Supporting Information

Photo-induced Coupling Reaction of Tetrazoles and Carboxylic Acids in Aqueous Solution: Application in the Protein Labelling

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1. *General information*

Yields refer to chromatographically and spectroscopically homogeneous materials. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by Thin Layer Chromatography on plates (GF254) supplied by Yantai Chemicals (China) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200-300 mesh) supplied by Tsingtao Haiyang Chemicals (China). NMR spectra were recorded on Brüker Advance 500 (^{1}H 500 MHz, ^{13}C 125 MHz) and Brüker Advance 400 (^{1}H 400 MHz, ^{13}C 100 MHz). TMS was used as internal standard for ^{1}H NMR (TMS, 0.00; $CDCl_3$, 7.26; DMSO-d_6, 2.50; MeOD-d_4, 3.31), and solvent signal was used as reference for ^{13}C NMR ($CDCl_3$, 77.0; DMSO-d_6, 39.5; MeOD-d_4, 49.0). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectrometric data were obtained using Brüker Apex IV FTMS using ESI (electrospray ionization) and Waters GCT (GC-MS) using EI (electron impact ionization).

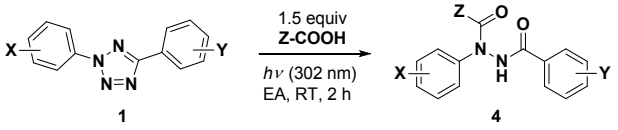
Human cell lines HepG2 was grown in RPMI medium 1640 containing 10% FBS and 1% PS. After harvesting, cell pellets were lysed with 0.1% NP-40 containing protease inhibitors and sonicated, followed by centrifugation at 21,000 x g (30 min) to provide soluble cellular proteome fractions. The soluble fractions were stored at -80 °C until use. For Western blotting experiments, the samples were run on tris-glycine gels and transferred to polyvinylidene fluoride. The blots were blocked with 5% BSA in TBST, probed with monoclonal HDAC1 and HDAC2 (1:10000 in TBST, Cell Signaling Technology, Danvers, MA), monoclonal α-Actin (1:10000 in TBST, Cell Signaling Technology, Danvers, MA) for 2h at RT, washed with TBST, incubated with goat-α-mouse IgG (H + L) HRP conjugate or goat-α-rabbit IgG (H + L) HRP conjugate (1:10000, Cell Signaling Technology, Danvers, MA) for 1 h at RT, washed again in TBST, and visualized using Chemi system (Bio-Red) after treated with Enhanced chemiluminescent reagent.

2. *Experimental procedures for chemical synthesis and spectroscopic data of the synthesized compounds*

All tetrazoles were synthesized according to literature procedures[1,2].

General procedure of the photo-induced coupling reaction of tetrazoles and carboxylic acids: The solution of carboxlic acid (1.5 equiv) and tetrazole (1 equiv) within a quartz test tubes was irradiated for 2 h using a hand-held 302 nm UV lamp under stirring. The organic solvents were evaporated under reduced pressure. The resulting residue was further purified by silica gel chromatography.

Table S1. Photo-induced Coupling Reactions of Tetrazoles with Carboxylic Acids



1 4

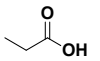
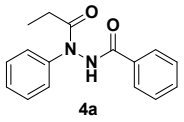
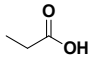
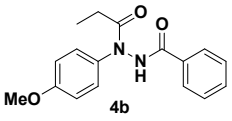
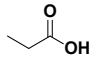
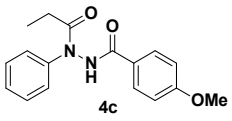
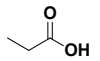
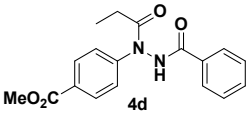
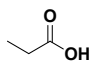
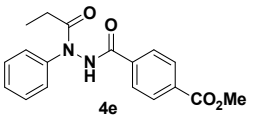
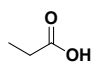
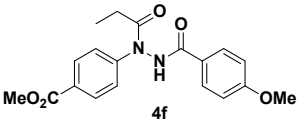
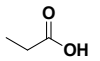
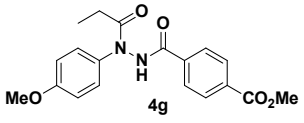
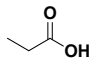
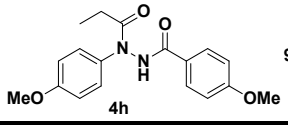
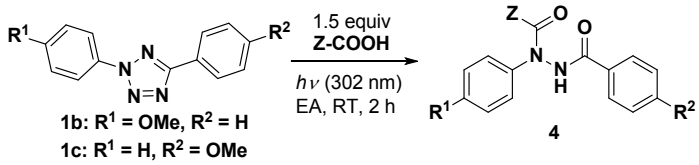
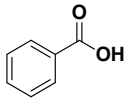
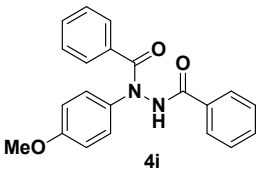
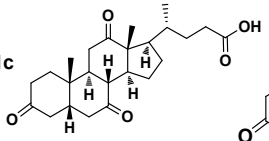
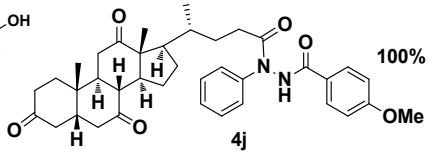
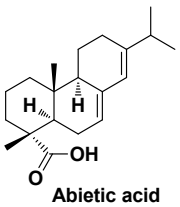
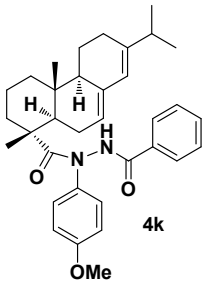
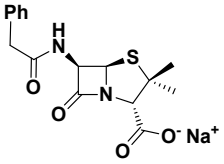
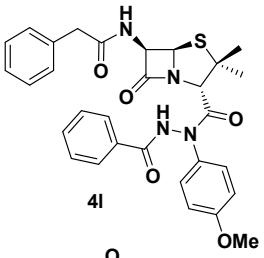
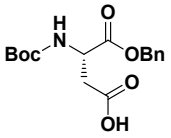
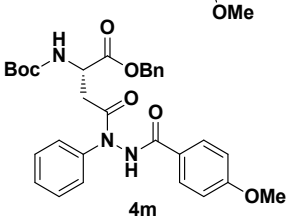
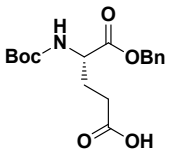
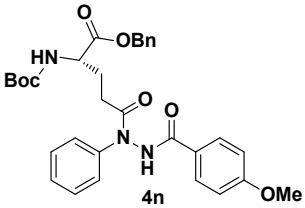
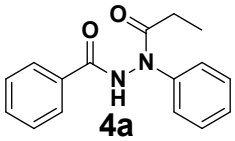
Tetrazole	Acid	Product	Yield[b]
1a		 4a	68%
1b		 4b	95%
1c		 4c	80%
1d		 4d	100%
1e		 4e	100%
1f		 4f	85%
1g		 4g	76%
1h		 4h	91%

Table S1. Photo-induced Coupling Reactions of Tetrazoles with Carboxylic Acids (continued)



Tetrazole	Acid	Product	Yield[b]
1b		 4i	100%
1c	 Dehydrocholic acid	 4j	100%
1b	 Abietic acid	 4k	78%
1b	 Penicillin G sodium salt	 4l	77%[c]
1c		 4m	99%[d]
1c		 4n	80%[d]

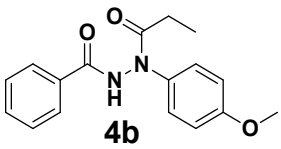
[a] Reactions were conducted by irradiating 0.011 M of tetrazole and 1.5 equiv of acid dissolving in EtOAc within a quartz test tubes for 2 h using a hand-held 302 nm UV lamp. [b] Isolated yield after column chromatography. [c] [**1b**] = 0.011 M in EtOH, 1.5 equiv penicillin G sodium salt, pH=2 by HCl. [d] 5 equiv acid was used.



4a

N'-phenyl-N'-propionylbenzohydrazide

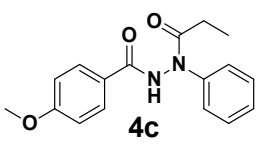
^{1}H NMR (400 MHz, DMSO-D_6) δ 11.51 (s, H), 7.92-7.94 (d, 2H, J = 7.93), 7.21-7.63 (m, 8H), 2.36-2.62 (br, 2H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 174.12, 165.61, 141.71, 132.43, 128.69, 128.49, 127.50, 125.70, 123.46, 26.07, 8.81. HRMS (ESI) calcd for $C_{16}H_{17}N_2O_2^+$ 269.1245[M+H]$^+$, $C_{16}H_{16}N_2O_2Na^+$ 291.1245[M+Na]$^+$, found 289.1289, 291.1109.



4b

N'-(4-methoxyphenyl)-N'-propionylbenzohydrazide:

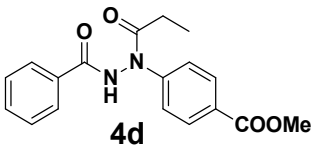
^{1}H NMR (400 MHz, DMSO-D_6) δ11.43 (s, H), 10.98* (s, H), 7.89-7.91 (d, 2H, J = 7.90), 7.85-7.86* (d, 2H, J = 7.86), 7.36-7.64 (m, 5H), 7.00-7.02* (d, 2H, J = 7.01), 6.92-6.94 (d, 2H, J = 6.93), 3.78* (s, 3H), 3.74 (s, 3H), 2.16-2.61 (br, 2H), 0.96-1.06 (m, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 174.09, 171.54, 165.56, 157.27, 134.80, 132.37, 131.81, 129.02, 128.69, 128.46, 127.46, 125.87, 114.47, 113.64, 55.23, 54.87, 26.70, 25.68, 9.28, 8.81. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_3^+$ 299.1351 [M+H]$^+$, found 299.13973. * represents the minor isomer.



4c

4-methoxy-N'-phenyl-N'-propionylbenzohydrazide:

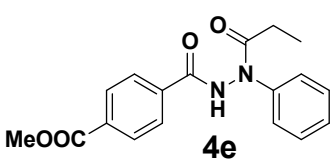
^{1}H NMR (400 MHz, DMSO-D_6) δ 11.35 (s, H), 7.92-7.93 (d, 2H, J = 7.93), 7.07-7.50 (m, 7H), 3.83 (s, 3H), 2.33-2.60 (br, 2H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 174.26, 165.07, 162.51, 141.85, 129.49, 128.44, 125.59, 123.77, 123.37, 113.94, 55.44, 26.08, 8.82. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_3^+$ 299.1351 [M+H]$^+$, found 299.13947.



4d

Methyl 4-(2-benzoyl-1-propionylhydrazinyl)benzoate:

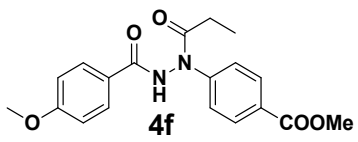
^{1}H NMR (400 MHz, DMSO-D_6) δ 11.58 (s, H), 7.95-7.99 (t, 4H, J = 7.97), 7.64-7.67 (t, 3H, J = 7.65), 7.55-7.58 (t, 2H, J = 7.57), 3.84 (s, 3H), 2.40-2.62 (br, 2H), 1.04-1.07 (t, 3H, J = 1.05); ^{13}C NMR (100 MHz, DMSO-D_6) δ 165.65, 165.61, 145.59, 132.59, 131.47, 129.83, 128.77, 127.59, 122.03, 54.86, 52.04, 26.54, 8.76. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_4^+$ 327.13393 [M+H]$^+$, found 327.13462.



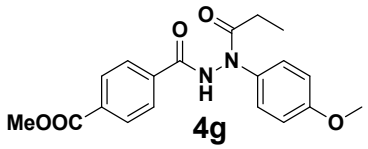
4e

Methyl 4-(2-phenyl-2-propionylhydrazinecarbonyl)benzoate:

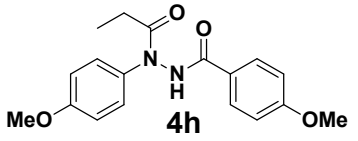
^{1}H NMR (400 MHz, DMSO-D_6) δ 11.72 (s, H), 11.29* (s, H), 7.95-8.11 (m, 4H), 7.22-7.68 (m, 5H), 3.89 (s, 3H), 3.84* (s, 3H), 2.37-2.62 (br, 2H), 1.04-1.08 (m, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 174.00, 165.51, 164.97, 141.55, 135.81, 132.77, 132.58, 131.47, 129.82, 128.75, 128.53, 127.95, 127.59, 125.86, 123.63, 54.85, 52.42, 52.03, 26.55, 26.02, 8.75. HRMS (ESI) calcd for $C_{18}H_{19}N_2O_4^+$ 327.13393 [M+H]$^+$, found 327.13471. * represents the minor isomer.



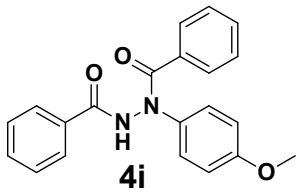
Methyl 4-(2-(4-methoxybenzoyl)-1-propionylhydrazinyl)benzoate: ^{1}H NMR (400 MHz, DMSO-D_6) δ 11.42 (s, H), 7.92-7.94 (m, 4H), 7.63-7.65 (d, 2H, J = 7.64), 7.08-7.11 (d, 2H, J = 7.09), 3.84 (d, 6H), 2.37-2.60 (br, 2H), 1.03-1.06 (t, 3H, J = 1.04); ^{13}C NMR (100 MHz, DMSO-D_6) δ 165.62, 165.07, 162.64, 145.73, 129.79, 129.59, 123.47, 121.93, 114.03, 55.51, 54.87, 52.04, 26.54, 8.76. HRMS (ESI) calcd for $C_{19}H_{21}N_2O_5^+$ 357.1445 $[M+H]^+$, found 357.14520.



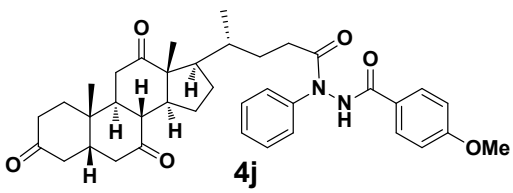
Methyl 4-(2-(4-methoxyphenyl)-2-propionylhydrazinecarbonyl)benzoate: ^{1}H NMR (400 MHz, DMSO-D_6) δ 11.63 (s, H), 11.19* (s, H), 7.97-8.11 (m, 4H), 7.45-7.47* (d, 2H, J = 7.46), 7.37-7.39 (d, 2H, J = 7.38), 7.00-7.02* (d, 2H, J = 7.01), 6.92-6.94 (d, 2H, J = 6.93), 3.88 (s, 3H), 3.77* (s, 3H), 3.74 (s, 3H), 2.17-2.59 (br, 2H), 0.98-1.06 (m, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 173.99, 171.53, 165.50, 164.89, 164.24, 158.90, 157.40, 135.87, 134.64, 132.74, 129.42, 129.29, 129.05, 127.91, 126.07, 114.51, 113.69, 55.32, 55.21, 52.41, 26.67, 25.64, 9.23, 8.77. HRMS (ESI) calcd for $C_{19}H_{21}N_2O_5^+$ 357.1445 $[M+H]^+$, found 357.14534. * represents the minor isomer.



4-methoxy-N'-(4-methoxyphenyl)-N'-propionylbenzohydrazide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, H), 9.42* (s, H), 7.80* (b, 2H), 7.69-7.71 (d, 2H, J = 7.70), 7.46-7.48 (d, 2H, J = 7.47), 7.40* (b, 2H), 6.88-6.90 (d, 2H, J = 6.89), 6.80* (b, 2H), 6.70-6.73 (d, 2H, J = 6.72), 3.78-3.80 (d, 6H, J = 3.79), 2.53* (b, 2H), 2.26-2.32 (m, 2H), 1.10-1.16 (t, 3H, J = 1.13); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.35, 165.80, 162.49, 159.59, 134.79, 129.36, 123.93, 114.58, 113.57, 55.50, 55.32, 27.43, 9.46. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_4^+$ 329.14958 $[M+H]^+$, found 329.15009. * represents the minor isomer.



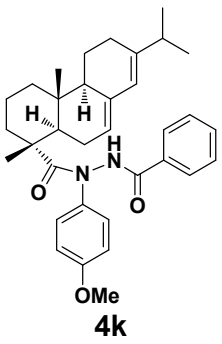
N'-(4-methoxyphenyl)-N'-benzoylbenzohydrazide: ^{1}H NMR (400 MHz, DMSO-D_6) δ 11.51 (s, H), 7.38-7.99 (m, 12H), 6.95 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 165.25, 157.64, 132.13, 131.86, 130.17, 128.55, 127.83, 127.26, 113.91, 55.25. HRMS (ESI) calcd for $C_{21}H_{19}N_2O_3^+$ 347.1351 $[M+H]^+$, found 347.13959.



N'-((R)-4-((5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoyl)-4-methoxy-N'-

phenylbenzohydrazide

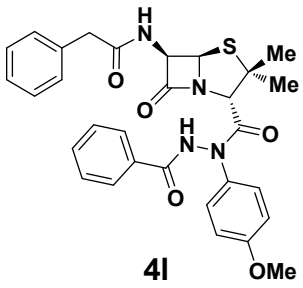
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, H), 7.71-7.83 (m, 2H), 7.42-7.53 (m, 5H), 6.75-6.90 (m, 2H), 3.80 (s, 3H), 2.78-2.92 (m, 3H), 1.91-2.29 (m, 16H), 1.58-1.63 (m, H),1.26-1.39 (m, 7H), 1.03 (s, 3H), 0.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.07, 209.22, 208.77, 173.49, 165.92, 162.60, 141.92, 129.42, 127.95, 123.89, 113.64, 56.90, 55.39, 51.71, 48.96, 46.79, 45.57, 44.96, 42.78, 38.62, 36.46, 35.98, 35.49, 35.22, 31.03, 27.55, 25.12, 21.88, 18.73, 11.85. HRMS (ESI) calcd for $C_{38}H_{47}N_2O_6^+$ 627.34286 $[M+H]^+$, found 627.34150.



4k

(1R,4aR,4bR,10aR)-N'-benzoyl-7-isopropyl-N-(4-methoxyphenyl)-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthrene-1-carbohydrazide:

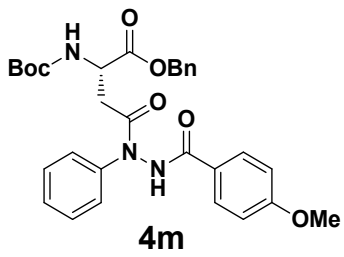
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, H), 7.73-7.75 (d, 2H, J = 7.74), 7.50-7.52 (d, 2H, J = 7.51), 7.30-7.38 (m, 3H), 6.85-6.87 (d, 2H, J = 6.86), 5.77 (s, H), 5.41 (s, H), 3.83 (s, 3H), 2.39-2.43 (m, H), 2.20-2.23 (m, H), 2.04-2.10 (m, 3H), 1.75-1.83 (m, 3H),1.60 (s, 2H), 1.48 (s, 2H), 1.26 (s, 3H), 1.12 (s, 3H), 1.01-1.02 (m, 6H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.09, 167.14, 163.58, 145.60, 145.07, 136.29, 130.20, 129.90, 129.41, 129.18, 125.40, 123.46, 121.86, 114.68, 56.26, 52.34, 49.28, 45.94, 38.81, 38.54, 38.08, 35.73, 35.57, 34.31, 30.55, 28.26, 26.76, 24.83, 23.34, 22.28, 21.74, 19.98, 19.07, 15.05. HRMS (ESI) calcd for $C_{34}H_{43}N_2O_3^+$ 527.3229 $[M+H]^+$, found 527.32790.



4l

N-((2S,5R,6R)-2-(2-benzoyl-1-(4-methoxyphenyl)hydrazinecarbonyl)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptan-6-yl)-2-phenylacetamide:

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48* (s, H), 10.20 (s, H), 7.86-7.88 (d, 2H, J = 7.87), 7.58-7.60 (d, 2H, J = 7.59), 7.40-7.48 (m, H), 7.28-7.35 (m, 5H), 7.20-7.24 (m, 2H), 6.93-6.95 (d, 2H, J = 6.94), 6.29-6.31 (d, H, J = 6.30), 5.59-5.60 (d, H, J = 5.59), 5.49-5.52 (m, H), 4.70 (s, H), 3.82 (s, 3H), 3.60-3.62 (d, 2H, J = 3.61), 1.72 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.48, 170.69, 167.19, 166.49, 160.08, 133.84, 133.63, 132.14, 131.83, 129.75, 129.58, 129.18, 128.95, 128.41, 127.76, 127.71, 127.58, 115.17, 68.44, 66.52, 65.28, 59.11, 55.53, 43.51, 34.06, 26.63. HRMS (ESI) calcd for $C_{30}H_{31}N_4O_5S^+$ 559.1970 $[M+H]^+$, found 559.20140.

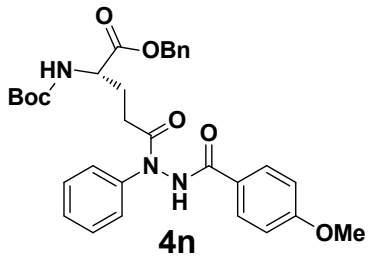


4m

(S)-benzyl 2-((tert-butoxycarbonyl)amino)-4-(2-(4-methoxybenzoyl)-1-phenylhydrazinyl)-4-oxobutanoate:

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.46* (s, H), 11.49 (s, H), 11.41* (s, H), 11.05* (s, H), 7.89-7.95 (m, 2H), 7.20-7.47 (m, 10H), 7.08-7.10 (m, 2H), 5.14 (s, 2H), 4.60 (br, H), 4.44* (br, H), 3.84 (s, 3H), 2.59-3.32 (br, 2H), 1.37 (s,

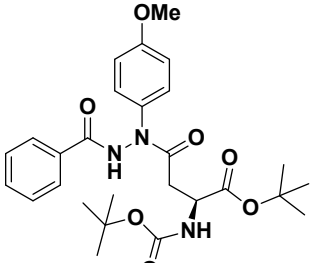
9H), 1.27* (s, 9H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 171.40, 170.89, 165.11, 162.61, 155.13, 141.34, 135.92, 129.62, 128.48, 128.29, 127.88, 127.54, 125.93, 123.54, 123.44, 113.97, 78.42, 65.99, 55.49, 49.94, 49.68, 35.43, 28.08. HRMS (ESI) calcd for $C_{30}H_{34}N_3O_7^+$ 548.2352 $[M+H]^+$, found 548.23893. * represents the minor isomer.



4n

(S)-benzyl 5-(2-benzoyl-1-(4-methoxyphenyl)hydrazinyl)-2-((tert-butoxycarbonyl)amino)-5-oxopentanoate:

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.18* (s, H), 11.38 (s, H), 10.98* (s, H), 7.93-7.94 (d, 2H, J = 7.93), 7.48-7.50 (d, 2H, J = 7.49), 7.34-7.37 (m, 8H), 7.20 (br, H), 7.06-7.08 (d, 2H, J = 7.07), 5.10 (s, 2H), 4.12 (br, H), 3.82 (s, 3H), 2.33-2.73 (br, 2H), 1.91-2.07 (br, 2H), 1.25-1.39 (m, 9H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 173.68, 172.23, 165.04, 162.55, 155.54, 141.67, 135.93, 129.54, 128.44, 128.33, 127.94, 127.73, 127.65, 125.73, 123.45, 113.91, 78.22, 65.80, 55.44, 53.08, 52.95, 29.94, 29.31, 28.08, 27.76, 25.85. HRMS (ESI) calcd for $C_{31}H_{36}N_3O_7^+$ 562.2509 $[M+H]^+$, found 562.25411. * represents the minor isomer.

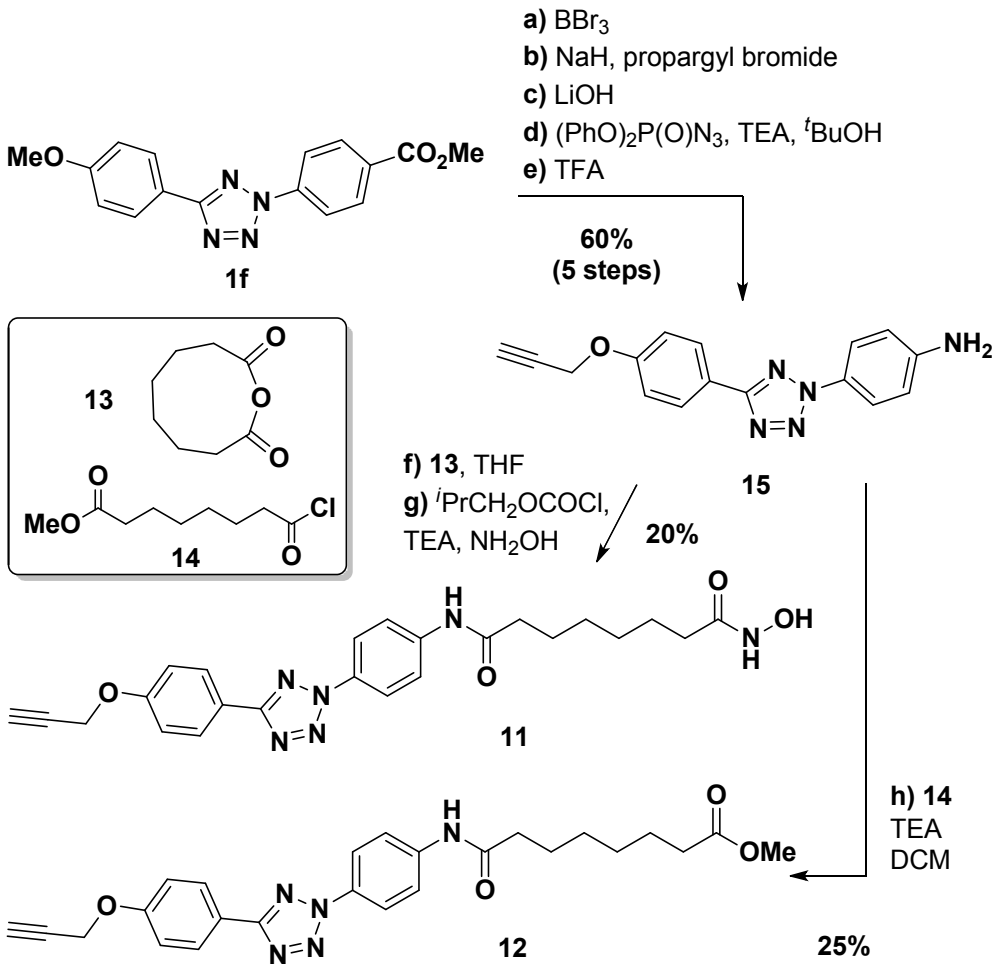


9

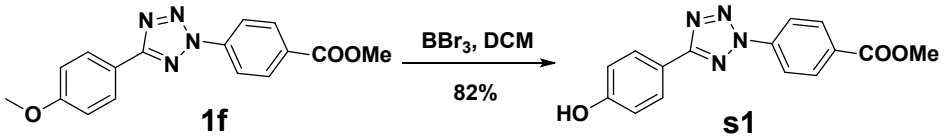
(S)-tert-butyl 4-(2-benzoyl-1-(4-methoxyphenyl)hydrazinyl)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoate:

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81* (s, H), 9.73 (s, H), 7.84-7.85* (d, 2H, J = 7.85), 7.867-7.69 (d, 2H, J = 7.68), 7.38-7.55 (m, 3H), 7.25-7.28 (m, 2H), 6.88-6.90 (d, 2H, J = 6.89), 6.79-6.81* (d, 2H, J = 6.80), 5.72-5.75 (d, H, J = 5.73), 4.38 (br, H), 3.80 (s, 3H), 3.74* (s, 3H), 2.94-3.00 (d, H, J = 2.97), 2.66-2.71 (d, H, J = 2.69), 1.40-1.48(m, 18H); ^{13}C NMR (100 MHz, CDCl3) δ 170.81, 170.56, 159.77, 158.33, 156.03, 155.74, 134.01, 132.61, 132.01, 131.62, 129.47, 128.83, 128.38, 127.54, 127.45, 126.58, 114.75, 114.02, 82.15, 79.72, 77.43, 77.31, 77.11, 76.79, 55.50, 55.40, 50.67, 36.86, 28.35, 28.32, 27.88. HRMS (ESI) calcd for $C_{27}H_{36}N_3O_7^+$ 514.2509 $[M+H]^+$, found 514.25504. * represents the minor isomer.

Scheme S1. Syntheses of Probe **11** and pseudo-Probe **12**

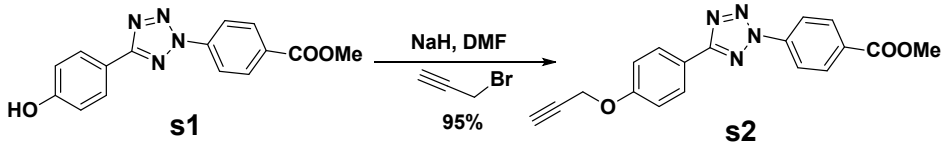


Reagents and conditions: a) BBr_3 (10 equiv), DCM, −78 °C to RT, 82%; b) NaH (1.2 equiv), propargyl bromide (1.2 equiv), DMF, 0 °C to RT, 95%; c) LiOH (5 equiv), THF/MeOH/H_2O, 65°C reflux, 95%; d) $(PhO)_2P(O)N_3$ (1.5 equiv), TEA (1.5 equiv), ^{t}BuOH/toluene (1:1), 3Å molecular sieves, reflux, 98%; e) TFA, DCM, RT, 82%; f) **13** (1 equiv), THF, RT; g) ^{i}PrCH$_2$OCOCl (5 equiv), TEA, THF, NH_2OH (5 equiv), 20%, purified by HPLC; h) **14** (1.2 equiv), TEA, DCM, 25%, purified by HPLC.



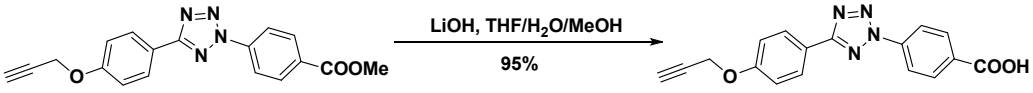
Under the N_2 atmosphere, **1f** (325 mg) was dissolved in dried DCM (6.3 mL) at -78 °C, and then added BBr_3 (10 equiv, diluted with dried DCM) slowly. After raising the temperature to RT gradually, the solution was stirred overnight. The reaction mixture was quenched with saturated sodium bicarbonate, extracted with EtOAc and dried over sodium sulfate. Then the organic solvent was removed under vacuum, and the resulting residue was purified by flash column chromatography on silica gel using PE/EtOAc as the eluent to give product **s1** (255 mg, 82% yield) ; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 10.13 (s, H), 8.30-8.32 (d, 2H, J = 8.31), 8.23-8.26 (d, 2H, J = 8.25), 8.01-8.03 (d, 2H, J = 8.02), 6.96-6.99 (d, 2H, J = 6.98), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.52, 160.47, 139.60, 131.67, 131.01, 128.99, 120.33, 117.40, 116.63, 53.01. HRMS (ESI) calcd for $C_{15}H_{13}N_4O_3^+$ 297.09822 $[M+H]^+$, found 297.09838.



