

Discovery of Natural Product Derived Labdane Appended Triazoles as Potent Pancreatic Lipase Inhibitors

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Contents

1. Experimental.....	(2)
1.1. Chemistry.....	(2-11)
1.2. Biology.....	(11-14)
2. Molecular docking studies of various triazole derivatives.....	(15-18)
3. Spectra of intermediates and triazole derivatives	(19-36)
4. References.....	(37-38)

1. Experimental

1.1. Chemistry

All reagents used for the isolation and triazole preparation were purchased from sigma-Aldrich and Spectrochem. Hep G2 Cell lines, human liver carcinoma-derived cell lines were purchased from American Type Cell Culture (ATCC, Manassas, VA, USA), Pancreatic lipase, p-nitrophenyl butyrate, Human Pancreatic lipase (EC 3.1.13), olive oil, taurochenodeoxycholate, taurocholate, cholesterol, L- α -phosphatidylcholine, calcium acetate, orlistat (Sigma Aldrich, USA) was used for biological study. Solvents were purchased from Merck and were distilled before use. TLC plates (silica gel 60 F₂₅₄) used for monitoring the purity of the isolated compounds and the reaction progress. Column chromatographic techniques were used for the isolation of natural compounds and its analogues. Heidolph rotary evaporator was used for the removal of solvents. The absorbance was recorded at 540 nm by the Elisa reader. The IR spectra was recorded on Bruker Alpha-T FT-IR spectrophotometer. The ¹H and ¹³C NMR spectra were recorded at 500MHz and 125MHz respectively on Bruker AMX 500 MHz FT NMR and 125 MHz spectrometer. Tetramethylsilane (TMS) was used as an internal standard, chemical shifts are expressed in δ scale and coupling constant in Hertz. In ¹H NMR the solvent (CDCl₃) peak appeared as singlet at 7.26 ppm and in ¹³C NMR the peak appeared as triplet at 77.0 ppm. Mass spectra were recorded under HRMS (ESI) using Thermo Scientific Exactive Orbitrap mass spectrometer.

1.1.1. Isolation of *E*-labda 8(17),12-diene -15,16-dial (1)

Two kilograms of the dried powdered rhizomes of *C.amada* was extracted four times with chloroform. After the removal of solvent, 90 g of the crude extract was obtained. 30g of the crude extract was chromatographed on silica gel (100-200 mesh). The column was eluted with mixture of ethylacetate-hexane of increasing polarity. The fraction obtained from 5% ethylacetate-hexane on subjected to crystallization using hexane to yield pure compound **1** (*E*-labda 8(17), 12-diene -15, 16-dial, 10 g) as colorless solid. The structure of the compound was confirmed by various spectroscopic and analytical techniques such as IR, ¹H NMR, ¹³C NMR, HRMS and comparison with the reported literature.^{1,2}

1.1.2. Procedure for the synthesis of Zerumin A (2)

To a stirred solution of compound *E*-labda 8(17),12-diene -15,16-dial (**1**) (1 g) in acetone, Jones' reagent (CrO_3 and H_2SO_4) was added drop wise until the reddish colour persisted. After the completion of the reaction as indicated by TLC, excess reagent was quenched by the addition of isopropanol. The reaction mixture was then filtered through celite, concentrated, further extracted with diethyl ether, washed with distilled water and dried with anhydrous Na_2SO_4 . Solvent was removed and the residue was subjected to column chromatography on silica gel afforded the compound Zerumin A (**2**) (1.5 g, 71% yield). The structure of the compound was confirmed by various spectroscopic data and comparison with the reported literature.

1.1.3. Procedure for the synthesis of (*E*)-prop-2-yn-1-yl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**3**)

The propargyl bromide (0.3736g, 1 equiv.) was added drop wise to a solution of Zerumin A (1 g, 1 equiv.) in DMF at 0 °C. K_2CO_3 (0.6510 g, 1.5 equiv.) was added and allowed to stir continuously at room temperature until the completion of the reaction monitored by TLC. The compound was extracted with ethylacetate, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure afforded the compound **3**. Yield: 97% (1.083 g). ^1H NMR(500MHz, CDCl_3) δ : 9.37(s, 1H), 6.69(t, $J = 6.5\text{Hz}$, 1H), 4.86(s, 1H), 4.69(d, $J = 2.5\text{Hz}$, 2H), 4.40(s, 1H), 3.37(d, $J = 8.5\text{Hz}$, 2H), 2.55-1.13(m, 15H), 0.89(s, 3H), 0.82(s, 3H), 0.74(s, 3H). ^{13}C NMR (125MHz, CDCl_3) δ : 193.29, 169.31, 159.19, 148.04, 135.78, 107.94, 77.44, 75.06, 56.35, 55.34, 52.42, 41.98, 39.56, 39.19, 37.84, 33.59, 29.42, 24.62, 24.09, 21.74, 19.28, 14.40. IR (NaCl, ν_{max} , cm^{-1}): 3279, 3080, 2933, 2845, 2719, 2130, 1747, 1686, 1644, 891. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{32}\text{O}_3$ is 379.2249, found 379.2235.

1.1.4. General procedure for synthesis of azides (**5a-5q**)

Benzyl/Phenacyl bromide (1 equiv.) was added drop wise to a stirred solution of NaN_3 (2 equiv.) in 3:1 mixture of acetone and water, and the resulting mixture was stirred at room temperature for 1 hr. The reaction was diluted with water and extracted with ethylacetate. The combined layer washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure.

1.1.5. General procedure for synthesis of triazole analogues (6a-6q)

To a solution of azide (1 equiv.) and compound **3** (1 equiv.) in ^tBuOH - water (1:2) mixture, CuSO₄·5H₂O (0.1 equiv.) and sodium ascorbate (0.25 equiv.) were added and the reaction mixture was allowed to stirred at room temperature, progress of the reaction was monitored by TLC. After completion of the reaction, the content was extracted with ethylacetate, washed with brine and the compound was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The product was purified by column chromatography using ethylacetate and hexane as solvents.

1.1.5.1. Synthesis of (*E*)-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) pent-3-enoate (**6a**)

The compound **6a** was prepared by the reaction of benzylazide (11.20 mg, 1 equiv.) and compound **3** (30 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 61% (25 mg). IR (NaCl, ν_{\max} , cm⁻¹): 3082, 2930, 2846, 2719, 2122, 1739, 1683, 1644, 891. ¹H NMR (500MHz, CDCl₃) δ : 9.33(s, 1H), 7.52(s, 1H), 7.38-7.27(m, 5H), 6.64(t, *J* = 6.5Hz, 1H), 5.51(s, 2H), 5.21(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.31(s, 2H), 2.53-1.04(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ¹³C NMR (125MHz, CDCl₃) δ : 193.42, 169.99, 159.06, 148.06, 143.12, 135.98, 134.40, 129.16, 128.84, 128.14, 123.62, 107.88, 58.26, 56.38, 55.36, 54.24, 41.98, 39.56, 39.22, 37.84, 33.58, 29.66, 24.58, 24.09, 21.74, 19.30, 14.40. HRMS (ESI) *m/z*: [M+Na]⁺ calcd for C₃₀H₃₉N₃O₃ is 512.2889, found 512.2885.

1.1.5.2. Synthesis of (*E*)-(1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6b**)

The compound **6b** was prepared by the reaction of 4-fluorobenzylazide (12.71 mg, 1 equiv.) and compound **3** (30mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 71% (32 mg). IR (NaCl, ν_{\max} , cm⁻¹): 3080, 2932, 2845, 2720, 2102, 1739, 1682, 1643, 892. ¹H NMR (500MHz, CDCl₃) δ : 9.33(s, 1H), 7.54(s, 1H), 7.29-7.27(m, 2H), 7.08-7.05(m, 2H), 6.65(t, *J* = 6.5Hz, 1H), 5.48(s, 2H), 5.22(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.32(s, 2H), 2.54-1.04(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ¹³C NMR (125MHz, CDCl₃) δ : 193.49, 170.04, 159.15, 148.06, 143.25, 135.96, 130.07, 130.00, 123.57, 116.26, 116.08, 107.88, 58.22, 56.37, 55.34, 53.46, 41.96, 39.54, 39.21, 37.83, 33.58,

33.57, 29.68, 24.58, 24.08, 21.74, 19.29, 14.40. HRMS (ESI) m/z : $[M+Na]^+$ calcd for $C_{30}H_{38}FN_3O_3$ is 530.2795, found 530.2775.

1.1.5.3. Synthesis of (*E*)-(1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6c**)

The compound **6c** was prepared by the reaction of 4-nitrobenzylazide (14.99 mg, 1 equiv.) and compound **3** (30 mg, 1 equiv.) in t BuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 73% (32 mg). IR (NaCl, ν_{max} , cm^{-1}): 3081, 2931, 2846, 2720, 2253, 1739, 1682, 1643, 893. 1H NMR (500MHz, $CDCl_3$) δ : 9.32(s, 1H), 8.24(d, J = 8.5Hz, 2H), 7.64(s, 1H), 7.42(d, J = 9Hz, 2H), 6.66(t, J = 6.5Hz, 1H), 5.64(s, 2H), 5.25(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.32(s, 2H), 2.55-1.05(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.72(s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ : 193.55, 170.09, 159.18, 148.10, 143.72, 141.46, 135.96, 128.67, 124.34, 124.06, 107.88, 58.16, 56.38, 55.34, 53.14, 41.96, 39.55, 39.23, 37.82, 33.57, 29.77, 24.59, 24.07, 21.72, 19.29, 14.41. HRMS (ESI) m/z : $[M+Na]^+$ calcd for $C_{30}H_{38}N_4O_5$ is 557.2740, found 557.2760.

1.1.5.4. Synthesis of (*E*)-(1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6d**)

The compound **6d** was prepared by the reaction of 2-chlorobenzylazide (14.10 mg, 1 equiv.) and compound **3** (30mg, 1 equiv.) in t BuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 80% (35 mg). IR (NaCl, ν_{max} , cm^{-1}): 3078, 2929, 2845, 2718, 2359, 1739, 1683, 1643, 891. 1H NMR (500MHz, $CDCl_3$) δ : 9.34(s, 1H), 7.62(s, 1H), 7.44-7.18(m, 4H), 6.65(t, J = 6.5Hz, 1H), 5.66(s, 2H), 5.22(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.32(d, J = 1.5Hz, 2H), 2.54-1.02(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ : 193.42, 169.98, 159.09, 148.05, 142.99, 135.98, 133.52, 132.25, 130.40, 130.32, 129.96, 127.64, 124.01, 107.90, 58.22, 56.37, 55.35, 51.46, 41.98, 39.54, 39.20, 37.84, 33.58, 33.57, 29.65, 24.58, 24.08, 21.74, 19.29, 14.40. HRMS (ESI) m/z : $[M+Na]^+$ calcd for $C_{30}H_{38}ClN_3O_3$ is 546.2499, found 546.2509.

1.1.5.5. Synthesis of (*E*)-(1-(4-(methylthio)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6e**)

The compound **6e** was prepared by the reaction of 4-thiomethylbenzylazide (15.08 mg, 1 equiv.) and compound **3** (30 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 53% (24 mg). IR (NaCl, ν_{\max} , cm^{-1}): 3082, 2930, 2846, 2720, 2100, 1739, 1682, 1643, 892. ¹H NMR (500MHz, CDCl₃) δ : 9.33(s, 1H), 7.52(s, 1H), 7.23(s, 2H), 7.21(s, 2H), 6.64(t, J = 6.5Hz, 1H), 5.46(s, 2H), 5.20(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.32(s, 2H), 2.48(s, 3H), 2.04-1.04(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ¹³C NMR (125MHz, CDCl₃) δ : 193.45, 170.00, 159.12, 148.06, 143.12, 139.80, 135.97, 130.86, 128.68, 126.78, 123.52, 107.89, 58.24, 56.37, 55.35, 53.79, 41.98, 39.54, 39.20, 37.84, 33.59, 33.57, 29.66, 24.59, 24.09, 21.74, 19.30, 15.52, 14.40. HRMS (ESI) m/z : [M+Na]⁺ calcd for C₃₁H₄₁N₃O₃S is 558.2766, found 558.2769.

1.1.5.6. Synthesis of (*E*)-(1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6f**)

The compound **6f** was prepared by the reaction of 4-chlorobenzylazide (14.10 mg, 1 equiv.) and compound **3** (30 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 52% (23 mg). IR (NaCl, ν_{\max} , cm^{-1}): 3083, 2931, 2845, 2720, 1739, 1682, 1643, 891. ¹H NMR (500MHz, CDCl₃) δ : 9.33(s, 1H), 7.54(s, 1H), 7.35(d, J = 8.5Hz, 2H), 7.22(d, J = 8.5Hz, 2H), 6.65(t, J = 6.5Hz, 1H), 5.48(s, 2H), 5.22(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.32(s, 2H), 2.54-1.04(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ¹³C NMR (125MHz, CDCl₃) δ : 193.46, 170.02, 159.10, 148.07, 143.34, 135.98, 134.90, 132.92, 129.44, 129.38, 123.62, 107.88, 58.22, 56.38, 55.36, 53.46, 41.98, 39.55, 39.22, 37.84, 33.58, 29.69, 24.58, 24.08, 21.74, 19.30, 14.40. HRMS (ESI) m/z : [M+Na]⁺ calcd for C₃₀H₃₈ClN₃O₃ is 546.2499, found 546.2512.

1.1.5.7. Synthesis of (*E*)-(1-(4-(*tert*-butyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6g**)

The compound **6g** was prepared by the reaction of 4-^tButylbenzylazide (10.65 mg, 1 equiv.) and compound **3** (20 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 50% (15 mg). IR (NaCl, ν_{\max} , cm^{-1}): 3081, 2957,

2867, 2718, 1739, 1684, 1643, 891. ¹H NMR (500MHz, CDCl₃) δ: 9.33(s, 1H), 7.52(s, 1H), 7.40(d, *J* = 8Hz, 2H), 7.22(d, *J* = 8.5Hz, 2H), 6.64(t, *J* = 6.5Hz, 1H), 5.48(s, 2H), 5.20(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.32(s, 2H), 2.54-1.05(m, 14H), 1.31(s, 9H), 0.89(s, 3H), 0.82(s, 3H), 0.72(s, 3H). ¹³C NMR (125MHz, CDCl₃) δ: 193.45, 170.01, 159.11, 151.98, 148.06, 135.98, 131.32, 127.98, 126.09, 107.90, 58.28, 56.38, 55.36, 53.95, 41.98, 39.56, 39.21, 37.84, 34.66, 33.59, 33.58, 31.26, 29.65, 24.59, 24.09, 21.74, 19.30, 14.41. HRMS (ESI) *m/z*: [M-H]⁺ calcd for C₃₄H₄₇N₃O₃ is 544.3534, found 544.3560.

1.1.5.8. (E)-(1-(2-bromo-5-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-((1*S*,4*aS*,8*aS*)-5,5,8*a*-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (6*h*)

The compound **6h** was prepared by the reaction of 2-bromo-5-fluorobenzylazide (14.77mg, 1 equiv.) and compound **3** (23 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 69% (25 mg). IR (NaCl, *v*_{max}, cm⁻¹): 3079, 2928, 2848, 2719, 1739, 1683, 1643, 891. ¹H NMR (500MHz, CDCl₃) δ: 9.34(s, 1H), 7.63-7.16(m, 4H), 6.65(t, *J* = 6.5Hz, 1H), 5.65(s, 2H), 5.22(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.32(s, 2H), 2.54-1.04(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ¹³C NMR (125MHz, CDCl₃) δ: 193.45, 170.00, 159.12, 148.06, 142.99, 135.97, 133.95, 133.26, 130.49, 130.40, 128.27, 124.06, 123.50, 107.91, 58.23, 56.38, 55.36, 53.88, 41.98, 39.55, 39.22, 37.84, 33.60, 33.58, 29.66, 24.60, 24.09, 21.75, 19.30, 14.42. HRMS (ESI) *m/z*: [M+Na]⁺ calcd for C₃₀H₃₇BrFN₃O₃ is 608.1900, found 608.1921.

1.1.5.9. Synthesis of (E)-(1-(2-hydroxy-5-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8*a*-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (6*i*)

The compound **6i** was prepared by the reaction of 2-hydroxy-5-nitrobenzylazide (10.88 mg, 1 equiv.) and compound **3** (20 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 77% (23 mg). IR (NaCl, *v*_{max}, cm⁻¹): 3081, 2928, 2847, 1740, 1681, 1644, 893. ¹H NMR (500MHz, CDCl₃) δ: 9.94 (bs, 1H), 9.30(s, 1H), 8.20(d, *J* = 2.5Hz 1H), 8.12(dd, *J* = 9Hz, 3Hz, 1H), 7.82(s, 1H), 7.04(d, *J* = 9Hz, 1H), 6.70(t, *J* = 6.5Hz, 1H), 5.58(s, 2H), 5.23(s, 2H), 4.81(s, 1H), 4.32(s, 1H), 3.30(s, 2H), 2.56-1.02(m, 14H), 0.88(s, 3H), 0.82(s, 3H), 0.70(s, 3H). ¹³C NMR (125MHz, CDCl₃) δ: 194.34, 170.09, 161.16, 160.51, 148.10, 142.80, 140.88, 135.82, 126.84, 126.78, 124.98, 121.89, 116.78, 107.88, 57.96, 56.38,

55.35, 49.53, 41.95, 39.56, 39.24, 37.81, 33.57, 29.76, 24.74, 24.06, 21.72, 19.28, 14.40. HRMS (ESI) m/z : $[M+Na]^+$ calcd for $C_{30}H_{38}N_4O_6$ is 573.2689, found 573.2689.

