-yl)ethan-1-amine (0.198 mL, 1.65 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 10 min while maintaining the temperature below 5 °C. After consumption of the starting material, as judged by TLC analysis, the solvent was evaporated *in vacuo* to give a crude mixture that was purified by silica gel chromatography (0% to 10% MeOH:EtOAc) to afford **CLIK-148** as a light yellow oil (94 mg, 15%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 3.91 Hz, 1H), 7.61 (td, *J* = 7.8, 2.0 Hz, 1H), 7.31–7.22 (m, 3H), 7.18–7.11 (m, 4H), 7.07 (t, *J* = 5.4 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.09 (td, *J* = 8.2, 6.4 Hz, 1H), 3.72–3.60 (m, 2H), 3.35 (d, *J* = 2.0 Hz, 1H), 3.28 (d, *J* = 2.0 Hz, 1H), 3.01-2.94 (m, 4H), 2.88 (s, 3H), 2.69 (s, 3H); $[\alpha]D^{25}$ + 31 (c = 0.53, $CHCl_3$) ^{13}C NMR (100 MHz CD_3OD) δ 170.4, 165.6, 165.2, 159.1, 149.2, 136.7, 135.6, 129.4, 128.5, 127.3, 123.4, 121.7, 54.8, 54.7, 49.4, 39.4, 38.0, 36.8, 36.3, 35.6; IR (thin film): 3279, 3069, 3040, 2931, 2159, 2031, 1977, 1629, 1593, 1526, 1476, 1436, 1418, 1284, 1237, 1149, 1052, 894, 773, 729, 700, 668, 505; HRMS (ESMS) calcd for $C_{22}H_{26}N_4O_4$ 411.1954 $[M+H]^+$, found : 411.2014.

(2*S*,3*S*)-*N*^{2}-(4-acetamidophenethyl)-*N*^{3}-((*S*)-1-(dimethylamino)-1-oxo-3-phenylpropan-2-yl)oxirane-2,3-dicarboxamide (CLIK-181). A mixture of **S6** (313 mg, 1.07 mmol), H-Phe-NMe_2·TFA (328 mg, 1.07 mmol), HBTU (447 mg, 1.18 mmol), EtOAc (30 mL) and IPA (20 mL) was maintained at rt for 5 min under nitrogen atmosphere. DIPEA (373 μL, 2.14 mmol) was added dropwise over a period of 20 min. The reaction mixture was stirred vigorously for 16 h. After consumption of the starting material, as judged by TLC analysis, solvent was evaporated *in vacuo* to obtain crude product. The crude product was purified by silica gel chromatography (0% to 20% MeOH:EtOAc) to afford **CLIK-181** as a white solid (338 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 7.8 Hz, 2H), 7.31−7.27 (m, 2H), 7.25−7.20 (m, 3H), 7.16 (d, *J* = 7.8 Hz, 2H), 5.06 (m, 1H), 3.47 (s, 1H), 3.43−3.39 (m, 3H), 3.02 (m, 1H), 2.95 (m, 1H), 2.84 (s, 3H), 2.81 (s, 3H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.10 (s, 3H); $[\alpha]D^{25}$ + 57.4. (c = 1.05, MeOH) ^{13}C NMR (100 MHz CD_3OD) δ 171.3, 170.2, 167.1, 166.6, 136.8, 136.2, 134.6, 129.0, 128.7, 128.1, 126.7, 120.1, 53.3, 53.0, 50.5, 40.4, 37.7, 36.0, 34.7, 34.3, 22.3; IR (thin layer): 3327, 3268, 3206, 2150, 2030, 1979, 1685, 1636, 1539, 1516, 1452, 1399, 1315, 1263, 1195, 900, 822, 768, 751, 702, 568, 503, 413; HRMS (ESMS) calcd for $C_{25}H_{30}N_4O_5$ 467.2216 $[M+H]^+$, found : 467.2290.

Photochemical studies

Photochemical experiments were performed with a 150 W Xe arc lamp (USHIO) housed in a MilliArc lamp housing unit that is powered by an LPS-220 power supply and an LPS-221 igniter (PTI). A 455 nm long pass filter (CVI Melles Griot) was used for the photolysis experiments. A 500 nm bandpass filter (Thorlabs) together with a 455 nm long-pass filter were used for the ligand exchange quantum yield experiments. For the UV-Vis experiments, the sample was dissolved in CH_3CN and placed in a 1 × 1 cm quartz cuvette, and the electronic

absorption spectra were recorded at various time points during irradiation. The photon flux of the lamp was determined using potassium tris(ferrioxalate) actinometer (λ_{irr} = 500 nm, flux = 2.56 × 10^{-8} mol photons/min).[6] The changes in absorption at very early times were monitored in calculating the quantum yields. For NMR studies, the samples were dissolved in D_2O and placed in an NMR tube, and the ^{1}H NMR was analyzed at various time intervals during irradiation. The ^{1}H NMR spectra were collected using a Bruker 400 MHz DPX spectrophotometer. Enzyme assays with photolysis were conducted using a 250 W Tungsten Halogen lamp (Osram Xenophot HLX) powered by a 24 V power source. The irradiation wavelength was selected by placing a longpass filter (395 nm cutoff) between the lamp and the sample, along with a 10 cm water cell to absorb infrared light.