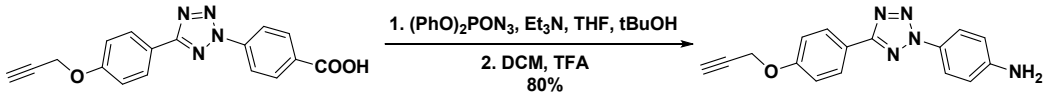
s1 s2

Under a nitrogen atmosphere, to a dry DMF solution (5 mL) of **s1** (150 mg) at 0 °C were added NaH (1.2 equiv) and propargyl bromide (1.2 equiv) slowly. After raising the reaction temperature to RT gradually, the solution was stirred overnight. The reaction mixture was quenched with saturated ammonium chloride, extracted with EtOAc and dried over sodium sulfate. Then the organic solvent was removed under vacuum, was purified by flash column chromatography on silica gel using PE/EtOAc as the eluent to give product **s2** (161 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.31 (m, 6H), 7.12-7.14 (d, 2H, J = 7.13), 4.78-4.79 (d, 2H, J = 4.79), 3.98 (s, 3H), 2.56-2.57 (t, H, J = 2.57); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.90, 165.33, 159.60, 139.80, 131.26, 131.00, 128.74, 120.32, 119.51, 115.43, 78.07, 75.99, 55.93, 52.49. HRMS (ESI) calcd for $C_{18}H_{15}N_4O_3^+$ 335.11387 $[M+H]^+$, found 335.11408.



s2 s3

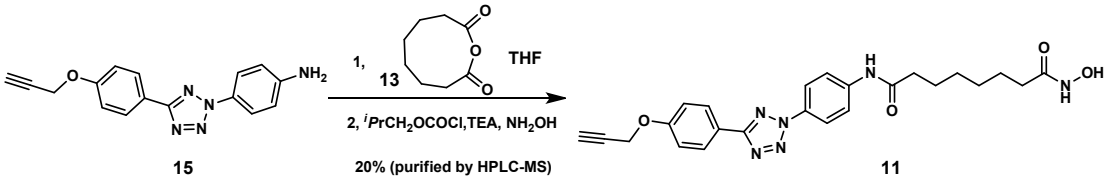
Compound **s2** (222 mg) was first dissolved in a mixture solution of THF/MeOH/H2O (3/1/1). Then LiOH (5 equiv) was added. The reaction mixture was reflux at 65 °C for 2 h. The reaction mixture was acidized with 2M HCl to obtain precipitates, which was collected by filtering to give product **s3** (202 mg, 95% yield). ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.27-8.29 (d, 2H, J = 8.28), 8.21-8.23 (d, 2H, J = 8.22), 8.12-8.14 (d, 2H, J = 8.13), 7.21-7.23 (d, 2H, J = 7.22), 4.92-4.92 (d, 2H, J = 4.92), 3.64-3.65 (t, 1H, J = 3.65); ^{13}C NMR (125 MHz, DMSO-D_6) δ 166.20, 164.55, 159.32, 138.84, 131.87, 131.26, 128.31, 119.76, 119.26, 115.69, 78.83, 78.63, 55.65. HRMS (ESI) calcd for $C_{17}H_{11}N_4O_3^-$ 319.082567 $[M+H]^-$, found 319.08239.



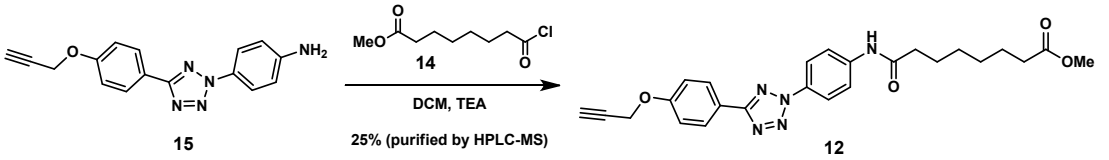
s3 15

Compound **s3** (150 mg) was first dissolved in a mixture solution of THF/t-BuOH (1:1). To this solution were added 2.1g/mmol 3Å molecular sieves, Et_3N (2.5 equiv) and $(PhO)_2PON_3$ (2.5 equiv) subsequently. The reaction mixture was reflux at 115 °C until complete conversion was observed (monitored by TLC). The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was

dissolved in DCM and TFA (10 equiv) was added. After complete conversion was observed (monitored by TLC) at RT, the reaction was quenched by $NaHCO_3$ (s, aq) and the extracted with EtOAc. The organic layer was concentrated under vacuum and purified by flash column chromatography on silica gel using PE/EtOAc as the eluent to give product **11** (109 mg, 80% yield). ^{1}H NMR (400 MHz, MeOD-D_4) δ 8.11-8.13 (d, 2H, J = 8.12), 7.84-7.86 (d, 2H, J = 7.85), 7.14-7.17 (d, 2H, J = 7.15), 6.82-6.84 (d, 2H, J = 6.83), 4.82-4.83 (d, 2H, J = 4.82), 2.99-3.00 (t, 1H, J = 2.99); ^{13}C NMR (125 MHz, DMSO-D_6) δ 164.10, 159.42, 151.12, 128.47, 125.90, 121.75, 120.50, 116.08, 114.19, 79.40, 79.30, 56.12. HRMS (ESI) calcd for $C_{16}H_{14}N_5O^+$ 292.11929 $[M+H]^+$, found 292.11917.



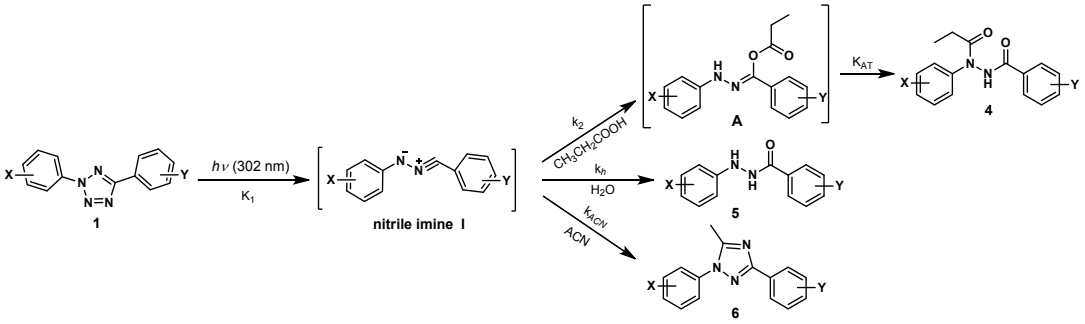
Under the N_2 atmosphere, compound **11** (25 mg) was dissolved in dry THF (0.3 mL). To this solution were added **12** (1.1 equiv). The reaction mixture was stirred at RT until complete conversion was observed (monitored by HPLC-MS). The reaction mixture was concentrated under vacuum. Under the N_2 atmosphere, the residue was dissolved in THF (0.3 mL). To this solution were added $iPrCH_2OCOCl$ (5 equiv), and Et_3N (5 equiv) at 0 °C. The mixture was stirred overnight at RT, after which NH_2OH (5 equiv) dissolved in MeOH was added. The reaction mixture was stirred at RT (monitored by HPLC-MS). The product **13** were purified by HPLC-MS (8 mg, 20% yield). ^{1}H NMR (400 MHz, MeOD-D_4) δ 8.11-8.16 (m, 4H), 7.84-7.86 (d, 2H, J = 7.85), 7.15-7.17 (d, 2H, J = 7.16), 4.83-4.84 (d, 2H, J = 4.84), 3.00-3.01 (t, 1H, J = 3.00), 2.40-2.44 (t, 2H, J = 2.42), 2.08-2.12 (t, 2H, J = 2.10), 1.71-1.75 (m, 2H), 1.61-1.66 (m, 2H), 1.40-1.42 (m, 4H); ^{13}C NMR (125 MHz, MeOD-D_4) δ 173.43, 171.56, 164.77, 159.76, 140.29, 132.38, 128.03, 120.31, 120.10, 115.17, 114.16, 78.00, 75.74, 55.38, 39.06, 36.51, 32.30, 28.50, 28.42, 25.17. HRMS (ESI) calcd for $C_{24}H_{27}N_6O_4^+$ 463.20883 $[M+H]^+$, found 463.20915; $C_{24}H_{26}N_6NaO_4^+$ 485.19077 $[M+Na]^+$, found 485.19102.



Under the N_2 atmosphere, compound **11** (30 mg) was dissolved in DCM (0.5 mL). To this solution were added **14** (1.2 equiv) and Et_3N (1.5 equiv). The reaction mixture was stirred at RT until complete conversion was observed (monitored by HPLC-MS). The product **15** were purified by HPLC-MS (11.7 mg, 25% yield). ^{1}H NMR (400 MHz, CDCl3) δ 8.18-8.21 (d, 2H, J = 8.19), 8.12-8.15 (d, 2H, J = 8.13), 7.75-7.77 (d, 2H, J = 7.76), 7.49 (s, H), 7.10-7.13 (d, 2H, J = 7.12), 4.77-4.78 (d, 2H, J = 4.78), 3.68 (s, 3H), 2.56-2.57(t, H, J = 2.57), 2.39-2.42 (t, 2H, J = 2.41), 2.31-2.35 (t, 2H, J = 2.33), 1.74-1.79 (m, 2H), 1.64-1.69 (m, 2H), 1.40-1.47 (m, 4H); ^{13}C NMR (100 MHz, CDCl3) δ 174.29, 172.34, 164.85, 159.33, 139.19, 128.57, 120.57, 120.22,

115.30, 78.12, 75.94, 55.88, 51.55, 37.52, 33.90, 28.66, 28.61, 25.15, 24.60. HRMS (ESI) calcd for $C_{25}H_{28}N_5O_4^+$ 462.2063 $[M+H]^+$, found 462.21405.

3. *Kinetic study of the photo-induced acid addition reaction between tetrazoles and propionic acid (10 equiv) upon 302-nm UV irradiation*



Aliquots of tetrazole **1** stock solution (100mM in DMSO) and propionic acid were added into 5 mL CH_3CN/PBS buffer (1:1 v/v) in quartz test tube to obtain the final tetrazole concentration of 100 μM and the final acid concentration of 1 mM. Under vigorous stirring, the reaction mixtures were photoirradiated with a handheld 302nm UV lamp for a period of seconds, respectively. Then, aliquots of 0.5 mL reaction mixtures from each sample were withdrawn and injected into a reverse phase HPLC-MS system (C_{18} column, 5 μm, 150×4.6 mm, gradient of 70:30 water/acetonitrile to 10:90 water/acetonitrile). The tetrazole **1**, nitrile imine intermediate **I** and product **4** in the mixtures were monitored by UV absorbance at 254 nm respectively. The integrated areas at high absorbance of product were compared to the standard curve in order to obtain the concentration of product.

The photolysis of tetrazoles were found to be very fast and almost all of **1** has been converted to the nitrile imine intermediate (**I**) within 40s, thus $k_1 >> k_{obs.}$ The subsequent reactions of the nitrile imine proceed through three pathways: (a) the addition and rearrangement reaction with propionic acid; (b) the water quenching reaction with bulk water; (c) the cycloaddition reaction with acetonitrile. For parallel reactions, the rate expression are:

$$-\frac{d[I]}{dt} = k_2[I] + k_h[I] + k_{ACN}[I] = k_{obs}[I]$$

Given the intramolecular O→N acyl transfer was very rapid, thus $k_{AT} >> k_2$, $k_{AT}[A] = k_2[I]$

$$\frac{d[4]}{dt'} = k_2[I]$$

$$\frac{d[5]}{dt} = k_h[I]$$

$$\frac{d[6]}{dt} = k_{ACN}[I]$$

According to the first-order rate law, the solution to the first equation is:

$$ln\frac{[I]}{[I]_0} = -(k_2 + k_h + k_{ACN})t = -k_{obs}t$$

$$[I] = [I]_0 e^{-(k_2 + k_h + k_{ACN})t}$$

To find out how products [4], [5] and [6] change with time, we substitute for [I] from the last equation:

$$\frac{d[4]}{dt} = k_2[I] = k_2[I]_0 e^{-(k_2 + k_h + k_{ACN})t}$$

$$\frac{d[5]}{dt} = k_h[I] = k_h[I]_0 e^{-(k_2 + k_h + k_{ACN})t}$$

$$\frac{d[6]}{dt} = k_{ACN}[I] = k_{ACN}[I]_0 e^{-(k_2 + k_h + k_{ACN})t}$$

Assuming $[4]_0 = [5]_0 = [6]_0 = 0$,

$$[4] = \frac{k_2[I]_0}{k_2 + k_h + k_{ACN}}(1 - e^{-(k_2 + k_h + k_{ACN})t})$$

$$[5] = \frac{k_h[I]_0}{k_2 + k_h + k_{ACN}}(1 - e^{-(k_2 + k_h + k_{ACN})t})$$

$$[6] = \frac{k_{ACN}[I]_0}{k_2 + k_h + k_{ACN}}(1 - e^{-(k_2 + k_h + k_{ACN})t})$$

Herein, we focus on the rate of acid addition product **4**. The change in concentration of **4** was fitted to an one phase decay equation:

$$Y = (Y_0 - Plateau)e^{(-KX)} + Plateau$$

When $Y_0 = 0$, $k_{obs} = k_2 + k_h + k_{ACN}$

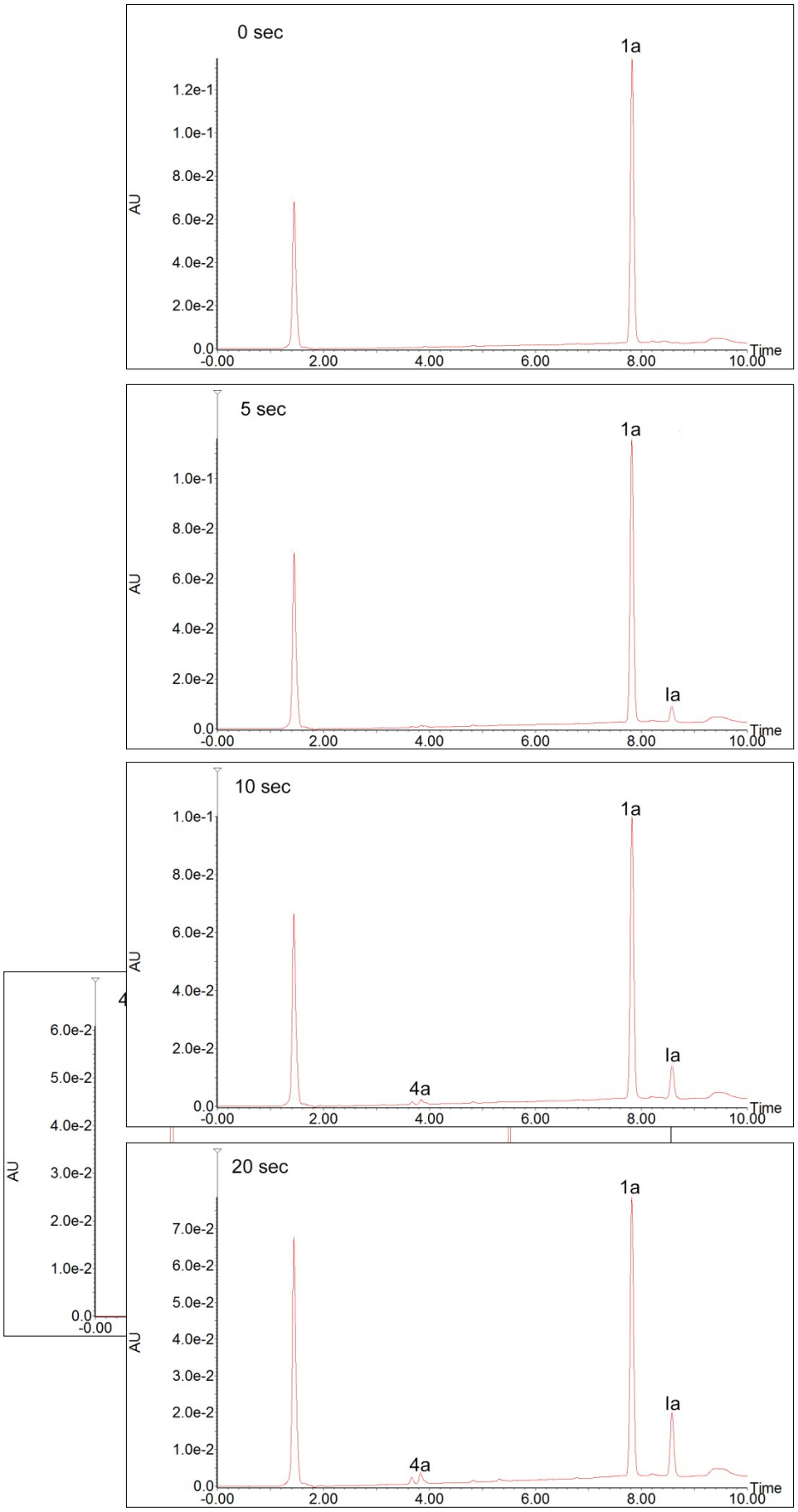
$$Plateau = \frac{k_2[I]_0}{k_2 + k_h + k_{ACN}} = \frac{k_2[I]_0}{k_{obs}}$$

$$k_2 = \frac{Plateau * k_{obs}}{[I]_0}$$

$$k_{COOH} = \frac{k_2}{[CH_3CH_2COOH]_0}$$

Table S2. Kinetic Study of Photo-induced reactions of tetrazoles with propionic acid

	Y_0	Plateau/$10^{-6}M^{-1}$	K_{obs}/ S^{-1}	R^2	$[I]_{0/10^{-6}M^{-1}}$	K_2/S^{-1}	$K_{COOH}/S^{-1}M^{-1}$
1a	0	56.06	0.005063	0.9797	100	0.002838	2.8
1b	0	58.65	0.009434	0.9027	100	0.005533	5.5
1c	0	95.73	0.007752	0.9955	100	0.007421	7.4
1d	0	5.582	0.005053	0.9392	100	0.0002821	0.28
1e	0	4.071	0.009374	0.4570	100	0.0003816	0.050
1f	0	35.54	0.002490	0.9772	100	0.00088495	0.88
1g	0	8.570	0.002490	0.8482	100	0.0002134	0.21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AU
Time
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la
10 sec
1a
la
4a
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la
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4a

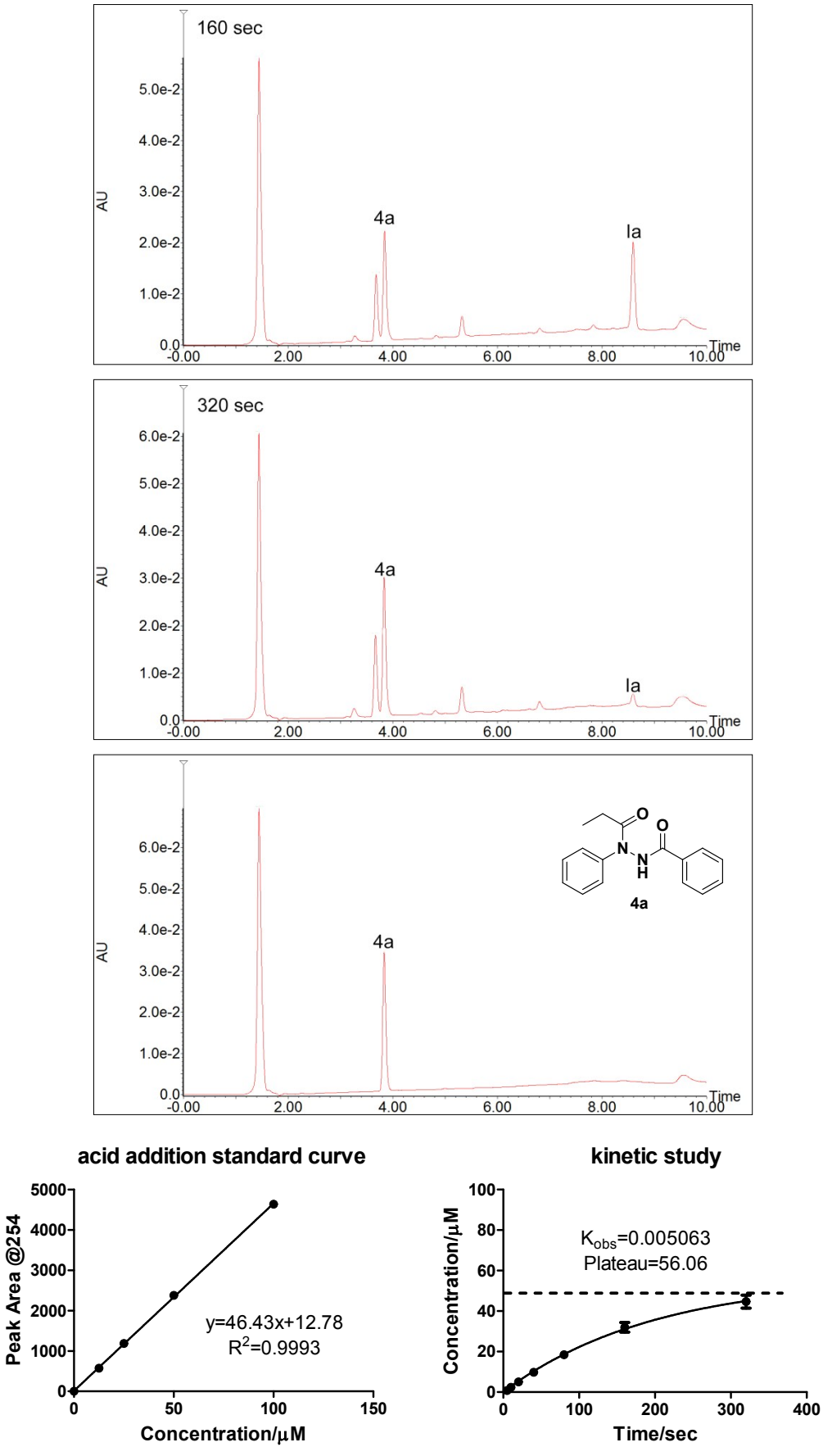
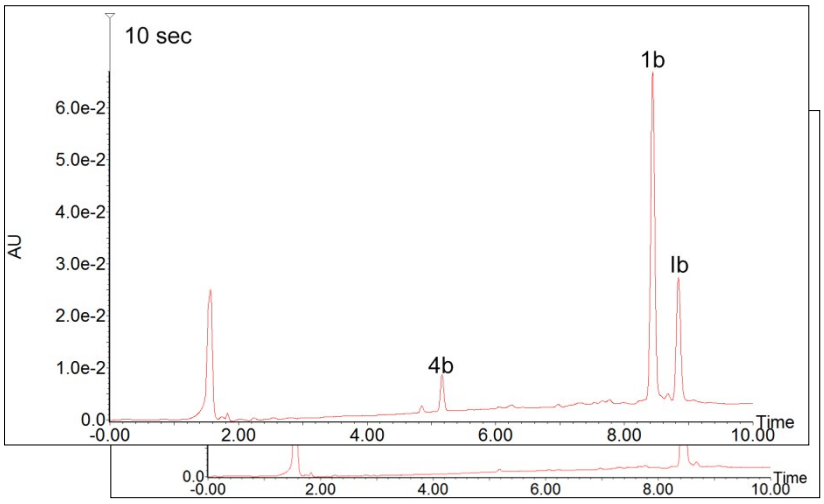


Fig. S1. Kinetic Study of Photo-induced reaction of tetrazole **1a** with propionic acid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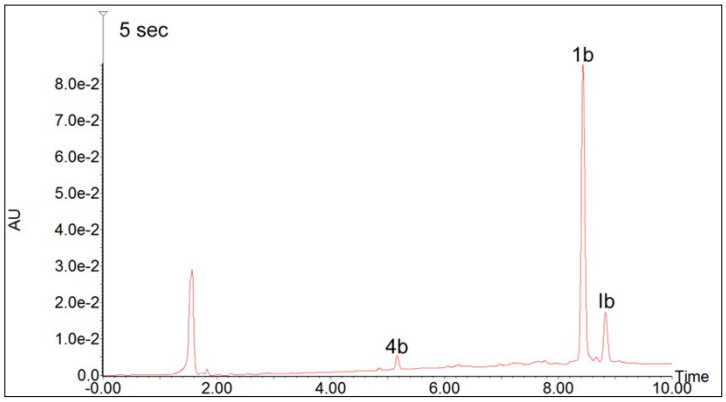
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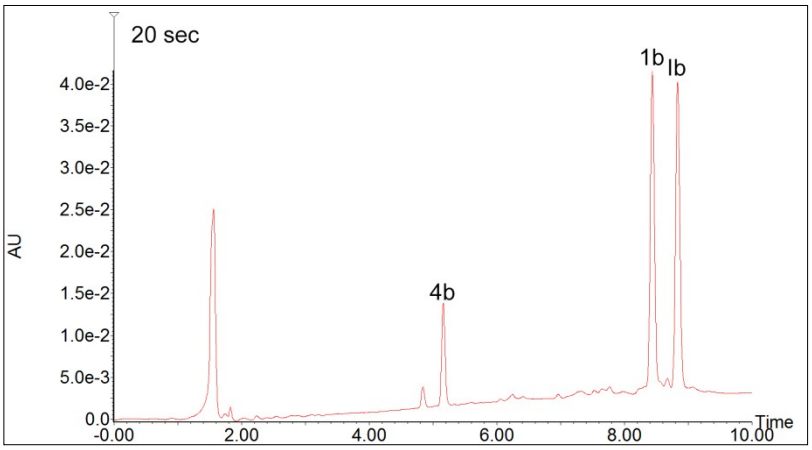
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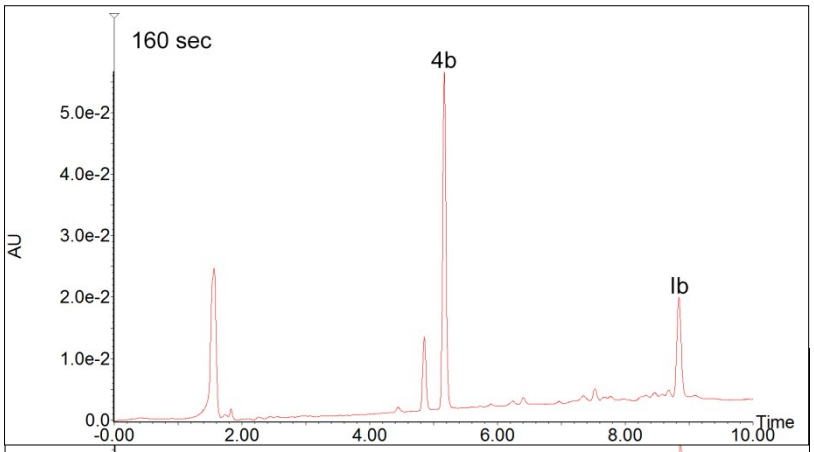
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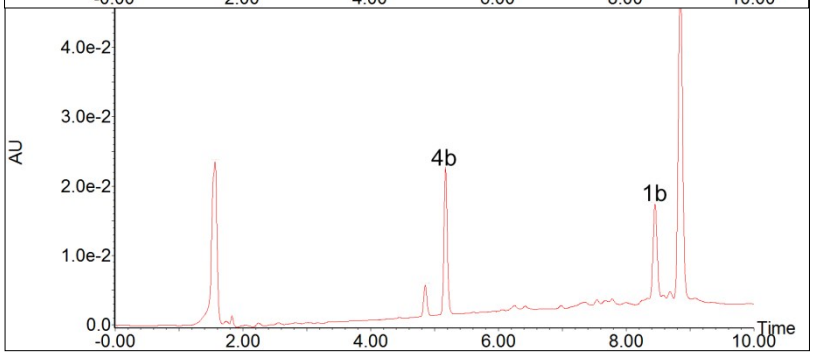
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1b
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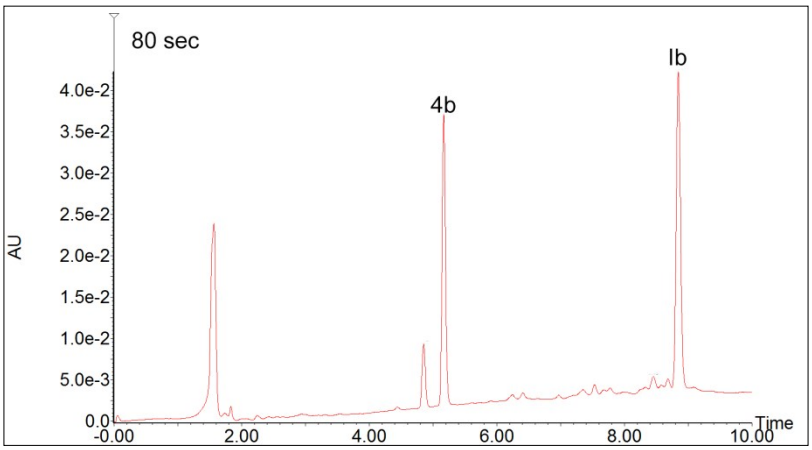
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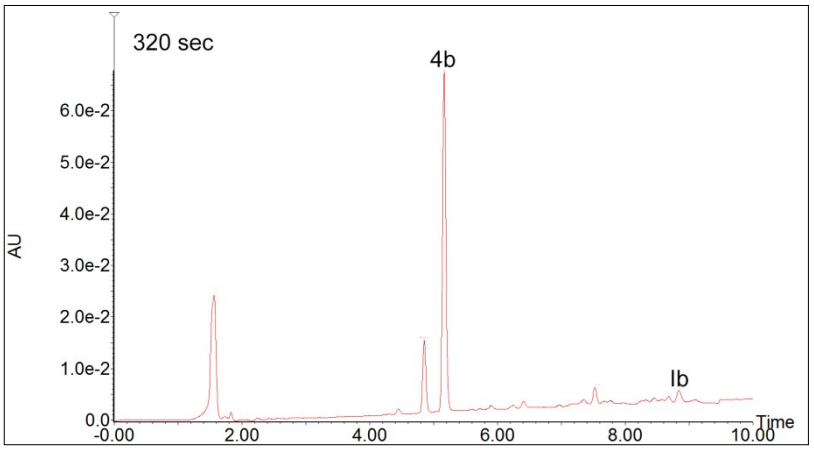
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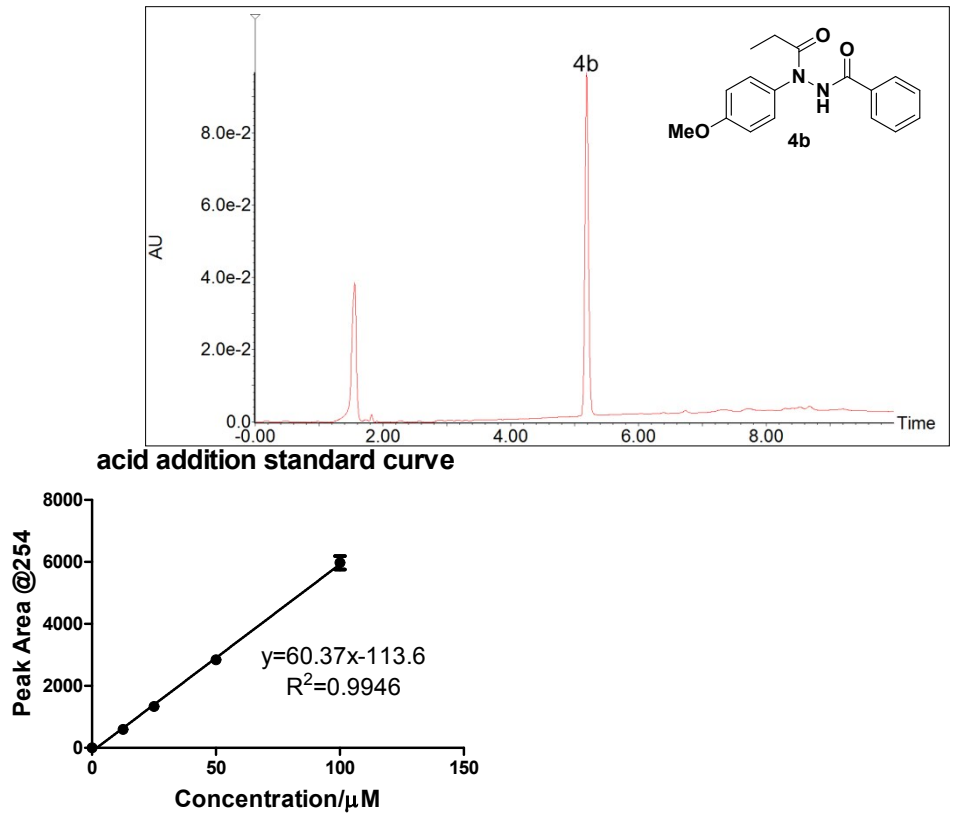
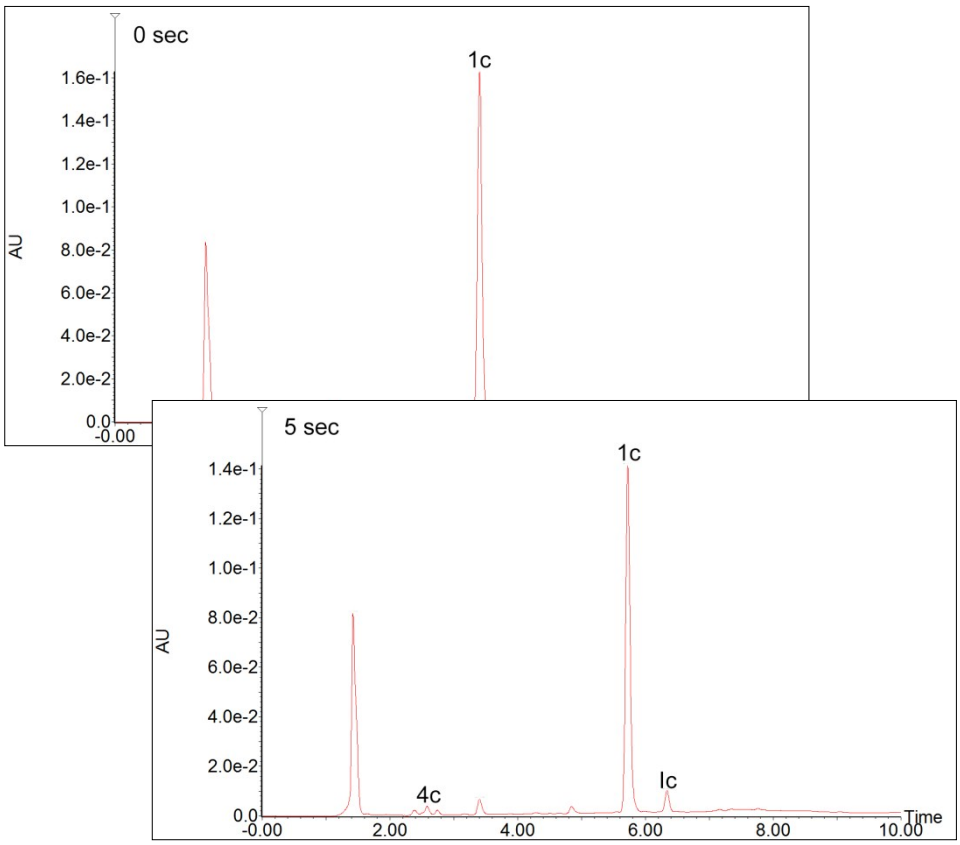
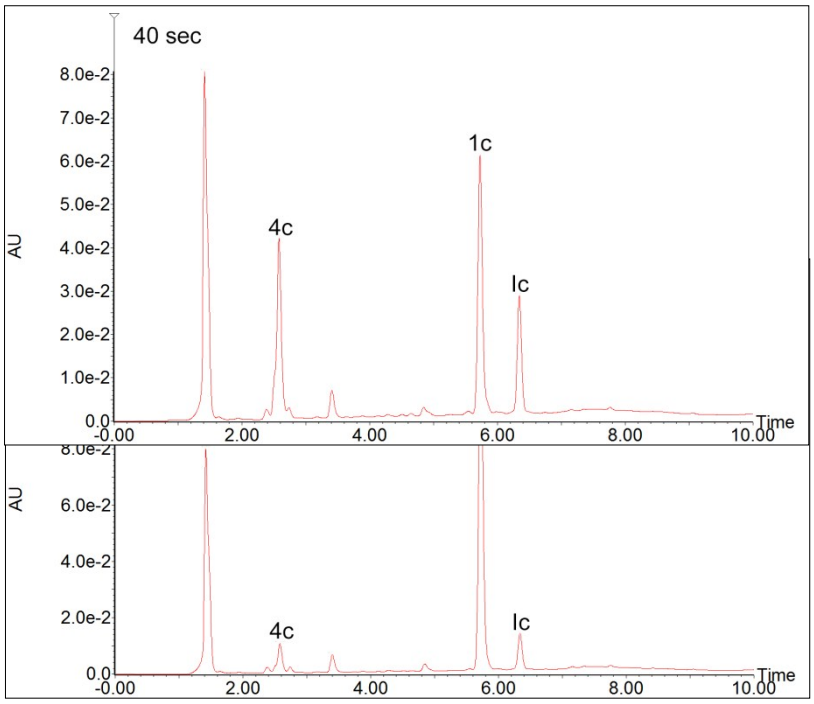


