

## Synthesis of Rigidified Shikimic Acid Derivatives by Ring-Closing Metathesis to Imprint Inhibitor Efficacy against Shikimate Kinase Enzyme

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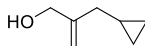
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## 1. PREPARATION OF ALCOHOLS 18, 20 AND 21



18

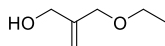
### Preparation of 2-(cyclopropylmethyl)prop-2-en-1-ol (18) from diethyl malonate (22)

**(a) Diethyl 2-(cyclopropylmethyl)malonate.** A solution of diethyl malonate (**22**) (0.29 mL, 1.71 mmol) in dry THF (3 mL), at 0 °C and under argon, was treated with NaH (75 mg, 1.87 mmol, *ca* 60% in mineral oil). The resultant mixture was stirred at room temperature for 30 min, and then cooled to 0 °C. Cyclopropylmethyl bromide (0.21 mL, 2.20 mmol) was then added and the reaction mixture was first stirred at room temperature for 1 h and then heated under reflux for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure and the crude was dissolved in a mixture of diethyl ether and saturated NH<sub>4</sub>Cl. The organic layer was separated and the aqueous layer was extracted with diethyl ether (×2). The combined organic extracts were washed with brine, dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography, eluting with (5:95) ethyl acetate/hexane, to give diethyl 2-(cyclopropylmethyl)malonate (245 mg, 67%) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 4.14 (q, *J* = 6.6 Hz, 4H, 2×CH<sub>2</sub>), 3.38 (t, *J* = 7.7 Hz, 1H, CH), 1.74 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 1.21 (t, *J* = 7.1 Hz, 6H, 2×CH<sub>3</sub>), 0.73–0.61 (m, 1H, CH<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>), 0.42–0.36 (m, 2H, cPr) and 0.06–0.01 (m, 2H, cPr) ppm.

**(b) 2-(Cyclopropylmethyl)malonic acid.** A solution of diethyl 2-(cyclopropylmethyl)malonate (1.357 g, 6.34 mmol) in NaOH (8.5 mL, 16.92 mmol, 2 M) was heated under reflux for 2 h. After cooling to room temperature, the reaction mixture was washed with hexane (x2), acidified with HCl (1 M) until pH 1 and then extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried (anh. MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to afford the corresponding 2-(cyclopropylmethyl)malonic acid (898 mg, 90%) as a white solid. <sup>1</sup>H NMR (300 MHz, DMSO) δ: 12.68 (br s, 2H, 2×OH), 3.26 (t, *J* = 7.5 Hz, 1H, CH), 1.61 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 0.74–0.61 (m, 1H, CH<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>), 0.40–0.35 (m, 2H, cPr) and 0.08–0.04 (m, 2H, cPr) ppm.

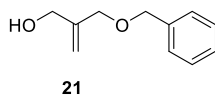
**(c) 2-(Cyclopropylmethyl)acrylic acid (23).** A solution of 2-(cyclopropylmethyl)malonic acid (878 mg, 5.55 mmol), piperidine (0.66 mL, 6.66 mmol) and HCHO (2 mL, 27.75 mmol, *ca* 37% wt) in ethanol (22 mL) was heated at 80 °C for 12 h. After cooling to room temperature, the organic solvent was removed under reduced pressure. The residue was diluted with diethyl ether and saturated NaHCO<sub>3</sub>. The aqueous phase was separated and the organic layer was extracted with saturated NaHCO<sub>3</sub>. The combined aqueous phases were washed with diethyl ether and then acidified with HCl (conc.) until pH 1. The solution was extracted with diethyl ether (x3). The combined organic extracts were washed with brine, dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to afford 2-(cyclopropylmethyl)acrylic acid (**23**) (663 mg, 95%) as a colorless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 9.96 (br s, 1H, OH), 6.30 (s, 1H, C=CHH), 5.80 (m, 1H, C=CHH), 2.18 (d, *J* = 6.8 Hz, 2H, CH<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>), 0.94–0.81 (m, 1H, CH<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>), 0.52–0.46 (m, 2H, cPr) and 0.08 (m, 2H, cPr) ppm.

**(e) 2-(Cyclopropylmethyl)prop-2-en-1-ol (18).** A solution of 2-(cyclopropylmethyl)acrylic acid (**23**) (651 mg, 5.16 mmol) in dry THF (52 mL), at 0 °C and under argon, was treated with BH<sub>3</sub>.Me<sub>2</sub>S complex (3 mL, 6.20 mmol, 2 M). The reaction mixture was stirred at room temperature for 5 h and then diluted with ethyl acetate and water (1:1). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (×3). The combined organic extracts were dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to afford 2-(cyclopropylmethyl)prop-2-en-1-ol (**18**) (350 mg, 60%) as a colorless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 5.02 (s, 2H, C=CH<sub>2</sub>), 4.13 (s, 2H, CH<sub>2</sub>OH), 1.97 (d, *J* = 6.8 Hz, 2H, CH<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>), 0.86–0.76 (m, 1H, CH<sub>2</sub>CH(CH<sub>2</sub>)<sub>2</sub>), 0.53–0.47 (m, 2H, cPr) and 0.09 (m, 2H, cPr) ppm.



20

**2-(Ethoxymethyl)prop-2-en-1-ol (20).** A solution of 2-methylene-1,3-propanediol (**19**) (50 mg, 0.57 mmol) in dry DMF (1.1 mL), at 0 °C and under argon, was treated with NaH (34 mg, 0.86 mmol, *ca* 60% w/w in mineral oil). After 30 min stirring, ethyl bromide (0.1 mL, 1.14 mmol) was added, the ice bath was removed and the reaction mixture was stirred for 1.5 h at room temperature. Ethyl acetate and water (4:1) were added, the aqueous phase was extracted with ethyl acetate (×3). The combined organic extracts were dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography, eluting with (60:40) ethyl acetate/hexane, to give compound **20** (29 mg, 44%) as a colorless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 5.15 (s, 1H, CHH), 5.10 (s, 1H, CHH), 4.15 (s, 2H, OCH<sub>2</sub>), 4.03 (s, 2H, OCH<sub>2</sub>), 3.48 (q, *J* = 7.0 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.17 (s, 1H, OH) and 1.20 (t, *J* = 7.0 Hz, 3H, CH<sub>3</sub>) ppm. IR (film): 3399 (OH) cm<sup>-1</sup>. MS (ESI) *m/z* = 117 (MH<sup>+</sup>). HRMS calcd for C<sub>6</sub>H<sub>13</sub>O<sub>2</sub> (MH<sup>+</sup>): 117.0910; found, 117.0909.



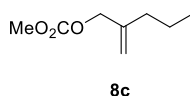
21

**2-(Benzyloxymethyl)prop-2-en-1-ol (21).** A solution of 2-methylene-1,3-propanediol (**19**) (50 mg, 0.57 mmol) in dry THF (1.9 mL), at 0 °C and under argon, was treated with NaH (34.2 mg, 0.86 mmol, *ca* 60% w/w in mineral oil). After 30 min stirring, benzyl bromide (0.1 mL, 0.9 mmol) was added, the ice bath was removed and the reaction mixture was stirred for 3 h at room temperature. Saturated aqueous solution of NH<sub>4</sub>Cl was added, the organic solvent was removed under reduced pressure and the aqueous extract was extracted with ethyl acetate (×3). The combined organic extracts were dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography, eluting with (60:40) ethyl acetate/hexane, to give compound **21** (28 mg, 28%) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.39–7.26 (m, 5H, 5×ArH), 5.21 (s, 1H, C=CHH), 5.16 (s, 1H, C=CHH), 4.52 (s, 2H, OCH<sub>2</sub>Ph), 4.17 (s, 2H, CH<sub>2</sub>OH), 4.09 (s, 2H, CH<sub>2</sub>OBn) and 2.55 (br s, 1H, OH) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 145.1 (C), 138.0 (C), 128.5 (2×CH), 127.8 (3×CH), 113.4 (CH<sub>2</sub>), 72.3 (CH<sub>2</sub>), 71.6 (CH<sub>2</sub>) and 64.2 (CH<sub>2</sub>) ppm. IR (film): 3372 (OH) cm<sup>-1</sup>. MS (ESI) *m/z* = 201 (MNa<sup>+</sup>). HRMS calcd for C<sub>11</sub>H<sub>14</sub>O<sub>2</sub>Na (MNa<sup>+</sup>): 201.0886; found, 201.0888.

## 2. PREPARATION OF CARBONATES **8**

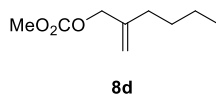
Methyl-2-methylallyl carbonate (**8a**) and methyl (2-methylenebutyl) carbonate (**8b**) were prepared as reported previously described by Dai *et al.*<sup>17</sup> from commercially available 2-methylprop-2-en-1-ol (**14**) and 2-methylenebutan-1-ol (**15**), which was prepared from commercially available ketone **11** as reported Sawayama *et al.*<sup>1</sup>

**General procedure for synthesis of carbonates 8a-h.** A solution of the alcohols **14–21** (1 mmol) and dry pyridine (3 mmol) in dry dichloromethane (0.4 mL/mmol of alcohol), at 0 °C and under argon, was treated with methyl chloroformate (2 mmol) and the resultant solution was stirred at room temperature for 2–2.5 h. The reaction mixture was washed with brine and the organic layer was extracted with diethyl ether (×3). The combined organic extracts, were washed with HCl (1 M), dried (anh. MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The reaction crude was purified by flash chromatography to give the carbonates **8a-h**.



8c

**Methyl (2-methylenepentyl) carbonate (8c).** It was prepared following the general procedure using 2-methylenepentan-1-ol (**16**)<sup>2</sup> (627 mg, 6.27 mmol), pyridine (1.5 mL), methyl chloroformate (1.0 mL, 12.54 mmol), dichloromethane (16 mL). Reaction time = 2.5 h. Eluent for chromatography = (75:25) diethyl ether/hexanes. Yield = 78% (919 mg). Colorless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 5.03 (br s, 1H, C=CHH), 4.92 (br s, 1H, C=CHH), 4.54 (s, 2H, OCH<sub>2</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 2.02 (t, *J* = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.46 (sext, *J* = 7.4 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 0.89 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 155.7 (C), 143.3 (C), 112.8 (CH<sub>2</sub>), 70.3 (CH<sub>2</sub>), 54.8 (OCH<sub>3</sub>), 35.1 (CH<sub>2</sub>), 20.7 (CH<sub>2</sub>) and 13.8 (CH<sub>3</sub>) ppm. FTIR (film): 1750 (CO) cm<sup>-1</sup>. MS (APCI) *m/z* = 159 (MH<sup>+</sup>). HMRS calcd for C<sub>8</sub>H<sub>15</sub>O<sub>3</sub> (MH<sup>+</sup>): 159.1016; found, 159.1014.

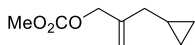


8d

**Methyl 2-(methylenehexyl) carbonate (8d).** It was prepared following the general procedure using 2-methylenehexyl-1-ol (**17**)<sup>2</sup> (3.16 g, 31.59 mmol), pyridine (5 mL), methyl chloroformate (7 mL, 94.77 mmol), dichloromethane (63 mL). Reaction time = 2.5 h. Yield = 94% (5.12 g). Colorless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 4.89 (br s, 1H, C=CHH), 4.78 (br s, 1H, C=CHH), 4.41 (s, 2H, OCH<sub>2</sub>), 3.61 (s, 3H, OCH<sub>3</sub>), 1.92 (t, *J* = 7.3 Hz, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 1.30 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.17 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 0.76 (t, *J* = 7.2 Hz, 3H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 155.3 (C), 143.4 (C), 111.9 (CH<sub>2</sub>), 69.7 (CH<sub>2</sub>), 54.2 (OCH<sub>3</sub>), 32.4 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>) and 13.5 (CH<sub>3</sub>) ppm. FTIR (film): 1750 (CO) cm<sup>-1</sup>. MS (APCI) *m/z* = 173 (MH<sup>+</sup>). HRMS calcd for C<sub>9</sub>H<sub>17</sub>O<sub>3</sub> (MH<sup>+</sup>): 173.1172; found, 173.1171.

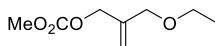
<sup>1</sup> Sawayama, A. M.; Tanaka, H.; Wandless, T. J. Total synthesis of ustiloxin D and considerations on the origin of selectivity of the asymmetric allylic alkylation. *J. Org. Chem.* **2004**, *69*, 8810–8820.

<sup>2</sup> Ma, W.; Fang, J.; Ren, J.; Wang, Z. Lewis acid catalyzed formal intramolecular [3 + 3] cross-cycloaddition of cyclopropane 1,1-diester for construction of benzobicyclo[2.2.2]octane skeletons. *Org. Lett.* **2015**, *17*, 4180–4183.