Part D. ^{1}H, ^{13}C NMR, HRMS spectra and for new compounds

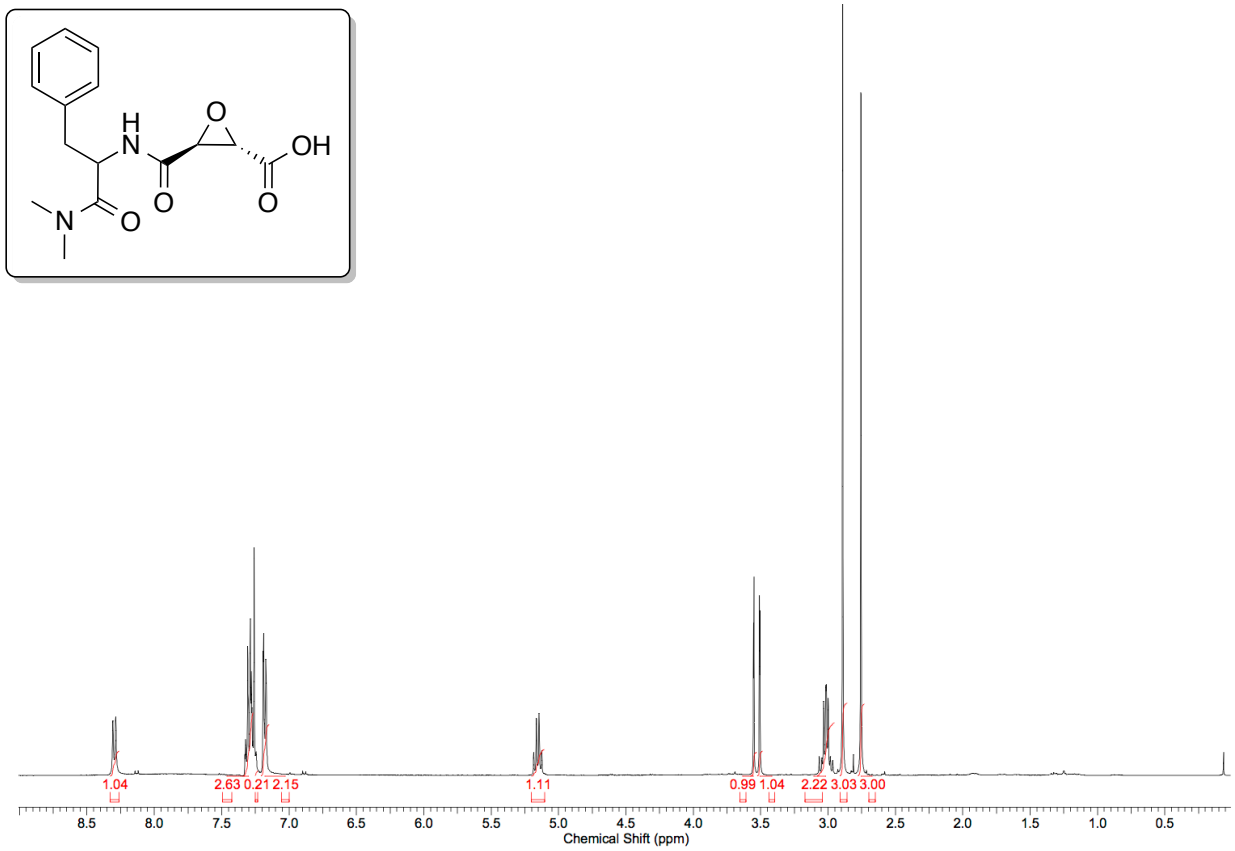


Figure S1: ^{1}H NMR ($CDCl_3$) for **S2**

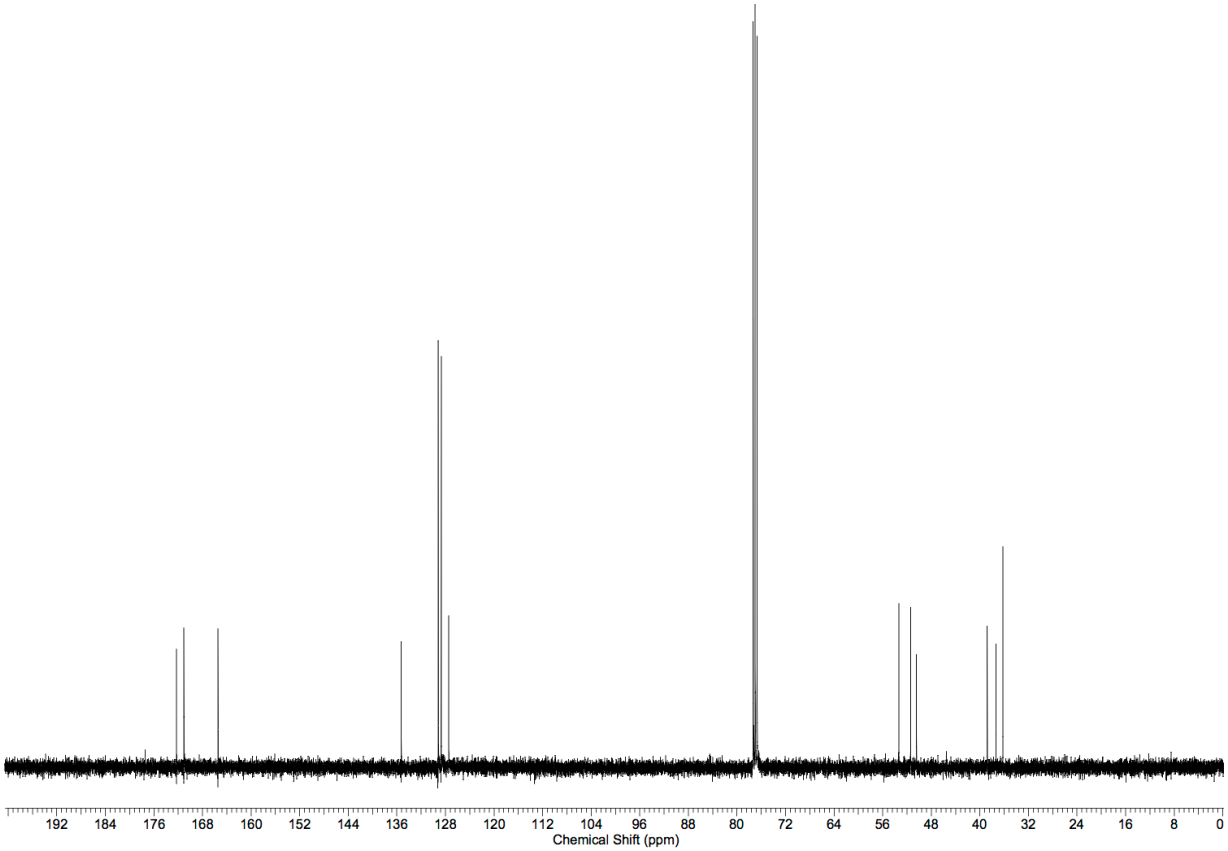


Figure S2: ^{13}C NMR ($CDCl_3$) for **S2**

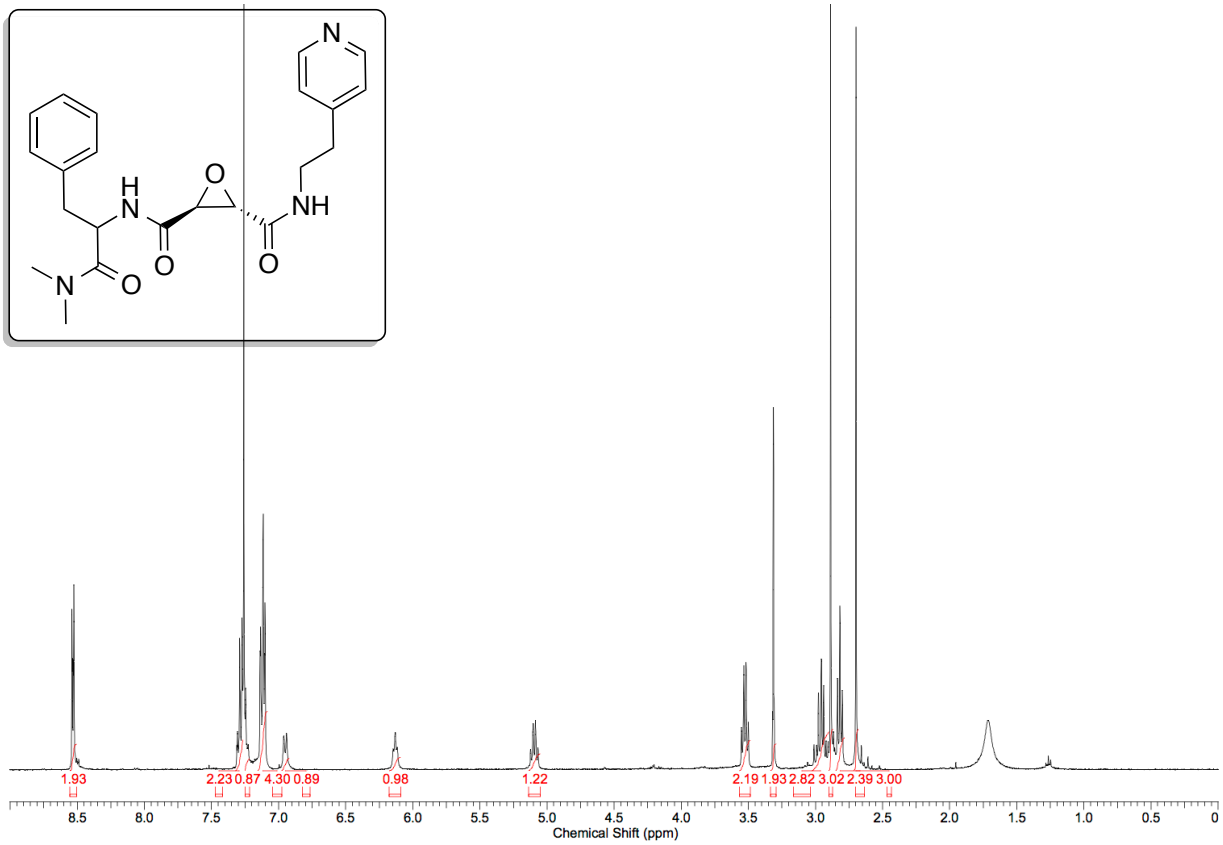


Figure S3: ^{1}H NMR ($CDCl_3$) for **1**

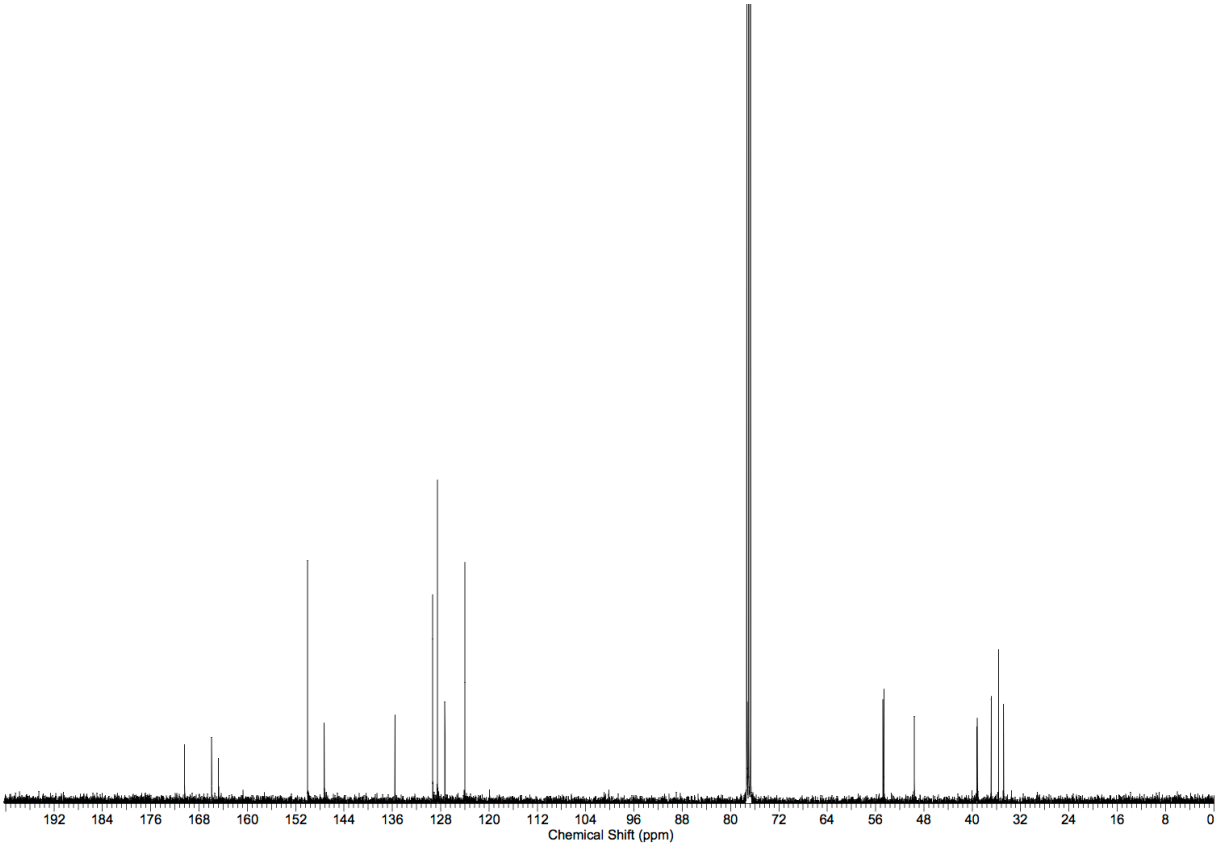


Figure S4: ^{13}C NMR ($CDCl_3$) for **1**

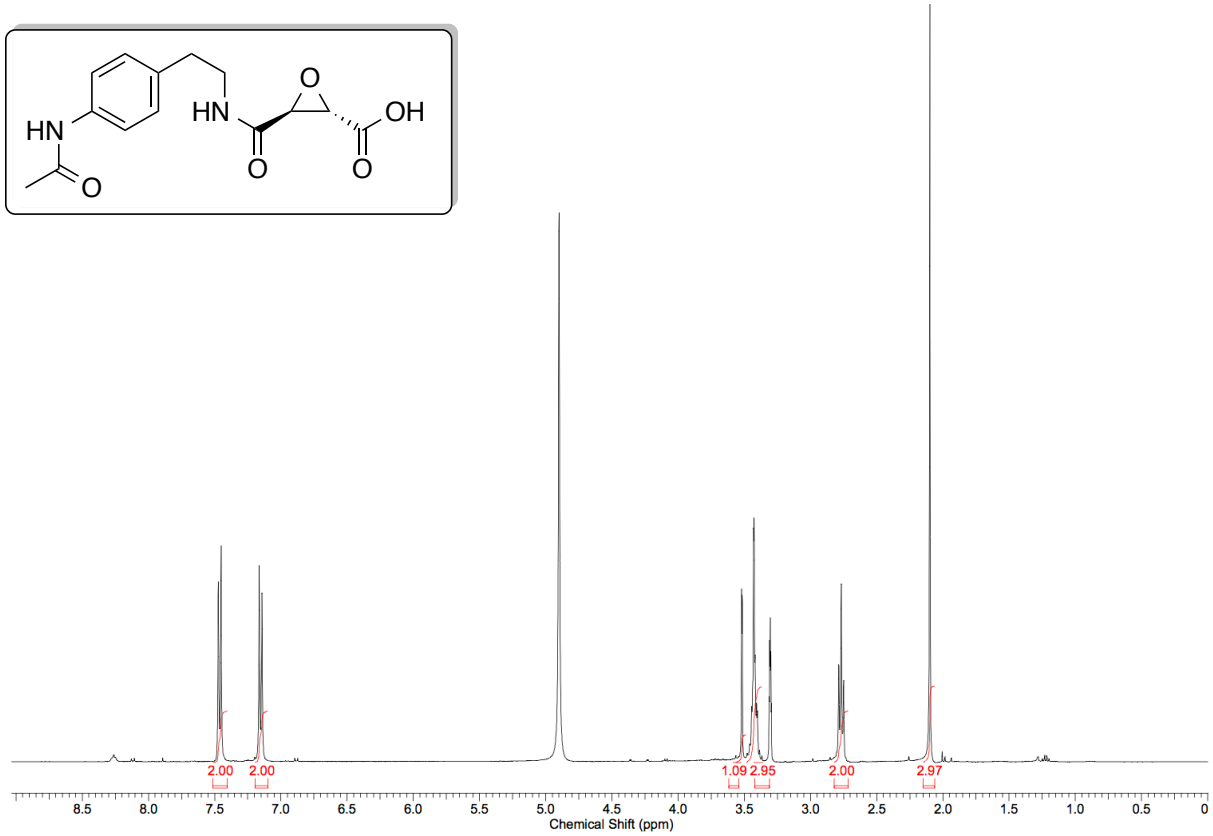


Figure S5: ^{1}H NMR (CD_3OD) for **S6**

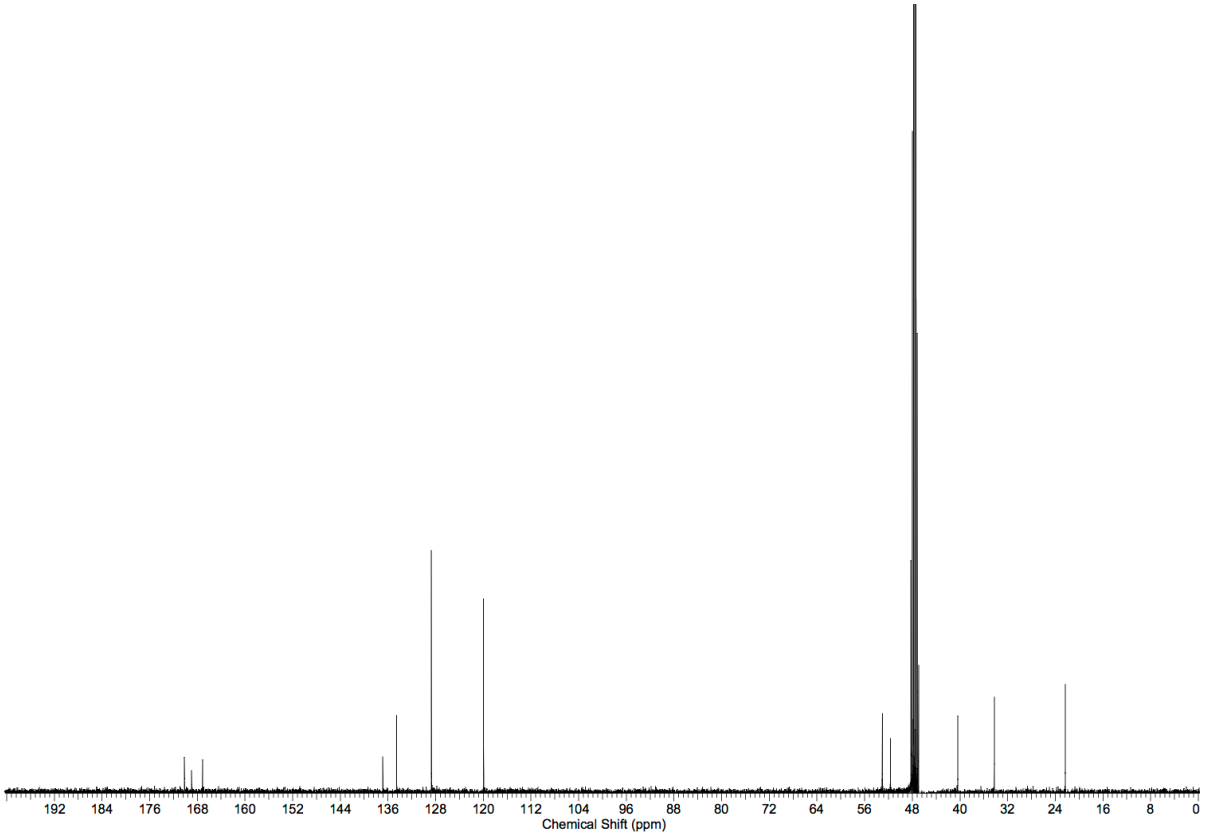


Figure S6: ^{13}C NMR (CD_3OD) for **S6**

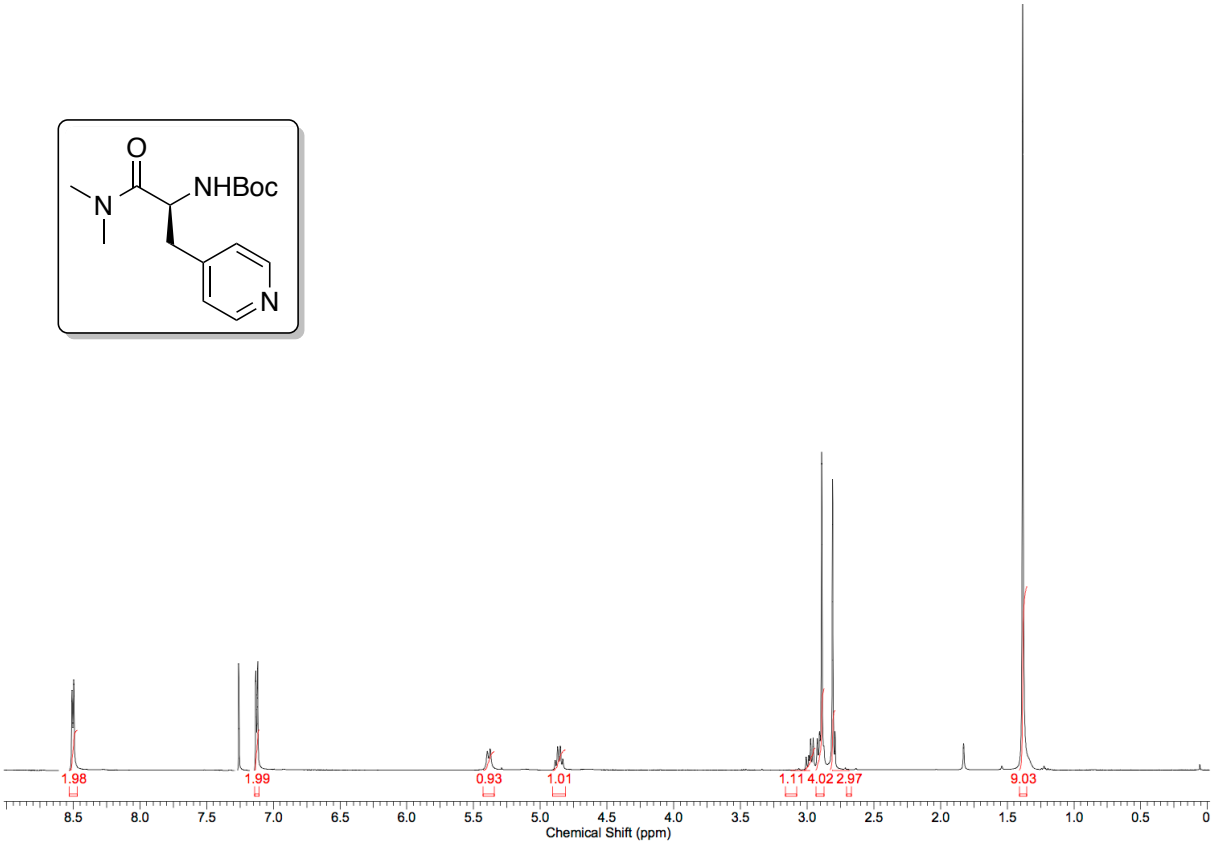


Figure S7: ^{1}H NMR ($CDCl_3$) for **S4**

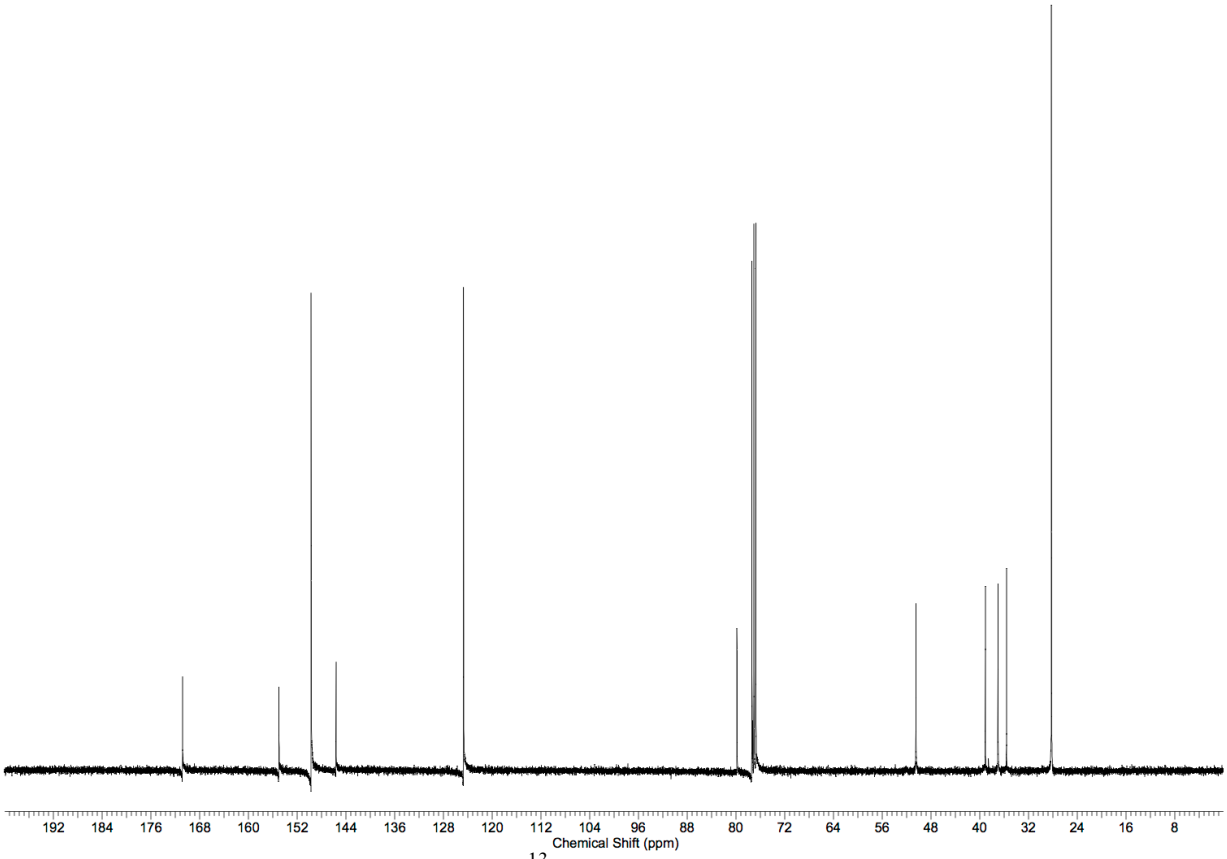


Figure S8: ^{13}C NMR ($CDCl_3$) for **S4**

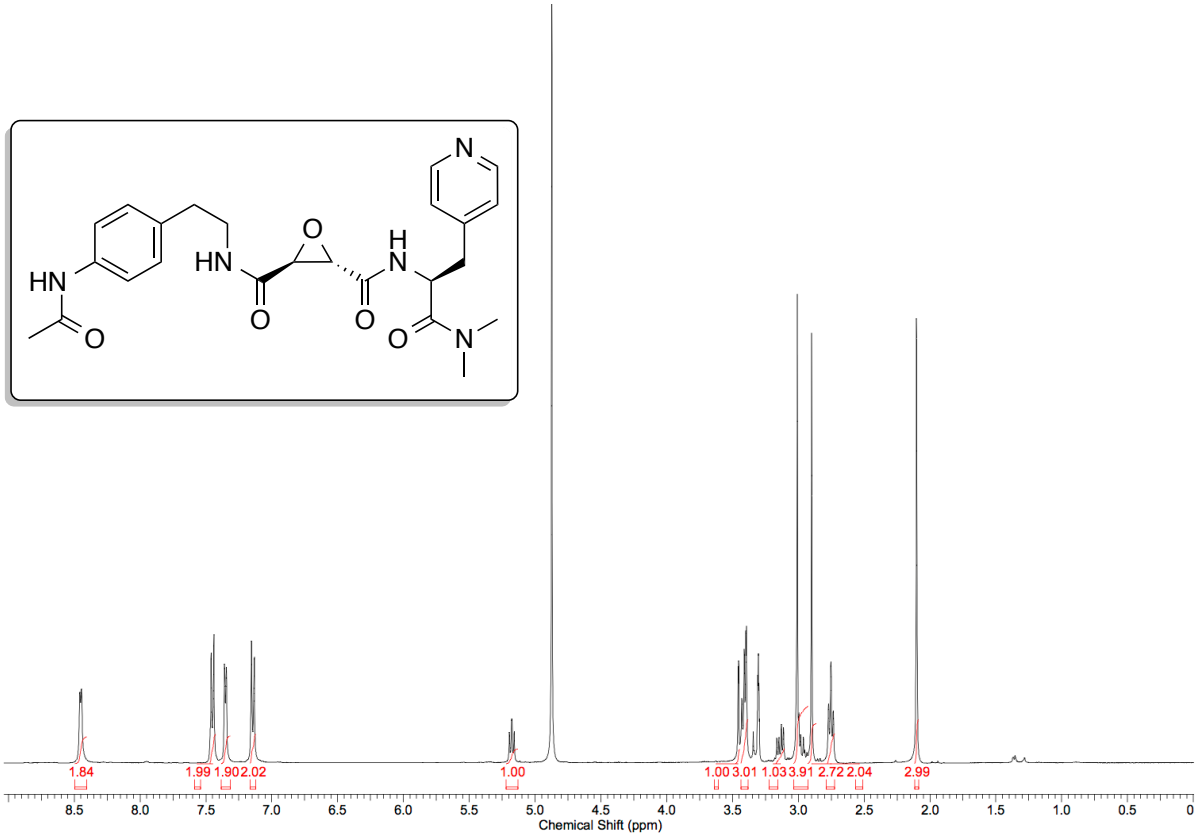


Figure S9: ^{1}H NMR (CD_3OD) for **2**

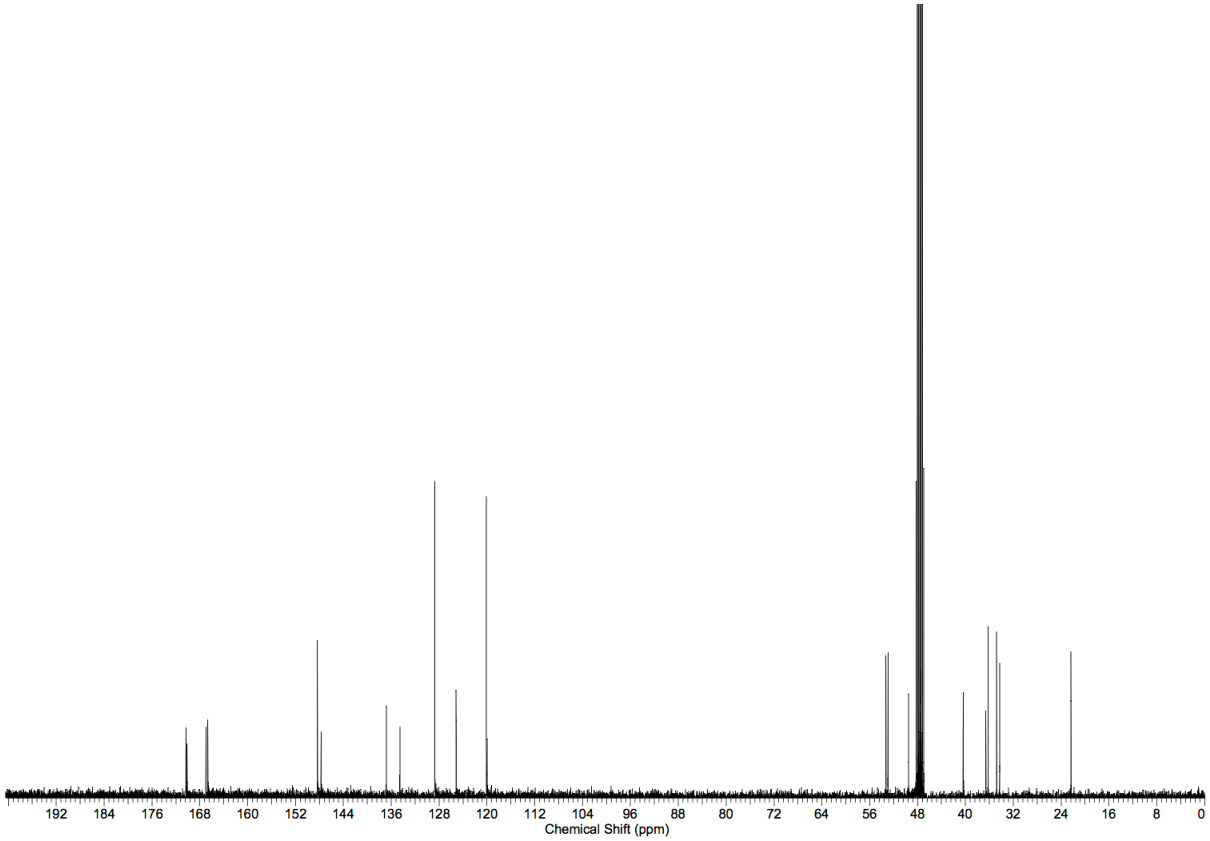


