

Macrocyclic Analogs of (+)-Saxitoxin: insights into the structure of Zeteketoxin AB

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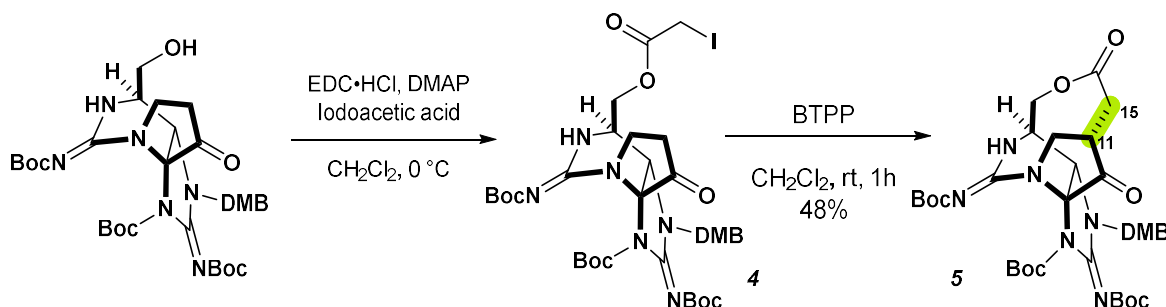
Supporting Information

1. General Experimental Considerations:

Solvents as dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), dimethylformamide (DMF) were degassed with N_2 and passed through a solvent purification system. Methanol (MeOH) was distilled from activated molecular sieves prior to use. Diglyme was commercially available.

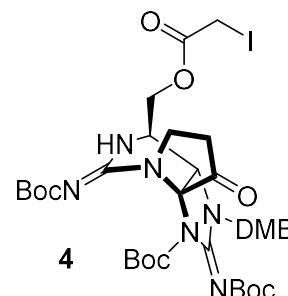
Mass spectroscopy data were obtained at the University of Utah Mass Spectrometry Facility. ^1H NMR and ^{13}C NMR spectra data were obtained at 500 MHz and 125 MHz, or 400 MHz and 101 MHz, respectively. Proton peaks for ^1H NMR were reported as chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplets, br = broad), coupling constants (Hz), integration, and relative to CDCl_3 peak (7.26 ppm), D_2O peak (4.80 ppm), deuterated MeOH- d_4 (3.31 ppm), dimethylsulfoxide- d_6 (2.49 ppm). ^{13}C NMR were reported as chemical shift (δ , ppm), and relative to CDCl_3 peak (77.0 ppm), deuterated MeOH- d_4 (49.1 ppm), and dimethylsulfoxide- d_6 (39.5 ppm). Optical rotations were collected on Perkin-Elmer PE-343 Polarimeter and reported as: $[\alpha]^{20}_{\text{D}}$ (c: g/100 mL, in solvent CHCl_3). Mass spectra were determined on a Micromass Quattro II (ESI/APCI-TOF) for HRMS at the University of Utah Mass Spectrometry Facility.

Experimental procedures:



Synthesis of tricyclic iodo-acetate (tert-butyl (2E,3aS,4R,6Z,10aR)-2,6-bis((tert-butoxycarbonyl)imino)-3-(2,4-dimethylbenzyl)-4-((2-iodoacetoxy)methyl)-10-oxooctahydro-1H,8H-pyrrolo[1,2-c]purine-1-carboxylate) (4)

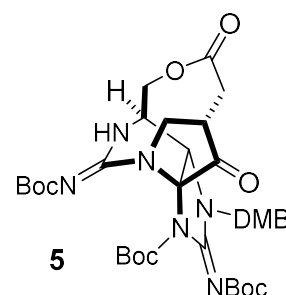
To a solution of the ketone-alcohol (1.3625 g, 1.98 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) at $0\text{ }^\circ\text{C}$ was added EDC·HCl (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) (0.759 g, 3.96 mmol, 2 equiv.), iodoacetic acid (0.5523 g, 2.97 mmol, 1.5 equiv.) and DMAP (4-Dimethylaminopyridine) (0.242 g, 1.98 mmol, 1 equiv.). The reaction mixture was allowed to stir for 1 h at $0\text{ }^\circ\text{C}$. The mixture was diluted with CH_2Cl_2 then was washed with water. The aqueous layer was



extracted with 2x CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give a colorless foam that was used in next step without further purification

Synthesis of macrocyclic lactone (tert-butyl (2E,4R,6Z,10aR)-2,6-bis((tert-butoxycarbonyl)imino)-3-(2,4-dimethylbenzyl)-10,12-dioxooctahydro-1H,8H-9,4-(ethanooxymethano)pyrrolo[1,2-c]purine-1-carboxylate) (5)

To a solution of tricyclic iodo-acetic acid (0.80 g, 0.9338 mmol, 1 equiv.) in CH₂Cl₂ (10 mL) was added BTTP (tert-Butylimino-tri(pyrrolidino)phosphorane) (0.57 mL, 1.868 mmol, 2 equiv.) at room temperature and the mixture was allowed to stir for 40 min. The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography gave macrocyclic lactone (0.373 g, 55%) as a colorless foam.



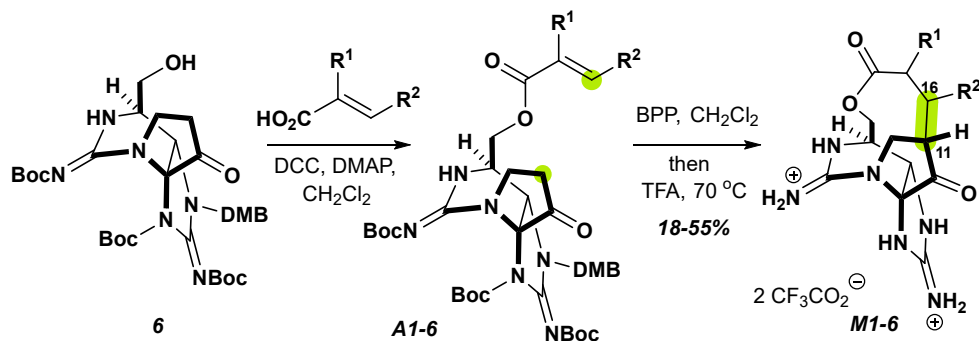
TLC R_f = 0.2 (3:2 EtOAc:Hexanes);

[α]_D²⁰ = −77.7° (c = 0.8, CHCl₃);

¹H NMR (400 MHz, CDCl₃) δ 9.23 (s, 1H), 7.26 (d, J = 8.3 Hz, 1H), 6.48 (dd, J = 8.4, 2.4 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 5.04 (d, J = 15.5 Hz, 1H), 4.99 (d, J = 12.3, 1H), 4.22 (d, J = 15.5 Hz, 1H), 4.17 (dd, J = 11.8, 6.5 Hz, 1H), 4.07 (s, 1H), 3.96 (d, J = 11.8 Hz, 1H), 3.83 (d, J = 4.3 Hz, 1H), 3.78 (d, J = 1.2 Hz, 6H), 3.42 (dd, J = 12.3, 4.5 Hz, 1H), 2.99 (q, J = 4.3 Hz, 1H), 2.80 (dd, J = 13.1, 3.4 Hz, 1H), 2.47 (dd, J = 13.2, 4.8 Hz, 1H), 1.47 (s, 9H), 1.46 (s, 9H), 1.44 (s, 9H);

¹³C NMR (126 MHz, CDCl₃) δ 207.2, 168.0, 163.8, 161.0, 160.1, 158.1, 157.9, 150.1, 131.5, 113.8, 105.2, 98.6, 86.6, 79.4, 79.0, 77.3, 77.3, 77.1, 76.8, 76.7, 66.5, 61.1, 56.0, 55.6, 55.4, 50.1, 48.1, 42.6, 41.0, 37.3, 29.7, 28.4, 28.3, 28.3, 28.0 ppm.

HRMS (ESI) calcd for C₃₅H₄₉N₆O₁₁ (M+H): 729.3454, found: 729.3459.



General procedure of synthesis of macrocycles (M1-M6)

To a solution of the tricyclic ketone (50 mg, 0.0726 mmol, 1 equiv.) in dry CH₂Cl₂ (1 mL) was added acrylic acid (0.109 mmol, 1.5 equiv.), EDC·HCl (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) (28 mg, 0.145 mmol, 2 equiv.) and DMAP (4-Dimethylaminopyridine) (14 mg, 0.109, 1.5 equiv.) at 0 °C. The mixture was allowed to stir for 1-4 h. Then the mixture was diluted with CH₂Cl₂ (2 mL) and washed with H₂O. The aqueous layer was extracted with CH₂Cl₂ (2 mL x2), and the combined organic layers were dried in Na₂SO₄ and

concentrated under reduced pressure to give white foam, which was used in next step without further purification. The white foam was dissolved in dry CH₂Cl₂ (1mL) and added BTPP (40 μ L, 0.128 mmol, 2 equiv.) at room temperature. The mixture was stirred for 40 min – 2h, then concentrated under reduced pressure, and purified by flash column chromatography to give N-Boc macrocycles **A1-A6** as white solids.

Trifluoroacetic acid (3mL, 0.008M) was added to the lactone (19 mg, 0.0269 mmol) and heated to 70 °C for 72 h. The reaction mixture was concentrated under reduced pressure, co-evaporated with CH₂Cl₂ until dried. The resulting mixture was diluted with H₂O (1mL) and washed with CH₂Cl₂ (2mL x3). The aqueous layers were combined and filtered through a 25-micron PTFE Acrodisc® syringe filter. The filter was washed with additional 1 mL of H₂O. The combined filtrates were evaporated under reduced pressure to give synthetic macrocyclic analogs **M1-M6**.