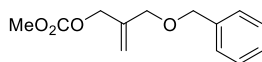
8e

**2-(Cyclopropylmethyl)allyl methyl carbonate (8e).** It was prepared following the general procedure using 2-(cyclopropylmethyl)prop-2-en-1-ol (**18**) (321 mg, 2.86 mmol), pyridine (0.7 mL), methyl chloroformate (0.4 mL), dichloromethane (7.2 mL). Reaction time = 2.5 h. Eluent for chromatography = (10:90) ethyl acetate/hexane. Yield = 72% (350 mg). Colorless liquid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.08 (br s, 1H, C=CHH), 5.04 (br s, 1H, C=CHH), 4.61 (br s, 2H,  $\text{OCH}_2$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 1.95 (d,  $J = 6.9$  Hz, 2H,  $\text{CH}_2\text{CH}(\text{CH}_2)_2$ ), 0.80–0.73 (m, 1H,  $\text{CH}_2\text{CH}(\text{CH}_2)_2$ ), 0.50–0.44 (m, 2H,  $\text{CH}_2\text{CHCH}_2\text{CH}_2$ ) and 0.06 (m, 2H,  $\text{CH}_2\text{CHCH}_2\text{CH}_2$ ) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.8 (C), 143.6 (C), 112.9 ( $\text{CH}_2$ ), 70.5 ( $\text{CH}_2$ ), 54.8 ( $\text{OCH}_3$ ), 38.1 ( $\text{CH}_2$ ), 9.1 (CH) and 4.7 ( $2\times\text{CH}_2$ ) ppm. IR (film): 1744 (CO)  $\text{cm}^{-1}$ . MS (ESI)  $m/z = 171$  ( $\text{MH}^+$ ). HRMS calcd for  $\text{C}_9\text{H}_{15}\text{O}_3$  ( $\text{MH}^+$ ): 171.1016; found, 171.1020.



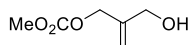
8f

**2-(Ethoxymethyl)allyl methyl carbonate (8f).** It was prepared following the general procedure using 2-(ethoxymethyl)prop-2-en-1-ol (**19**) (251 mg, 1.16 mmol), pyridine (0.3 mL), methyl chloroformate (0.18 mL, 2.27 mmol), solution of methyl chloroformate in dry dichloromethane (2.4 mL, 1.0 M), dichloromethane (2.1 mL). Reaction time = 2 h. Eluent for chromatography = (30:70) ethyl acetate/hexane. Yield = 78% (240 mg). Colorless liquid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.16 (s, 2H, C=CH<sub>2</sub>), 4.58 (s, 2H,  $\text{OCH}_2$ ), 3.91 (s, 2H,  $\text{CH}_2$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 3.40 (q,  $J = 7.0$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ) and 1.12 (d,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.5 (C), 140.5 (C), 115.2 ( $\text{CH}_2$ ), 71.0 ( $\text{CH}_2$ ), 68.0 ( $\text{CH}_2$ ), 65.7 ( $\text{CH}_2$ ), 54.7 ( $\text{OCH}_3$ ) and 15.0 ( $\text{CH}_3$ ) ppm. IR (film): 1751 (CO)  $\text{cm}^{-1}$ . MS (ESI)  $m/z = 175$  ( $\text{MH}^+$ ). HRMS calcd for  $\text{C}_8\text{H}_{15}\text{O}_4$  ( $\text{MH}^+$ ): 175.0965; found, 175.0964.



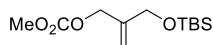
8g

**2-(Benzyloxymethyl)allyl methyl carbonate (8g).** It was prepared following the general procedure using 2-(benzyloxymethyl)prop-2-en-1-ol (**20**) (207 mg, 1.16 mmol), pyridine (0.3 mL), methyl chloroformate (0.2 mL), dichloromethane (2.9 mL). Reaction time = 2.5 h. Eluent for chromatography = (20:80) ethyl acetate/hexane. Yield = 94% (257 mg). Colorless liquid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.34–7.26 (m, 5H, 5 $\times$ ArH), 5.30 (s, 2H, C=CH<sub>2</sub>), 4.71 (s, 2H,  $\text{OCH}_2$ ), 4.51 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 4.07 (s, 2H,  $\text{CH}_2\text{OBn}$ ) and 3.78 (s, 3H,  $\text{CH}_3$ ) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.6 (C), 140.2 (C), 138.0 (C), 128.4 ( $2\times\text{CH}$ ), 127.7 ( $2\times\text{CH}$ ), 127.7 (CH), 115.9 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 70.6 ( $\text{CH}_2$ ), 68.1 ( $\text{CH}_2$ ) and 54.8 ( $\text{CH}_3$ ) ppm. IR (film): 1744 (CO)  $\text{cm}^{-1}$ . MS (ESI)  $m/z = 259$  ( $\text{MNa}^+$ ). HRMS calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_4\text{Na}$  ( $\text{MNa}^+$ ): 259.0941; found, 259.0941.



8h

**2-(Hydroxymethyl)allyl methyl carbonate (8h).** It was prepared following the general procedure using 2-methylene-1,3-propanediol (**19**) (205 mg, 2.33 mmol), pyridine (0.4 mL), methyl chloroformate (0.2 mL), dichloromethane (2.3 mL). Reaction time = 2.5 h. Eluent for chromatography = 40:60 ethyl acetate/hexane. Yield = 55% (188 mg). Colorless liquid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.19 (m, 1H, C=CHH), 5.14 (s, 1H, C=CHH), 4.61 (s, 2H,  $\text{OCH}_2$ ), 4.08 (s, 1H, CHHOH), 4.07 (s, 1H, CHHOH) and 3.72 (s, 3H,  $\text{OCH}_3$ ) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 155.7 (C), 142.8 (C), 114.4 ( $\text{CH}_2$ ), 68.1 ( $\text{CH}_2$ ), 63.2 ( $\text{CH}_2$ ) and 54.9 ( $\text{OCH}_3$ ) ppm. IR (film)  $\nu$ : 3390 (OH) and 1747 (CO)  $\text{cm}^{-1}$ .



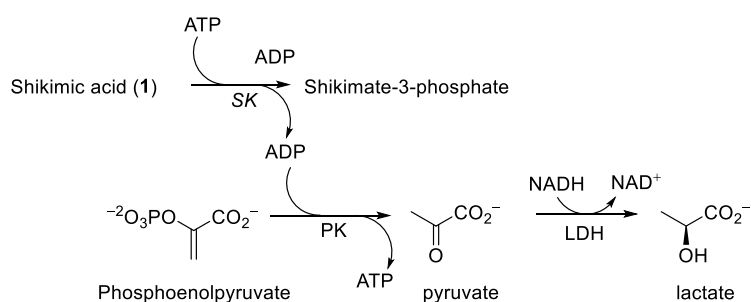
8i

**2-((tert-Butyl)dimethylsilyloxy)methyl allyl methyl carbonate (8i).** A solution of 2-(hydroxymethyl)allyl methyl carbonate (**8h**) (180 mg, 1.23 mmol), DMAP (42 mg, 0.35 mmol), TBAI (46 mg, 0.12 mmol) and dry triethylamine (0.2 mL, 1.35 mmol) in dry DMF (2.0 mL), at 0 °C and under argon, was treated with *tert*-butyldimethylsilyl chloride (204 mg, 1.35 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 3 h. The resultant suspension was diluted with

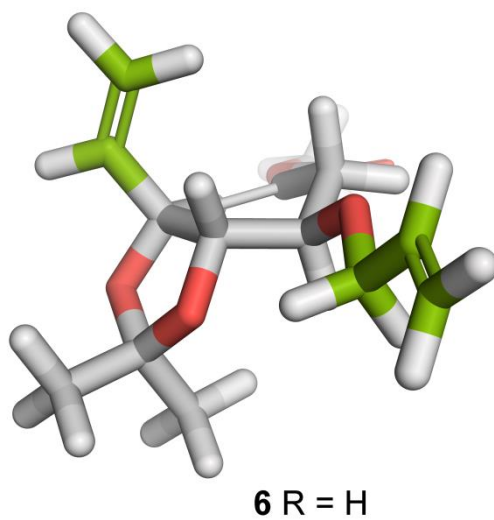
ethyl acetate and filtered over a plug of Celite®. The filtrate and the washings were washed with HCl (1 M, ×3) followed by brine (×3). The organic extract was dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography, eluting with (7:93) ethyl acetate/hexane, to give the silyl ether **22** (297 mg, 93%) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 5.21 (m, 1H, C=CHH), 5.12 (m, 1H, C=CHH), 4.61 (s, 2H, OCH<sub>2</sub>), 4.14 (br s, 2H, CH<sub>2</sub>OTBS), 3.74 (s, 3H, OCH<sub>3</sub>), 0.87 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) and 0.03 (s, 6H, 2×CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 155.7 (C), 142.8 (C), 113.5 (CH<sub>2</sub>), 68.1 (CH<sub>2</sub>), 63.7 (CH<sub>2</sub>), 54.8 (OCH<sub>3</sub>), 25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 18.4 (C(CH<sub>3</sub>)<sub>3</sub>) and 5.4 (2×CH<sub>3</sub>) ppm. IR (film): 1751 (CO) cm<sup>-1</sup>. MS (ESI) *m/z* = 283 (MNa<sup>+</sup>). HRMS calcd for C<sub>12</sub>H<sub>24</sub>O<sub>4</sub>SiNa (MNa<sup>+</sup>): 283.1336; found, 283.1336.

### 3. SHIKIMATE KINASE ASSAY

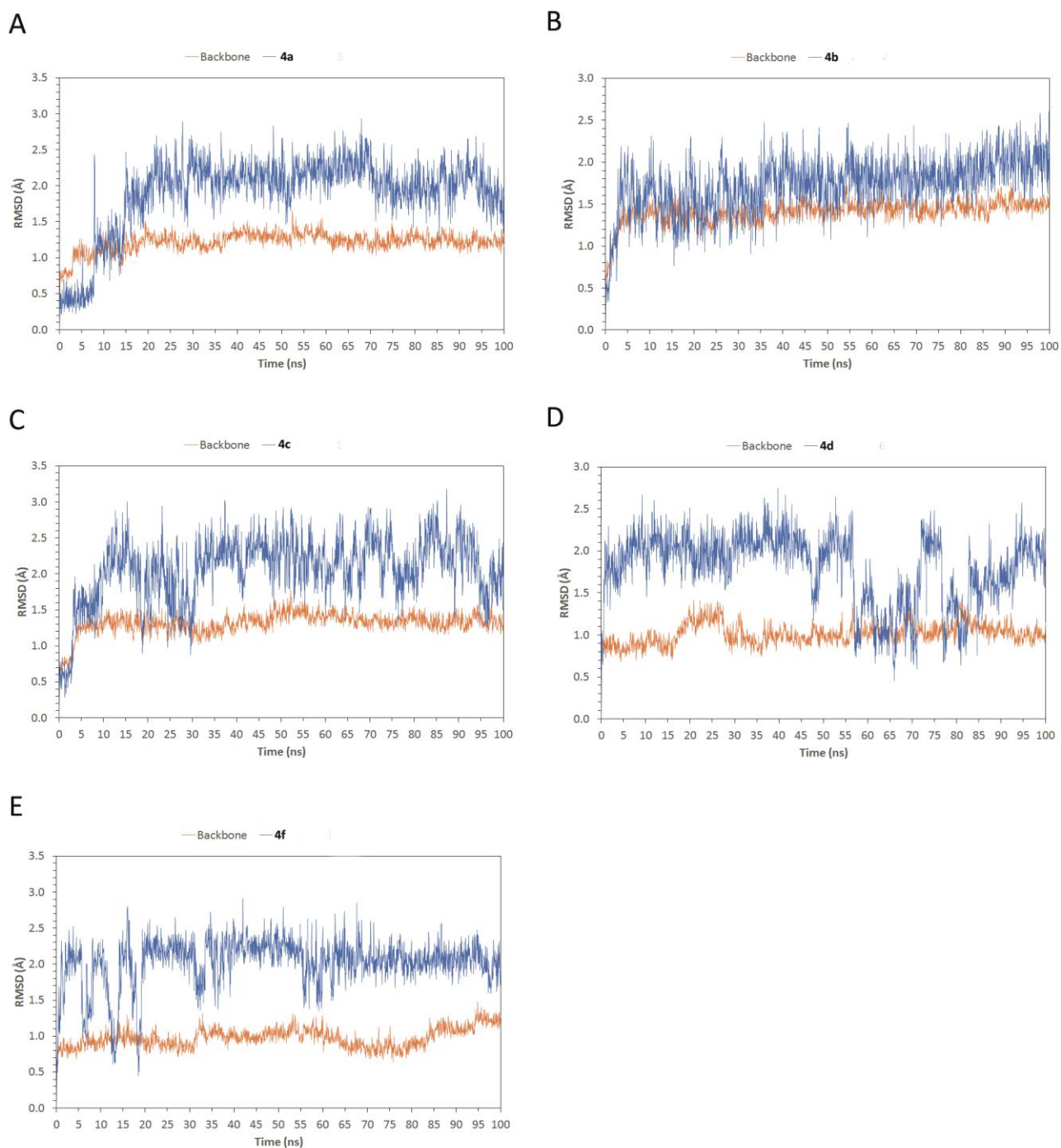
Both enzymes were purified as described previously.<sup>3,18</sup> Concentrated solutions of *Hp*-SK (7.4 mg mL<sup>-1</sup>) or *Mt*-SK (1.5 mg mL<sup>-1</sup>) were stored in potassium phosphate buffer (50 mM, pH 7.2), DTT (1 mM) and NaCl (150 mM). When required for assays, aliquots of the enzyme stock solutions were diluted in water and buffer and stored on ice. Enzyme activity was measured by monitoring the decrease in absorbance at 340 nm in the UV spectrum due to the absorbance of NADH ( $\epsilon/M^{-1} \text{ cm}^{-1}$  6 220) in a coupled assay format wherein ADP formed after the formation of shikimate-3-phosphate was detected using pyruvate kinase (PK) and lactate dehydrogenase (LDH). Oxidation of NADH to NAD during PK-LDH activity was monitored at 340 nm. Standard assay conditions for shikimate kinase were 100 mM Tris.HCl pH 7.7, 100 mM KCl, 5 mM MgCl<sub>2</sub>, 2.5 mM ATP, 1 mM shikimic acid, 1 mM PEP, 0.20 mM NADH, ~2.8 units of PK-LDH and 0.03 unit of SK protein. One unit of enzyme is defined as the amount of enzyme required to convert 1  $\mu\text{mol}$  of substrate to product in 1 min. Each assay was initiated by addition of shikimic acid. Solutions of ATP ( $\epsilon/M^{-1} \text{ cm}^{-1}$  15 400) and NADH ( $\epsilon/M^{-1} \text{ cm}^{-1}$  6220) were calibrated by measuring the absorbance at 259 nm and 340 nm in the UV spectrum, respectively. Solutions of shikimic acid were calibrated by equilibration with SK and measurement of the change in the UV absorbance at 340 nm due to the disappearance of NADH. The *K<sub>i</sub>* values of compounds **2–5** against SK were obtained from Dixon plots (1/*v* vs [I]) of assay data. The initial rates at fixed enzyme and substrate concentrations (0.25–1.2 *K<sub>m</sub>*) were measured in the absence and in the presence of various inhibitor concentrations.