1.1.5.10. Synthesis of (*E*)-(1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (6j)

The compound **6j** was prepared by the reaction of 4-methoxybenzylazide (10.06 mg, 1 equiv.) and compound **3** (22 mg, 1 equiv.) in t BuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 75% (24 mg). IR (NaCl, ν_{max} , cm^{-1}): 3081, 2933, 2843, 1739, 1682, 1643, 891. 1H NMR (500MHz, $CDCl_3$) δ : 9.33(s, 1H), 7.50(bs, 1H), 7.23(d, J = 8.5Hz, 2H), 6.90(d, J = 8.5Hz, 2H), 6.64(t, J = 6.5Hz, 1H), 5.44(s, 2H), 5.20(s, 2H), 4.82(s, 1H), 4.34(s, 1H), 3.80(s, 3H), 3.32(s, 2H), 2.52-1.04(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ : 193.48, 170.02, 159.98, 159.18, 148.06, 135.97, 129.76, 126.33, 114.51, 107.90, 58.26, 56.36, 55.34, 53.84, 41.98, 39.54, 39.20, 37.84, 33.60, 33.58, 29.64, 24.59, 24.08, 21.74, 19.29, 14.41. HRMS (ESI) m/z : $[M+Na]^+$ calcd for $C_{31}H_{41}N_3O_4$ is 542.2995, found 542.3003.

1.1.5.11. Synthesis of (*E*)-(1-(2-bromo-5-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (6k)

The compound **6k** was prepared by the reaction of 2-bromo-5-methoxybenzylazide (16.89 mg, 1 equiv.) and compound **3** (25 mg, 1 equiv.) in t BuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 66% (27 mg). IR (NaCl, ν_{max} , cm^{-1}): 3080, 2932, 2844, 1739, 1682, 1643, 890. 1H NMR (500MHz, $CDCl_3$) δ : 9.34(s, 1H), 7.65(s, 1H), 7.49(d, J = 9Hz, 1H), 6.79(dd, J_I = 9Hz, 3Hz, 1H), 6.72(d, J = 3Hz, 1H), 6.65(t, J = 6.5Hz, 1H), 5.60(s, 2H), 5.22(s, 2H), 4.82(s, 1H), 4.35(s, 1H), 3.75(s, 3H), 3.33(s, 2H), 2.54-1.04(m, 14H), 0.90(s, 3H), 0.82(s, 3H), 0.71(s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ : 193.47, 169.99, 159.44, 159.18, 148.05, 142.98, 135.96, 134.70, 133.86, 124.02, 116.32, 115.96, 113.63, 107.92, 58.22, 56.36, 55.58, 55.34, 53.94, 41.97, 39.54, 39.20, 37.83, 33.60, 33.57, 29.64, 24.60, 24.08, 21.75, 19.30, 14.41. HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{31}H_{40}BrN_3O_4$ is 598.2280, found 598.2278.

1.1.5.12. Synthesis of (E)-(1-([1,1'-biphenyl]-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl 5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (6l)

The compound **6l** was prepared by the reaction of 1,1'-biphenylazide (15.82 mg, 1 equiv.) and compound **3** (27 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 86% (36 mg). IR (NaCl, ν_{\max} , cm^{-1}): 3060, 2932, 2844, 2719, 1740, 1684, 1643, 891. ¹H NMR (500MHz, CDCl_3) δ : 9.33(s, 1H), 7.44-7.24(m, 10H), 6.64(t, $J = 6.5\text{Hz}$, 1H), 5.48(s, 2H), 5.16(s, 2H), 4.80(s, 1H), 4.33(s, 1H), 3.30(s, 2H), 2.52-1.01(m, 14H), 0.88(s, 3H), 0.82(s, 3H), 0.70(s, 3H). ¹³C NMR (125MHz, CDCl_3) δ : 193.40, 169.96, 159.07, 148.05, 142.64, 141.99, 139.80, 135.98, 131.86, 130.50, 129.09, 129.03, 128.70, 128.64, 128.22, 127.79, 123.80, 107.90, 58.20, 56.37, 55.34, 51.76, 41.98, 39.54, 39.20, 37.83, 33.59, 33.57, 29.63, 24.58, 24.08, 21.74, 19.28, 14.40. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{36}\text{H}_{43}\text{N}_3\text{O}_3$ is 588.3202, found 588.3181.

1.1.5.13. Synthesis of (E)-(1-(2-oxo-2-phenylethyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (6m)

The compound **6m** was prepared by the reaction of phenacylazide (10.39 mg, 1 equiv.) and compound **3** (23 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 55% (18 mg). IR (NaCl, ν_{\max} , cm^{-1}): 3082, 2929, 2848, 2121, 1738, 1682, 1643, 892. ¹H NMR (500MHz, CDCl_3) δ : 9.36(s, 1H), 8.00(d, $J = 7\text{Hz}$, 2H), 7.78(s, 1H), 7.68(t, $J = 7.5\text{Hz}$, 1H), 7.56(t, $J = 8\text{Hz}$, 2H), 6.67(t, $J = 6.5\text{Hz}$, 1H), 5.86(s, 2H), 5.30(s, 2H), 4.84(s, 1H), 4.38(s, 1H), 3.36(d, $J = 4\text{Hz}$, 2H), 2.56-1.06(m, 14H), 0.88(s, 3H), 0.82(s, 3H), 0.72(s, 3H). ¹³C NMR (125MHz, CDCl_3) δ : 193.52, 189.96, 169.99, 159.15, 148.06, 135.99, 134.65, 133.90, 129.20, 128.14, 125.63, 107.90, 58.28, 56.39, 55.38, 55.36, 41.98, 39.56, 39.20, 37.84, 33.56, 29.68, 24.60, 24.09, 21.72, 19.28, 14.40. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_4$ is 540.2838, found 540.2828.

1.1.5.14. Synthesis of (E)-(1-(2-(4-bromophenyl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (6n)

The compound **6n** was prepared by the reaction of 4-bromophenacylazide (17.43 mg, 1 equiv.) and compound **3** (26 mg, 1 equiv.) in ^tBuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 72% (31 mg). IR (NaCl, ν_{\max} , cm^{-1}): 3086, 2929,

2848, 1738, 1683, 1644, 911. ^1H NMR (500MHz, CDCl_3) δ : 9.35(s, 1H), 7.86(d, J = 8.5Hz, 2H), 7.76(s, 1H), 7.70(d, J = 8.5Hz, 2H), 6.67(t, J = 6.5Hz, 1H), 5.81(s, 2H), 5.29(s, 2H), 4.84(s, 1H), 4.37(s, 1H), 3.34(d, J = 3.5Hz, 2H), 2.57-1.06(m, 14H), 0.88(s, 3H), 0.82(s, 3H), 0.72(s, 3H). ^{13}C NMR (125MHz, CDCl_3) δ : 193.53, 189.18, 169.99, 159.17, 148.06, 135.98, 132.60, 130.11, 129.57, 125.60, 107.89, 58.23, 56.39, 55.36, 55.27, 41.98, 39.56, 39.20, 37.84, 33.56, 29.70, 24.60, 24.09, 21.72, 19.28, 14.40. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{38}\text{BrN}_3\text{O}_4$ is 618.1943, found 618.1917.

1.1.5.15. Synthesis of (*E*)-(1-(2-(4-chlorophenyl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6o**)

The compound **6o** was prepared by the reaction of 4-chlorophenacylazide (7.65 mg, 1 equiv.) and compound **3** (14 mg, 1 equiv.) in $t\text{BuOH}$ - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 62% (13 mg). IR (NaCl, ν_{max} , cm^{-1}): 3085, 2930, 2847, 1739, 1705, 1683, 1643, 891. ^1H NMR (500MHz, CDCl_3) δ : 9.35(s, 1H), 7.94(d, J = 9Hz, 2H), 7.77(s, 1H), 7.53(d, J = 8.5Hz, 2H), 6.67(t, J = 6.5Hz, 1H), 5.82(s, 2H), 5.29(s, 2H), 4.84(s, 1H), 4.38(s, 1H), 3.35(d, J = 3.5Hz, 2H), 2.57-1.06(m, 14H), 0.88(s, 3H), 0.82(s, 3H), 0.72(s, 3H). ^{13}C NMR (125MHz, CDCl_3) δ : 193.52, 188.92, 169.99, 159.14, 148.06, 141.34, 135.98, 132.19, 129.60, 129.54, 125.66, 107.89, 99.99, 58.24, 56.40, 55.36, 55.28, 41.98, 39.56, 39.20, 37.84, 33.56, 29.70, 24.59, 24.09, 21.72, 19.29, 14.40. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{38}\text{ClN}_3\text{O}_4$ is 574.2438, found 574.2438.

1.1.5.16. Synthesis of (*E*)-(1-(2-(4-fluorophenyl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6p**)

The compound **6p** was prepared by the reaction of 4-fluorophenacylazide (6.53 mg, 1 equiv.) and compound **3** (13 mg, 1 equiv.) in $t\text{BuOH}$ - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 53% (10 mg). IR (NaCl, ν_{max} , cm^{-1}): 3079, 2927, 2850, 1739, 1683, 1644, 891. ^1H NMR (500MHz, CDCl_3) δ : 9.36(s, 1H), 8.06-8.03(m, 2H), 7.77(s, 1H), 7.23(t, J = 8.5Hz, 2H), 6.67(t, J = 6.5Hz, 1H), 5.82(s, 2H), 5.30(s, 2H), 4.84(s, 1H), 4.38(s, 1H), 3.35(d, J = 4Hz, 2H), 2.56-1.06(m, 14H), 0.88(s, 3H), 0.82(s, 3H), 0.72(s, 3H). ^{13}C NMR (125MHz, CDCl_3) δ : 193.51, 188.46, 169.91, 159.13, 152.06, 148.06, 144.75, 135.98, 130.92, 116.62, 116.45, 107.90, 58.26, 56.40, 55.36, 55.23, 41.98, 39.75, 39.20, 37.84, 33.56,

29.69, 24.59, 24.09, 21.72, 19.29, 14.40. HRMS (ESI) m/z : $[M+Na]^+$ calcd for $C_{31}H_{38}FN_3O_4$ is 558.2744, found 558.2737.

1.1.5.17. Synthesis of (*E*)-(1-(2-(4-cyanophenyl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl 3-formyl-5-(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)pent-3-enoate (**6q**)

The compound **6q** was prepared by the reaction of 4-cyanophenacylazide (17.74 mg, 1 equiv.) and compound **3** (34 mg, 1 equiv.) in t BuOH - water (1:2) mixture (3 ml) as per the method described in the section 1.1.5. Yield: 35% (18 mg). IR (NaCl, ν_{max} , cm^{-1}): 3095, 2928, 2848, 2232, 1738, 1683, 1643, 892. 1H NMR (500MHz, $CDCl_3$) δ : 9.34(s, 1H), 8.10(d, J = 8.5Hz, 2H), 7.86(d, J = 8.5Hz, 2H), 7.78(s, 1H), 6.68(t, J = 6.5Hz, 1H), 5.86(s, 2H), 5.30(s, 2H), 4.84(s, 1H), 4.38(s, 1H), 3.34(d, J = 2.5Hz, 2H), 2.57-1.04(m, 14H), 0.89(s, 3H), 0.82(s, 3H), 0.73(s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ : 193.60, 189.12, 170.03, 159.26, 148.08, 136.74, 135.97, 133.02, 128.64, 125.56, 117.94, 117.42, 107.90, 58.20, 56.40, 55.52, 55.36, 41.98, 39.58, 39.22, 37.84, 33.58, 29.74, 24.61, 24.09, 21.73, 19.30, 14.42. HRMS (ESI) m/z : $[M-H]^+$ calcd for $C_{32}H_{38}N_4O_4$ is 541.2809, found 541.2828.

1.2. Biology

1.2.1. In vitro cytotoxic evaluation of compounds by MTT assay.

In vitro toxicity of the synthesized compounds was assessed by standard MTT bioassay³ in Hep G2 Cell line (American Type Cell Culture, ATCC, Manassas, VA, USA) at 24 h of drug administration. In brief, the cells were seeded in 96-well plates (10^4 cells/well in 200 μ L of medium) and incubated for 24 h for attachment. Test compounds were prepared prior to the experiment by dissolving in 0.1% DMSO and diluted with the medium. The cells were then exposed to different concentrations of the compounds (0.5-100 μ M) in the volume of 200 μ L/well. Cells in the control wells received the same volume of medium containing 0.1% DMSO. After 24 h, the medium was removed, and cell cultures were incubated with 100 μ L MTT reagent (5mg/mL) for 4 h at 37 $^{\circ}C$. The formazan crystals formed by the viable cells was solubilized by addition of 200 μ L DMSO. The suspension was placed on the shaker for 5 min, and absorbance was recorded at 540 nm by the plate reader (Biotek, USA). The experiment was

performed in triplicate. The percentage of cytotoxicity and percentage cell viability was calculated using the following formula.

$$\text{Cell viability (\%)} = [\text{Abs sample} / \text{Abs Control}] \times 100$$

Where Abs (absorbance) is calculated as, Abs_{sample} = OD of sample-blank, Abs_{control} = OD of control-blank.

1.2.2. Pancreatic lipase inhibitory activity assay

Method A

The pancreatic lipase assay was performed as described Bustanji *et al.* with some modifications.⁴ Briefly, a volume of 50 µL porcine pancreatic lipase (Sigma, St. Louis, MO) (1 mg/mL in 2.5 mM tris-hydrochloride buffer pH 7.4 with 0.125 mM sodium chloride) was pre-mixed with 100 µL of different concentration of compounds (Stock solutions of the isolates, synthetic derivatives and orlistat were prepared in DMSO with concentrations ranging from 0.25 µM-20 µM and 0.2 to 1.4 µM, respectively) and incubated at 37 °C for 15 min. Following pre-incubation, 100 µL p-nitrophenyl butyrate (PNPB) (25 mM) was added to the enzyme-sample mixture, and the volume was made up to 300 µL using tris hydrochloride buffer. The amount of DMSO in the final concentration did not exceed 1%. The reaction mixture was incubated at 37 °C for 60 min, and the amount of p-nitro-phenol produced was measured at 405 nm using a plate reader (Biotek, USA). The percentage inhibition of pancreatic lipase was calculated as follows

$$\% \text{ inhibition} = \frac{\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}}}{\text{OD}_{\text{control}}} \times 100$$

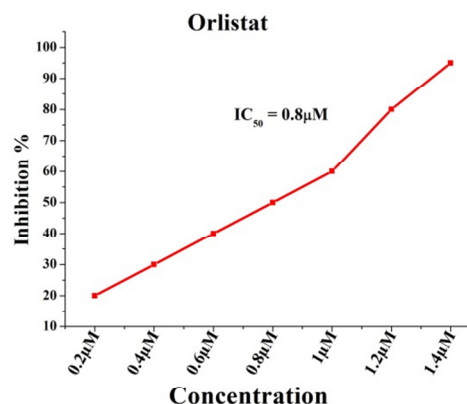
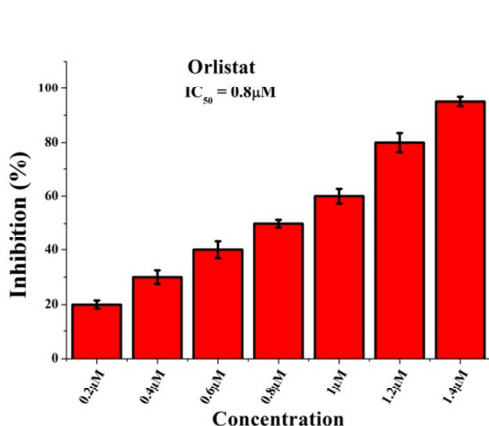
Absorbance (Abs) of control (DMSO) or sample was calculated by subtracting ODs for each sample from their corresponding blank. A Bar diagram was plotted with % inhibition against test compounds (concentrations 1, 5, 10, 20 µM) where n=4.

The IC₅₀, the concentration of the compounds /positive control that causes 50% inhibition of the enzyme were calculated from the results of isolated and synthetic derivatives of concentrations 0.25 µM -20 µM) for both method A and B from the dose-response curves using a logistic model in Origin software (Origin Lab Corp.).