Figure S10: ^{13}C NMR (CD_3OD) for **2**

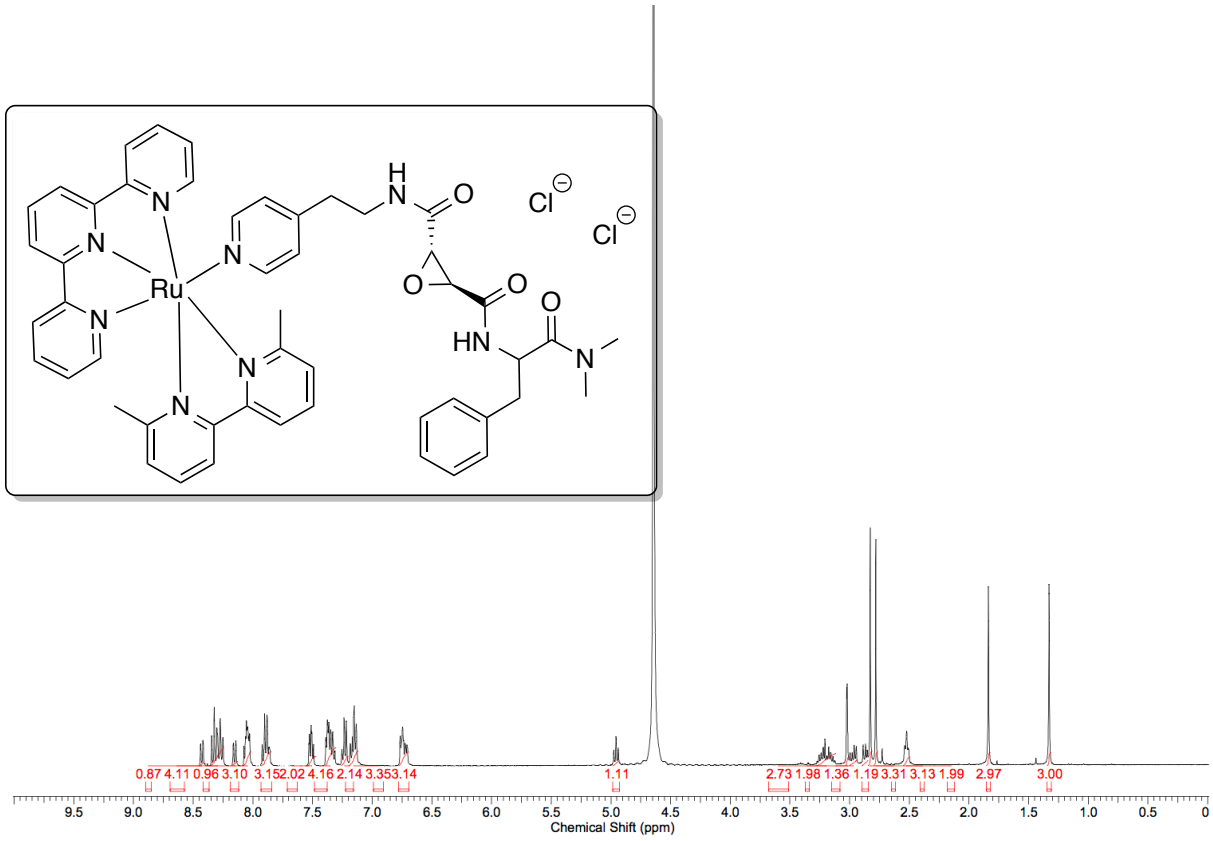


Figure S11: ^{1}H NMR (D_2O) for **3**

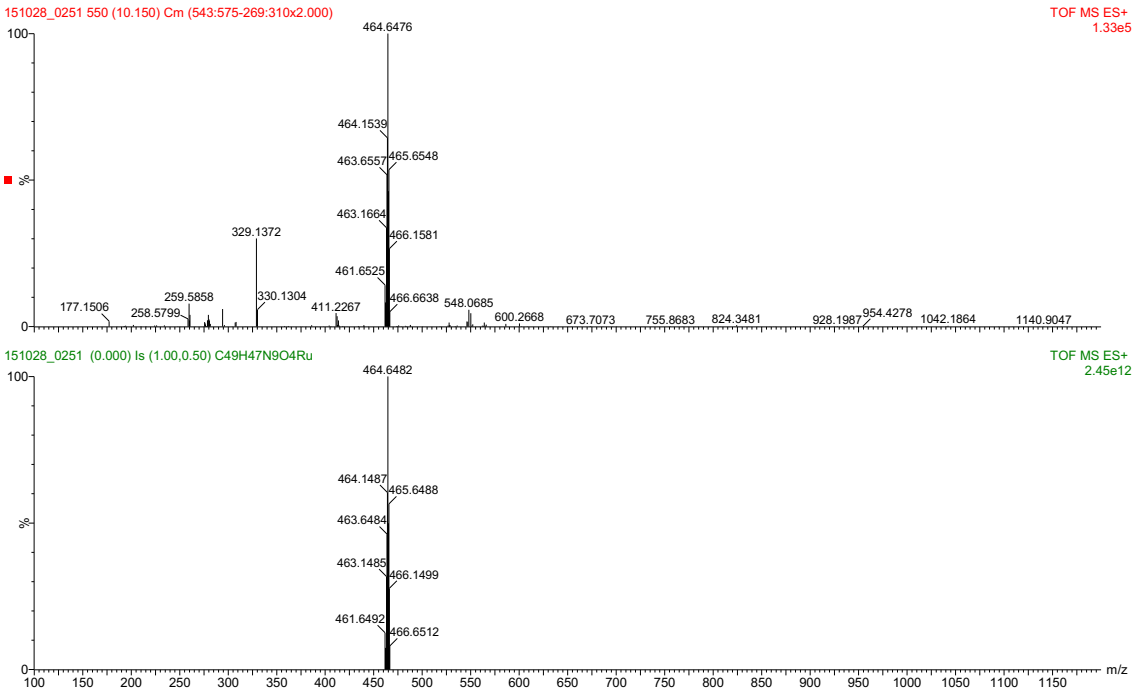


Figure S12: Observed (top) and calculated (bottom) HRMS ESMS spectra of **3**

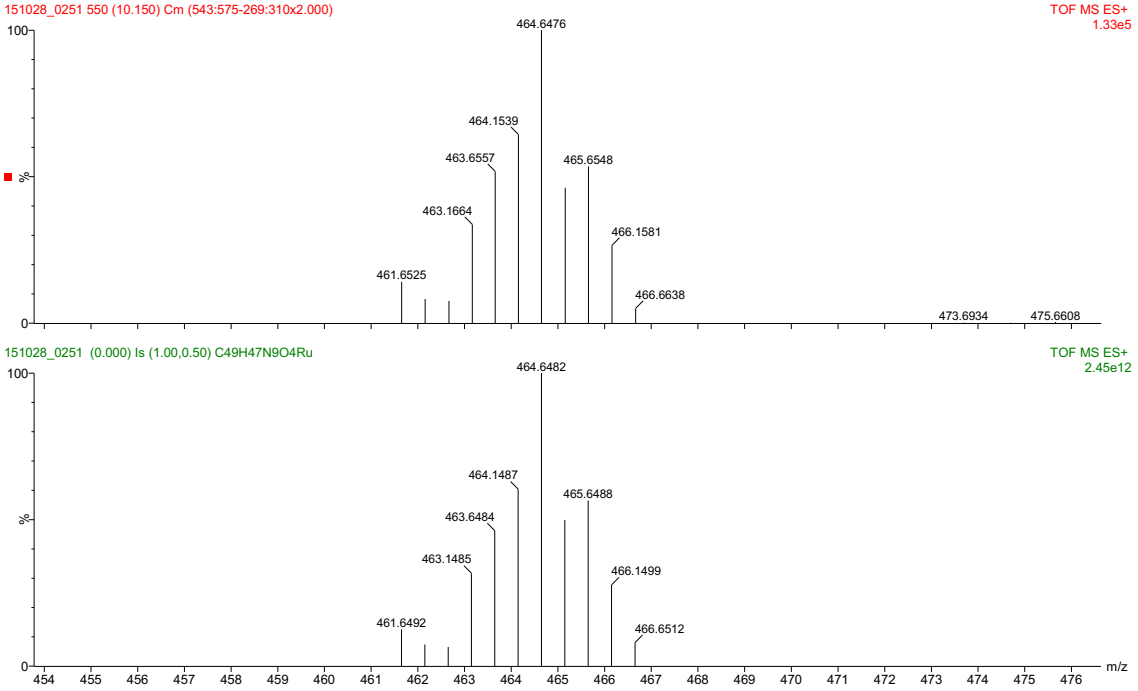


Figure S13: Expansion of HRMS (ESMS) spectrum of **3** showing observed (top) and calculated (bottom) isotope pattern for major peak with *m/z* = 465

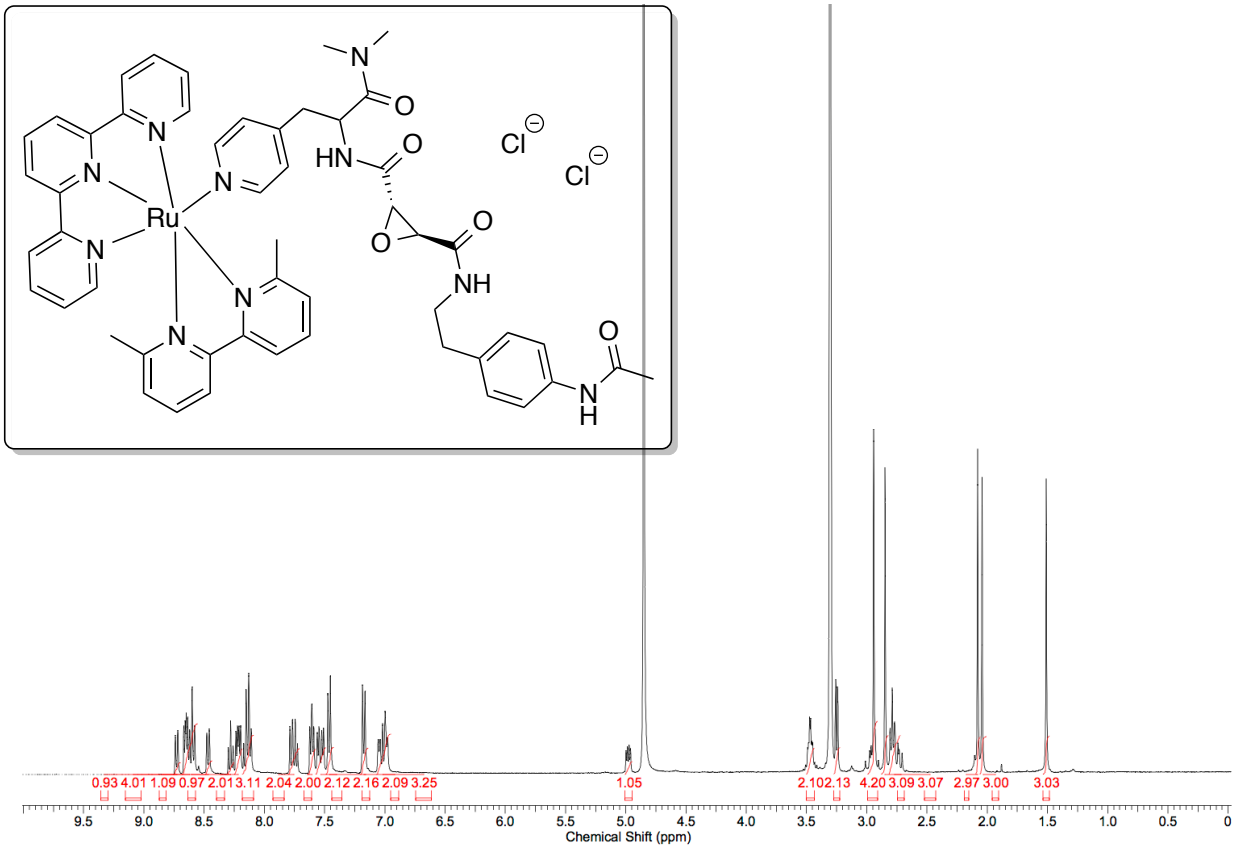


Figure S14: ^{1}H NMR (CD_3OD) for **4**

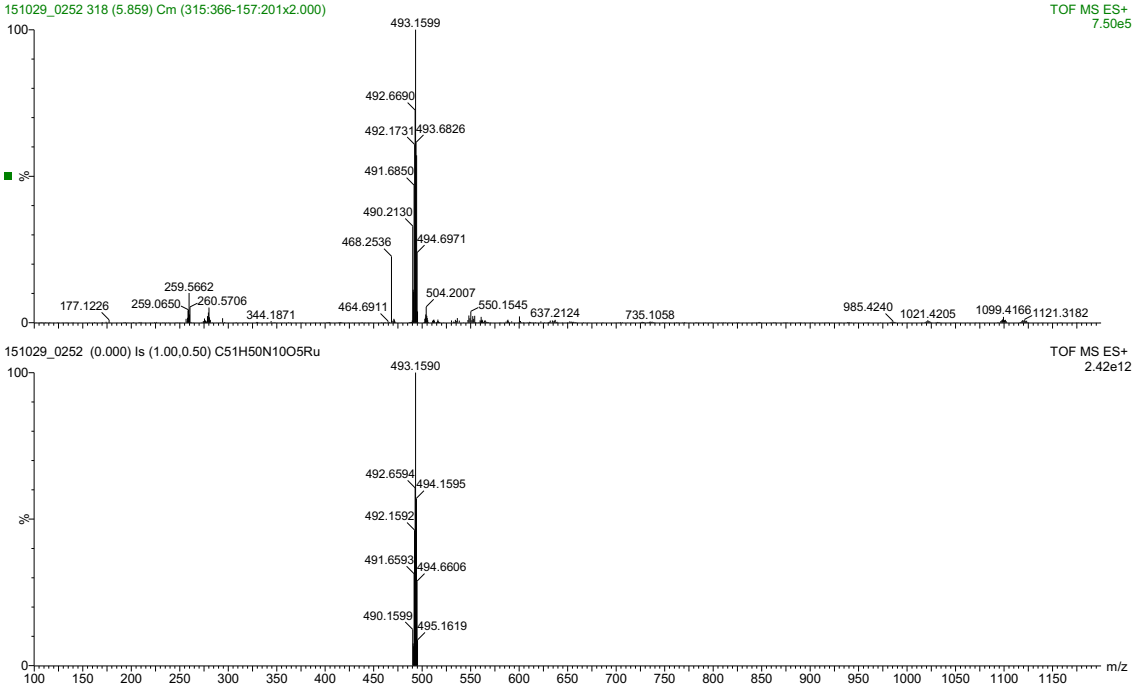


Figure S15: Observed (top) and calculated (bottom) HRMS ESMS spectra of **4**

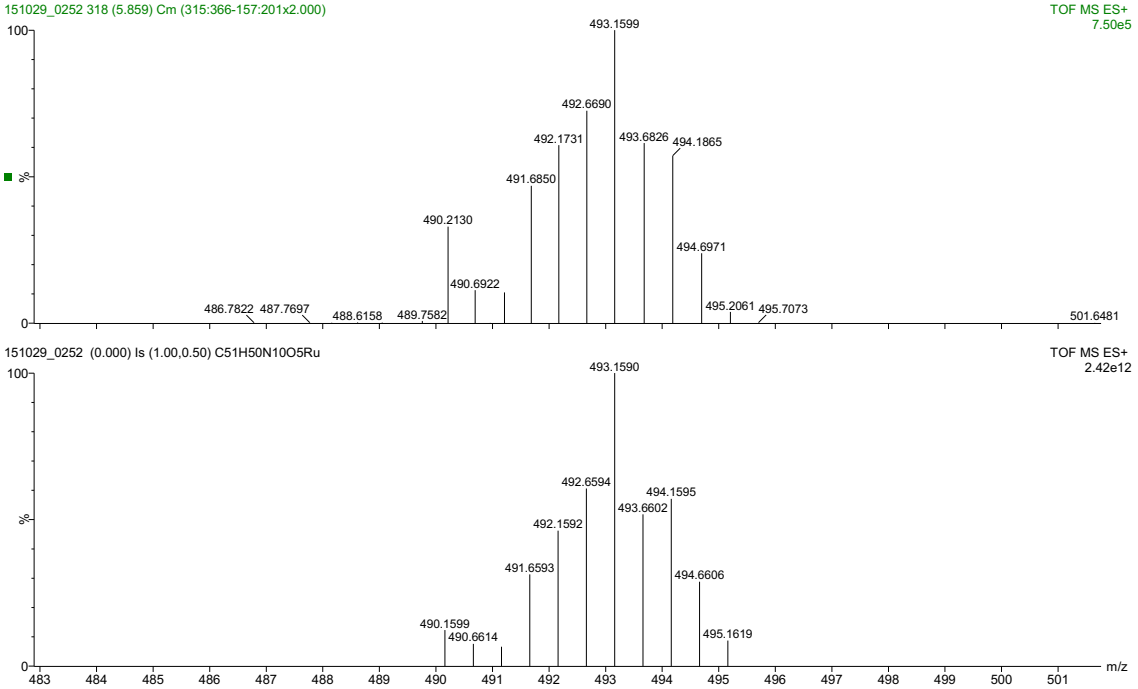


Figure S16: Expansion of HRMS (ESMS) spectrum of **4** showing observed (top) and calculated (bottom) isotope pattern for major peak with *m/z* = 493