Cyclopentanelactonemacrocycle (A1) (tert-butyl (2E,3aR,6aS,13R,15Z)-2,15-bis((tert-butoxycarbonyl)imino)-1-(2,5-dimethoxybenzyl)-10,16-dioxododecahydro-13,4-(epiminomethano)-3a,6-methanocyclopenta[i]imidazo[4,5-d][1]oxa[6]azacycloundecine-3(2H)-carboxylate)

55% yield 2 steps;

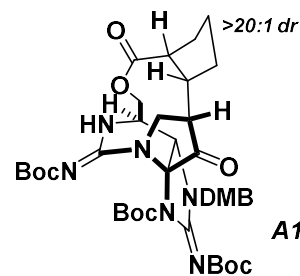
TLC R_f = 0.5 (2:3 Hexanes: EtOAc);

[α]_D²⁰ = –48.1° (c = 1, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 9.33 (s, 1H), 7.25 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.52 (dt, *J* = 8.3, 2.6 Hz, 1H), 6.47 (t, *J* = 2.2 Hz, 1H), 5.11 – 4.99 (m, 1H), 4.28 – 4.20 (m, 1H), 4.16 (td, *J* = 11.8, 7.9 Hz, 1H), 3.85 – 3.79 (m, 7H), 3.79 – 3.73 (m, 1H), 3.45 (dd, *J* = 12.3, 4.1 Hz, 1H), 3.03 (ddq, *J* = 21.0, 10.2, 3.6 Hz, 1H), 2.07 – 1.98 (m, 2H), 1.92 – 1.76 (m, 2H), 1.57 – 1.48 (m, 27H), 1.48 – 1.38 (m, 2H);

¹³C NMR (126 MHz, CDCl₃) δ 207.98, 172.82, 172.61, 163.91, 161.13, 160.93, 160.71, 158.44, 158.33, 158.03, 156.90, 151.87, 150.56, 131.58, 131.34, 114.87, 114.02, 105.10, 104.98, 98.60, 98.58, 85.88, 79.42, 79.04, 78.74, 77.32, 77.27, 77.07, 76.92, 76.81, 75.10, 66.92, 66.74, 61.86, 60.86, 60.38, 55.60, 55.57, 55.39, 49.07, 48.96, 48.63, 47.84, 47.15, 45.56, 43.28, 43.26, 42.90, 42.41, 41.89, 39.74, 33.95, 33.83, 30.32, 29.71, 28.53, 28.37, 28.34, 28.23, 28.16, 28.03, 27.86, 27.81, 25.64, 24.96, 24.84, 24.58, 21.04, 14.19.;

HRMS (ESI) calc for C₃₉H₅₅N₆O₁₁ (M+H): 783.3929, found 783.3937

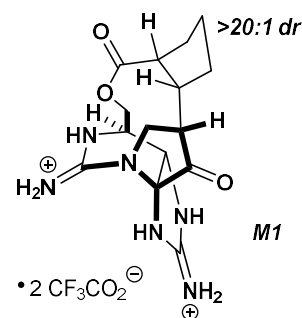


Cyclopentanelactonemacrocycle (M1) ((3aS,6aS,13R)-10,16-dioxododecahydro-13,4-(epiminomethano)-3a,6-methanocyclopenta[i]imidazo[4,5-d][1]oxa[6]azacycloundecine-2,15(3H)-diiminium)

^1H NMR (500 MHz, D_2O) δ 4.91 (d, J = 1.0 Hz, 1H), 4.90 – 4.83 (m, 1H), 3.96 – 3.86 (m, 3H), 3.37 (dd, J = 12.3, 3.4 Hz, 1H), 3.21 (dt, J = 9.6, 3.3 Hz, 1H), 3.05 (dtd, J = 10.4, 7.6, 3.2 Hz, 1H), 2.88 (ddd, J = 10.6, 10.6, 7.7 Hz, 1H), 1.97 (tt, J = 9.4, 3.8 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.75 – 1.61 (m, 2H), 1.36 – 1.22 (m, 2H).;

^{13}C NMR (126 MHz, D_2O) δ 207.09, 175.83, 163.00, 162.72, 156.01, 117.40, 115.09, 76.46, 66.86, 61.46, 50.37, 45.96, 43.49, 42.43, 33.69, 30.02, 24.15.;

HRMS (ESI) calc for $\text{C}_{15}\text{H}_{21}\text{N}_6\text{O}_3$ ($\text{M}+\text{H}$): 333.1670, found 333.1675



Lactonemacrocycle (A2) (tert-butyl (2E,4R,6Z,10aR)-2,6-bis((tert-butoxycarbonyl)imino)-3-(2,5-dimethoxybenzyl)-10,13-dioxooctahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-1-carboxylate)

18% yield 2 steps;

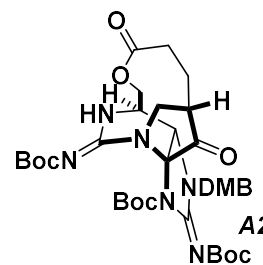
TLC R_f = 0.35 (2:3 Hexanes: EtOAc);

$[\alpha]^{20}_{\text{D}} = -93.0^\circ$ (c = 1, CHCl_3);

^1H NMR (500 MHz, CDCl_3) δ 9.34 (s, 1H), 7.25 (d, J = 8.3 Hz, 1H), 6.50 (dd, J = 8.3, 2.4 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 4.98 (d, J = 15.2 Hz, 1H), 4.27 (d, J = 15.2 Hz, 1H), 4.20 (dd, J = 11.7, 8.9 Hz, 1H), 4.02 – 3.97 (m, 3H), 3.96 (s, 1H), 3.82 (s, 6H), 3.77 (s, 1H), 3.17 (tt, J = 9.0, 2.8 Hz, 1H), 2.59 (ddd, J = 16.8, 12.4, 4.5 Hz, 1H), 2.41 (ddt, J = 16.9, 13.0, 4.1 Hz, 2H), 2.06 – 1.96 (m, 1H), 1.52 – 1.46 (m, 27H);

^{13}C NMR (126 MHz, CDCl_3) δ 209.51, 170.19, 164.04, 162.05, 161.17, 158.30, 157.94, 151.25, 150.42, 131.48, 113.76, 105.04, 98.55, 85.94, 79.44, 78.84, 77.29, 77.04, 76.78, 75.98, 66.56, 61.38, 55.51, 55.40, 48.79, 48.58, 42.49, 41.72, 29.88, 29.69, 28.50, 28.35, 27.91, 25.28;

HRMS (ESI) calc for $\text{C}_{36}\text{H}_{51}\text{N}_6\text{O}_{11}$ ($\text{M}+\text{H}$): 743.3616, found: 743.3621

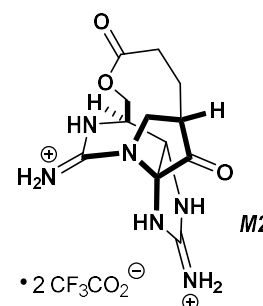


Lactonemacrocycle (M2) ((4R,10aS)-10,13-dioxohexahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-2,6-diiminium)

^1H NMR (500 MHz, D_2O) δ 4.72 (s, 1H), 4.30 (d, J = 12.0 Hz, 1H), 4.20 (dt, J = 12.1, 2.1 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.95 (s, 1H), 3.89 (dd, J = 12.5, 3.0 Hz, 1H), 3.20 – 3.13 (m, 1H), 2.58 (ddd, J = 17.0, 12.1, 4.6 Hz, 1H), 2.43 (dt, J = 17.4, 4.7 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.07 (ddt, J = 14.1, 8.9, 5.0 Hz, 1H);

^{13}C NMR (126 MHz, D_2O) δ 209.30, 172.48, 163.10, 162.81, 157.41, 156.95, 75.65, 69.54, 66.30, 61.78, 49.40, 47.00, 41.36, 29.25, 25.13;

HRMS (ESI) calc for $\text{C}_{12}\text{H}_{17}\text{N}_6\text{O}_3$ ($\text{M}+\text{H}$): 293.1362, found 293.1367



17-Methylactonemacrocyclic (A3) (tert-butyl (2E,4R,6Z,10aR,11R)-2,6-bis((tert-butoxycarbonyl)imino)-3-(2,5-dimethoxybenzyl)-11-methyl-10,13-dioxooctahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-1-carboxylate)

34% yield 2 steps;

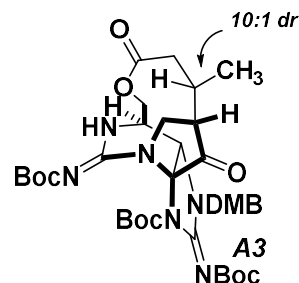
TLC Rf = 0.5 (2:3 Hexanes: EtOAc);

$[\alpha]^{20}_D = -57.4^\circ$ (c = 1, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 9.30 (s, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.53 – 6.46 (m, 2H), 4.91 (d, *J* = 15.0 Hz, 1H), 4.29 (d, *J* = 15.1 Hz, 1H), 4.24 – 4.12 (m, 2H), 4.03 (s, 1H), 3.87 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.83 (d, *J* = 7.7 Hz, 6H), 3.78 (dd, *J* = 11.9, 2.3 Hz, 1H), 3.66 (s, 1H), 3.06 – 2.99 (m, 1H), 2.84 – 2.74 (m, 1H), 2.37 (dd, *J* = 14.4, 12.0 Hz, 1H), 2.29 (dd, *J* = 14.5, 4.8 Hz, 1H), 1.57 – 1.45 (m, 27H), 1.09 (d, *J* = 7.0 Hz, 3H);

¹³C NMR (126 MHz, CDCl₃) δ 208.66, 169.95, 161.26, 158.39, 157.87, 156.78, 151.24, 150.44, 139.43, 131.61, 125.43, 113.74, 104.96, 98.52, 98.50, 85.90, 79.54, 78.81, 77.29, 77.24, 77.04, 76.79, 75.84, 66.13, 62.06, 55.48, 55.41, 49.86, 49.71, 49.10, 46.38, 42.16, 37.60, 36.71, 33.96, 33.32, 33.23, 29.70, 28.49, 28.35, 28.33, 28.03, 27.88, 25.62, 25.55, 24.96, 24.86, 23.36, 22.69, 17.66.