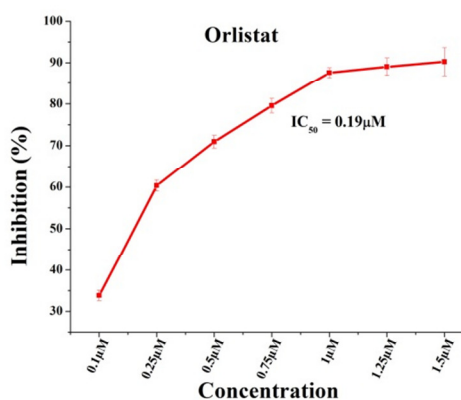
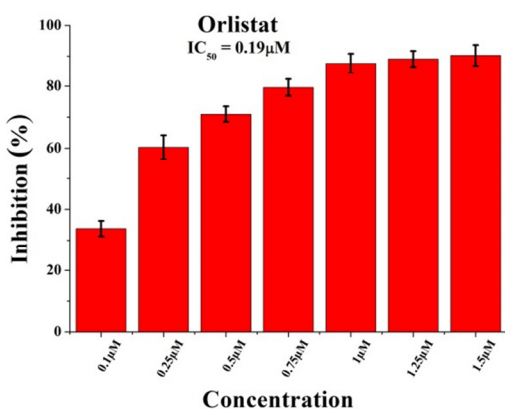
Method B

The pancreatic lipase activity was assayed as narrated by Kido *et al* (2003) with slight modifications.⁵ The activity was measured based on the amount of free fatty acids released from the emulsified olive oil substrate. Emulsion mixture consisting of bile salts, cholesterol and phospholipid were taken to imitate *in vivo* conditions. The bile salts concentration was adjusted to approximate that of duodenal aspirates.⁶ The substrate emulsion (0.6 mL) was formulated by ultrasonification of olive oil (48 g/L) in a solution containing 1 mmol/L taurochenodeoxycholate, 9 mmol/L taurocholate, 0.1 mmol/L cholesterol, 0.8 g/L L- α -phosphatidylcholine, 1 mmol/L calcium acetate and 100 mmol/L Tris-HCl (pH 8.0). After addition of the test compounds in 75 μ L of 100 mmol/L Tris- HCl (pH 8.0), or vehicle alone, the assay mixture was pre-incubated for 5 min at 37 °C. The reaction was initiated by the addition of 75 μ L lipase solution containing 0.1 g/L of 100 mmol/L Tris-HCl (pH 8.0). After incubation for 30 min at 37 °C, free fatty acids concentration in the reaction was calculated as described by Duncombe (1963).⁷ Human pancreatic lipase was used in all experiments. The inhibitory activity of test materials was calculated from the relative fatty acid concentration liberated compared with the control value. The concentration ranges of isolates and synthetic derivatives tested in the method B were in the range 0.25-20 μ M. A Bar diagram was plotted with % inhibition against Test compound (concentrations 0.5, 1, 5, 10, 15 μ M) since the results of method A showed IC₅₀ values starting from 0.77 μ M concentration.

The IC₅₀ values were calculated from the dose-response curves (Test compounds concentration ranging from .25 μ M to 20 μ M using a logistic model in Origin software (Origin Lab Corp.).



Method A: The percentage inhibition of Orlistat against pancreatic lipase in various concentrations.



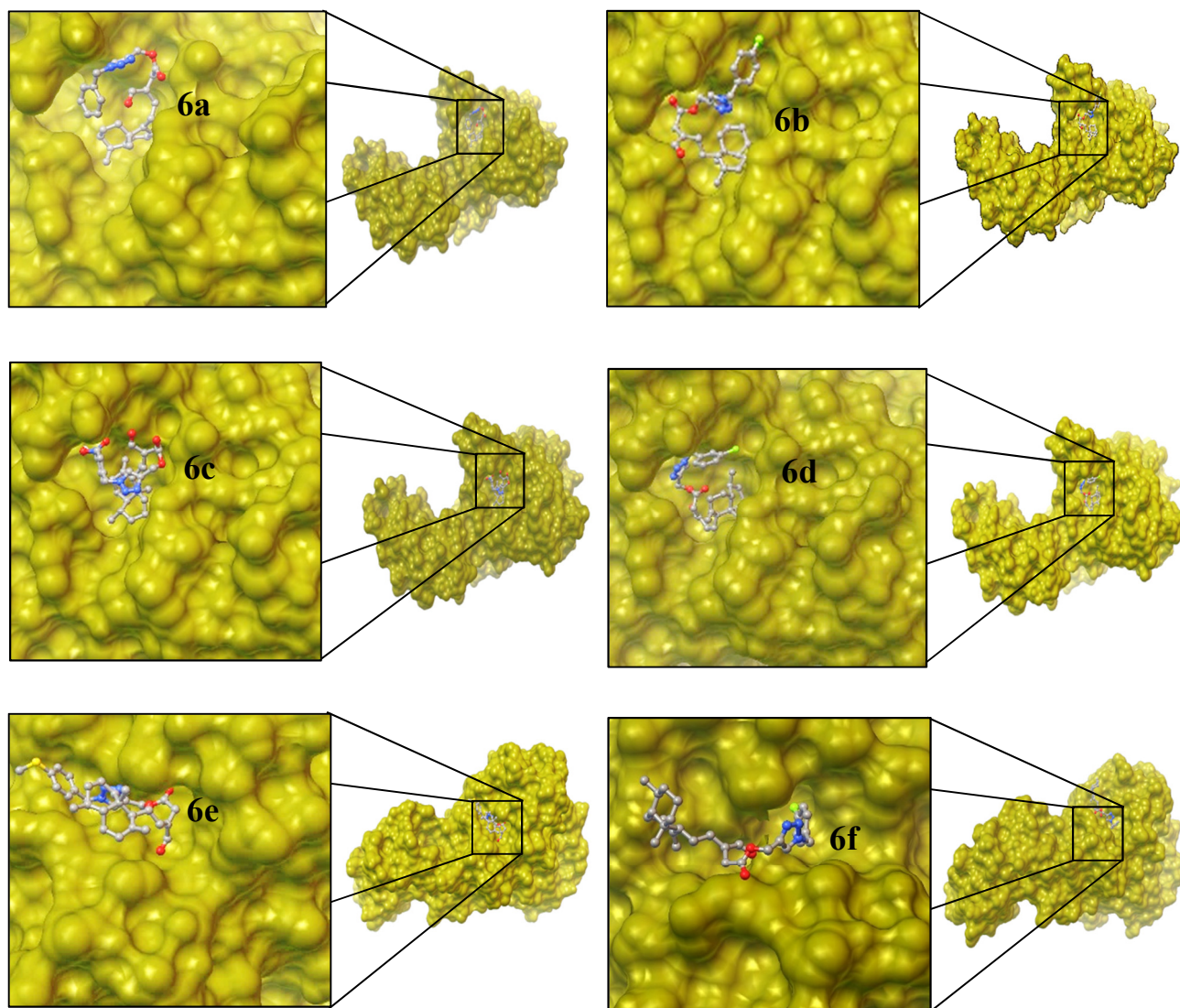
Method B: The percentage inhibition of Orlistat against human pancreatic lipase in various concentrations

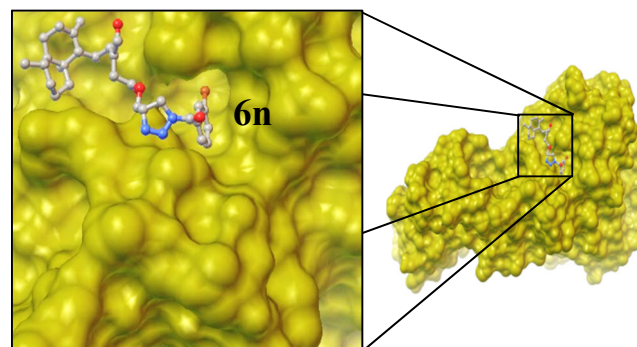
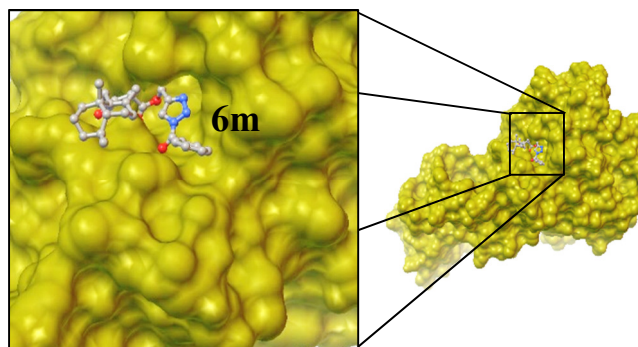
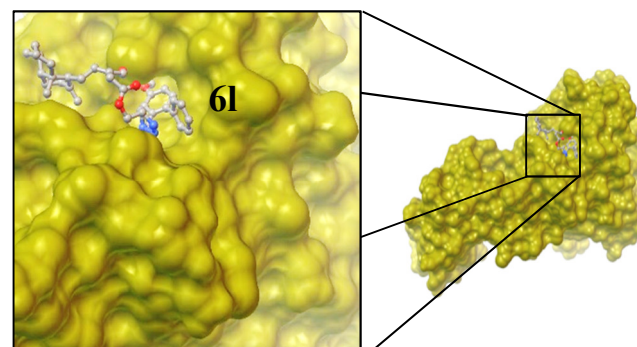
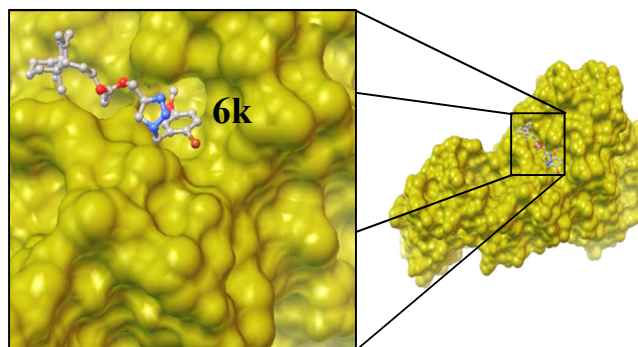
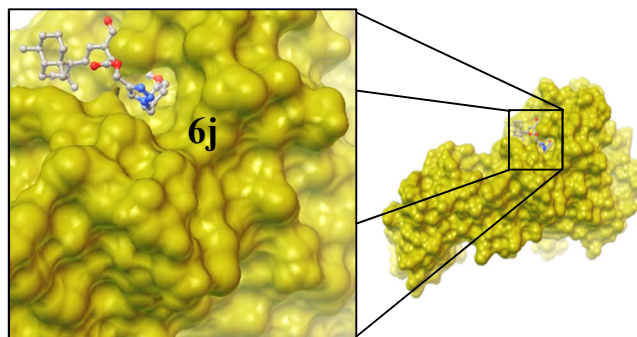
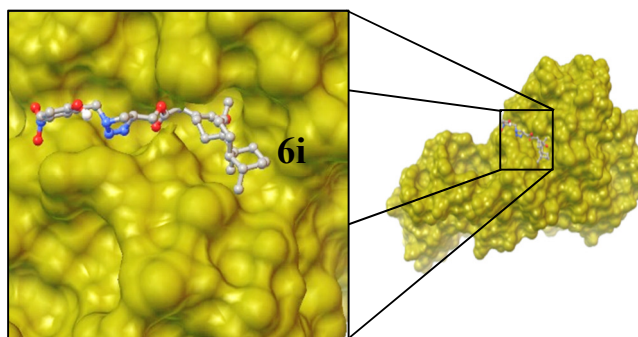
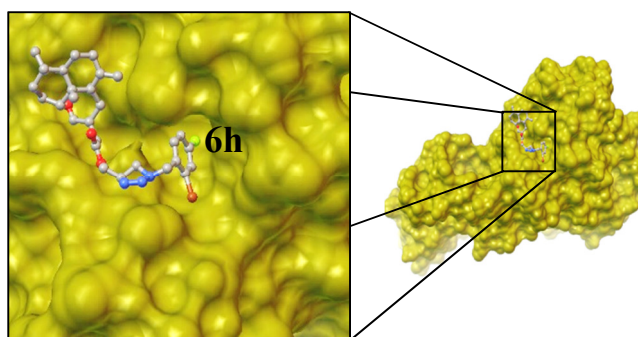
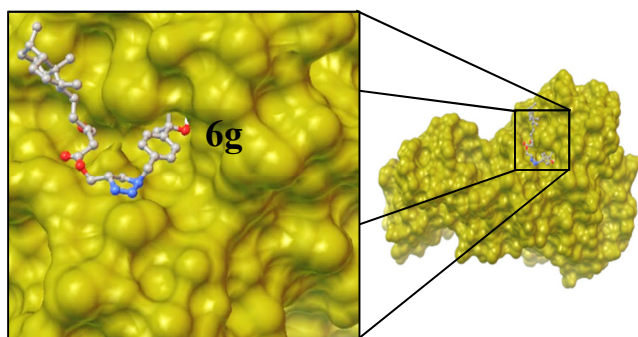
2. Molecular docking studies of various triazole derivatives

The molecular docking studies of various triazole derivatives were carried out using Autodock 3.0 version (Morris et al., 1998).⁸ In brief, the X-ray Human pancreatic lipase

structure coordinates were obtained from protein databank (PDB ID: 1LPA_B; Van Tilbeurgh et al., 1993),⁹ and the 2D structures of compounds were created using JME editor (Bienfait and Ertl, 2013).¹⁰ The protonation state and energy minimizations of these compounds were done with PRODRG tool (Schuttelkopf and Alten., 2004).¹¹ The predefined grid space on lipase structure was created using autogrid program. The docking was carried out using Lamarckian genetic algorithm. The total 50 GA runs were performed, and the Gibbs's free energy of binding was evaluated best ranked conformation of compound/s. the possible binding site of compound/s was visualized using MGL software (Michel, 1999).

Figure S: Molecular docking studies of various triazole derivatives and intermediate compounds.





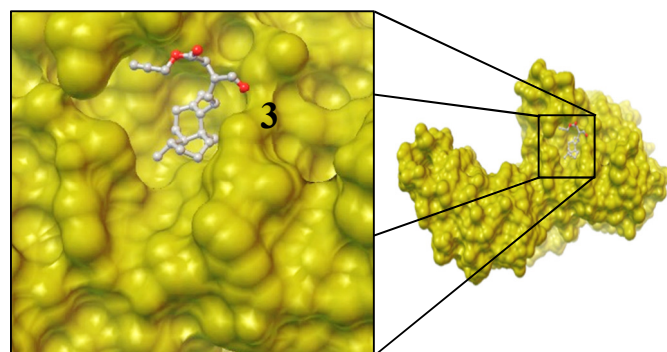
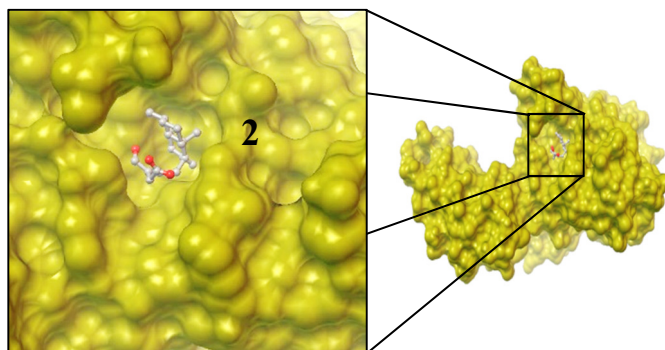
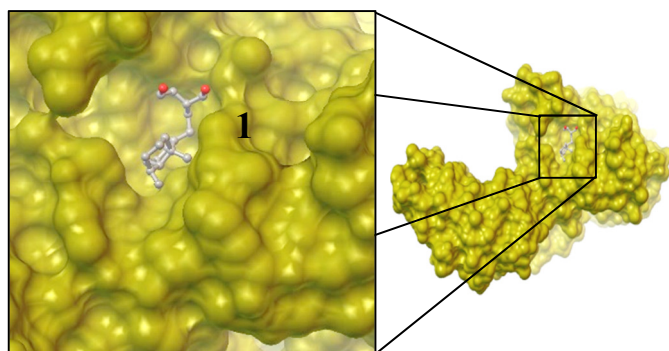
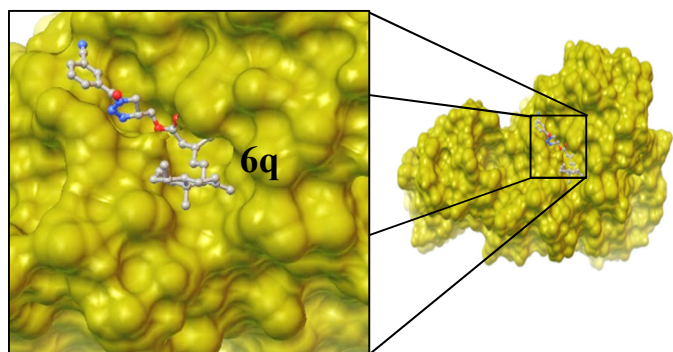
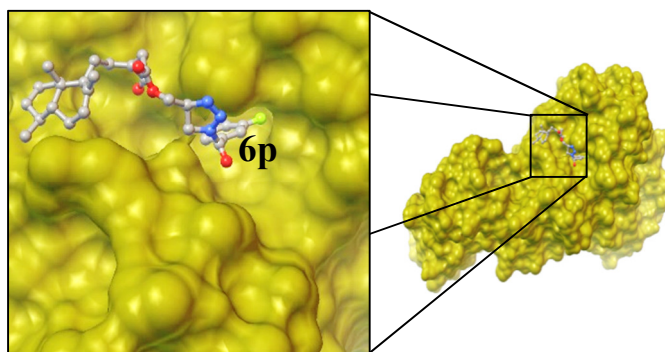
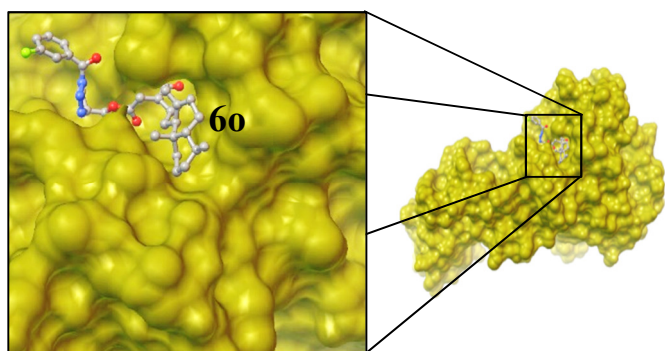


Table S: List of compounds used in docking study and the estimated free energy of binding.

