Supporting Information

Evaluation of Oxetan-3-ol, Thietan-3-ol and Derivatives Thereof as Bio-isosteres of the Carboxylic Acid Functional Group.

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Experimental Section

Materials and methods. All solvents were reagent grade. All reagents were purchased from Aldrich or Fisher Scientific and used as received. Thin layer chromatography (TLC) was performed with 0.25 mm E. Merck pre-coated silica gel plates. Silica gel column chromatography was performed with silica gel 60 (particle size 0.040–0.062 mm) supplied by Silicycle and Sorbent Technologies. TLC spots were detected by viewing under a UV light (254 nm), or using $KMnO_4$ or ceric ammonium molybdate stains. Melting points (mp) were acquired on a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts were reported relative to the residual solvent's peak. High-resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. Single-crystal X-ray structure determinations were performed at the University of Pennsylvania with an Enraf Nonius CAD-4 diffractometer. Analytical reverse-phase (Sunfire™ C18; 4.6×50 mm, 5 mL) high-performance liquid chromatography (HPLC) was performed with a Waters binary gradient module 2525 equipped with Waters 2996 PDA and Waters micromass ZQ. All samples were analyzed employing a linear gradient from 10% to 90% of CH_3CN in H_2O over 8 min and flow rate of 1 mL/min, and unless otherwise stated, the purity level was >95%. Preparative reverse-phase HPLC purifications were performed on a Gilson instrument (*i.e.*, Gilson 333 pumps, a 215 liquid handler, 845Z injection module, and PDA detector) employing Waters SunFire™ preparative C_{18} OBD™ columns (5 μm 19×50 or 19×100 mm). Purifications were carried out employing a linear gradient from 10% to 90% of CH_3CN in H_2O for 15 min with a flow rate of 20 mL/min. Unless otherwise stated, all final compounds were found to be >95% pure as determined by HPLC/MS and NMR.
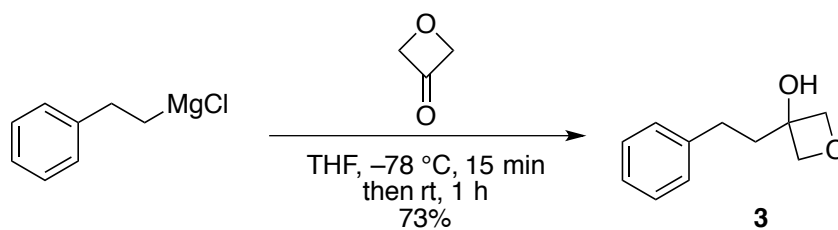
3-Phenethyloxetan-3-ol (**3**): To a stirred solution of oxetan-3-one (50 μL, 0.780 mmol, 1 equiv) in THF

(2 mL) at −78 °C under N_2 was added dropwise phenethylmagnesium chloride (940 μL of a 1 M

solution in THF, 1.2 equiv). The reaction was stirred at this temperature for 10 min, then at room

temperature for 1 h. The reaction was quenched with satd. aq. NH_4Cl, then extracted with Et_2O (× 3).

The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in

vacuo. Purification by silica gel flash column chromatography (Hexanes/EtOAc 88/12 to 0/10) afforded

the title compound (102 mg, 0.572 mmol, 73%) as a colorless low-melting solid. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.34–7.27 (m, 2H), 7.25–7.18 (m, 3H), 4.56 (d, $J = 6.8$ Hz, 2H), 4.49 (d, $J = 7.2$ Hz, 2H), 2.89

(s, 1H), 2.78–2.71 (m, 2H), 2.21–2.14 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4, 128.7, 128.5,

126.3, 84.1, 74.6, 39.6, 29.9 ppm. IR (KBr) ν 3389, 3026, 2950, 2872, 2359, 2344, 1603, 1495 cm^{-1}.

HRMS (CI$^+$) calculated for $C_{10}H_{12}O$ [M–CH$_2$O]$^+$ 148.0888, found 148.0892.
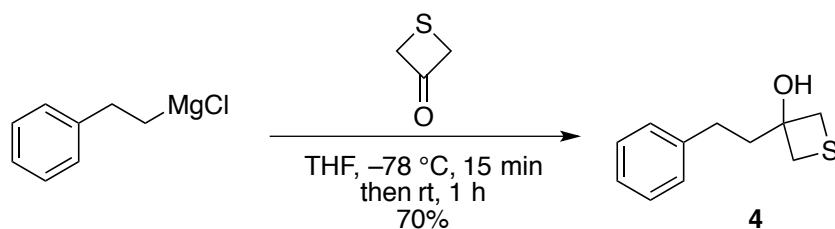
3-Phenethylthietan-3-ol (**4**): To a stirred solution of thietan-3-one (367 mg, 4.17 mmol, 1.0 equiv) in

THF (10 mL) at −78 °C under N_2 was added dropwise phenethylmagnesium chloride (5 mL of a 1M

solution in THF, 5.0 mmol, 1.2 equiv). The solution was stirred at this temperature for 15 min, then at

room temperature for 1.5 h. The reaction was quenched with satd. aq. NH_4Cl, then extracted with Et_2O

(× 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and

concentrated in vacuo. Purification by silica gel flash chromatography (Hexanes/EtOAc 95/5 to 6/4) afforded the title compound (570 mg, 2.93 mmol, 70%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33–7.30 (m, 2H), 7.26–7.20 (m, 3H), 3.36 (d, J = 10.4 Hz, 2H), 3.20 (d, J = 10.4 Hz, 2H), 2.78–2.74 (m, 2H), 2.67 (s, 1H), 2.24–2.21 (m, 2H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.68, 128.62, 128.49, 126.10, 77.95, 41.28, 41.17, 29.42 ppm. IR (KBr) ν 3406, 2933, 2848, 1495, 1453 cm^{-1}. HRMS (CI$^+$) calculated for C$_{11}$H$_{14}$OS [M$^+$] 194.0765, found 194.0768.
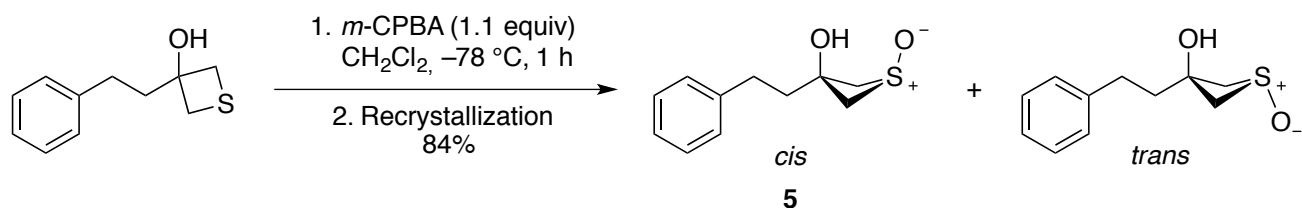
3-Hydroxy-3-phenethylthietane 1-oxide (**5**): 3-Phenethylthietan-3-ol (200 mg, 1.03 mmol, 1.0 equiv) was dissolved in anhydrous CH$_2$Cl$_2$ (9 mL) under N$_2$ at room temperature, then cooled to –78 °C and stirred for 10 min. Then, a solution of *m*-CPBA (~75% wt, 261 mg, 1.13 mmol, 1.1 equiv) in CH$_2$Cl$_2$ (6 mL) was added dropwise in 15 min and the mixture was stirred at the same temperature for 1 h. The reaction was diluted with CH$_2$Cl$_2$, then quenched with satd. aq. NaHCO$_3$ at room temperature and extracted with CH$_2$Cl$_2$ (× 4). The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. ^{1}H NMR of the crude material indicated a *cis*/*trans* ratio of >98/2. Recrystallization from a mixture of CH$_2$Cl$_2$ and hexanes afforded the pure *cis* sulfoxide **5** as a colorless solid (182 mg, 0.867 mmol, 84%). X-Ray quality crystals were formed by slow diffusion of hexanes into a CH$_2$Cl$_2$ solution. mp = 127–128 °C (CH$_2$Cl$_2$/Hexanes). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31–7.28 (m, 2H), 7.22–7.18 (m, 3H), 4.65 (br s, 1H), 3.89 (d, J = 13.0 Hz, 2H), 3.48 (d, J = 13.0 Hz, 2H), 2.72–2.69 (m, 2H), 1.82–1.79 (m, 2H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.96, 128.73, 128.45, 126.34, 66.20, 65.21, 43.88, 29.52 ppm. IR (KBr) ν 3342, 3029, 2919, 2848, 1453 cm^{-1}. HRMS (ES$^+$) calculated for C$_{11}$H$_{14}$O$_2$SNa [M+Na]$^+$ 233.0612, found 233.0623.
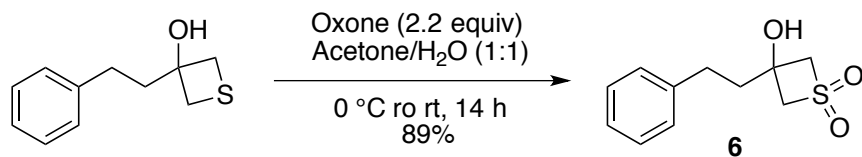
3-Hydroxy-3-phenethylthietane 1,1-dioxide (**6**): To a stirred solution of 3-phenethylthietan-3-ol in acetone (1 mL) at 0 °C was added in one portion a solution of Oxone® (271 mg, 0.442 mmol, 2.2 equiv) in H_2O (1 mL). The resulting mixture was slowly warmed to room temperature and stirred for 14 h. The reaction was quenched with 1M aq. Na_2SO_3, then extracted with CH_2Cl_2 (× 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (Hexanes/EtOAc 6/4) afforded the title compound (41 mg, 0.179 mmol, 89%) as a colorless solid. X-Ray quality crystals were formed by slow diffusion of hexanes into a CH_2Cl_2 solution. mp = 101–101.5 °C (CH_2Cl_2/Hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.30 (m, 2H), 7.24–7.20 (m, 3H), 4.09 (d, J = 13.1 Hz, 2H), 4.04 (d, J = 13.1 Hz, 2H), 3.09 (s, 1H), 2.79 (t, J = 7.7 Hz, 2H), 2.22 (t, J = 7.7 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.12, 128.90, 128.55, 126.70, 76.38, 63.37, 42.31, 30.61 ppm. IR (KBr) ν 3446, 3037, 2966, 2920, 1457 cm^{-1}. HRMS (ES$^-$) calculated for $C_{11}H_{13}O_3S$ [M–H]$^-$ 225.0585, found 225.0583.
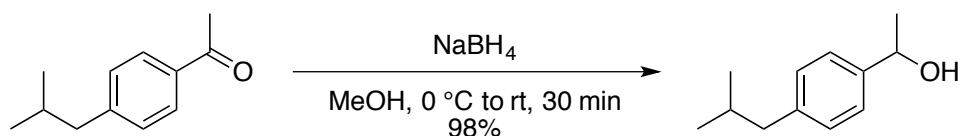
1-(4-Isobutylphenyl)ethan-1-ol:[1] To a stirred solution of 1-(4-isobutylphenyl)ethan-1-one (5.0 mL, 27.2 mmol, 1.0 equiv) in MeOH (140 mL) at 0 °C was added portionwise $NaBH_4$ (2.06 g, 54.5 mmol, 2.0 equiv) in 10 min. Once the bubbling subsided (approx. 10 min), the mixture was warmed to room temperature and stirred for 10 min. The reaction was quenched with H_2O, then the volatile solvents were removed in vacuo and the residue was extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Filtration through a pad of

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[1] Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 4665–4668.

silica gel (eluting with Hexanes/EtOAc 7/3) afforded the title compound (4.73 g, 26.6 mmol, 98%) as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (t, J = 6.7 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 4.85 (q, J = 6.5 Hz, 1H), 2.48 (d, J = 7.2 Hz, 2H), 2.15 (s, 1H), 1.87 (hept, J = 6.7 Hz, 1H), 1.48 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.7 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 143.19, 141.01, 129.28, 125.30, 70.31, 45.18, 30.34, 25.11, 22.48 ppm. MS (EI$^+$) calculated for C$_{12}$H$_{18}$O [M]$^+$ 178.1, found 178.2.
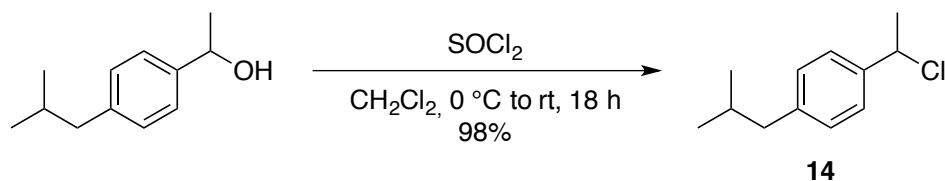

1-(1-Chloroethyl)-4-isobutylbenzene (**14**):[1] To a stirred solution of 1-(4-isobutylphenyl)ethan-1-ol (2.0 g, 11.22 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (60 mL) under N$_2$ at 0 °C was added thionyl chloride (1.2 mL, 16.44 mmol, 1.47 equiv). The resulting solution was stirred at 0 °C for 5 min, then warmed to room temperature and stirred for 19 h. The reaction was *carefully* quenched with H$_2$O (30 mL) and stirred vigorously for 5 min. The aqueous layer was discarded, and the organic layer was shaken with 0.2 M Na$_2$HPO$_4$ and neutralized with 2 M NaOH until pH = 7. The organic layer was separated, washed with H$_2$O, brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. Evaporation of the solvents in vacuo afforded the title compound (2.17 g, 11.03 mmol, 98%) as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 5.11 (q, J = 6.8 Hz, 1H), 2.49 (d, J = 7.2 Hz, 2H), 1.88 (hept, J = 6.7 Hz, 1H), 1.87 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.7 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.02, 140.22, 129.45, 126.39, 59.01, 45.21, 30.31, 26.60, 22.51 ppm. MS (EI$^+$) calculated for C$_{12}$H$_{17}$Cl [M]$^+$ 196.1, found 196.1.