HRMS (ESI) calc for C₃₇H₅₂N₆O₁₁ (M+H): 757.3772, found: 757.3777

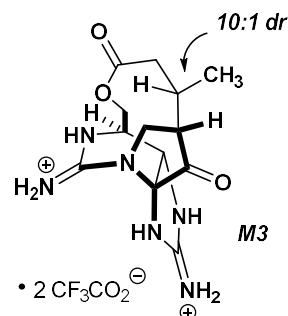


17-Methylactonemacrocyclic (M3) ((4R,10aS,11R)-11-methyl-10,13-dioxohexahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-2,6-diiminium)

¹H NMR (500 MHz, D₂O) δ 4.52 (d, *J* = 12.1 Hz, 1H), 4.19 – 4.05 (m, 3H), 4.05 – 3.98 (m, 1H), 3.95 (dd, *J* = 12.2, 3.7 Hz, 1H), 3.15 (ddd, *J* = 9.6, 3.7, 1.9 Hz, 1H), 2.82 (dtd, *J* = 15.0, 7.4, 3.8 Hz, 1H), 2.49 – 2.43 (m, 2H), 1.08 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, D₂O) δ 208.01, 171.97, 163.10, 162.81, 157.41, 157.38, 117.51, 115.19, 75.80, 66.87, 65.86, 62.17, 49.68, 49.06, 48.13, 44.69, 37.14, 36.77, 33.49, 21.61, 20.96;

HRMS (ESI) calc for C₁₃H₁₉N₆O₃ (M+H): 307.1513, found 307.1519

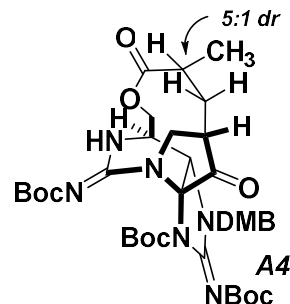


16-Methylactonemacrocyclic(A4) (tert-butyl (2E,4R,6Z,10aR)-2,6-bis((tert-butoxycarbonyl)imino)-3-(2,5-dimethoxybenzyl)-12-methyl-10,13-dioxooctahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-1-carboxylate)

46% yield 2 steps;

$[\alpha]^{20}_D = -120^\circ$ (c = 1, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 9.42 (s, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.50 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 5.07 (d, *J* = 15.5 Hz, 1H), 4.29 – 4.20 (m, 2H), 4.05 – 3.90 (m, 5H), 3.82 (d, *J* = 3.5 Hz, 7H),



3.20 – 3.10 (m, 1H), 2.83 (dq, $J = 10.9, 7.1, 3.4$ Hz, 1H), 2.22 (ddd, $J = 14.3, 10.4, 3.7$ Hz, 1H), 1.85 (ddd, $J = 14.4, 11.6, 4.9$ Hz, 1H), 1.52 (s, 9H), 1.49 (s, 18H), 1.14 (d, $J = 7.2$ Hz, 3H);

^{13}C NMR (126 MHz, CDCl_3) δ 173.02, 161.02, 158.15, 131.77, 131.24, 113.94, 105.22, 105.10, 98.58, 98.51, 78.93, 77.30, 77.25, 77.04, 76.79, 74.97, 67.08, 60.13, 55.57, 55.53, 55.51, 55.39, 55.37, 49.08, 47.36, 47.07, 42.45, 41.40, 41.15, 37.15, 35.99, 35.35, 34.87, 33.96, 28.50, 28.36, 28.34, 28.00, 27.92, 27.90, 25.62, 24.96, 17.73, 17.59;

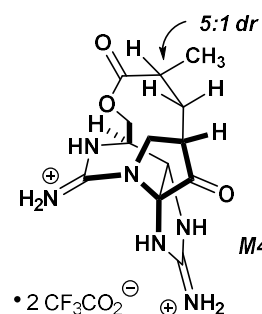
HRMS (ESI) calc for $\text{C}_{37}\text{H}_{52}\text{N}_6\text{O}_{11}$ ($\text{M}+\text{H}$): 757.3772, found: 757.3770

16-Methylactonemacrocyclic (M4) ((4R,10aS,12R)-12-methyl-10,13-dioxohexahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-2,6-diiminium)

^1H NMR (500 MHz, d_2O) δ 4.35, 4.35, 4.33, 4.32, 4.15, 4.15, 4.13, 4.12, 4.01, 4.00, 4.00, 4.00, 3.99, 3.97, 3.97, 3.96, 3.95, 3.94, 3.93, 3.93, 3.92, 3.92, 3.90, 3.88, 3.79, 3.78, 3.76, 3.76, 3.11, 3.10, 3.10, 3.09, 3.09, 3.08, 3.08, 3.07, 3.07, 3.06, 3.06, 2.72, 2.71, 2.70, 2.70, 2.69, 2.68, 2.67, 2.32, 2.32, 2.30, 2.29, 2.29, 2.27, 2.27, 1.84, 1.83, 1.81, 1.81, 1.80, 1.79, 1.78, 1.01, 0.99;

^{13}C NMR (126 MHz, d_2O) δ 208.50, 175.52, 162.94, 162.66, 115.05, 76.37, 67.11, 52.06, 49.16, 41.16, 35.80, 35.16, 16.72.;

HRMS (ESI) calc for $\text{C}_{13}\text{H}_{19}\text{N}_6\text{O}_3$ ($\text{M}+\text{H}$): 307.1513, found 307.1527



17-Phenyllactonemacrocyclic (A5) (tert-butyl (2E,4R,6Z,10aR,11R)-2,6-bis((tert-butoxycarbonyl)imino)-3-(2,5-dimethoxybenzyl)-10,13-dioxo-11-phenyloctahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-1-carboxylate)

30% yield 2 steps;

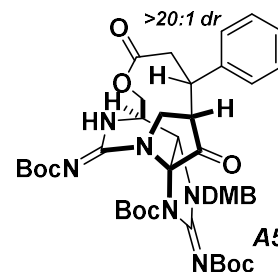
TLC $R_f = 0.5$ (2:3 Hexanes: EtOAc);

$[\alpha]^{20}_D = -24.9^\circ$ ($c = 1$, CHCl_3);

^1H NMR (500 MHz, CDCl_3) δ 7.35 – 7.22 (m, 5H), 7.19 – 7.13 (m, 2H), 6.52 (dd, $J = 8.3, 2.5$ Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 4.95 (d, $J = 15.0$ Hz, 1H), 4.35 (t, $J = 10.3$ Hz, 1H), 4.29 (d, $J = 15.0$ Hz, 1H), 4.25 – 4.15 (m, 2H), 4.07 (s, 1H), 3.94 (dd, $J = 11.9, 2.1$ Hz, 1H), 3.86 (s, 3H), 3.83 (d, $J = 12.1$ Hz, 1H), 3.83 (s, 3H), 3.72 (s, 1H), 3.37 (dd, $J = 10.6, 7.4$ Hz, 1H), 2.88 (dd, $J = 14.9, 13.0$ Hz, 1H), 2.52 (dd, $J = 14.9, 4.1$ Hz, 1H), 1.54 (s, 9H), 1.48 (s, 9H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 208.55, 169.49, 161.28, 158.40, 157.90, 154.00, 151.20, 150.35, 143.65, 131.64, 129.22, 127.39, 126.58, 113.69, 104.96, 98.53, 86.07, 79.67, 78.90, 77.30, 77.25, 77.05, 76.79, 75.63, 66.49, 62.24, 60.44, 55.54, 55.44, 49.61, 49.40, 47.37, 43.82, 42.17, 37.77, 33.94, 32.76, 30.80, 29.72, 28.48, 28.37, 27.82, 26.40, 25.60, 25.50, 25.30, 24.95, 24.70, 14.22.;

HRMS (ESI) calc for $\text{C}_{42}\text{H}_{55}\text{N}_6\text{O}_{11}$ ($\text{M}+\text{H}$): 819.3923, found: 819.3925

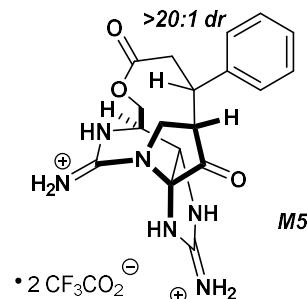


17-Phenyllactonemacrycycle (M5) ((4R,10aS,11R)-10,13-dioxo-11-phenylhexahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-2,6-diiminium)

^1H NMR (500 MHz, D_2O) δ 7.35 – 7.10 (m, 5H), 4.80 (s, 1H), 4.38 (dt, J = 12.1, 1.7 Hz, 1H), 4.25 (dt, J = 12.1, 2.2 Hz, 1H), 4.21 – 4.04 (m, 2H), 3.97 (d, J = 2.1 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.36 (ddd, J = 9.2, 4.1, 1.8 Hz, 1H), 2.99 (dd, J = 15.4, 13.2 Hz, 1H), 2.60 (ddd, J = 15.8, 4.0, 1.9 Hz, 1H).

^{13}C NMR (126 MHz, D_2O) δ 207.22, 171.04, 163.07, 142.53, 129.25, 127.60, 126.54, 75.50, 66.19, 62.31, 49.37, 48.14, 45.51, 43.10, 36.27, 30.22.;

HRMS (ESI) calc for $\text{C}_{18}\text{H}_{21}\text{N}_6\text{O}_3$ ($\text{M}+\text{H}$): 369.1670, found: 369.1675



17-Phenyldioxolelactonemacrocyclic (A6) (tert-butyl (2E,4R,6Z,10aR,11R)-11-(benzo[d][1,3]dioxol-5-yl)-2,6-bis((tert-butoxycarbonyl)imino)-3-(2,5-dimethoxybenzyl)-10,13-dioxooctahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-1-carboxylate)

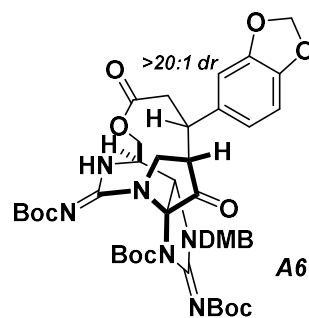
30% yield 2 steps;

TLC R_f = 0.5 (2:3 Hexanes: EtOAc);