Compound code	Predicted free energy of binding (kcal/mol)
6a	-8.24
6b	-8.50
6c	-6.08
6d	-6.80
6e	-7.00
6f	-4.90
6g	-5.43
6h	-4.90
6i	-6.16
6j	-8.09
6k	-3.75
6l	-2.17
6m	-3.77
6n	-3.29
6o	-5.04
6p	-7.25
6q	-6.14
1	-4.13
2	-1.19
3	-7.07

3. Spectra of intermediates and triazole derivatives.

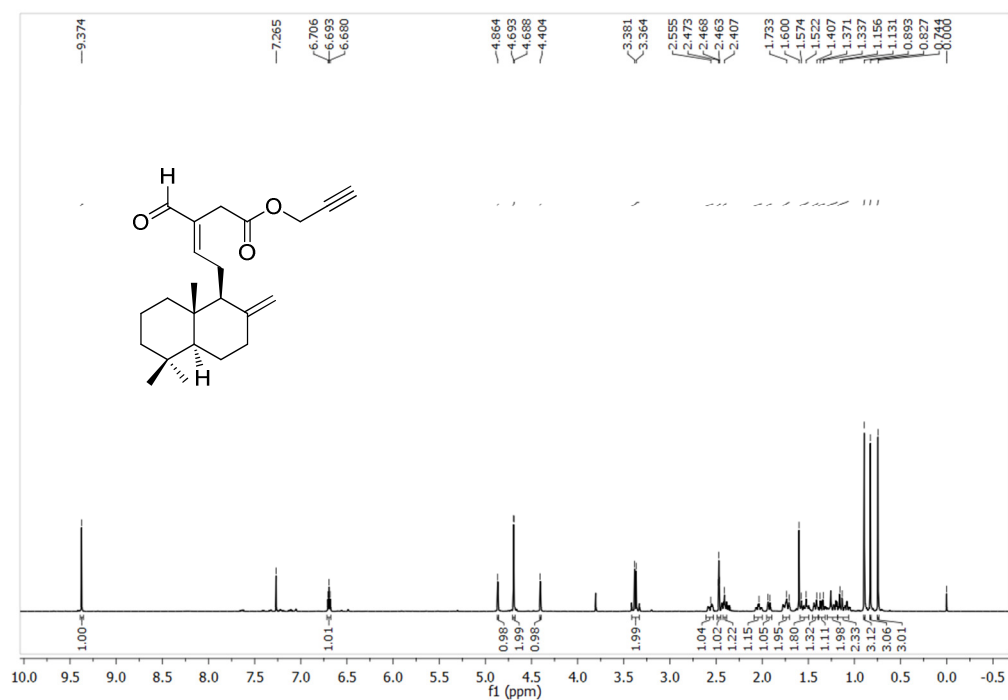


Figure S₁. ¹H NMR Spectrum of Compound **3**

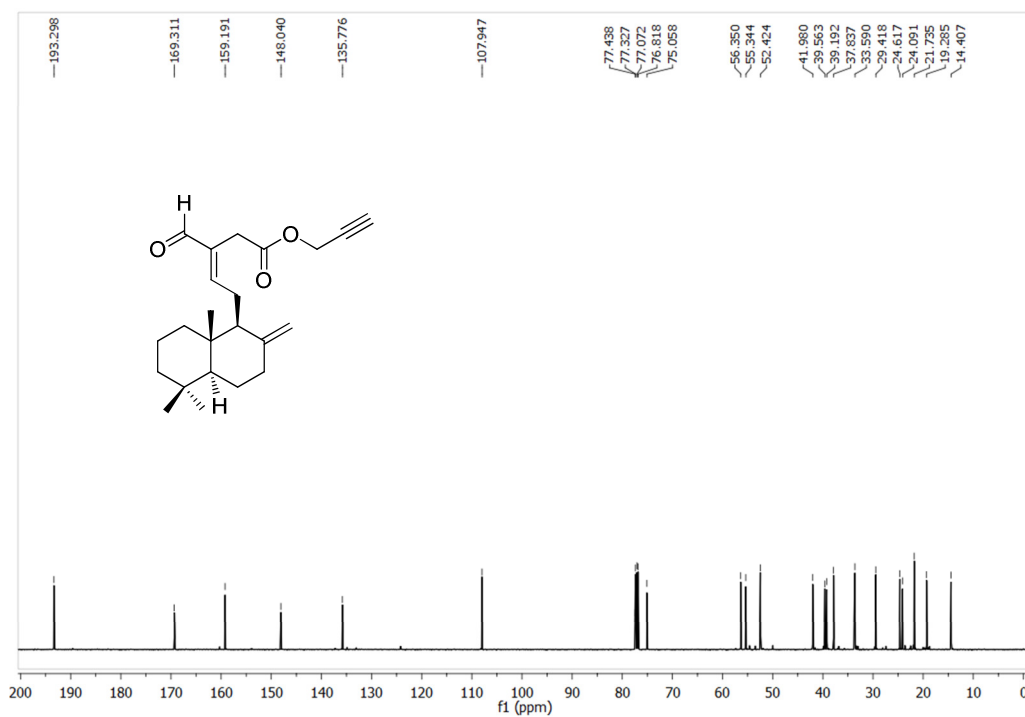


Figure S₂. ¹³C NMR Spectrum of Compound **3**

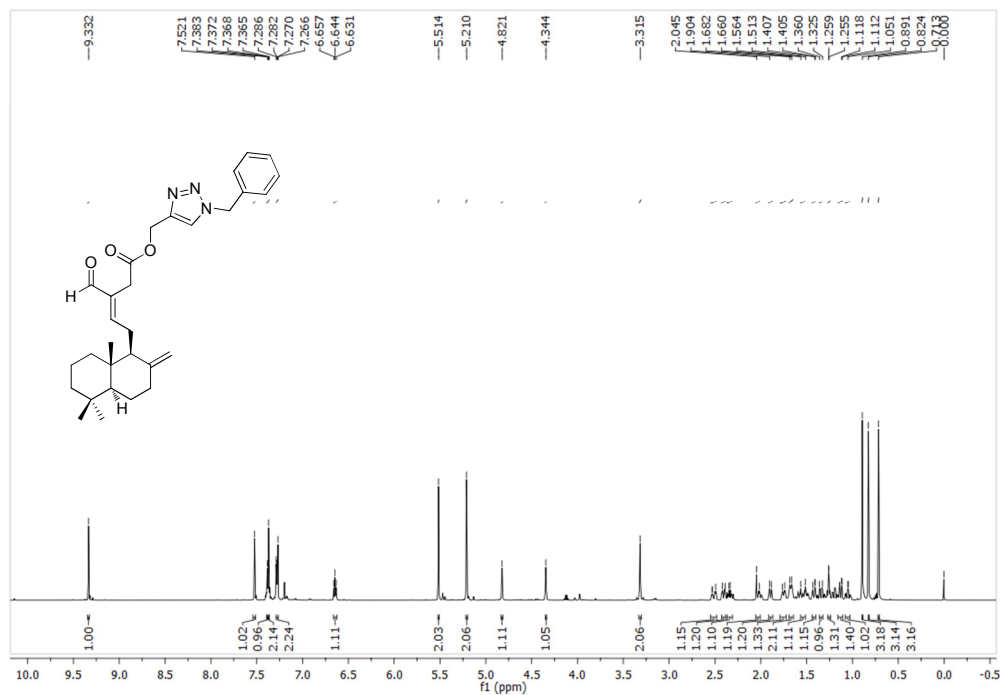


Figure S3. ^1H NMR Spectrum of Compound **6a**

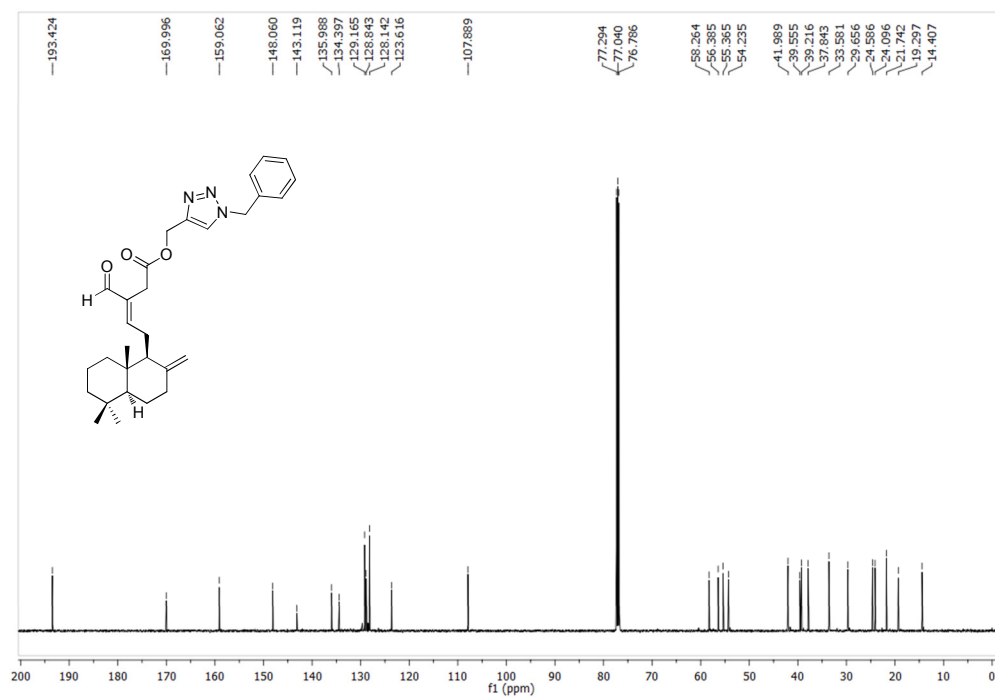


Figure S4. ^{13}C NMR Spectrum of Compound **6a**

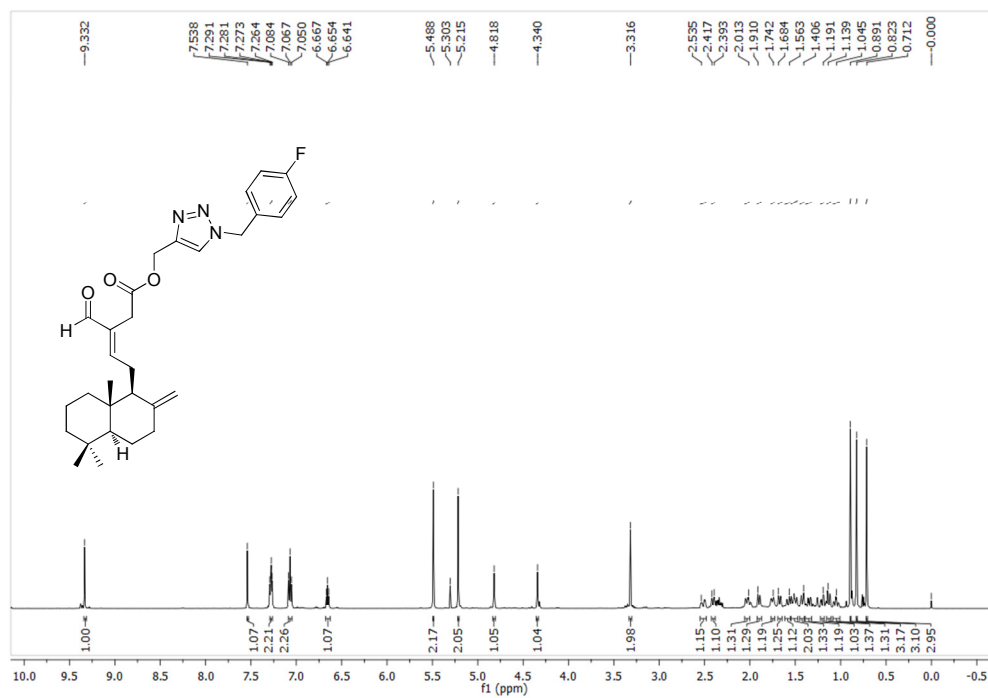