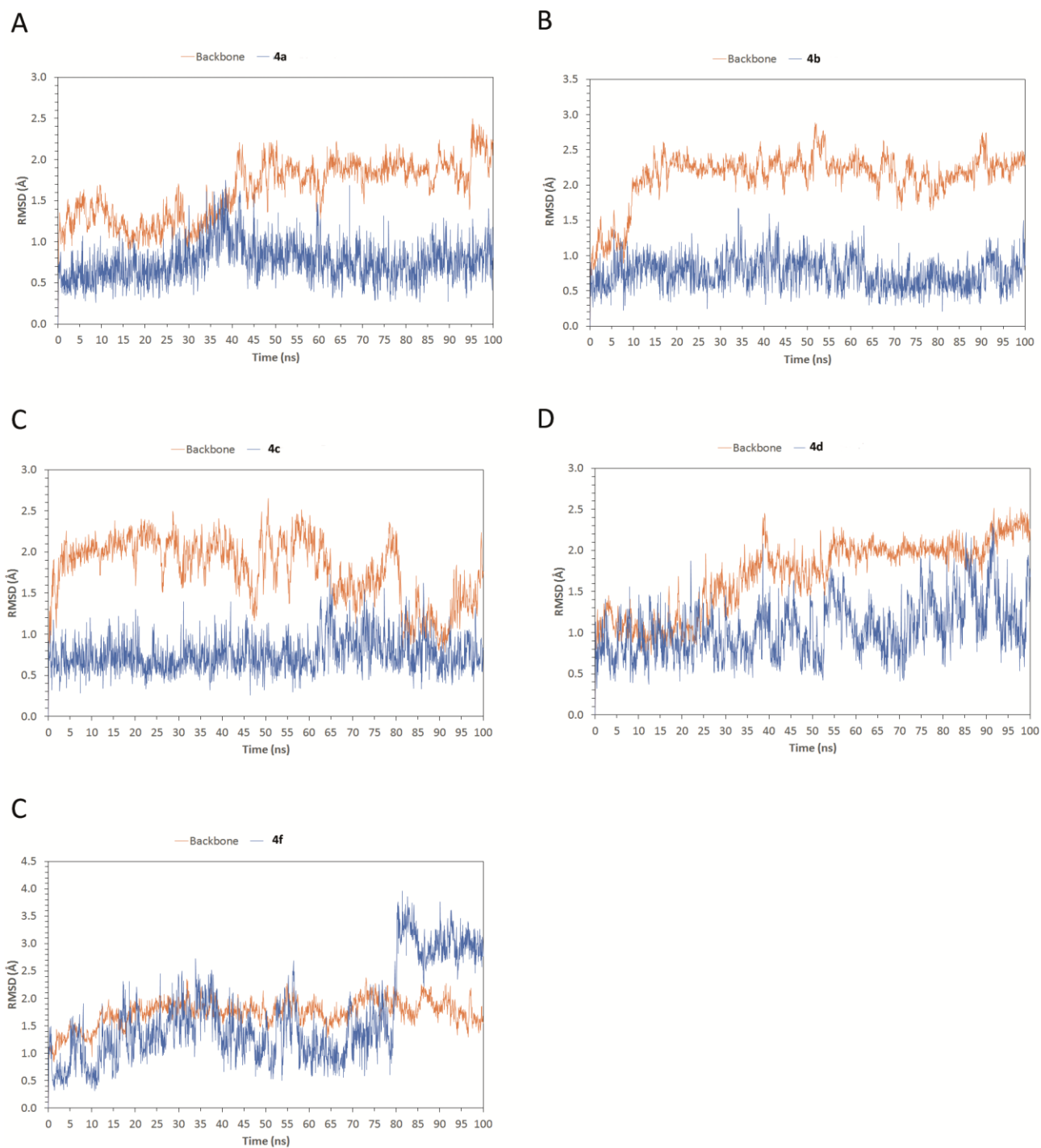
<sup>3</sup> Krell, T.; Maclean, J.; Boam, D. J.; Cooper, A.; Resmini, M.; Brocklehurst, K.; Kelly, S. M.; Price, N. C.; Laphorn, A. J.; Coggins, J. R. Biochemical and X-ray crystallographic studies on shikimate kinase: The important structural role of the P-loop lysine. *Protein Science* **2001**, *10*, 1137–1149.



**Figure S1.** Conformation of minimum energy of **6** (R = H) obtained by computational calculations (Gaussian 09, AM1).

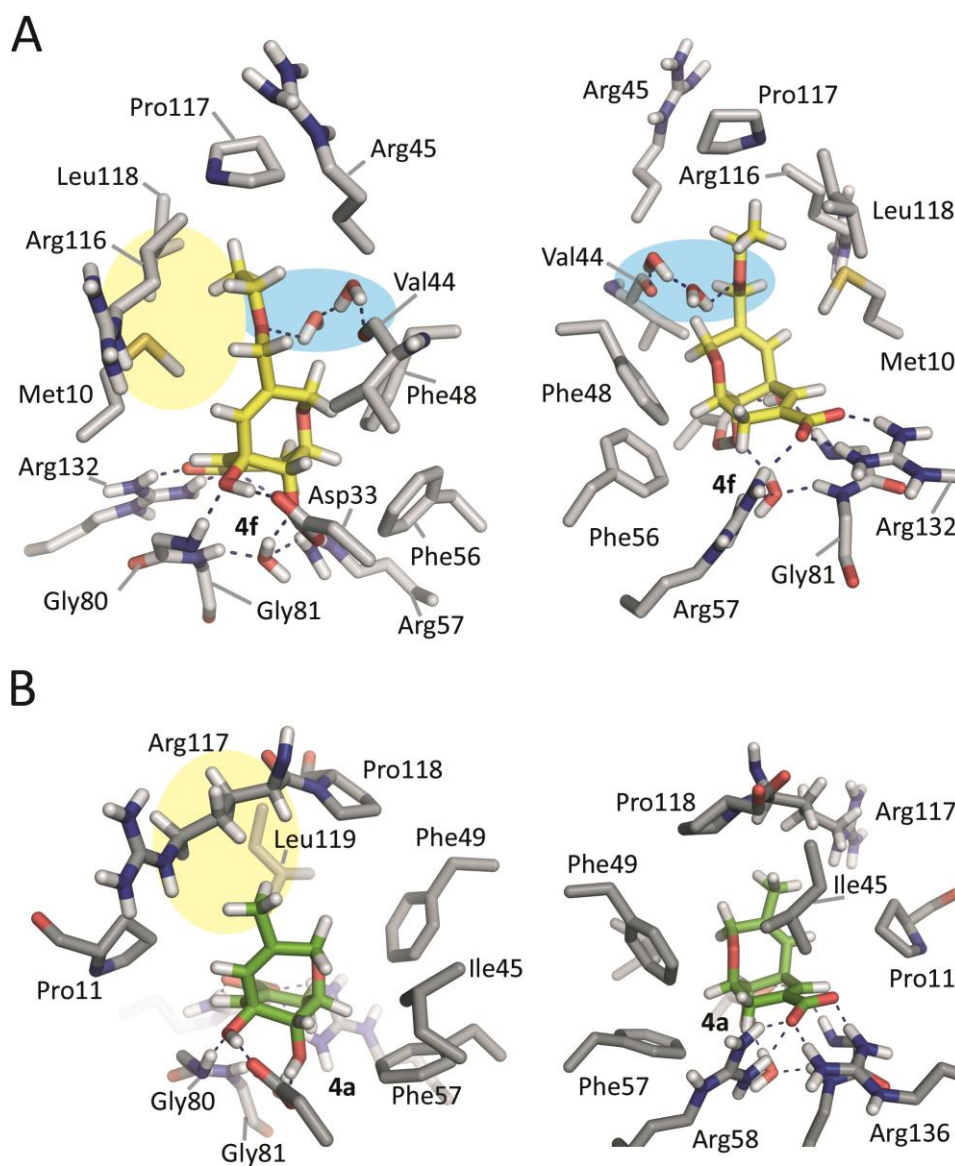


**Figure S2.** The rmsd plots for the protein backbone (C $\alpha$ , C, N and O atoms) (orange line) and ligand (blue line) calculated for the *Hp*-SK/ATP/Mg<sup>2+</sup>/ligand complex obtained from MD simulation studies. A. *Hp*-SK/ATP/Mg<sup>2+</sup>/4a complex. B. *Hp*-SK/ATP/Mg<sup>2+</sup>/4b complex. C. *Hp*-SK/ATP/Mg<sup>2+</sup>/4c complex. D. *Hp*-SK/ATP/Mg<sup>2+</sup>/4d complex. E. *Hp*-SK/ATP/Mg<sup>2+</sup>/4f complex.

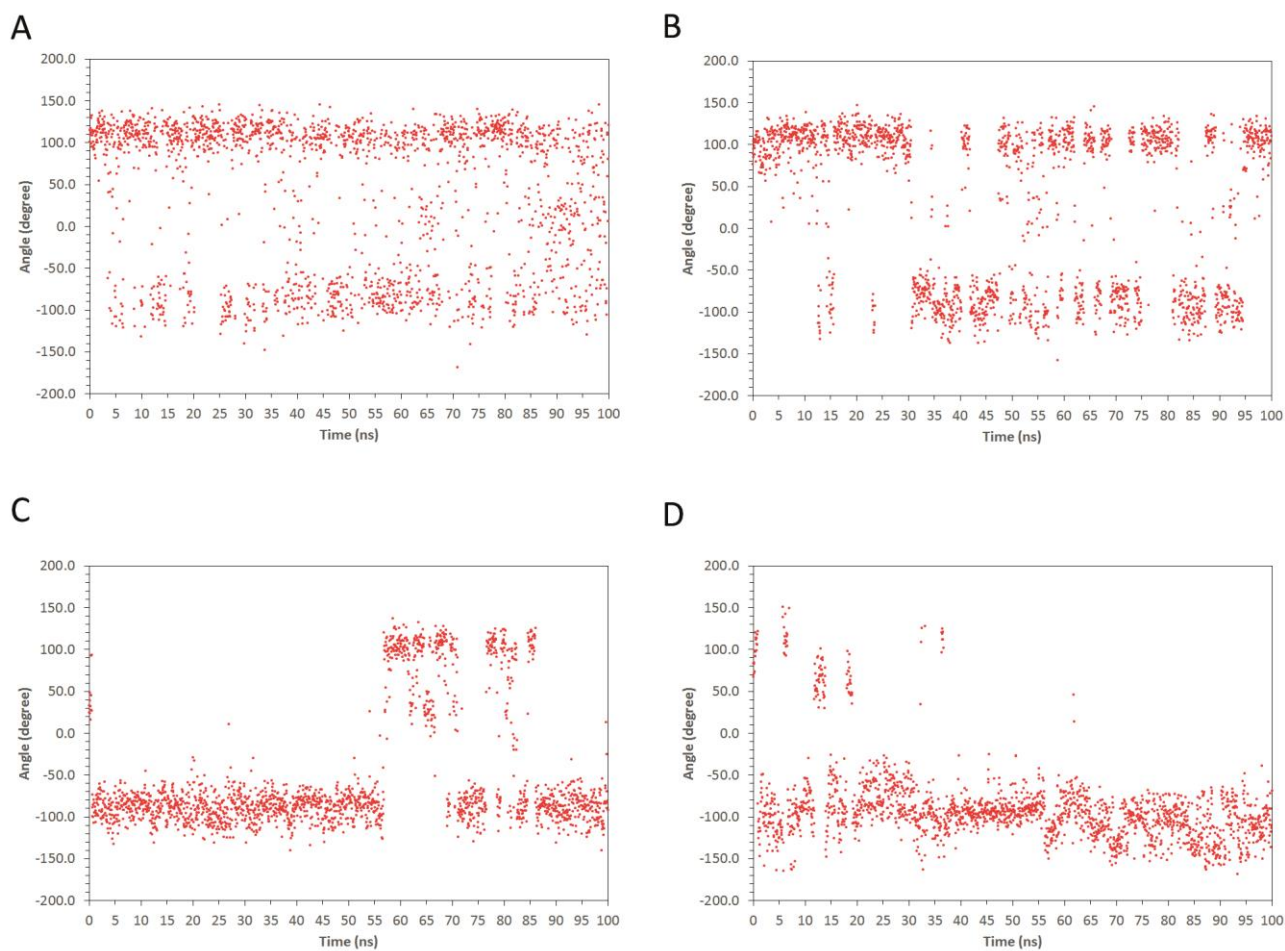
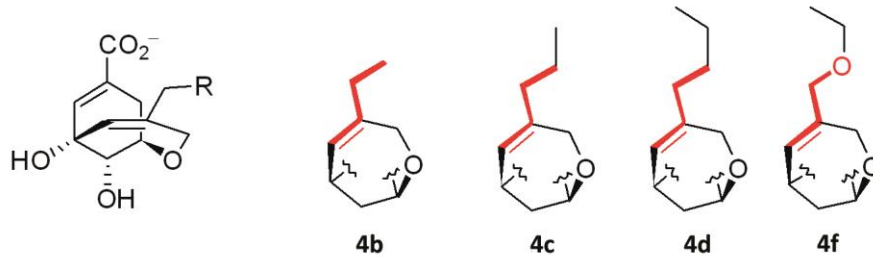