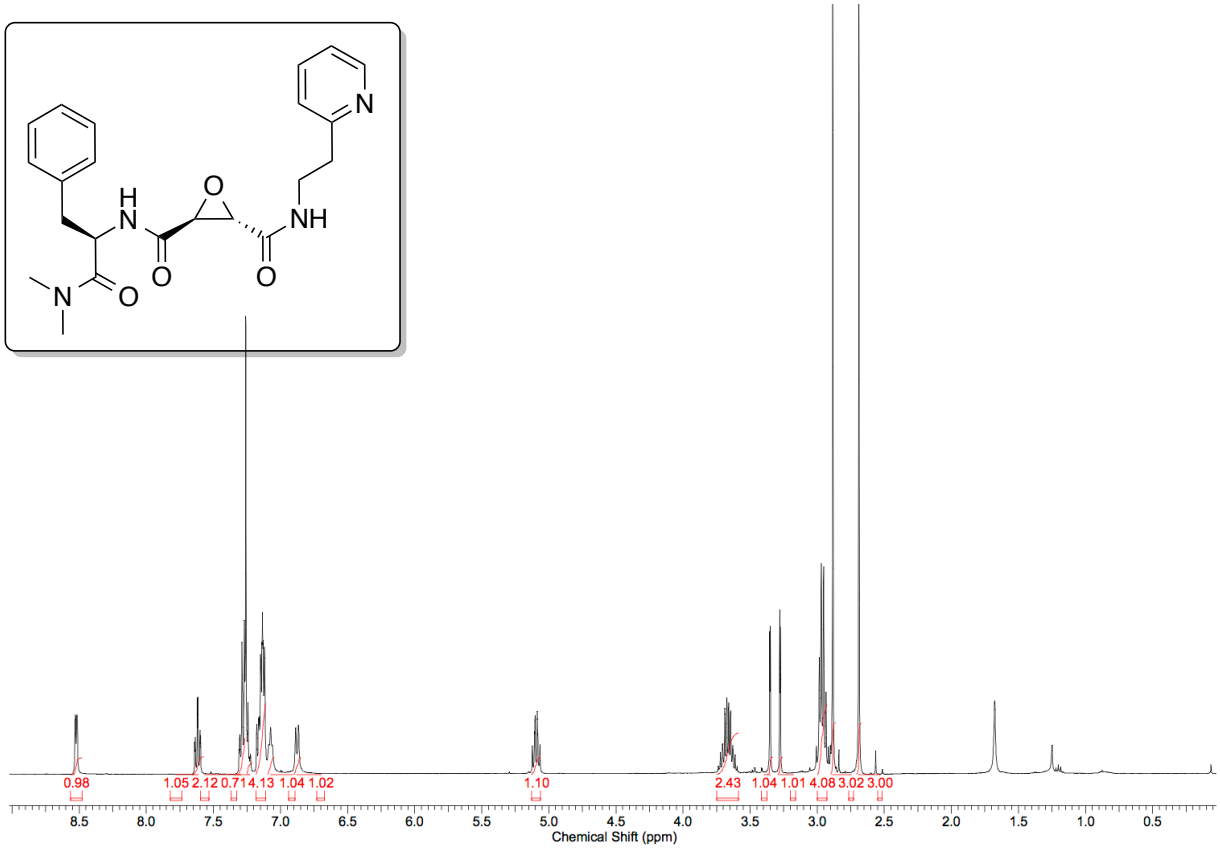


Figure S17: ^{1}H NMR ($CDCl_3$) for **CLIK-148**

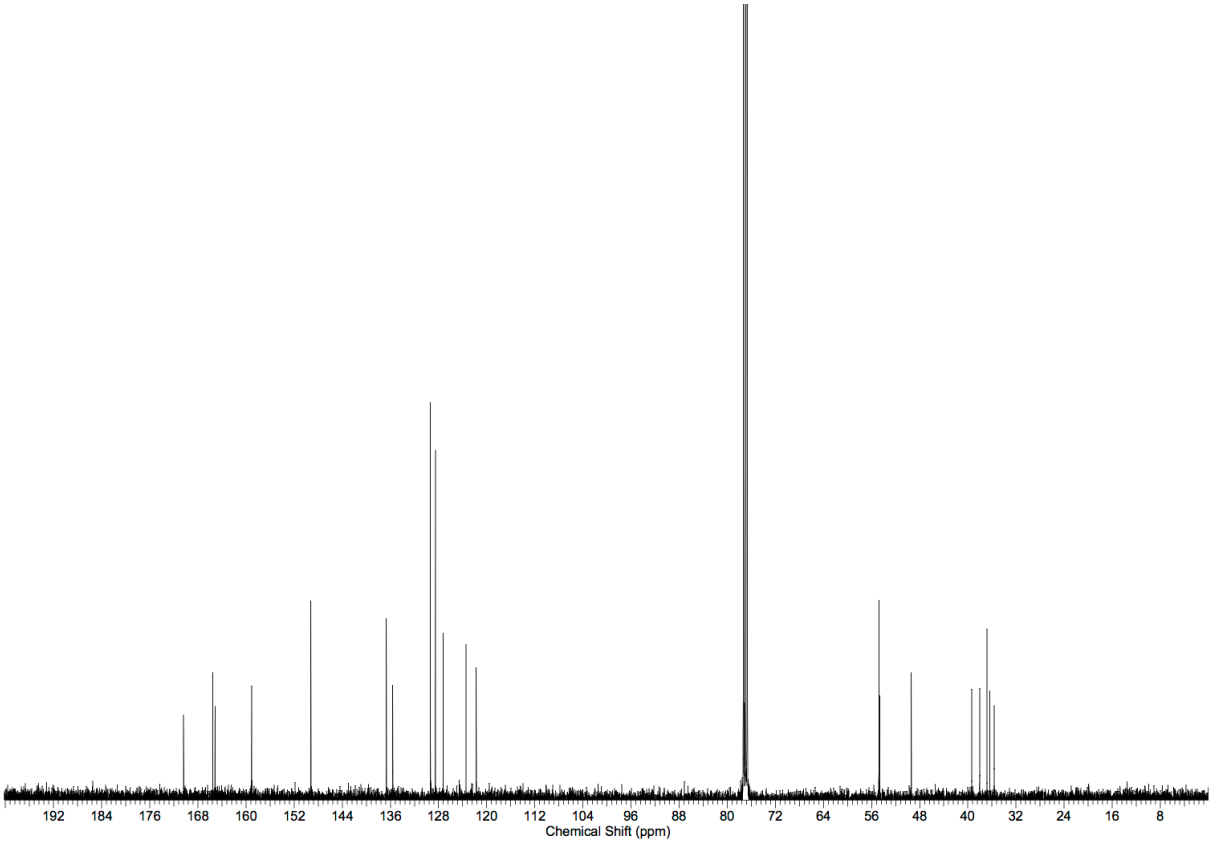


Figure S18: ^{13}C NMR ($CDCl_3$) for **CLIK-148**

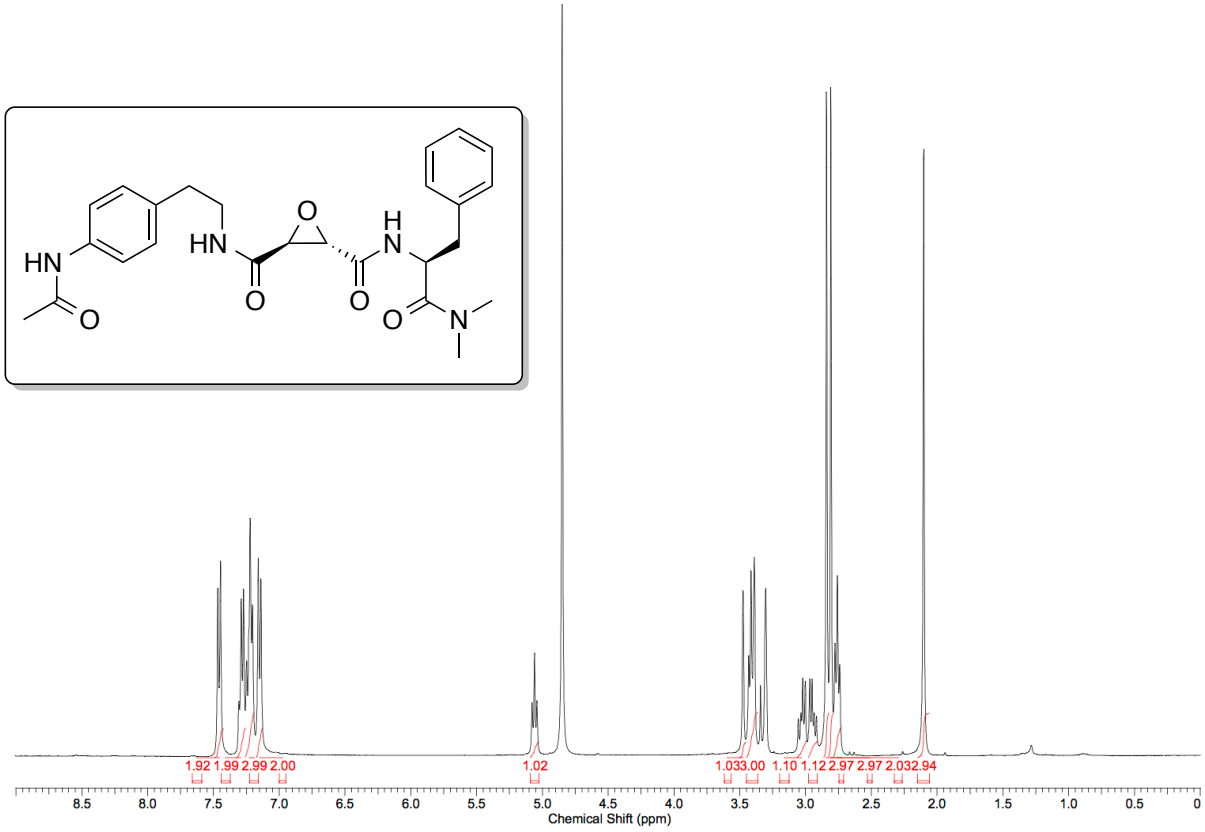


Figure S19: ^{1}H NMR (CD_3OD) for **CLIK-181**

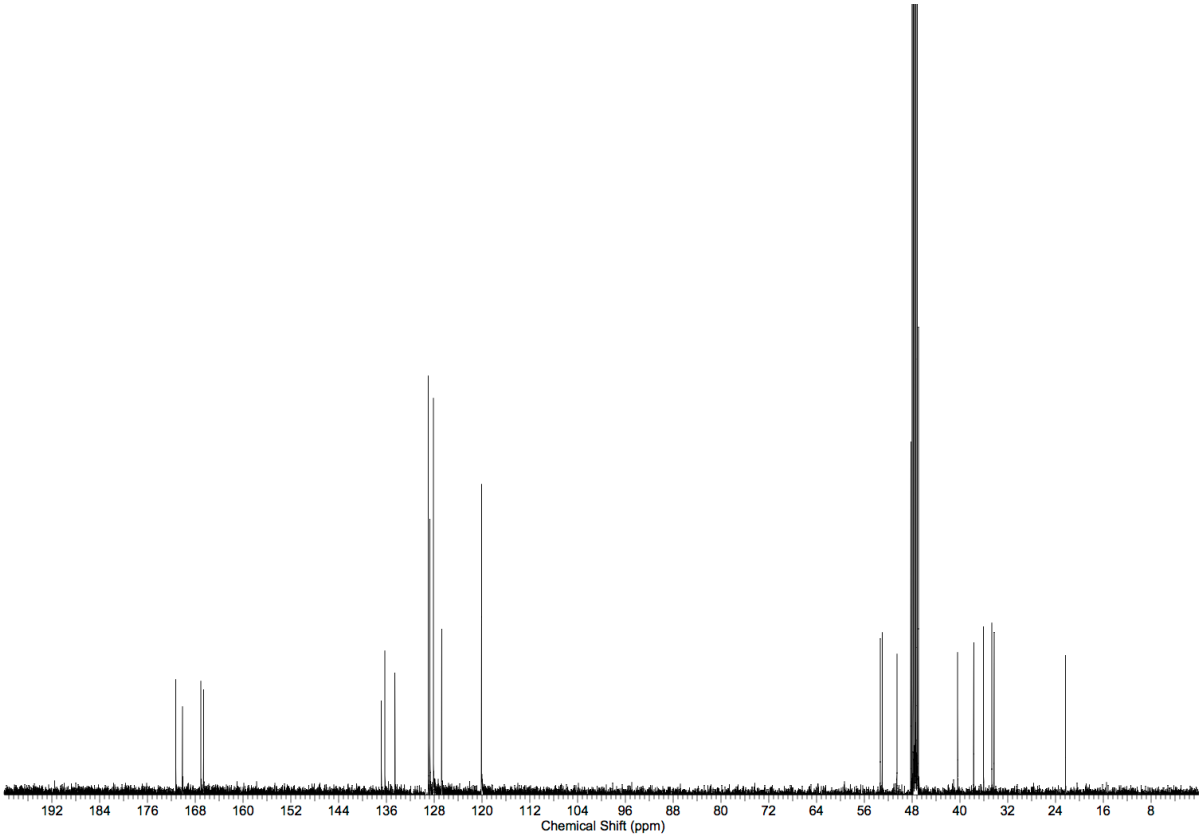


Figure S20: ^{13}C NMR (CD_3OD) for **CLIK-181**

Part E. Enzyme Inhibition Studies

Progress curves with cathepsin L and 1-4

Progress curves for hydrolysis of Z-Phe-Arg-AMC by cathepsin L were collected in the presence of inhibitors **1-4** at 25 °C in the dark. A 11.1 μM stock solution of cathepsin L was prepared by diluting commercially available human cathepsin L (20 mM malonate, pH 5.5, 1 mM EDTA, 400 mM NaCl) in assay buffer. The cathepsin L stock was diluted 694-fold in assay buffer (400 mM sodium acetate, 4 mM EDTA, 0.01% Triton-X 100, pH 5.5) containing 32 mM DTT, and activated for 30 min at 25 °C. Inhibitors were prepared as < 1% DMSO stock solutions in assay buffer and plated (Corning 96-well clear bottom black polystyrene TC-treated microplates), 25 μL per well, to achieve final concentrations ranging from 0.1-25 μM. Assay buffer (25 μL) was added as a blank. The substrate Z-Phe-Arg-AMC in assay buffer (20 μM, 50 μL) was added to each well, to achieve a final concentration of 10 μM. Using a multichannel pipet, activated enzyme (25 μL) was added to each well, to achieve a final enzyme concentration of 4 nM, and kinetic measurements were performed immediately by fluorometric detection of the hydrolysis product AMC, using λ_{ex} = 360 nm and λ_{em} = 430 nm, 5 flashes per well, every 30 sec for 15 min. Raw data were fit to a competitive, two-step irreversible inhibition model (Figure S21) using Dynafit. An example script used in the fitting is shown in Figure S22, individual fits for **1-4** are shown in Figures S23-26.

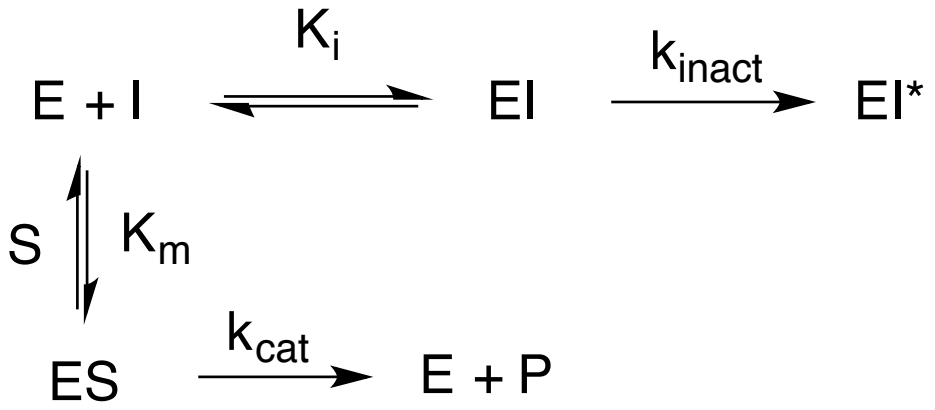


Figure S21. Model for competitive, irreversible inactivation of cathespin L by epoxysuccinyl inhibitors with reversible formation of the enzyme inhibitor complex (EI) and irreversible formation of the covalent complex (EI*).

```
            Cathepsin L:
;_____________________________________________________________________________
[task]
  data = progress
  task = fit
  model = two steps ?
[mechanism]
  E + S <==> E.S    :   ka.S  kd.S
  E.S ---> E + P    :   kd.P
  E + I <==> E.I    :   ka.I  kd.I
  E.I --> E-I       :   k.inact
[constants]
  ka.S = 10, kd.S  = 30 ?
  kd.P = 10 ?
  ka.I = 1 ?, kd.I = 0.1 ?
  k.inact = 0.1 ?
[concentrations] | E = 0.004 ?, S = 10 ?
[responses]
  P = 800 ? (500 .. 2000)
[progress]
  directory  ./CatL/012116/MH-181/data
  sheet     data-2.csv
  column 2 | conc I = 0.000 | offset auto ? | label I = 0
  column 3 | conc I = 0.1 ? (0.08 .. 0.12) | offset auto ? | label I = 100nm
  column 4 | conc I = 0.5 ? (0.4 .. 0.6) | offset auto ? | label I = 500nm
  column 5 | conc I = 1.0 ? (0.8 .. 1.2) | offset auto ? | label I = 1.0um
  column 6 | conc I = 1.5 ? (1.2 .. 1.8) | offset auto ? | label I = 1.5um
  column 7 | conc I = 2.0 ? (1.6 .. 2.4) | offset auto ? | label I = 2.0um
  column 8 | conc I = 2.5 ? (2.0 .. 3.0)| offset auto ? | label I = 2.5um

[settings] {Constraints} | Concentrations = 0.01
[output]
  directory  ./CatL/012116/MH-181/output/2h
;_____________________________________________________________________________
[task]
  data = progress
  task = fit
  model = equilibrium ?
[constants]
  ka.S = 10, kd.S  = 30 ?
  kd.P = 10 ?
  ka.I = 10, kd.I = 0.1 ?
  k.inact = 0.1 ?

[end]
;_____________________________________________________________________________
;_____________________________________________________________________________
```

Figure S22. Example of Dynafit script used in fitting progress curve for inhibitor **2**.

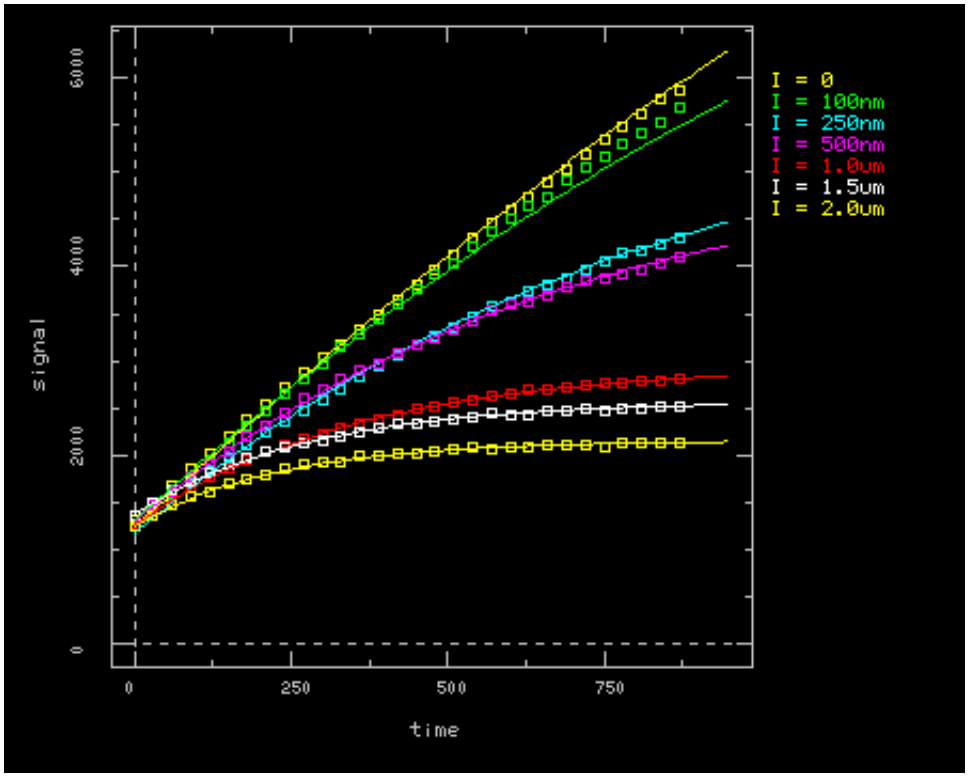


Figure S23. Experimental data (squares) vs. estimated fit (lines) for **1** (0-2.0 μM) using the competitive, two-step irreversible inhibition model shown in Figure S21.