Figure S₅. ¹H NMR Spectrum of Compound **6b**

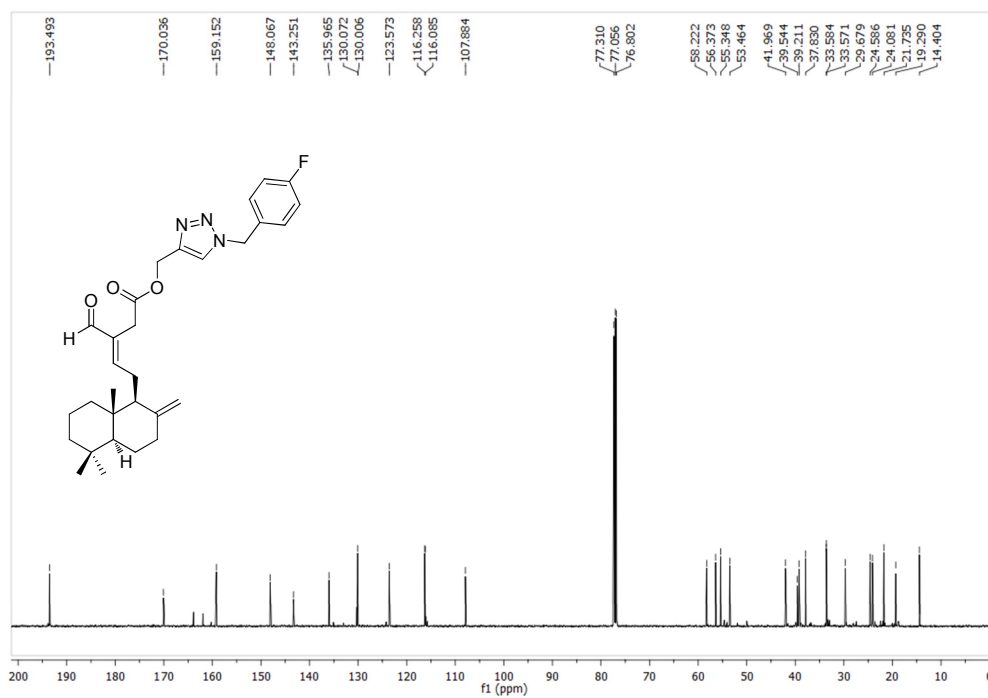


Figure S₆. ¹³C NMR Spectrum of Compound **6b**

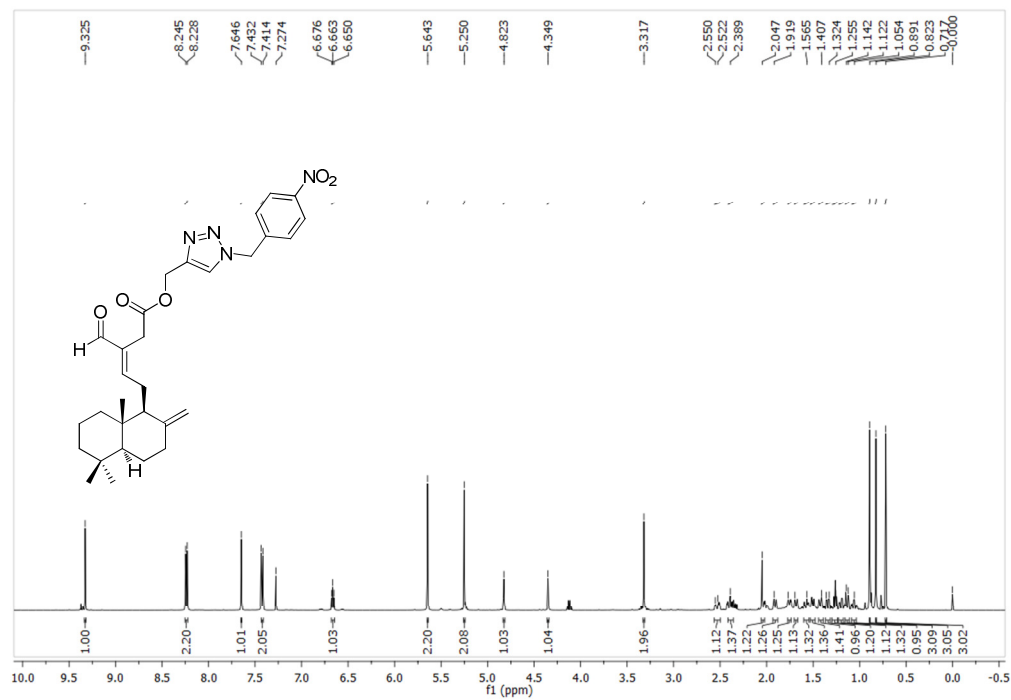


Figure S7. ¹H NMR Spectrum of Compound **6c**

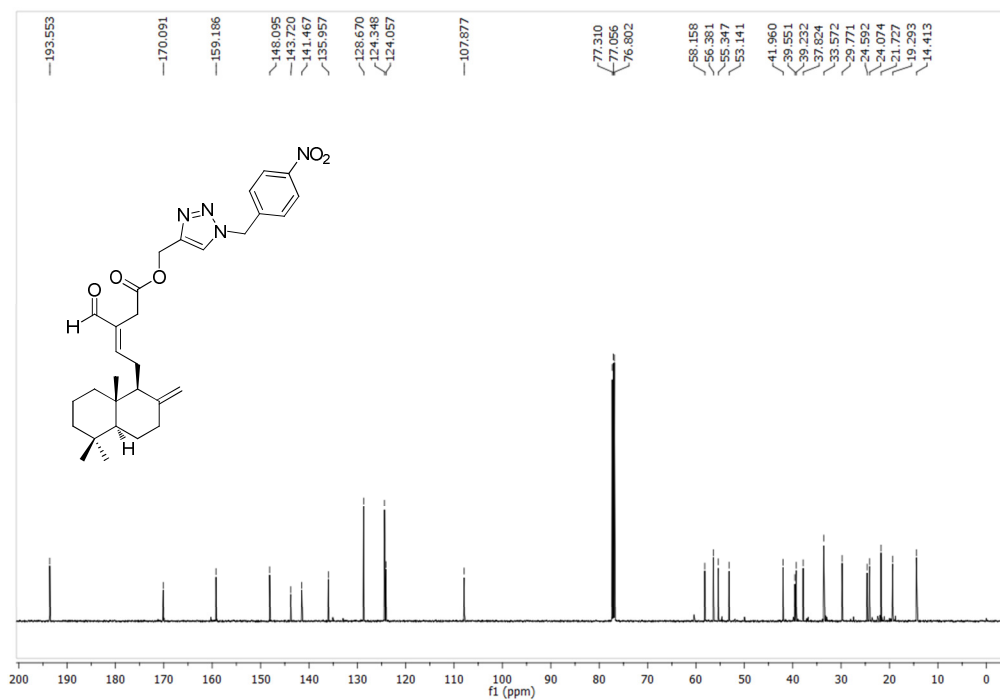


Figure S8. ¹³C NMR Spectrum of Compound **6c**

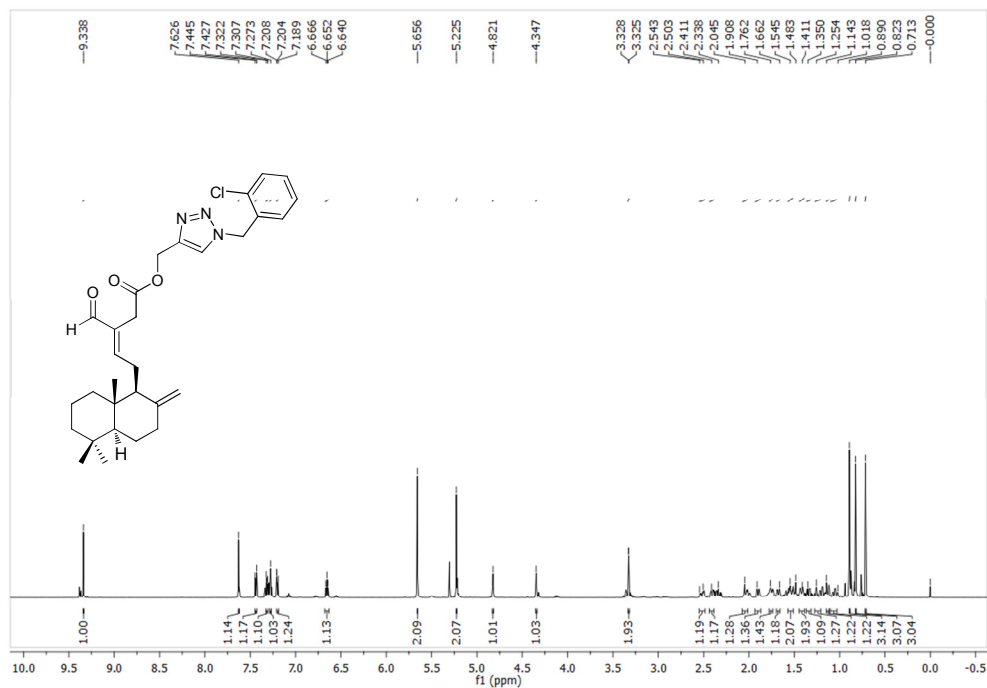


Figure S9. ¹H NMR Spectrum of Compound **6d**

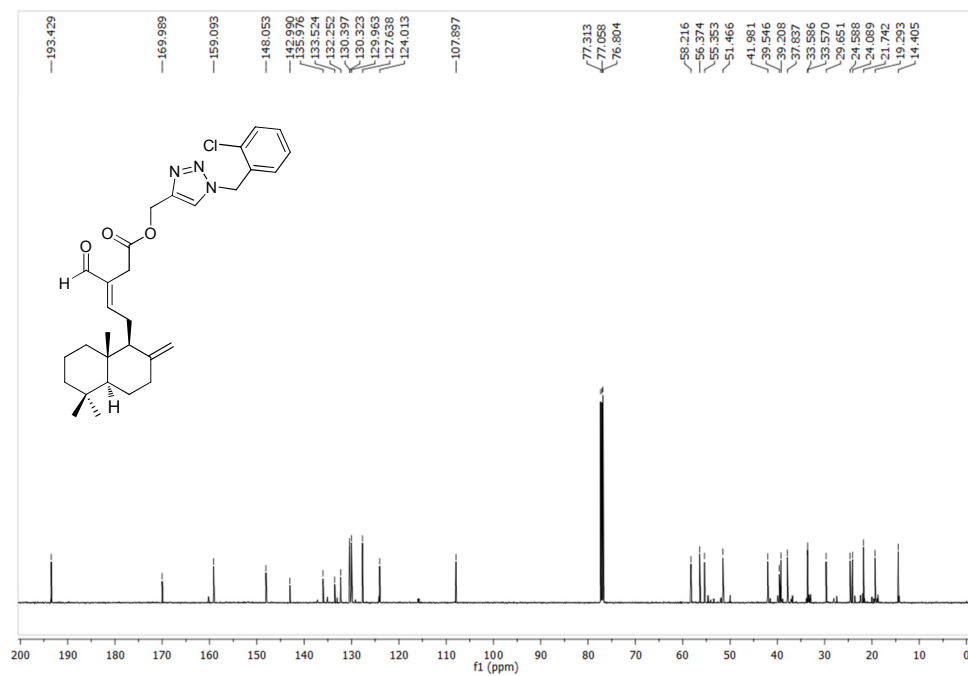


Figure S10. ¹³C NMR Spectrum of Compound **6d**

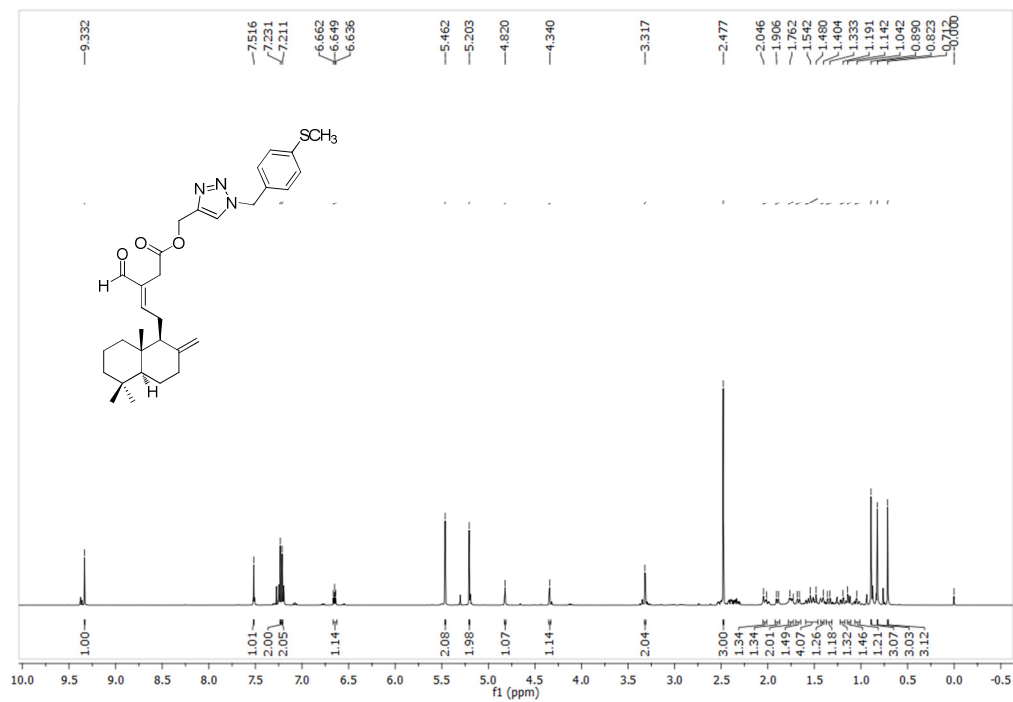


Figure S₁₁. ¹H NMR Spectrum of Compound **6e**

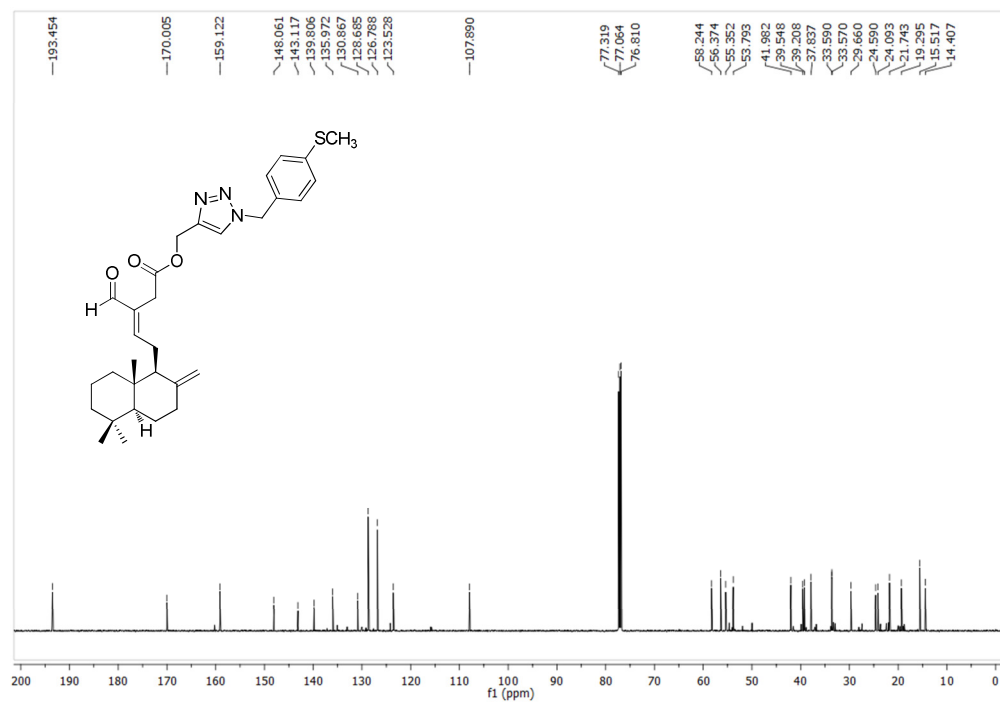


Figure S₁₂. ¹³C NMR Spectrum of Compound **6e**

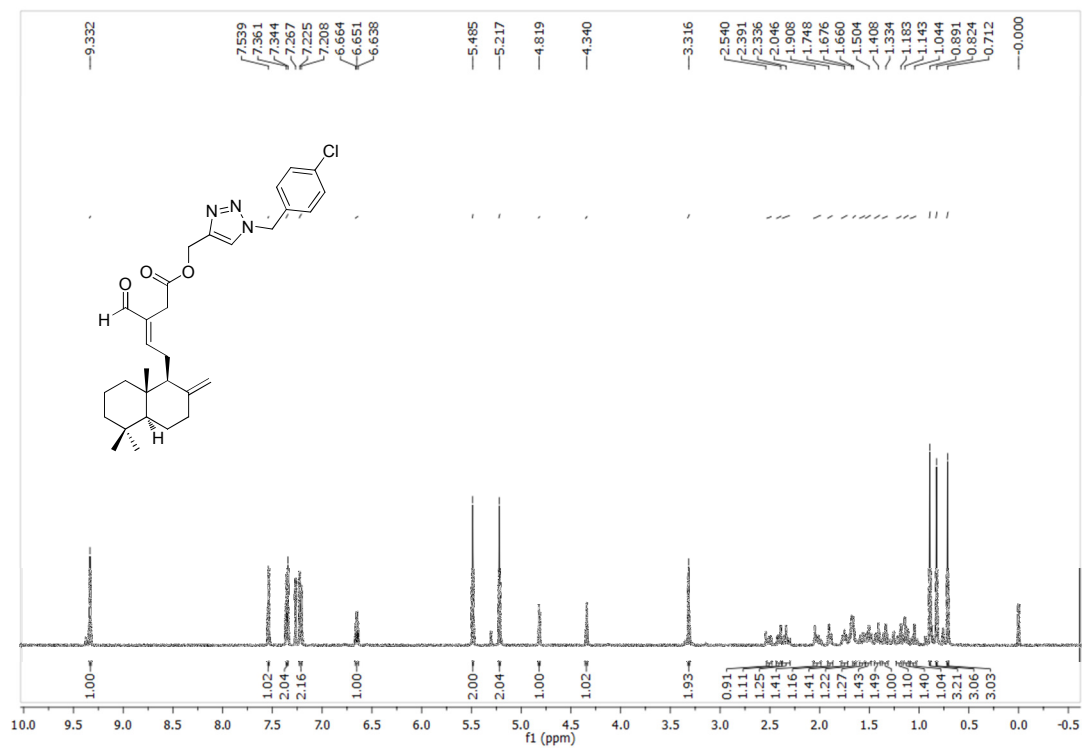