^1H NMR (500 MHz, CDCl_3) δ 9.34 (s, 1H), 7.26 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.65 – 6.58 (m, 2H), 6.51 (dd, J = 8.3, 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 5.95 (s, 2H), 4.93 (d, J = 15.0 Hz, 1H), 4.29 (d, J = 15.1 Hz, 1H), 4.25 – 4.16 (m, 2H), 4.16 – 4.08 (m, 2H), 4.05 (s, 1H), 3.96 – 3.90 (m, 1H), 3.84 (d, J = 11.6 Hz, 8H), 3.79 – 3.67 (m, 3H), 3.37 – 3.30 (m, 1H), 2.88 – 2.77 (m, 1H), 2.49 (dd, J = 14.9, 4.1 Hz, 1H), 2.22 (s, 1H), 2.05 (s, 1H), 1.96 – 1.90 (m, 1H), 1.53 (s, 9H), 1.48 (s, 9H), 1.45 (s, 9H).;

^{13}C NMR (126 MHz, CDCl_3) δ 161.29, 158.40, 157.89, 151.22, 148.19, 146.70, 131.63, 119.51, 113.66, 108.67, 107.07, 104.95, 101.26, 98.53, 86.06, 79.67, 78.90, 77.31, 77.25, 77.05, 76.80, 66.47, 62.22, 60.44, 55.53, 55.43, 49.73, 49.61, 43.56, 42.21, 37.89, 33.94, 32.76, 30.80, 29.72, 28.48, 28.37, 27.83, 26.40, 25.60, 25.30, 24.95, 24.70, 14.21.;

HRMS (ESI) calc for $\text{C}_{43}\text{H}_{55}\text{N}_6\text{O}_{13}$ ($\text{M}+\text{H}$): 863.3822, found: 863.3822

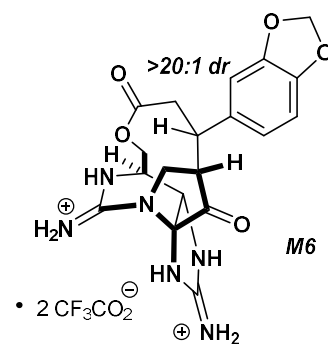


17-Phenyldioxolelactonemacrocycle (M6) ((4R,10aS,11R)-11-(benzo[d][1,3]dioxol-5-yl)-10,13-dioxohexahydro-1H,8H-9,4-(propanooxymethano)pyrrolo[1,2-c]purine-2,6-diiminium)

¹H NMR (500 MHz, D₂O) δ 6.80 – 6.50 (m, 3H), 5.81 (d, J = 1.7 Hz, 2H), 4.81 – 4.74 (m, 1H), 4.37 (ddd, J = 12.0, 8.2, 1.7 Hz, 1H), 4.27 – 4.20 (m, 1H), 4.10 (dd, J = 8.2, 3.8 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.82 – 3.70 (m, 1H), 3.31 (ddd, J = 8.3, 4.4, 1.8 Hz, 1H), 2.93 (ddd, J = 15.3, 13.0, 8.5 Hz, 1H), 2.59 – 2.49 (m, 1H).

¹³C NMR (126 MHz, D₂O) δ 207.11, 170.97, 162.82, 157.36, 147.57, 146.22, 136.54, 119.72, 116.45, 108.73, 107.11, 101.18, 75.50, 66.16, 62.30, 49.37, 48.43, 45.43, 42.86, 36.37.;

HRMS (ESI) calc for C₁₉H₂₁N₆O₅ (M+H): 413.1568, found 413.1574



2. Constellation pharmacology experiments

Calcium imaging based constellation pharmacology experiments were done as described before^{1, 2}. Lumbar dorsal root ganglion (DRG) L1-L6 were isolated from 40-70 day old mice, digested with 0.25% trypsin for 20 minutes and dissociated to obtain primary cell culture plated on poly-D-lysine coated plates overnight, supplemented with minimal essential media + supplements. Cells were loaded with 2.5 μM FURA-2AM for an hour before experiment. Calcium imaging was performed using Nikon-Eclipse microscope and fluorescence from FURA-2 was monitored by ratiometric imaging. Video was captured every 2 s and the ratio of excitation wavelengths 340 nM/380 nM was monitored for an hour. In each trial, ~1000 neurons were simultaneously monitored. The changes to intracellular calcium levels were monitored in response extracellular application of pharmacological stimulus. Cells were stimulated with 20mM KCl for 15 s, every 7 minute. After the first KCl application, cells were pre-treated with 1uM ATX-II for 1 minute just before the next KCl stimulus pulse. Cells were incubated for 5-minutes with the test drug (either analog A4 or A5) at 100 nM or 1 uM concentration. The effects of the test drug were monitored on the subsequent KCl+ATX-II pulse. Two more stimulus pulses were given to observe recovery from the effect of test drug and cells were incubated with either 100 nM or 1uM saxitoxin (STX). The effects of test drug were compared with STX in the same experiment.

Analysis of data from Constellation pharmacology experiments

A single calcium imaging experiment measures the intracellular calcium concentration (ICC) for 100s-1000s of cells at 2 second intervals over a time course of minutes to hours. During the experiment specific modifications are made to the cell culture to test for induced changes in ICC. The ICC values for each cell across the entire experiment is referred to as the phenotype of the cell. 20 nM K⁺ is added at regular intervals to induce a depolarization phenotype (KDP). The KDP is very specific for each cell and highly reproducible but is conditional upon a complex set of cellular variables.

We test for activity of a toxin of interest by incubating the cell culture in the toxin between K⁺ pulses and testing for a significant change in the phenotype of all or a subset of cells. A change that alters the KDP after incubation is referred to as a toxin effect (TXE).

-Relative ratio as a measure of the fractional impact of the toxin (Amp Stat). We use the relative ratio of the affected KDP to all other KDPs as a measure of the fractional impact of the toxin (Amp Stat). This is calculated as $(\text{KDPe}-\text{KDPmean})/(\text{KDPe}+\text{KDPmean})$ where KDPe is the KDP of the pulse immediately after the application of the toxin and KDPmean is the mean of the KDP values across all other pulses. This value varies from -1, complete block to 1, complete amplification, and is roughly analogous to a signed R^2 value. The Amp Stat values from each cell are ranked from lowest to highest according to the Amp Stat values to form a cumulative distribution function (CDF) graph, used to visualize the distribution of the results.

3. Computational Details and Methods

All Saxitoxin, (+)-STX, derivatives were subjected to the following general workflow: conformational searching in water, density functional theory (DFT) optimization in water, single point energy calculation in water, triple-zeta energy correction. Conformational searches were conducted for the ketone and hydrate forms of all reported analogs using Macromodel (part of the Schrödinger Suite) and the OPLS4 (release 2022-1)³ force field (10,000 steps, 5 kcal/mol energy window) in water. At this stage, all conformers arising from this search were optimized at the ω b97XD/def2-SVP/SMD(water) level of theory using Gaussian 16 (Revision C.01).⁴ All optimized geometries were verified by frequency computations as minima (zero imaginary frequencies) at the optimization level of theory. Single point calculations were run using M062X-D3/def2-TZVP/SMD(water) and parameters were acquired from these ground state structures (*vide infra*).⁵ Triple-zeta energy corrections were computed using Paton GoodVibes (v3.2) and the quasi-harmonic Gibbs free energy correction.⁶ NBO charges were calculated using NBO 3.1 at the M062X-D3/def2-TZVP/SMD(water) level as implemented in Gaussian 16.⁷ ChelpG and Hirshfeld charges (and its derivatives) as well as NMR shifts (GIAO method) were computed as implemented in Gaussian 16 at the M062X-D3/def2-TZVP/SMD(water) level.⁸⁻¹² Water (H_2O) was computed in the same manner for hydration analysis. In total, 1215 conformers were optimized in this study. Coordinates for the lowest energy conformer (LEC) for each analog (ketone and hydrate forms), are included in the supplemental information. Coordinates for the minimum buried volume conformers $\text{Vbur}(\text{C12})_{1.5\text{\AA}}$ are also present (used for modeling). all related calculations can be found on Sigman GitHub organization page: https://github.com/SigmanGroup/STX_Hydration_Equilibria. An atom numbering scheme for the atoms used for modeling is provided (**Figure S1**).

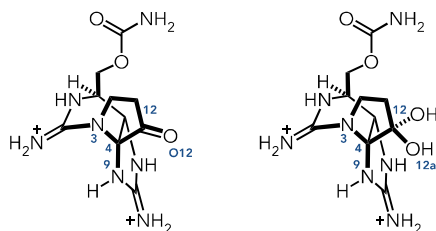
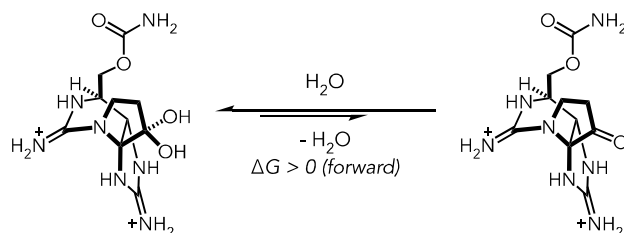


Figure S1. Atom labeling of (+)-STX used for DFT parameterization. Only atoms featuring correlations relevant to this study are displayed.

Gibbs free energy of ketone hydration ($\Delta G_{\text{Hydration}}$)



Scheme S1. Example of hydration equilibrium of (+)-STX in the presence of water. For this study, $\Delta G > 0$ denotes preference for the ketone.

Hydration energies ($\Delta G_{\text{Hydration}}$) were computed by first identifying the lowest energy conformer (LEC) for the ketone and hydrate of each respective analog. The energy for the LEC ketone was added to water, providing a corrected energy that could be compared directly to the hydrate. This sum was subtracted from the energy of the hydrate (**Scheme S1** & **Equation S1**). This provides positive ΔG values when the hydrate is disfavored, and negative ΔG values when the hydrate is favored. The full table can be found in the main text (**Table 1**). **Note:** gas phase-based conformer models have successfully been applied to the calculation of ketone hydration equilibria by computing the solvation energy (Henry's constant) upon placement in water.¹³ However, this technique does not account for the effect of water on conformation, which was found to have a consequential impact on the computed ΔG of ketone hydration.