1. Mg, LiCl, ZnCl$_2$
THF, rt, 6 h

2. oxetan-3-one
THF, rt, 17 h
15%

14

7
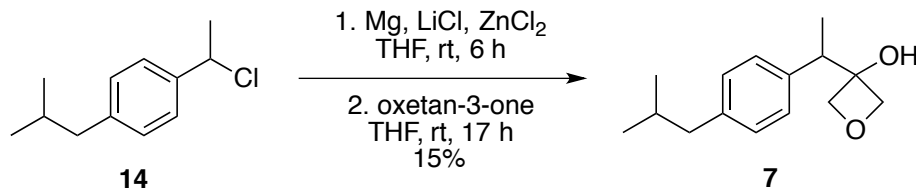
3-(1-(4-Isobutylphenyl)ethyl)oxetan-3-ol (**7**):[1] LiCl (50 mg, 1.17 mmol, 1.5 equiv) and ZnCl$_2$ (117 mg, 0.857 mmol, 1.1 equiv) were flame-dried under high vacuum, then cooled to room temperature (this procedure was repeated twice). Mg turnings (57 mg, 2.34 mmol, 3.0 equiv) were added under N$_2$, followed by THF (2.25 mL), then all the solids were dissolved under sonication. In a separate flask, 1-(1-chloroethyl)-4-isobutylbenzene **14** (184 mg, 0.935 mmol, 1.2 equiv) was dissolved in THF (0.5 mL) under N$_2$, then the solution was cannulated dropwise onto the Mg suspension at room temperature. The vial was rinsed with THF (2 × 0.250 mL). The resulting mixture was briefly sonicated (approx. 1 min), then vigorously stirred at room temperature for 2 h. In a separate vial, a solution of oxetan-3-one (50 µL, 0.779 mmol, 1.0 equiv) in THF (1 mL) was cooled to –78 °C under N$_2$. The crude zinc reagent was slowly cannulated to the oxetan-3-one solution in 5 min (the vial was rinsed with 0.5 mL of THF). The solution was stirred at –78 °C for 5 min, then warmed to room temperature and stirred for 1 h. The reaction was quenched with satd. aq. NH$_4$Cl, then extracted with Et$_2$O (× 3). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (Hexanes/EtOAc 94/6 to 5/5) afforded the title compound (27 mg, 0.115 mmol, 15%) as a colorless low melting solid. Further purification by preparative HPLC (H$_2$O/Acetonitrile 8/2 to 0/1 in 12 min) afforded 20.12 mg of analytically pure product. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 4.38 (d, *J* = 6.9 Hz, 1H), 3.26 (q, *J* = 7.1 Hz, 1H), 2.45 (d, *J* = 7.2 Hz, 2H), 2.24 (br s, 1H), 1.84 (m, 1H), 1.35 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.76, 138.13, 129.51, 127.92, 82.74, 82.42, 76.96, 45.22, 45.11, 30.29, 22.55, 22.52, 14.53 ppm. IR (KBr) *ν* 3397, 2953, 2928, 2869, 1512, 1462 cm^{-1}. HRMS (CI⁻) calculated for C$_{15}$H$_{21}$O [M–OH]⁻ 217.1592, found 217.1590.
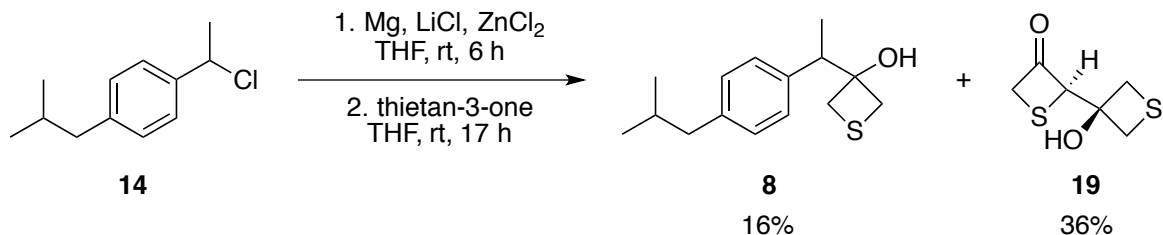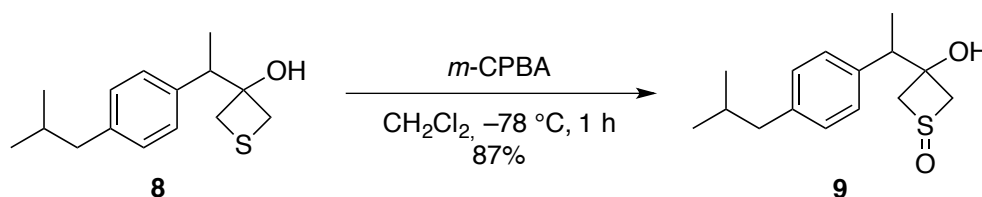
3-(1-(4-Isobutylphenyl)ethyl)thietan-3-ol (**8**): LiCl (50 mg, 1.17 mmol, 1.5 equiv) and $ZnCl_2$ (117 mg, 0.857 mmol, 1.1 equiv) were flame-dried under high vacuum, then cooled to room temperature (this procedure was repeated twice). Mg turnings (57 mg, 2.34 mmol, 3.0 equiv) were added under N_2, followed by THF (2.25 mL), then all the solids were dissolved under sonication. In a separate flask, 1-(1-chloroethyl)-4-isobutylbenzene **14** (184 mg, 0.935 mmol, 1.2 equiv) was dissolved in THF (0.5 mL) under N_2, then the solution was cannulated dropwise onto the Mg suspension at room temperature. The vial was rinsed with THF (2 × 0.250 mL). The resulting mixture was briefly sonicated (approx. 1 min), then vigorously stirred at room temperature for 2.5 h. In a separate vial, a solution of thietan-3-one (69 mg, 0.779 mmol, 1.0 equiv) in THF (1 mL) was cooled to –78 °C under N_2. The crude zinc reagent was slowly cannulated to the oxetan-3-one solution in 5 min (the vial was rinsed with 0.5 mL of THF). The solution was stirred at –78 °C for 5 min, then warmed to room temperature and stirred for 1 h. The reaction was quenched with satd. aq. NH_4Cl, then extracted with Et_2O (× 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (Hexanes/EtOAc 95/5 to 6/4) afforded the title compound (31 mg, 0.124 mmol, 16%) as a colorless low melting solid, and by-product **19**, which was crystallized and analyzed via X-ray diffraction analyses.[2] Further purification of **8** by preparative HPLC (H_2O/Acetonitrile 8/2 to 0/1 in 12 min) afforded 23.12 mg of analytically pure product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.41 (d, *J* = 9.8 Hz, 1H), 3.31

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[2] X-Ray quality crystals were formed by slow diffusion of hexanes into a CH_2Cl_2 solution. mp = 77.5–78.5 °C (CH_2Cl_2/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (t, *J* = 1.8 Hz, 1H), 4.20–4.20 (m, 2H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.41 (d, *J* = 9.7 Hz, 2H), 3.25 (s, 1H), 2.85 (dd, *J* = 9.6, 2.3 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.98, 78.10, 76.41, 53.11, 40.19, 37.67 ppm. IR (KBr) ν 3455, 2935, 2853, 1768 cm^{-1}. HRMS (ESI$^-$) calculated for $C_6H_7O_2S_2$ [M–H]$^-$ 174.9887, found 174.9881.

(q, J = 7.1 Hz, 1H), 3.26 (m, 2H), 2.96 (d, J = 10.0 Hz, 1H), 2.45 (d, J = 7.2 Hz, 2H), 2.19 (br s, 1H), 1.85 (m, 1H), 1.34 (d, J = 7.1 Hz, 3H), 0.90 (dd, J = 6.7, 2.2 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.61, 138.24, 129.29, 128.50, 80.26, 46.36, 45.14, 39.56, 39.54, 30.31, 22.57, 22.52, 14.21 (the quaternary carbon of thietane does not appear) ppm. IR (KBr) ν 3446, 2952, 2865, 1509, 1465 cm^{-1}. HRMS (CI$^+$) calculated for C$_{15}$H$_{22}$OS [M$^+$] 250.1391, found 250.1392.

3-Hydroxy-3-(1-(4-isobutylphenyl)ethyl)thietane 1-oxide (**9**): A solution of *m*-CPBA (75% wt, 9.1 mg, 0.040 mmol, 1.1 equiv) in CH$_2$Cl$_2$ (0.30 mL) was dried over MgSO$_4$, then added dropwise in 10 min to a stirred solution of 3-(1-(4-isobutylphenyl)ethyl)thietan-3-ol **8** (9 mg, 0.036 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.430 mL) at –78 °C under N$_2$. The resulting solution was stirred at –78 °C for 1 h. The reaction was quenched with satd. aq. NaHCO$_3$, then extracted with CH$_2$Cl$_2$ (× 4). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and K$_2$CO$_3$, filtered, and concentrated in vacuo. Purification by flash chromatography (Hexanes/EtOAc 2/8) afforded the title compound (*cis/trans* >20:1, 8.32 mg, 0.031 mmol, 87%) as a colorless solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.15–7.09 (m, 4H), 4.00 (dd, J = 12.4, 5.3 Hz, 1H), 3.88 (dd, J = 12.6, 5.3 Hz, 1H), 3.37 (d, J = 12.4 Hz, 1H), 3.24 (d, J = 12.6 Hz, 1H), 2.63 (q, J = 7.0 Hz, 1H), 3.59 (bs, 1H), 2.45 (d, J = 7.2 Hz, 2H), 1.84 (h, J = 6.6 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.20, 137.22, 129.52, 128.61, 70.06, 63.84, 63.35, 48.34, 45.11, 30.31, 22.53, 22.51, 14.58 ppm. IR (KBr) ν 3321, 2951, 2920, 2865, 1456 cm^{-1}. HRMS (ES$^+$) calculated for C$_{15}$H$_{22}$O$_2$NaS [M+Na]$^+$ 289.1238, found 289.1234.

8 → **10**

Oxone

Acetone/H₂O (1:1)
0 °C to rt, 20 h
82%
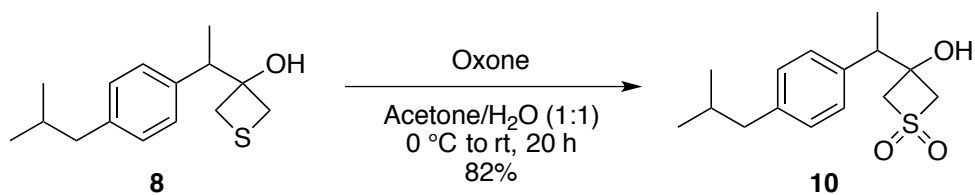
3-Hydroxy-3-(1-(4-isobutylphenyl)ethyl)thietane 1,1-dioxide (**10**): A solution of Oxone® (49 mg, 0.079 mmol, 2.2 equiv) in H_2O (0.200 mL) was added in one portion to a stirred solution of 3-(1-(4-isobutylphenyl)ethyl)thietan-3-ol **8** (9 mg, 0.036 mmol, 1.0 equiv) in acetone (0.200 mL) at 0 °C, and the solution was stirred at 0 °C for 1 h, then at room temperature for 3 h. The reaction was quenched with 1M Na_2SO_3, then extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. ¹H NMR of the crude material showed a mixture of the desired sulfone with sulfoxide **9** (2:1). The crude was taken up in acetone (0.200 mL) and cooled to 0 °C, then a solution of Oxone® (18 mg, 0.026 mmol, 2.2 equiv/sulfoxide) in H_2O (0.200 mL) was added in one portion. The resulting solution was stirred for 50 min, then warmed to room temperature and stirred for 20 h. The reaction was quenched with 1M Na_2SO_3, then extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (Hexanes/EtOAc 9/1 to 8/2) afforded the title compound (8.30 mg, 0.029 mmol, 82%) as a colorless solid. ¹H NMR (500 MHz, CDCl₃) δ 7.20 (app d, *J* = 8.0 Hz, 2H), 7.15 (app d, *J* = 7.9 Hz, 2H), 4.26 (d, *J* = 13.6 Hz, 1H), 4.23 (d, *J* = 14.0 Hz, 1H), 4.07 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.71 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.11 (q, *J* = 7.1 Hz, 1H), 2.59 (br s, 1H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.87 (hept, *J* = 6.6 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 141.64, 137.00, 129.85, 128.06, 75.29, 74.91, 66.03, 48.04, 45.11, 30.29, 22.53, 22.50, 15.26 ppm. IR (KBr) ν 3481, 2955, 2926, 2872 cm⁻¹. HRMS (ES⁺) calculated for $C_{15}H_{22}O_3NaS$ [M+Na]⁺ 305.1187, found 305.118.
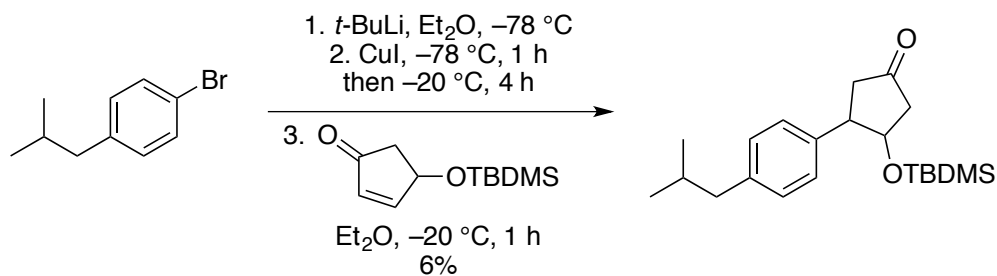
3-((tert-Butyldimethylsilyl)oxy)-4-(4-isobutylphenyl)cyclopentan-1-one: To a solution of 1-bromo-4-isobutylbenzene (1.4 g, 6.69 mmol, 2.0 equiv) in Et$_2$O (10 mL) at –78 °C, *tert*-butyl lithium (4.5 mL, 1.5 M, 2.02 equiv) was added dropwise over 20 min. The resulting solution was added to a suspension of CuI (636 mg, 3.34 mmol, 1.0 equiv) in Et$_2$O (10 mL) under N$_2$, and the reaction mixture was stirred at –78 °C for 1 h, then at –20 °C for 1 h. To this solution was slowly added 4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one[3] (710 mg 3.34 mmol, 1.0 equiv) and the mixture was stirred for 1 h. The reaction was quenched with H$_2$O (10 mL), then extracted with Et$_2$O (× 3). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (gradients of Hexanes/EtOAc) afforded the title compound as a colorless solid (69 mg, 0.199 mmol, 6%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13 (m, 4 H), 4.28 (q, *J* = 6.8 Hz, 1H), 3.31 (m, 1H), 2.77 (m, 1H), 2.65 (m, 1H), 2.48 (m, 3H), 2.29 (m, 1 H), 1.86 (n, 1H), 0.91 (d, *J* = 6.5 Hz, 6H), 0.82 (s, 9H), –0.10 (s, 3H), –0.17 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 215.31, 140.71, 138.12, 129.54, 127.39, 51.11, 47.76, 45.21, 43.99, 30.46, 25.88, 22.50, 18.18, –4.89, –4.93 ppm.
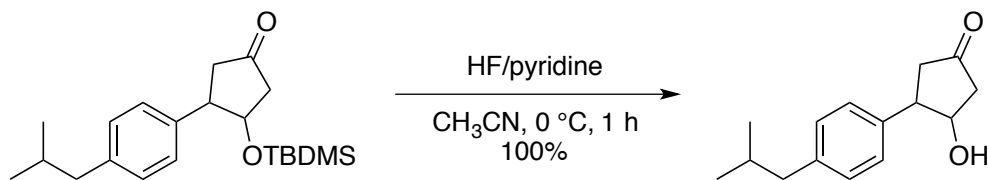
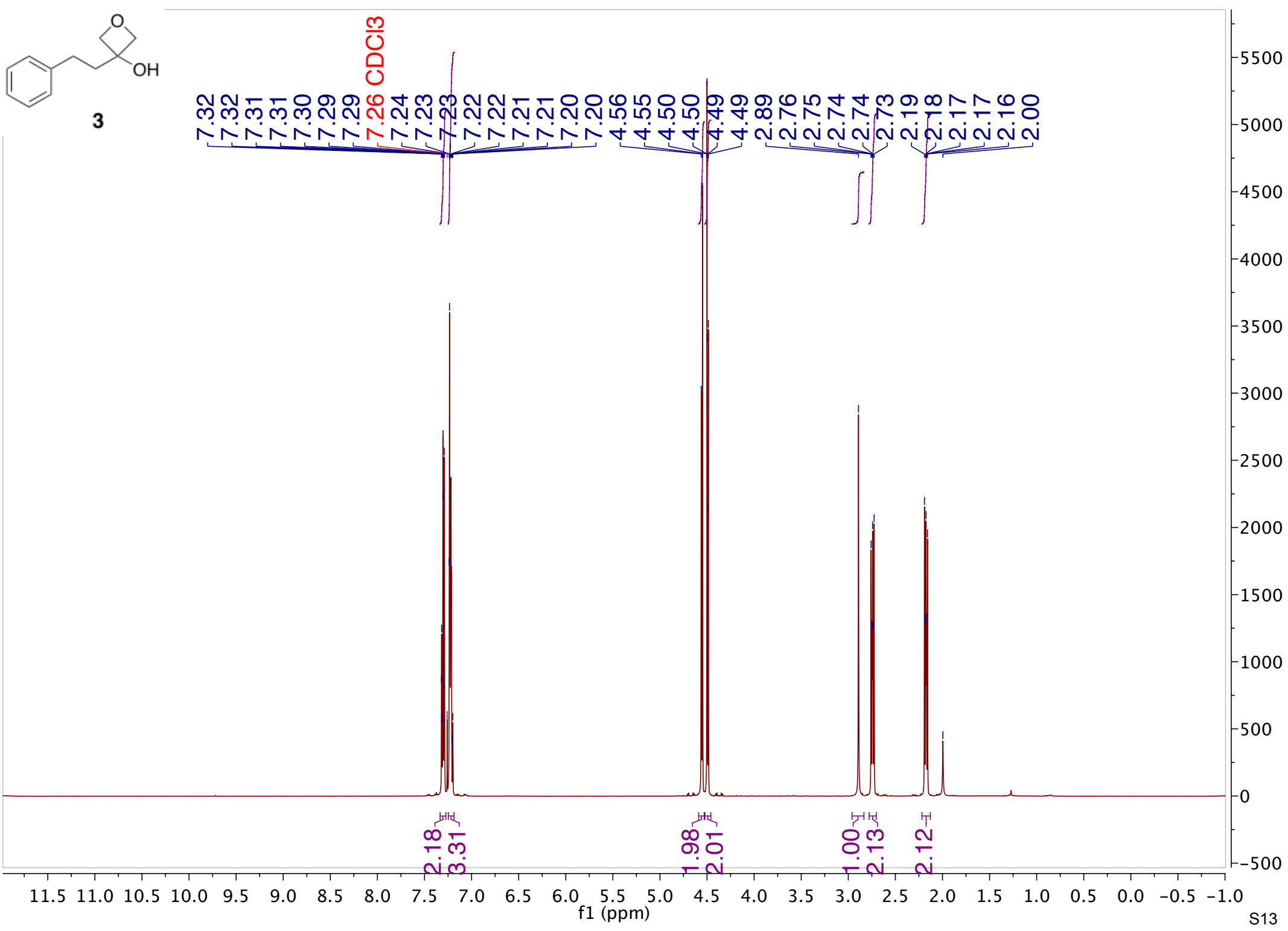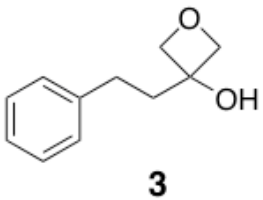*3-Hydroxy-4-(4-isobutylphenyl)cyclopentan-1-one:* To a solution of 3-((*tert*-butyldimethylsilyl)oxy)-4-(4-isobutylphenyl)cyclopentan-1-one (25 mg, 0.072 mmol, 1.0 equiv) in CH$_3$CN (2 mL), HF-pyridine