**Figure S3.** The rmsd plots for the protein backbone (C $\alpha$ , C, N and O atoms) (orange line) and ligand (blue line) calculated for the *Mt*-SK/ATP/Mg<sup>2+</sup>/ligand complex obtained from MD simulation studies. A. *Mt*-SK/ATP/Mg<sup>2+</sup>/4a complex. B. *Mt*-SK/ATP/Mg<sup>2+</sup>/4b complex. C. *Mt*-SK/ATP/Mg<sup>2+</sup>/4c complex. D. *Mt*-SK/ATP/Mg<sup>2+</sup>/4d complex. E. *Mt*-SK/ATP/Mg<sup>2+</sup>/4f complex.

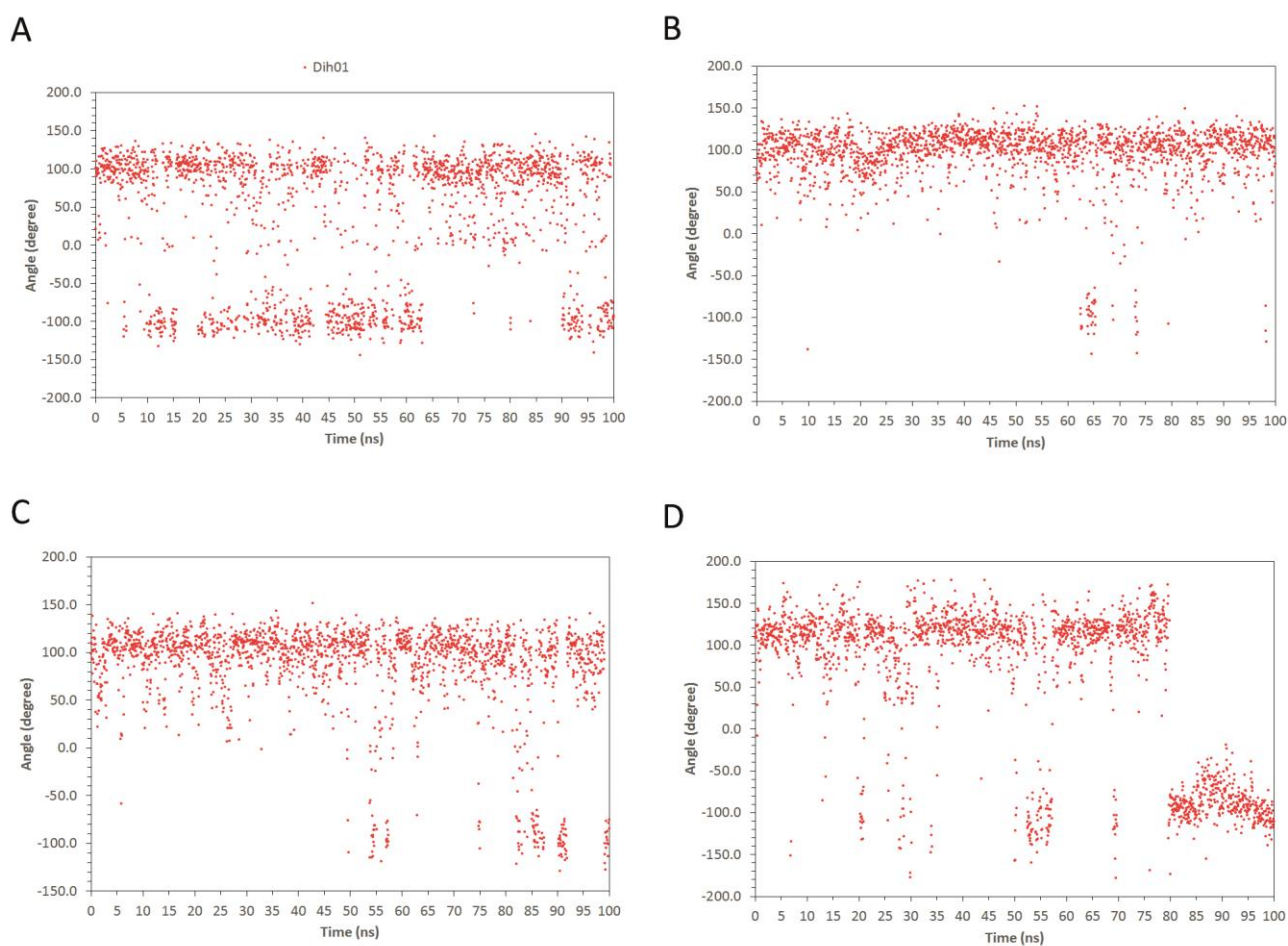
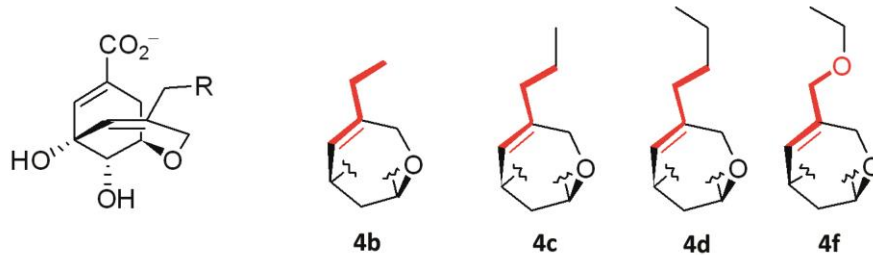




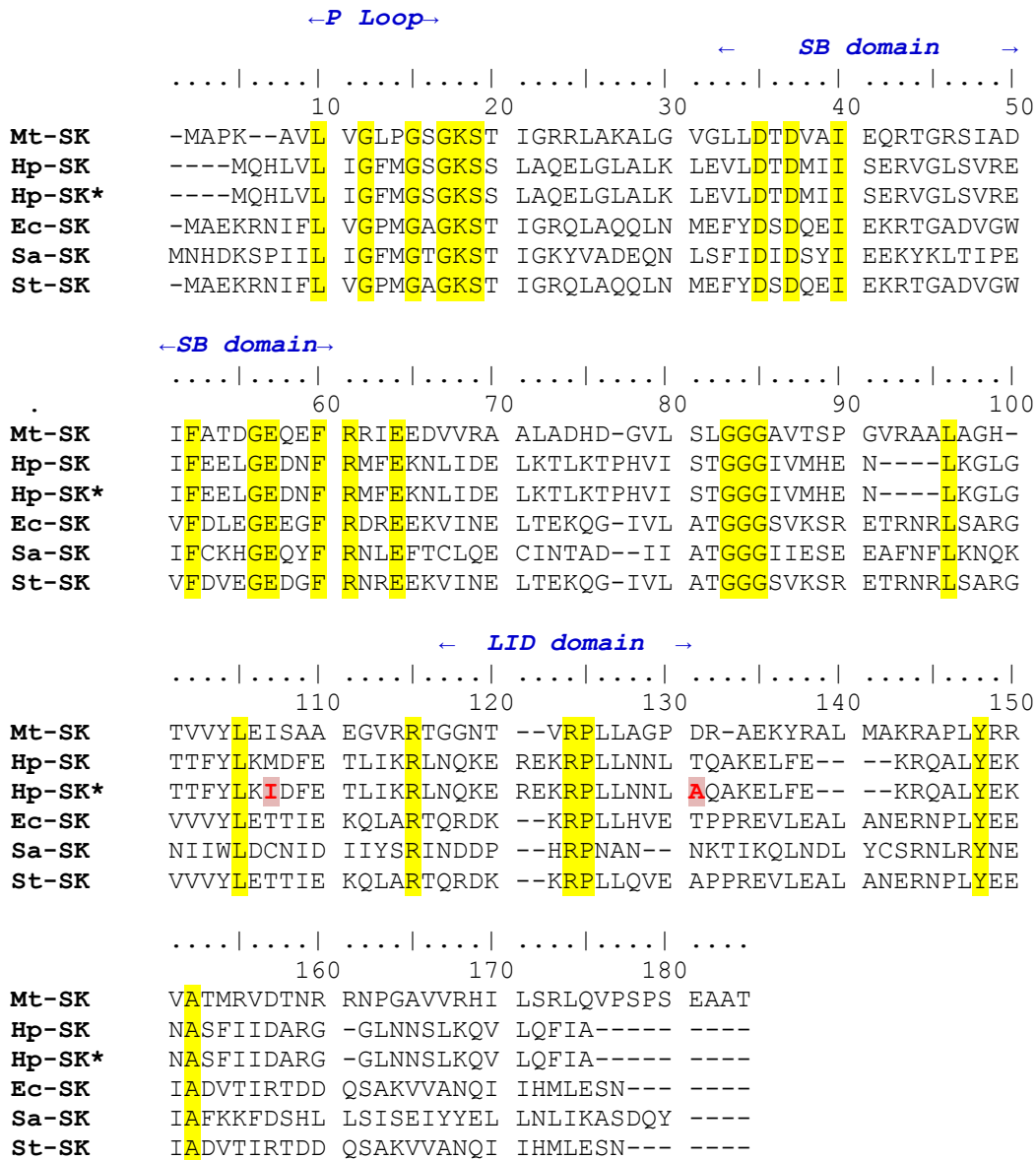
**Figure S4.** Detailed view of the binding mode of the most potent compounds against *Hp*-SK (A, compound **4f**) and *Mt*-SK (B, compound **4a**) in *Hp*-SK/ATP/Mg<sup>2+</sup>/**4f** and *Mt*-SK/ATP/Mg<sup>2+</sup>/**4a** enzyme complexes, respectively. Two perspectives are provided. Snapshots after 80 ns of simulation are shown. Relevant side chain residues are shown and labelled. Polar contacts are shown as blue dashed lines. The indirect interaction of the oxygen atom of the substituent in the ether bridge in **4f** with the Val44 side chain through a water network is highlighted with blue shading. The proximity of the methyl group in **4a** to the carbon chain of the catalytic residue Arg117 is shown as yellow shading.