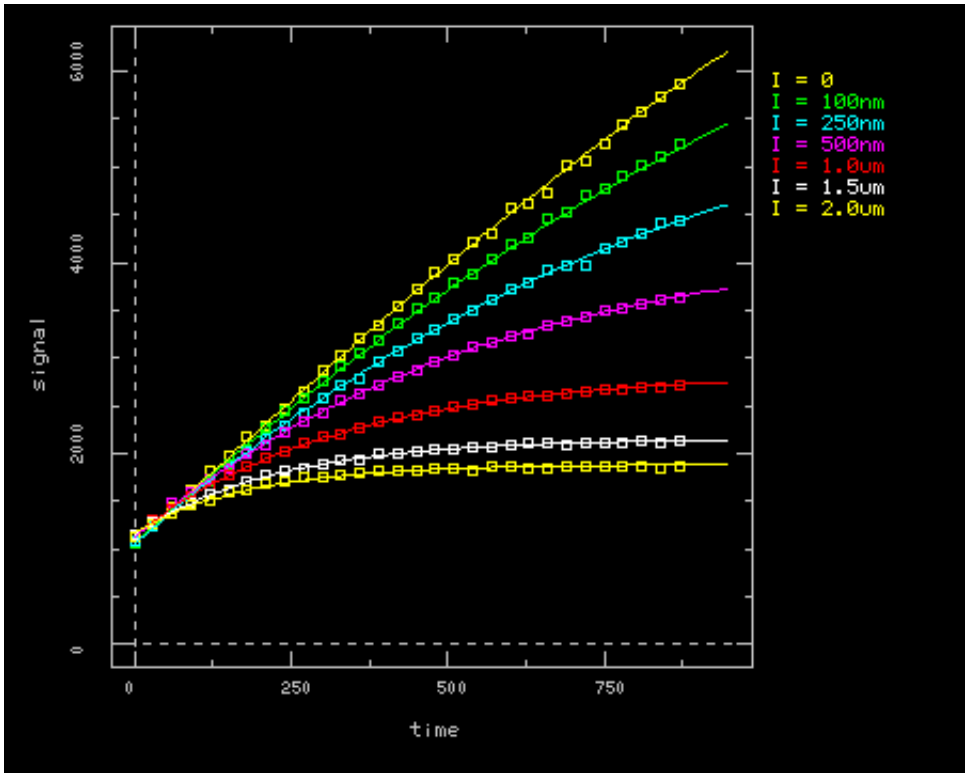


Figure S24. Experimental data (squares) vs. estimated fit (lines) for **3** (0-2.0 μM) using the competitive, two-step irreversible inhibition model shown in Figure S21.

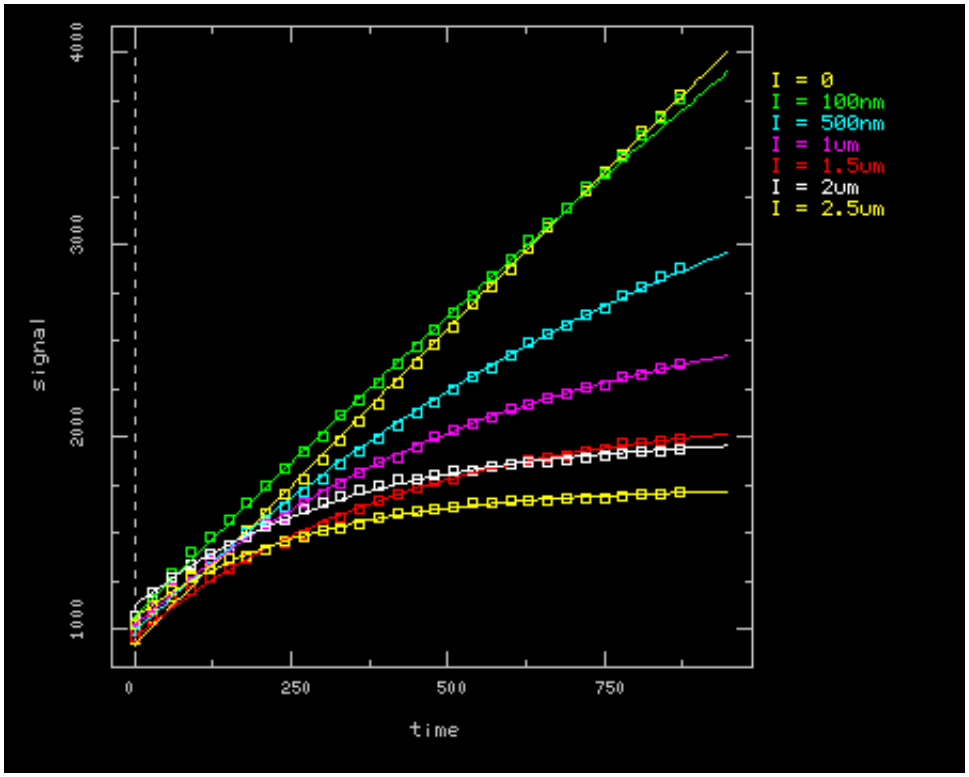


Figure S25. Experimental data (squares) vs. estimated fit (lines) for **2** (0-2.5 μM) using the competitive, two-step irreversible inhibition model shown in Figure S21.

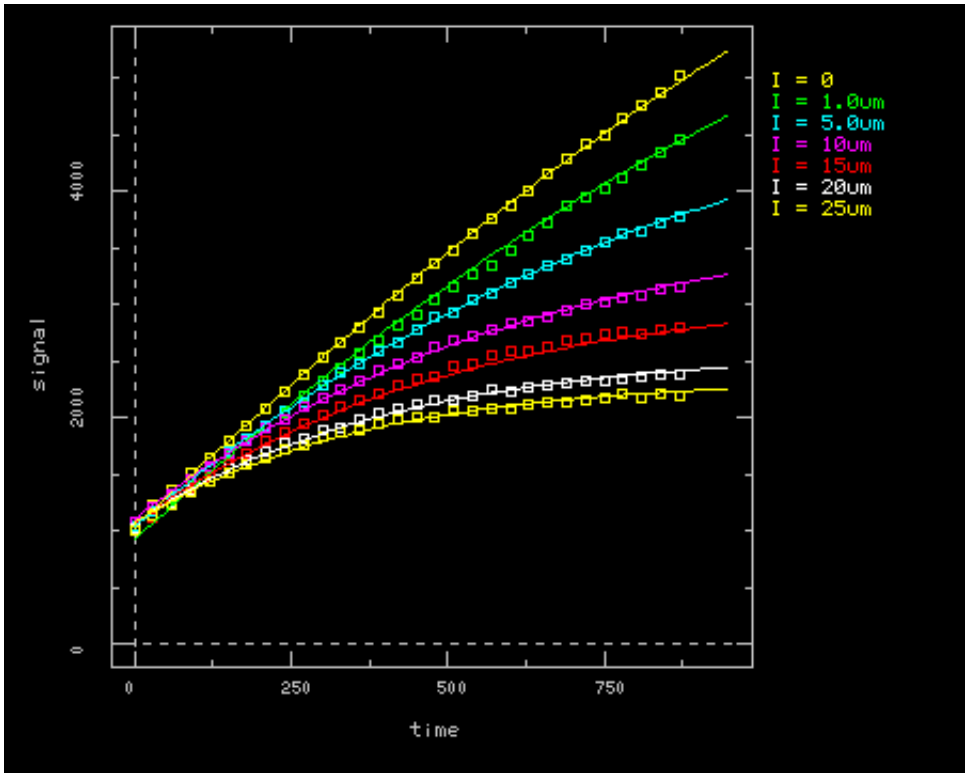


Figure S26. Experimental data (squares) vs. estimated fit (lines) for **4** (0-25 μM) using the competitive, two-step irreversible inhibition model shown in Figure S21.

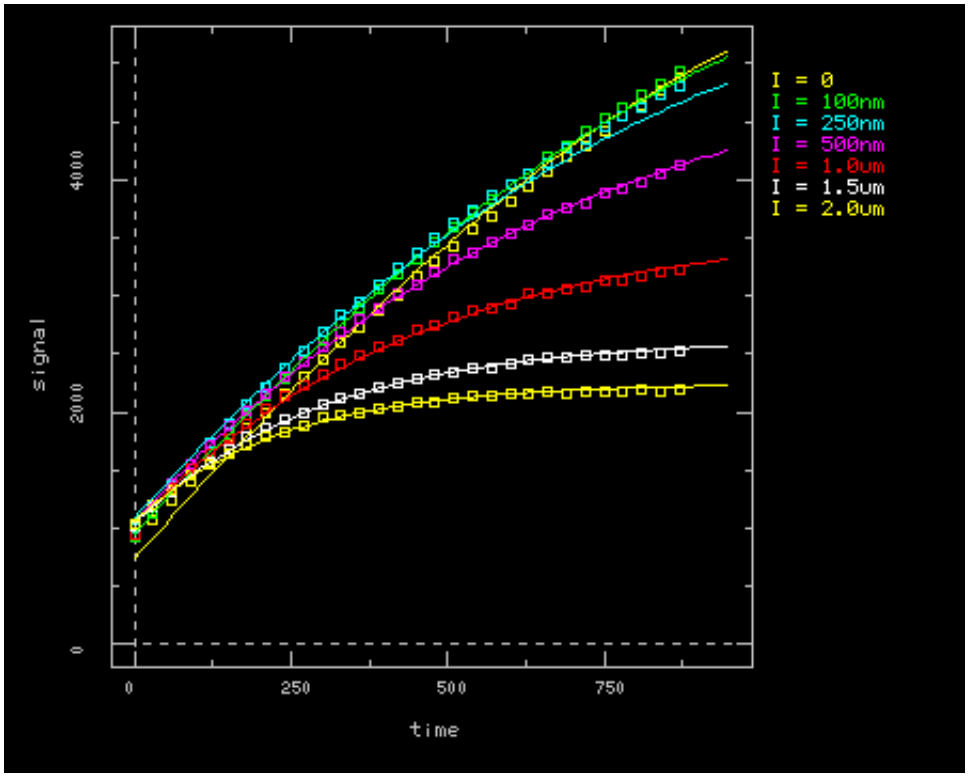


Figure S27. Experimental data (squares) vs. estimated fit (lines) for **CLIK-148** (0-2.0 μM) using the competitive, two-step irreversible inhibition model shown in Figure S21.

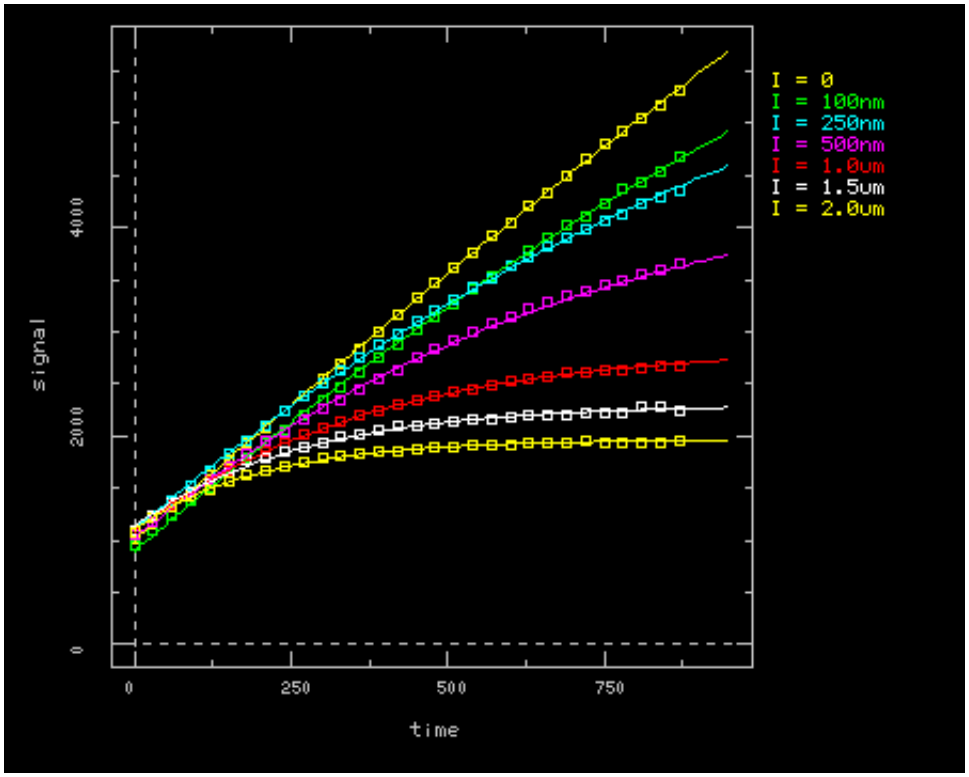


Figure S28. Experimental data (squares) vs. estimated fit (lines) for **CLIK-181** (0-2.0 μM) using the competitive, two-step irreversible inhibition model shown in Figure S21.

Time-dependent incubation studies with cathepsin L and 1-4

Incubation assays of compounds **1-4** under light and dark conditions were carried out on black 96-well plates with each inhibitor reaction done in 100 μL volumes in triplicate. Each plate contained a negative control, containing only buffer and substrate, and a positive control, containing buffer, Z-Phe-Arg-AMC as the substrate, and cathepsin L. A portion of the buffer (400 mM sodium acetate, 4 mM EDTA, 0.01% Triton-X 100, pH 5.5) was first activated with 32 mM DTT and the human cathepsin L was diluted to 16 nM (4 nM final well concentration) in this activated reaction buffer and incubated for 30 minutes at 25 °C with shaking. Dilutions of compounds **1-4** were made separately in the non-activated reaction buffer at the single concentration of 1 μM (final well concentration of 250 nM). Stock solutions of inhibitors in non-activated buffer were kept at room temperature either covered in foil for the dark experiments or were irradiated with visible light ($\lambda_{irr} > 395$ nm) for 10 min in an open glass vial. Photolysis was achieved using a 250 W tungsten halogen lamp powered by a 24 V power supply, using a longpass filter with a 395 nm cutoff and a 10 cm water cell between the light source and the plate to filter out UV and IR irradiation. A stock solution of substrate Z-Phe-Arg-AMC in assay buffer was prepared at 20 μM (final well concentration 10 μM) in non-activated reaction buffer. Non-activated reactions buffer was added to the wells corresponding to the controls (50 μL into the positive control and 25 μL into the negative controls). Inhibitors were added to the non-control wells (25 μL per well), designating 3 wells to each concentration of each inhibitor. Cathepsin L was then added (25 μL of the 16 nM stock per well) to the designated rows of the plate at 0, 10, 20, 30, 40, 50, and 60 minutes at room temperature. After the incubation of the plate, substrate (50 μL) was added to each well. Fluorescence intensity was then read at 25 °C every 2 min for

10 min, with λ_{ex} = 360 nm and λ_{em} = 430 nm. Percent activities were calculated using change in fluorescence over time, with 100% activity equal to activity present in control wells with no inhibitor added.

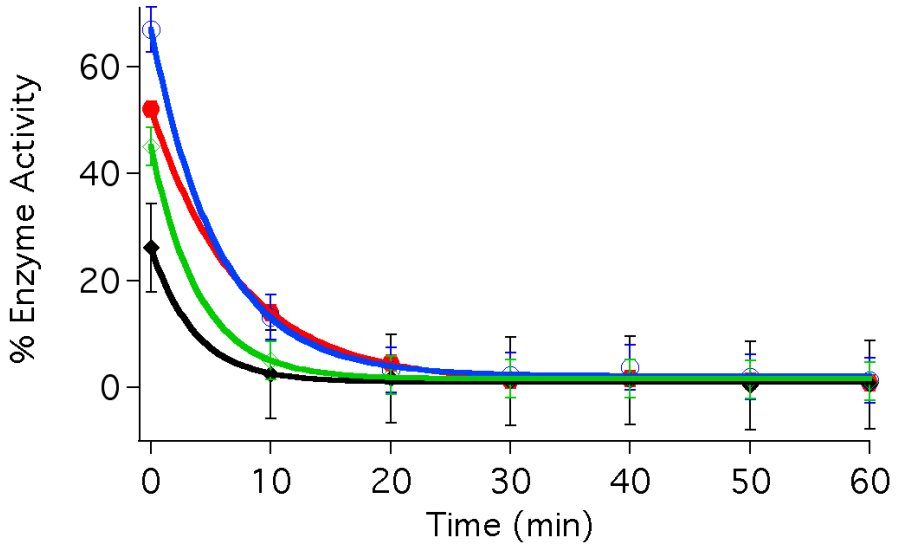


Figure S29 Time-dependent inactivation of cathepsin L by **1** (blue with irradiation, red without) and **3** (green with irradiation and black without). Solutions of **1** or **3** (250 nM) were irradiated with visible light ($\lambda_{irr} \geq$ 395 nm, 10 min) or left in the dark and incubated with cathepsin L (4 nM) at 25 °C for 0-60 min. Inhibition data were acquired using cathepsin L (4 nM), Z-Phe-Arg-AMC (10 μM), and inhibitor (250 nM) in 0.4 M acetate buffer, pH 5.5, <1% DMSO, 4 mM EDTA, 0.01% Triton X-100, DTT = 8 mM at 25 °C.