[3] Kumar, R. J.; Chebib, M.; Hibbs, D. E.; Kim, H.-L.; Johnston, G. A. R.; Salam, N. K.; Hanrahan, J. R. *J. Med. Chem.* **2008**, *51*, 3825–3840.

(0.45 mL, 70% hydrogen fluoride basis) was added dropwise at 0 °C, and the solution was stirred at 0 °C for 1 h. The reaction was diluted with EtOAc (10 mL), and the organic layer was washed with H_2O (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (gradients of Hexanes/EtOAc) afforded the title compound as a colorless solid (16.7 mg, 0.072 mmol, 100%). ^1H NMR (500 MHz, CDCl$_3$) δ 7.17 (m, 4H), 4.42 (q, J = 7.5 Hz, 1H), 3.30 (m, 1H), 2.79 (m, 2H), 2.47 (m, 3H), 2.32 (m, 1H), 2.26 (bs, 1H), 1.87 (m, 1H), 0.92 (d, J = 6.5 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 214.21, 141.05, 137.36, 75.98, 50.75, 46.79, 45.16, 44.88, 30.35, 22.53 ppm. IR (KBr) v 3412, 2922, 1741 cm^{-1}. HRMS (ES$^-$) calculated for $C_{15}H_{19}O_2$ [M–H]$^-$ 231.1391, found 231.1387.
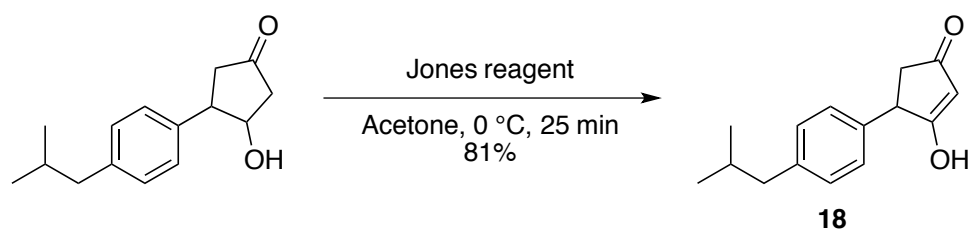
4-(4-Isobutylphenyl)cyclopentane-1,3-dione (18): NB: Jones reagent was prepared by adding 5 g of anhydrous CrO$_3$ to 5 mL of H$_2$SO$_4$ in a round-bottom flask under stirring at 0°C, followed by the slow addition of 15 mL of ice cold H$_2$O. To a solution of 3-hydroxy-4-(4-isobutylphenyl)cyclopentan-1-one (10 mg, 0.043 mmol) in acetone (5 mL), 20 drops of freshly prepared Jones reagent was added over 5 min at 0 °C. The solution turned orange-red quickly. After 20 min, the reaction mixture was diluted with H$_2$O (5 mL) and extracted with 20 mL CHCl$_3$ (× 3). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by silica gel preparative TLC (CH$_2$Cl$_2$/MeOH 95/5) afforded the title compound as a colorless solid (8 mg, 0.035 mmol, 81%). ^1H NMR (500 MHz, CDCl$_3$) δ 7.13–6.97 (m, 4H), 5.35 (s, 1H), 3.80 (d, J = 6.3 Hz, 1H), 3.02 (dd, J = 18.5, 7 Hz, 1H), 2.56 (d, J = 18.5 Hz, 1H), 2.44 (d, J = 7 Hz, 2H), 1.84 (dt, J = 13.5, 6.8 Hz, 1H), 0.90 (d, J = 6.6 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ 202.91, 201.69, 141.06, 136.62, 129.86, 127.35, 105.85, 49.26, 45.26, 41.73, 30.36, 22.58 ppm. IR (KBr) v 3411, 2955, 2923, 1721 cm^{-1}. HRMS (ES$^+$) calculated for $C_{15}H_{19}O_2$ [M+H]$^+$ 231.1385, found 231.1374.

7.32, 7.32, 7.31, 7.31, 7.30, 7.29, 7.29, 7.26 CDCl3, 7.24, 7.23, 7.23, 7.22, 7.22, 7.21, 7.21, 7.20, 7.20, 4.56, 4.55, 4.50, 4.50, 4.49, 4.49, 2.89, 2.76, 2.75, 2.74, 2.74, 2.73, 2.19, 2.18, 2.17, 2.17, 2.16, 2.00

2.18, 3.31, 1.98, 2.01, 1.00, 2.13, 2.12

f1 (ppm)

S13

3

141.44

128.67
128.47
126.25

84.14
77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
74.60

39.57

29.86

f1 (ppm)

S14

7.33, 7.31, 7.29, 7.28, 7.26 CDCl3, 7.22, 7.20, 7.19, 7.18, 7.13

4.65, 4.65, 3.90, 3.89, 3.88, 3.87, 3.49, 3.49, 3.47, 3.47, 2.72, 2.71, 2.71, 2.70, 2.69, 2.66, 2.65, 1.86, 1.82, 1.81, 1.80, 1.80, 1.79, 1.74

2.24, 3.35, 1.00, 2.30, 2.32, 2.30, 2.28

S17

140.95
128.72
128.44
126.33
77.41 CDCl3
77.15 CDCl3
76.90 CDCl3
66.20
65.21
43.87
29.52

5

S18

PL-II-049.10.fid
PL-II-049 F1

7.33 7.32 7.31 7.31 7.30 7.29 7.26 CDCl3 7.26 7.24 7.24 7.23 7.23 7.22 7.21 7.20 4.12 4.11 4.11 4.10 4.09 4.08 4.08 4.07 4.06 4.05 4.05 4.05 4.03 4.03 4.02 3.09 2.81 2.81 2.80 2.79 2.79 2.78 2.78 2.24 2.24 2.23 2.22 2.22 2.21 2.21 2.20

6

2.00 3.07 4.40 1.11 2.03 2.06

f1 (ppm)

S19

7.26 CDCl3
7.19
7.19
7.17
7.16
7.11
7.10
7.08
4.71
4.70
4.69
4.63
4.62
4.59
4.58
4.56
4.56
4.39
4.37
4.36
3.29
3.27
3.26
3.24
2.47
2.45
2.44
2.42
2.24
1.89
1.87
1.86
1.85
1.83
1.82
1.81
1.81
1.80
1.36
1.35
1.33
0.93
0.92
0.92
0.91
0.91
0.89
0.89
0.89
0.88

7

1.88
1.94
0.95
0.84
0.99
1.00
1.00
1.99
0.89
1.04
2.76
6.19

f1 (ppm)

7

140.75
138.13
129.51
127.92

82.74
82.42
77.41 CDCl3
77.16 CDCl3
76.96
76.90 CDCl3

45.22
45.11

30.29
22.55
22.52
14.53

S22

PhII-193.30.fid
PhII-193 purif 1 f1 hplc

7.26 CDCl3
7.23
7.23
7.22
7.22
7.21
7.20
7.20
7.11
7.10
7.09
7.09
3.42
3.42
3.42
3.40
3.40
3.40
3.33
3.31
3.30
3.28
3.28
3.27
3.27
3.27
3.26
3.25
3.25
2.97
2.95
2.47
2.45
2.44
2.43
2.19
1.89
1.88
1.86
1.85
1.83
1.82
1.81
1.35
1.33
0.91
0.90
0.89
0.89
0.87

8

1.94
1.92

0.99
0.98
2.00
0.96
1.89
1.12
1.00
2.96
5.77

f1 (ppm)

S23

140.61
138.24
129.29
128.50

80.26
77.41 CDCl3
77.16 CDCl3
76.90 CDCl3

46.36
45.14
39.56
39.54
30.31
22.57
22.52
14.21

8

f1 (ppm)

S24

141.20
137.22
129.52
128.61

77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
70.06
63.84
63.35
48.34
45.11
30.31
22.53
22.51
14.58

9

OH

S
O

f1 (ppm)

S26

10

141.64
137.00
129.85
128.05

77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
75.29
74.91
66.03

48.04
45.11

30.28
22.53
22.50
15.26

f1 (ppm)

S28

7.26 CDCl3
7.16
7.15
7.08
7.07
4.51
4.49
4.48
4.47
2.42
2.41
1.82
1.81
1.80
1.78
0.87
0.86

17

2.15
2.10
1.00
2.13
4.47
6.47

f1 (ppm)

S29

141.48
137.93
129.97
127.19
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
45.06
35.42
30.28
29.84
22.46
20.34

17

S30

18

7.27 CDCl3
7.10
7.08
7.06
7.04
5.35
5.31
3.81
3.80
3.79
3.04
3.01
3.00
2.63
2.59
2.58
2.55
2.45
2.43
1.85
1.84
1.83
1.27
0.91
0.90
0.89
0.88

4.31
0.91
0.99
1.00
1.03
2.11
1.13
6.47

f1 (ppm)

S31

LH-237-3.2.fid

202.90
201.68
141.06
136.62
129.85
127.35
105.86
77.48 CDCl3
77.23 CDCl3
76.97 CDCl3
49.27
45.27
41.74
30.37
29.92
22.59