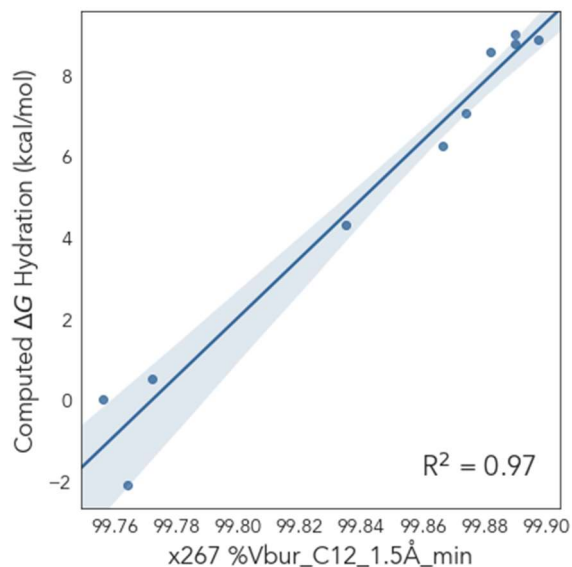
$$\Delta G_{\text{Hydration}} = G_{\text{Hydrate}} - (G_{\text{Water}} + G_{\text{Ketone}}) \quad \text{Equation S1}$$

Univariate Correlations of DFT Descriptors to Computed ΔG of Ketone Hydration ($\Delta G_{\text{Hydration}}$)

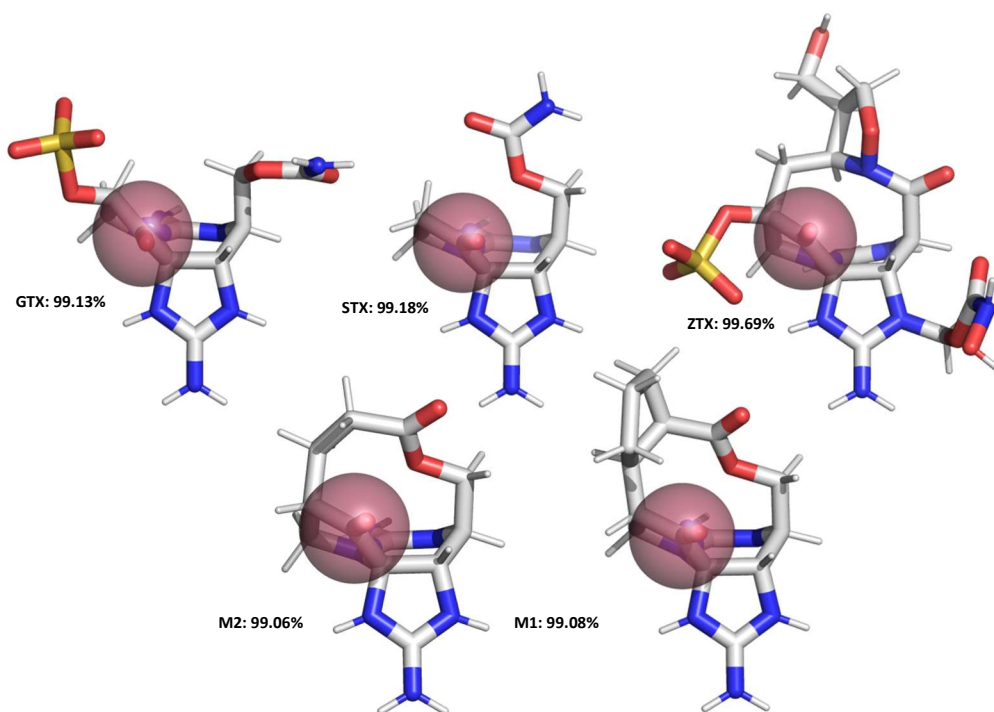
All univariate correlations were generated using the parameters found in **Supplemental_Document1.xlsx**. Sheet 1 contains all ketone descriptors and Sheet 2 contains all hydrate descriptors. Maximum and minimum descriptor values were obtained for each analog, as well as a LEC set of descriptors, and a 4D Boltzmann-weighted average set of descriptors. **In all cases, the minimum descriptor value is used for ketone modeling.** A combination of descriptor types was used for hydrate modeling.

All correlations were achieved by analyzing analogs in their respective ketone and hydrate forms to enable direct comparison. For example, *ketone* models use parameters derived from **(+)-STX** in its **ketone** form and *hydrate* models use parameters derived from **M1** in its **hydrate** form, respectively. This allows for direct comparison stabilizing/destabilizing interactions across the ketone and hydrate forms independently. Identification of strong univariate correlations was accomplished using an in-house Jupyter notebook with an R^2 threshold of 0.93 for the ketone model search and 0.97 for the hydrate model search.

Steric Ketone Model (Vbur(C12) at 1.5 Å)



Vbur(C12, 1.5 Å) across several representative intermediates



Sample Figure. Range of vbur is very small (~1%). Trend suggests substitution alpha to C12 is not directly influencing vbur (GTX), but the macrocycle impacts this term more heavily. Visualizing does not provide the greatest insight into this correlation since the differences are so small and vDW radii are used for vbur.

Additional Univariate Correlations Between Ketone Descriptors and ΔG of Hydration ($\Delta G_{\text{Hydration}}$)

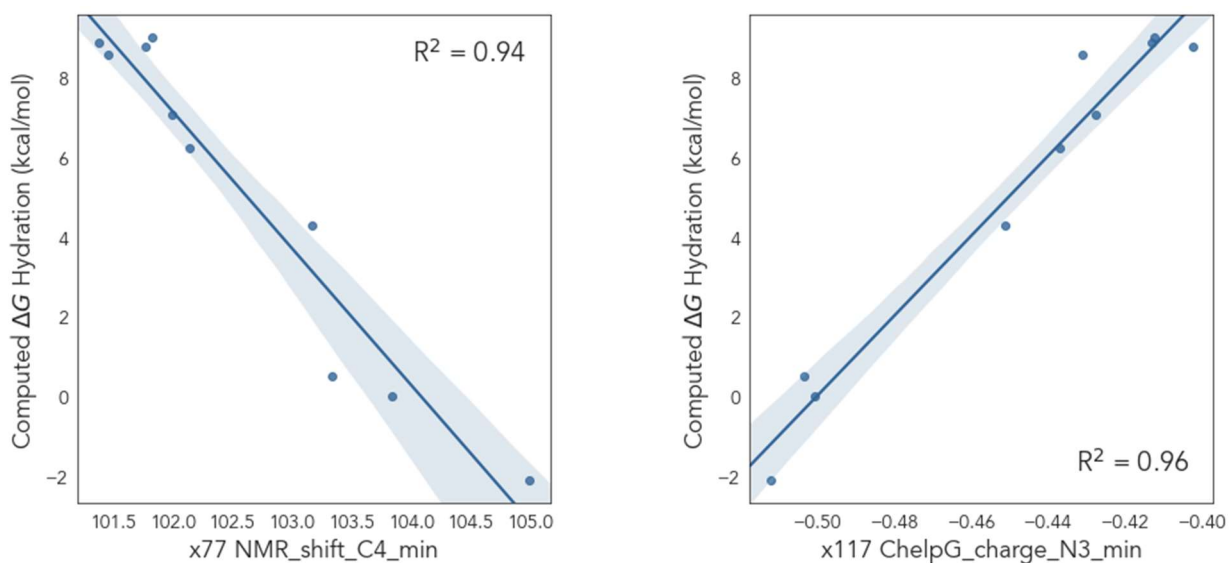


Figure S2. Correlation between ΔG of ketone hydration and computed NMR shift of C4 (left) and ChelpG charge of N3 (right).

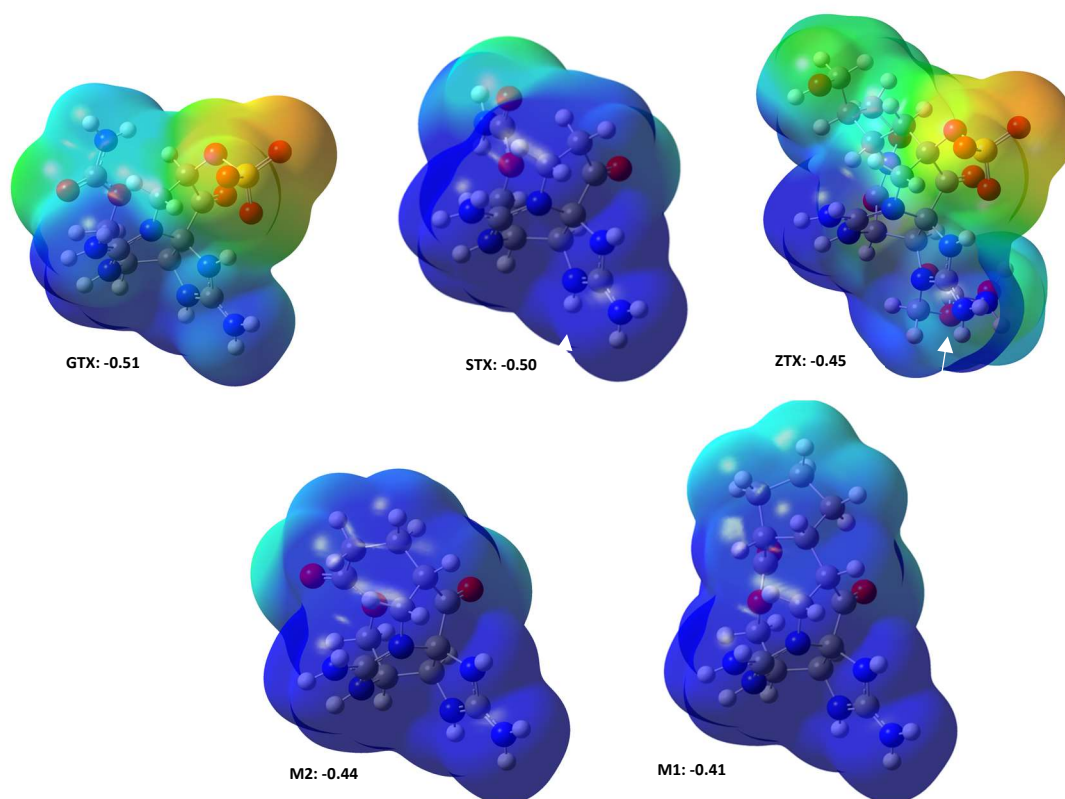


Figure S3. Trend of partial charge build up on .N3 position visualized by electrostatic potential map (ESP).