Figure S13. ¹H NMR Spectrum of Compound **6f**

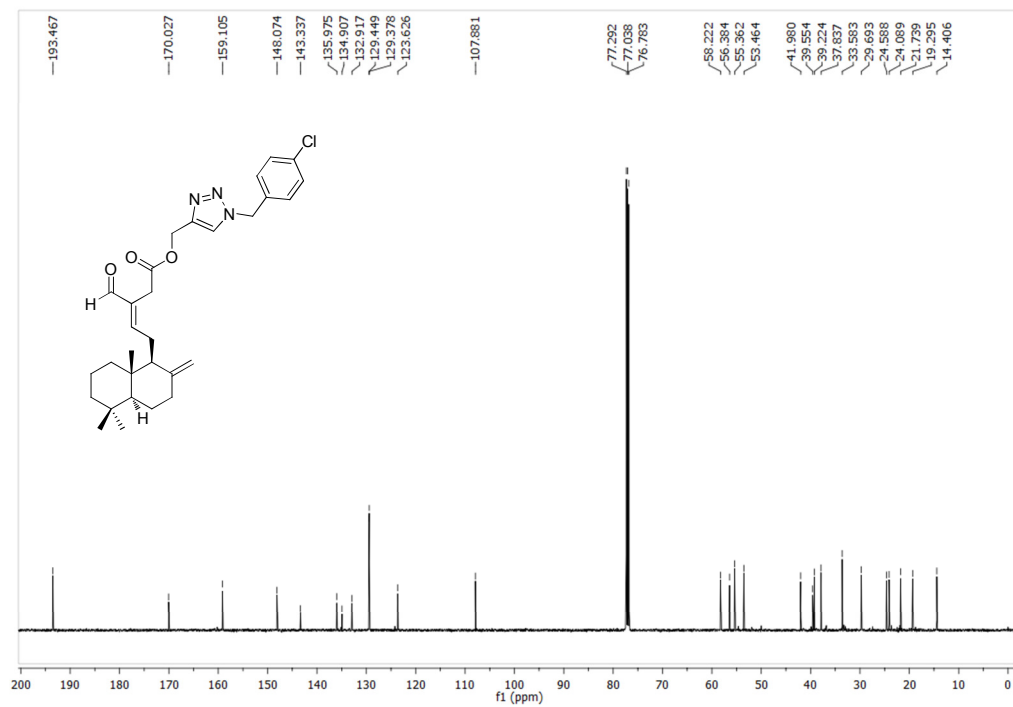


Figure S14. ¹³C NMR Spectrum of Compound **6f**

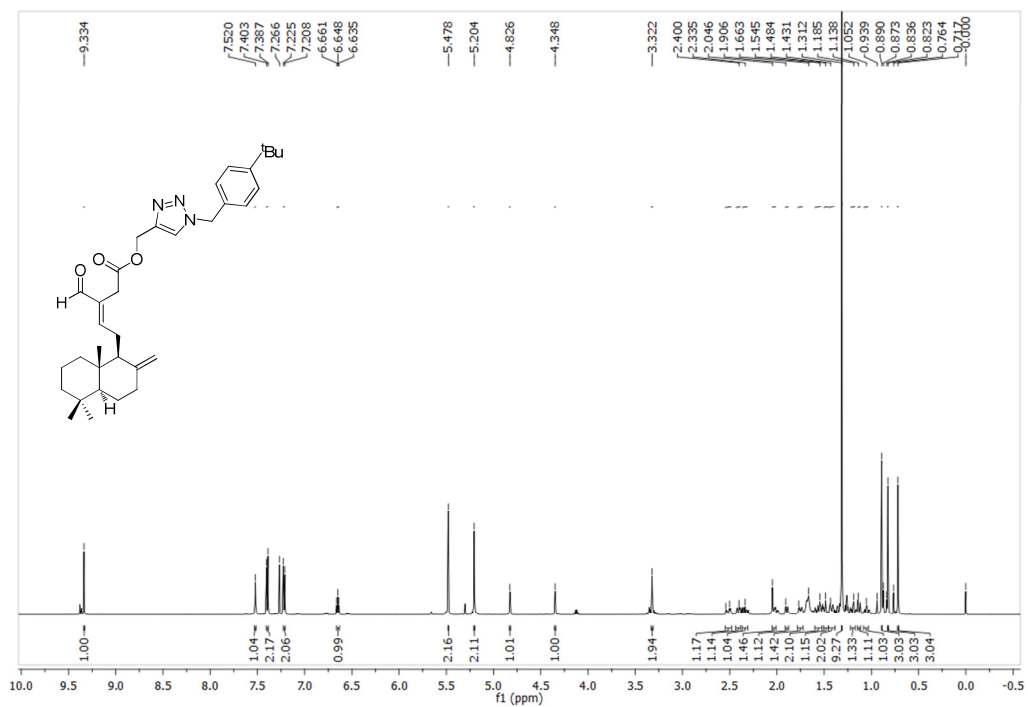


Figure S₁₅. ¹H NMR Spectrum of Compound 6g

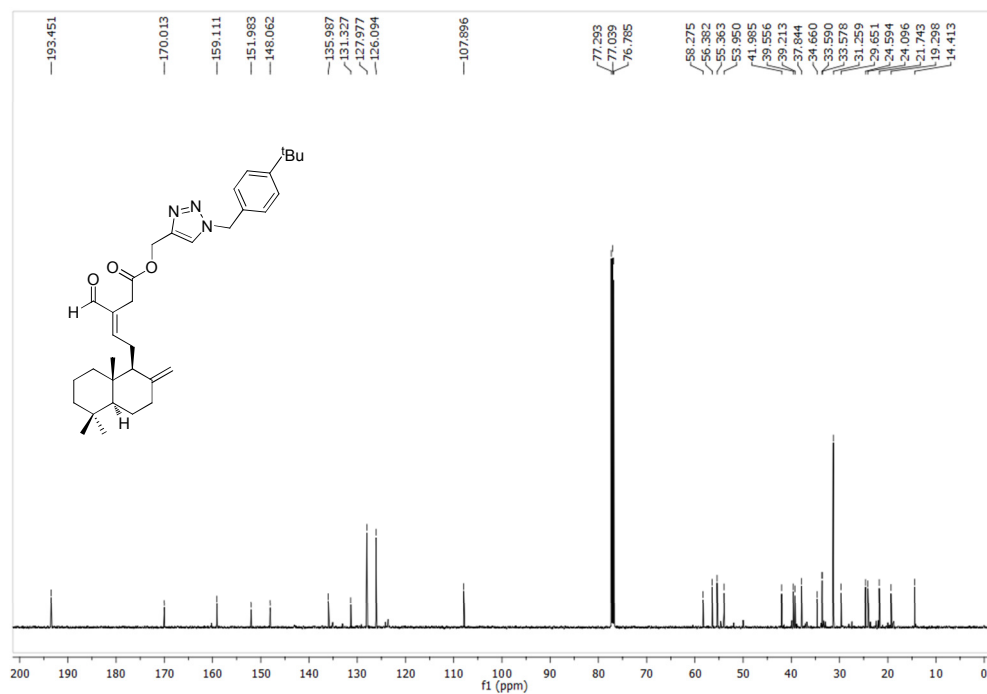


Figure S₁₆. ¹³C NMR Spectrum of Compound 6g

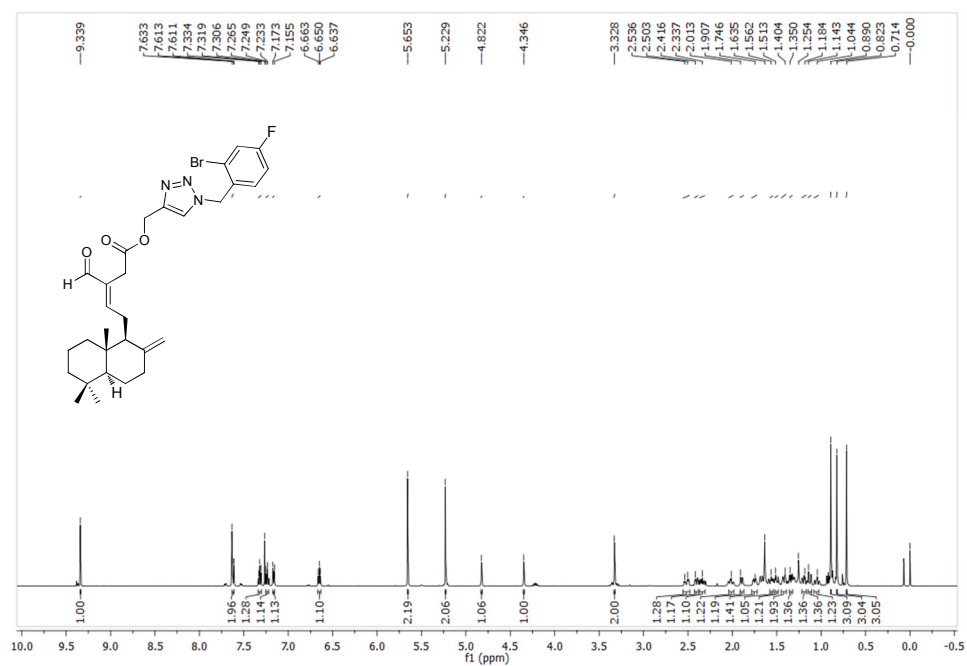


Figure S₁₇. ¹H NMR Spectrum of Compound **6h**

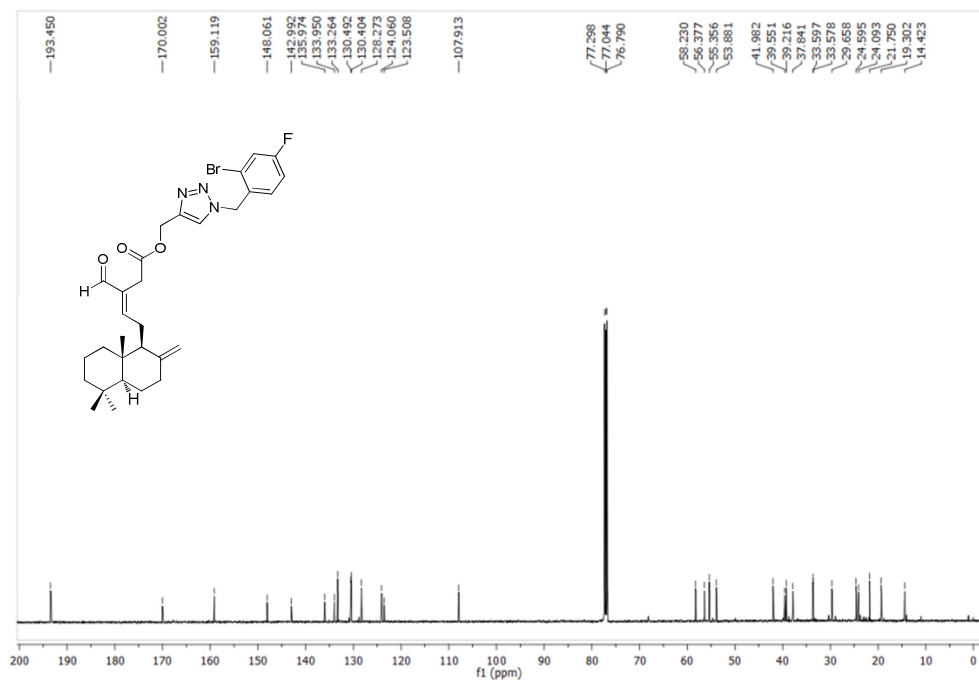


Figure S₁₈. ¹³C NMR Spectrum of Compound **6h**

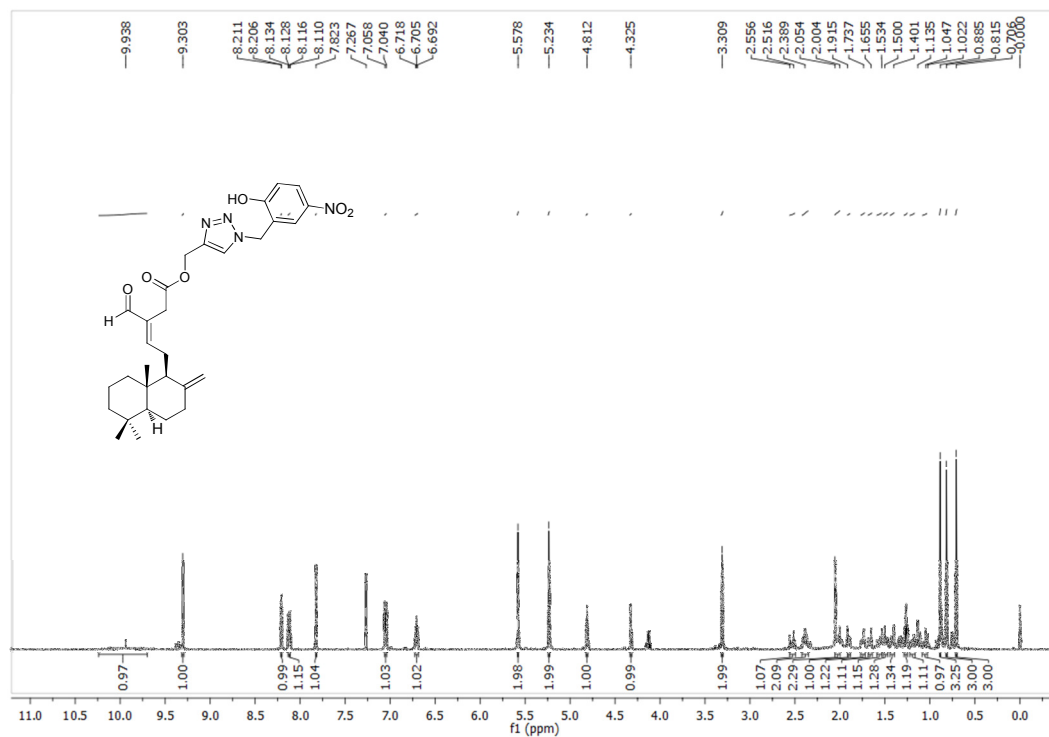


Figure S₁₉. ¹H NMR Spectrum of Compound 6i

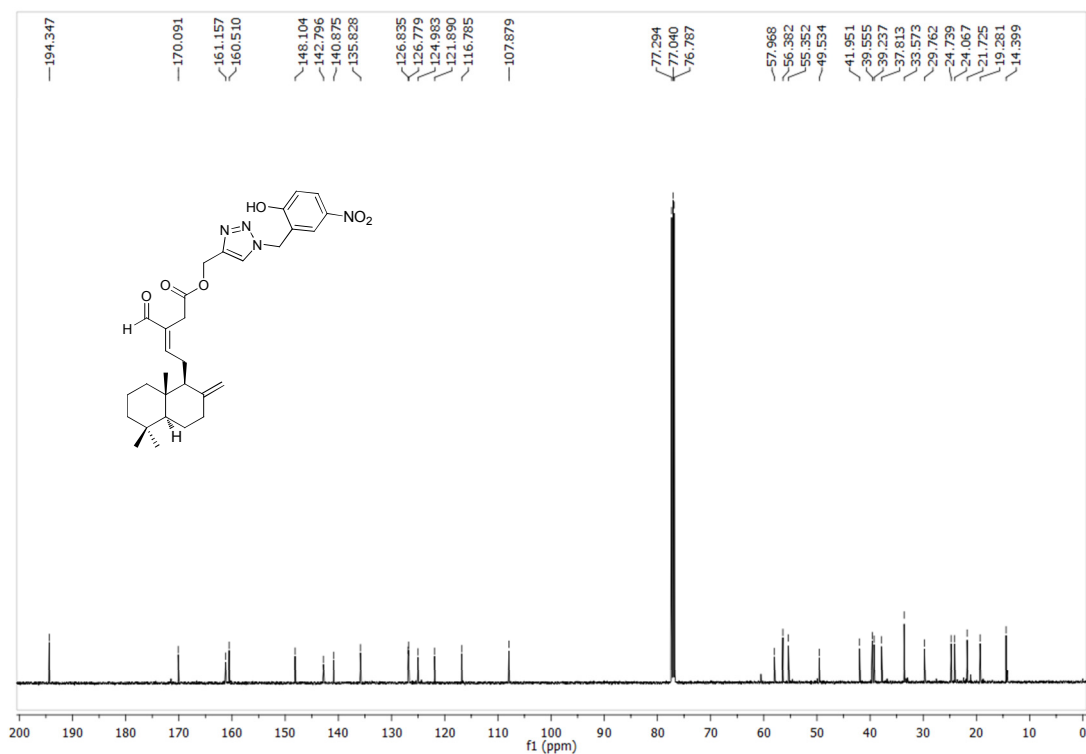


Figure S₂₀. ¹³C NMR Spectrum of Compound 6i

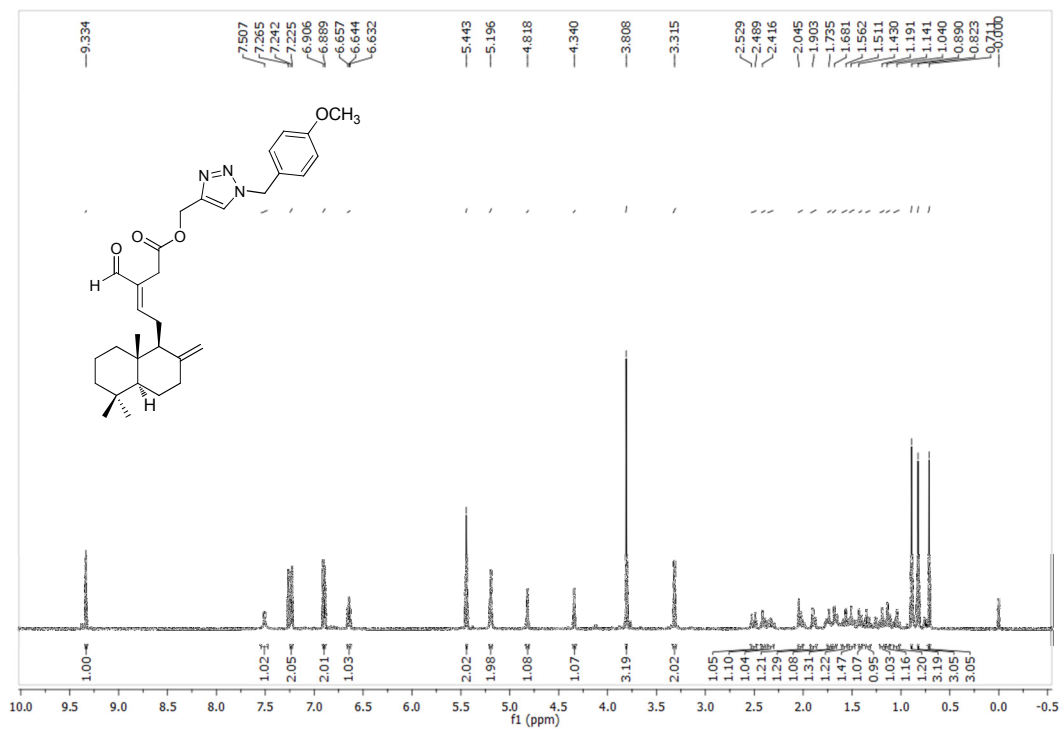