18

S32
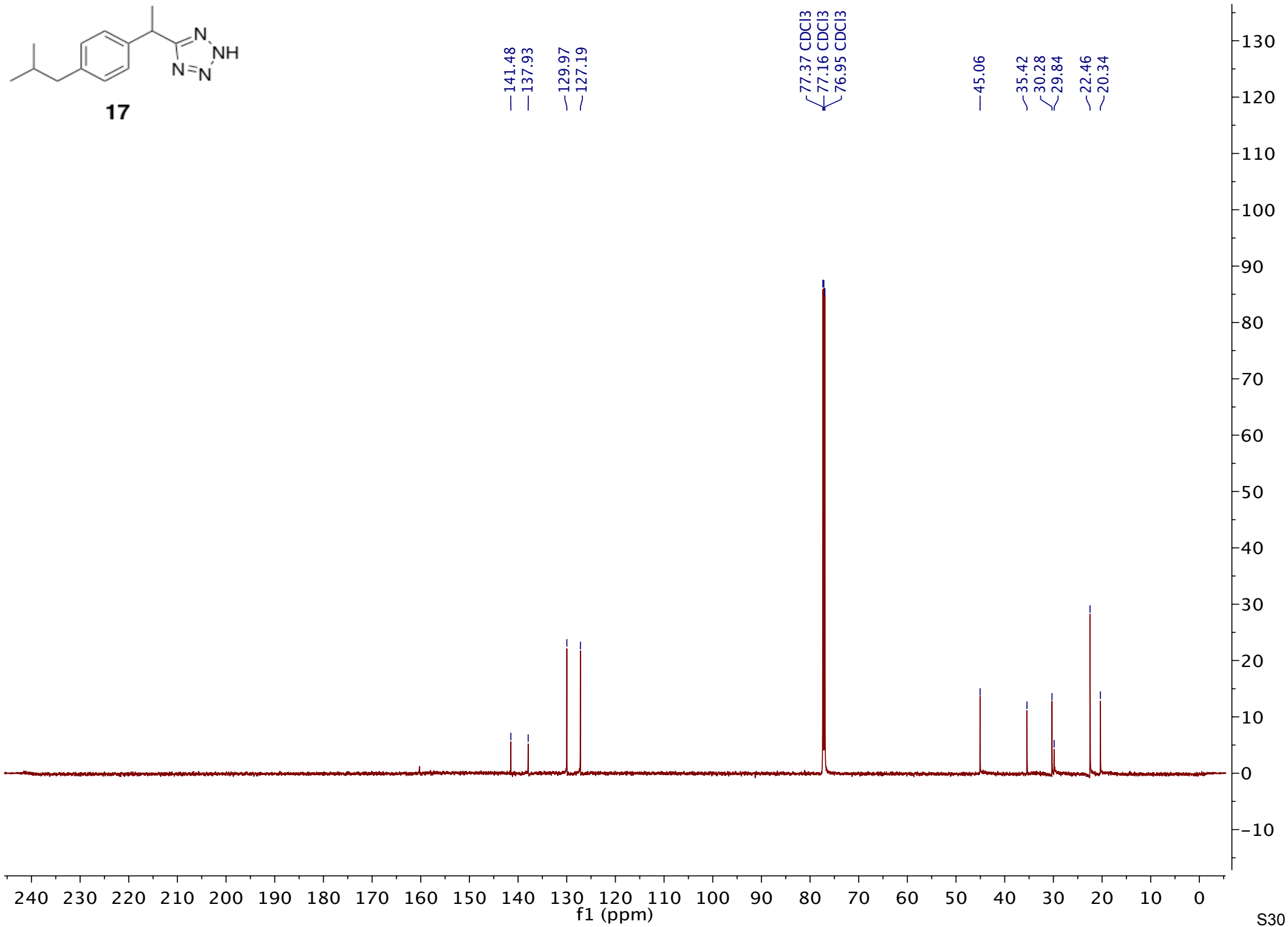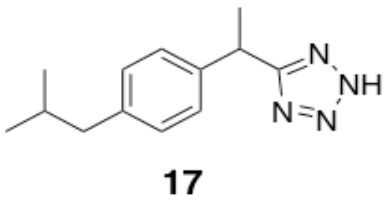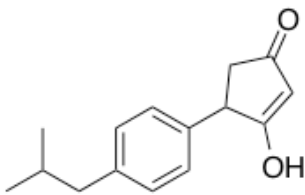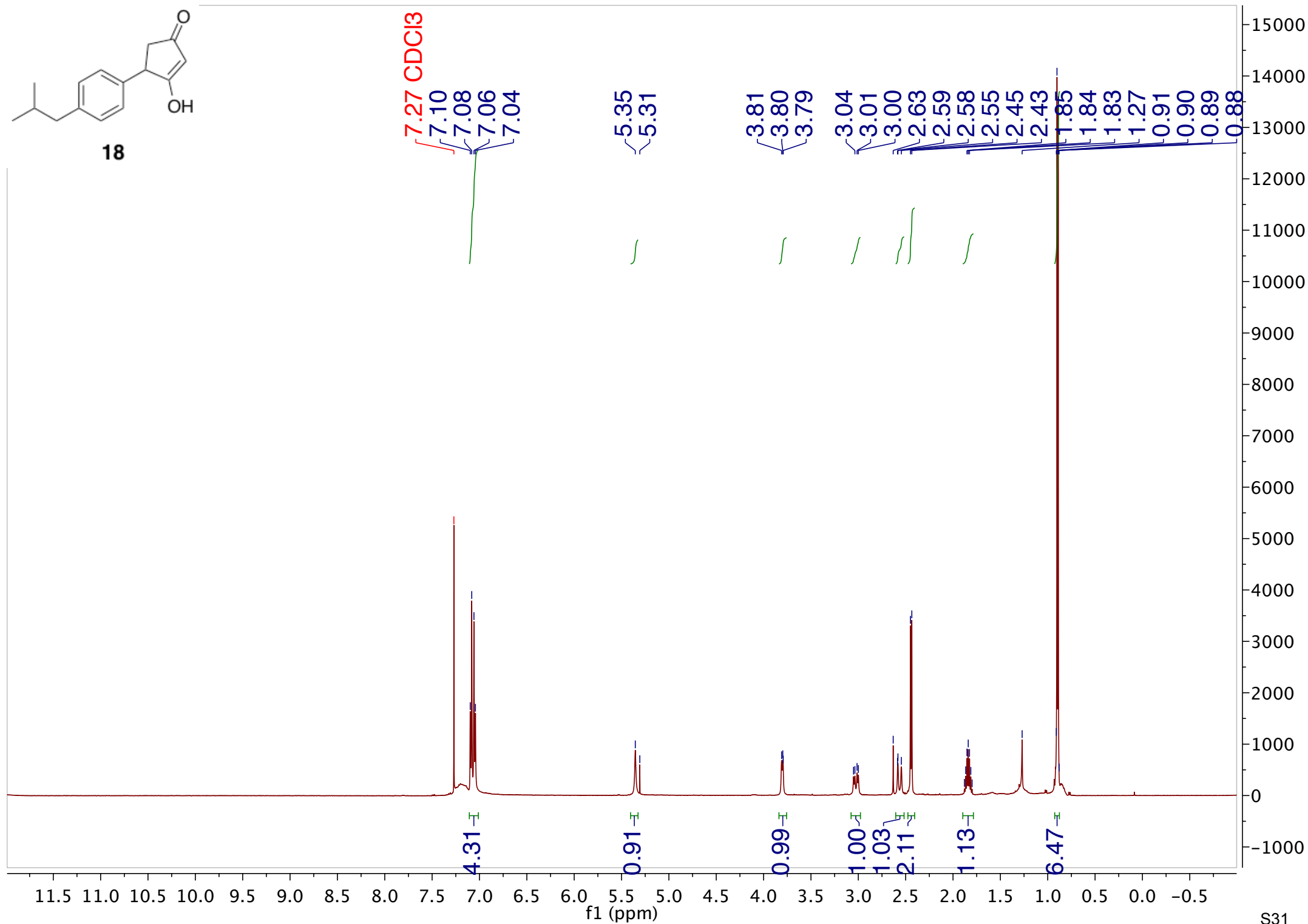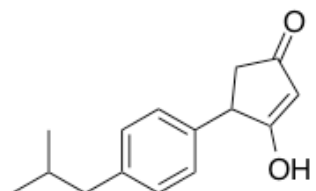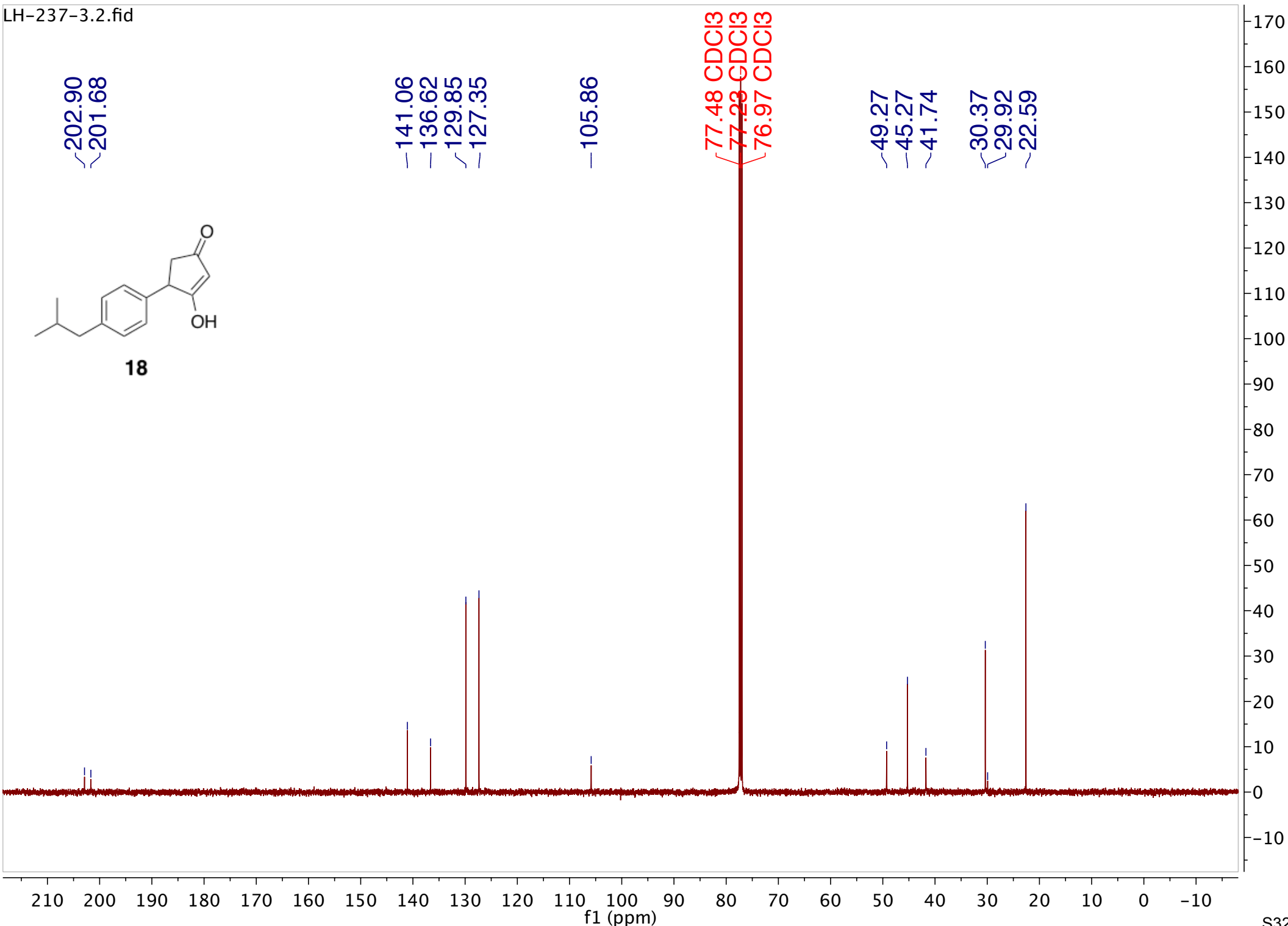
X-ray Structure Determination of Compound 1395 (compound 5 in the manuscript, CCDC 1543000)
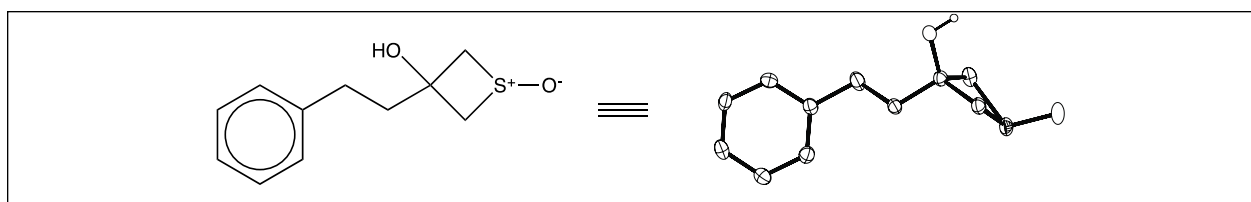
Compound 1395, $C_{11}H_{14}SO_2$, crystallizes in the monoclinic space group $P2_1$ (systematic absences 0k0: k=odd) with a=12.1555(7)Å, b=5.7786(4)Å, c=15.1633(10)Å, β=98.221(2)°, V=1054.15(12)Å^3, Z=4, and d$_{calc}$=1.325 g/cm^3 . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 100(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 1602 frames were collected with a crystal to detector distance of 37.5 mm, rotation widths of 0.5° and exposures of 5 seconds:

scan type	2θ	ω	ϕ	χ	frames
ϕ	-23.00	315.83	12.48	28.88	739
ω	-20.50	332.84	178.64	-31.86	148
ϕ	-23.00	334.21	50.50	73.66	715

Rotation frames were integrated using SAINT[i], producing a listing of unaveraged F^2 and σ(F^2) values which were then passed to the SHELXTL[ii] program package for further processing and structure solution. A total of 13556 reflections were measured over the ranges $2.01 \leq \theta \leq 25.49°$, $-13 \leq h \leq 14$, $-6 \leq k \leq 6$, $-18 \leq l \leq 18$ yielding 3824 unique reflections (Rint = 0.0230). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[iii] (minimum and maximum transmission 0.6883, 0.7452).

The structure was solved by direct methods (SHELXS-97[iv]). The CH$_2$-phenyl group was disordered by a small rotation about the C9-C8 single bond; the occupancy factors for the two disordered moieties refined to values of 0.62(2) and 0.38(2). Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[v] All reflections were used during refinement. The weighting scheme used was w=1/

$[\sigma^2(F_o^2) + (0.0277P)^2 + 0.4121P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model.   Refinement converged to R1=0.0285 and wR2=0.0658 for 3564 observed reflections for which F > 4σ(F) and R1=0.0315 and wR2=0.0677 and GOF =1.040 for all 3824 unique, non-zero reflections.[vi] The maximum Δ/σ in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were +0.226 and -0.202 e/Å^3.

   Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4.   Tables 5. and 6. list bond distances and bond angles. Figures 1. and 2. are ORTEP[vii] representations of the molecule with 50% probability thermal ellipsoids displayed.
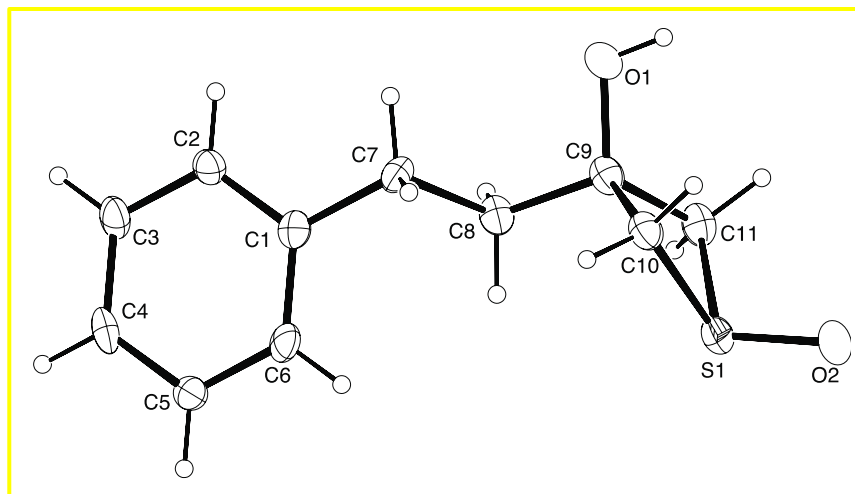
Figure 1. ORTEP drawing of molecule no. 1 of the asymmetric unit with 50% probability thermal ellipsoids.
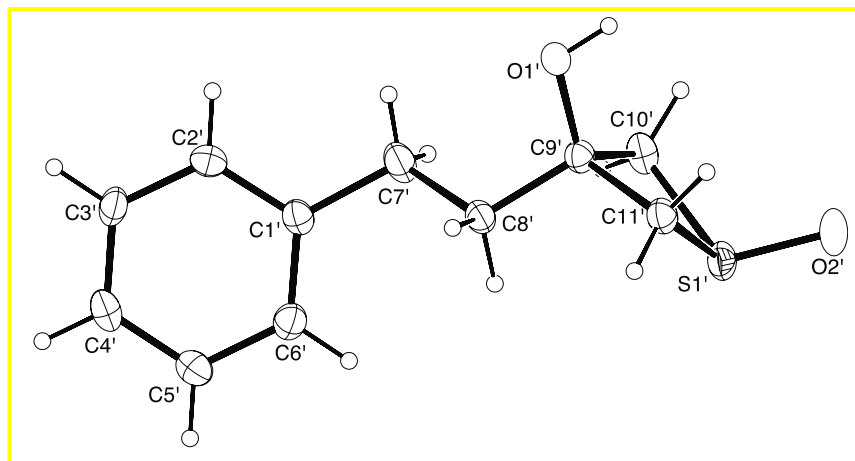
Figure 2. ORTEP drawing of molecule no. 2 of the asymmetric unit with 50% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 1395

Empirical formula	$C_{11}H_{14}SO_2$
Formula weight	210.28
Temperature	100(1) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1$
Cell constants:	
a	12.1555(7) Å
b	5.7786(4) Å
c	15.1633(10) Å
β	98.221(2)°
Volume	1054.15(12) Å^3
Z	4
Density (calculated)	1.325 Mg/m^3
Absorption coefficient	0.278 mm^{-1}
F(000)	448
Crystal size	0.45 x 0.10 x 0.08 mm^3
Theta range for data collection	2.01 to 25.49°
Index ranges	-13 ≤ h ≤ 14, -6 ≤ k ≤ 6, -18 ≤ l ≤ 18
Reflections collected	13556
Independent reflections	3824 [R(int) = 0.0230]
Completeness to theta = 25.49°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6883
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3824 / 3 / 247
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0285, wR2 = 0.0658
R indices (all data)	R1 = 0.0315, wR2 = 0.0677
Absolute structure parameter	-0.02(6)
Largest diff. peak and hole	0.226 and -0.202 e.Å^{-3}

Table 2. Refined Positional Parameters for Compound 1395

Atom	x	y	z	U_{eq}, Å^2
C1	0.8087(4)	0.6284(7)	-0.0627(2)	0.0177(5)
C2	0.8359(5)	0.8205(7)	-0.1110(3)	0.0201(8)
C3	0.9332(5)	0.8203(10)	-0.1498(3)	0.0233(14)
C4	1.0034(4)	0.6281(12)	-0.1403(3)	0.0228(14)
C5	0.9762(5)	0.4361(10)	-0.0921(4)	0.0227(10)
C6	0.8788(5)	0.4362(8)	-0.0532(4)	0.0211(6)
C7	0.7026(4)	0.6286(13)	-0.0204(4)	0.0196(12)
C1*	0.8002(6)	0.6171(14)	-0.0648(4)	0.0177(5)
C2*	0.8100(6)	0.8310(12)	-0.1056(6)	0.0201(8)
C3*	0.9012(7)	0.8762(12)	-0.1493(6)	0.0233(14)
C4*	0.9827(6)	0.7075(16)	-0.1521(5)	0.0228(14)
C5*	0.9729(8)	0.4935(15)	-0.1113(7)	0.0227(10)
C6*	0.8817(8)	0.4483(13)	-0.0677(6)	0.0211(6)
C7*	0.7008(7)	0.568(2)	-0.0173(6)	0.0196(12)
C8	0.73358(15)	0.6034(4)	0.08344(12)	0.0210(4)
C9	0.63520(14)	0.5776(4)	0.13413(12)	0.0207(4)
C10	0.57804(15)	0.3381(4)	0.12158(13)	0.0217(4)
C11	0.67495(16)	0.5414(4)	0.23457(13)	0.0233(4)
O1	0.56460(11)	0.7691(2)	0.11267(9)	0.0262(4)
O2	0.59662(11)	0.1248(3)	0.28563(10)	0.0299(3)
S1	0.66501(4)	0.22644(9)	0.22030(3)	0.02332(13)
C1'	0.16711(14)	1.2456(3)	0.53590(12)	0.0196(4)
C2'	0.16699(16)	1.4423(3)	0.58825(13)	0.0215(4)
C3'	0.09706(16)	1.4617(4)	0.65251(13)	0.0232(4)
C4'	0.02598(16)	1.2821(4)	0.66591(13)	0.0247(5)
C5'	0.02615(15)	1.0836(4)	0.61552(13)	0.0235(4)
C6'	0.09547(15)	1.0663(4)	0.55016(13)	0.0226(4)

C7'	0.24084(17)	1.2384(4)	0.46355(13)	0.0281(5)
C8'	0.30508(15)	1.0129(3)	0.45826(13)	0.0199(4)
C9'	0.38139(15)	1.0189(3)	0.38683(12)	0.0183(4)
C10'	0.31848(16)	1.0152(4)	0.29067(13)	0.0233(4)
C11'	0.43951(15)	0.7842(3)	0.37837(13)	0.0208(4)
O1'	0.45415(10)	1.2082(3)	0.40550(8)	0.0237(3)
O2'	0.39213(11)	0.6410(3)	0.20400(9)	0.0322(4)
S1'	0.33696(4)	0.70170(9)	0.28374(3)	0.02469(13)

$U_{eq}=\frac{1}{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 3. Positional Parameters for Hydrogens in Compound 1395

Atom	x	y	z	U_{iso}, Å^2
H2	0.7891	0.9486	-0.1173	0.027
H3	0.9514	0.9483	-0.1820	0.031
H4	1.0683	0.6280	-0.1662	0.030
H5	1.0229	0.3079	-0.0858	0.030
H6	0.8607	0.3082	-0.0210	0.028
H7a	0.6553	0.5011	-0.0437	0.026
H7b	0.6623	0.7719	-0.0344	0.026
H2*	0.7556	0.9435	-0.1037	0.027
H3*	0.9077	1.0189	-0.1764	0.031
H4*	1.0435	0.7377	-0.1812	0.030
H5*	1.0273	0.3811	-0.1132	0.030
H6*	0.8752	0.3057	-0.0405	0.028
H7a*	0.6759	0.4098	-0.0290	0.026
H7b*	0.6401	0.6709	-0.0394	0.026
H8a	0.7814	0.4694	0.0957	0.028
H8b	0.7760	0.7385	0.1060	0.028
H8a*	0.7902	0.4913	0.1058	0.028
H8b*	0.7652	0.7567	0.0941	0.028
H10a	0.5899	0.2607	0.0670	0.029
H10b	0.4996	0.3420	0.1272	0.029
H11a	0.6242	0.6033	0.2725	0.031
H11b	0.7501	0.5957	0.2537	0.031
H1	0.5125	0.7628	0.1415	0.039
H2'	0.2148	1.5636	0.5801	0.029
H3'	0.0979	1.5955	0.6867	0.031
H4'	-0.0215	1.2953	0.7086	0.033
H5'	-0.0201	0.9609	0.6252	0.031

H6'	0.0938	0.9330	0.5156	0.030
H7a'	0.2937	1.3648	0.4732	0.037
H7b'	0.1951	1.2644	0.4066	0.037
H8a'	0.3492	0.9830	0.5156	0.026
H8b'	0.2527	0.8865	0.4457	0.026
H10a'	0.3557	1.1014	0.2487	0.031
H10b'	0.2413	1.0620	0.2867	0.031
H11a'	0.4390	0.6849	0.4299	0.028
H11b'	0.5142	0.7989	0.3635	0.028
H1'	0.4981	1.2113	0.3693	0.036

Table 4. Refined Thermal Parameters (U's) for Compound 1395

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0189(10)	0.0220(11)	0.0113(9)	-0.0026(8)	-0.0013(8)	-0.0028(8)
C2	0.022(2)	0.0227(12)	0.0159(12)	-0.0014(9)	0.0040(15)	0.0029(13)
C3	0.032(3)	0.020(3)	0.0203(12)	-0.0046(18)	0.013(2)	-0.003(2)
C4	0.020(2)	0.035(4)	0.0151(16)	-0.004(2)	0.0082(15)	-0.004(2)
C5	0.0250(11)	0.032(3)	0.011(3)	0.0014(19)	0.0002(15)	0.0109(17)
C6	0.0291(11)	0.0234(12)	0.0107(19)	0.0010(10)	0.0029(12)	0.0004(9)
C7	0.0200(10)	0.020(4)	0.0183(11)	0.0055(16)	0.0020(8)	-0.0017(16)
C1*	0.0189(10)	0.0220(11)	0.0113(9)	-0.0026(8)	-0.0013(8)	-0.0028(8)
C2*	0.022(2)	0.0227(12)	0.0159(12)	-0.0014(9)	0.0040(15)	0.0029(13)
C3*	0.032(3)	0.020(3)	0.0203(12)	-0.0046(18)	0.013(2)	-0.003(2)
C4*	0.020(2)	0.035(4)	0.0151(16)	-0.004(2)	0.0082(15)	-0.004(2)
C5*	0.0250(11)	0.032(3)	0.011(3)	0.0014(19)	0.0002(15)	0.0109(17)
C6*	0.0291(11)	0.0234(12)	0.0107(19)	0.0010(10)	0.0029(12)	0.0004(9)
C7*	0.0200(10)	0.020(4)	0.0183(11)	0.0055(16)	0.0020(8)	-0.0017(16)
C8	0.0176(8)	0.0270(10)	0.0182(10)	-0.0015(8)	0.0020(7)	-0.0015(8)
C9	0.0174(9)	0.0260(11)	0.0187(10)	-0.0027(8)	0.0029(7)	-0.0004(8)
C10	0.0177(9)	0.0270(11)	0.0211(10)	-0.0012(9)	0.0046(8)	0.0006(8)
C11	0.0226(9)	0.0291(12)	0.0190(10)	-0.0032(8)	0.0050(8)	-0.0024(8)
O1	0.0252(7)	0.0269(9)	0.0281(8)	0.0006(6)	0.0097(6)	0.0057(6)
O2	0.0289(7)	0.0325(8)	0.0317(8)	0.0039(7)	0.0164(6)	0.0006(6)
S1	0.0200(2)	0.0284(3)	0.0232(2)	0.0021(2)	0.00854(18)	0.0028(2)
C1'	0.0212(9)	0.0207(10)	0.0174(9)	0.0036(8)	0.0044(7)	0.0050(8)
C2'	0.0227(9)	0.0203(10)	0.0217(10)	0.0037(8)	0.0034(8)	-0.0010(8)
C3'	0.0317(11)	0.0206(10)	0.0177(10)	-0.0043(8)	0.0053(8)	0.0039(8)
C4'	0.0245(10)	0.0318(12)	0.0191(10)	0.0012(8)	0.0080(8)	0.0049(8)
C5'	0.0214(9)	0.0270(11)	0.0225(10)	0.0017(9)	0.0046(8)	-0.0025(9)
C6'	0.0268(10)	0.0210(11)	0.0200(10)	-0.0013(8)	0.0031(8)	0.0016(8)

C7'	0.0361(10)	0.0253(11)	0.0266(11)	0.0077(10)	0.0169(9)	0.0108(10)
C8'	0.0227(9)	0.0197(10)	0.0187(10)	0.0017(8)	0.0073(8)	0.0021(8)
C9'	0.0185(9)	0.0186(10)	0.0183(10)	0.0003(8)	0.0039(8)	0.0020(8)
C10'	0.0226(9)	0.0291(11)	0.0188(10)	0.0003(8)	0.0052(8)	0.0055(8)
C11'	0.0215(9)	0.0215(11)	0.0204(10)	0.0005(8)	0.0063(8)	0.0032(7)
O1'	0.0271(7)	0.0219(7)	0.0246(7)	-0.0044(7)	0.0128(5)	-0.0041(7)
O2'	0.0275(7)	0.0416(10)	0.0298(8)	-0.0181(7)	0.0124(6)	-0.0053(6)
S1'	0.0203(2)	0.0295(3)	0.0261(3)	-0.0104(2)	0.00961(18)	-0.0041(2)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 5. Bond Distances in Compound 1395, Å

C1-C6	1.3950	C1-C2	1.3951	C1-C7	1.5201
C2-C3	1.3949	C3-C4	1.3950	C4-C5	1.3950
C5-C6	1.3950	C7-C8	1.572(6)	C1*-C6*	1.3950
C1*-C2*	1.3951	C1*-C7*	1.5200	C2*-C3*	1.3951
C3*-C4*	1.3950	C4*-C5*	1.3950	C5*-C6*	1.3951
C7*-C8	1.536(9)	C8-C9	1.519(2)	C9-O1	1.410(2)
C9-C11	1.545(3)	C9-C10	1.548(3)	C10-S1	1.823(2)
C11-S1	1.835(2)	O2-S1	1.5010(14)	C1'-C2'	1.386(3)
C1'-C6'	1.390(3)	C1'-C7'	1.513(2)	C2'-C3'	1.386(3)
C3'-C4'	1.384(3)	C4'-C5'	1.378(3)	C5'-C6'	1.393(3)
C7'-C8'	1.527(3)	C8'-C9'	1.524(2)	C9'-O1'	1.409(2)
C9'-C11'	1.543(3)	C9'-C10'	1.547(3)	C10'-S1'	1.830(2)
C11'-S1'	1.824(2)	O2'-S1'	1.5056(13)		

Table 6. Bond Angles in Compound 1395, °

C6-C1-C2	120.0	C6-C1-C7	120.0	C2-C1-C7	120.0
C3-C2-C1	120.0	C2-C3-C4	120.0	C5-C4-C3	120.0
C4-C5-C6	120.0	C5-C6-C1	120.0	C1-C7-C8	109.0(2)
C6*-C1*-C2*	120.0	C6*-C1*-C7*	120.0	C2*-C1*-C7*	120.0
C1*-C2*-C3*	120.0	C4*-C3*-C2*	120.0	C3*-C4*-C5*	120.0
C4*-C5*-C6*	120.0	C1*-C6*-C5*	120.0	C1*-C7*-C8	109.6(4)
C9-C8-C7*	112.3(3)	C9-C8-C7	115.0(2)	C7*-C8-C7	13.1(6)
O1-C9-C8	107.67(16)	O1-C9-C11	115.34(15)	C8-C9-C11	110.75(14)
O1-C9-C10	115.20(14)	C8-C9-C10	113.44(16)	C11-C9-C10	94.12(15)
C9-C10-S1	91.04(12)	C9-C11-S1	90.68(12)	O2-S1-C10	111.70(9)

O2-S1-C11	110.11(9)	C10-S1-C11	76.49(9)	C2'-C1'-C6'	118.03(16)
C2'-C1'-C7'	119.13(18)	C6'-C1'-C7'	122.79(18)	C3'-C2'-C1'	121.31(18)
C4'-C3'-C2'	120.08(18)	C5'-C4'-C3'	119.48(17)	C4'-C5'-C6'	120.20(19)
C1'-C6'-C5'	120.87(18)	C1'-C7'-C8'	114.94(17)	C9'-C8'-C7'	112.69(15)
O1'-C9'-C8'	107.64(15)	O1'-C9'-C11'	114.65(14)	C8'-C9'-C11'	111.81(15)
O1'-C9'-C10'	114.29(15)	C8'-C9'-C10'	113.62(15)	C11'-C9'-C10'	94.59(15)
C9'-C10'-S1'	91.12(12)	C9'-C11'-S1'	91.47(12)	O2'-S1'-C11'	111.09(8)
O2'-S1'-C10'	110.45(9)	C11'-S1'-C10'	76.82(9)		

[i]Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

[ii]Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.