Fig. S2. Kinetic Study of Photo-induced reaction of tetrazole **1b** with propionic acid

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1.0e-2
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1c
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4.00
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8.00
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Time
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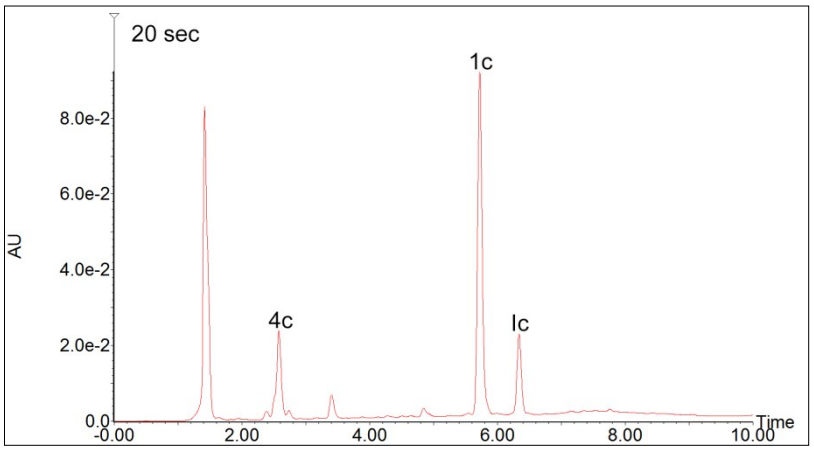
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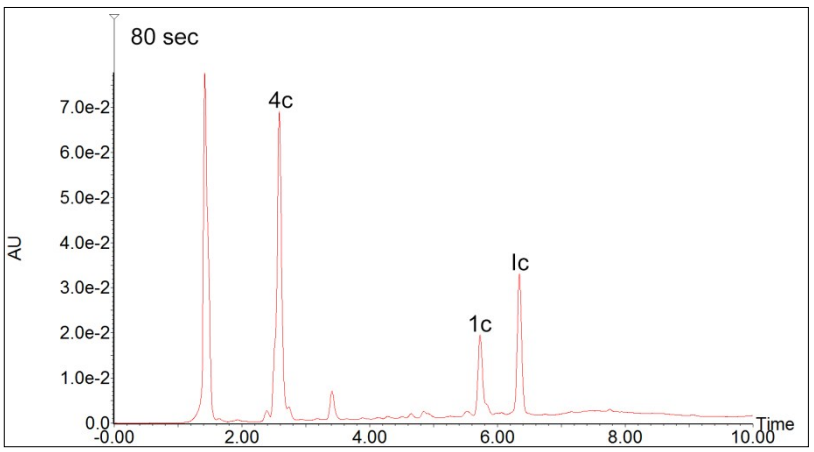
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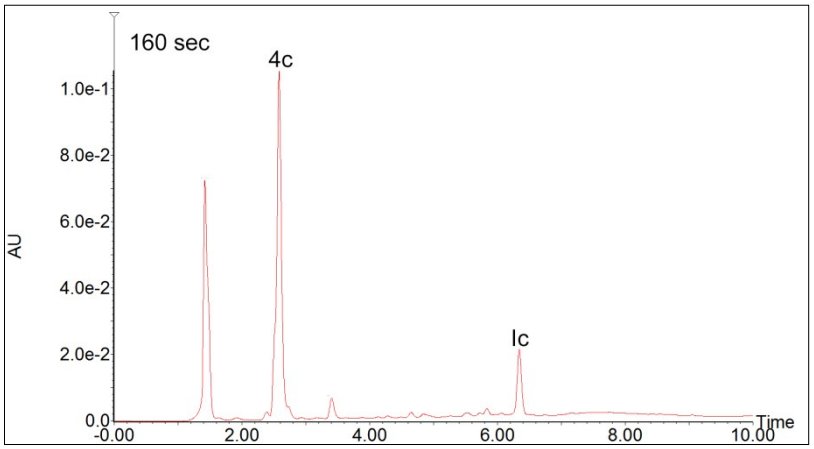
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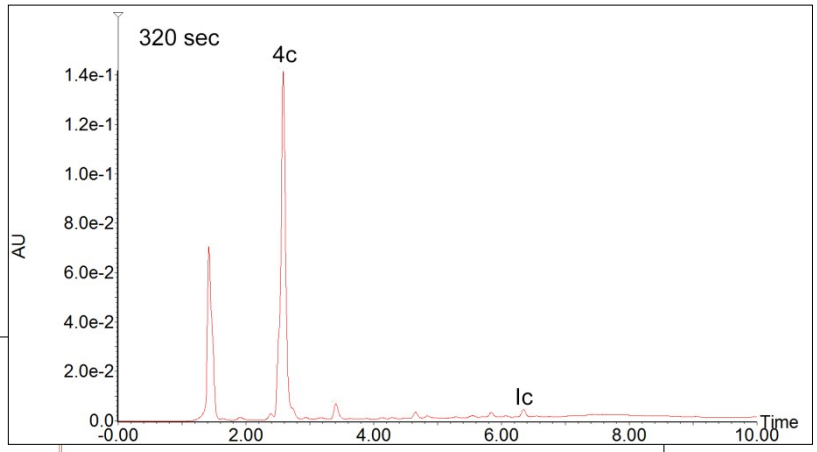
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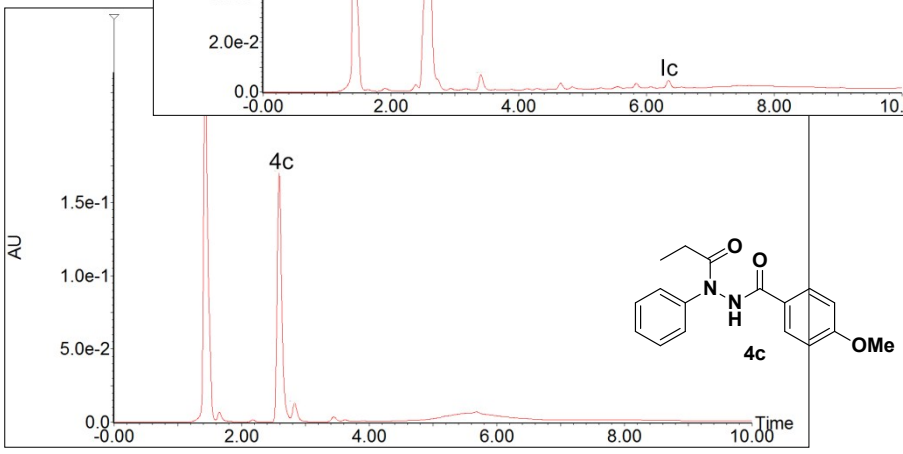
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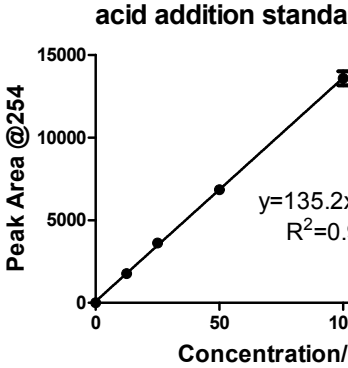

acid addition standa
Peak Area @254
Concentration/

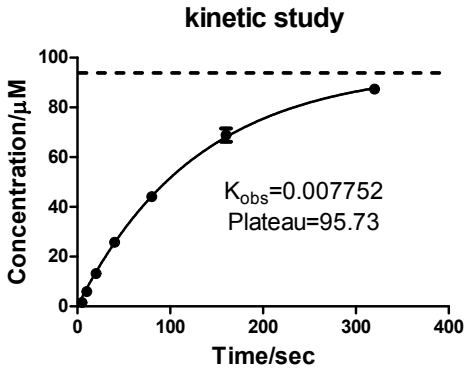
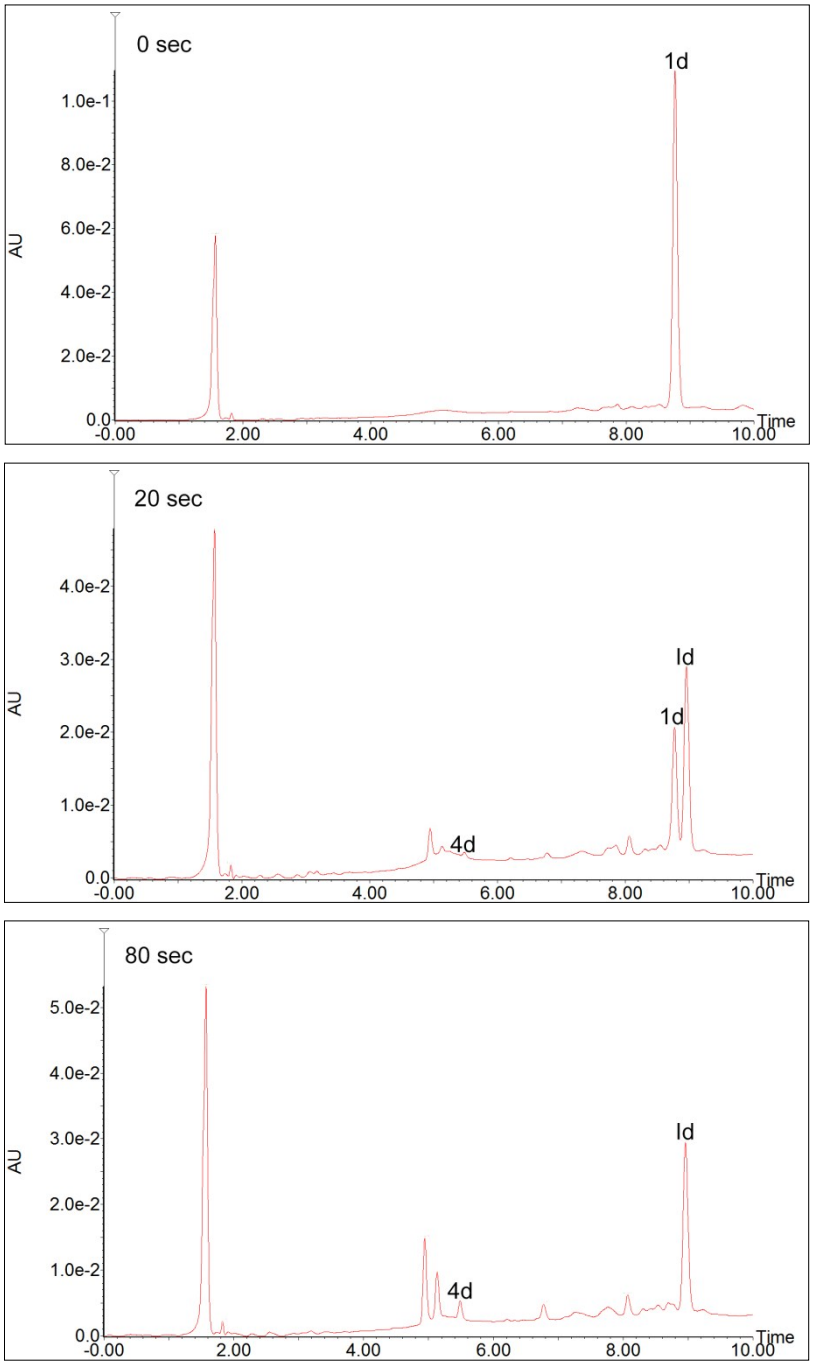


Fig. S3. Kinetic Study of Photo-induced reaction of tetrazole **1c** with propionic acid



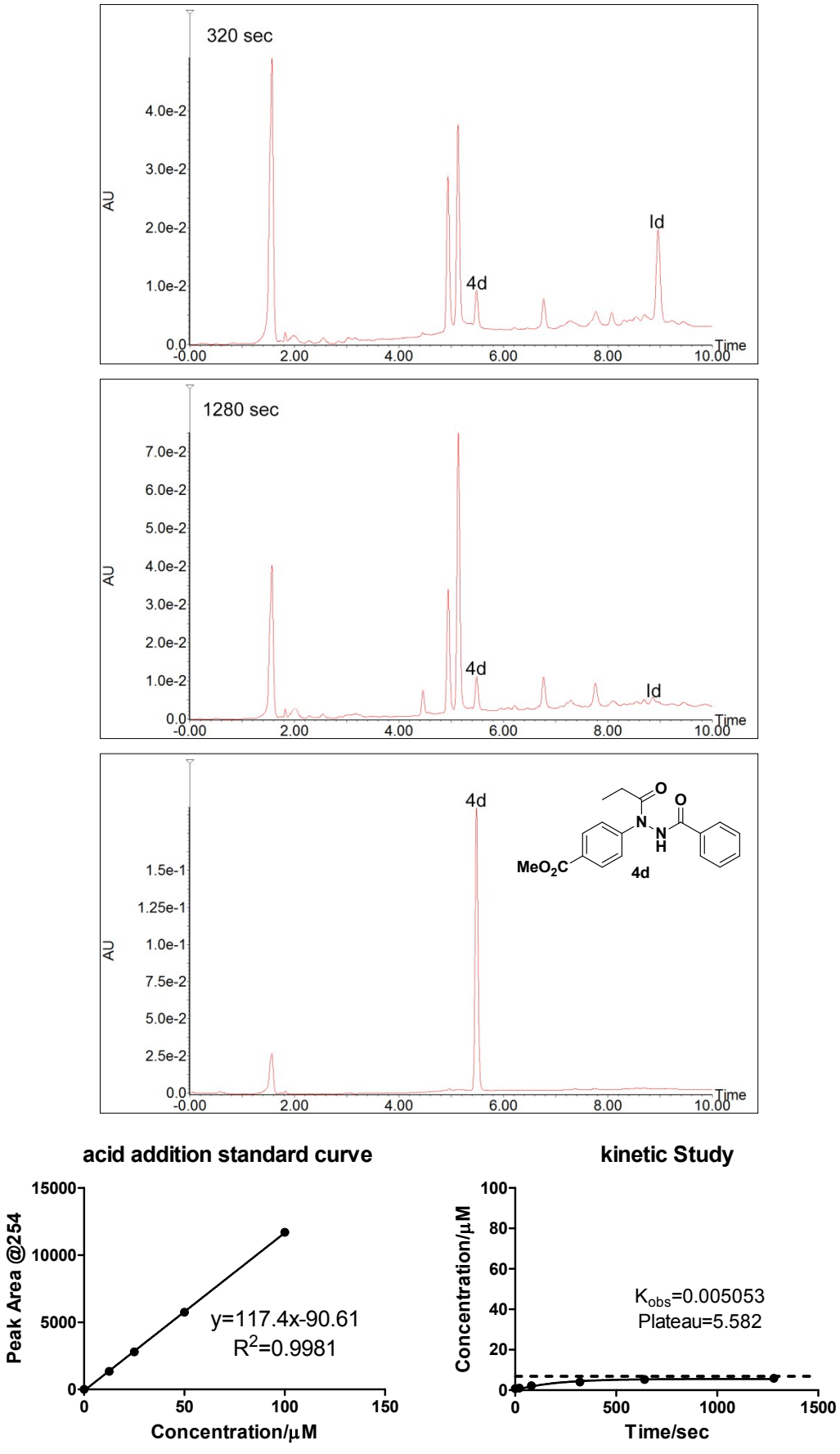


Fig. S4. Kinetic Study of Photo-induced reaction of tetrazole **1d** with propionic acid

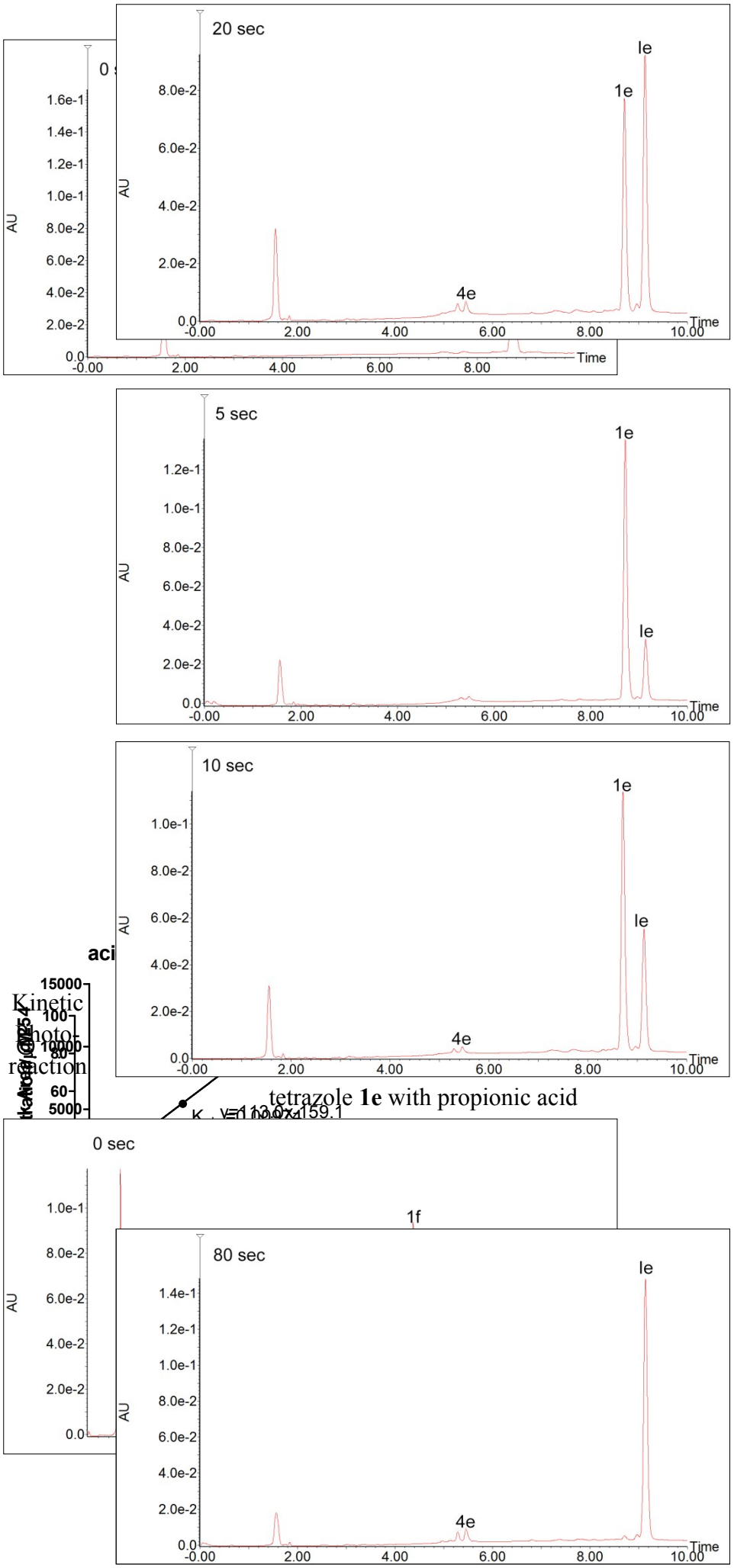
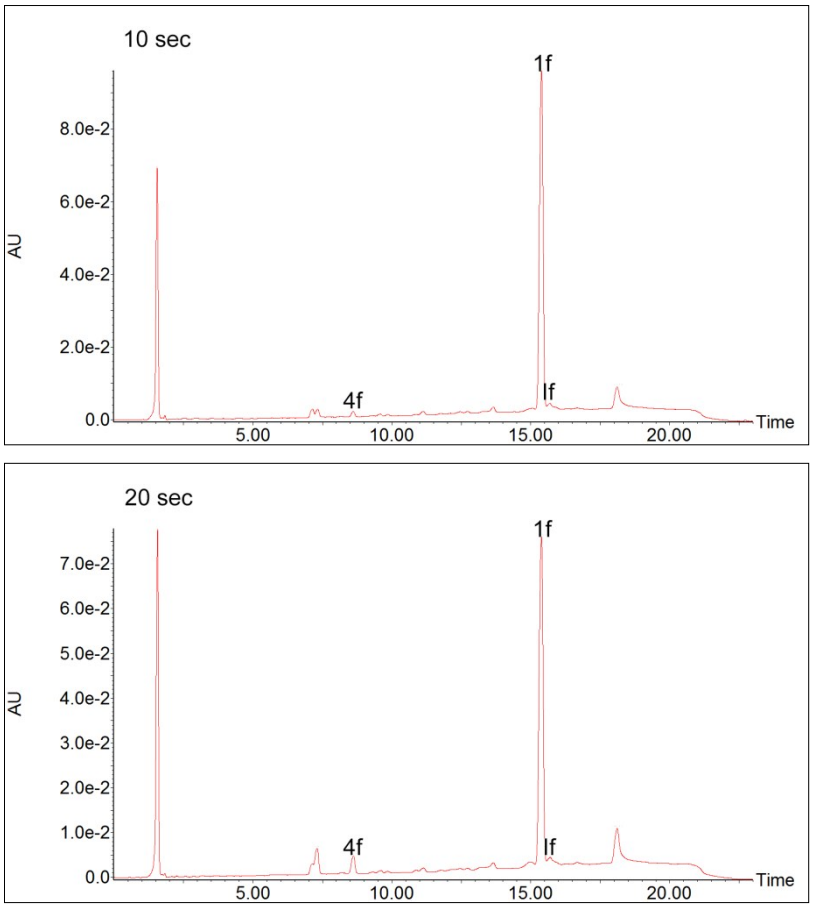


Fig. S5. Kinetic study of photo-induced reaction of tetrazole **1e** with propionic acid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15.00
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Time

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If
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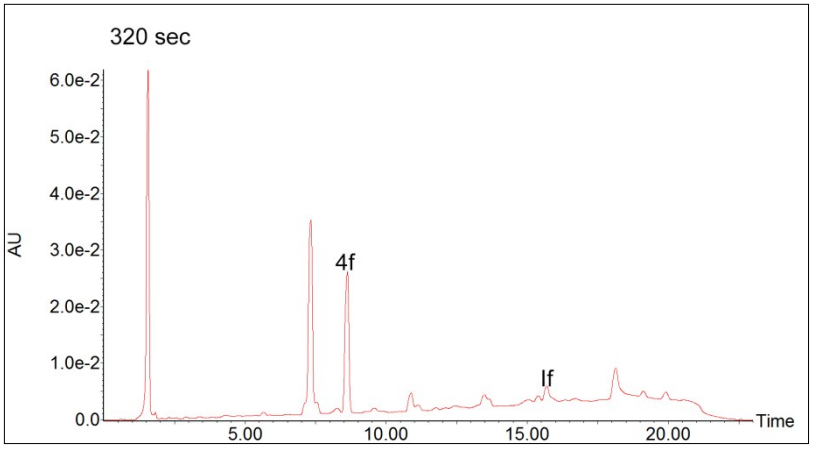
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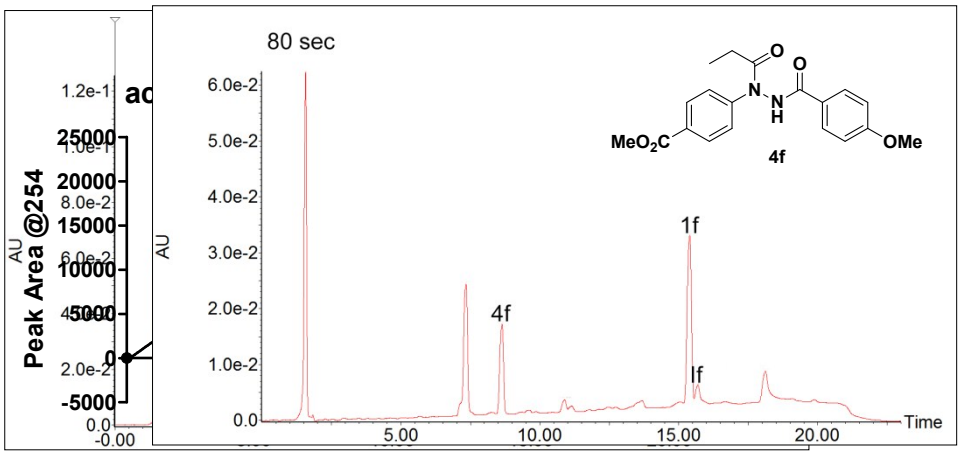
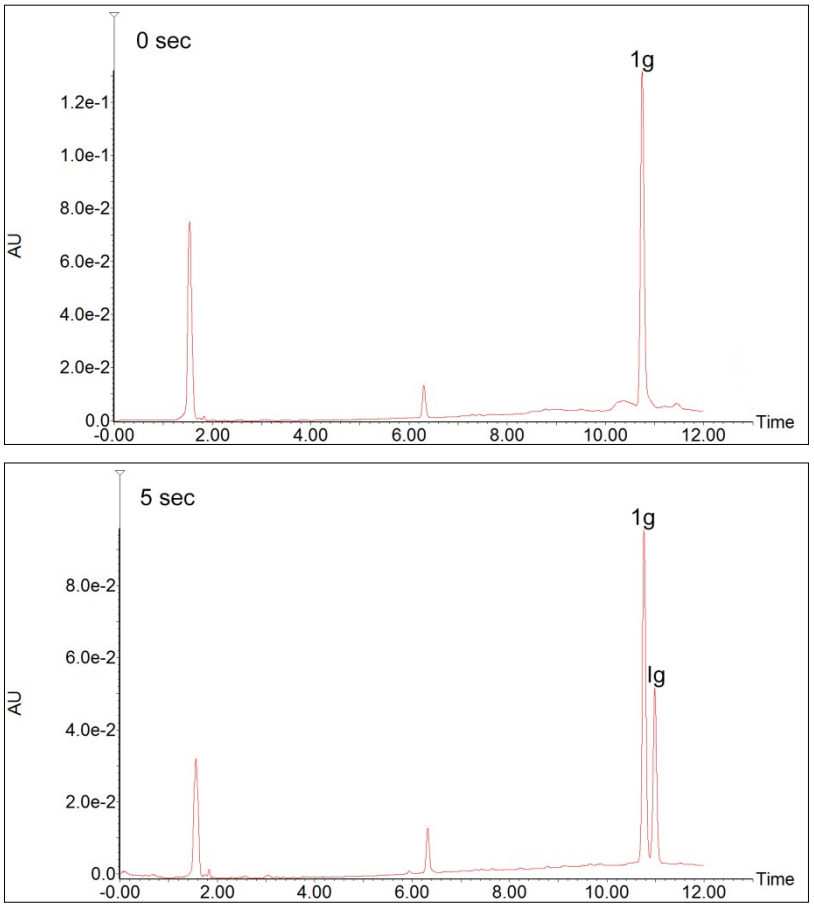
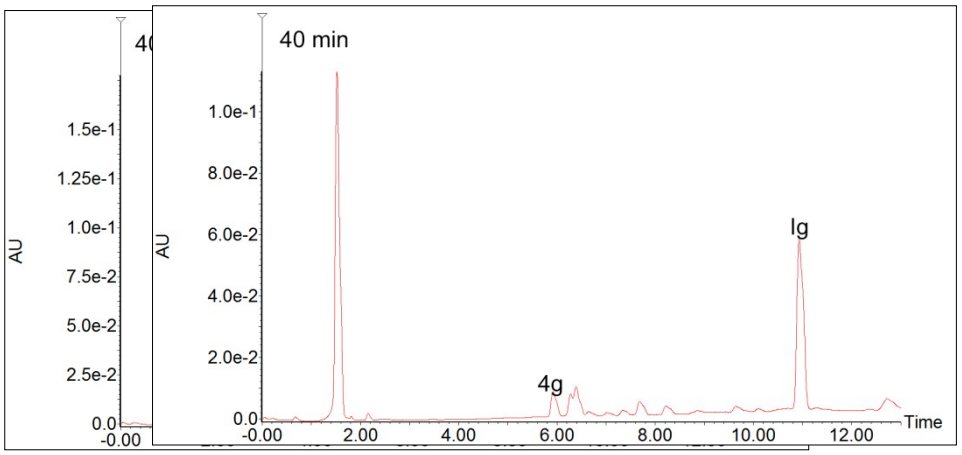