Univariate Correlations Between Hydrate Descriptors and ΔG of Hydration ($\Delta G_{\text{Hydration}}$)

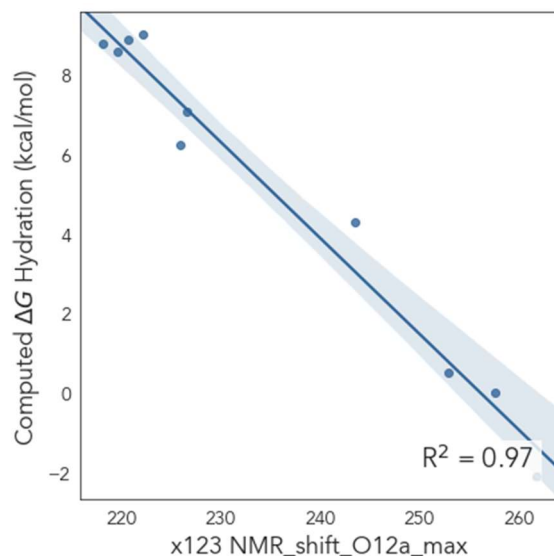


Figure S4. Correlation between ΔG of ketone hydration and computed NMR shift of O12a (left).

While a strong univariate correlation is observed with the computed NMR shift of O12a, this correlation was ultimately deemed difficult to interpret due to the complex quadrupolar interactions arising from ^{17}O bearing a spin of nucleus 5/2.¹⁴

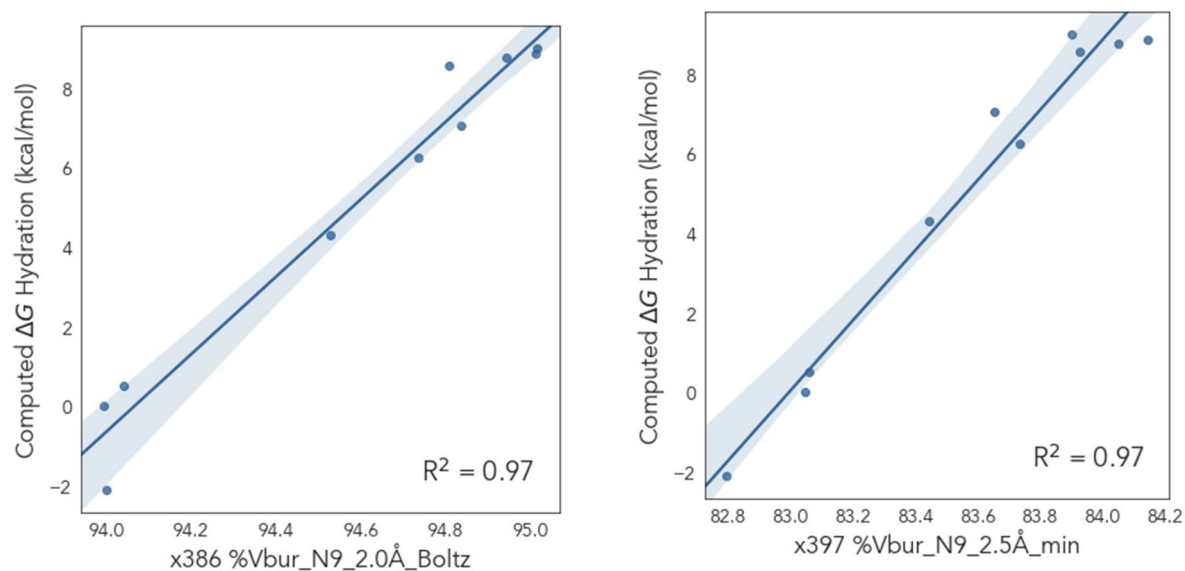
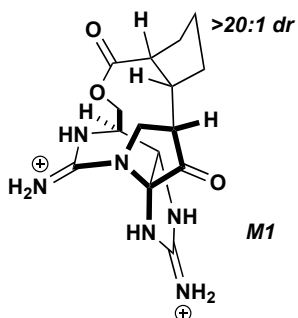


Figure S5. Correlation between ΔG of ketone hydration and computed Vbur(N9) at 2.0 Å (left) and 2.5 Å (right).

XYZ Coordinates for LEC Analog Conformers



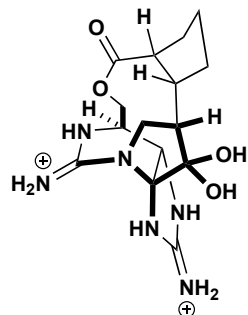
M1 – Ketone

computed as single diastereomer

Energy: -714616.4630019

C	-1.49169	1.59171	-1.16097
N	-1.79228	2.12376	0.16026
C	-1.33535	1.52198	1.26120
C	-0.05453	1.86781	-1.58992
H	-2.14664	2.09416	-1.88339
N	-1.20438	2.19304	2.39266
H	-1.34669	3.19778	2.41100
H	-1.05457	1.70813	3.27095
H	-2.09815	3.08920	0.23850
N	-1.00618	0.21540	1.21939
C	0.04143	-1.35943	-0.15298
C	0.87877	-1.26853	1.09923
C	0.07926	-0.35082	2.04224
O	0.29781	-1.91413	-1.18835
H	0.69585	0.46697	2.43487
H	-0.33619	-0.90808	2.89186
H	0.16109	1.37303	-2.54620
H	0.11028	2.94900	-1.69627
O	0.80371	1.37750	-0.56365
C	2.03625	0.93505	-0.84231
O	2.48031	0.88908	-1.96456

C	-1.81909	0.10605	-1.17690
C	-1.30136	-0.62612	0.07737
N	-2.37816	-1.56632	0.33420
C	-3.49630	-1.19842	-0.31349
N	-3.24401	-0.17327	-1.12708
H	-1.36955	-0.36301	-2.06479
N	-4.66556	-1.77866	-0.16246
H	-2.38846	-2.17287	1.15001
H	-3.88234	0.12006	-1.86048
H	-5.46460	-1.46935	-0.70604
H	-4.77982	-2.54189	0.49617
H	0.87197	-2.29747	1.49735
C	2.74396	0.52780	0.42900
C	2.36244	-0.89276	0.92684
C	3.18822	-1.81937	0.02529
C	4.51201	-1.06576	-0.20981
C	4.25885	0.39477	0.23106
H	2.48477	1.28577	1.18164
H	2.78504	-0.94736	1.94326
H	3.32777	-2.80718	0.48767
H	2.66311	-1.97710	-0.92619
H	4.80687	-1.11916	-1.26711
H	5.33253	-1.50645	0.37397
H	4.64483	1.13257	-0.48506
H	4.74490	0.59229	1.19685



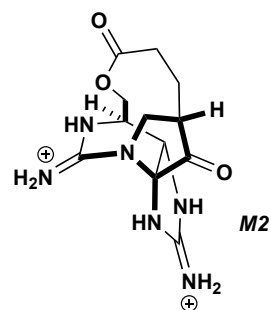
M1 – Hydrate

computed as single diastereomer

Energy: -762588.4831617

C	-1.44908	1.74916	-1.07471
N	-1.78479	2.20893	0.26320
C	-1.29485	1.56252	1.32576
C	-0.02056	2.11640	-1.46864
H	-2.10891	2.26818	-1.78110
N	-1.16422	2.18078	2.48995
H	-1.33483	3.17876	2.55749
H	-1.00072	1.65917	3.34376
H	-2.08485	3.17081	0.38885
N	-0.93316	0.27788	1.19923
C	0.00016	-1.45511	-0.15872
C	0.86183	-1.27790	1.12435
C	0.04602	-0.37398	2.06188
O	-0.33075	-2.80425	-0.25503
H	0.66974	0.38490	2.55125
H	-0.46015	-0.95812	2.84408
H	0.24440	1.65067	-2.42654
H	0.06192	3.20775	-1.56990
O	0.86427	1.69208	-0.44025
C	2.04194	1.14279	-0.75106
O	2.49885	1.16206	-1.87146
C	-1.76704	0.25925	-1.17195
C	-1.28693	-0.55307	0.06096
N	-2.45171	-1.36826	0.34992
C	-3.52309	-0.97973	-0.34757
N	-3.20106	0.01401	-1.17333
H	-1.31136	-0.15091	-2.08072
N	-4.72258	-1.51073	-0.23084
H	-2.46496	-2.09049	1.06259
H	-3.81011	0.33653	-1.91806
H	-5.48695	-1.18204	-0.81067
H	-4.89007	-2.25630	0.43606

H	0.91531	-2.27745	1.57377
C	2.72427	0.59850	0.48372
C	2.32237	-0.83143	0.96680
C	3.23628	-1.81420	0.19376
C	4.36469	-0.95516	-0.40898
C	4.23038	0.41889	0.26001
H	2.50525	1.32253	1.28201
H	2.69661	-0.83261	2.00232
H	3.62236	-2.57198	0.89088
H	2.70344	-2.38344	-0.58325
H	5.35978	-1.39515	-0.25368
H	4.21999	-0.85104	-1.49401
H	4.67208	1.23319	-0.33083
H	4.72539	0.41418	1.24314
O	0.58752	-1.00903	-1.33768
H	-0.89428	-2.92714	-1.03292
H	1.37611	-1.53647	-1.51956

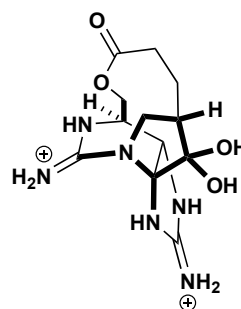


M2 – Ketone

Energy: -641373.4526724

C	-0.42665	-0.46842	-1.94749
N	-0.66529	0.96489	-2.02528
C	-0.52737	1.78424	-0.98031
C	1.04459	-0.83644	-2.05970
H	-0.93633	-0.93283	-2.80119
N	-0.36052	3.08343	-1.17472
H	-0.24178	3.44323	-2.11612