[iii]Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.

[iv]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[v]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[vi]$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$
$wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$
$GOF = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$
where n = the number of reflections and p = the number of parameters refined.

[vii]"ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

X-ray Structure Determination of Compound 1398 (compound 6 in the manuscript, CCDC 1543001)
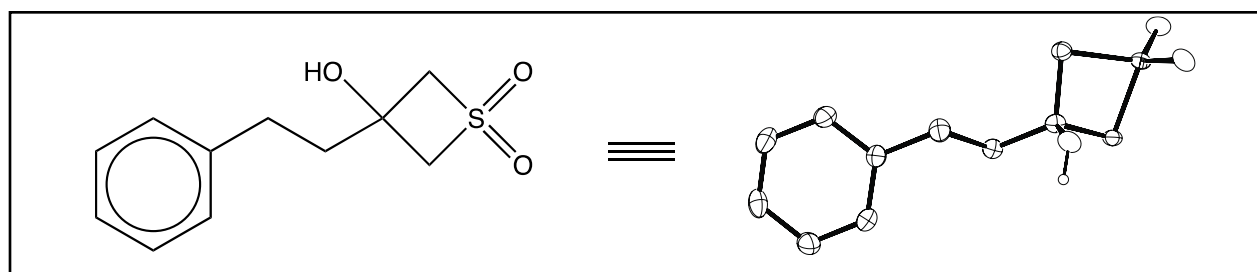
Compound 1398, $C_{11}H_{14}SO_3$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=5.9892(2)Å, b=8.7813(2)Å, c=20.9331(6)Å, V=1100.93(5)Å^3, Z=4, and d_{calc}=1.365 g/cm^3 . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 100(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 842 frames were collected with a crystal to detector distance of 37.4 mm, rotation widths of 0.5° and exposures of 10 seconds:

scan type	2θ	ω	ϕ	χ	frames
ϕ	-23.00	315.83	12.48	28.88	739
ω	12.00	322.46	290.21	72.15	103

Rotation frames were integrated using SAINT[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the SHELXTL[ii] program package for further processing and structure solution. A total of 7905 reflections were measured over the ranges $1.95 \leq \theta \leq 25.38°$, $-7 \leq h \leq 7$, $-10 \leq k \leq 10$, $-25 \leq l \leq 25$ yielding 2016 unique reflections (Rint = 0.0141). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[iii] (minimum and maximum transmission 0.6855, 0.7452).

The structure was solved by direct methods (SHELXS-97[iv]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[v] All reflections were used during refinement. The weighting scheme used was w=1/[$\sigma^2(F_o^2)$+ (0.0296P)^2 + 0.2886P] where P = (F_o^2 + 2F_c^2)/3. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement

converged to R1=0.0210 and wR2=0.0560 for 1992 observed reflections for which F > 4σ(F) and R1=0.0214 and wR2=0.0565 and GOF =1.105 for all 2016 unique, non-zero reflections and 138 variables.[vi] The maximum Δ/σ in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were +0.224 and -0.254 e/$Å^3$.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4. Tables 5. and 6. list bond distances and bond angles. Figure 1. is an ORTEP[vii] representation of the molecule with 50% probability thermal ellipsoids displayed.

Figure 1. ORTEP drawing of the title compound with 50% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 1398

Empirical formula	$C_{11}H_{14}SO_3$
Formula weight	226.28
Temperature	100(1) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell constants:	
a	5.9892(2) Å
b	8.7813(2) Å
c	20.9331(6) Å
Volume	1100.93(5) $Å^3$
Z	4
Density (calculated)	1.365 Mg/m^3
Absorption coefficient	0.278 mm^{-1}
F(000)	480
Crystal size	0.42 x 0.18 x 0.05 mm^3
Theta range for data collection	1.95 to 25.38°
Index ranges	$-7 \le h \le 7$, $-10 \le k \le 10$, $-25 \le l \le 25$
Reflections collected	7905
Independent reflections	2016 [R(int) = 0.0141]
Completeness to theta = 25.38°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6855
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2016 / 0 / 138
Goodness-of-fit on F^2	1.105
Final R indices [I>2sigma(I)]	R1 = 0.0210, wR2 = 0.0560
R indices (all data)	R1 = 0.0214, wR2 = 0.0565
Absolute structure parameter	0.00(6)
Largest diff. peak and hole	0.224 and -0.254 $e.Å^{-3}$

Table 2. Refined Positional Parameters for Compound 1398

Atom	x	y	z	U_{eq}, Å^2
C1	0.8559(2)	0.16336(16)	0.78347(7)	0.0192(3)
C2	0.6675(3)	0.25350(19)	0.79194(7)	0.0287(4)
C3	0.5105(3)	0.2699(2)	0.74412(8)	0.0308(4)
C4	0.5398(3)	0.19669(19)	0.68591(7)	0.0273(4)
C5	0.7275(3)	0.10957(18)	0.67641(7)	0.0289(4)
C6	0.8848(3)	0.09278(18)	0.72479(7)	0.0245(3)
C7	1.0293(3)	0.14707(18)	0.83546(7)	0.0230(3)
C8	0.9357(2)	0.09075(16)	0.89951(6)	0.0173(3)
C9	1.1165(2)	0.08233(16)	0.95030(7)	0.0162(3)
C10	1.0404(2)	0.02169(15)	1.01706(7)	0.0162(3)
C11	1.2983(3)	-0.04096(15)	0.93854(6)	0.0184(3)
O1	1.22940(16)	0.22355(10)	0.95765(5)	0.0203(2)
O2	1.27673(18)	-0.23750(11)	1.04033(5)	0.0231(2)
O3	1.46645(18)	0.00883(11)	1.05480(5)	0.0240(2)
S1	1.29743(6)	-0.07990(4)	1.022376(15)	0.01651(9)

$U_{eq}=\frac{1}{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 3. Positional Parameters for Hydrogens in Compound 1398

Atom	x	y	z	U_{iso}, Å^2
H2	0.6467	0.3038	0.8306	0.038
H3	0.3850	0.3301	0.7509	0.041
H4	0.4336	0.2065	0.6538	0.036
H5	0.7495	0.0615	0.6373	0.038
H6	1.0110	0.0334	0.7177	0.033

H7a	1.1004	0.2450	0.8421	0.031
H7b	1.1432	0.0764	0.8211	0.031
H8a	0.8188	0.1593	0.9137	0.023
H8b	0.8703	-0.0094	0.8938	0.023
H10a	0.9096	-0.0433	1.0155	0.022
H10b	1.0235	0.1007	1.0491	0.022
H11a	1.4386	-0.0004	0.9229	0.024
H11b	1.2479	-0.1256	0.9125	0.024
H1	1.1376	0.2924	0.9607	0.030

Table 4.   Refined Thermal Parameters (U's) for Compound 1398

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0202(7)	0.0196(7)	0.0176(7)	0.0030(6)	0.0022(6)	-0.0034(6)
C2	0.0326(9)	0.0359(9)	0.0176(7)	-0.0025(7)	0.0020(6)	0.0078(8)
C3	0.0266(8)	0.0411(9)	0.0246(8)	0.0045(7)	0.0033(6)	0.0103(7)
C4	0.0267(8)	0.0370(9)	0.0183(7)	0.0069(6)	-0.0024(6)	-0.0063(8)
C5	0.0331(9)	0.0353(9)	0.0183(7)	-0.0045(6)	0.0022(6)	-0.0014(8)
C6	0.0243(7)	0.0265(8)	0.0226(7)	-0.0009(6)	0.0039(6)	0.0025(7)
C7	0.0191(7)	0.0284(8)	0.0214(7)	0.0021(6)	0.0016(6)	-0.0025(6)
C8	0.0170(7)	0.0152(6)	0.0197(7)	-0.0006(6)	-0.0004(5)	-0.0021(6)
C9	0.0155(6)	0.0125(6)	0.0205(7)	-0.0017(6)	0.0002(5)	-0.0029(6)
C10	0.0151(6)	0.0149(6)	0.0187(7)	-0.0019(5)	-0.0001(6)	0.0030(5)
C11	0.0181(6)	0.0179(6)	0.0191(6)	0.0007(5)	0.0020(6)	0.0008(6)
O1	0.0193(5)	0.0122(4)	0.0293(5)	0.0006(4)	-0.0043(4)	-0.0036(4)
O2	0.0272(5)	0.0149(5)	0.0273(5)	0.0032(4)	0.0037(4)	0.0043(4)
O3	0.0221(5)	0.0214(5)	0.0286(5)	0.0015(4)	-0.0068(4)	0.0010(4)
S1	0.01653(16)	0.01331(15)	0.01968(16)	0.00049(13)	0.00024(14)	0.00224(14)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 5. Bond Distances in Compound 1398, Å

C1-C6	1.387(2)	C1-C2	1.390(2)	C1-C7	1.511(2)		
C2-C3	1.381(2)	C3-C4	1.389(2)	C4-C5	1.374(2)		
C5-C6	1.391(2)	C7-C8	1.5351(19)	C8-C9	1.5192(18)		
C9-O1	1.4208(16)	C9-C11	1.5549(19)	C9-C10	1.5634(19)		
C10-S1	1.7826(13)	C11-S1	1.7880(14)	O2-S1	1.4394(10)		

O3-S1	1.4466(11)

Table 6. Bond Angles in Compound 1398, °

C6-C1-C2	117.96(14)	C6-C1-C7	120.65(14)	C2-C1-C7	121.34(13)
C3-C2-C1	121.33(14)	C2-C3-C4	120.11(16)	C5-C4-C3	119.21(15)
C4-C5-C6	120.51(14)	C1-C6-C5	120.86(15)	C1-C7-C8	114.12(12)
C9-C8-C7	111.52(11)	O1-C9-C8	111.86(12)	O1-C9-C11	106.96(11)
C8-C9-C11	114.97(11)	O1-C9-C10	109.83(11)	C8-C9-C10	115.75(11)
C11-C9-C10	96.22(10)	C9-C10-S1	88.54(8)	C9-C11-S1	88.61(9)
O2-S1-O3	117.11(6)	O2-S1-C10	115.03(7)	O3-S1-C10	111.35(6)
O2-S1-C11	116.13(6)	O3-S1-C11	110.82(7)	C10-S1-C11	81.11(7)

[i]Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

[ii]Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.

[iii]Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.

[iv]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[v]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

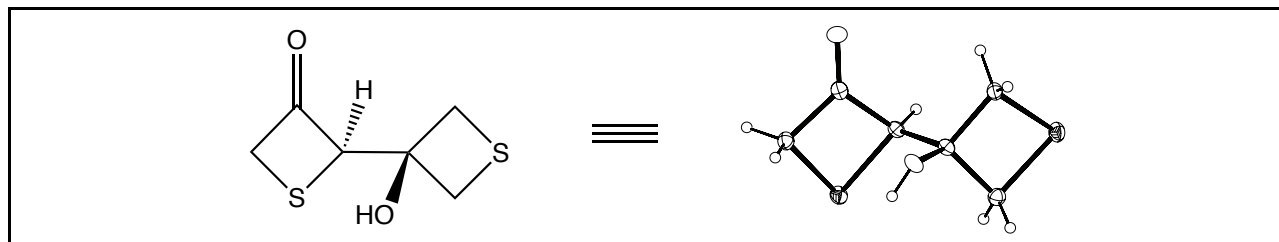[vi]$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$
$wR2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$
$GOF = [\Sigma w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2}$
where n = the number of reflections and p = the number of parameters refined.

[vii]"ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

X-ray Structure Determination of Compound 1405 (compound 17 in the manuscript, CCDC 1543002)

Compound 1405, $C_6H_8S_2O_2$, crystallizes in the monoclinic space group $P2_1/c$ (systematic absences 0k0: k=odd and h0l: l=odd) with a=14.3735(4)Å, b=5.1523(2)Å, c=10.0932(3)Å, β=101.9260(10)°, V=731.33(4)Å^3, Z=4, and d_{calc}=1.601 g/cm^3 . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 100(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 1895 frames were collected with a crystal to detector distance of 59.8 mm, rotation widths of 0.5° and exposures of 5seconds:

scan type	2θ	ω	φ	χ	frames
φ	-23.00	334.99	345.26	-33.72	739
φ	32.00	33.96	343.46	-56.95	715
φ	32.00	13.64	203.15	70.63	69
ω	-30.50	311.33	246.51	-76.00	106
φ	-30.50	357.57	326.35	-66.87	266

Rotation frames were integrated using SAINT[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the SHELXTL[ii] program package for further processing and structure solution. A total of 6083 reflections were measured over the ranges $1.45 \le \theta \le 25.37°$, $-17 \le h \le 16$, $-6 \le k \le 6$, $-12 \le l \le 12$ yielding 1341 unique reflections (Rint = 0.0173). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[iii] (minimum and maximum transmission 0.6631, 0.7452).