Fig. S6. Kinetic Study of Photo-induced reaction of tetrazole **1f** with propionic acid

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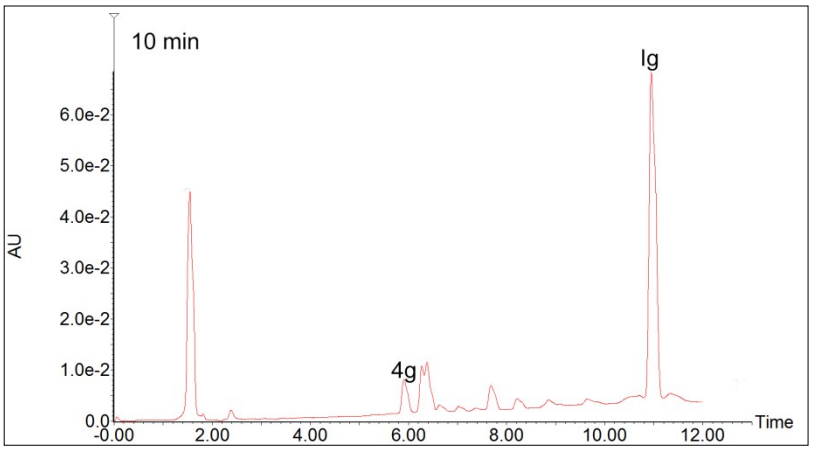
Time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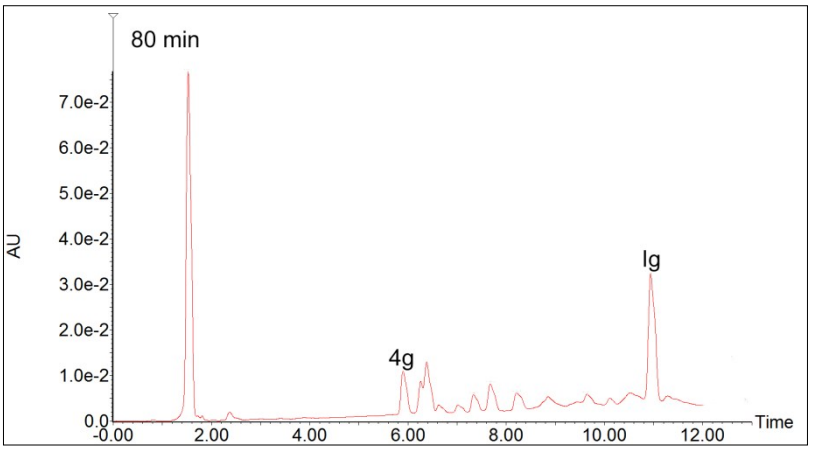
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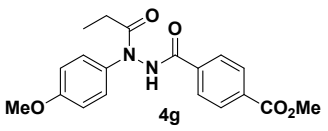
4g
-0.00
2.00
4.00
6.00
8.00
10.00
12.00
Time


O
O
N
N
H
MeO
CO2Me

4g

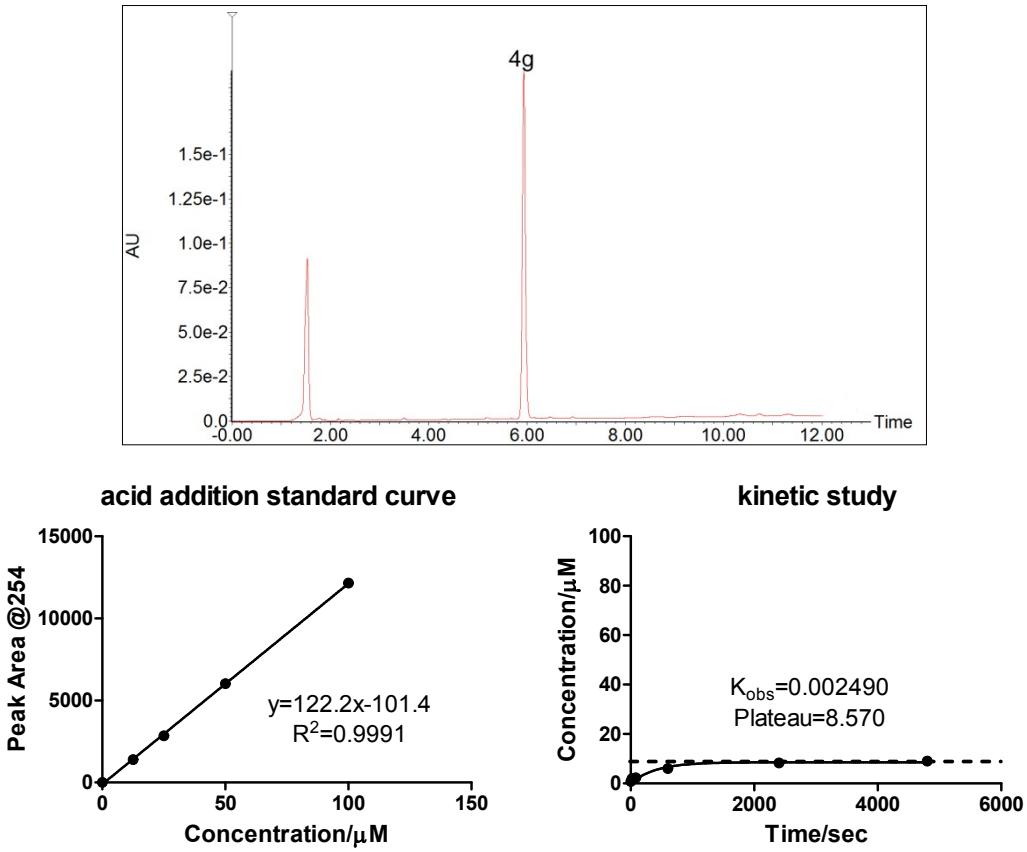
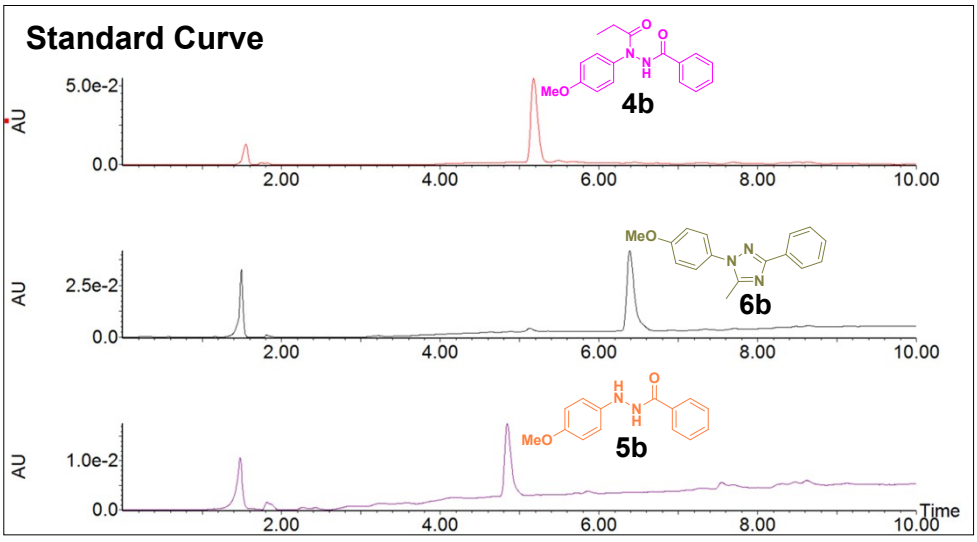


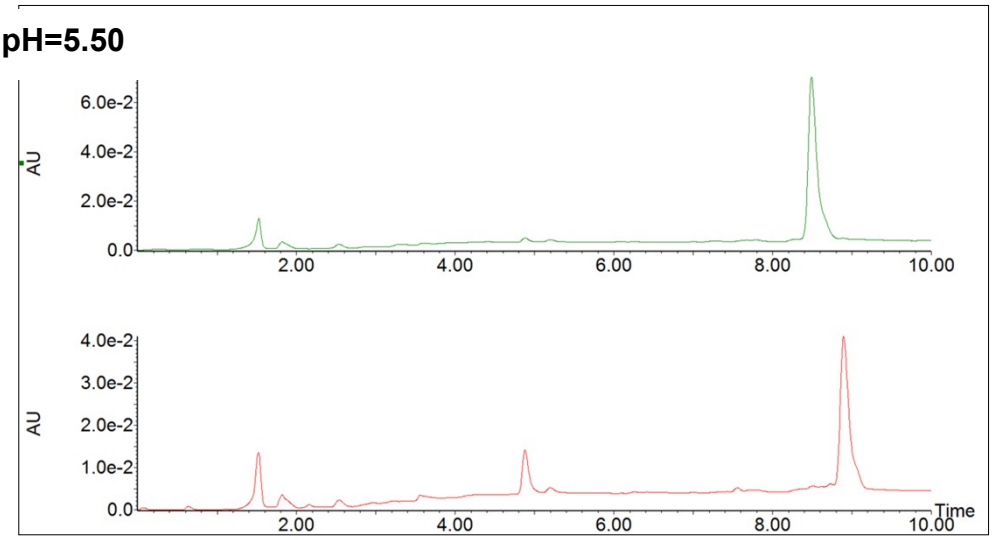
Fig. S7. Kinetic Study of Photo-induced reaction of tetrazole **1g** with propionic acid

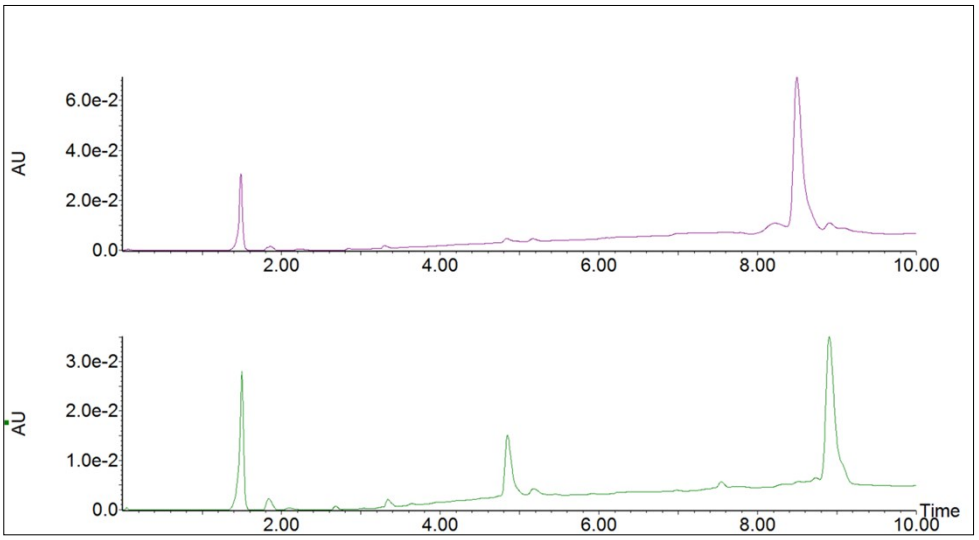
4. *The effect of pH on the product distribution of reaction of propionic acid with tetrazole 1b*

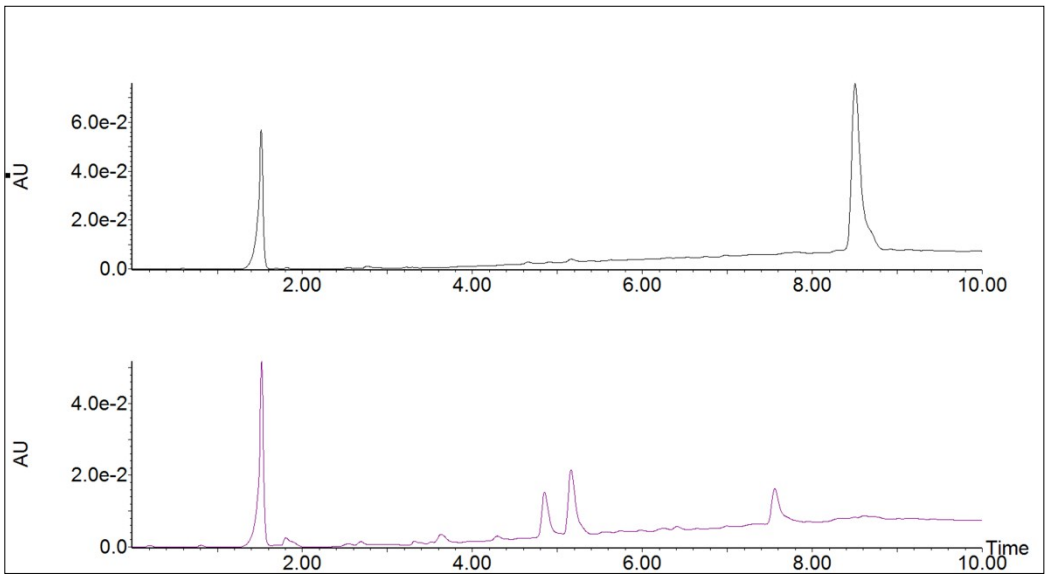


pH=2.52

pH=5.50


AU
6.0e-2
4.0e-2
2.0e-2
0.0
2.00
4.00
6.00
8.00
10.00
AU
4.0e-2
3.0e-2
2.0e-2
1.0e-2
0.0
Time


AU
6.0e-2
4.0e-2
2.0e-2
0.0
2.00
4.00
6.00
8.00
10.00
AU
3.0e-2
2.0e-2
1.0e-2
0.0
Time


AU
6.0e-2
4.0e-2
2.0e-2
0.0
2.00
4.00
6.00
8.00
10.00
AU
4.0e-2
2.0e-2
0.0
Time

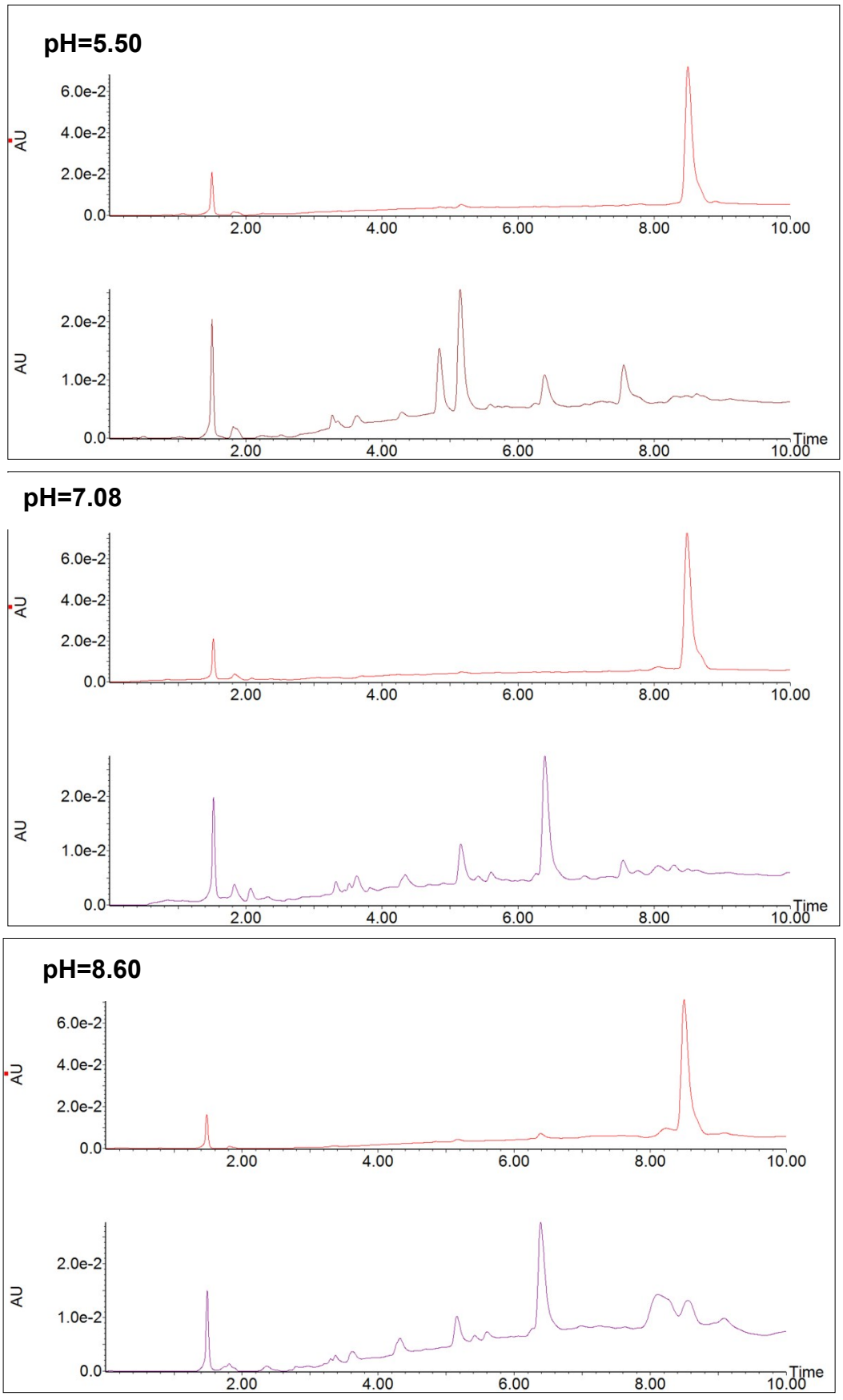
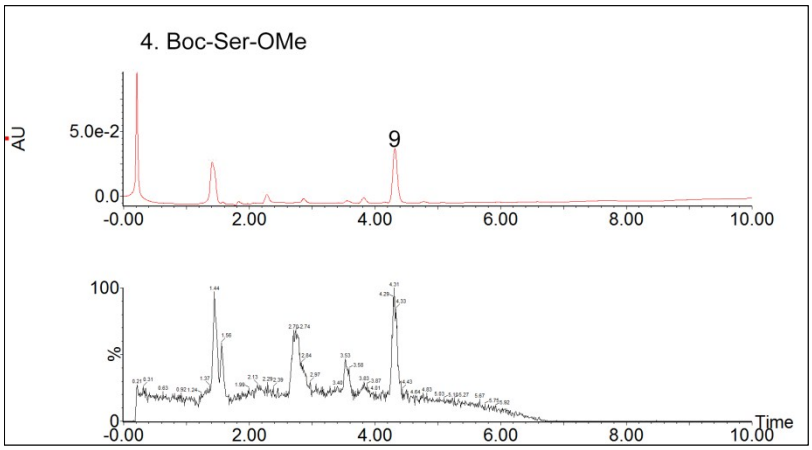
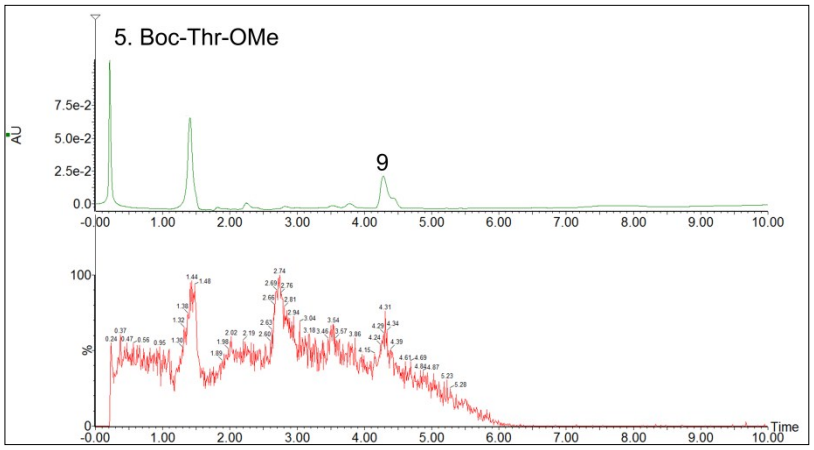
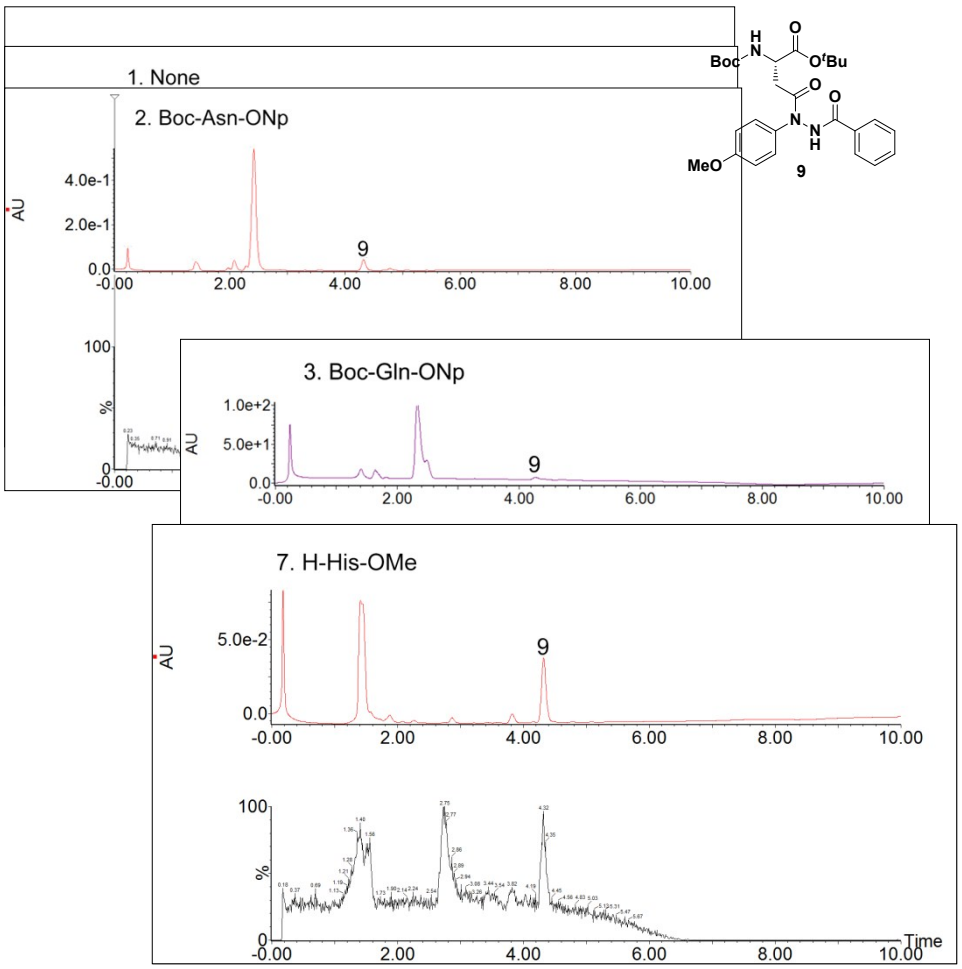


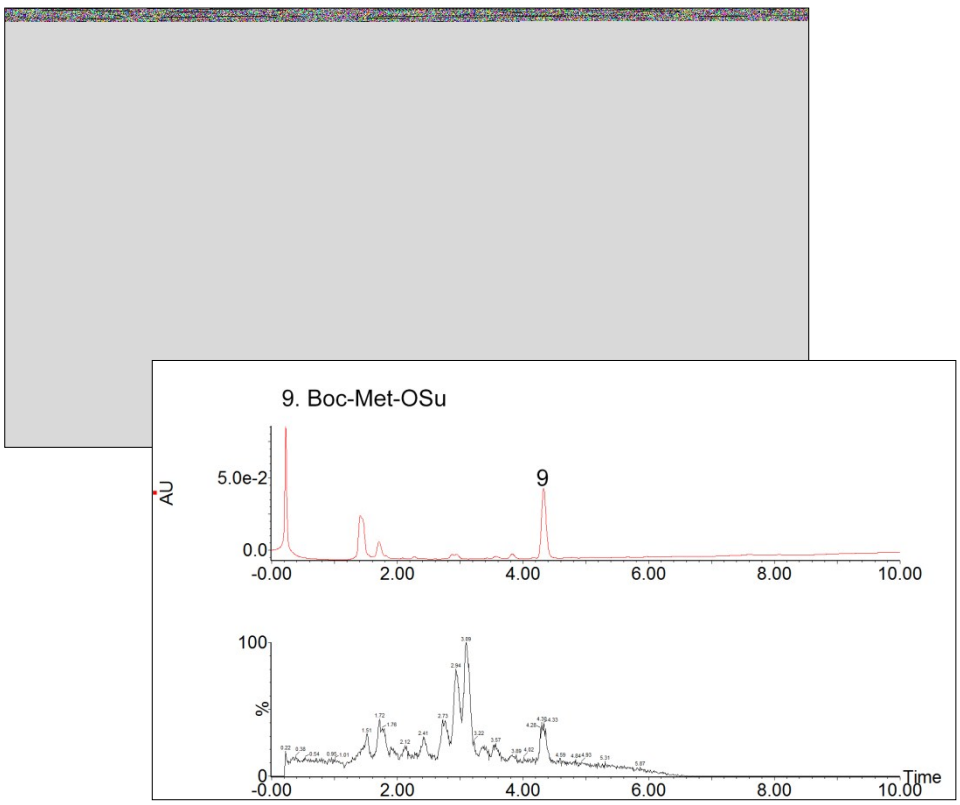
Fig. S8. HPLC-MS analysis of the reactions of tetrazole **1b** and propionic acid in varied pH solution





5. *Evaluating the functional group compatibility of the coupling reaction by HPLC-MS*




9. Boc-Met-OSu
AU
5.0e-2
0.0
9
-0.00
2.00
4.00
6.00
8.00
10.00
100
%
0
Time

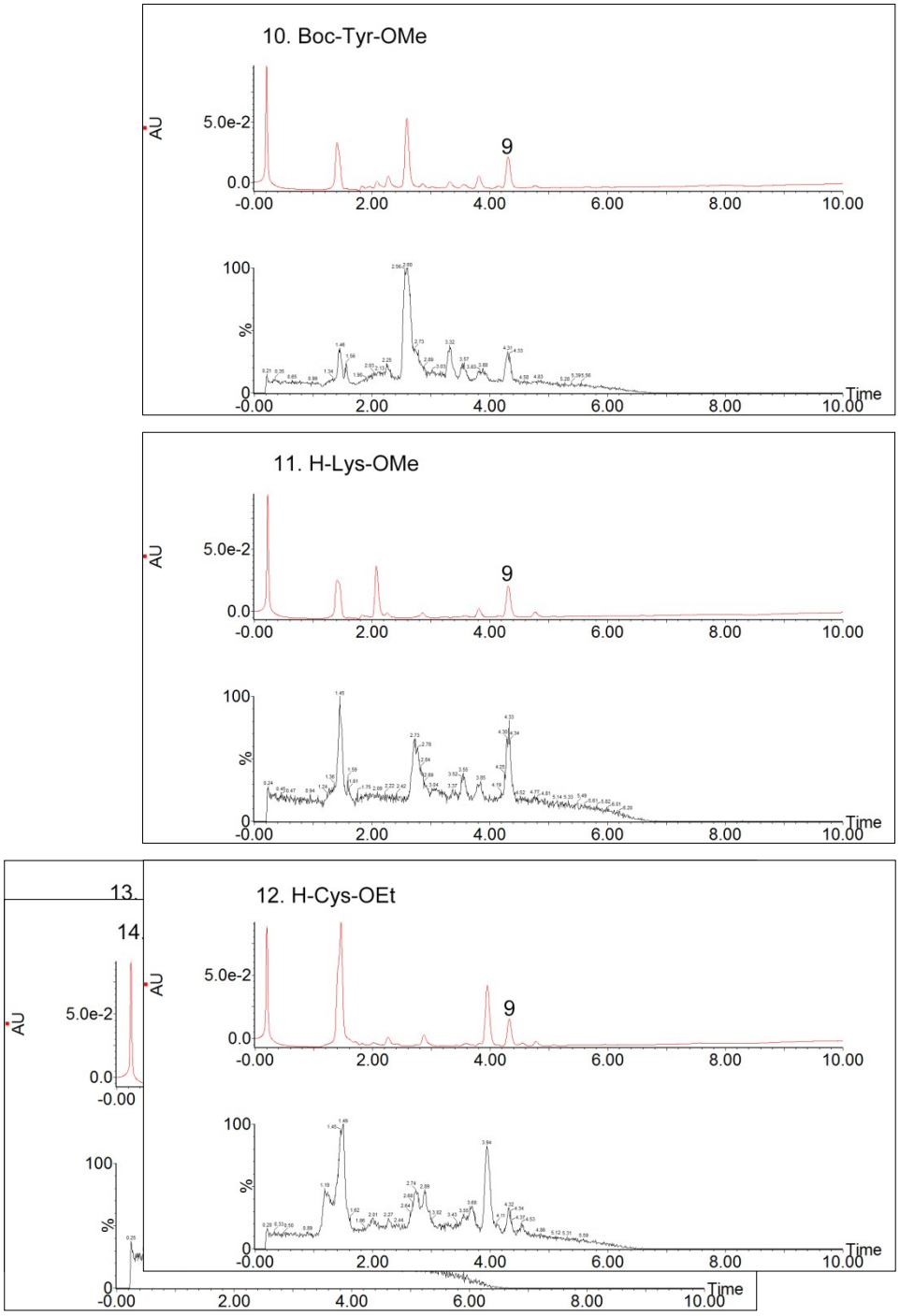


Fig. S9. HPLC-MS analysis of tetrazole **1b** reacting with Boc-Asp-OtBu **8** in the presence of various additives

6. *Photo-labelling of Myoglobin*

Tetrazole **1b** (3 mM) and myoglobin protein (150 μM) in water was UV-irradiated for 10 min at room temperature, followed by trypsin digestion and peptide extraction. The peptides samples were desalted by C18 column and dried. LC-MS/MS analysis was performed on a nanoAcquity (Waters) LC system coupled with Q-Exactive Orbitrap mass spectrometer (Thermo Scientific Inc.).

Table S3.

VEADIAGHGQEVLIR VR-3791

Res.	mass	b ion	b++	y ion	y++	z	m/z
V	99.1			1830.9		2	915.9745
E_Z	353.1	453.2		1731.9	866.4	3	610.9830
A	71.0	524.3	262.6	1378.7	689.9	4	458.4873
D	115.0	639.3	320.1	1307.7	654.4		
I	113.1	752.4	376.7	1192.7	596.8		
A	71.0	823.4	412.2	1079.6	540.3		
G	57.0	880.4	440.7	1008.6	504.8		
H	137.1	1017.5	509.2	951.5	476.3		
G	57.0	1074.5	537.8	814.5	407.7		
Q	128.1	1202.6	601.8	757.5	379.2		
E	129.0	1331.6	666.3	629.4	315.2		
V	99.1	1430.7	715.8	500.4	250.7		
L	113.1	1543.8	772.4	401.3	201.1		
I	113.1	1656.8	828.9	288.2			
R	156.1	1812.9	907.0	175.1			

Table S4.