H	-0.48517	3.74715	-0.41840
H	-0.69941	1.38825	-2.94817
N	-0.58585	1.28959	0.27028
C	0.35007	-0.48080	1.46585
C	1.05501	0.78825	1.89515
C	0.08457	1.88695	1.43893
O	0.61273	-1.61322	1.77047
H	0.60018	2.81266	1.16373
H	-0.66428	2.12230	2.20741
H	1.15808	-1.92818	-2.09249
H	1.48580	-0.40108	-2.96675
O	1.70519	-0.30484	-0.91637
C	2.74146	-0.95394	-0.37068
O	3.21086	-1.95995	-0.84566
C	-1.04522	-1.02146	-0.67024
C	-0.85121	-0.10959	0.55612
N	-2.10717	-0.29874	1.25919
C	-3.04028	-0.80650	0.43702
N	-2.49368	-1.13276	-0.73452
H	-0.60090	-2.00271	-0.44223
N	-4.30534	-0.96241	0.75400
H	-2.34037	0.20758	2.10957
H	-2.95610	-1.74423	-1.40115
H	-4.95195	-1.37813	0.09165
H	-4.65086	-0.65565	1.65755
H	1.13217	0.74236	2.99047
C	3.23238	-0.27724	0.88336
C	2.47435	0.97930	1.29098
H	4.28804	-0.02648	0.69676
H	2.39528	1.63650	0.41375
H	3.23956	-1.04113	1.67607
H	3.07261	1.52040	2.03548

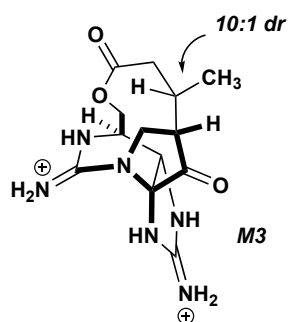


M2 – Hydrate

Energy: -689347.1564024

C	0.49414	-1.84819	-1.01795
N	0.66046	-2.32311	0.34690
C	0.30648	-1.54010	1.37286
C	-0.96829	-1.88219	-1.46219
H	1.03804	-2.53409	-1.67935
N	-0.00914	-2.07081	2.54431
H	-0.11554	-3.07570	2.63617
H	-0.07966	-1.49861	3.37824
H	0.70885	-3.32373	0.51248
N	0.28225	-0.21099	1.20148
C	-0.10454	1.67081	-0.21323
C	-1.03878	1.75213	1.02896
C	-0.49708	0.71427	2.02222
O	0.58350	2.87870	-0.30048
H	-1.29522	0.17214	2.54502
H	0.14710	1.18423	2.77960
H	-1.09668	-1.36345	-2.42145
H	-1.29438	-2.92564	-1.57431
O	-1.75051	-1.27228	-0.44751
C	-2.74317	-0.42940	-0.74218
O	-3.19728	-0.29696	-1.85498
C	1.15992	-0.47952	-1.14491
C	0.88327	0.46081	0.06186
N	2.21616	0.93769	0.37942
C	3.16258	0.29596	-0.31089

N	2.61033	-0.58731	-1.13904
H	0.82082	0.00236	-2.06897
N	4.45581	0.51192	-0.18402
H	2.39974	1.66795	1.05980
H	3.12858	-1.06748	-1.86743
H	5.11876	0.00554	-0.76087
H	4.79859	1.19436	0.48300
H	-0.87509	2.75167	1.44837
C	-3.20574	0.29295	0.49332
C	-2.54751	1.66104	0.74014
H	-3.04901	-0.36685	1.35782
H	-3.05710	2.08323	1.61858
H	-4.28604	0.45950	0.38625
H	-2.79321	2.33901	-0.09196
O	-0.75323	1.38525	-1.40867
H	1.18654	2.83203	-1.05689
H	-1.38355	2.09264	-1.60241



M3 – Ketone

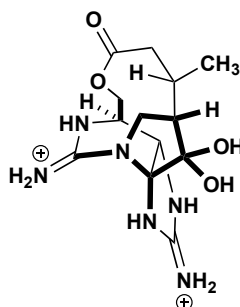
computed as single diastereomer

Energy: -666040.0893259

C	-0.96806	1.77091	0.93571
N	-1.03448	0.85002	2.06013
C	-0.63439	-0.42170	1.98384
C	0.41219	2.38130	0.74535
H	-1.65506	2.59958	1.14836
N	-0.33278	-1.08751	3.08773

H	-0.31066	-0.60639	3.98114
H	-0.23836	-2.09675	3.08203
H	-1.14582	1.24751	2.98821
N	-0.56939	-1.03201	0.78566
C	0.32386	-0.56421	-1.31755
C	1.22864	-1.57282	-0.64644
C	0.33590	-2.14871	0.46141
O	0.49546	0.00744	-2.36092
H	0.90930	-2.45994	1.34104
H	-0.25607	-3.00688	0.11494
H	0.38589	3.12825	-0.05896
H	0.75330	2.86152	1.67267
O	1.30675	1.32485	0.41230
C	2.30611	1.52924	-0.45595
O	2.54931	2.61015	-0.93603
C	-1.45090	1.07136	-0.32735
C	-0.95342	-0.38047	-0.45536
N	-2.09575	-1.02267	-1.07835
C	-3.20475	-0.28284	-0.91061
N	-2.89395	0.89846	-0.37643
H	-1.10702	1.63110	-1.21124
N	-4.41458	-0.67784	-1.23548
H	-2.12689	-2.02046	-1.27188
H	-3.53322	1.68792	-0.37922
H	-5.20717	-0.05539	-1.11671
H	-4.56629	-1.60738	-1.61282
H	1.46997	-2.32442	-1.41263
C	3.07578	0.26603	-0.74256
C	2.56173	-1.00409	-0.06608
H	4.10646	0.46415	-0.40702
H	2.36449	-0.74837	0.98554
H	3.13034	0.16219	-1.83760
C	3.62143	-2.10152	-0.09319
H	4.52901	-1.78043	0.43889

H	3.24834	-3.01649	0.39123
H	3.89918	-2.35277	-1.12893



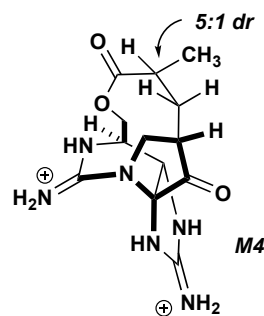
M3 – Hydrate

computed as single diastereomer

Energy: -714010.7913017

C	-0.88001	2.10455	0.10880
N	-0.94948	1.78709	1.52616
C	-0.54212	0.61625	2.02652
C	0.48453	2.61922	-0.32284
H	-1.58408	2.92681	-0.07338
N	-0.22377	0.52570	3.31110
H	-0.18466	1.36325	3.88239
H	-0.13349	-0.37439	3.76815
H	-1.04021	2.56182	2.17682
N	-0.48398	-0.46129	1.23206
C	0.17688	-1.29852	-0.90063
C	1.22100	-1.66356	0.19339
C	0.34937	-1.64762	1.45308
O	0.60179	-0.53767	-1.97670
H	0.93594	-1.56059	2.37407
H	-0.29162	-2.53724	1.53397
H	0.46177	2.89921	-1.38426
H	0.75911	3.50070	0.27298
O	1.44212	1.59910	-0.09603
C	2.29890	1.24345	-1.06015
O	2.45017	1.87658	-2.07946

C	-1.36523	0.90986	-0.71068
C	-0.96983	-0.48197	-0.14119
N	-2.23125	-1.19729	-0.22452
C	-3.25655	-0.39156	-0.51502
N	-2.81916	0.84533	-0.72895
H	-0.98129	0.99562	-1.73471
N	-4.51380	-0.77686	-0.58142
H	-2.33131	-2.17284	0.03710
H	-3.39389	1.57904	-1.13058
H	-5.23849	-0.11808	-0.84518
H	-4.76411	-1.74268	-0.39933
H	1.53597	-2.68789	-0.04425
C	3.08138	0.01759	-0.68019
C	2.49854	-0.81689	0.46109
H	4.06799	0.39227	-0.35764
H	2.25750	-0.10077	1.25984
H	3.26944	-0.56300	-1.59504
C	3.57267	-1.75749	1.01090
H	3.18468	-2.35570	1.84952
H	3.92036	-2.45441	0.23152
H	4.44207	-1.19017	1.37525
O	-0.31801	-2.52754	-1.34462
H	1.23198	-1.06209	-2.49012
H	-0.99934	-2.36113	-2.01207

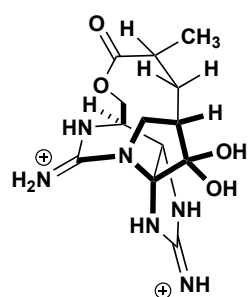


M4 – Ketone

computed as single diastereomer

	Energy: -666040.7151788		
C	-0.90368	1.74360	-0.96586
N	-1.08874	2.16689	0.41412
C	-0.74020	1.37048	1.42709
C	0.55709	1.79038	-1.40167
H	-1.45723	2.43866	-1.60892
N	-0.48242	1.87520	2.62167
H	-0.42261	2.88018	2.75109
H	-0.40675	1.27699	3.43733
H	-1.22481	3.15449	0.60892
N	-0.64999	0.03839	1.23159
C	0.09997	-1.50228	-0.35458
C	0.94750	-1.71750	0.87130
C	0.35838	-0.78073	1.93740
O	0.28916	-1.93848	-1.45843
H	1.11762	-0.11639	2.36877
H	-0.11041	-1.34298	2.75487
H	0.66321	1.39588	-2.42125
H	0.93222	2.82287	-1.37262
O	1.30251	1.00238	-0.47667
C	2.49233	0.49210	-0.81634
O	2.98213	0.64936	-1.90847
C	-1.50168	0.35533	-1.13461
C	-1.09906	-0.59835	0.00629
N	-2.31507	-1.36926	0.18590
C	-3.36369	-0.73887	-0.36935
N	-2.95214	0.32809	-1.05580
H	-1.16257	-0.08093	-2.08613
N	-4.61239	-1.13126	-0.25263
H	-2.41636	-2.06347	0.92163
H	-3.54136	0.79985	-1.73557
H	-5.35588	-0.62225	-0.71958
H	-4.84538	-1.94071	0.31318
H	0.74091	-2.76317	1.15483