The structure was solved by direct methods (SHELXS-97[iv]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[v] All reflections were used during refinement. The weighting scheme used was w=1/[$\sigma^2(F_o^2$)+ (0.0266P)^2 + 0.4240P] where P = (F_o^2 + 2F_c^2)/3. Non-hydrogen atoms

were refined anisotropically and hydrogen atoms were refined using a riding model.   Refinement converged to R1=0.0214 and wR2=0.0559 for 1309 observed reflections for which F > 4σ(F) and R1=0.0218 and wR2=0.0562 and GOF =1.107 for all 1341 unique, non-zero reflections and 93 variables.[vi] The maximum Δ/σ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.334 and -0.207 e/Å^3.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4.   Tables 5. and 6. list bond distances and bond angles.   Figure 1. is an ORTEP[vii] representation of the molecule with 50% probability thermal ellipsoids displayed.
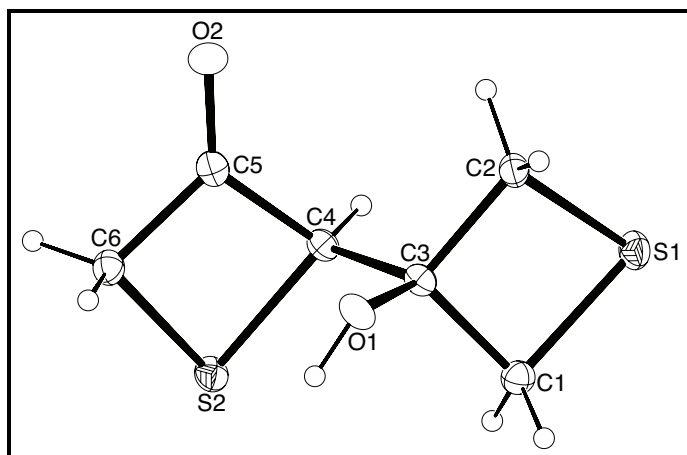

Figure 1. ORTEP drawing of the title compound with 50% probability thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 1405

Empirical formula	$C_6H_8S_2O_2$
Formula weight	176.24
Temperature	100(1) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1/c$
Cell constants:	
a	14.3735(4) Å
b	5.1523(2) Å
c	10.0932(3) Å
β	101.9260(10)°
Volume	731.33(4) Å^3
Z	4
Density (calculated)	1.601 Mg/m^3
Absorption coefficient	0.658 mm^{-1}
F(000)	368
Crystal size	0.30 x 0.20 x 0.10 mm^3
Theta range for data collection	1.45 to 25.37°
Index ranges	$-17 \leq h \leq 16, -6 \leq k \leq 6, -12 \leq l \leq 12$
Reflections collected	6083
Independent reflections	1341 [R(int) = 0.0173]
Completeness to theta = 25.37°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.6631
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1341 / 0 / 93
Goodness-of-fit on F^2	1.107
Final R indices [I>2sigma(I)]	R1 = 0.0214, wR2 = 0.0559
R indices (all data)	R1 = 0.0218, wR2 = 0.0562
Largest diff. peak and hole	0.334 and -0.207 e.Å^{-3}

Table 2. Refined Positional Parameters for Compound 1405

Atom	x	y	z	U_{eq}, Å^2
S1	0.44857(2)	0.64811(7)	0.33834(3)	0.01537(12)
S2	0.12809(2)	0.72352(6)	0.11893(3)	0.01427(12)
O1	0.26774(7)	0.23925(17)	0.14394(9)	0.0135(2)
O2	0.14053(7)	0.2708(2)	0.38995(10)	0.0192(2)
C1	0.36656(9)	0.6438(3)	0.17275(13)	0.0135(3)
C2	0.37178(9)	0.3699(3)	0.35414(13)	0.0128(3)
C3	0.29975(9)	0.4567(3)	0.22695(12)	0.0112(3)
C4	0.21525(9)	0.5978(3)	0.26529(12)	0.0119(3)
C5	0.14028(9)	0.4069(3)	0.29359(12)	0.0129(3)
C6	0.06365(9)	0.4417(3)	0.16724(12)	0.0139(3)

$U_{eq}={}^1/_3[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 3. Positional Parameters for Hydrogens in Compound 1405

Atom	x	y	z	U_{iso}, Å^2
H1	0.2334	0.2886	0.0732	0.018
H1a	0.3381	0.8114	0.1459	0.018
H1b	0.3941	0.5698	0.1012	0.018
H2a	0.4010	0.2035	0.3438	0.017
H2b	0.3464	0.3732	0.4360	0.017
H4	0.2342	0.7264	0.3373	0.016
H6a	0.0019	0.4847	0.1857	0.019
H6b	0.0589	0.2976	0.1043	0.019

Table 4. Refined Thermal Parameters (U's) for Compound 1405

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	0.01298(19)	0.0147(2)	0.01739(19)	-0.00025(12)	0.00067(13)	-0.00293(13)
S2	0.01358(19)	0.01150(19)	0.01701(19)	0.00280(12)	0.00151(13)	0.00198(12)
O1	0.0153(5)	0.0108(5)	0.0129(5)	-0.0024(3)	-0.0006(4)	0.0013(4)
O2	0.0187(5)	0.0234(6)	0.0150(5)	0.0036(4)	0.0023(4)	-0.0047(4)
C1	0.0133(6)	0.0137(7)	0.0136(6)	0.0014(5)	0.0030(5)	0.0008(5)
C2	0.0118(6)	0.0119(6)	0.0142(6)	0.0014(5)	0.0014(5)	-0.0004(5)
C3	0.0122(6)	0.0092(6)	0.0119(6)	-0.0012(5)	0.0017(5)	-0.0001(5)
C4	0.0128(6)	0.0106(6)	0.0117(6)	0.0000(5)	0.0013(5)	0.0009(5)
C5	0.0126(6)	0.0120(6)	0.0142(6)	-0.0032(5)	0.0029(5)	0.0012(5)
C6	0.0125(6)	0.0130(7)	0.0159(6)	0.0008(5)	0.0020(5)	0.0000(5)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 5. Bond Distances in Compound 1405, Å

S1-C1	1.8355(13)	S1-C2	1.8361(13)	S2-C6	1.8413(14)
S2-C4	1.8457(12)	O1-C3	1.4175(15)	O2-C5	1.1985(16)
C1-C3	1.5389(17)	C2-C3	1.5395(17)	C3-C4	1.5324(17)
C4-C5	1.5286(18)	C5-C6	1.5136(17)		

Table 6. Bond Angles in Compound 1405, °

C1-S1-C2	77.59(6)	C6-S2-C4	78.85(6)	C3-C1-S1	90.82(8)
C3-C2-S1	90.78(8)	O1-C3-C4	110.29(10)	O1-C3-C1	115.80(10)
C4-C3-C1	112.20(11)	O1-C3-C2	110.10(10)	C4-C3-C2	111.02(10)
C1-C3-C2	96.71(10)	C5-C4-C3	111.60(11)	C5-C4-S2	89.27(8)
C3-C4-S2	114.00(8)	O2-C5-C6	129.24(12)	O2-C5-C4	130.09(12)
C6-C5-C4	100.65(10)	C5-C6-S2	89.89(8)		

[i]Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

[ii]Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.

[iii]Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.

[iv]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[v]Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.

[vi]$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$
$wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$
$GOF = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$
where n = the number of reflections and p = the number of parameters refined.

[vii]"ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

RBL-1 Cell PG and LT Assay

Inhibition of PG and LT synthesis by test compounds was determined through the utilization of an established RBL-1 cell assay.[4] RBL-1 cells (ATCC) were grown in RPMI 1640 medium (Mediatech Inc., Manassas, VA) with 10% fetal bovine serum (FBS) (Atlanta Biologicals, Lawrenceville, GA), 1 mM L-glutamine (Mediatech), 50 U/mL penicillin, and 0.05 mg/mL streptomycin (Thermo Fisher Scientific). For assessment of compound activity, RBL-1 cells were plated at a density of 9 x 10^5 cells/well in 24-well plates and after 2 h incubation at 37 ˚C, cells were treated with the indicated concentrations of test compounds. After a 2 h incubation with compounds, cells were treated with 12 µM calcium ionophore, A23187, for 15 min to induce arachidonic acid formation. Culture supernatants (200 µL/well) were collected and treated with 0.6 ml of MeOH containing 0.01% BHT (Butylated Hydroxytoluene) to extract eicosanoids. After centrifugation in a microfuge, the supernatant was dried by vacuum centrifugation and dissolved in 0.2 ml of 50% acetonitrile. Enzyme products were quantified with an Acquity UPLC-TQ MS system (Waters Corporation, Milford, MA). Injections (10 µL) were separated on an Acquity BEH C18, 1.7 µm, 2.1 x 50 mm column at 37 ˚C using a gradient from 5 to 95% acetonitrile with 10 mM ammonium formate over 2 min at 0.6 mL/min. Combined PGD_2+PGE_2, as well as LTB_4, were detected in negative ion mode using compound specific collision induced mass transitions (PGD_2 and PGE_2: 351 > 315, LTB_4: 335 > 195). To separate the isomeric PGD_2 and PGE_2, a gradient from 5 to 60% acetonitrile over 3 min at 0.6 mL/min was used. The cysteinyl leukotriene LTC_4 was separated using a gradient from 5 to 95% acetonitrile with 0.1% formic acid over 2 min at 0.6 mL/min. LTC_4 was detected using electrospray ionization in positive mode while monitoring for a compound specific mass transition (626 > 189). Chromatograms are integrated and peak areas used to quantitate unknowns against a curve of standards (Cayman Chemical, Ann Arbor, MI) from 1 to 50 ng/mL in 50% acetonitrile. The IC_{50} values and 95% confidence intervals of compound concentration-response curves were determined in GraphPad Prism from triplicate samples at each concentration using a sigmoidal fit allowing for variable slope.

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[4] Tries, S.; Neupert, W.; Laufer, S. The mechanism of action of the new antiinflammatory compound ML3000: inhibition of 5-LOX and COX-1/2. *Inflammation Res*. **2002**, *51*, 135–143.

Supplemental Table 1. Inhibitory activity of ibuprofen isosteres for multiple COX- and 5-LOX pathway eicosanoids (data expressed as % inhibition).

| Compound	PGE2 (100 μM cmpd)	PGD2 (100 μM cmpd)	LTB4 (50 μM cmpd)	LTC4 (50 μM cmpd)
7	79 ± 4	88 ± 4	96 ± 1	99 ± 1
8	40 ± 10	70 ± 20	98 ± 1	96 ± 4
9	70 ± 10	89 ± 5	92 ± 2	98 ± 2
10	95 ± 2	99 ± 2	86 ± 1	92 ± 4
17	89 ± 6	92 ± 1	18 ± 7	30 ± 20
18	60 ± 20	80 ± 8	30 ± 10	60 ± 10
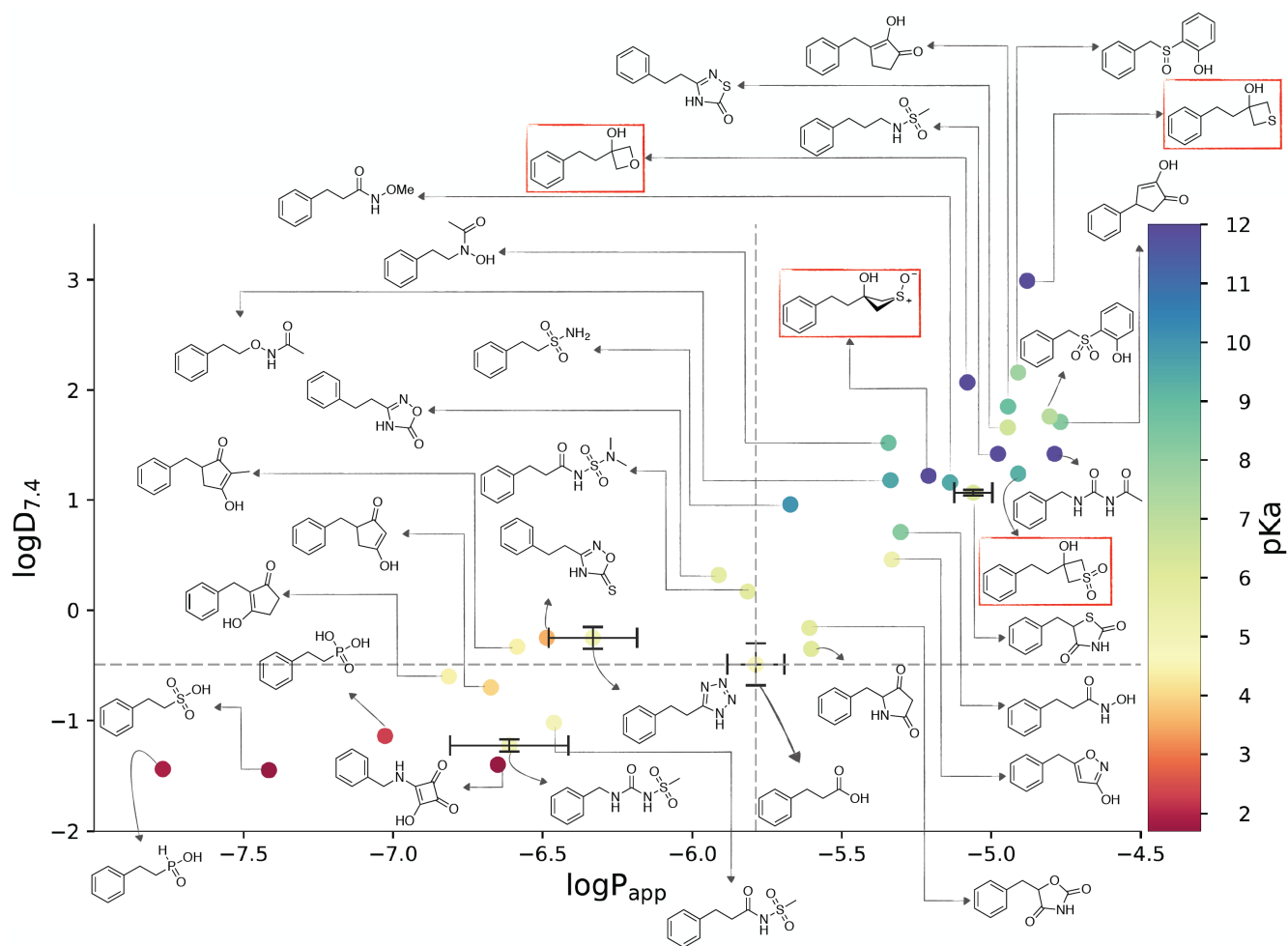
Supplemental Figure 1. Comparison of physicochemical properties of phenylpropionic acid derivatives **3–6** (compounds shown in red boxes), with a set of corresponding model compounds bearing other known carboxylic acid bio-isosteres that had been previously tested in the same assays and under identical assay conditions (Lassalas, *et al*. J. Med. Chem., **2016**, *59*, 3183-203).