VEADIAGHGQEVLIR VR-4440

Res.	mass	b ion	b++	y ion	y++	z	m/z
V	99.1			1830.9		2	915.9745
E	129.0	229.1		1731.9	866.4	3	610.9830
A	71.0	300.2		1602.8	801.9	4	458.4873
D	115.0	415.2	208.1	1531.8	766.4		
I	113.1	528.3	264.6	1416.8	708.9		
A	71.0	599.3	300.2	1303.7	652.3		
G	57.0	656.3	328.7	1232.7	616.8		
H	137.1	793.4	397.2	1175.6	588.3		
G	57.0	850.4	425.7	1038.6	519.8		
Q	128.1	978.5	489.7	981.6	491.3		
Ez	353.1	1331.6	666.3	853.5	427.2		
V	99.1	1430.7	715.8	500.4	250.7		
L	113.1	1543.8	772.4	401.3	201.1		
I	113.1	1656.8	828.9	288.2			
R	156.1	1812.9	907.0	175.1			

Table S5.
VEADIAGHGQEVLIR

VR-3905

Res.	mass	b ion	b++	y ion	y++	z	m/z
V	99.1			1830.9		2	915.9745
E	129.0	229.1		1731.9	866.4	3	610.9830
A	71.0	300.2		1602.8	801.9	4	458.4873
D	115.0	415.2	208.1	1531.8	766.4		
I	113.1	528.3	264.6	1416.8	708.9		
A	71.0	599.3	300.2	1303.7	652.3		
G	57.0	656.3	328.7	1232.7	616.8		
H	137.1	793.4	397.2	1175.6	588.3		
G	57.0	850.4	425.7	1038.6	519.8		
Q	128.1	978.5	489.7	981.6	491.3		
Ez	353.1	1331.6	666.3	853.5	427.2		
V	99.1	1430.7	715.8	500.4	250.7		
L	113.1	1543.8	772.4	401.3	201.1		
I	113.1	1656.8	828.9	288.2	144.6		
R	156.1	1812.9	907.0	175.1	88.1		

Table S6.
LFTGHPETLEK

LK-3788

Res.	mass	b ion	b++	y ion	y++	z	m/z
L	113.1			1495.8		2	748.3787
F	147.1	261.2		1382.7	691.8	3	499.2525
T	101.0	362.2		1235.6	618.3	4	374.6893
G	57.0	419.2	210.1	1134.6	567.8		
H	137.1	556.3	278.6	1077.5	539.3		
P	97.1	653.3	327.2	940.5	470.7		
Ez	353.1	1006.5	503.7	843.4	422.2		
T	101.0	1107.5	554.3	490.3	245.6		
L	113.1	1220.6	610.8	389.2	195.1		
E	129.0	1349.7	675.3	276.2			
K	128.1	1477.7	739.4	147.1			

Table S7.
LFTGHPETLEK LK-3872

Res.	mass	b ion	b++	y ion	y++	z	m/z
L	113.1			1495.8		2	748.3787
F	147.1	261.2		1382.7	691.8	3	499.2525
T	101.0	362.2		1235.6	618.3	4	374.6893
G	57.0	419.2	210.1	1134.6	567.8		
H	137.1	556.3	278.6	1077.5	539.3		
P	97.1	653.3	327.2	940.5	470.7		
E	129.0	782.4	391.7	843.4	422.2		
T	101.0	883.4	442.2	714.4	357.7		
L	113.1	996.5	498.8	613.3	307.2		
E_z	353.1	1349.7	675.3	500.2			
K	128.1	1477.7	739.4	147.1			

7. *In Vitro and In Situ Proteome Labelling Experiments*

***In vitro* Proteome labelling.** HepG2 cell lysate samples were diluted in PBS to a final concentration of 1 mg protein per mL. The total volume with small molecule probes was 800 µL for gel analysis, 2 ml for MS analysis. All samples were placed into the wells of an ice-cooled 24-well plate. After incubating at room temperature for 30min, samples were irradiated using a hand-held 302 nm light for 10min, then incubating at room temperature for another 30min. Next, the proteins were precipitated with methanol/CCl_4 (4:1) and water, dissolved in 240 µL 1.2% SDS/PBS. After distributing 20 µL sample as input samples, 20 µL sample for SDS-PAGE analysis and 200 µL sample for western blotting analysis, reporter-tagged azide reagents (rhodamine-azide for SDS-PAGE analysis, biotin-azide for western blotting) were added, followed by TCEP and ligand. Samples were gently vortexed and the cycloaddition initiated by the addition of $CuSO_4$. The reactions were incubated at RT for 1 h. For gel-based ABPP, standard SDS loading buffer was added and the samples separated by 1D SDS-PAGE and visualized by in-gel fluorescent scanning using a Bio-RAD ChemiDocMP Imager. For protein input samples, standard SDS loading buffer was added and the samples separated by 1D SDS-PAGE. For western blotting, the samples were added streptavidin beads (Sigma) and incubated for 3 h at room temperature to bind and enrich biotin-labeled proteins. The beads were then washed with 0.2% SDS/PBS (1 x 1 mL), PBS (3 x 1 mL) and water (3 x 1 mL). Then SDS loading buffer was added to the beads for heating at 90 °C for 5-10 min. The samples were separated by SDS-PAGE and immunoblotted with anti-HDAC1 or anti-HDAC2 antibodies.

***In situ* Proteome labelling.** 90% confluent 10mm dishes of HepG2 cells were washed with PBS (3 x 5 mL) and subjected to tetrazole-SAHA (10 µM in complete medium) or tetrazole-SAHA and excess SAHA (10 µM tetrazole-SAHA and 200 µM

SAHA in complete medium) (5 mL total volume). The cells were incubated at 37°C for 2h, washed with PBS (3 x 5 mL) and irradiated at 302 nm at RT for 10min. After irradiation, the cells were incubated at RT for 30min, scraped, and pelleted by centrifugation. The cell pellet was lysed with NP-40 containing protease inhibitors and resuspended in PBS and homogenized by sonication, and diluted to 2 mg/mL with PBS. The lysates were then subjected to the gel-based ABPP and western blotting procedures as described above in the section of "in vitro proteome labeling".

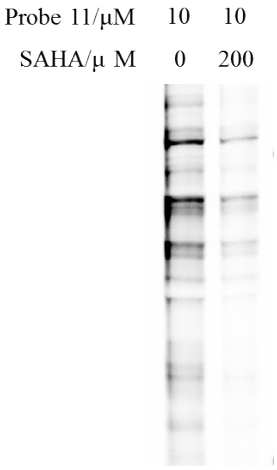


Fig. S10. In-gel fluorescence protein profiling in living HepG2 cells with Probe 11.

8. *LC-MS/MS Site-Mapping Analysis of HDAC1 by SAHA-tetrazole probe 11*

The purified HDAC1 protein (5 μg protein in 50 μL PBS buffer) was incubated with probe 11 (10 μM) for 30 min at room temperature, then UV-irradiated for 10 min on ice, and incubated for 30 min at room temperature again. The samples were then subjected to in-solution trypsin digestion. Briefly, the samples were denatured in 8 M urea (150 μL of 100mg urea in PBS was added), reduced by 10 mM of dithiothreitol for 30 min at room temperature (10 μL of 200 mM stock in water was added) and alkylated by 10 mM iodoacetamide for 30 min at room temperature in dark (20 μL of 100 mM stock in water was added). The samples were diluted with ammonium bicarbonate (25 mM, 460 μL) to 2 M urea and subjected to trypsin digestion (Promega; 4 μL of 0.5 μg/μL) overnight at 37 °C in the presence of 2 mM CaCl2. Digested peptide samples were desalted and re-solubilized in 50uL Buffer A (95% water, 5% acetonitrile, 0.1% formic acid). 25uL of each sample was analyzed by LC-MS/MS on a Ultimate 3000 LC system coupled with Q-Exactive Orbitrap mass spectrometer (Thermo Scientific Inc.). Peptides were eluted from the C18 column using a 75 min gradient of 96.3%-0 Buffer B (80% acetonitrile, 20% water, 0.1% formic acid) and 3.7%-100% Buffer C (95% water, 5% acetonitrile, 0.1% formic acid, 500mM ammonium acetate). The flow rate through the column was 5 μL/min and the spray voltage was 2.0 kV. The QE-Orbitrap was operated in data-dependent scanning

mode, with one full MS scan (400–1800 m/z) in the orbitrap followed by MS/MS scans of the 20 most abundant ions using the linear ion trap with dynamic exclusion enabled. The MS data was analyzed by Mascot v2.3.02 using a SwissProt database with two differential modifications: Carbamidomethyl modification of 57.02146 on cysteine (C) and SAHA-tetrazole probe modification of 418.2005 on aspartic acid (D) or glutamic acid (E).

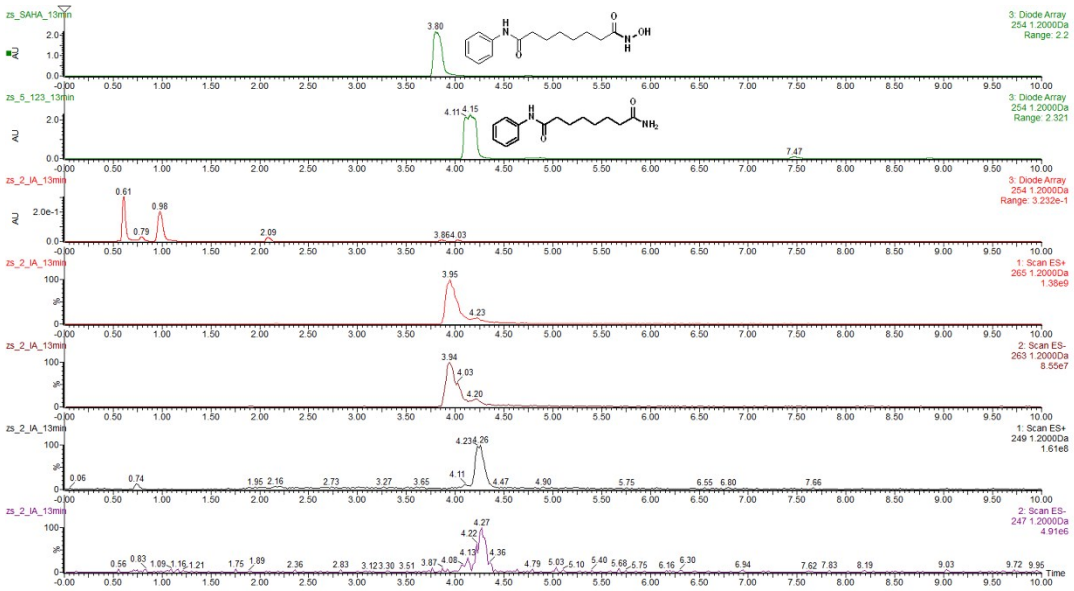


Fig. S11. HPLC-MS analysis of SAHA after the treatment of the MS sample preparation

Table S8. MS/MS spectrum and b/y ion assignments by Mascot confirming 203E of HDAC1 was labeled by probe **11**

YGEYFPGTGDLR

Res.	mass	b ion	b++	y ion	y++	z	m/z
Y	163.1	164.1	82.5			2	895.9129
G	57.0	221.1	111.0	1629.8	815.4	3	597.2752
E_Z	101.0	768.3	384.7	1572.7	786.9	4	447.9564
Y	163.1	931.4	466.2	1025.5	513.3		
F	147.1	1078.5	539.7	862.4	431.7		
P	97.1	1175.5	588.3	715.4	358.2		
G	128.1	1232.5	616.7	618.3	309.7		
T	101.0	1333.6	667.3	561.3	281.2		
G	128.1	1390.6	695.8	460.3	230.6		
D	115.0	1505.6	753.8	403.2	202.1		
L	113.1	1618.7	809.9	288.2	144.6		
R	156.1			175.1	88.1		

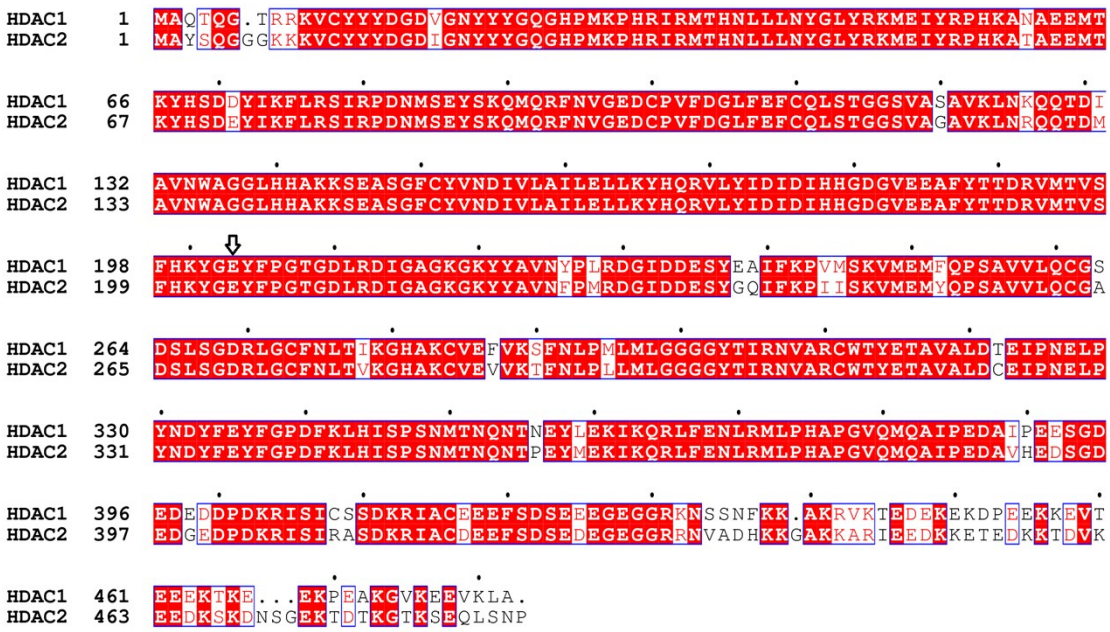


Fig. S12. The amino acid sequences of HDAC1 were aligned with HDAC2. The 203E (HDAC1) is marked by the arrow.

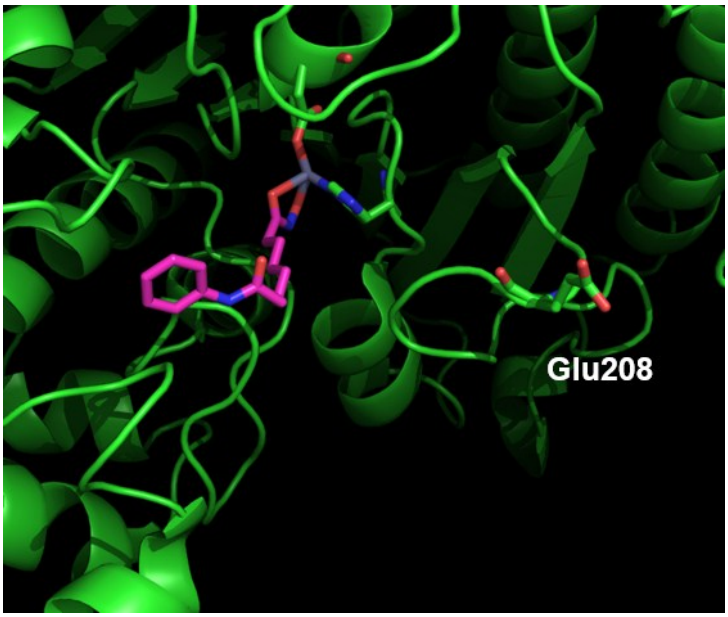
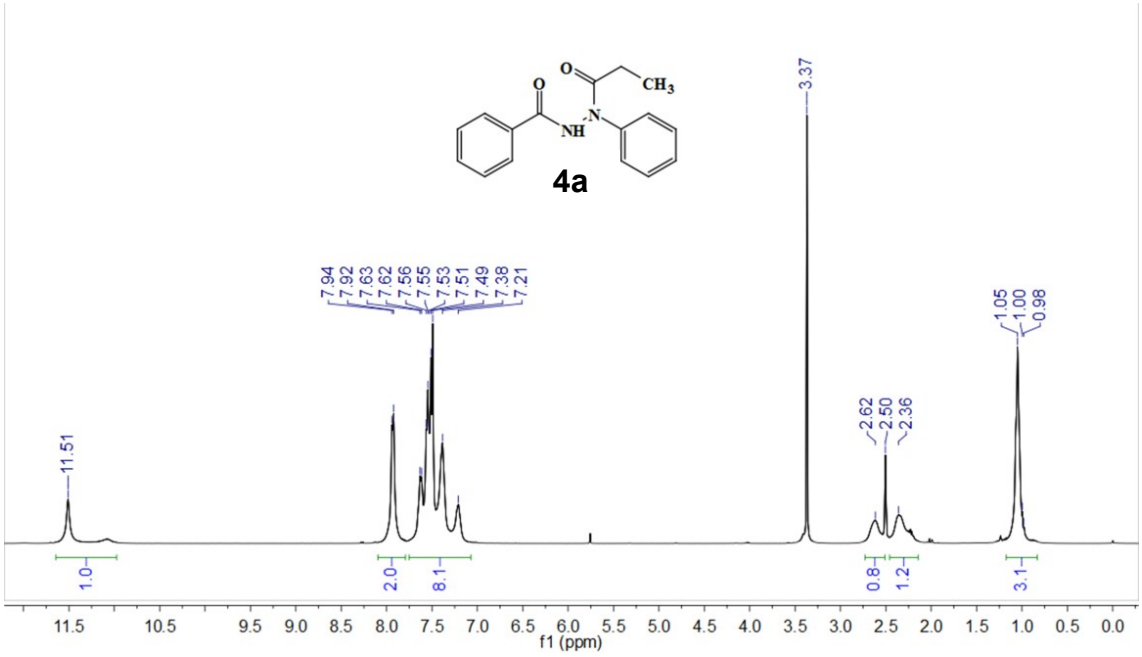
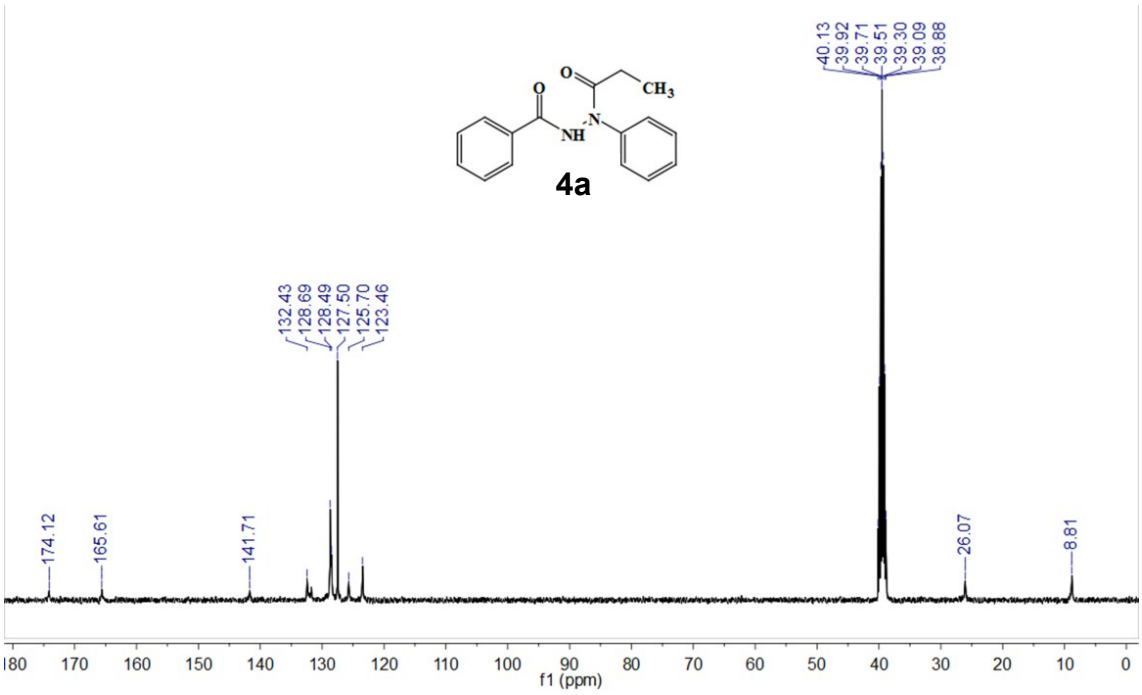
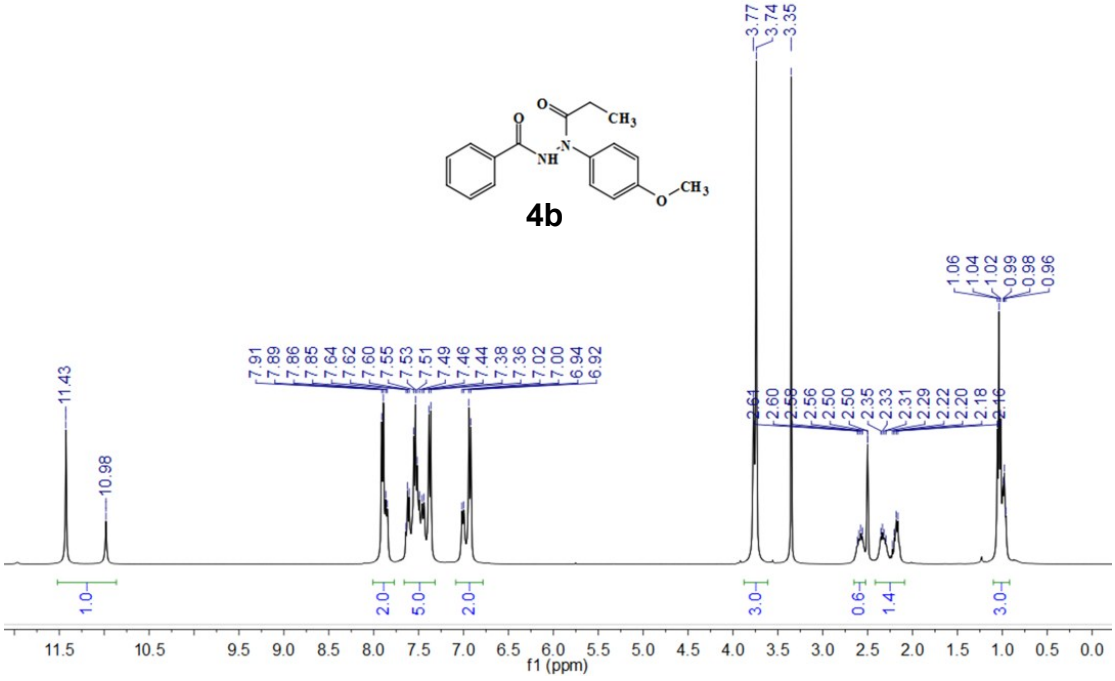


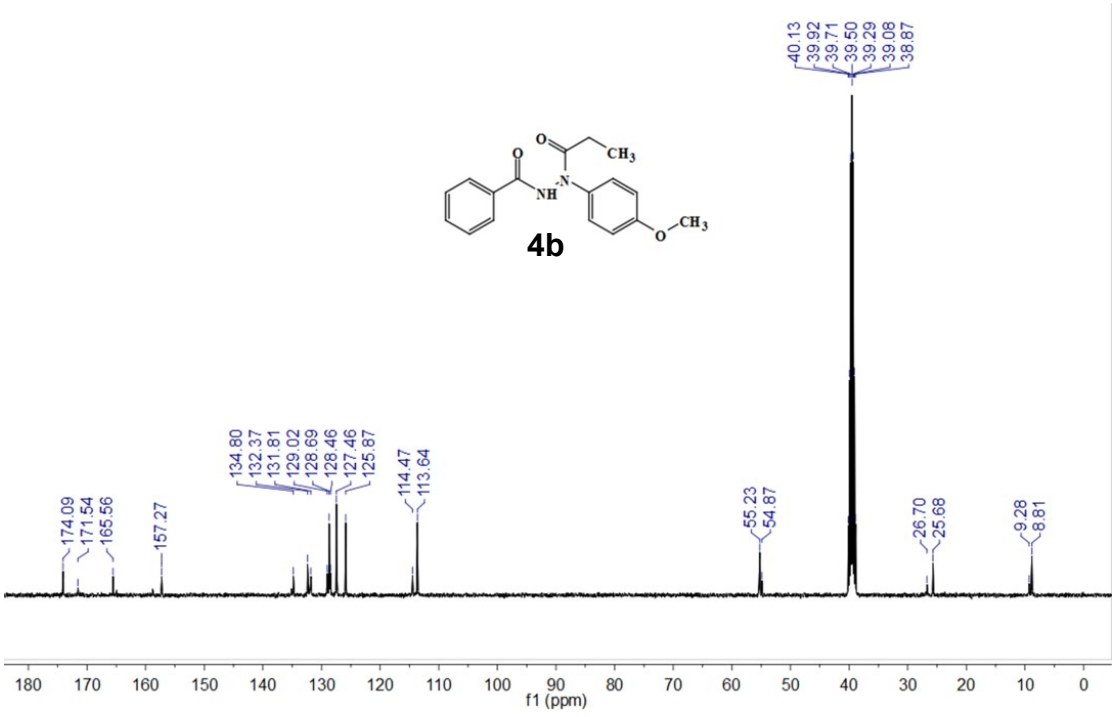
Fig. S13. The 208E residue of HDAC2 is spatially close to the phenyl ring of SAHA. View derived from the X-ray structure of HDAC2-SAHA complex (PDB ID: 4LXZ)

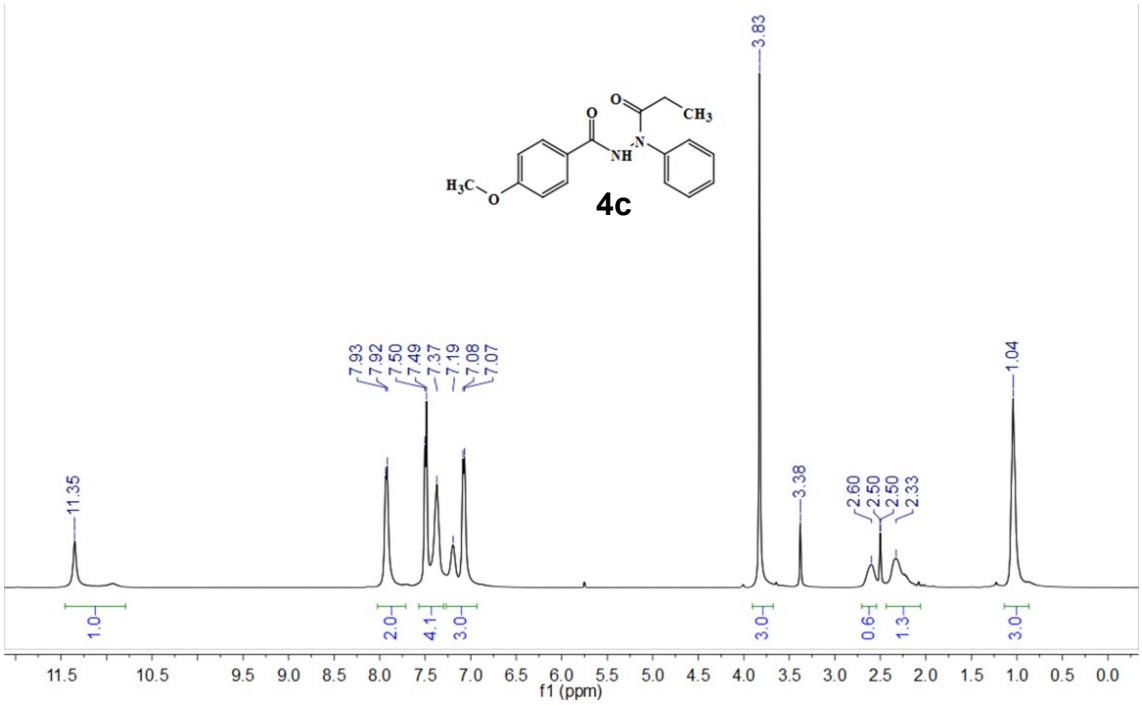
9. *^{1}H and ^{13}C NMR Spectra of Compounds*

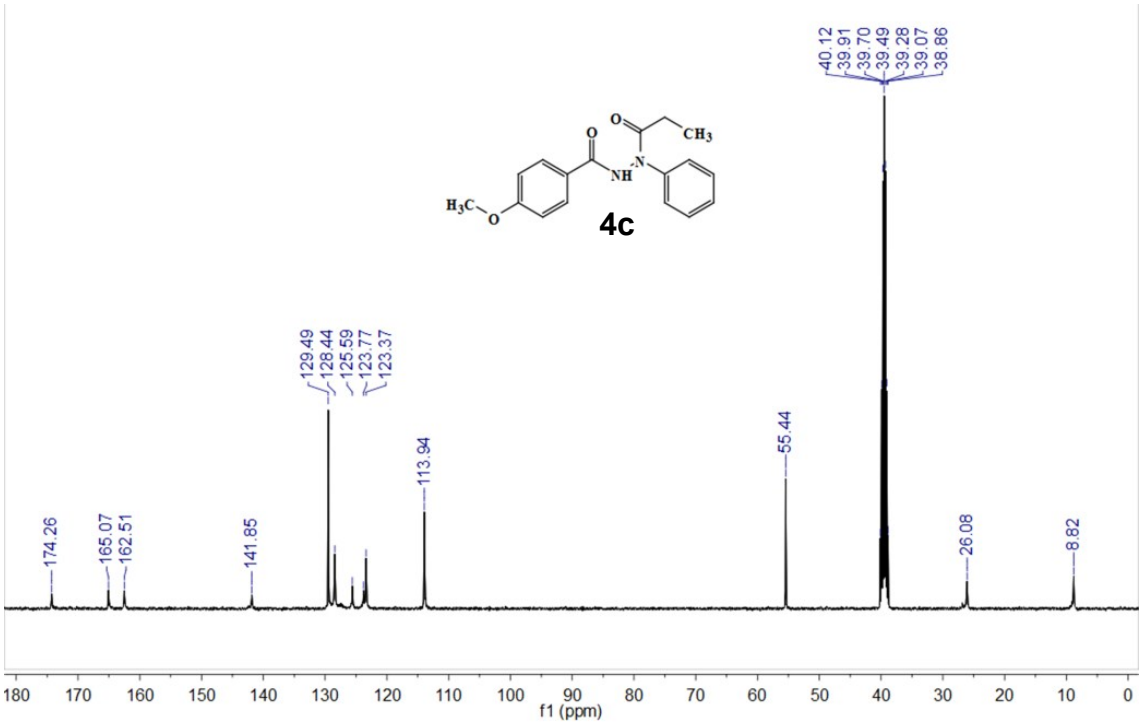


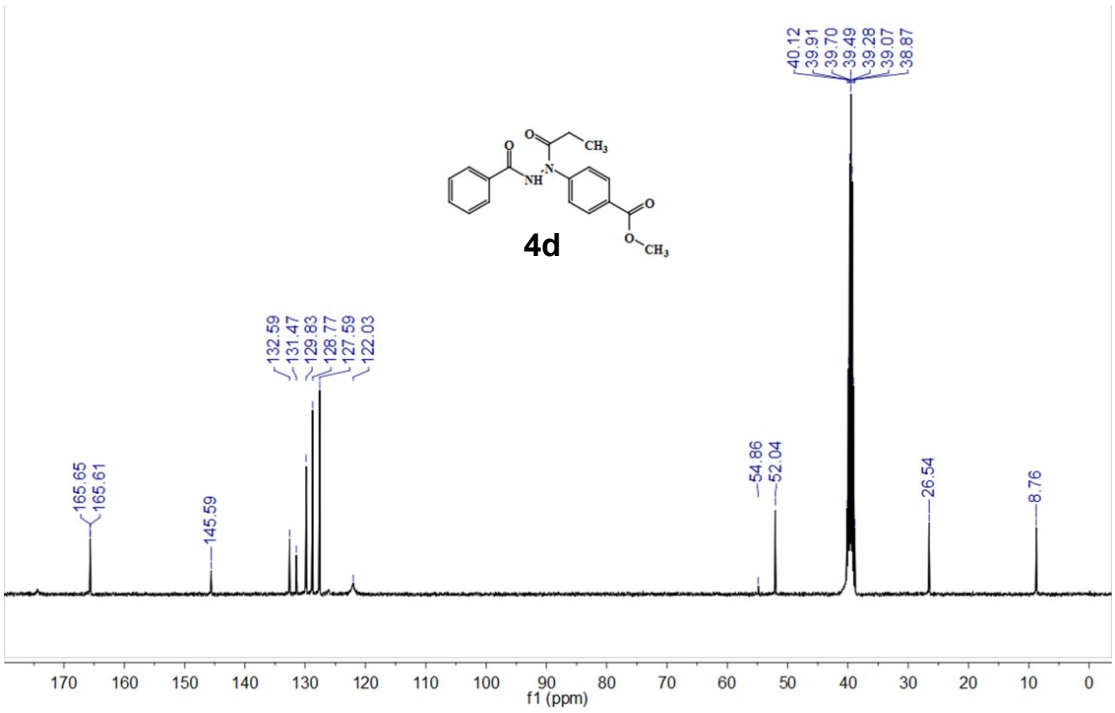


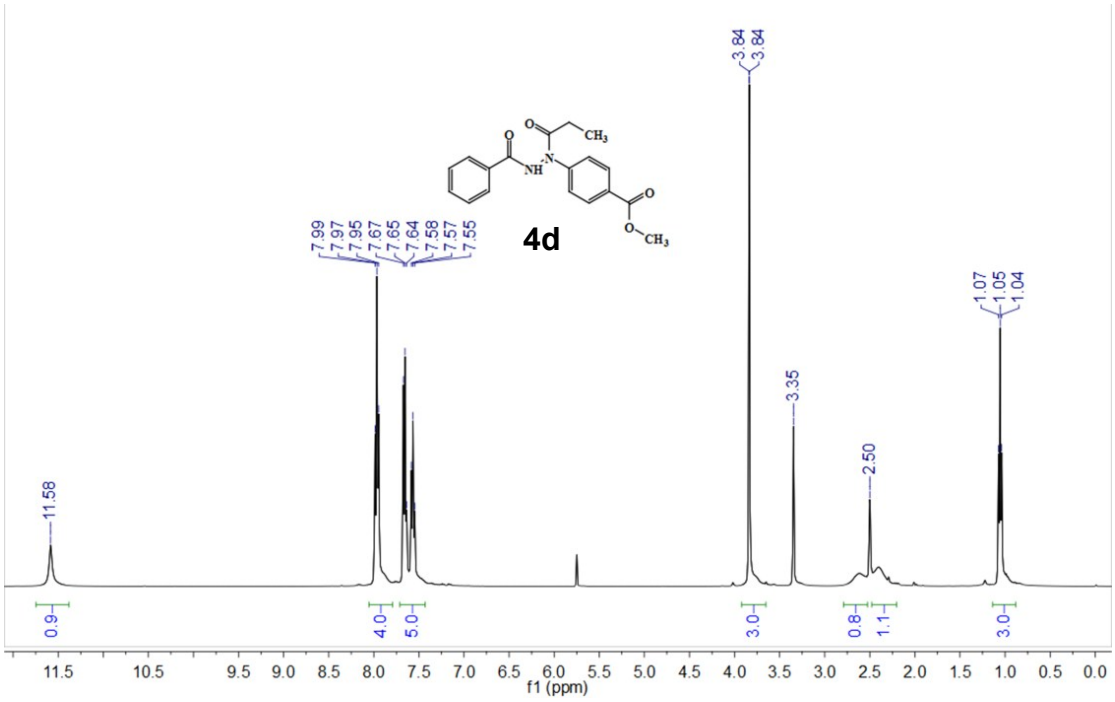

4b
11.43
10.98
7.91
7.89
7.86
7.85
7.64
7.62
7.60
7.55
7.53
7.51
7.49
7.46
7.44
7.38
7.36
7.02
7.00
6.94
6.92
3.77
3.74
3.35
2.61
2.60
2.58
2.56
2.50
2.50
2.35
2.33
2.31
2.29
2.22
2.20
2.18
2.16
1.06
1.04
1.02
0.99
0.98
0.96
1.0
2.0
5.0
2.0
3.0
0.6
1.4
3.0
f1 (ppm)