Part F. Photochemical studies

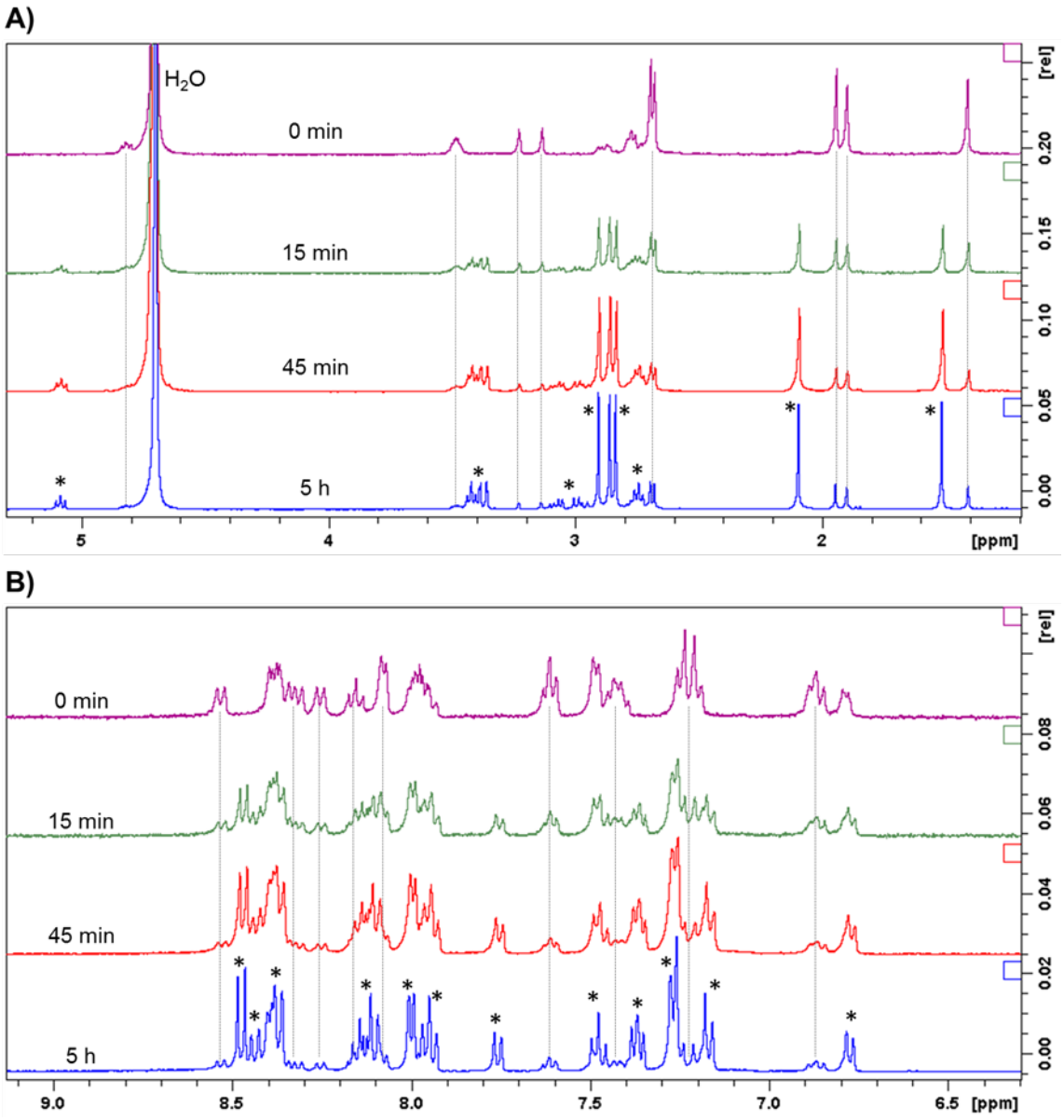


Figure S30. Aliphatic region (A) and aromatic region (B) of the ^{1}H NMR spectra of **4** in D_2O irradiated with $\lambda_{irr} \geq 455$ nm for 0−5 h.

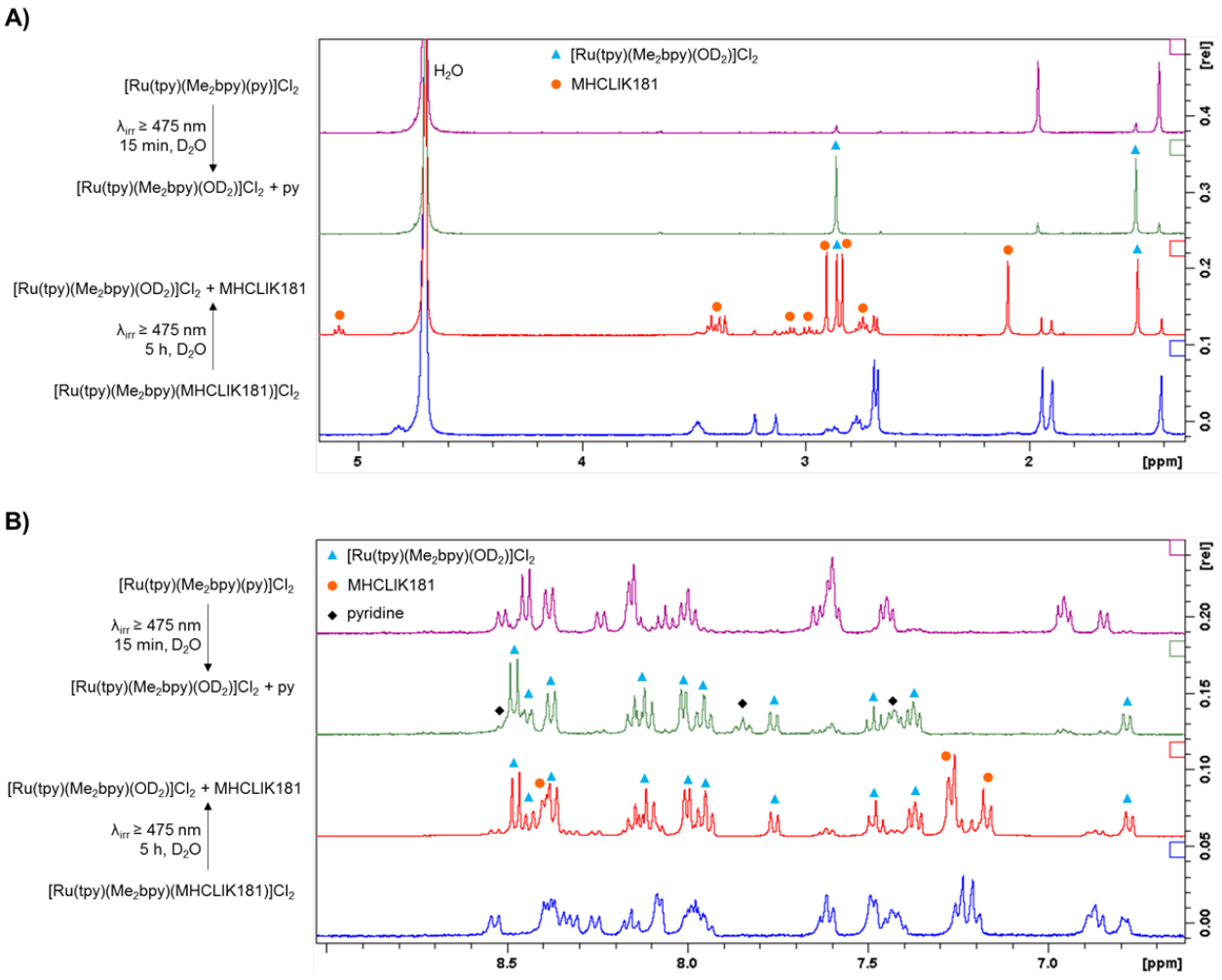


Figure S31. Aliphatic region (A) and aromatic region (B) of the ^{1}H NMR spectra of [Ru(tpy)(Me$_2$bpy)(py)]Cl$_2$ and **4** in D$_2$O irradiated with $\lambda_{irr} \geq 455$ nm for 0−15 min and 0−5 h, respectively.

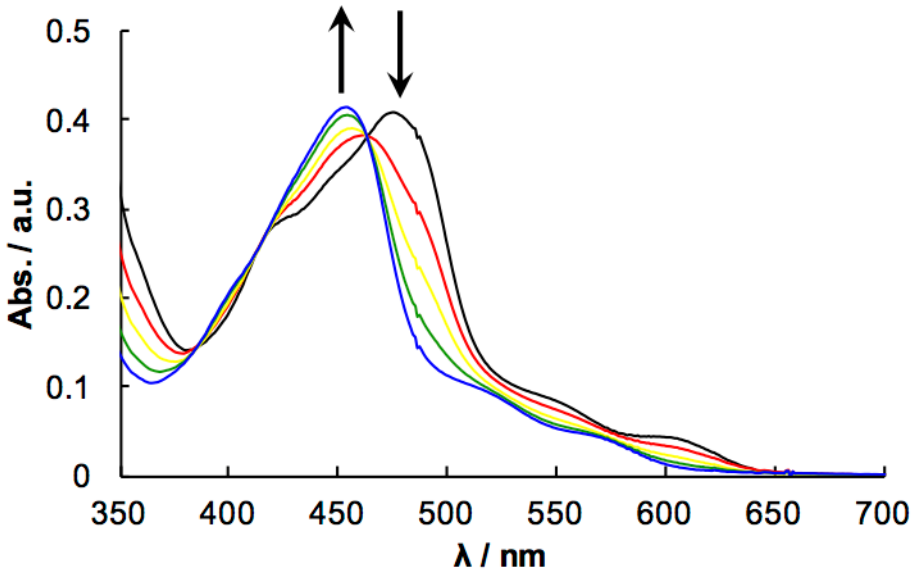


Figure S32. Electronic absorption spectra of **3** in CH_3CN irradiated with $\lambda_{irr} \geq 455$ nm for 0−4 min.

Part G. Papain conjugates and LCMS analysis

Preparation of Papain-Inhibitor Conjugates.

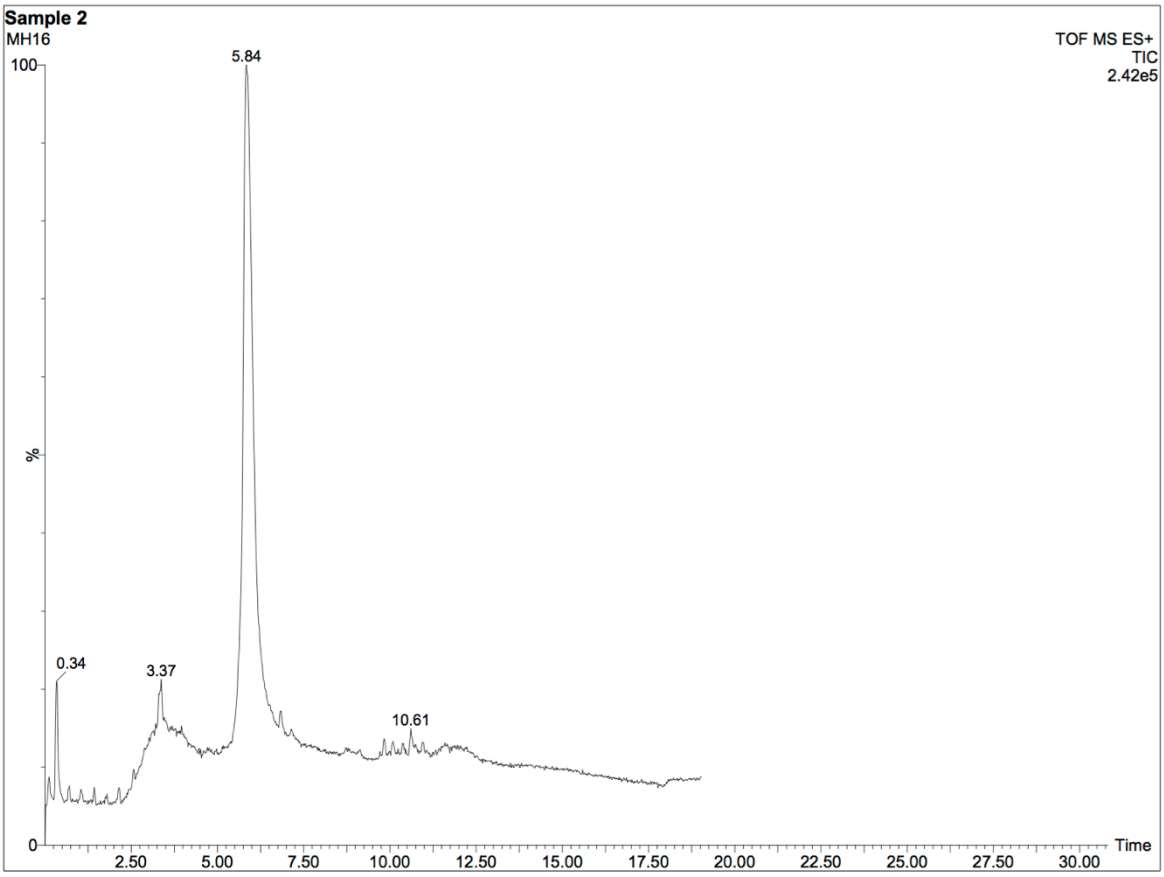
A literature procedure was adapted to prepare papain conjugates with inhibitors **1**-**3**.[7] A concentrated solution of papain (from papaya latex, Sigma Aldrich, P4762) was prepared in 20% DMSO/H_2O (20 mg/mL), resulting in a suspension that was filtered through a 0.2 μM membrane. The filtrate (50 μL) was added to a solution of L-cysteine hydrochloride (2 mg/mL, 200 μL) and inhibitors **1**-**3** (2 mg/mL, 200 μL) in the dark. Solutions were incubated at rt for 18 h in the dark, and were concentrated to a volume of ~50 μL using 10 kD centrifugal filters (Amicon Ultra Ultracel® 10K membrane) at 4 °C, 14,000 g for 30 min. Samples were diluted in 0.2% AcOH/H_2O (400 μL) and concentrated to ~50 μL four times to remove excess inhibitor and L-cysteine. Samples were diluted to a final volume of 450 μL in 0.2% AcOH/H_2O and stored in the dark for analysis by LCMS. In the case of caged inhibitor **3**, 200 μL of the papain-**3** conjugate solution was irradiated for 20 min with visible light (λ_{irr} > 395 nm, see pg S47 for details) in a 1.5 mL Ependorf microcentrifuge tube with the cap off and this sample was analyzed by LCMS.

Liquid Chromatography/Mass Spectrometry (LCMS) Analysis of Protein Samples.

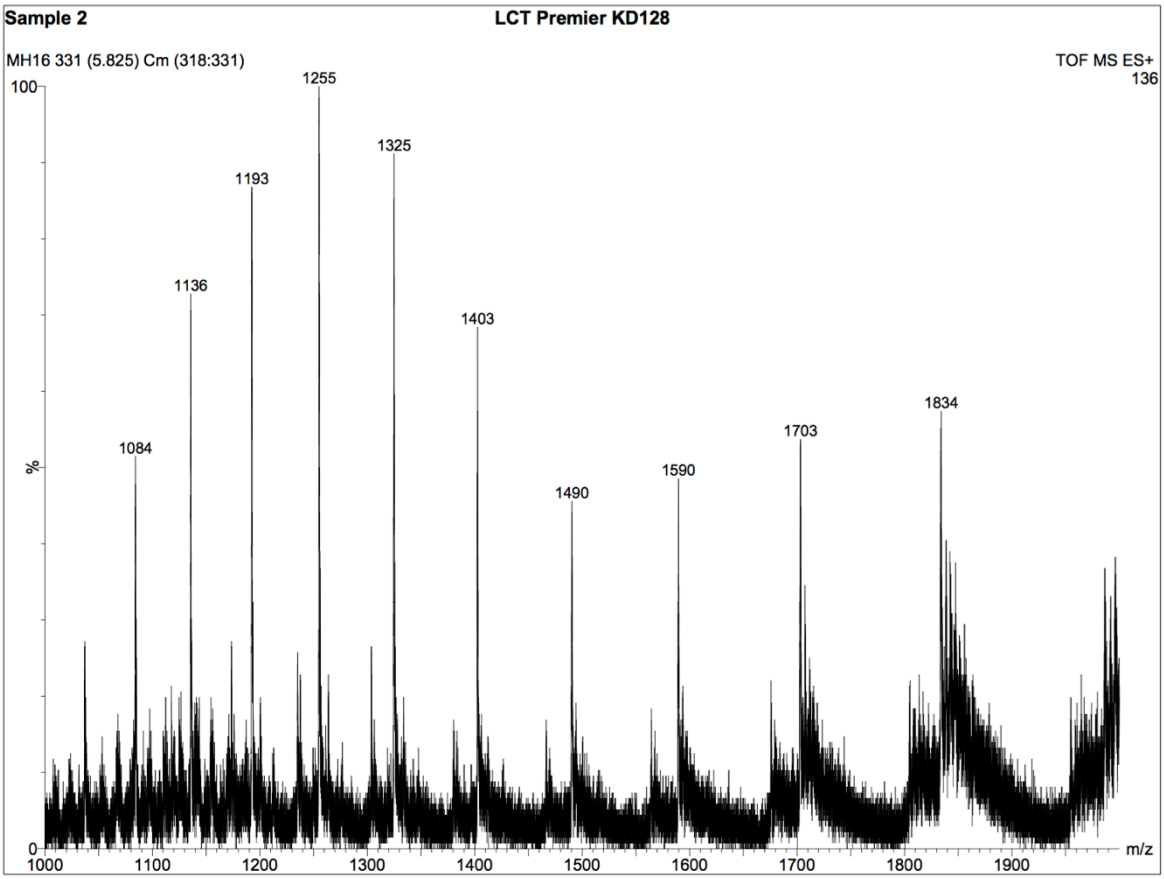
LC-MS was performed on a Waters LCT Premier XE Micromass KD128 Time of Flight mass-spectrometer with an electrospray source and Waters Alliance 2695 liquid chromatograph. Approximately 100 pmol of the sample was injected onto a Aeris^{TM} 3.6 μm widepore C4 200 50 x 2.1 mm column (Phenomenex) with a flow rate of 0.45 mL/min and the column heated to 40 °C. Mobile phase A was a solution of 0.1% formic acid in acetonitrile:water (20:0).

Separation was achieved using a gradient of: CH_3CN 0.1% HCO_2H and water 0.1% HCO_2H; 0–1.5 min, 0-20% CH_3CN 1.5–10 min, 20–80% CH_3CN 10–15 min and 80-20% CH_3CN 15–20 min. A H_2O (blank) was injected after each sample to minimize any carryover. Spectra were collected from 1,000 to 2,000 m/z and the signal was deconvoluted using Masslynx.