Figure S21. ^1H NMR Spectrum of Compound 6j

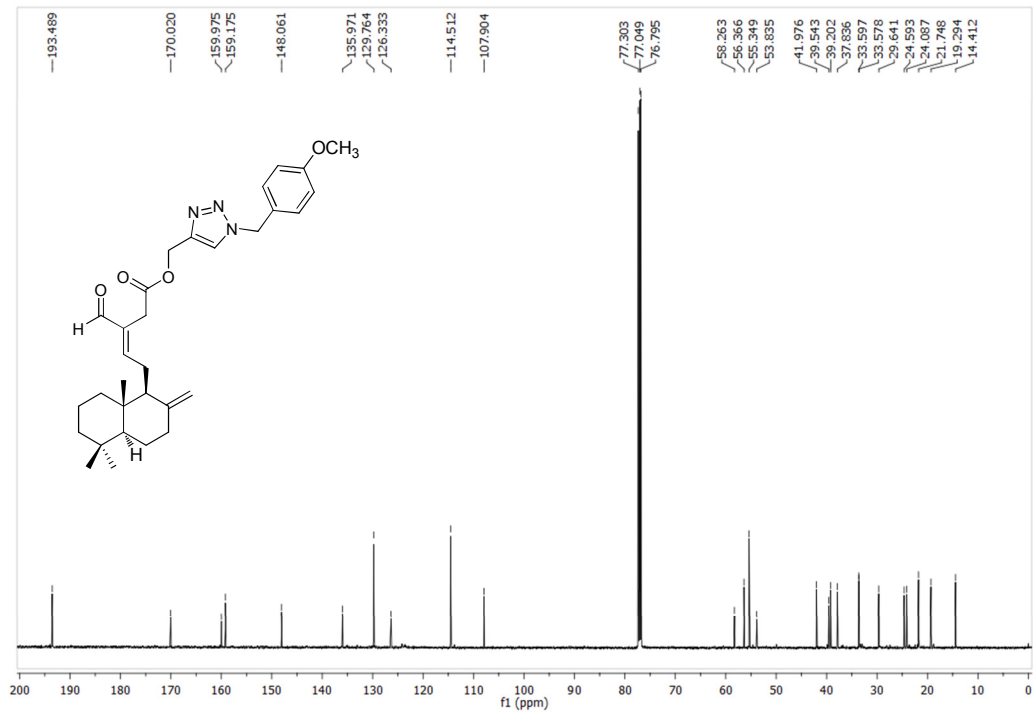


Figure S22. ^{13}C NMR Spectrum of Compound 6j

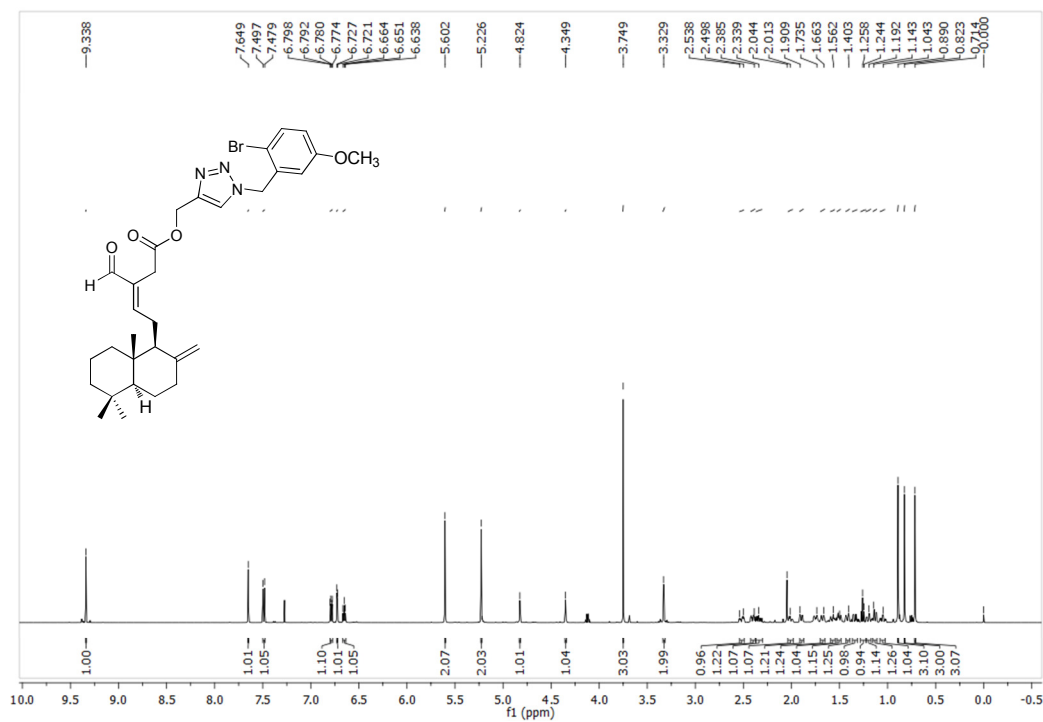


Figure S₂₃. ¹H NMR Spectrum of Compound **6k**

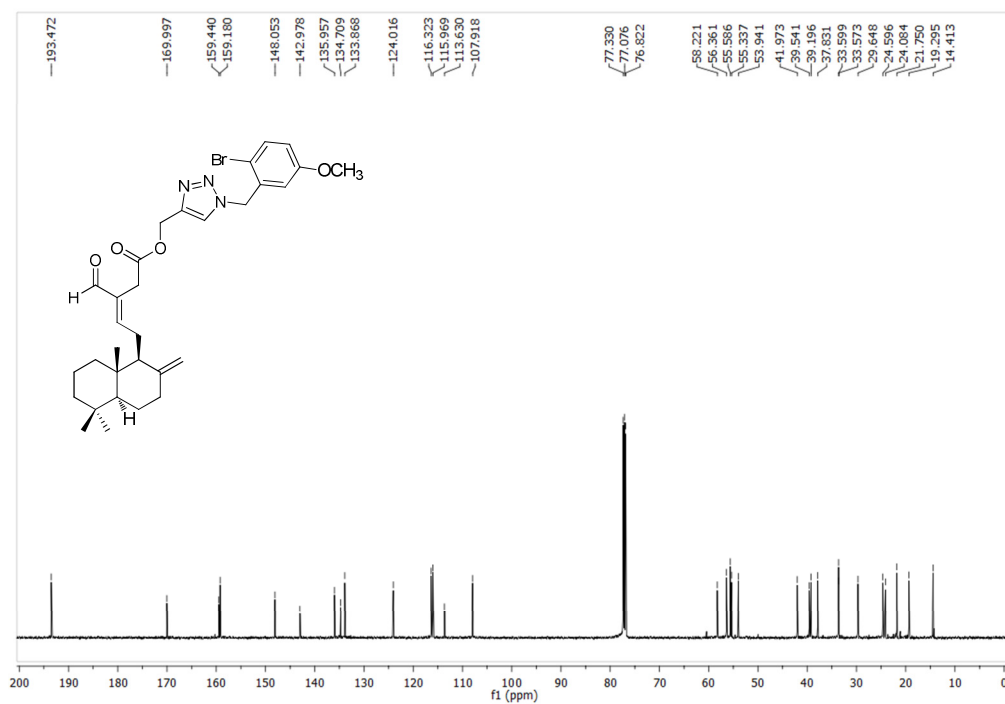


Figure S₂₄. ¹³C NMR Spectrum of Compound **6k**

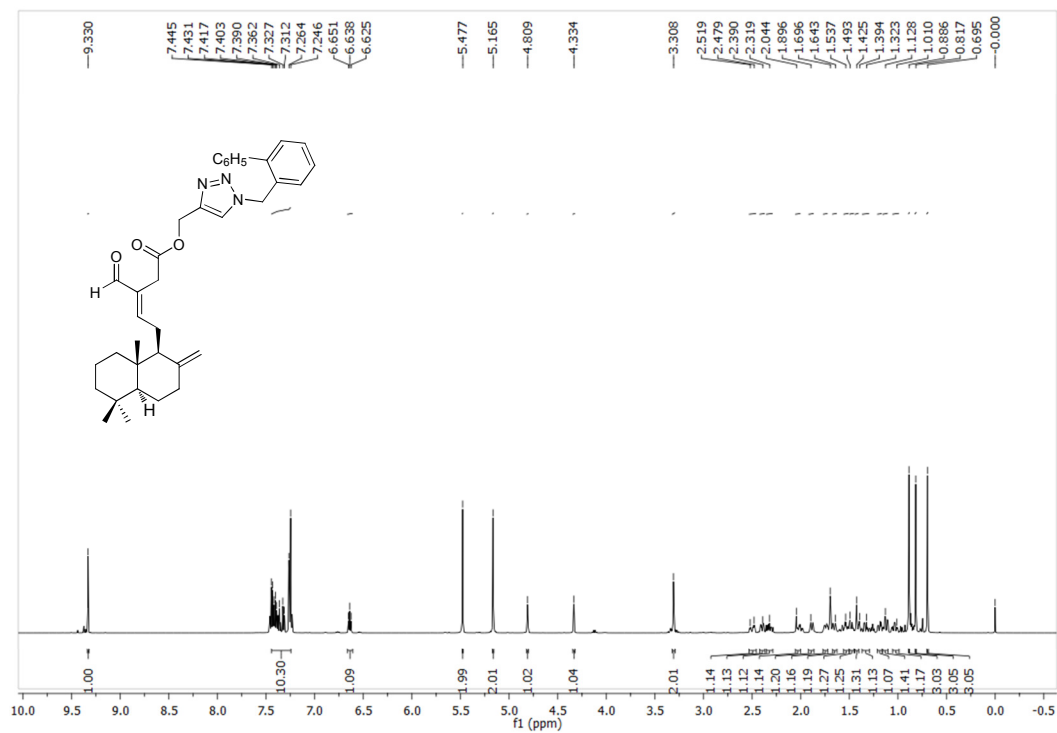


Figure S₂₅. ¹H NMR Spectrum of Compound 6l

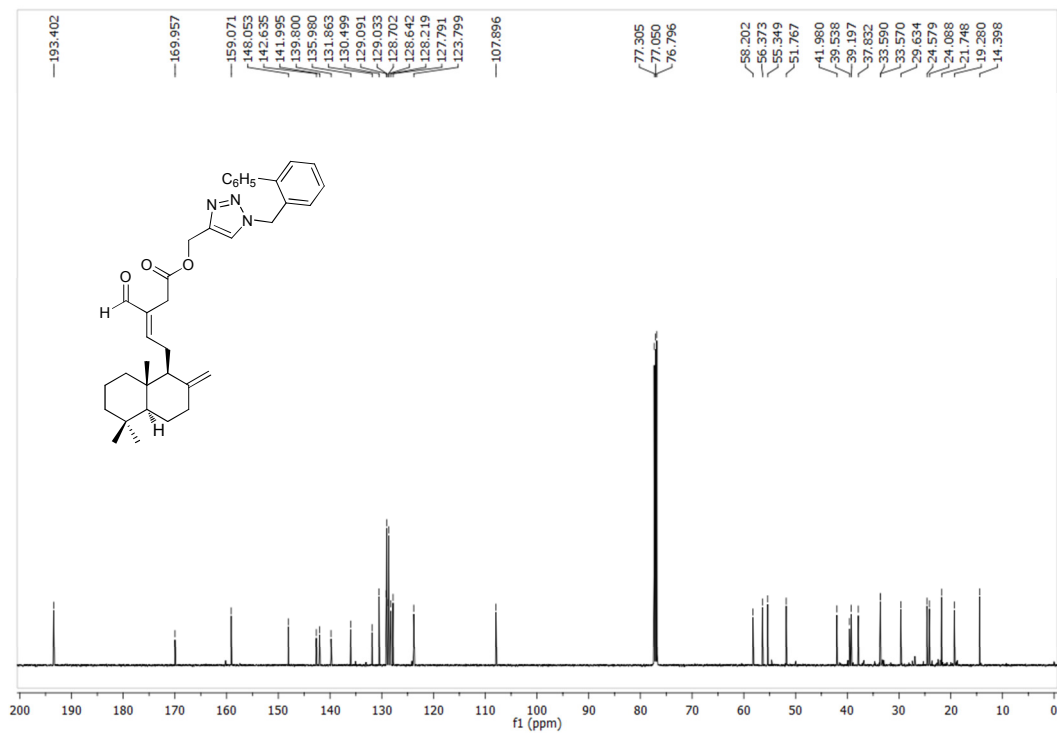


Figure S₂₆. ¹³C NMR Spectrum of Compound 6l

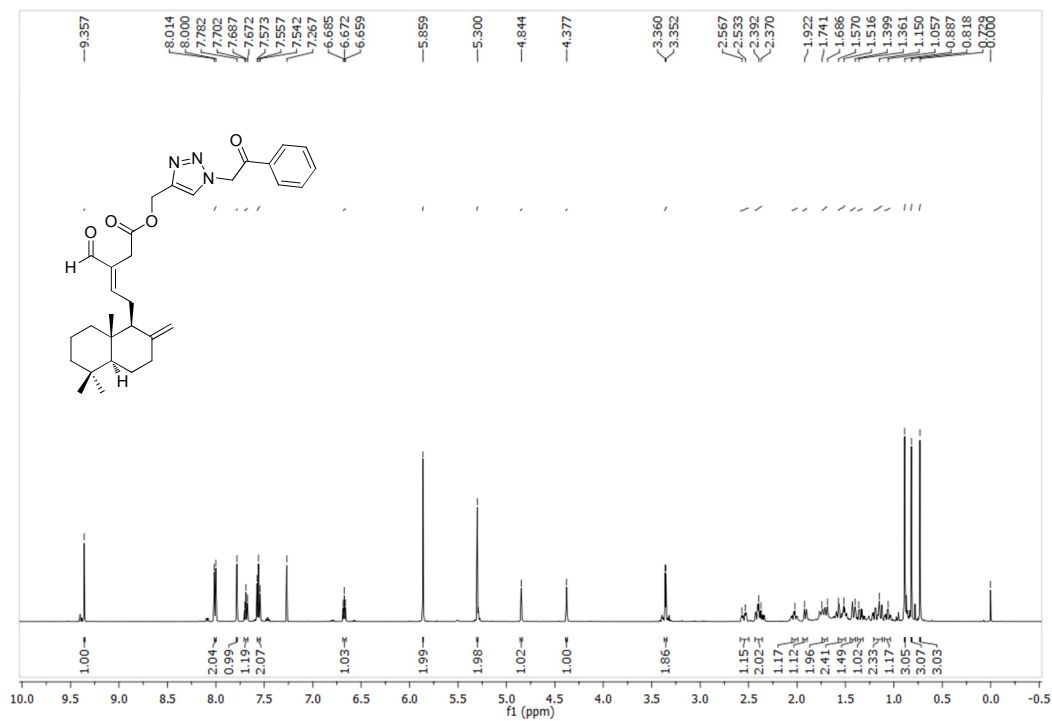


Figure S27. ¹H NMR Spectrum of Compound **6m**

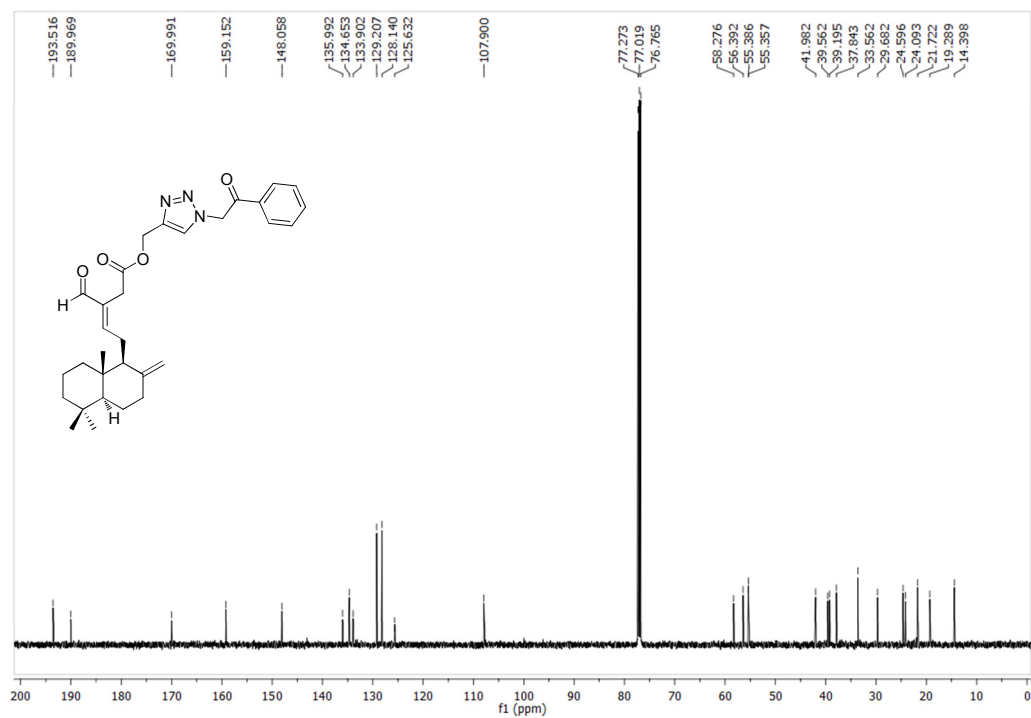


Figure S28. ¹³C NMR Spectrum of Compound **6m**

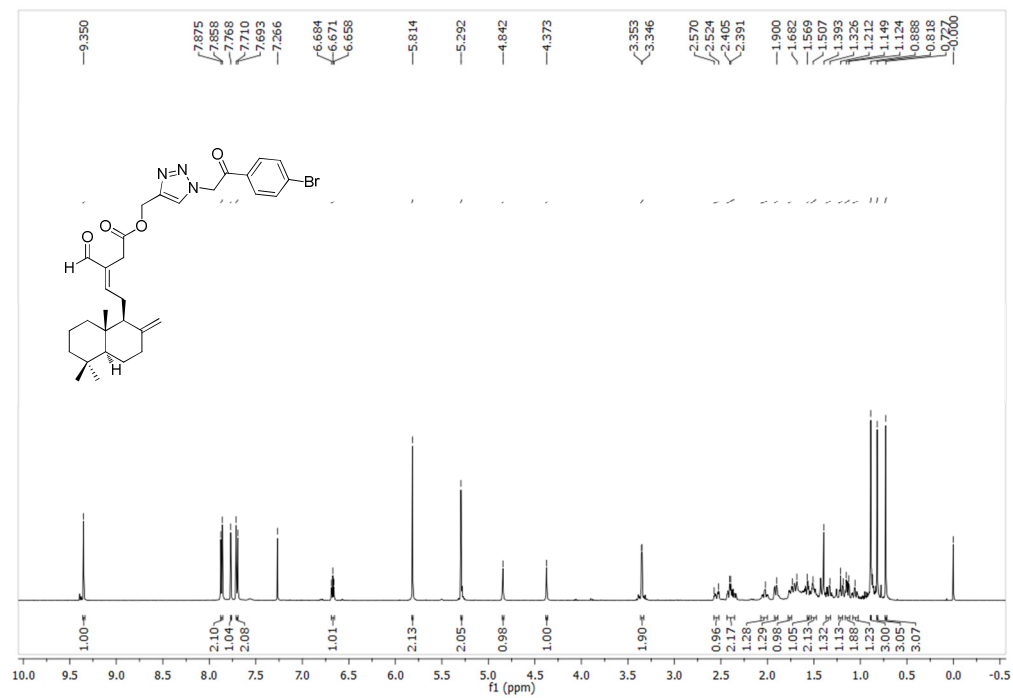