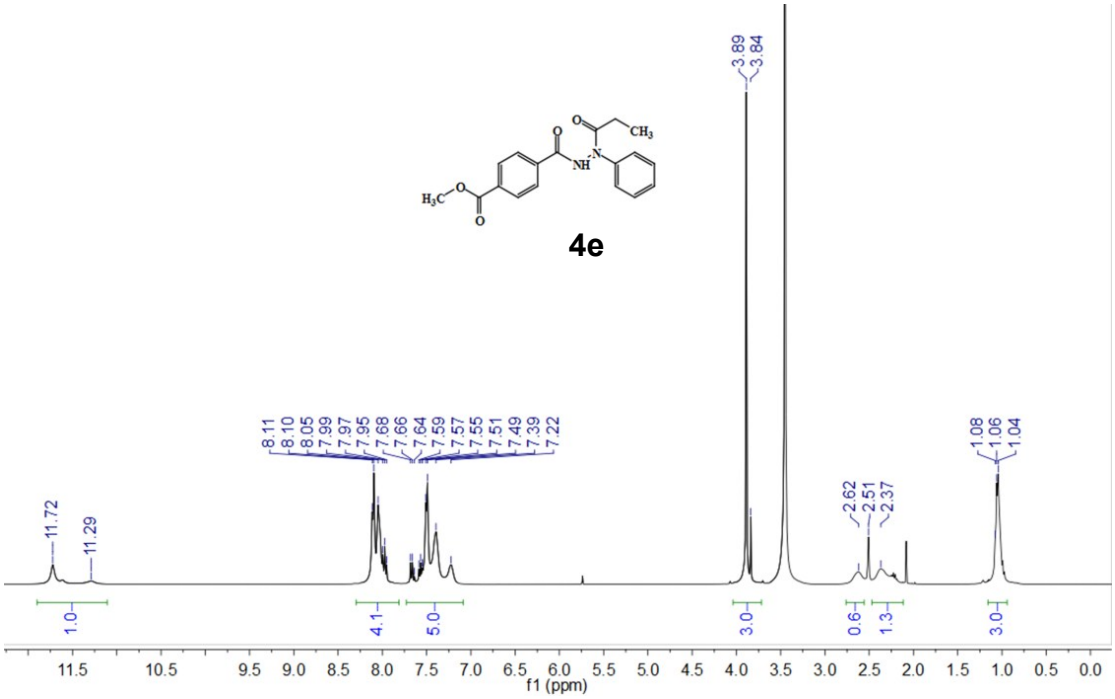

4b
174.09
171.54
165.56
157.27
134.80
132.37
131.81
129.02
128.69
128.46
127.46
125.87
114.47
113.64
55.23
54.87
40.13
39.92
39.71
39.50
39.29
39.08
38.87
26.70
25.68
9.28
8.81
f1 (ppm)

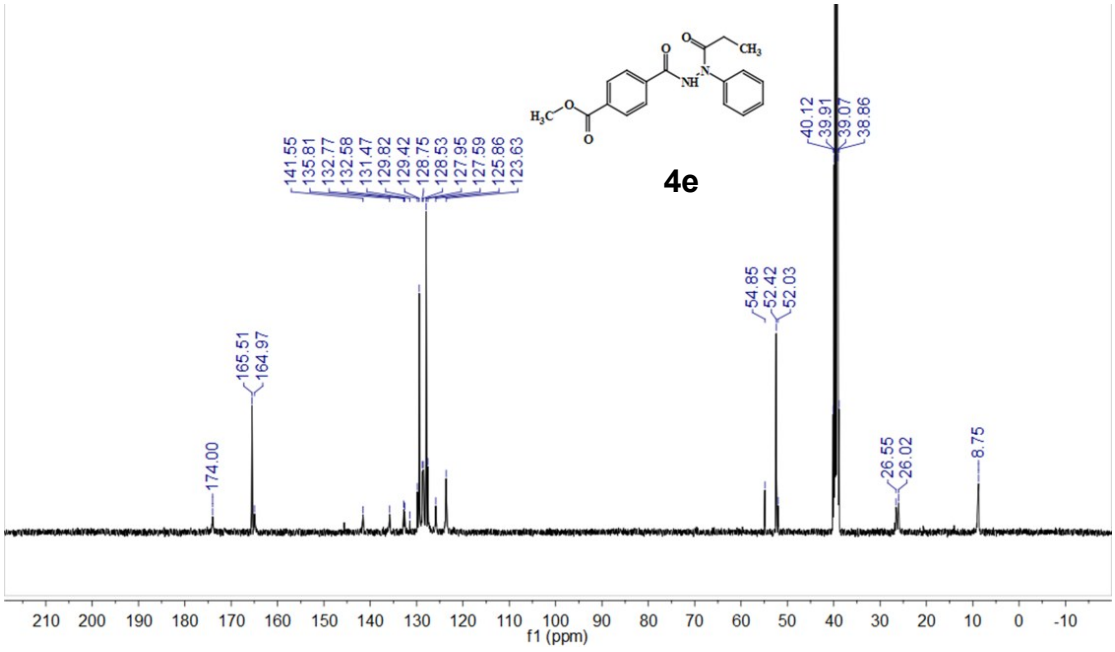

4c
11.35
7.93
7.92
7.50
7.49
7.37
7.19
7.08
7.07
3.83
3.38
2.60
2.50
2.50
2.33
1.04
1.0
2.0
4.1
3.0
3.0
0.6
1.3
3.0
f1 (ppm)

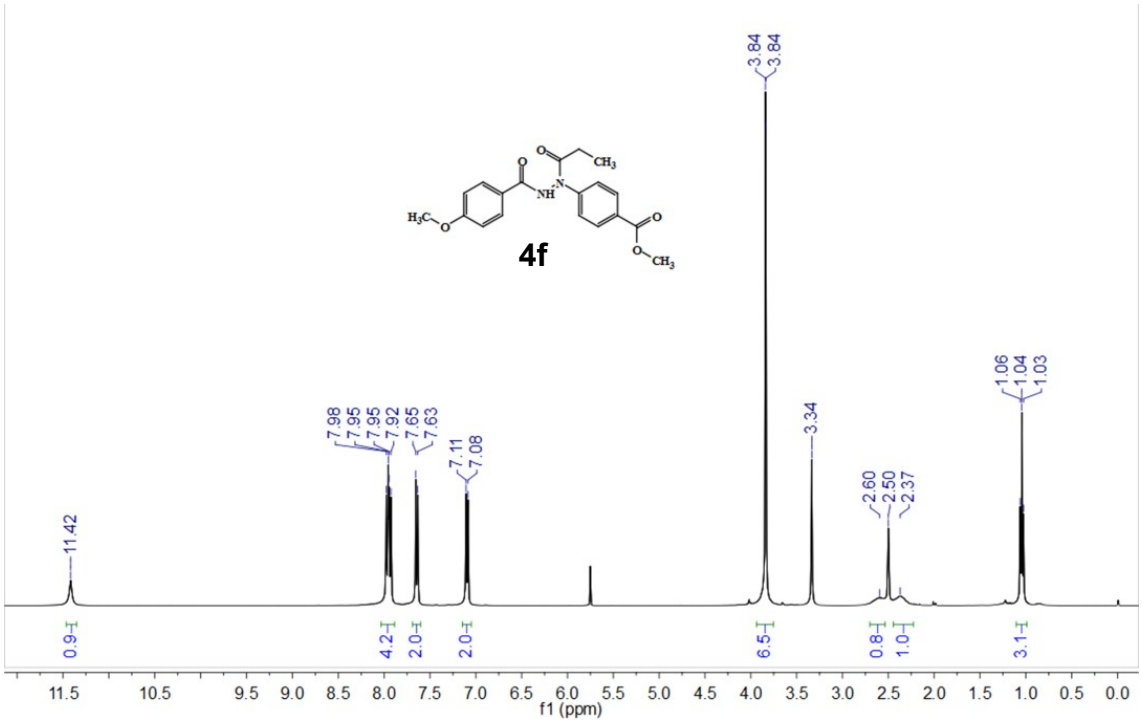

4c
40.12
39.91
39.70
39.49
39.28
39.07
38.86
129.49
128.44
125.59
123.77
123.37
113.94
55.44
174.26
165.07
162.51
141.85
26.08
8.82
f1 (ppm)

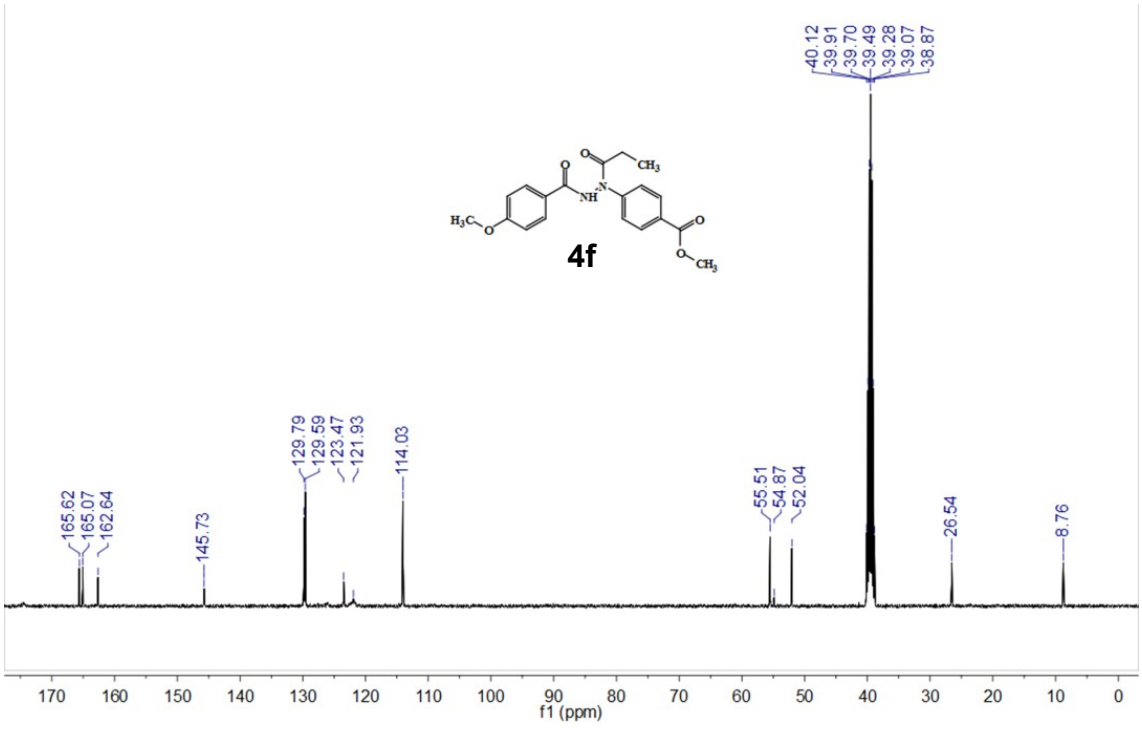

4d
40.12
39.91
39.70
39.49
39.28
39.07
38.87
132.59
131.47
129.83
128.77
127.59
122.03
165.65
165.61
145.59
54.86
52.04
26.54
8.76
f1 (ppm)

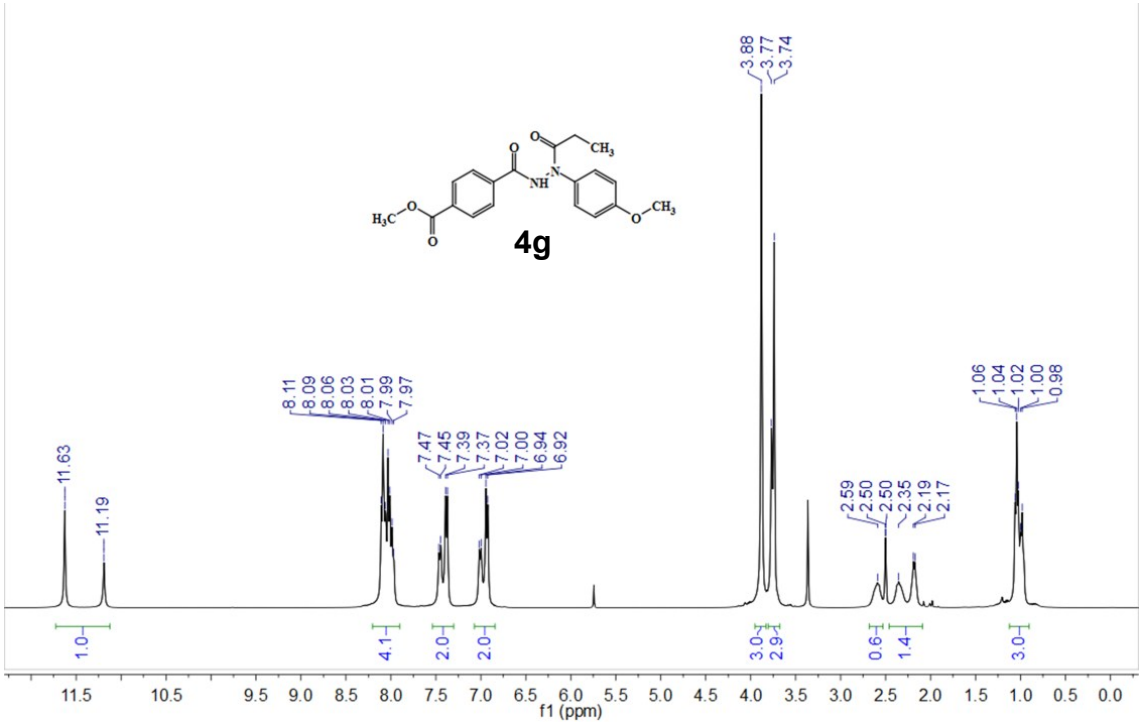

4d
3.84
3.84
7.99
7.97
7.95
7.67
7.65
7.64
7.58
7.57
7.55
1.07
1.05
1.04
3.35
2.50
11.58
0.9
4.0
5.0
3.0
0.8
1.1
3.0
f1 (ppm)

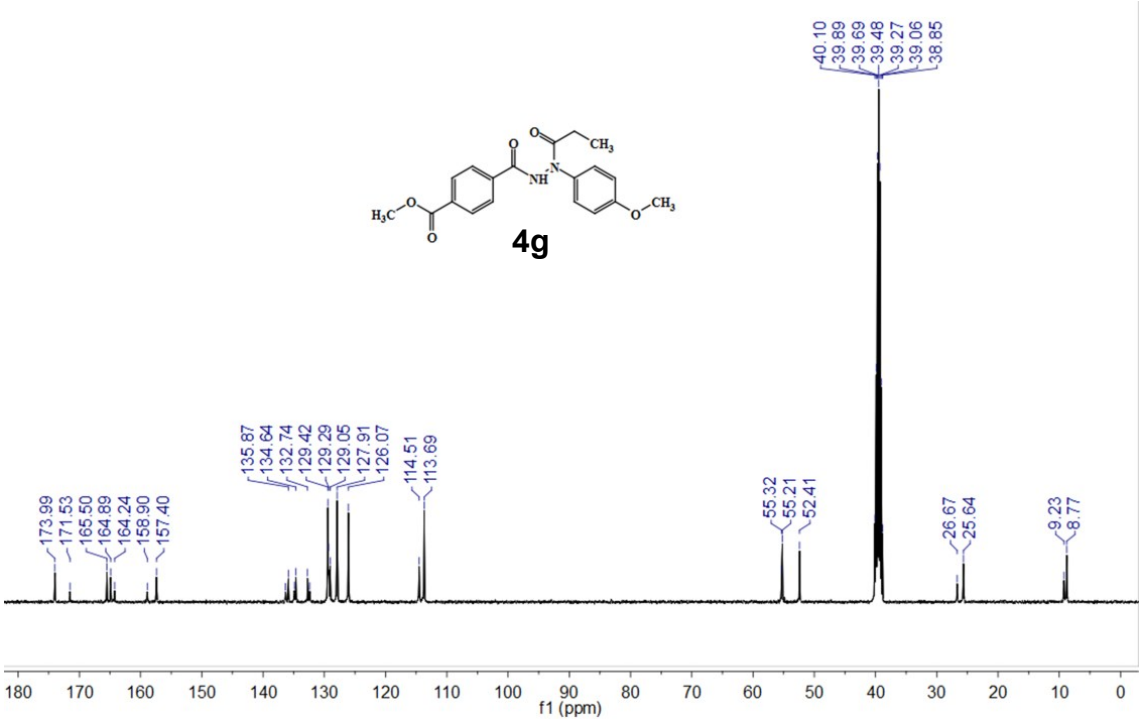

4e
3.89
3.84
8.11
8.10
8.05
7.99
7.97
7.95
7.68
7.66
7.64
7.59
7.57
7.55
7.51
7.49
7.39
7.22
11.72
11.29
2.62
2.51
2.37
1.08
1.06
1.04
1.0
4.1
5.0
3.0
0.6
1.3
3.0
f1 (ppm)

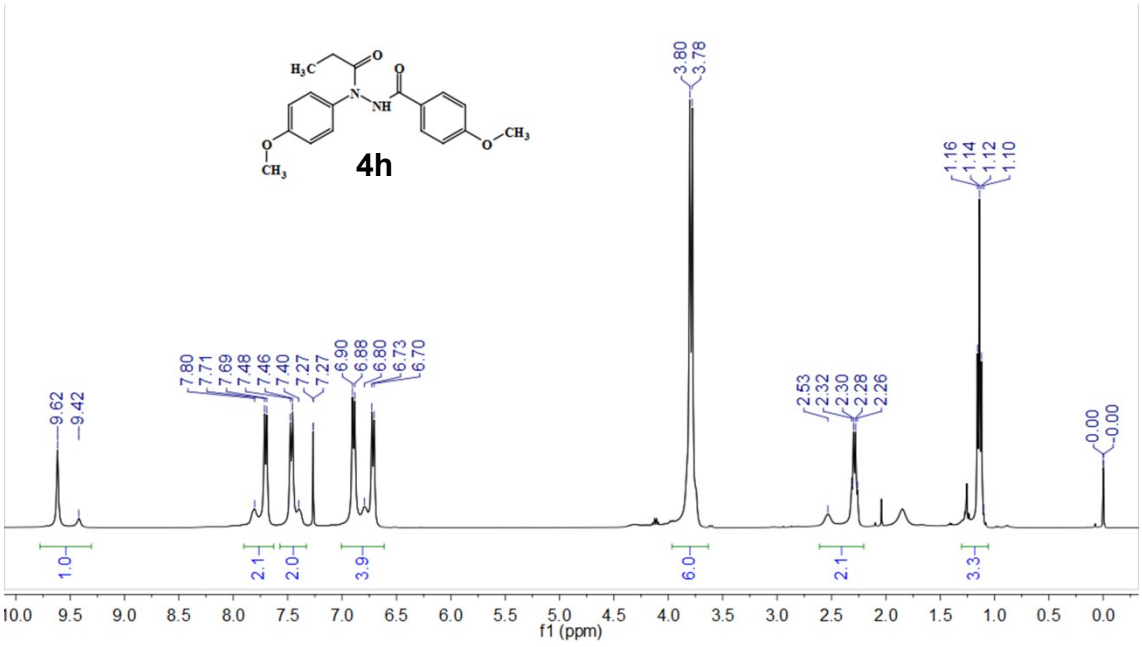

4e
141.55
135.81
132.77
132.58
131.47
129.82
129.42
128.75
128.53
127.95
127.59
125.86
123.63
40.12
39.91
39.07
38.86
54.85
52.42
52.03
165.51
164.97
174.00
26.55
26.02
8.75
f1 (ppm)

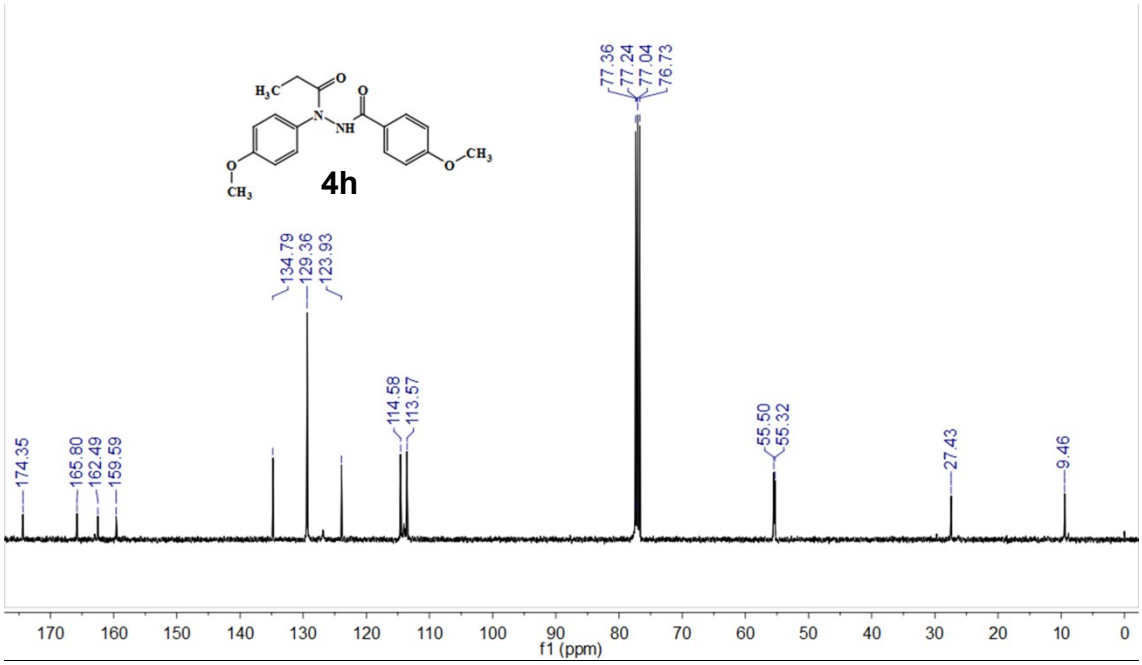

4f
11.42
7.98
7.95
7.95
7.92
7.65
7.63
7.11
7.08
3.84
3.84
3.34
2.60
2.50
2.37
1.06
1.04
1.03
0.9
4.2
2.0
2.0
6.5
0.8
1.0
3.1
f1 (ppm)

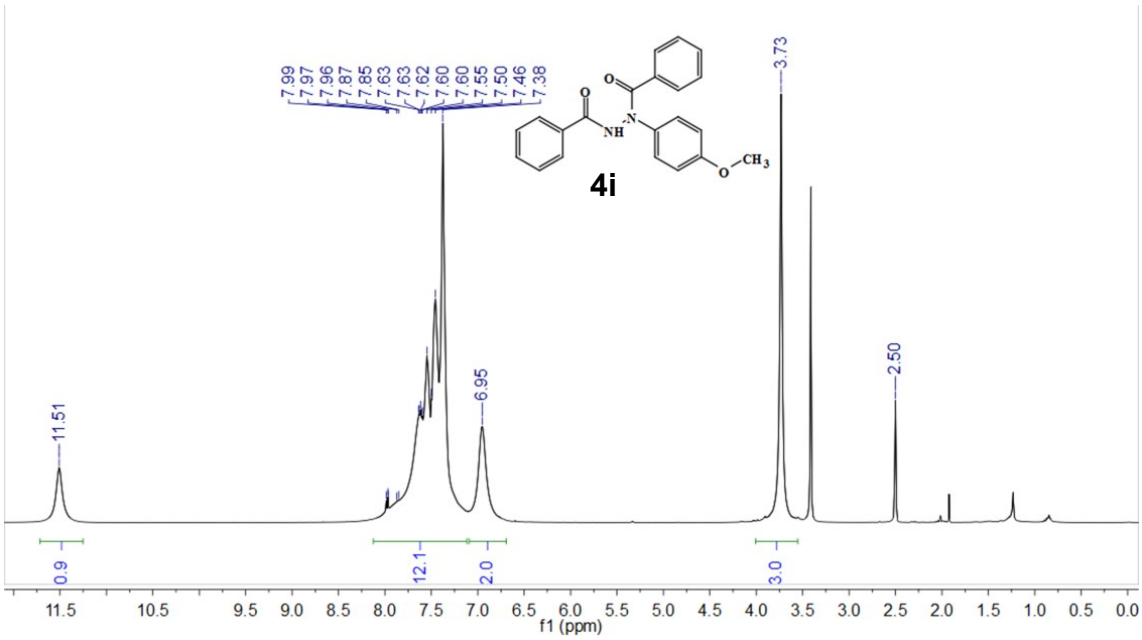

4f
165.62
165.07
162.64
145.73
129.79
129.59
123.47
121.93
114.03
55.51
54.87
52.04
40.12
39.91
39.70
39.49
39.28
39.07
38.87
26.54
8.76
f1 (ppm)

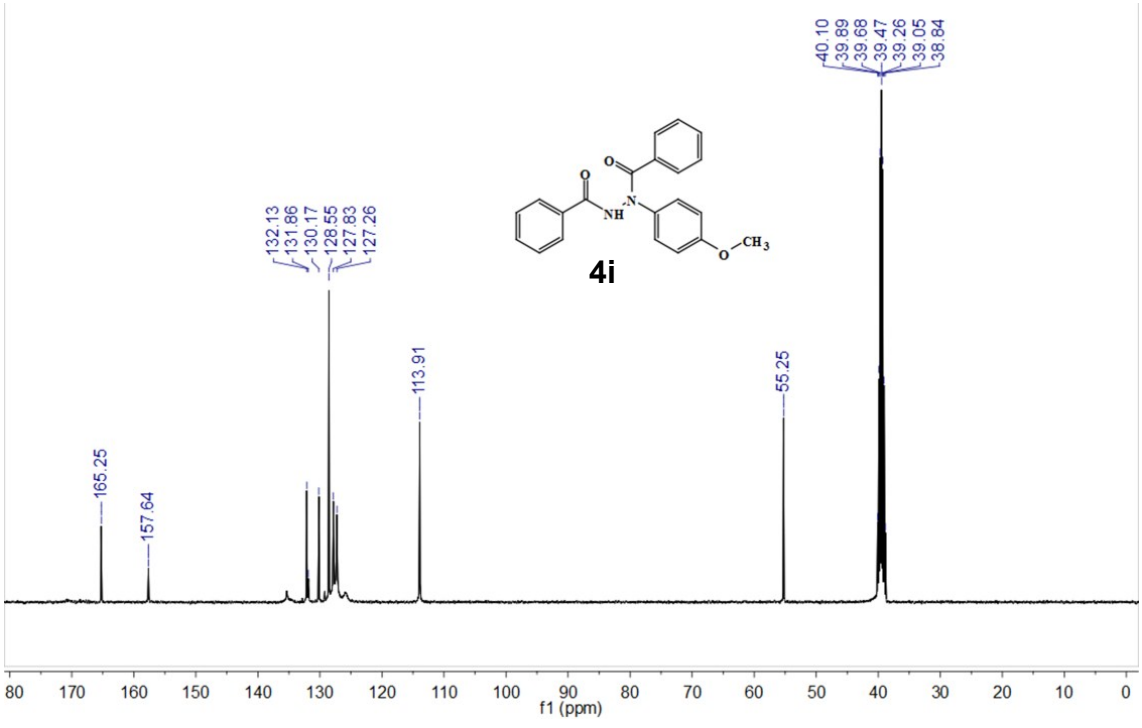

4g
11.63
11.19
8.11
8.09
8.06
8.03
8.01
7.99
7.97
7.47
7.45
7.39
7.37
7.02
7.00
6.94
6.92
3.88
3.77
3.74
2.59
2.50
2.50
2.35
2.19
2.17
1.06
1.04
1.02
1.00
0.98
1.0
4.1
2.0
2.0
3.0
2.9
0.6
1.4
3.0
f1 (ppm)