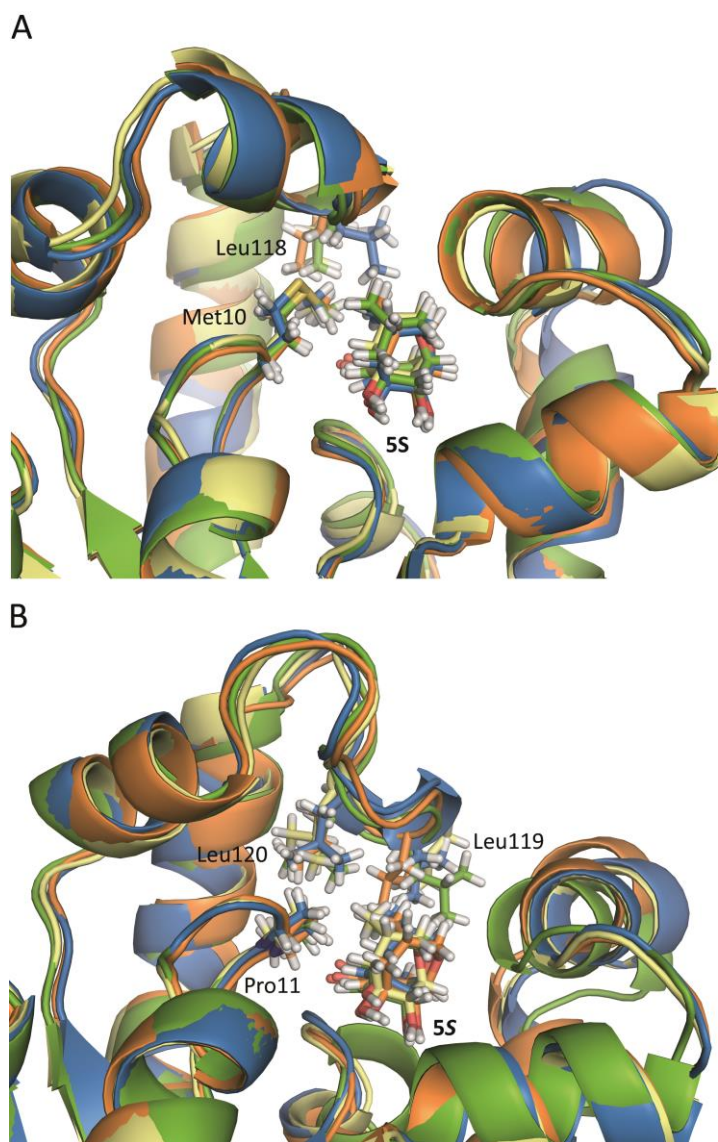
**Figure S5.** Variation of the dihedral angle shown in red in ligands **4b** (A), **4c** (B), **4d** (C) and **4f** (D) calculated for the *Hp*-SK/ATP/Mg<sup>+2</sup>/ligand complex obtained from MD simulation studies.



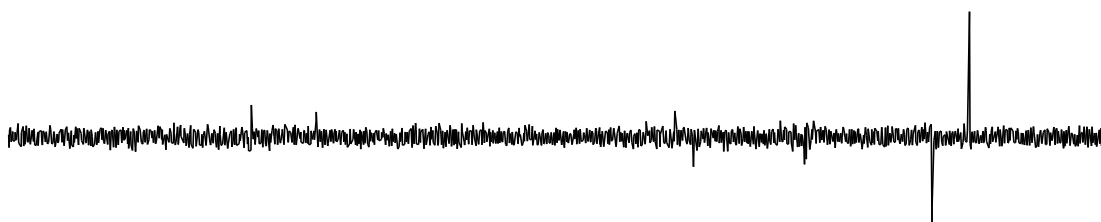
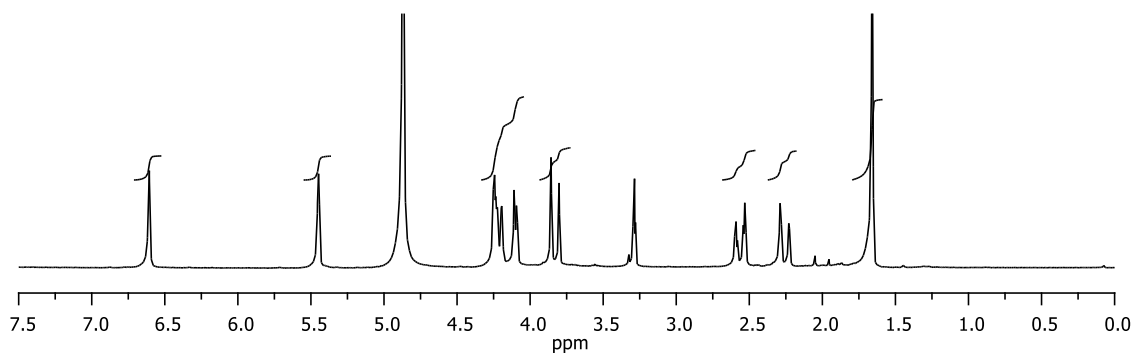
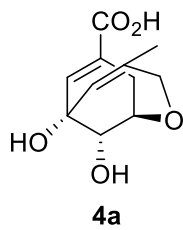
**Figure S6.** Variation of the dihedral angle shown in red in ligands **4b** (A), **4c** (B), **4d** (C) and **4f** (D) calculated for the *Mt*-SK/ATP/Mg<sup>+2</sup>/ligand complex obtained from MD simulation studies.

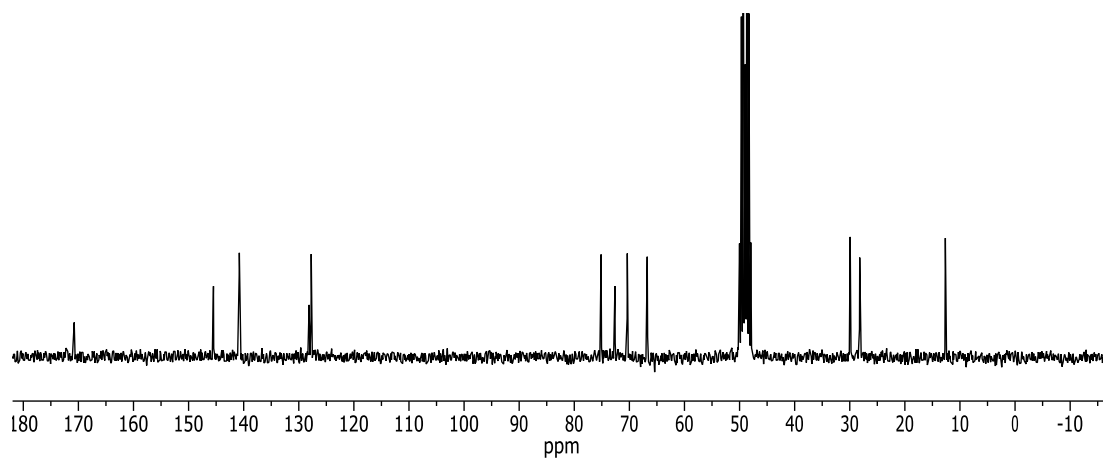
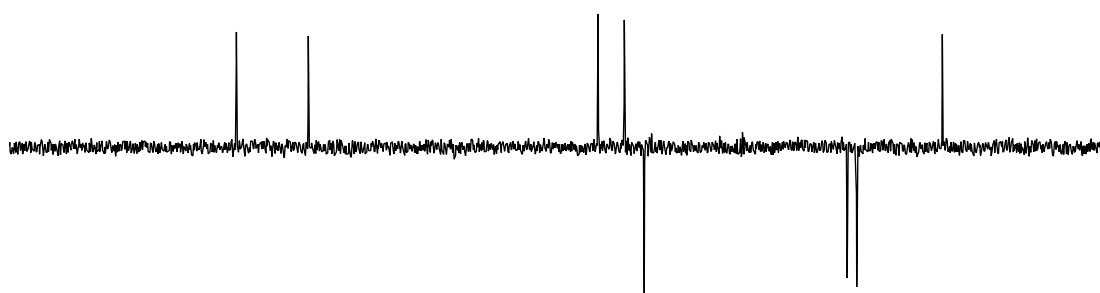
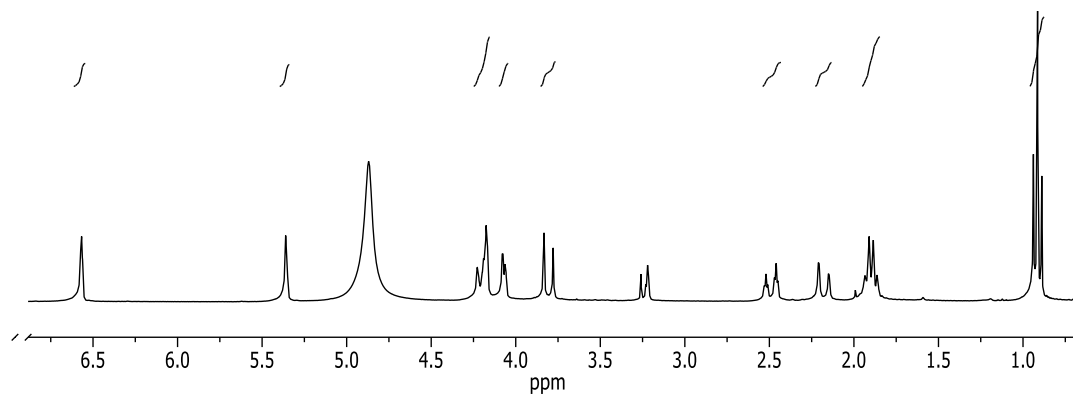
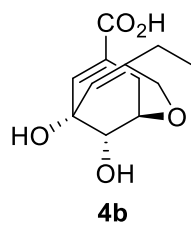


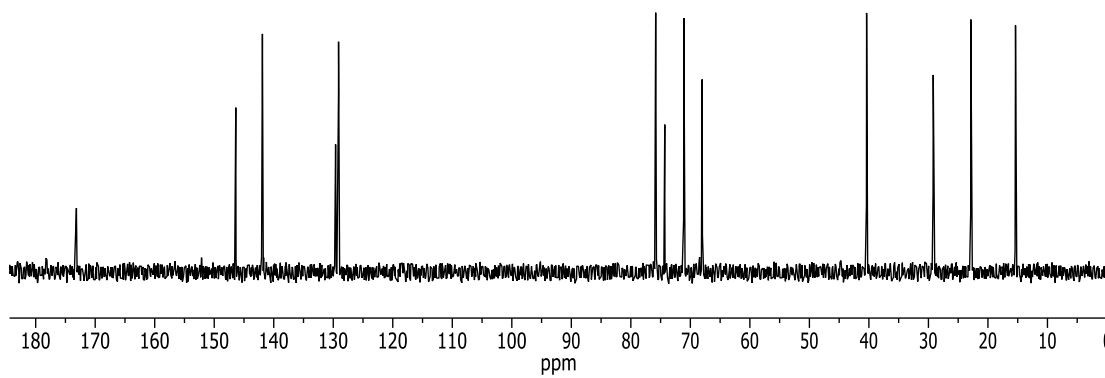
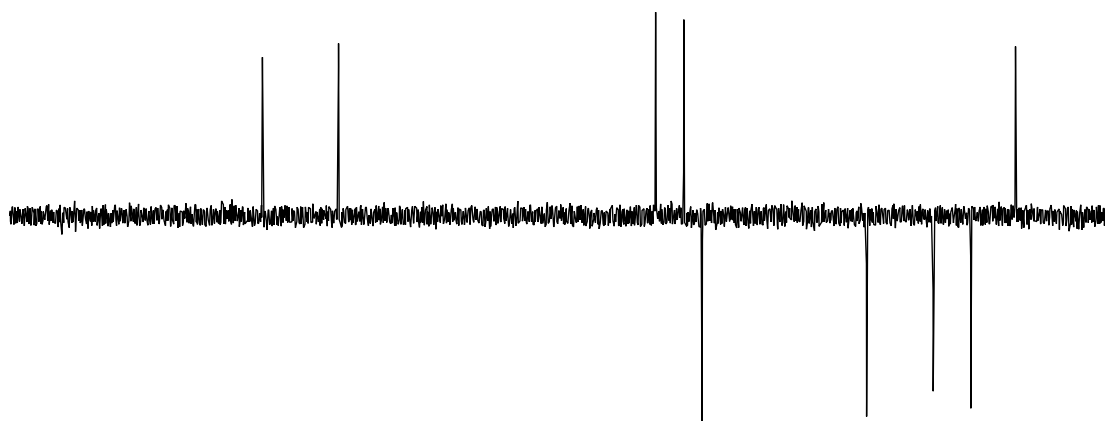
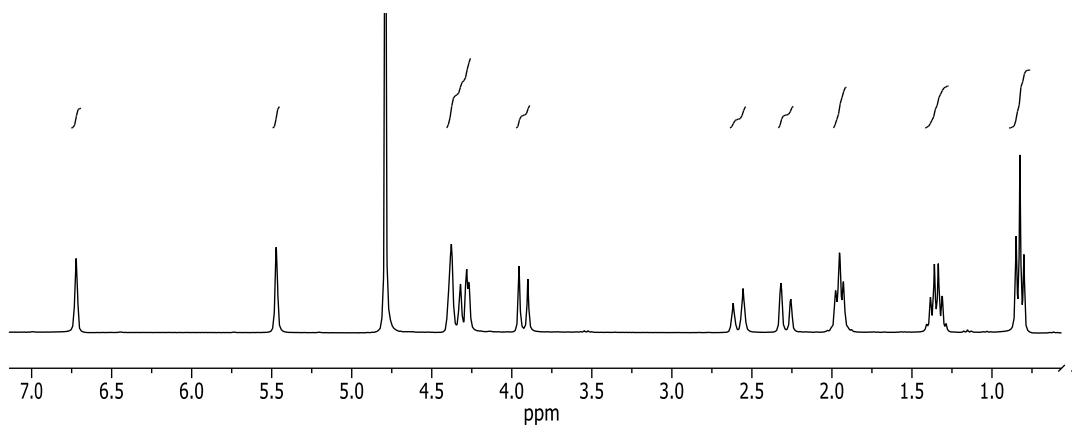
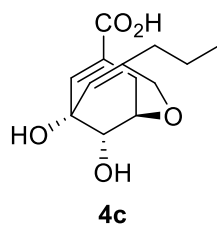
**Figure S7.** Amino acid sequence alignments for *M. tuberculosis*, *H. pylori*, *E. coli*, *S. aureus* and *S. typhi* shikimate kinase. For the *H. pylori* enzyme, two strains are shown: AROK\_HELJPJ, Q9ZMS3 (strain J99 / ATCC 700824) and clinically isolated strain from Guadalajara Hospital (Spain), which was employed in these studies. Protein sequences were aligned using the CLUSTAL Omega multiple sequence alignment (<http://www.ebi.ac.uk/Tools/msa/clustalo/>). Changed residues in the clinically isolated strain used in these studies are highlighted in red. Conserved residues are highlighted in yellow. The P loop, SB and LID domains are also indicated.