A)


Sample 2
MH16
TOF MS ES+
TIC
2.42e5
100
%
0
5.84
0.34
3.37
10.61
2.50
5.00
7.50
10.00
12.50
15.00
17.50
20.00
22.50
25.00
27.50
30.00
Time

B)


Sample 2
LCT Premier KD128
MH16 331 (5.825) Cm (318:331)
TOF MS ES+
136
100
%
0
1255
1325
1193
1136
1403
1834
1703
1084
1590
1490
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

C)

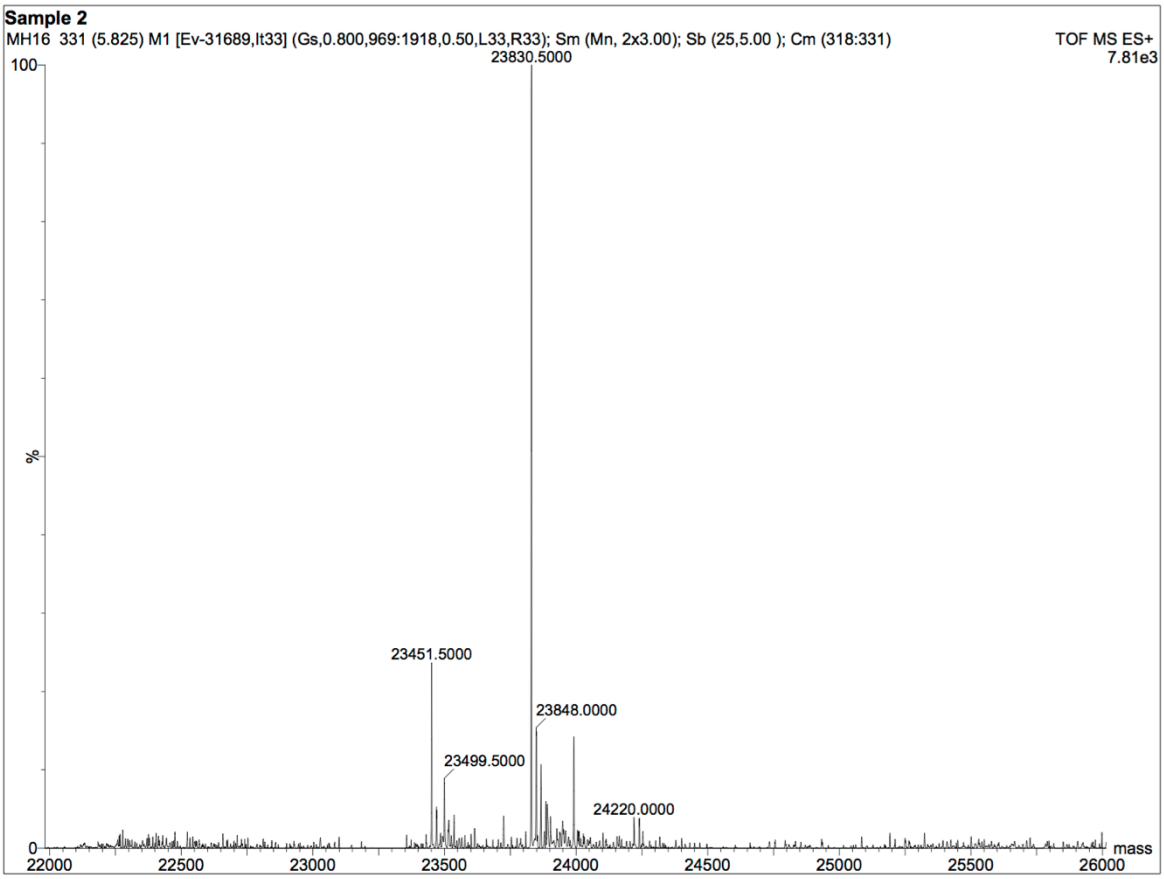
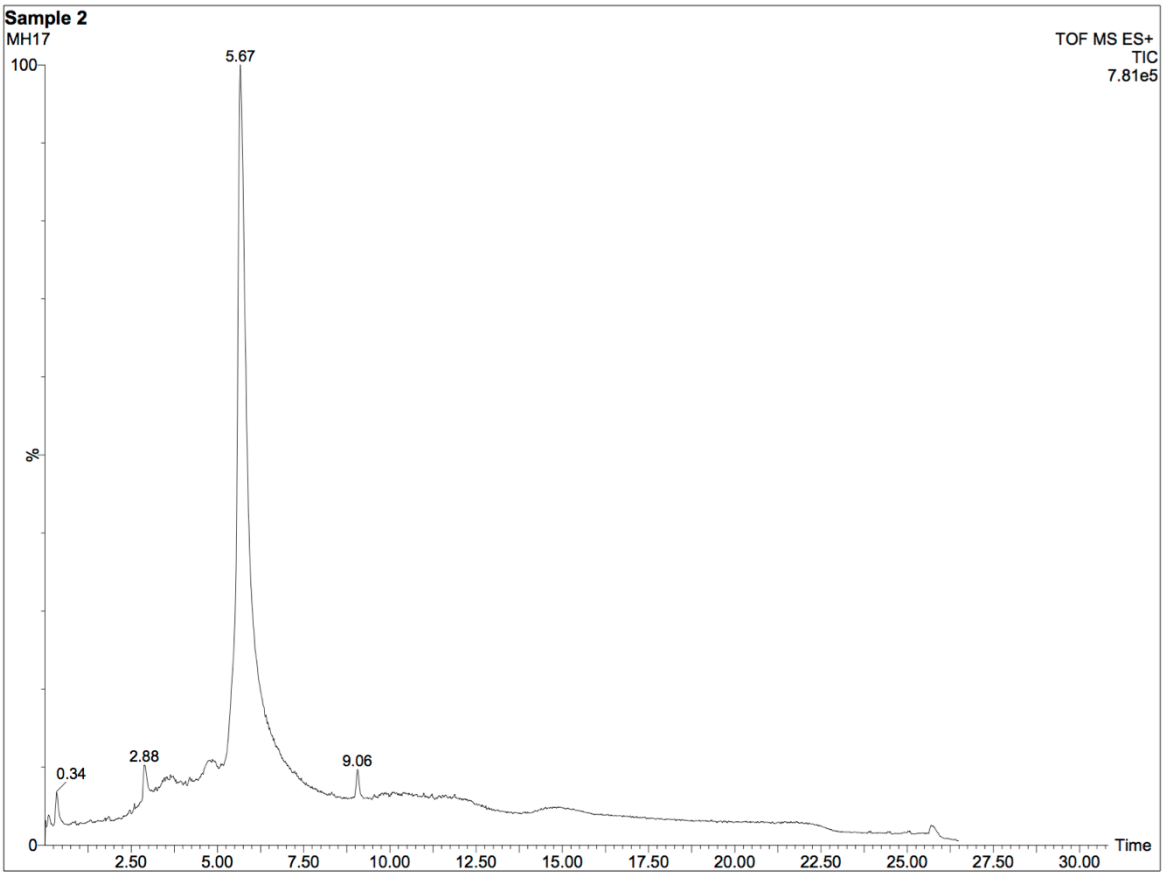
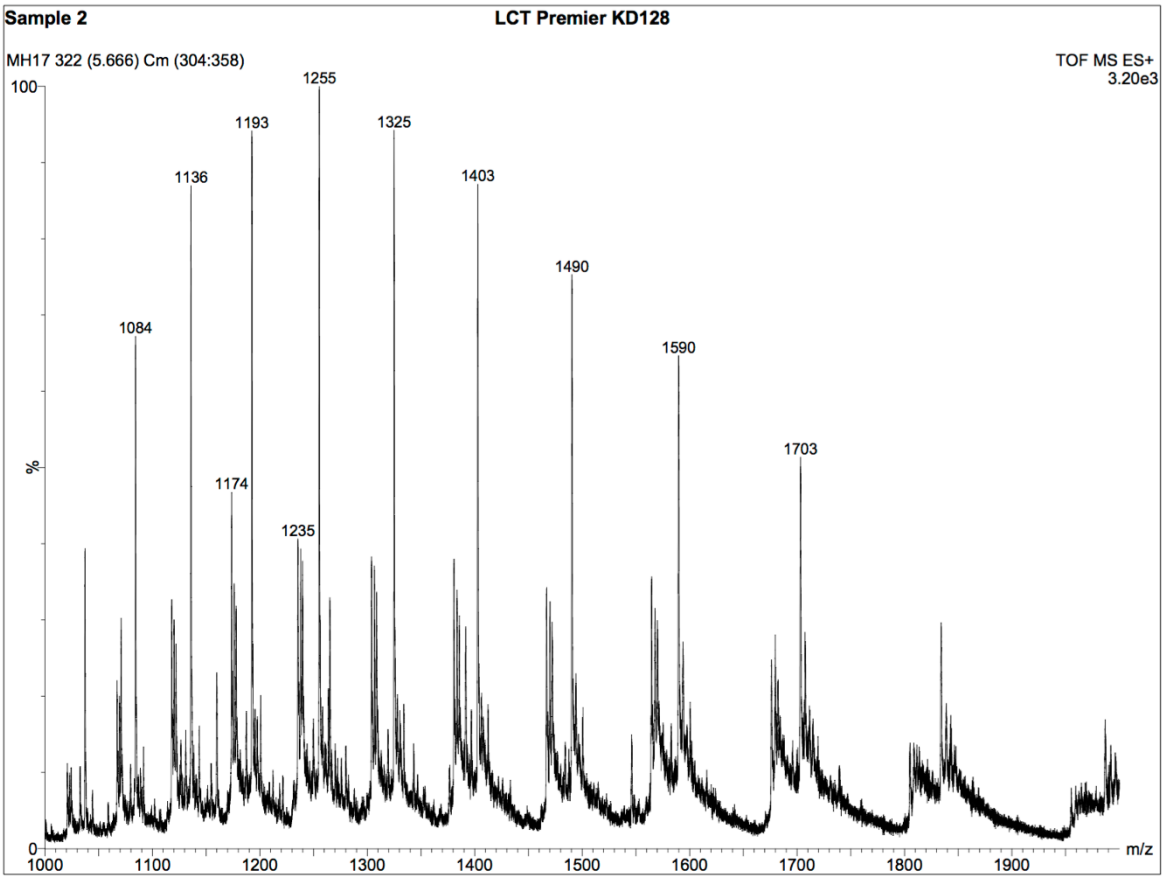


Figure S33. A) LC chromatogram B) raw and C) deconvoluted LC-MS data for commercial Papain-**1** conjugate. Calculated mass of Papain-**1** conjugate: 23830, observed 23831.

A)


Sample 2
MH17
TOF MS ES+
TIC
7.81e5
100
%
0
5.67
2.88
0.34
9.06
2.50
5.00
7.50
10.00
12.50
15.00
17.50
20.00
22.50
25.00
27.50
30.00
Time

B)


Sample 2
LCT Premier KD128
MH17 322 (5.666) Cm (304:358)
TOF MS ES+
3.20e3
100
%
0
1084
1136
1174
1193
1235
1255
1325
1403
1490
1590
1703
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

C)

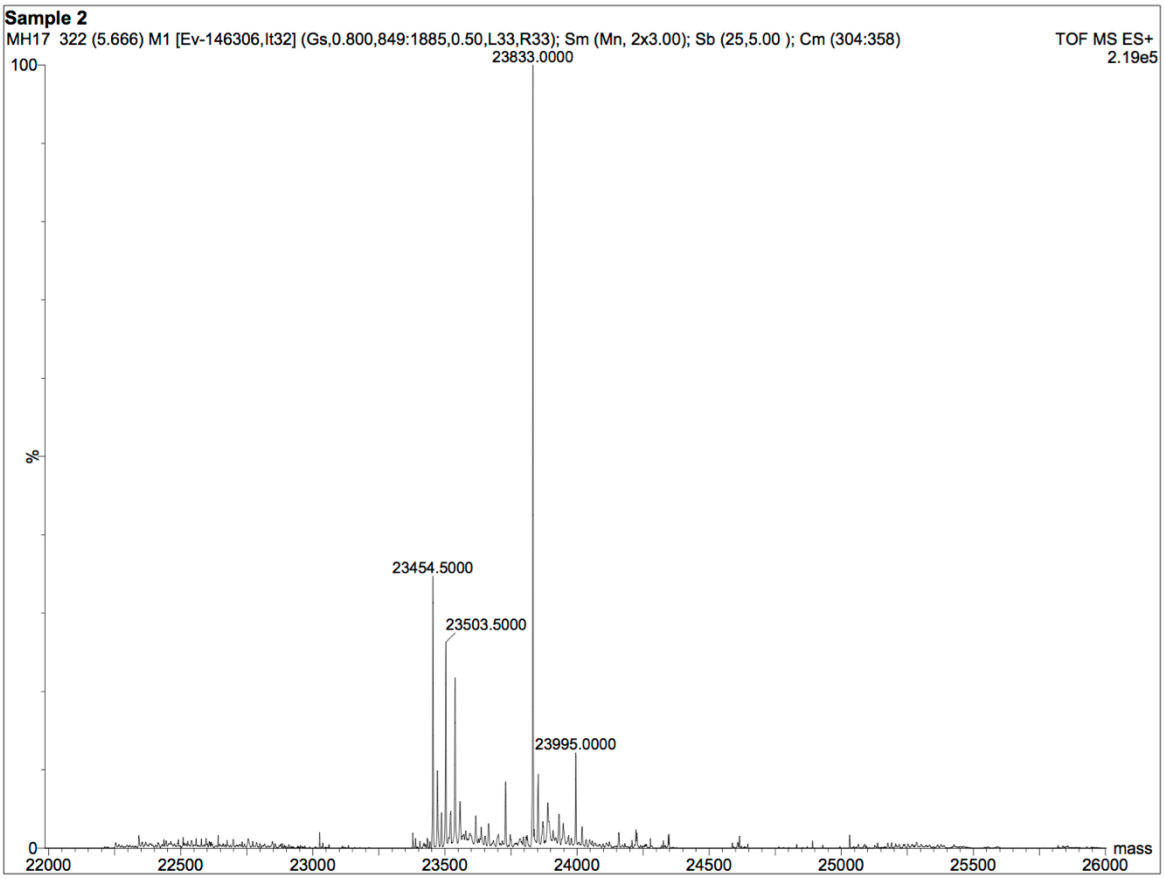
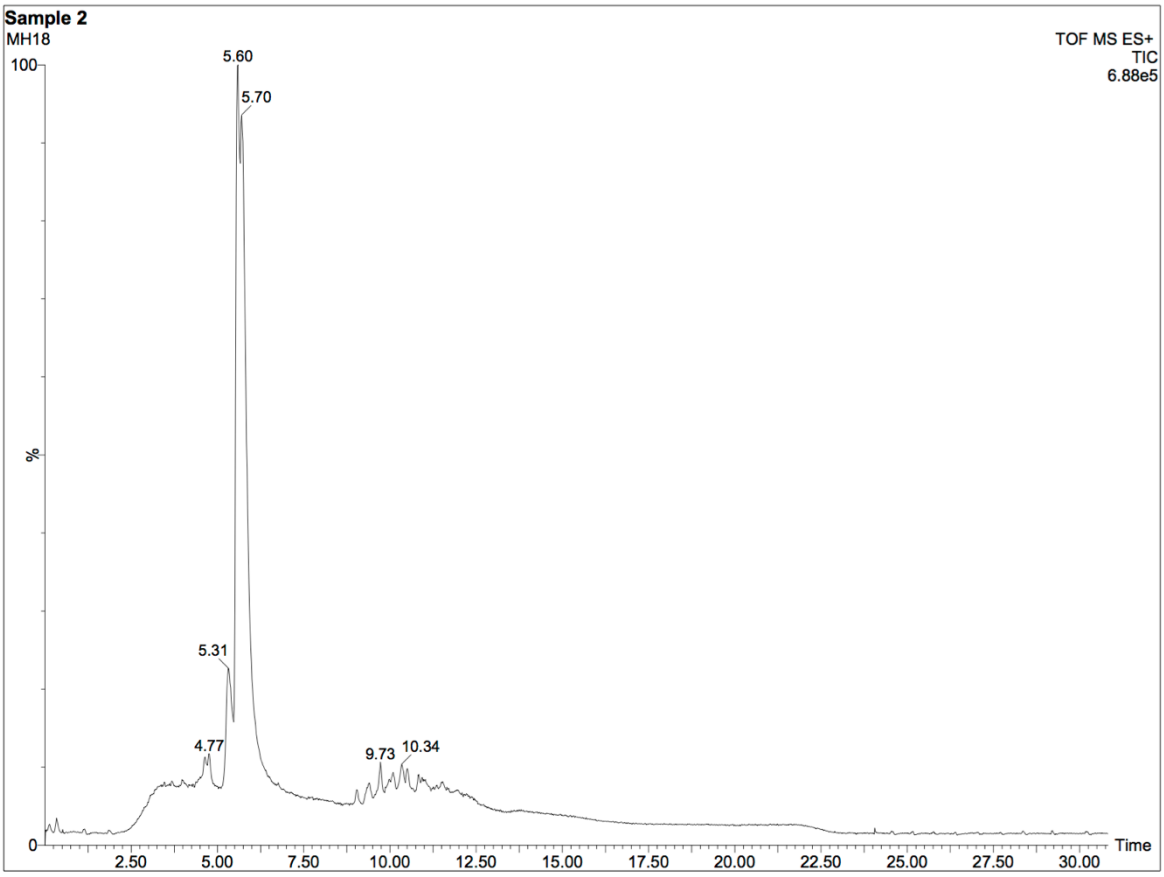
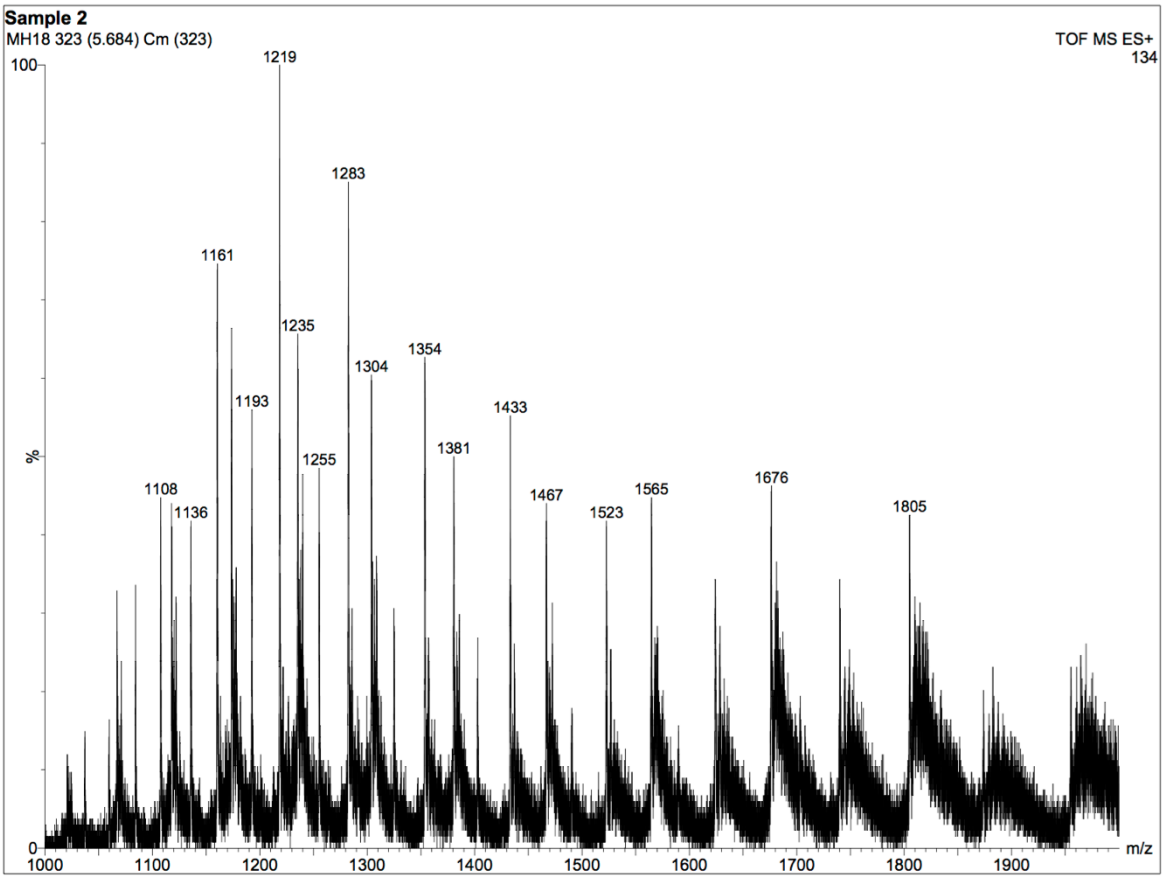


Figure S34. A) LC chromatogram B) raw and C) deconvoluted LC-MS data for Papain-**3** conjugate (light). Calculated mass of Papain-**1** conjugate: 23830, observed 23833. The peak at 24350 was not observed, consistent with photochemical release of fragment [Ru(tpy)(Me_2bpy)] = 517 amu.