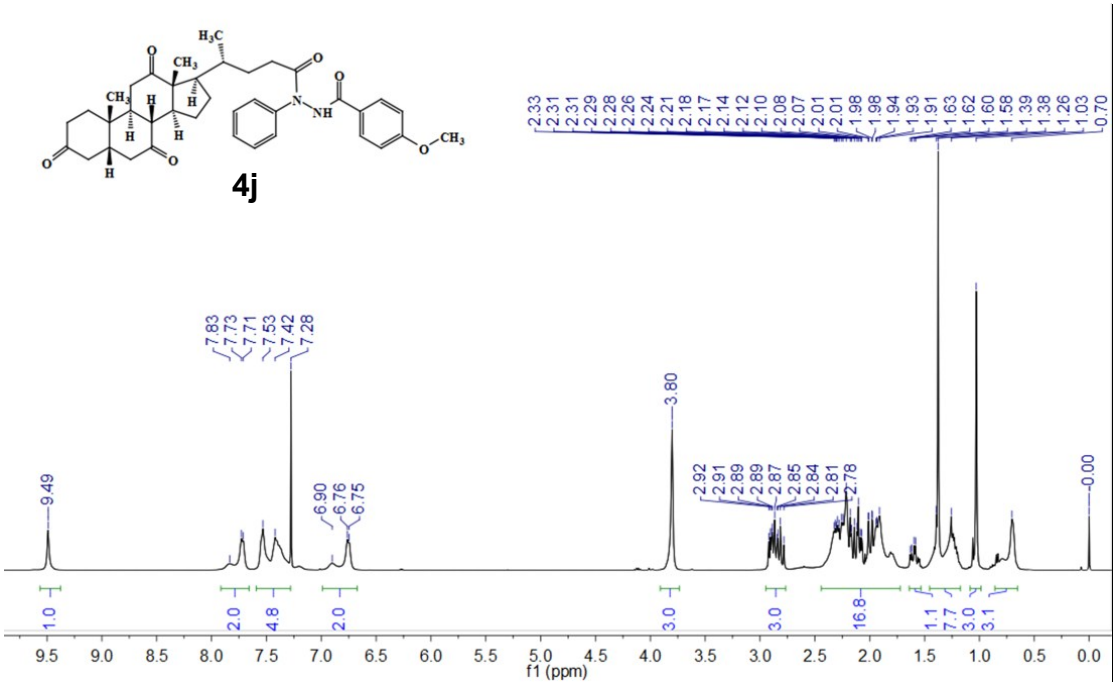

4g
40.10
39.89
39.69
39.48
39.27
39.06
38.85
135.87
134.64
132.74
129.42
129.29
129.05
127.91
126.07
114.51
113.69
173.99
171.53
165.50
164.89
164.24
158.90
157.40
55.32
55.21
52.41
26.67
25.64
9.23
8.77
f1 (ppm)

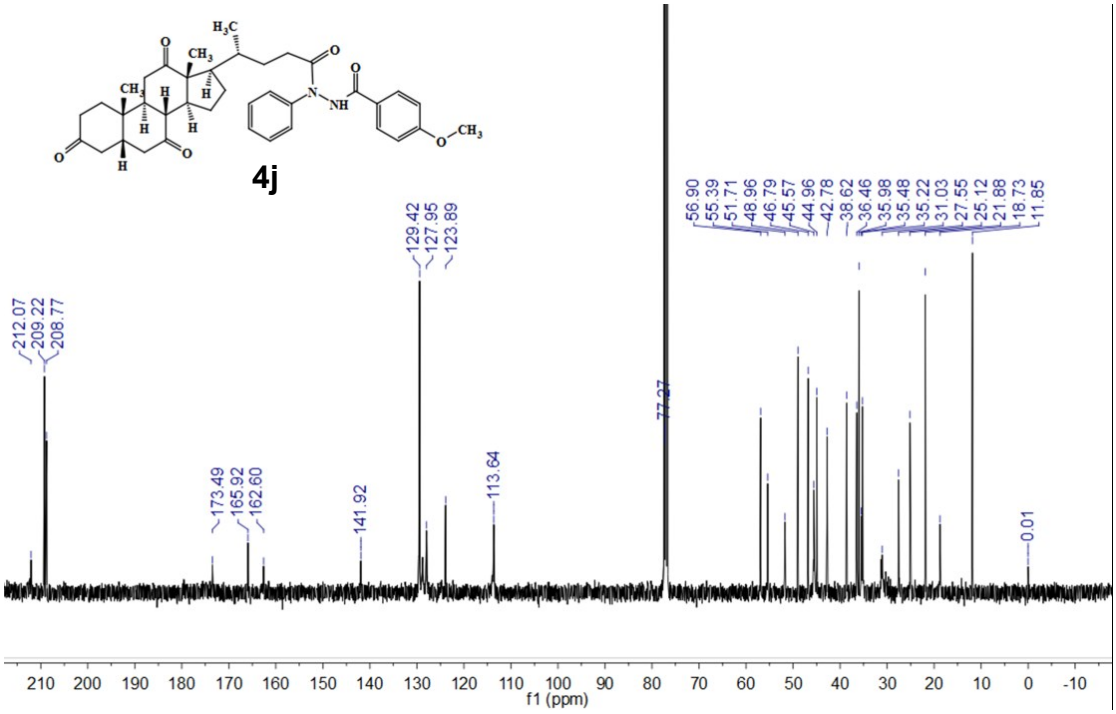

4h
9.62
9.42
7.80
7.71
7.69
7.48
7.46
7.40
7.27
7.27
6.90
6.88
6.80
6.73
6.70
3.80
3.78
2.53
2.32
2.30
2.28
2.26
1.16
1.14
1.12
1.10
0.00
0.00
1.0
2.1
2.0
3.9
6.0
2.1
3.3
f1 (ppm)

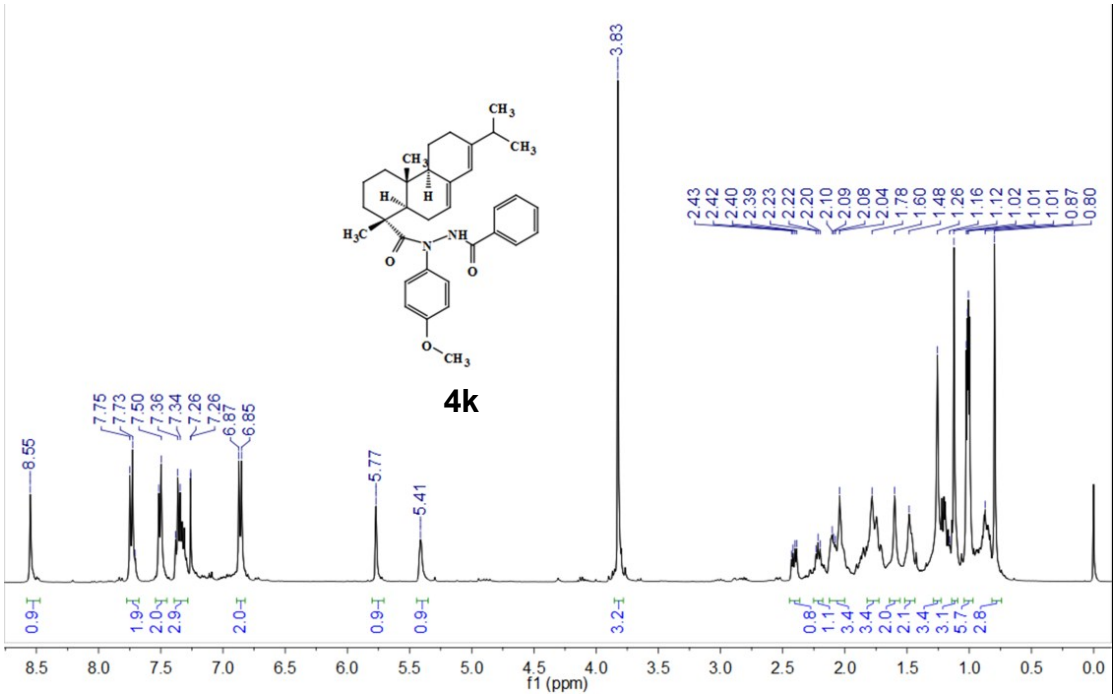

4h
77.36
77.24
77.04
76.73
134.79
129.36
123.93
114.58
113.57
55.50
55.32
27.43
9.46
174.35
165.80
162.49
159.59
f1 (ppm)

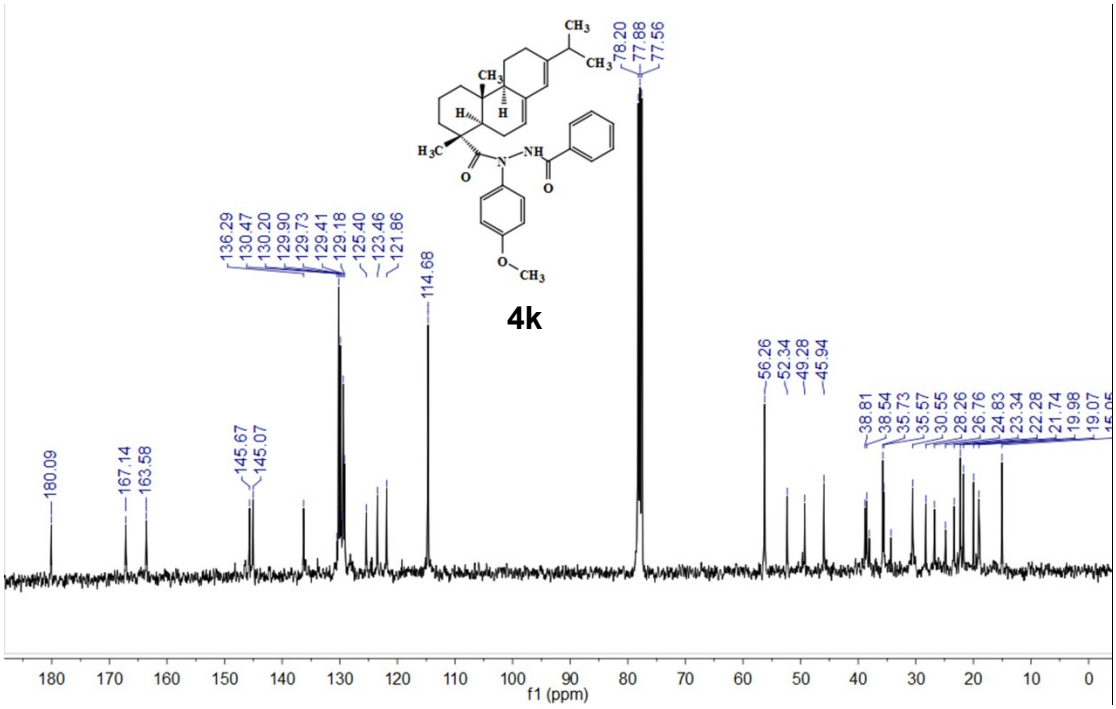

7.99
7.97
7.96
7.87
7.85
7.63
7.63
7.62
7.60
7.60
7.55
7.50
7.46
7.38
3.73
2.50
6.95
11.51
0.9
12.1
2.0
3.0
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
4i

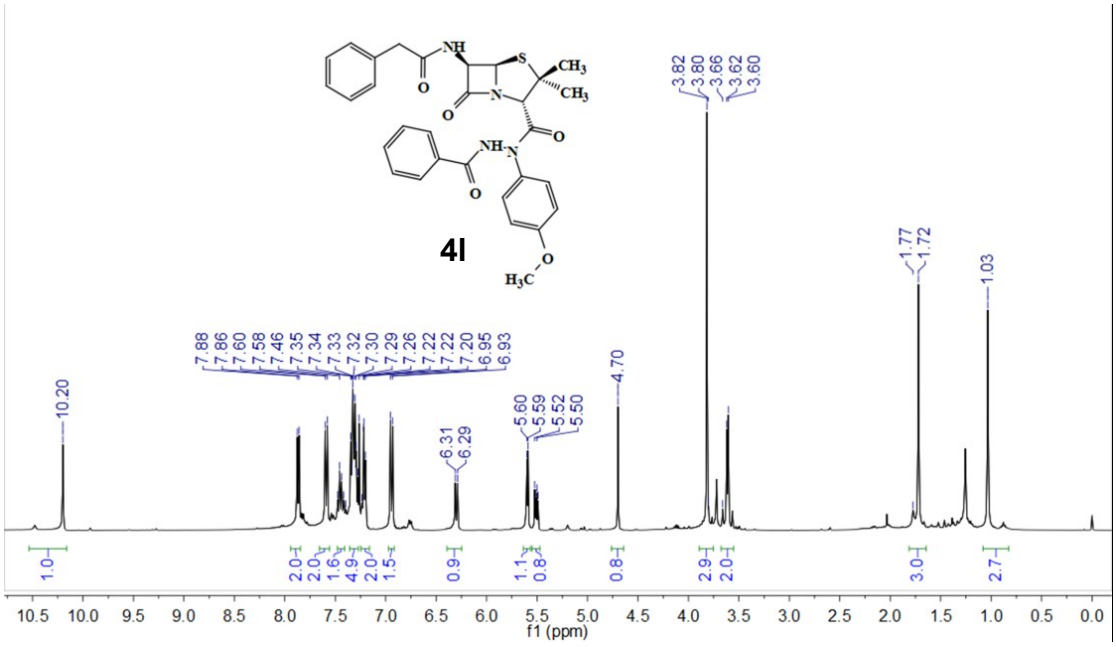

40.10
39.89
39.68
39.47
39.26
39.05
38.84
132.13
131.86
130.17
128.55
127.83
127.26
113.91
55.25
165.25
157.64
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
4i

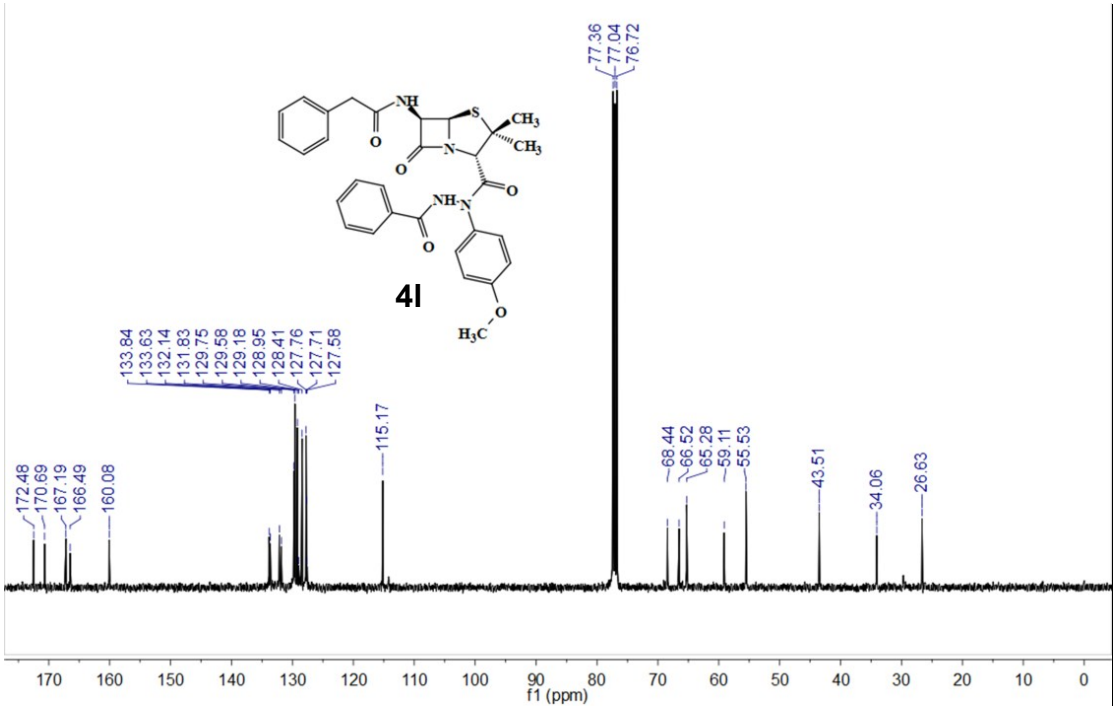

4j
2.33
2.31
2.31
2.29
2.28
2.26
2.24
2.21
2.18
2.17
2.14
2.12
2.10
2.08
2.07
2.01
2.01
1.98
1.98
1.94
1.93
1.91
1.63
1.62
1.60
1.58
1.39
1.38
1.26
1.03
0.70
7.83
7.73
7.71
7.53
7.42
7.28
3.80
9.49
6.90
6.76
6.75
2.92
2.91
2.89
2.89
2.87
2.85
2.84
2.81
2.78
0.00
1.0
2.0
4.8
2.0
3.0
3.0
16.8
1.1
7.7
3.0
3.1
f1 (ppm)

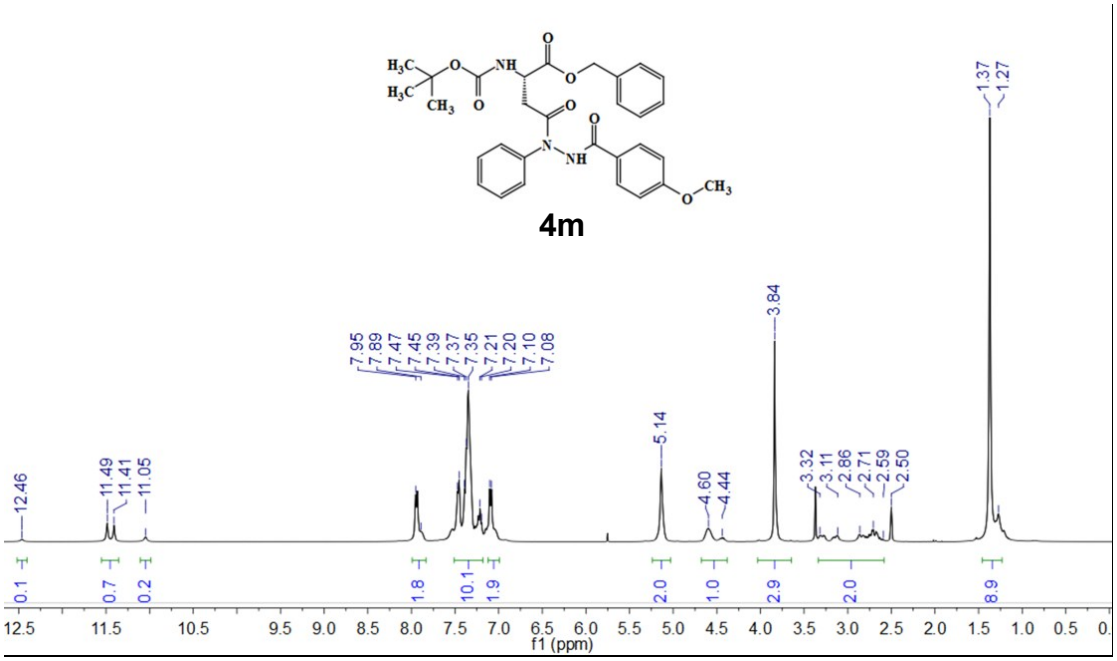

4j
56.90
55.39
51.71
48.96
46.79
45.57
44.96
42.78
38.62
36.46
35.98
35.48
35.22
31.03
27.55
25.12
21.88
18.73
11.85
129.42
127.95
123.89
212.07
209.22
208.77
77.37
173.49
165.92
162.60
141.92
113.64
0.01
f1 (ppm)

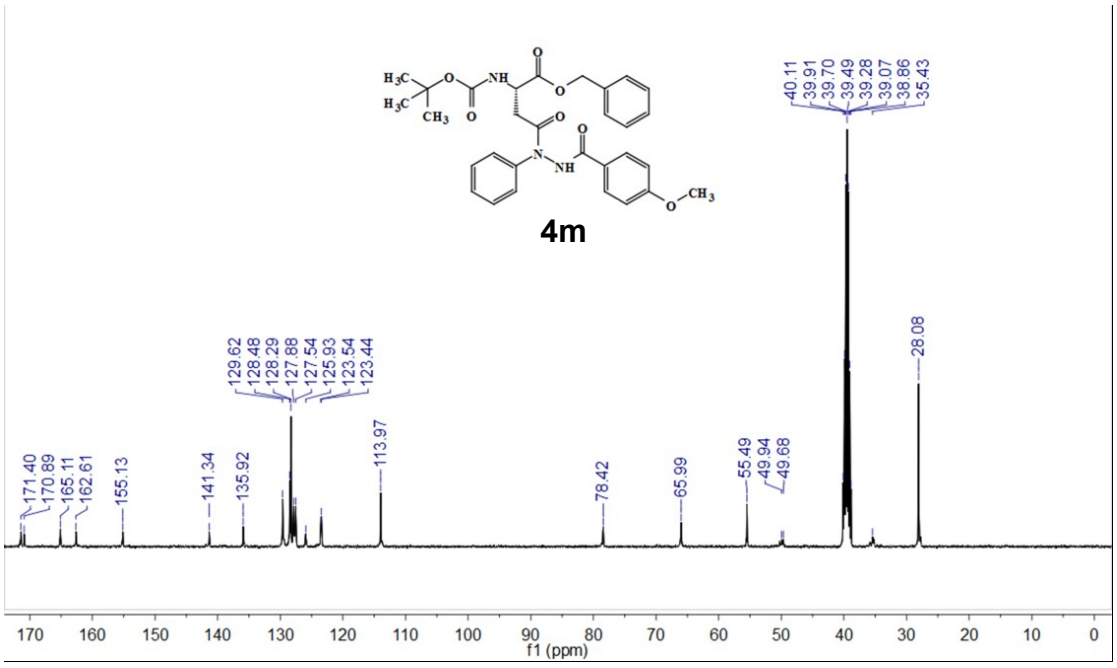

4k
8.55
7.75
7.73
7.50
7.36
7.34
7.26
7.26
6.87
6.85
5.77
5.41
3.83
2.43
2.42
2.40
2.39
2.23
2.22
2.20
2.10
2.09
2.08
2.04
1.78
1.60
1.48
1.26
1.16
1.12
1.02
1.01
1.01
0.87
0.80
f1 (ppm)

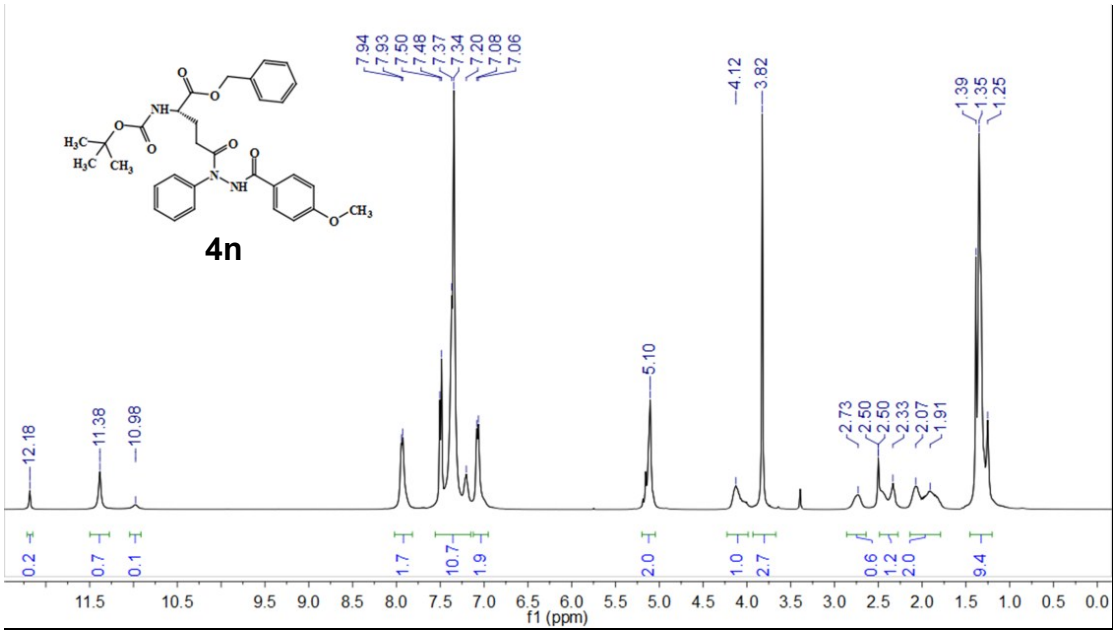

4k
78.20
77.88
77.56
136.29
130.47
130.20
129.90
129.73
129.41
129.18
125.40
123.46
121.86
114.68
180.09
167.14
163.58
145.67
145.07
56.26
52.34
49.28
45.94
38.81
38.54
35.73
35.57
30.55
28.26
26.76
24.83
23.34
22.28
21.74
19.98
19.07
f1 (ppm)

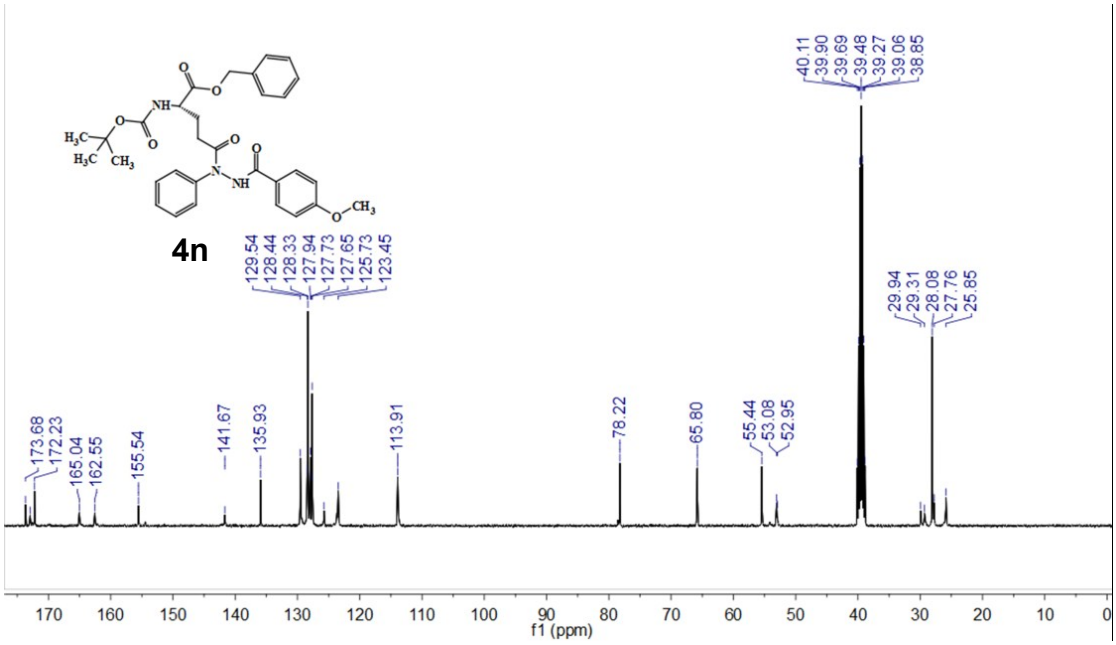

4l
10.20
7.88
7.86
7.60
7.58
7.46
7.35
7.34
7.33
7.32
7.30
7.29
7.26
7.22
7.22
7.20
6.95
6.93
6.31
6.29
5.60
5.59
5.52
5.50
4.70
3.82
3.80
3.66
3.62
3.60
1.77
1.72
1.03
1.0
2.0
2.0
1.6
4.9
2.0
1.5
0.9
1.1
0.8
0.8
2.9
2.0
3.0
2.7
f1 (ppm)

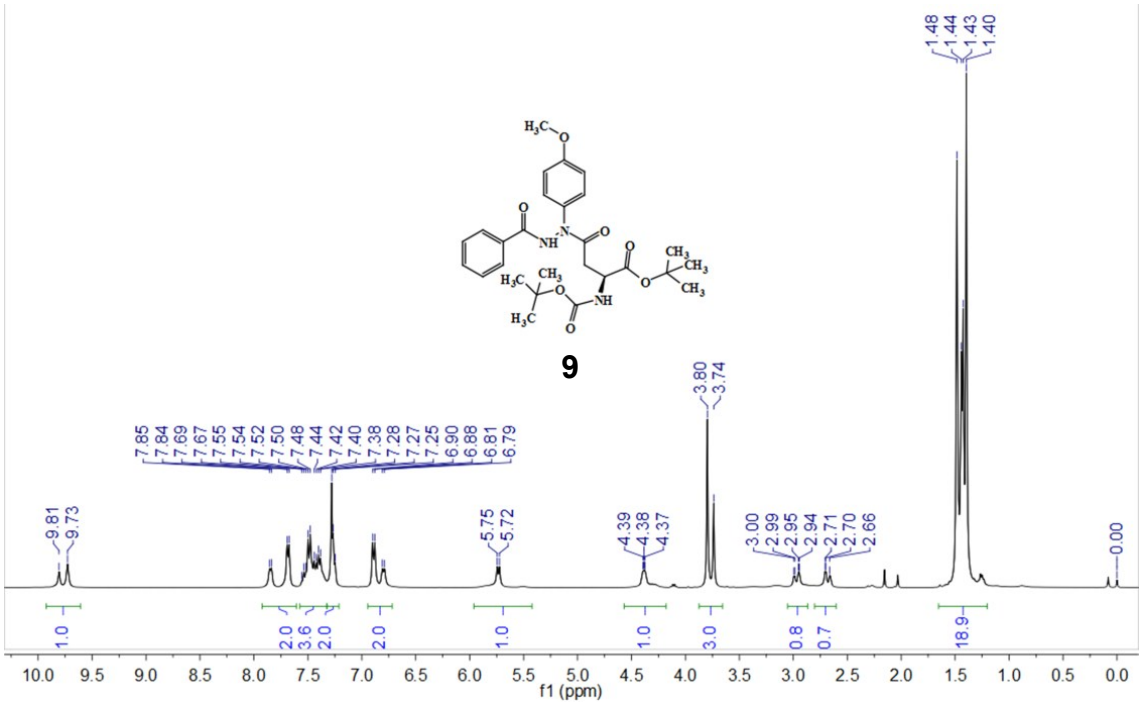

4l
77.36
77.04
76.72
133.84
133.63
132.14
131.83
129.75
129.58
129.18
128.95
128.41
127.76
127.71
127.58
115.17
172.48
170.69
167.19
166.49
160.08
68.44
66.52
65.28
59.11
55.53
43.51
34.06
26.63
f1 (ppm)

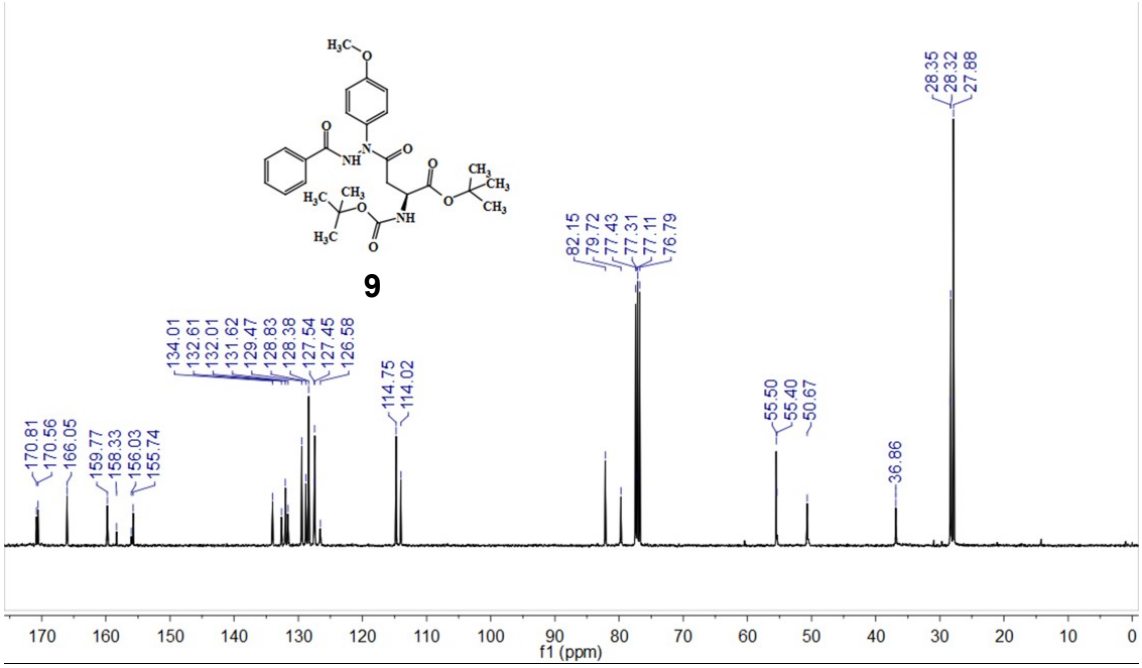

4m
12.46
11.49
11.41
11.05
7.95
7.89
7.47
7.45
7.39
7.37
7.35
7.21
7.20
7.10
7.08
5.14
4.60
4.44
3.84
3.32
3.11
2.86
2.71
2.59
2.50
1.37
1.27
0.1
0.7
0.2
1.8
10.1
1.9
2.0
1.0
2.9
2.0
8.9
f1 (ppm)