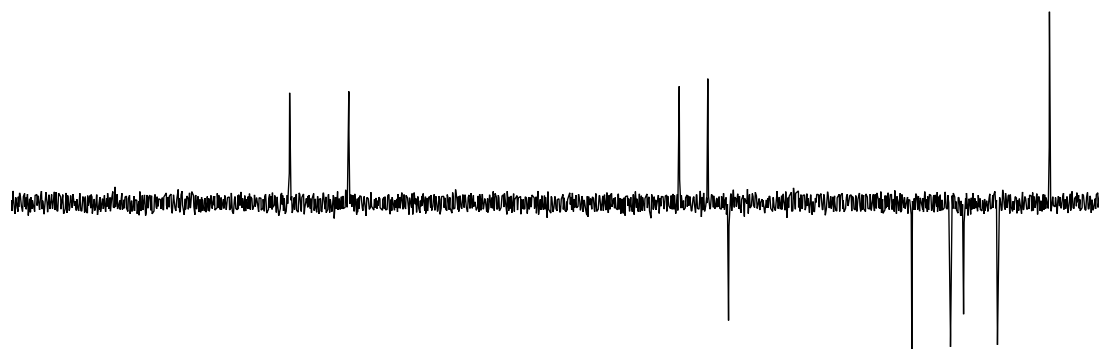
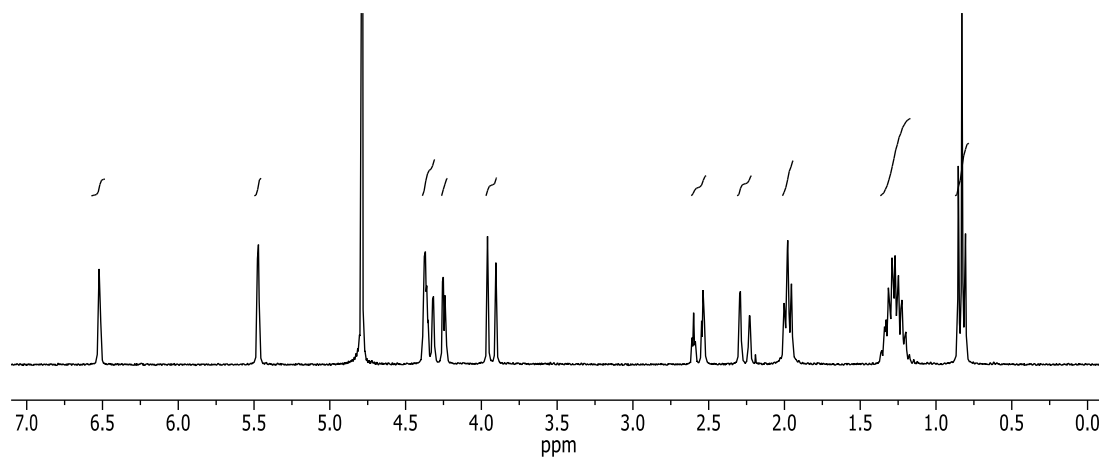
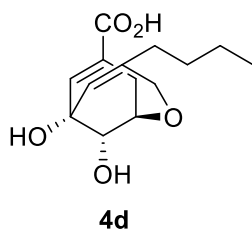
**Figure S8.** Superposition of several snapshots of *Hp*-SK/ATP/Mg<sup>+2</sup>/5S (A) and *Mt*-SK/ATP/Mg<sup>+2</sup>/5S (B) complexes. Note how the methyl group would interact with the side chain of apolar residues of the lid and P-loop (Leu118 and Met10 for *Hp*-SK and Leu119, Leu120 and Pro11 for *Mt*-SK). No interaction with the carbon chain of the essential arginine was identified.

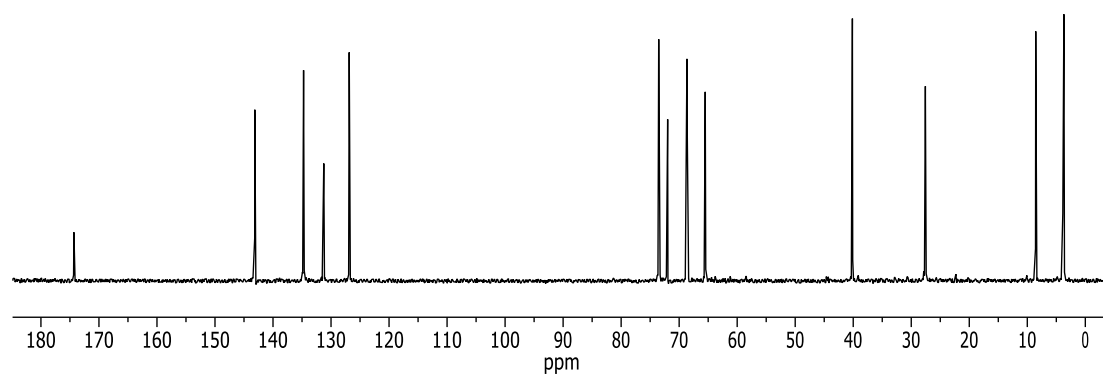
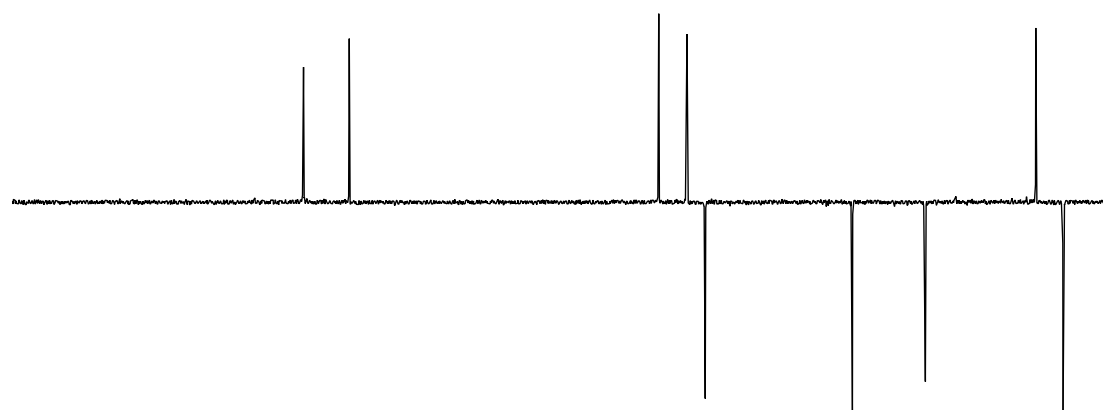
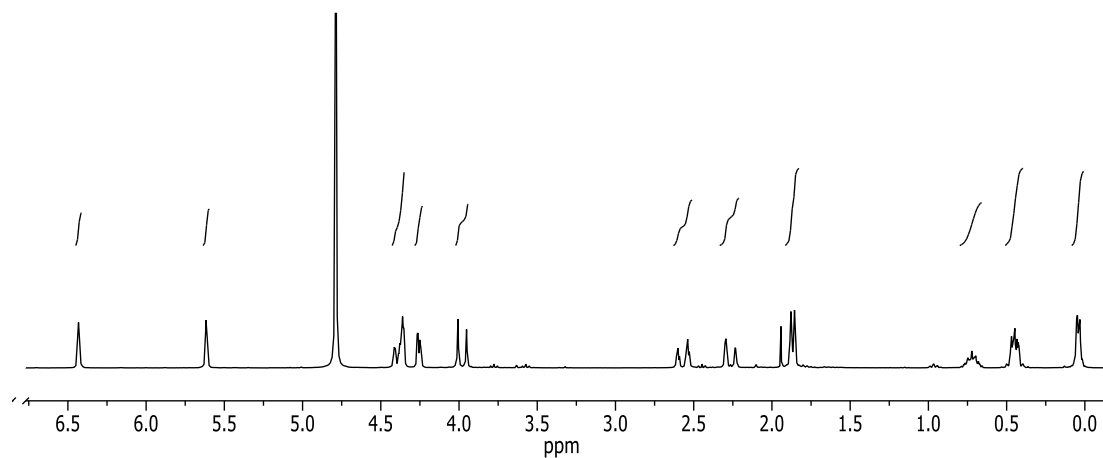
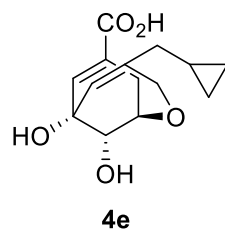


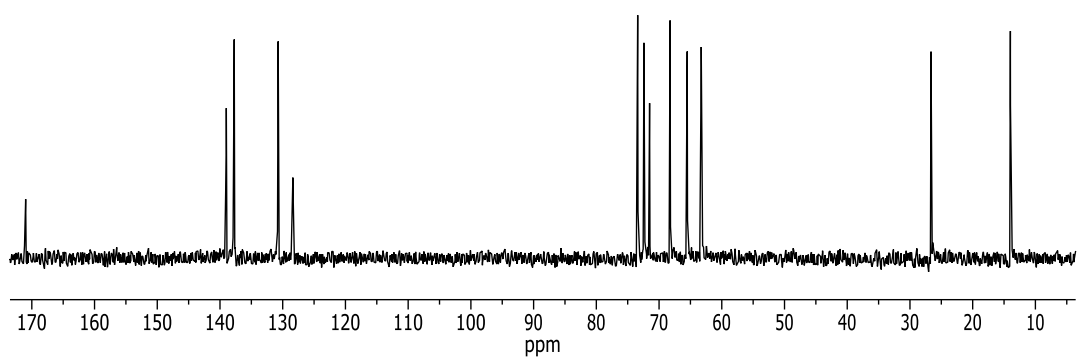
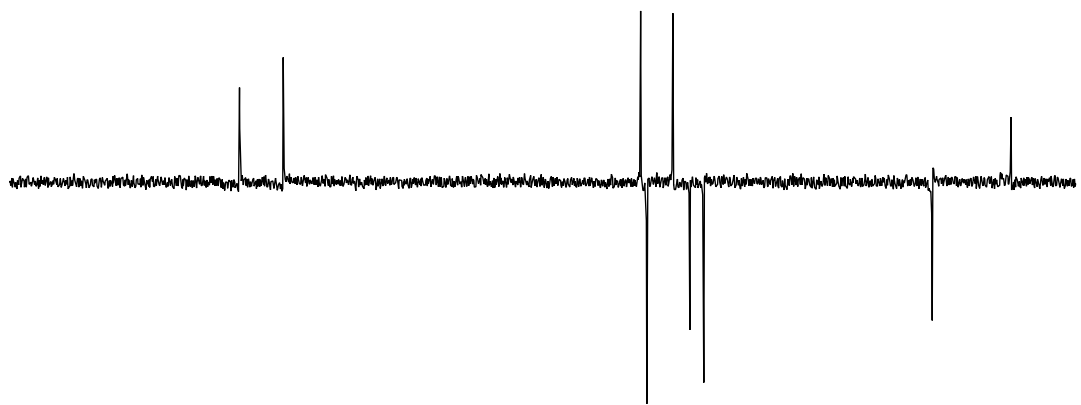
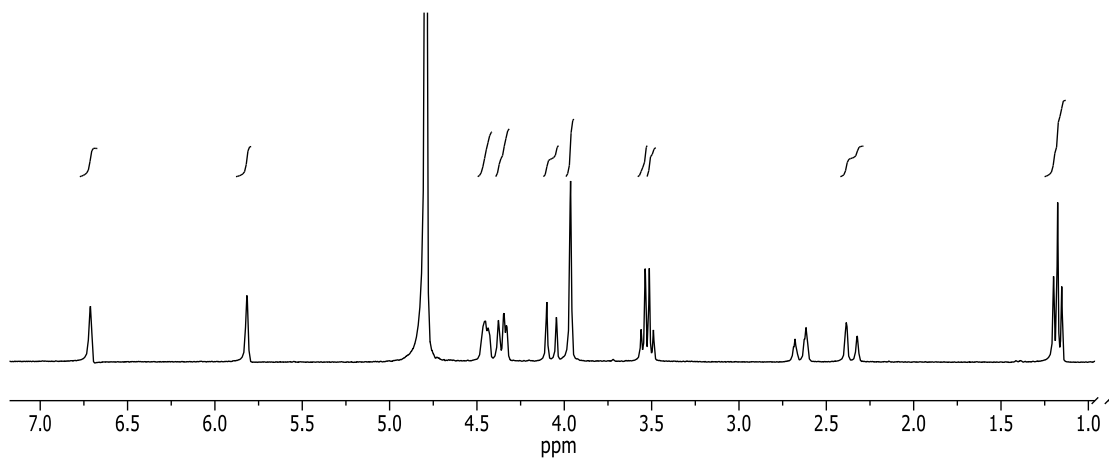
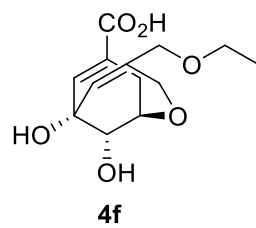