Figure S₂₉. ¹H NMR Spectrum of Compound **6n**

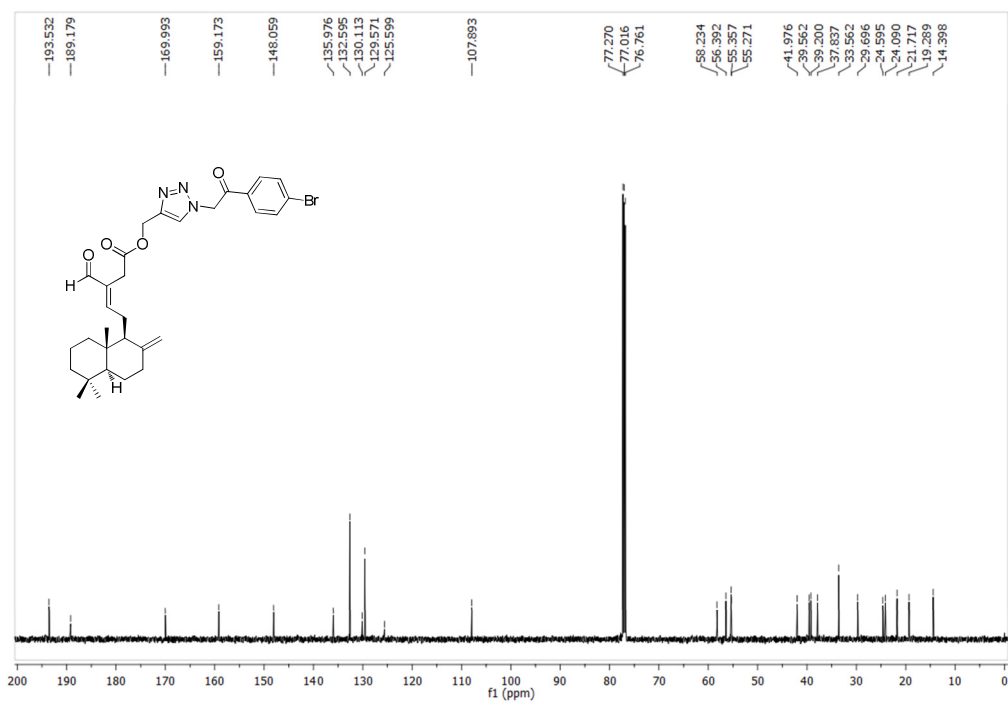


Figure S₃₀. ¹³C NMR Spectrum of Compound **6n**

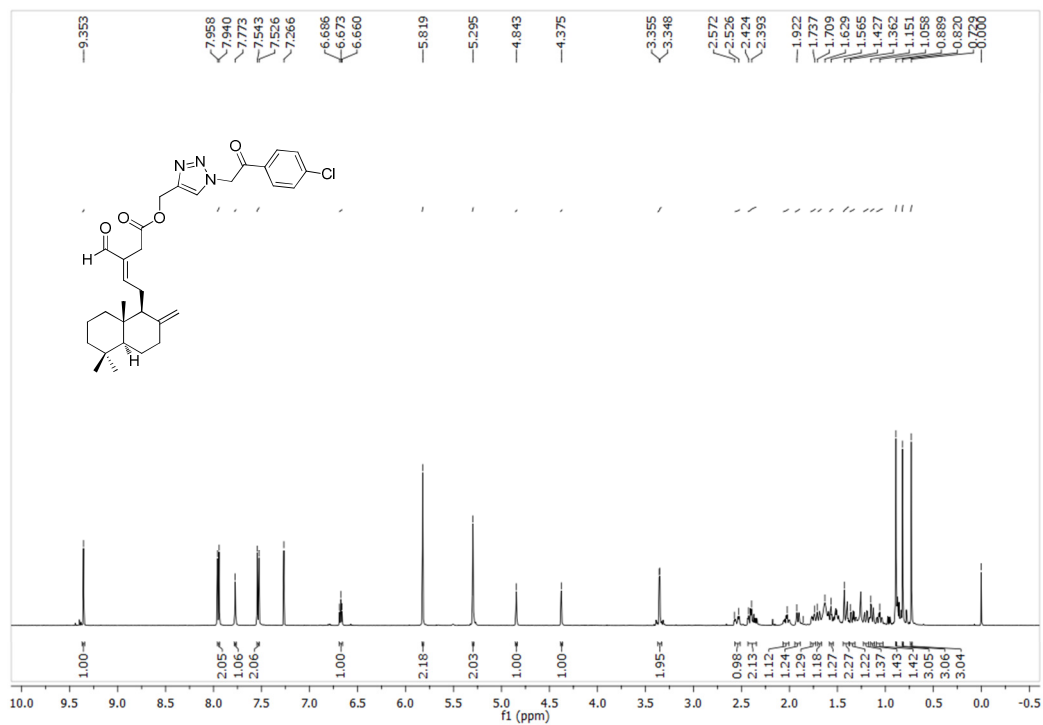


Figure S₃₁. ¹H NMR Spectrum of Compound 60

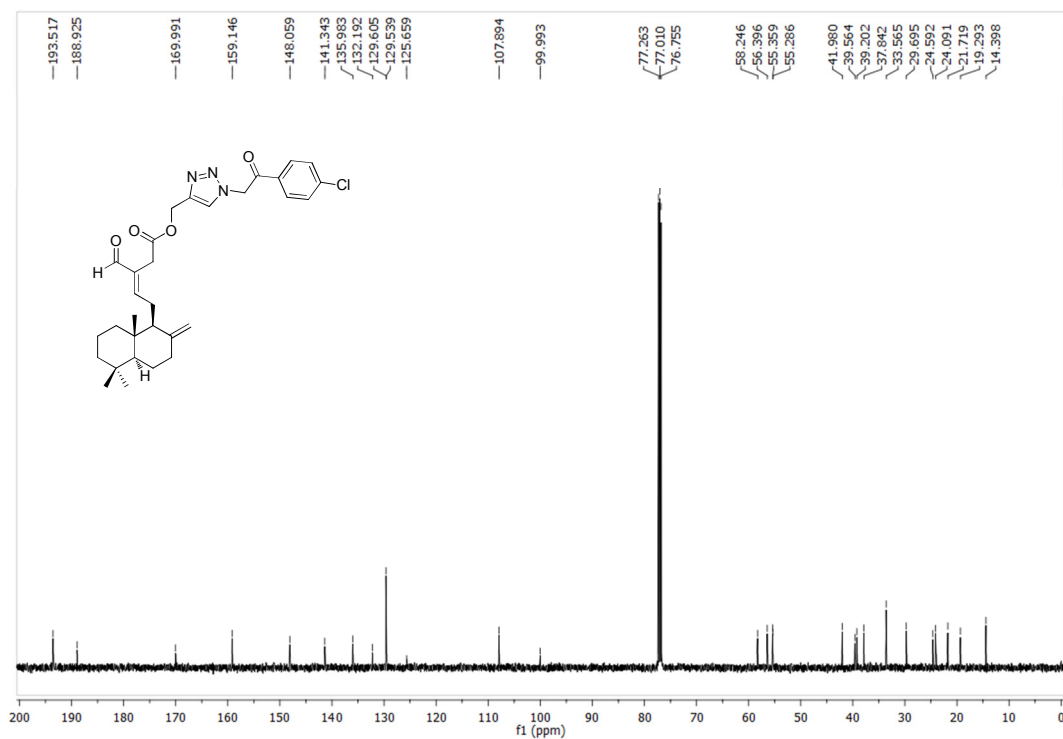


Figure S₃₂. ¹³C NMR Spectrum of Compound 60

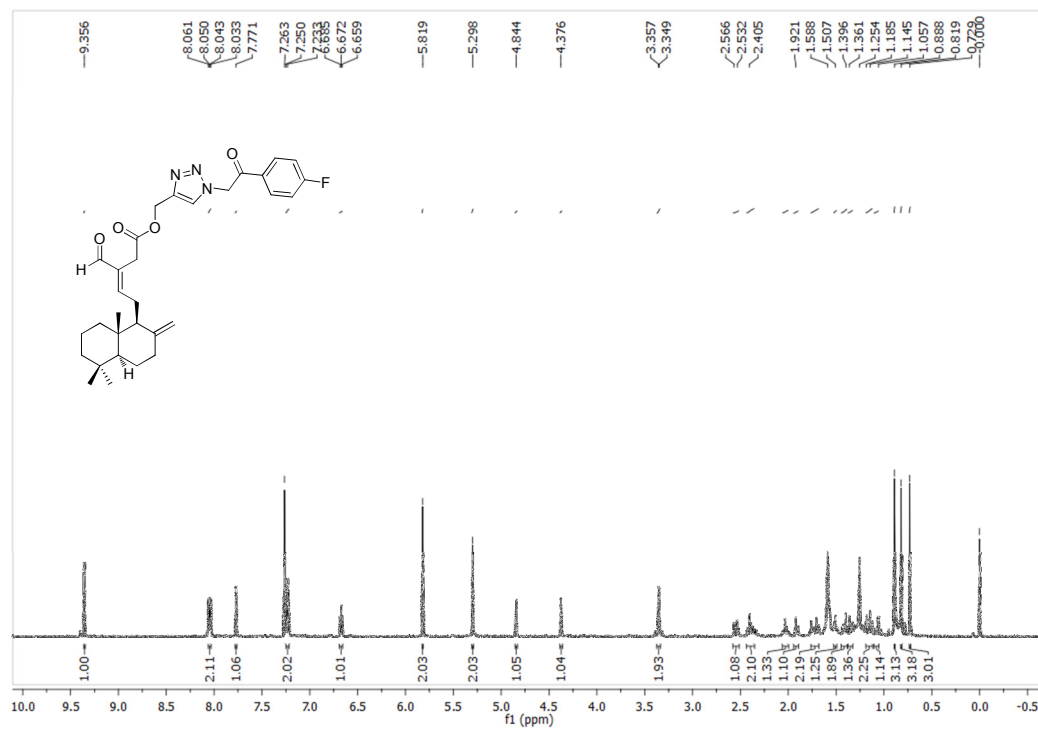


Figure S33. ^1H NMR Spectrum of Compound 6p

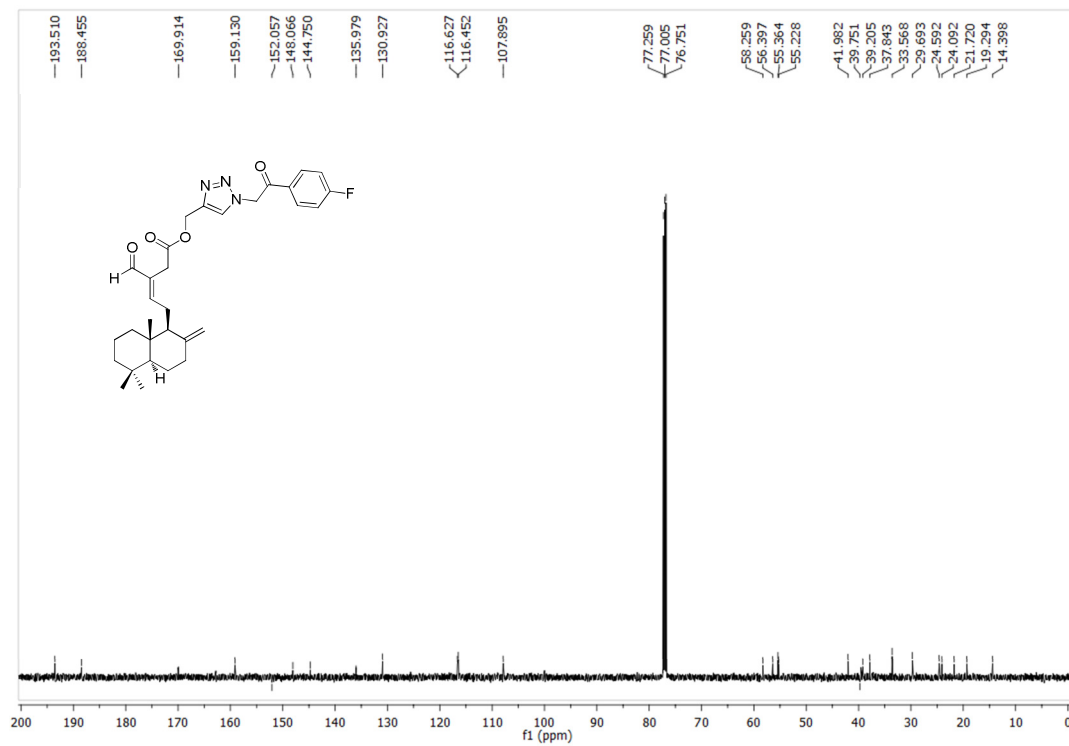


Figure S34. ^{13}C NMR Spectrum of Compound 6p

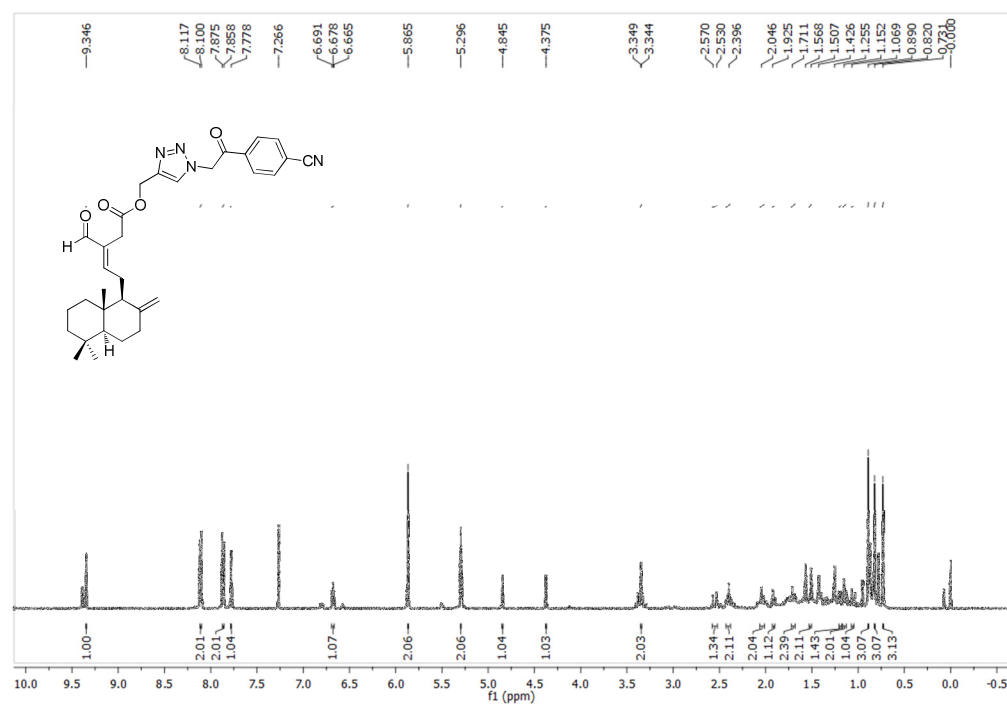


Figure S₃₅. ¹H NMR Spectrum of Compound 6q

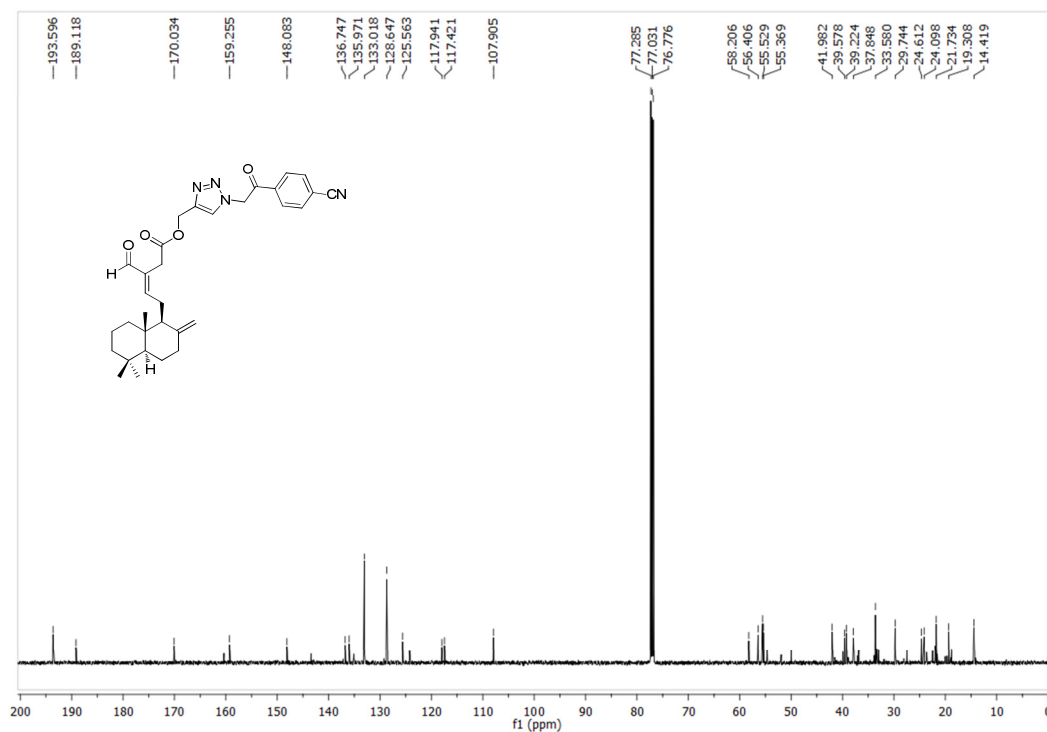


Figure S₃₆. ¹³C NMR Spectrum of Compound 6q

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