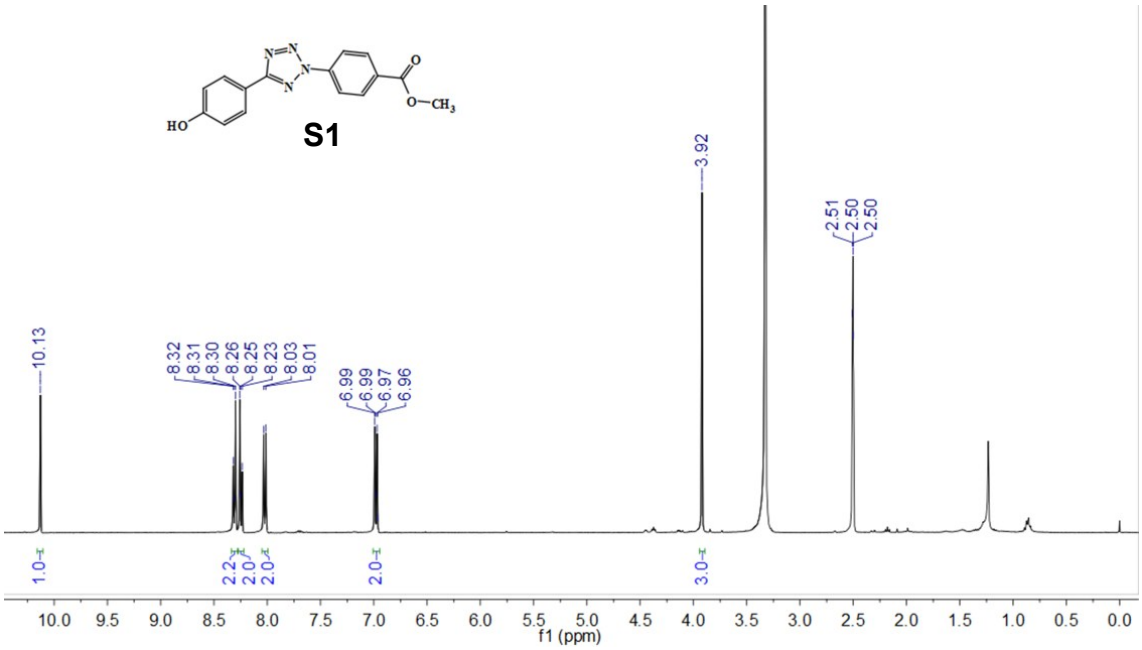

4m
171.40
170.89
165.11
162.61
155.13
141.34
135.92
129.62
128.48
128.29
127.88
127.54
125.93
123.54
123.44
113.97
78.42
65.99
55.49
49.94
49.68
40.11
39.91
39.70
39.49
39.28
39.07
38.86
35.43
28.08
f1 (ppm)

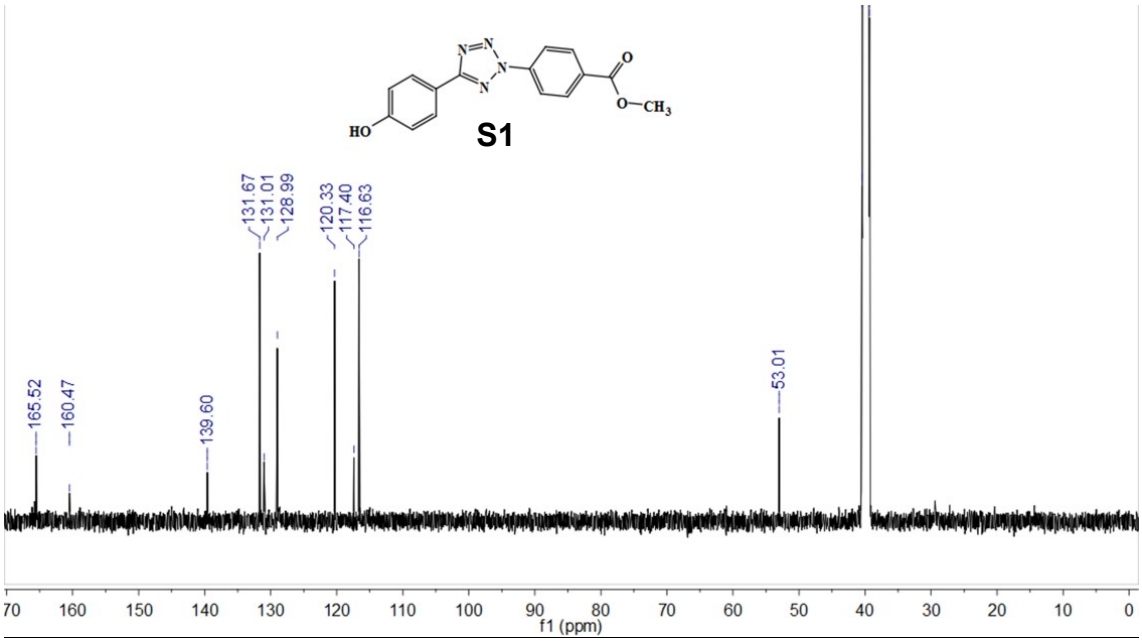

4n
12.18
11.38
10.98
7.94
7.93
7.50
7.48
7.37
7.34
7.20
7.08
7.06
5.10
4.12
3.82
2.73
2.50
2.50
2.33
2.07
1.91
1.39
1.35
1.25
f1 (ppm)

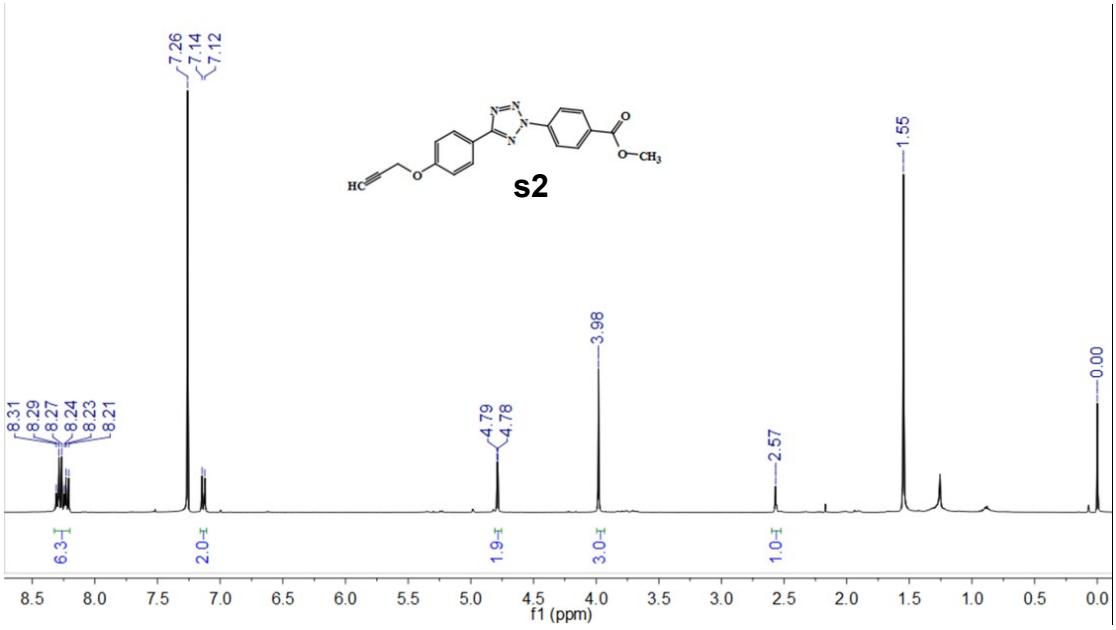

4n
173.68
172.23
165.04
162.55
155.54
141.67
135.93
129.54
128.44
128.33
127.94
127.73
127.65
125.73
123.45
113.91
78.22
65.80
55.44
53.08
52.95
40.11
39.90
39.69
39.48
39.27
39.06
38.85
29.94
29.31
28.08
27.76
25.85
f1 (ppm)


9
1.48
1.44
1.43
1.40
3.80
3.74
7.85
7.84
7.69
7.67
7.55
7.54
7.52
7.50
7.48
7.44
7.42
7.40
7.38
7.28
7.27
7.25
6.90
6.88
6.81
6.79
9.81
9.73
5.75
5.72
4.39
4.38
4.37
3.00
2.99
2.95
2.94
2.71
2.70
2.66
0.00
1.0
2.0
3.6
2.0
2.0
1.0
1.0
3.0
0.8
0.7
18.9
f1 (ppm)

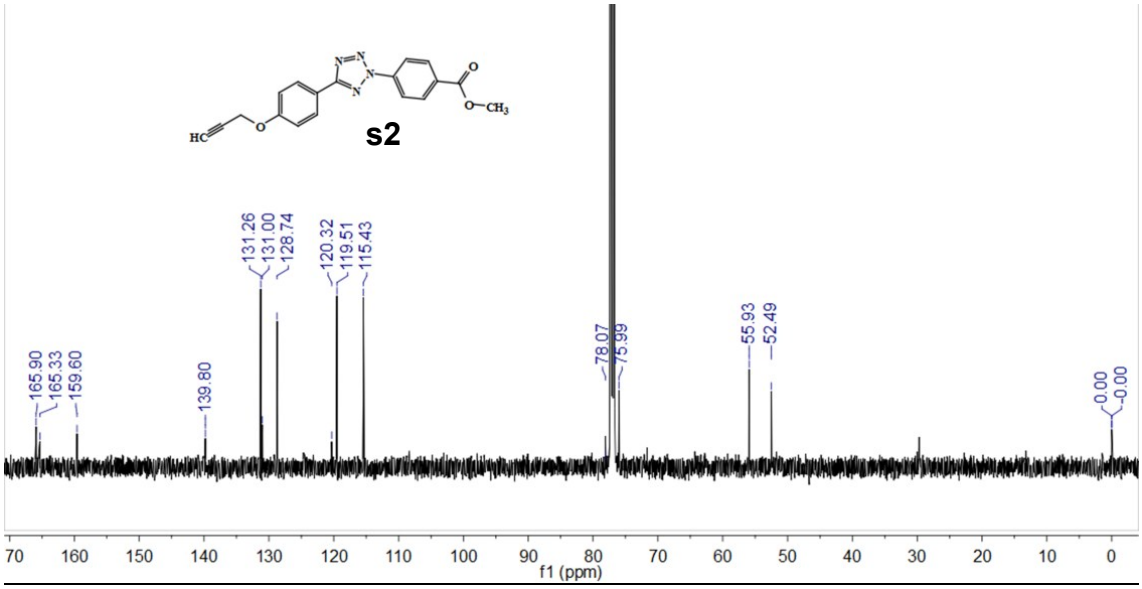

9
28.35
28.32
27.88
82.15
79.72
77.43
77.31
77.11
76.79
134.01
132.61
132.01
131.62
129.47
128.83
128.38
127.54
127.45
126.58
114.75
114.02
55.50
55.40
50.67
36.86
170.81
170.56
166.05
159.77
158.33
156.03
155.74
f1 (ppm)


S1
HO
O
O—CH3
10.13
8.32
8.31
8.30
8.26
8.25
8.23
8.03
8.01
6.99
6.99
6.97
6.96
3.92
2.51
2.50
2.50
1.0
2.2
2.0
2.0
2.0
3.0
f1 (ppm)

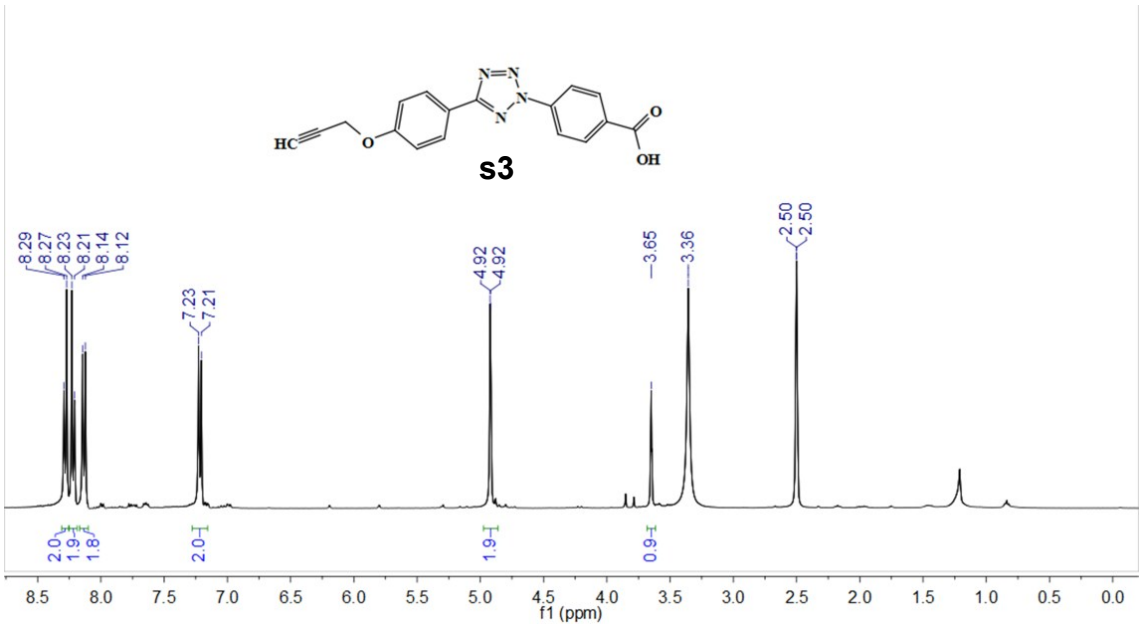

S1
HO
O
O—CH3
131.67
131.01
128.99
120.33
117.40
116.63
165.52
160.47
139.60
53.01
f1 (ppm)

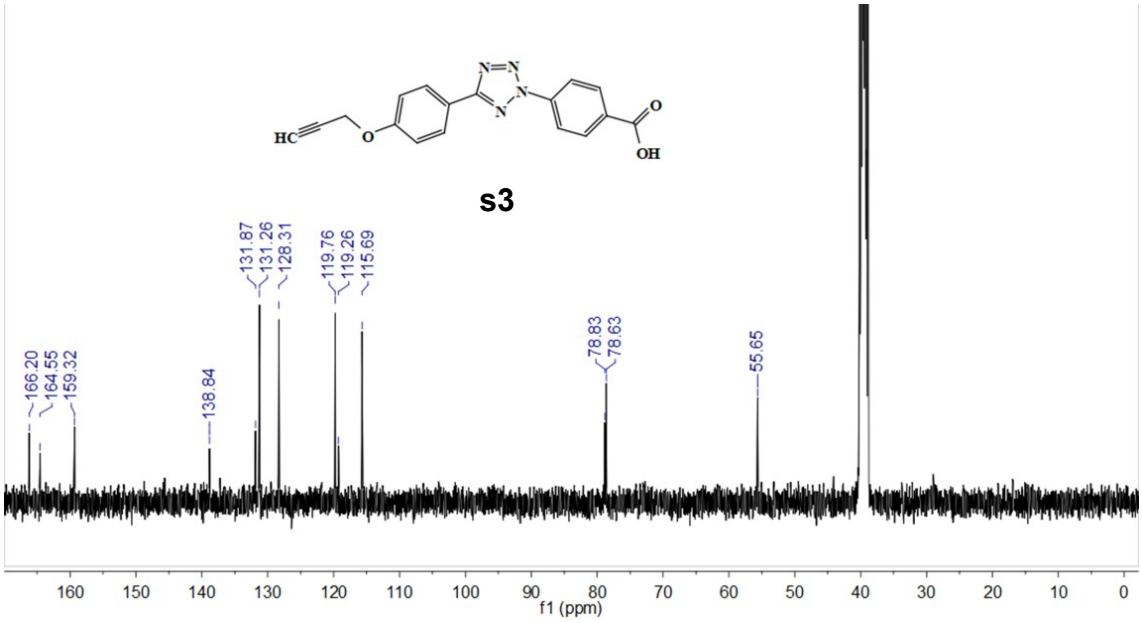

7.26
7.14
7.12
8.31
8.29
8.27
8.24
8.23
8.21
4.79
4.78
3.98
2.57
1.55
0.00
6.3
2.0
1.9
3.0
1.0
f1 (ppm)

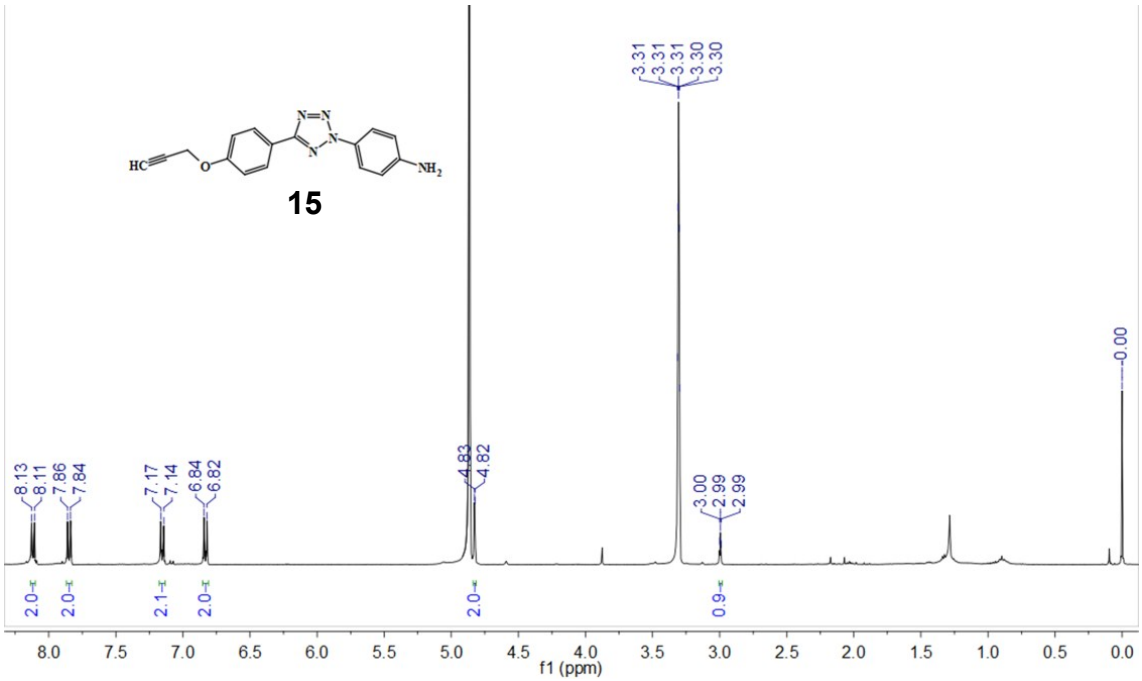
s2

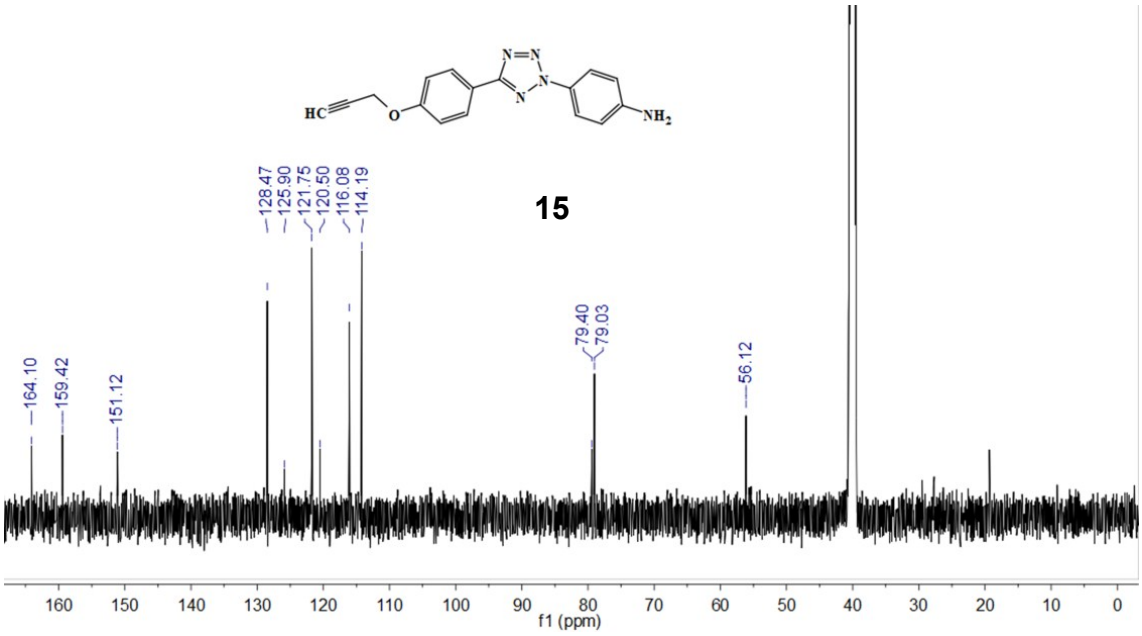

165.90
165.33
159.60
139.80
131.26
131.00
128.74
120.32
119.51
115.43
78.07
75.99
55.93
52.49
0.00
0.00
f1 (ppm)

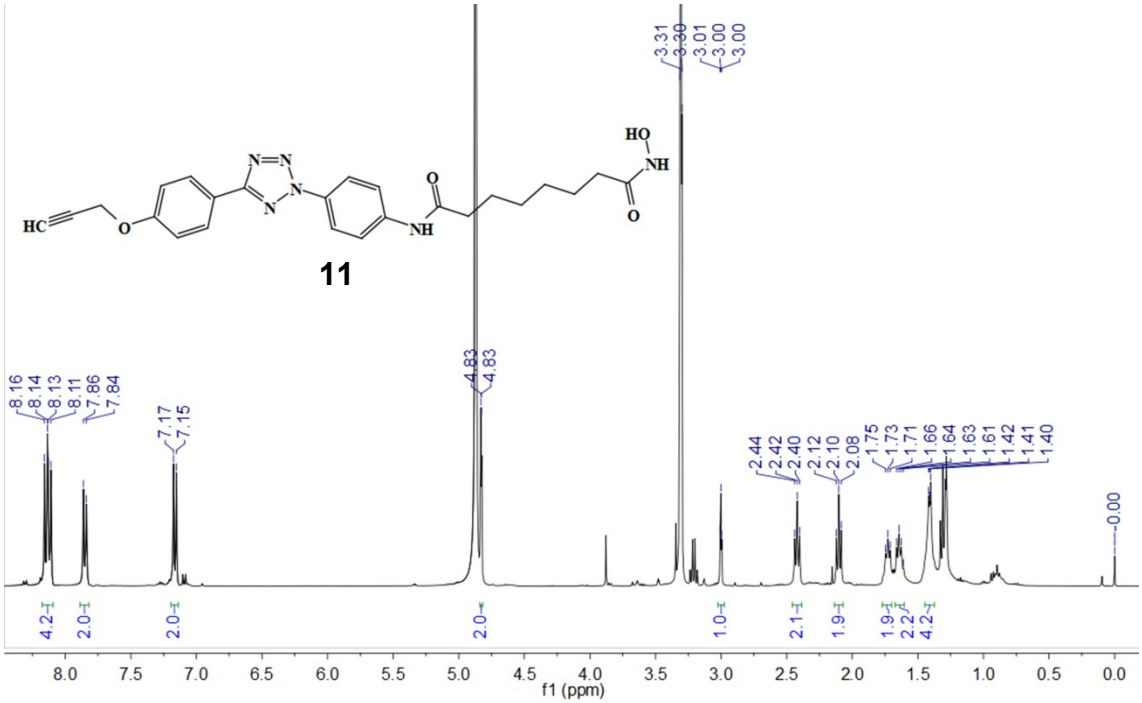
s2

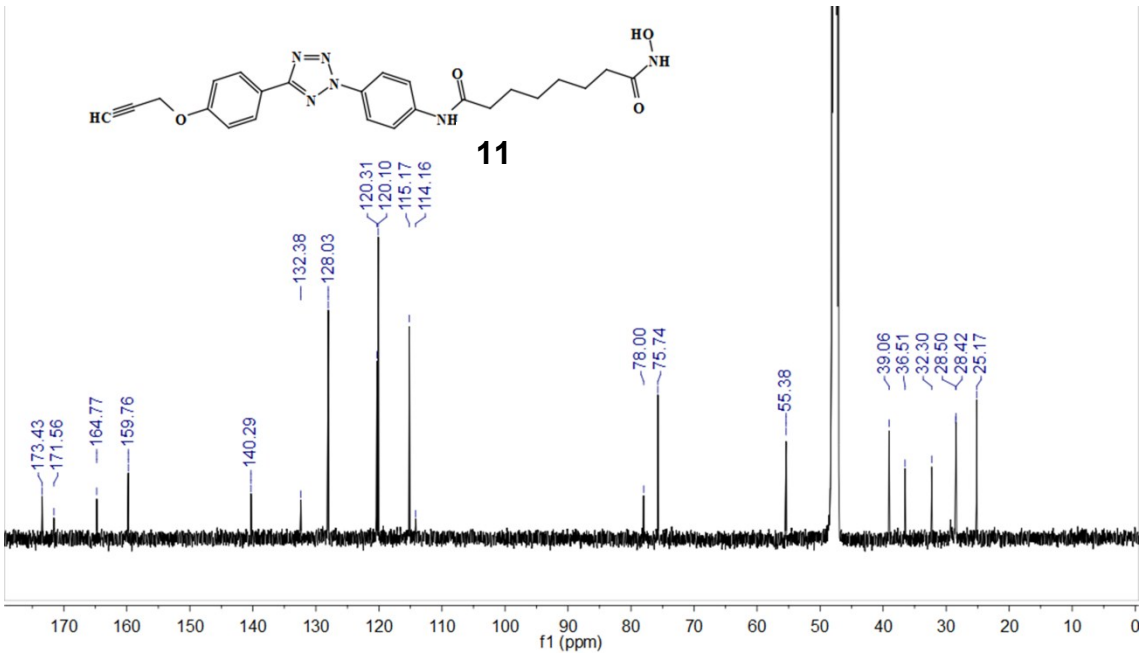

s3
8.29
8.27
8.23
8.21
8.14
8.12
7.23
7.21
4.92
4.92
3.65
3.36
2.50
2.50
2.0
1.9
1.8
2.0
1.9
0.9
f1 (ppm)

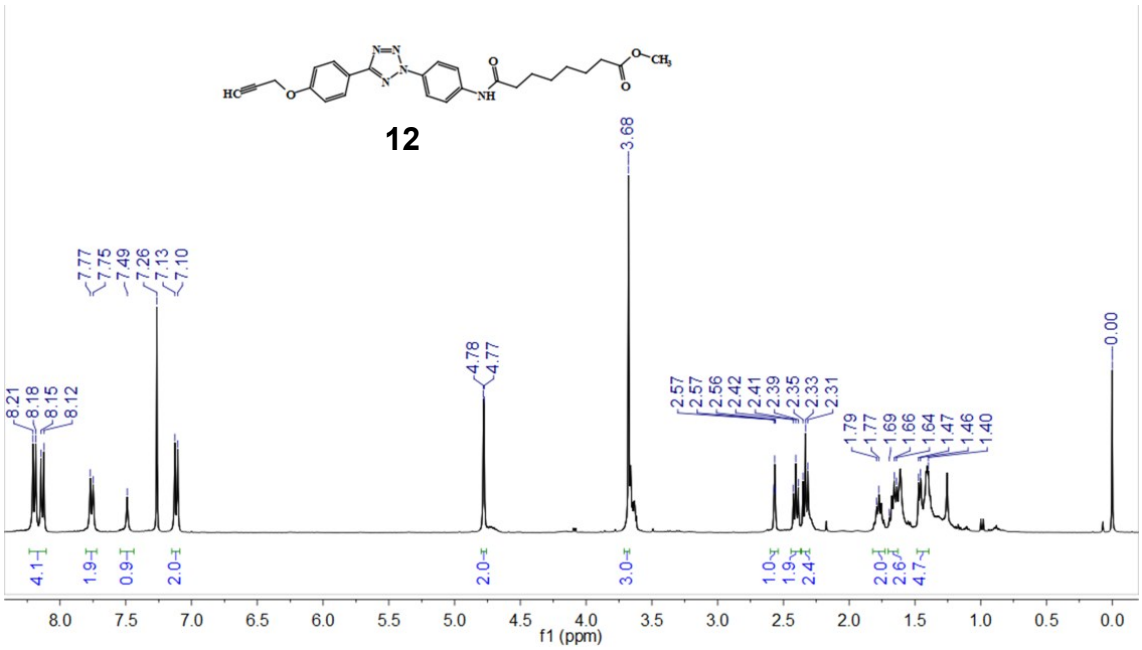

s3
166.20
164.55
159.32
138.84
131.87
131.26
128.31
119.76
119.26
115.69
78.83
78.63
55.65
f1 (ppm)

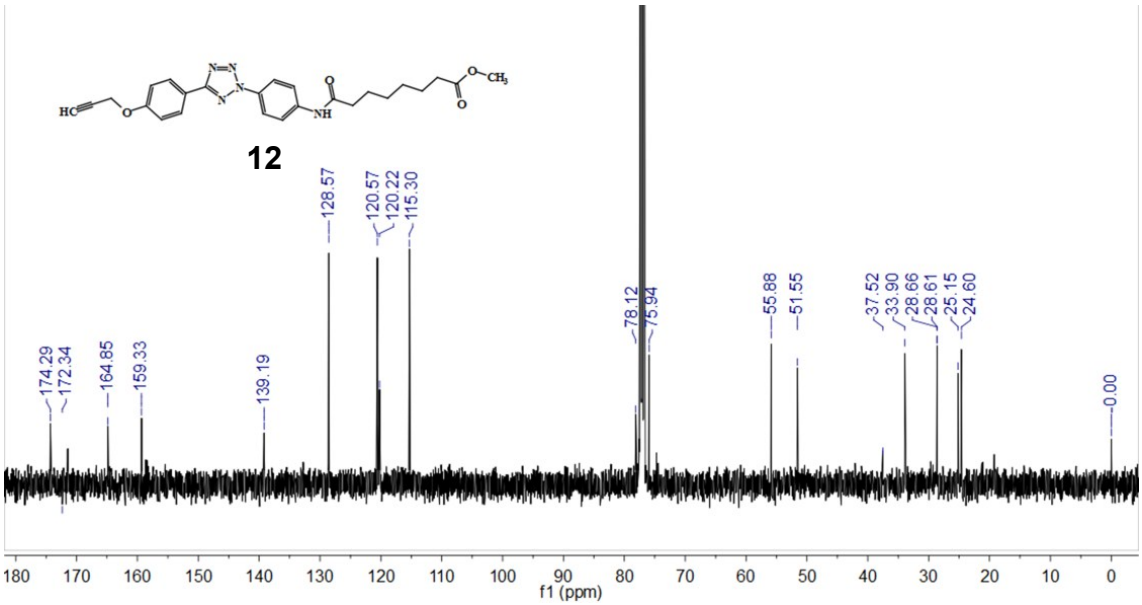

15
8.13
8.11
7.86
7.84
7.17
7.14
6.84
6.82
4.83
4.82
3.31
3.31
3.31
3.30
3.30
3.00
2.99
2.99
0.00
2.0
2.0
2.1
2.0
2.0
0.9
f1 (ppm)


15
164.10
159.42
151.12
128.47
125.90
121.75
120.50
116.08
114.19
79.40
79.03
56.12
f1 (ppm)


11
8.16
8.14
8.13
8.11
7.86
7.84
7.17
7.15
4.83
4.83
3.31
3.30
3.01
3.00
3.00
2.44
2.42
2.40
2.12
2.10
2.08
1.75
1.73
1.71
1.66
1.64
1.63
1.61
1.42
1.41
1.40
0.00
4.2
2.0
2.0
2.0
1.0
2.1
1.9
1.9
2.2
4.2
f1 (ppm)


11
173.43
171.56
164.77
159.76
140.29
132.38
128.03
120.31
120.10
115.17
114.16
78.00
75.74
55.38
39.06
36.51
32.30
28.50
28.42
25.17
f1 (ppm)





10. *References*

(1) Suketaka Ito, Y. T., Akikazu Kakehi, Ken-ichi Kondo *Bull. Chem. Soc. Jpn.* **1976**, *49*, 4.

(2) Suketaka Ito, Y. T., Akikazu Kakehi *Bull. Chem. Soc. Jpn.* **1976**, *49*, 5.