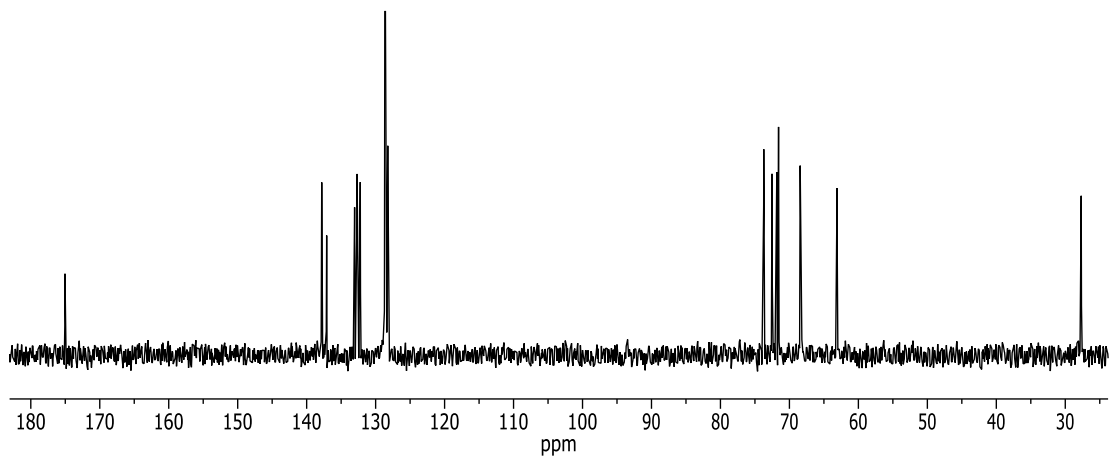
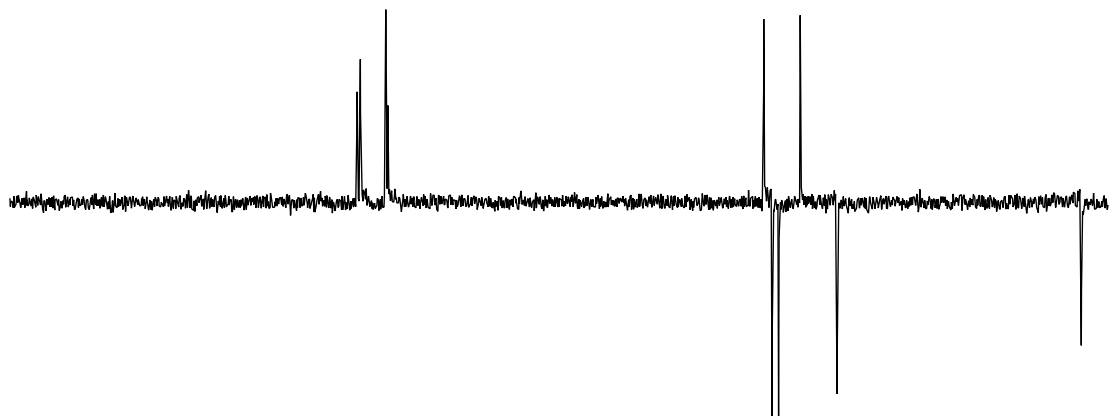
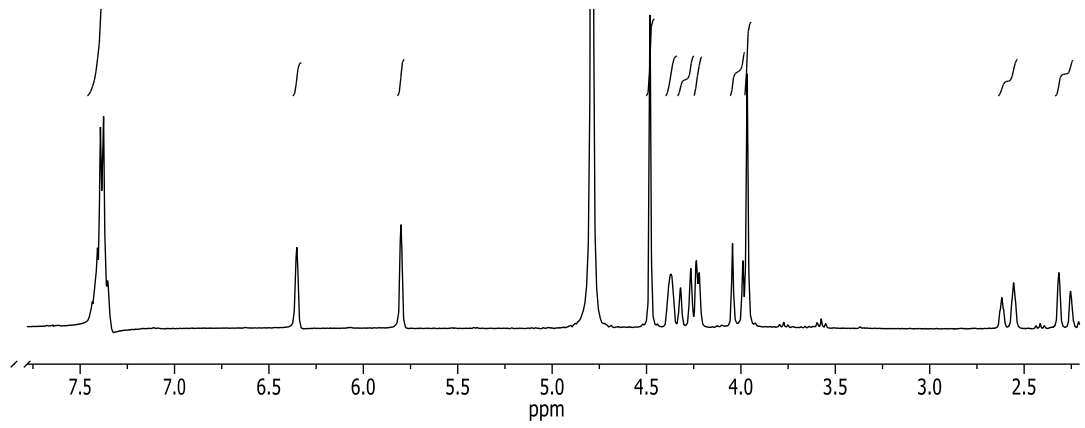
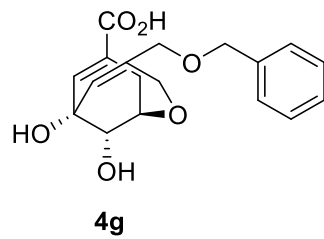


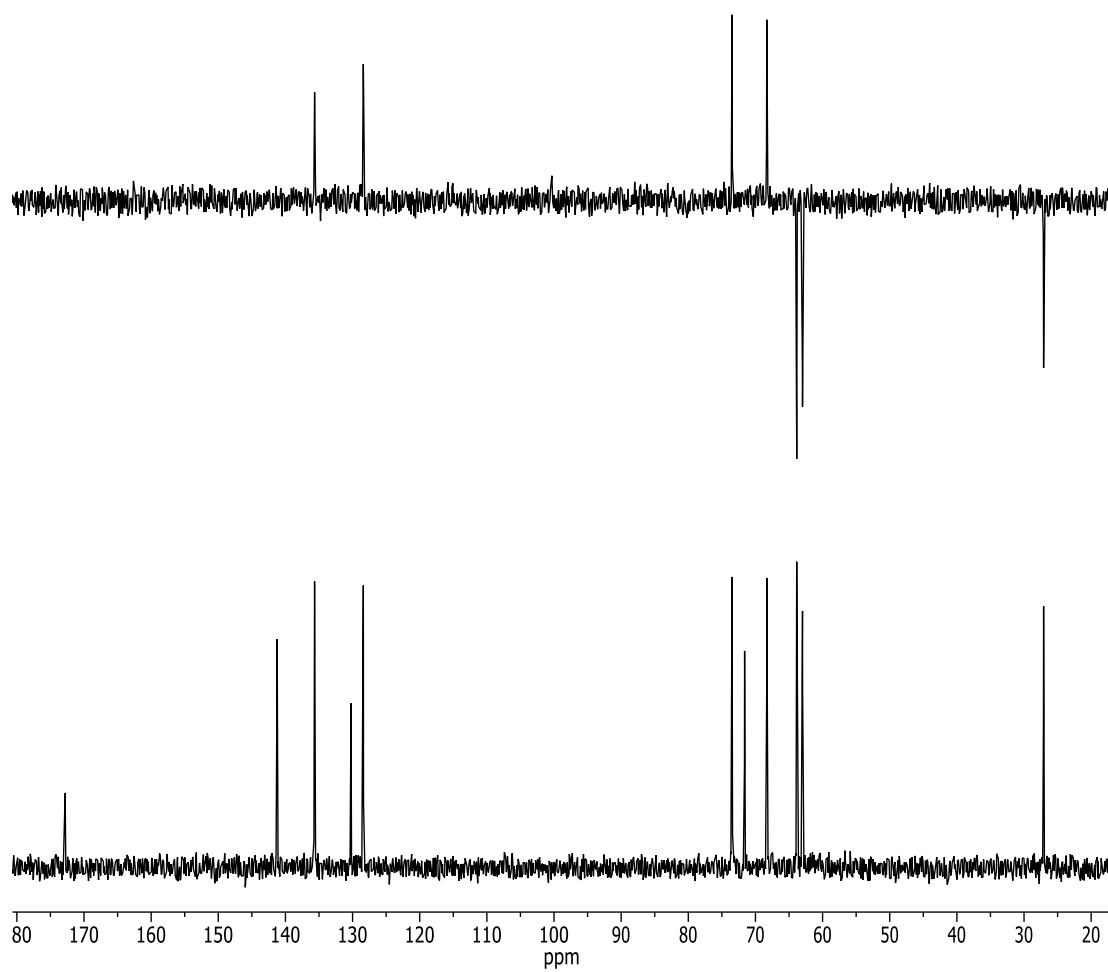
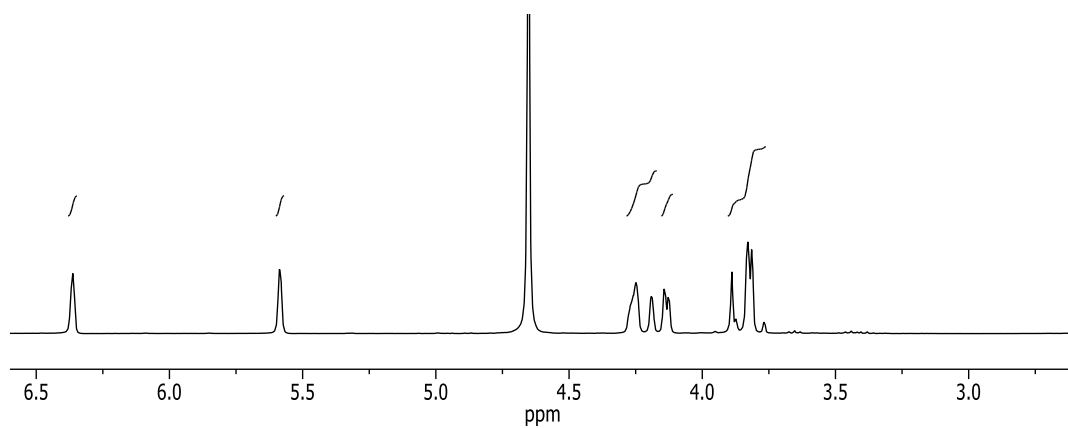
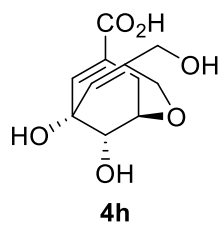


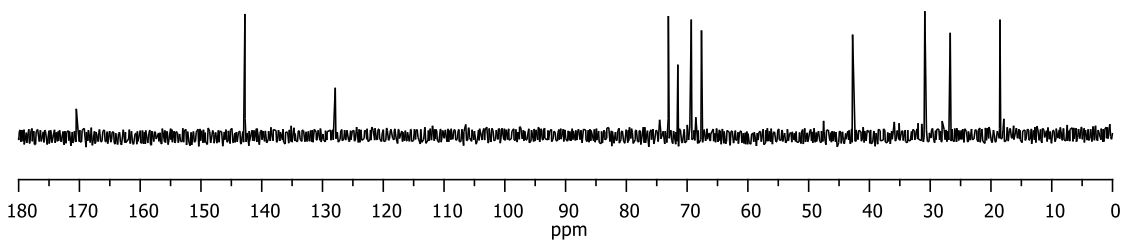
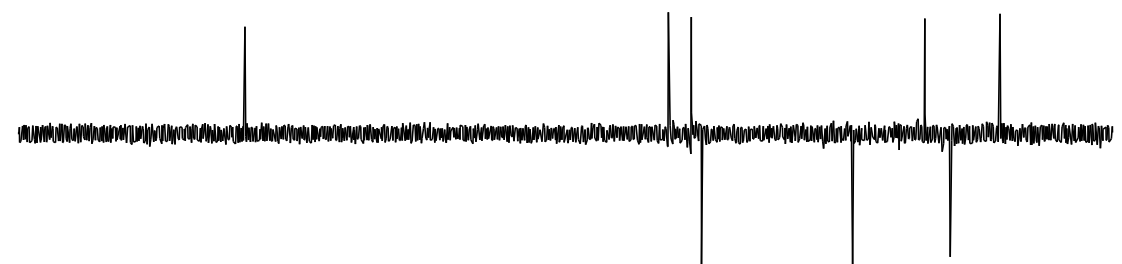
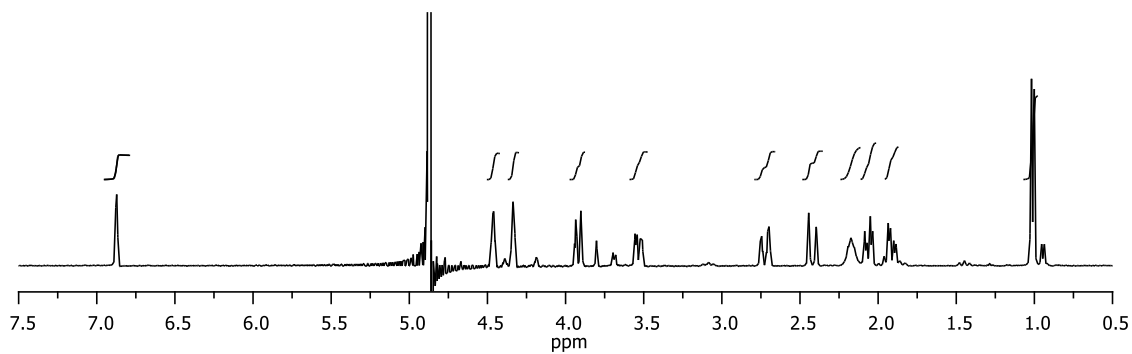
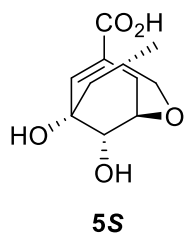