A)


Sample 2
MH18
TOF MS ES+
TIC
6.88e5
100
%
0
5.60
5.70
5.31
4.77
9.73
10.34
2.50
5.00
7.50
10.00
12.50
15.00
17.50
20.00
22.50
25.00
27.50
30.00
Time

B)


Sample 2
MH18 323 (5.684) Cm (323)
TOF MS ES+
134
100
%
0
1219
1283
1161
1235
1354
1304
1193
1433
1381
1255
1108
1136
1467
1523
1565
1676
1805
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

C)

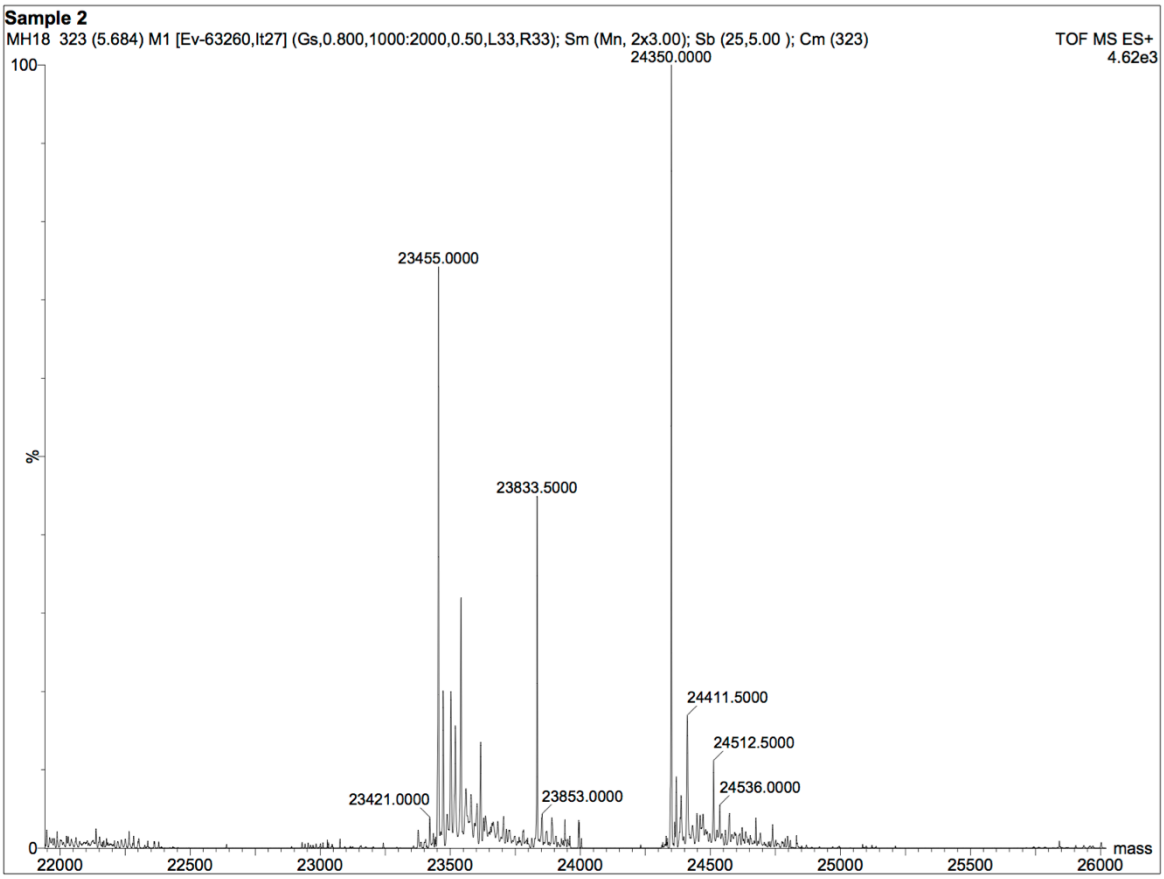
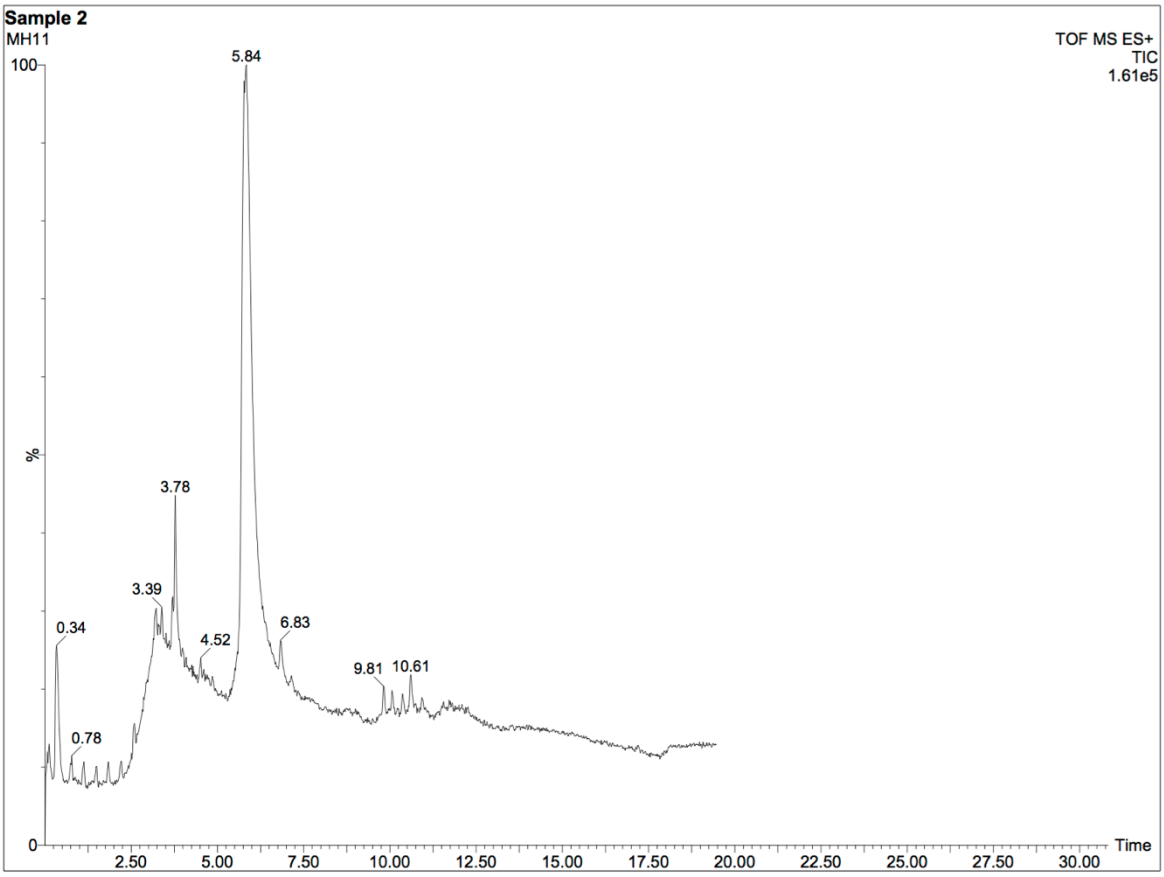
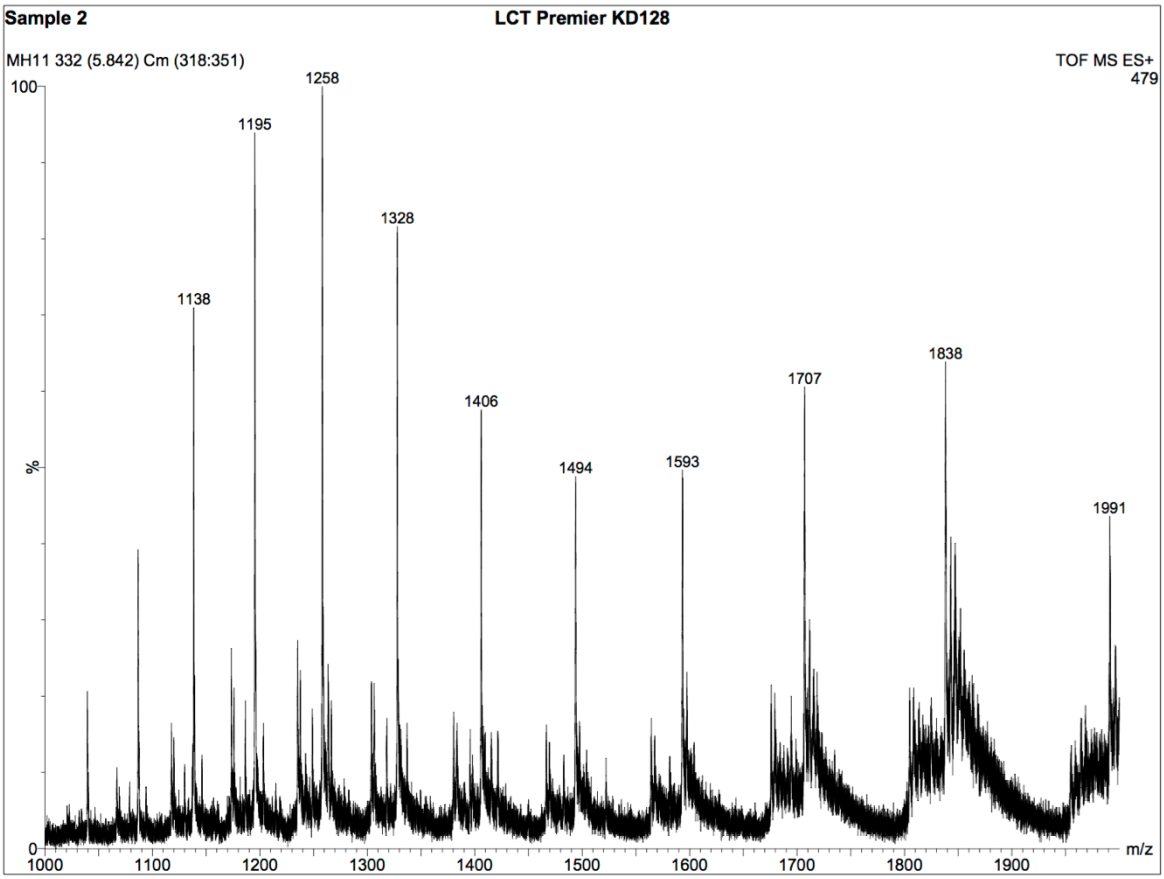


Figure S35. A) LC chromatogram B) raw and C) deconvoluted LC-MS data for Papain-**3** conjugate (dark). Calculated mass of Papain-**3** conjugate: 24349, observed 24350. Calculated mass of Papain-**1** conjugate: 23830, observed 23834. The LC chromatogram and deconvoluted MS data indicate the presence of unmodified papain (t_R = 5.70 min) and papain-**3** conjugate (t_R = 5.60 min). Commercially available papain shows peaks at 23421 ± 1 (papain) and 23455 ± 1 (papain + dioxygen) that were observed previously.[8]

A)


Sample 2
MH11
TOF MS ES+
TIC
1.61e5
100
%
0
5.84
3.78
3.39
0.34
4.52
6.83
9.81
10.61
0.78
2.50
5.00
7.50
10.00
12.50
15.00
17.50
20.00
22.50
25.00
27.50
30.00
Time

B)


Sample 2
LCT Premier KD128
MH11 332 (5.842) Cm (318:351)
TOF MS ES+
479
100
%
0
1258
1195
1328
1138
1406
1838
1707
1494
1593
1991
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
m/z

C)

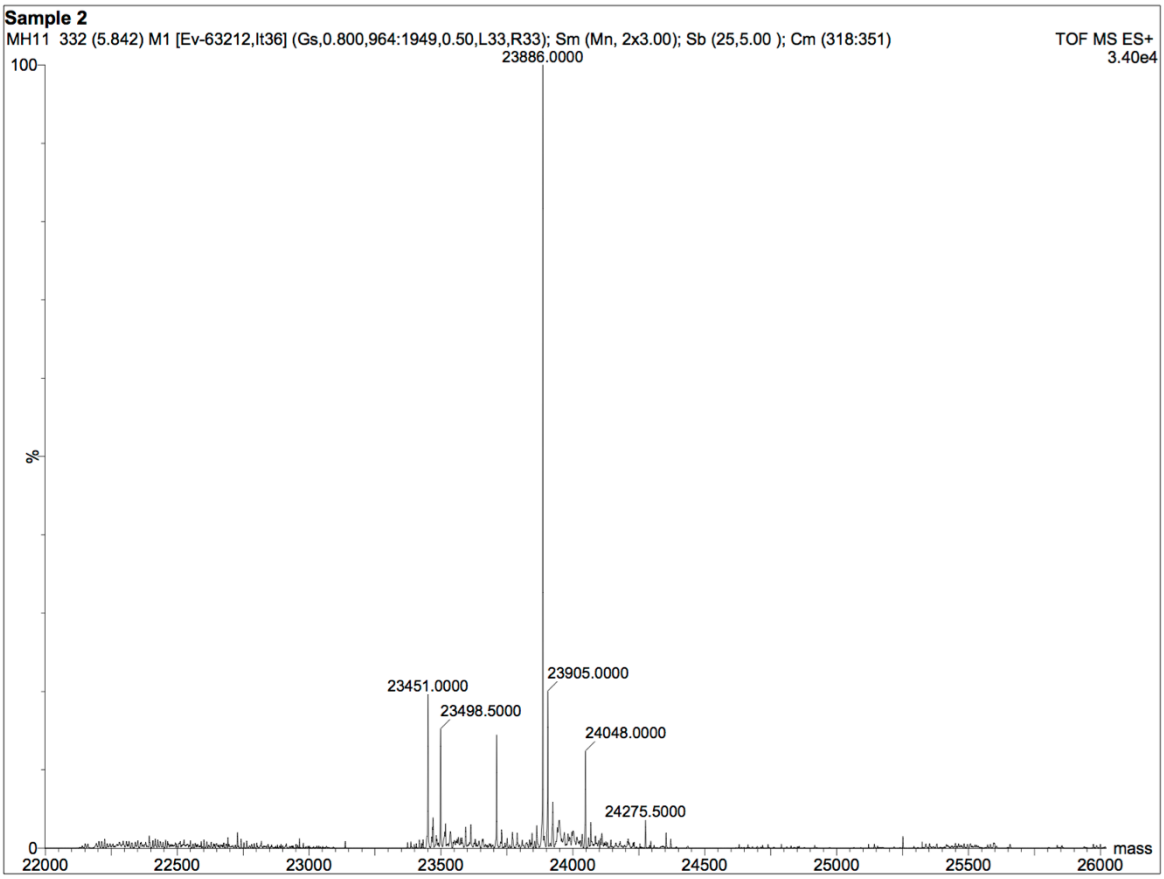


Figure S36. A) LC chromatogram B) raw and C) deconvoluted LC-MS data for Papain-**2** conjugate. Calculated mass of Papain-**2** conjugate: 23887, observed 23886.

Part H. Stability Studies for **3** and **4**

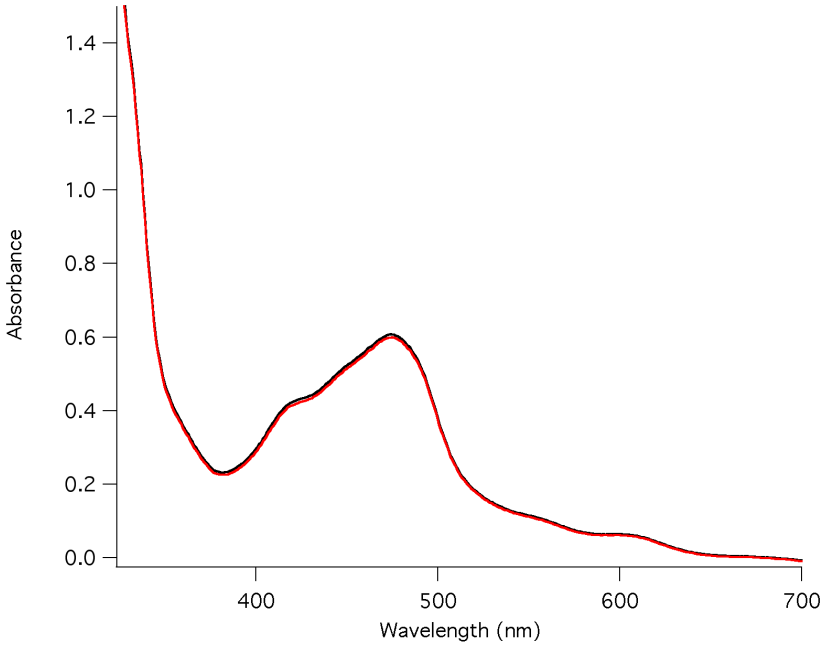


Figure S37. Electronic absorption spectra of **3** incubated at 293±2 K in assay buffer (400 mM sodium acetate, 4 mM EDTA, 0.01% Triton-X 100, pH 5.5) at t = 0 (black) and 8 h (red).

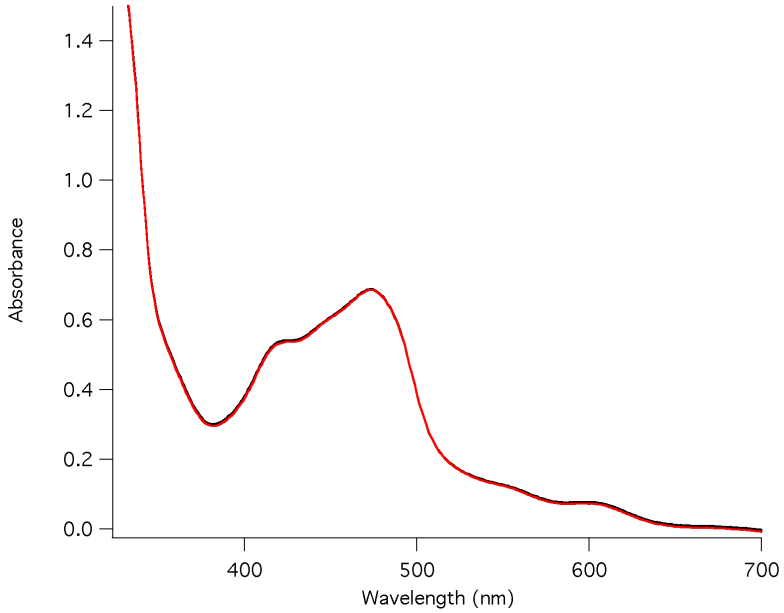


Figure S38. Electronic absorption spectra of **4** incubated at 293±2 K in assay buffer (400 mM sodium acetate, 4 mM EDTA, 0.01% Triton-X 100, pH 5.5) at t = 0 (black) and 8 h (red).

Part I. References

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