Docking Studies

Docking studies were conducted employing the COX-1 crystal structure (PDB code:1EQG). Each ibuprofen derivate (**7–10**, enantiomer S and R) and (S)-ibuprofen was evaluated using the MOE docking induced fit protocol (*Molecular Operating Environment (MOE)*, 2013.08; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, **2017**). Ligand poses were ranked according to (i) their calculated docking binding energy relative to that of ibuprofen (-8.27 kcal/mol) and (ii) the proximity of the four membered ring heterocycle to Arg120 and or Tyr355. Selected plausible poses are shown for each ibuprofen derivate (**7–10**).
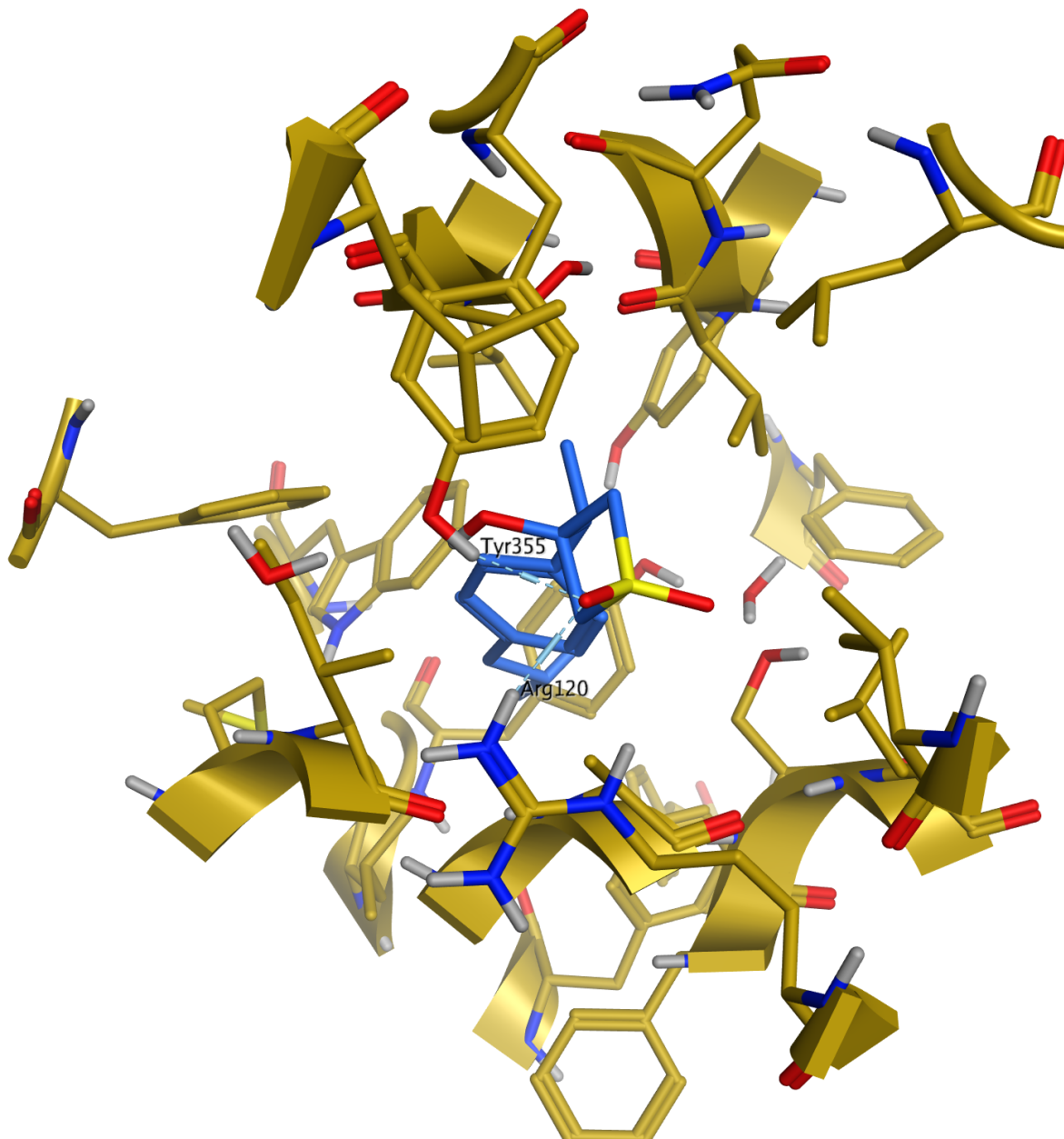
Tyr355

Arg120
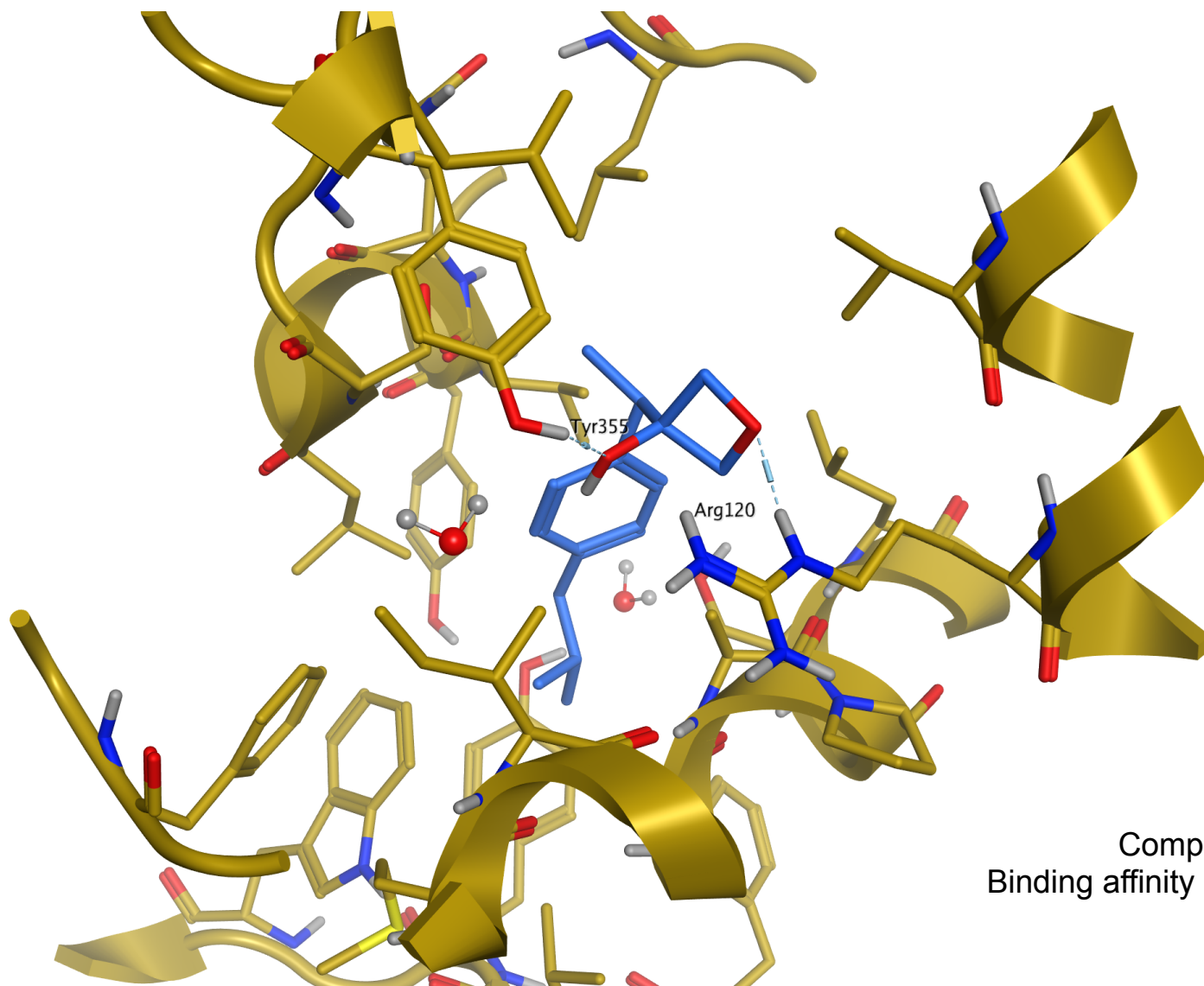
Compound **7**
Binding affinity = -8.00 kcal/mol
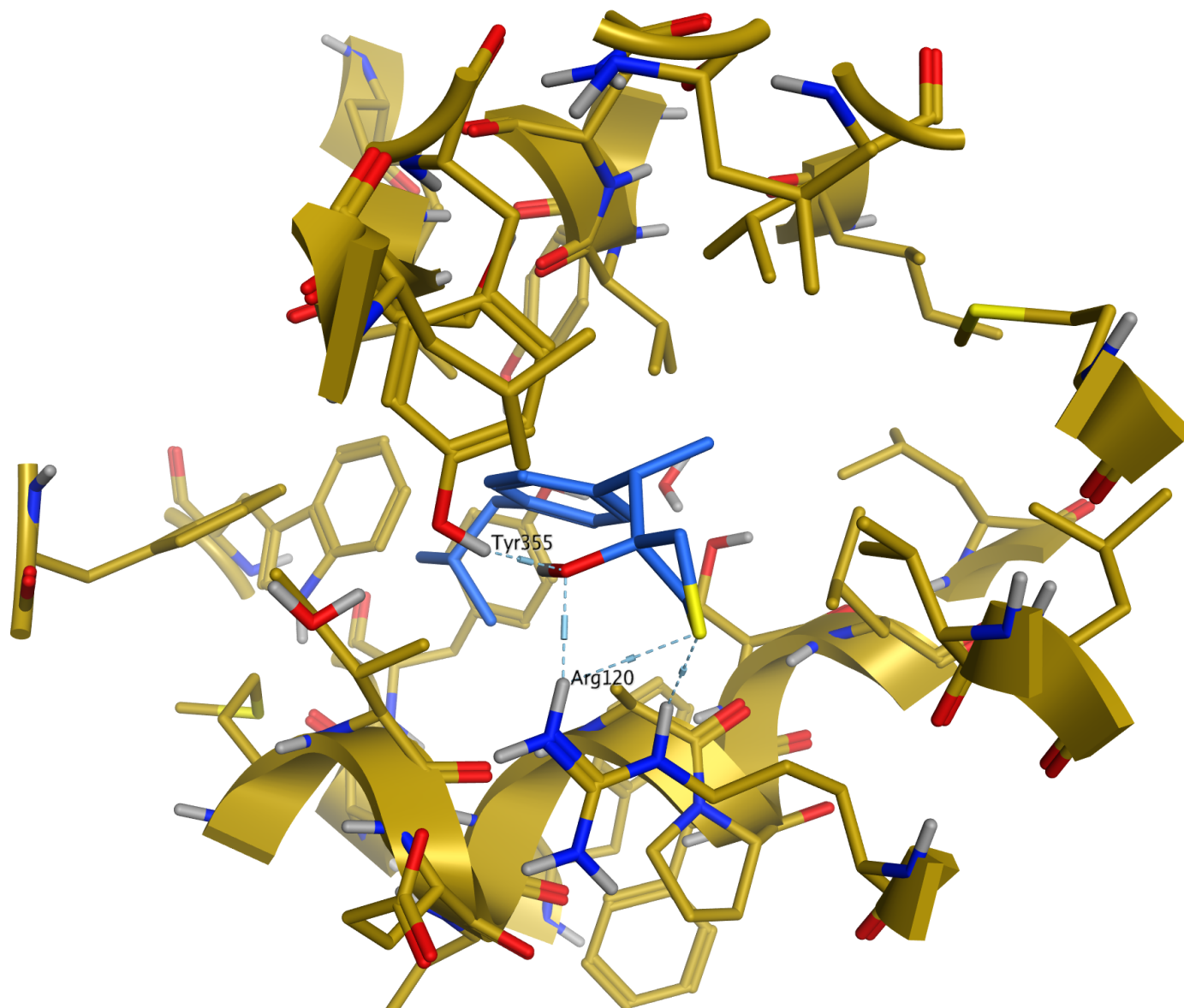
Compound **8**
Binding affinity = -8.00 kcal/mol
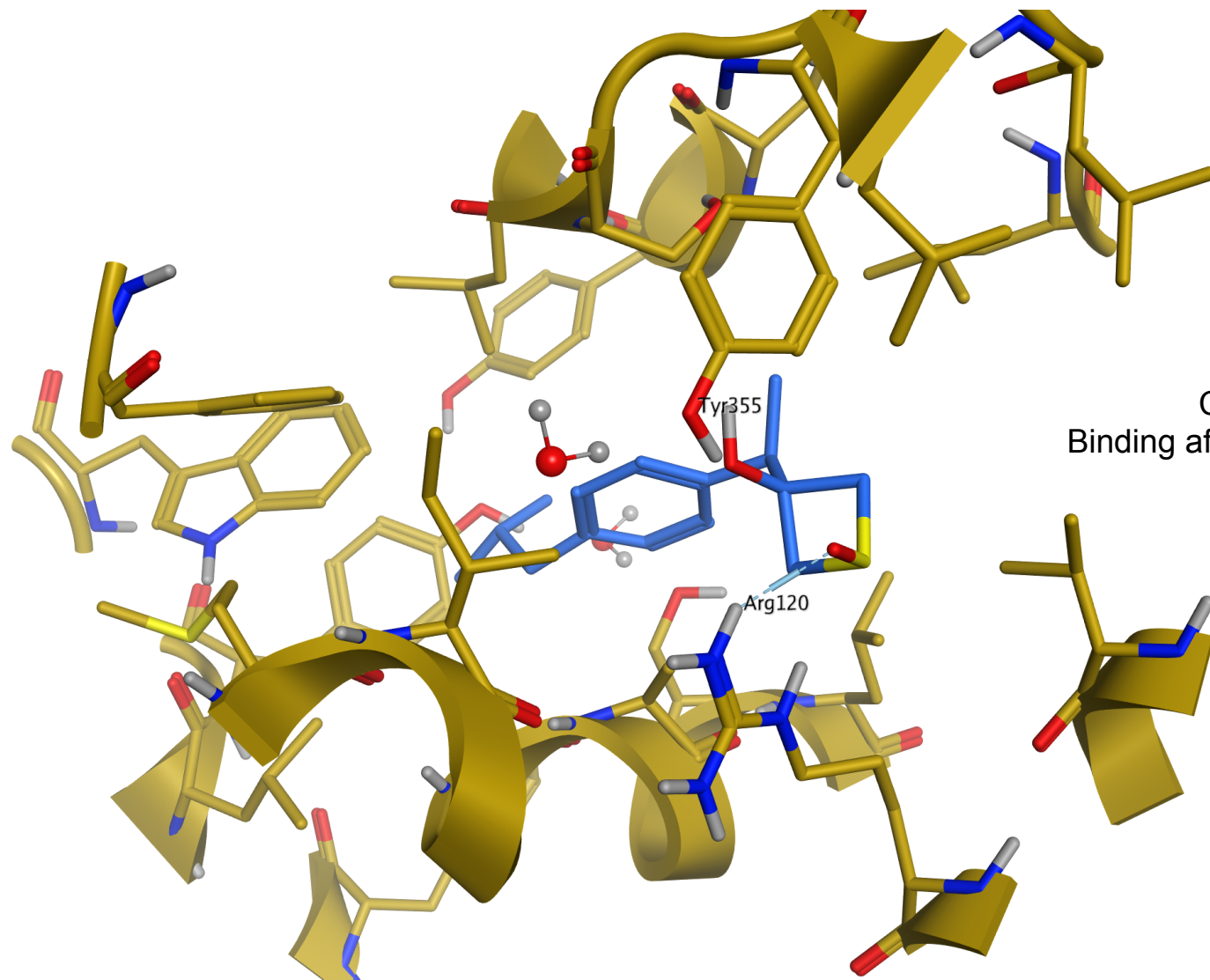
Compound **9**
Binding affinity = -8.11 kcal/mol

Tyr355

Arg120

Compound **10**
Binding affinity = -8.05 kcal/mol