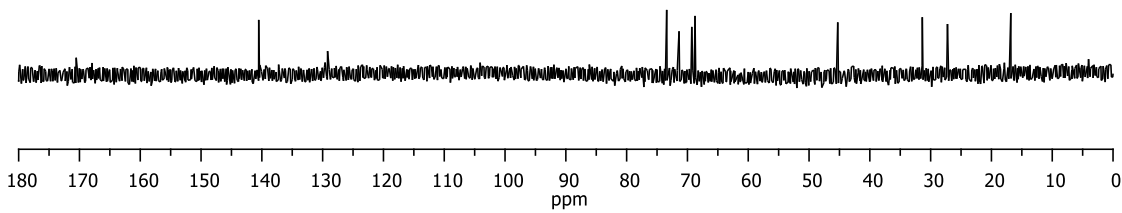
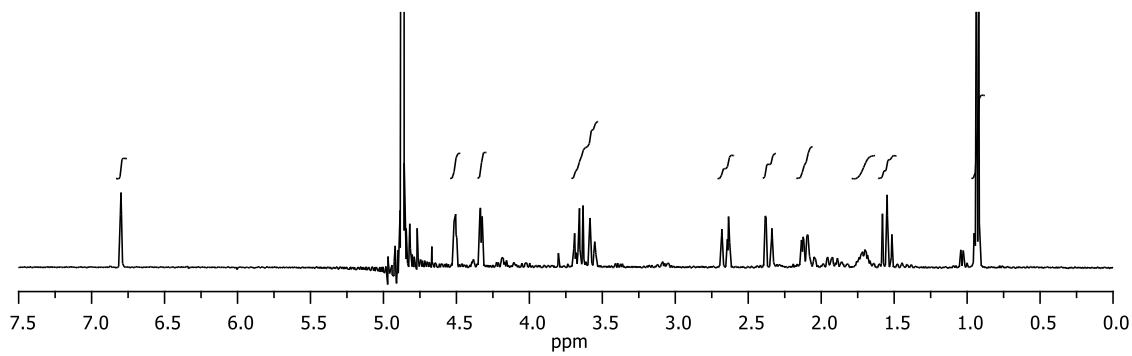
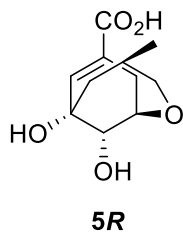




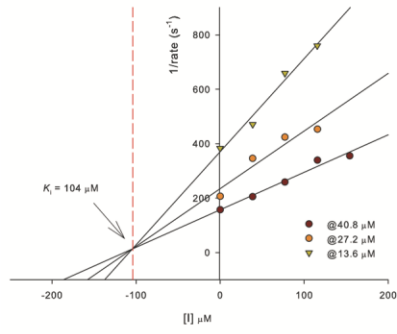




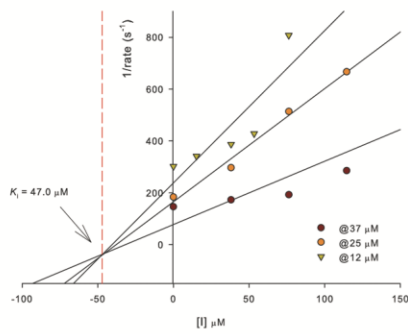




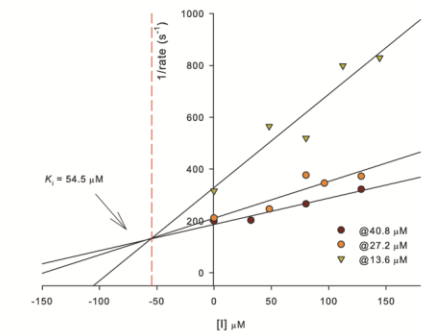
(A) ligand 2



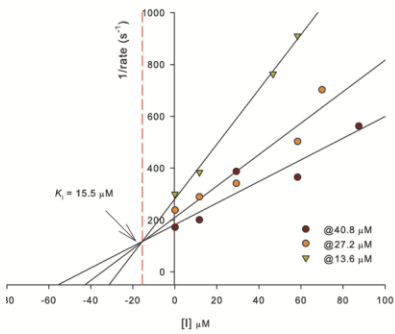
(B) ligand 3



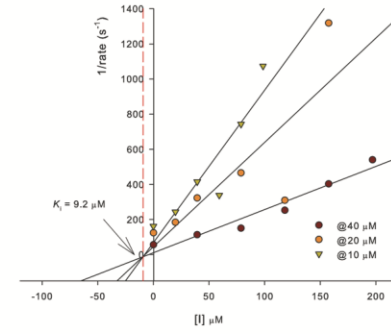
(C) ligand 4a



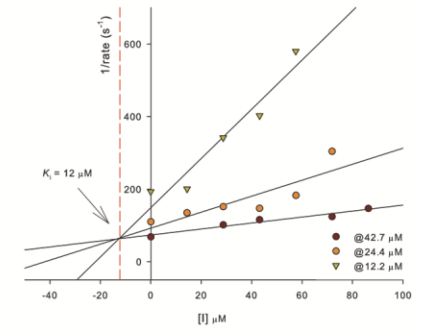
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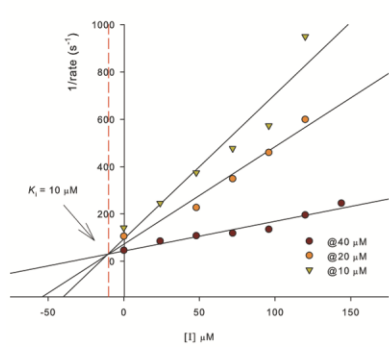
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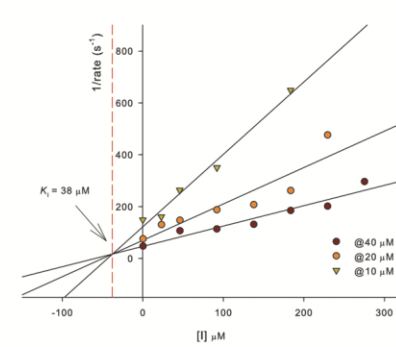
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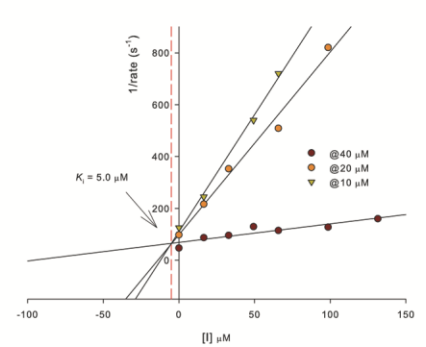
(G) ligand 4e



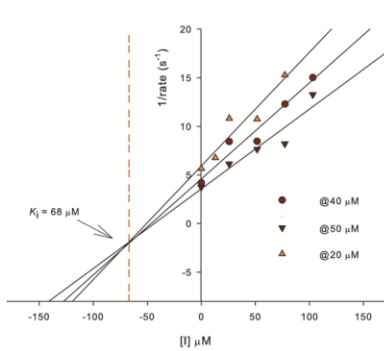
(H) ligand 4h



(I) ligand 4f



(J) ligand 4g



(K) ligand 5S

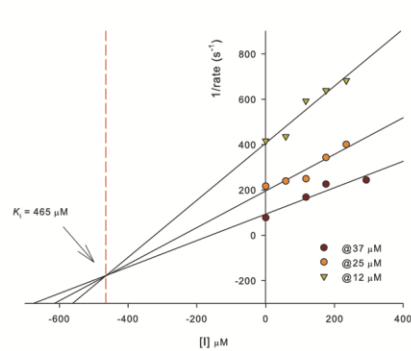


Figure S9. Dixon plots of compounds 2–5 against *Hp*-SK.



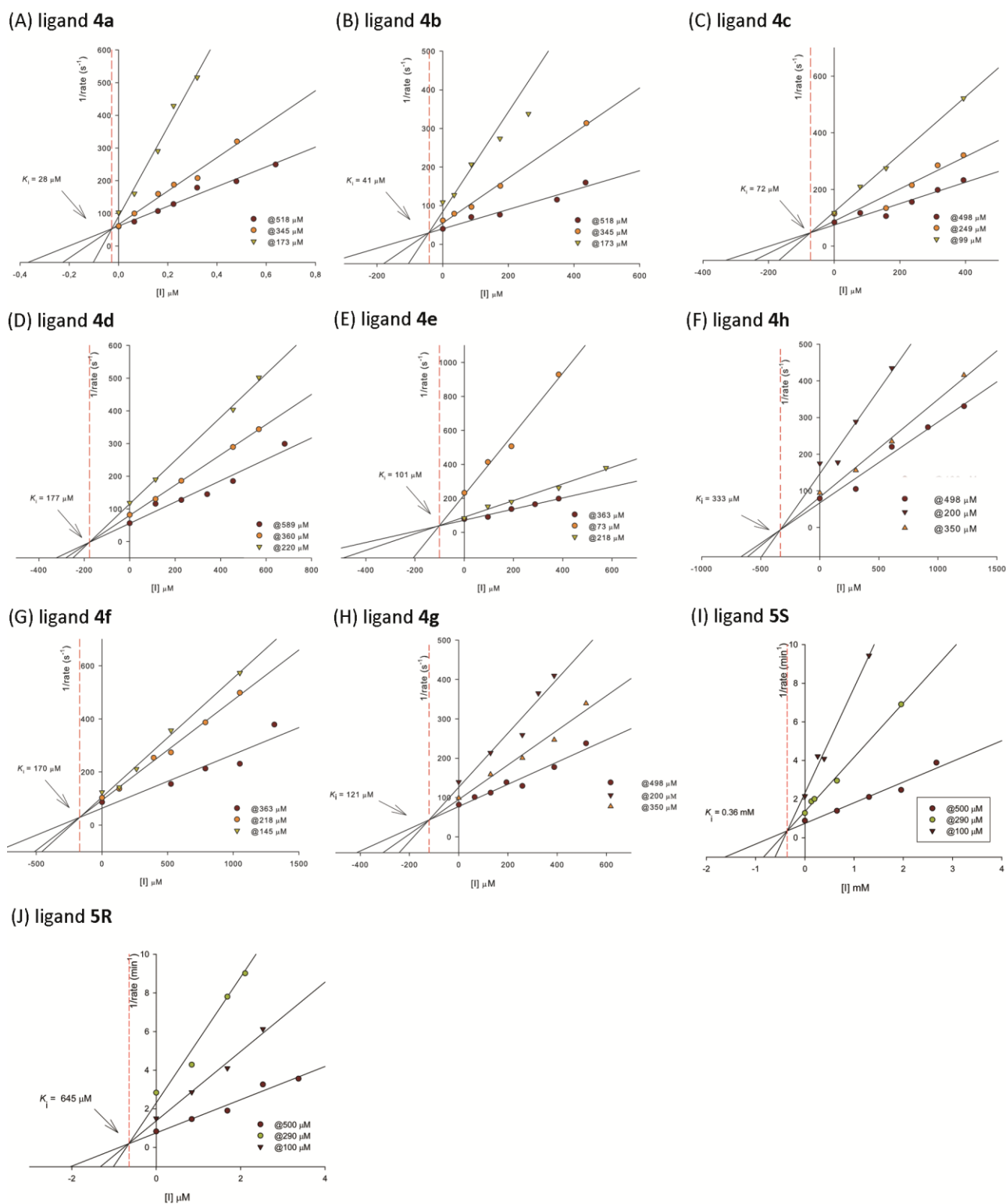


Figure S10. Dixon plots of compounds 4–5 against *Mt-SK*.