C	3.10375	-0.26357	0.34572
C	2.45563	-1.64272	0.58868
H	2.91897	0.36412	1.23167
H	2.98025	-2.08907	1.44529
C	4.60646	-0.42226	0.14513
H	2.65830	-2.29278	-0.27722
H	5.05368	-0.90908	1.02318
H	4.82194	-1.04150	-0.73823
H	5.09418	0.55329	0.00807

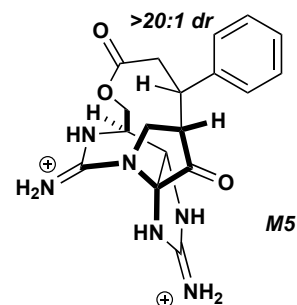


M4 – Hydrate

computed as single diastereomer

	Energy: -714013.6573257		
C	0.81420	-1.84433	-1.01262
N	0.95832	-2.31185	0.35683
C	0.55361	-1.53807	1.37069
C	-0.63497	-1.92108	-1.49307
H	1.39442	-2.51535	-1.65814
N	0.22221	-2.07762	2.53373
H	0.14559	-3.08529	2.62393
H	0.11206	-1.50832	3.36519
H	1.03309	-3.31015	0.52662
N	0.49352	-0.21068	1.19530
C	0.06809	1.64474	-0.24523
C	-0.89990	1.69517	0.97171
C	-0.33701	0.69261	1.98935
O	0.70912	2.87914	-0.32290
H	-1.12325	0.12803	2.50611

H	0.27486	1.19775	2.75081
H	-0.75534	-1.40620	-2.45525
H	-0.92724	-2.97371	-1.61223
O	-1.46121	-1.33608	-0.49759
C	-2.48025	-0.53869	-0.82034
O	-2.90626	-0.42507	-1.94641
C	1.44377	-0.45764	-1.12446
C	1.09668	0.47802	0.06627
N	2.40023	1.01152	0.41569
C	3.38974	0.39504	-0.23626
N	2.89586	-0.52119	-1.06653
H	1.12314	0.00999	-2.06248
N	4.66971	0.66110	-0.07727
H	2.53582	1.74997	1.09832
H	3.45290	-0.97841	-1.78099
H	5.36741	0.16681	-0.62285
H	4.96903	1.36212	0.59164
H	-0.78897	2.70456	1.38465
C	-3.02691	0.15420	0.40846
C	-2.39712	1.54273	0.65293
H	-2.78272	-0.49432	1.26282
H	-2.93499	1.95618	1.51944
C	-4.54369	0.28902	0.29676
H	-2.65397	2.20498	-0.19007
H	-4.95261	0.73985	1.21218
H	-4.81685	0.93020	-0.55453
H	-5.02088	-0.69149	0.15447
O	-0.53550	1.32552	-1.45532
H	1.33457	2.85240	-1.06200
H	-1.19153	2.00298	-1.66925



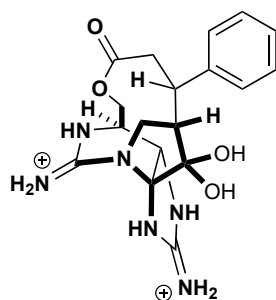
M5 – Ketone

computed as single diastereomer

Energy: -786353.0985479

C	-2.59059	1.27041	1.02361
N	-2.25205	0.33272	2.08257
C	-1.35620	-0.64519	1.93620
C	-1.61065	2.42815	0.91082
H	-3.56712	1.70594	1.27082
N	-0.81802	-1.21362	3.00468
H	-1.00068	-0.83192	3.92709
H	-0.32055	-2.09507	2.93757
H	-2.54655	0.55835	3.02827
N	-1.02297	-1.06885	0.70165
C	-0.42317	-0.10695	-1.33688
C	0.83156	-0.66912	-0.70356
C	0.28277	-1.64975	0.34154
O	-0.51475	0.55357	-2.33637
H	0.93341	-1.72937	1.21866
H	0.13512	-2.65688	-0.07118
H	-1.96214	3.14698	0.15905
H	-1.50305	2.93964	1.87705
O	-0.35065	1.88725	0.52746
C	0.46698	2.57742	-0.27659
O	0.22804	3.69846	-0.65472
C	-2.72888	0.52156	-0.29491
C	-1.65203	-0.55905	-0.50549
N	-2.40541	-1.58243	-1.20834

C	-3.72485	-1.41158	-1.01646
N	-3.95344	-0.25736	-0.38962
H	-2.66756	1.23558	-1.13107
N	-4.64772	-2.26346	-1.40029
H	-2.00055	-2.48095	-1.45882
H	-4.87197	0.17622	-0.36094
H	-5.63066	-2.05161	-1.26235
H	-4.38751	-3.13156	-1.85679
H	1.37330	-1.18392	-1.50957
C	1.70334	1.79400	-0.63744
C	1.78099	0.38459	-0.04371
H	2.55359	2.39148	-0.27350
H	1.47090	0.46927	1.00638
H	1.77637	1.79661	-1.73564
C	5.80919	-1.19401	-0.04579
C	5.24576	-0.71221	-1.22959
C	3.95064	-0.19893	-1.23052
C	3.19932	-0.15309	-0.04840
C	3.77263	-0.63668	1.13161
C	5.06893	-1.15597	1.13444
H	6.82403	-1.59803	-0.04575
H	5.81948	-0.73785	-2.15888
H	3.51678	0.16801	-2.16470
H	3.19631	-0.60498	2.06023
H	5.50071	-1.53072	2.06528



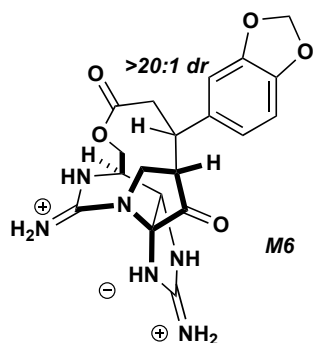
M5 – Hydrate

****computed as single diastereomer****

Energy: -834324.8389891

C	-2.48663	1.18453	-1.23287
N	-3.13876	1.44818	0.04042
C	-2.51690	1.12642	1.17884
C	-1.35709	2.17205	-1.51555
H	-3.23184	1.32529	-2.02569
N	-2.81369	1.74596	2.31093
H	-3.42795	2.55346	2.30510
H	-2.50980	1.37528	3.20478
H	-3.87475	2.14643	0.08032
N	-1.57954	0.16751	1.16159
C	0.17040	-0.98999	0.01098
C	0.72283	-0.40161	1.33993
C	-0.49414	0.09245	2.13435
O	0.48446	-2.34640	-0.00435
H	-0.33620	1.07993	2.58611
H	-0.74808	-0.61028	2.94080
H	-0.80900	1.88014	-2.42094
H	-1.77321	3.17899	-1.65961
O	-0.49136	2.19501	-0.38812
C	0.83001	2.27988	-0.54609
O	1.34696	2.55926	-1.60415
C	-2.05560	-0.28059	-1.26888
C	-1.39885	-0.75910	0.05680
N	-2.09666	-2.00618	0.30044
C	-3.12562	-2.18254	-0.53227
N	-3.19377	-1.17652	-1.40159
H	-1.35583	-0.43040	-2.09921
N	-3.94885	-3.20970	-0.49019
H	-1.85168	-2.64411	1.05059
H	-3.79317	-1.18616	-2.22026
H	-4.69691	-3.29669	-1.16937
H	-3.83696	-3.92564	0.21924

H	1.13467	-1.26015	1.87984
C	1.54296	2.05865	0.76604
C	1.88533	0.61897	1.22281
H	0.91162	2.51564	1.54031
H	2.19789	0.76605	2.26932
H	2.47730	2.63427	0.73152
C	5.33398	-1.26835	-0.64224
C	4.79235	-0.11745	-1.20664
C	3.68639	0.50581	-0.62131
C	3.09603	-0.01472	0.53705
C	3.66022	-1.17190	1.09902
C	4.76322	-1.79169	0.51986
H	6.19794	-1.75506	-1.09999
H	5.22991	0.30858	-2.11229
H	3.28116	1.40307	-1.09068
H	3.23723	-1.59202	2.01494
H	5.18289	-2.68845	0.98140
O	0.63213	-0.36975	-1.14488
H	0.13256	-2.73113	-0.82068
H	1.59039	-0.50180	-1.20382



M6 – Ketone

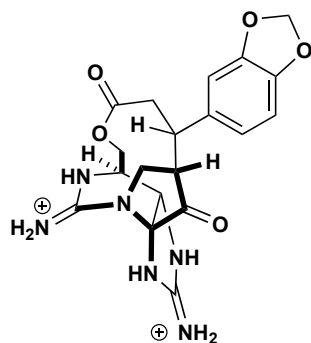
computed as single diastereomer

Energy: -904671.0897564

C	-3.45862	1.23431	0.73851
N	-3.10059	0.49518	1.93931
C	-2.11518	-0.40412	1.98145

C	-2.58158	2.45477	0.50484
H	-4.48401	1.60109	0.87270
N	-1.58652	-0.75154	3.14511
H	-1.86253	-0.26498	3.99169
H	-1.01917	-1.58639	3.23587
H	-3.46640	0.83108	2.82577
N	-1.68186	-0.97729	0.84217
C	-1.03183	-0.26027	-1.27957
C	0.21923	-0.61374	-0.50510
C	-0.31923	-1.49747	0.62749
O	-1.11142	0.24460	-2.36699
H	0.28463	-1.42458	1.53843
H	-0.37622	-2.55492	0.33642
H	-2.94073	3.01519	-0.36836
H	-2.58923	3.11200	1.38500
O	-1.25490	1.98877	0.28410
C	-0.44676	2.61292	-0.58107
O	-0.75435	3.62763	-1.15768
C	-3.44617	0.29802	-0.46229
C	-2.27252	-0.69931	-0.45648
N	-2.89173	-1.87531	-1.03937
C	-4.23050	-1.79776	-0.95281
N	-4.59455	-0.59318	-0.51227
H	-3.38691	0.89129	-1.38810
N	-5.05208	-2.77297	-1.26738
H	-2.39942	-2.75871	-1.14466
H	-5.54502	-0.24441	-0.59607
H	-6.05597	-2.63578	-1.20944
H	-4.68959	-3.67145	-1.56947
H	0.86343	-1.17138	-1.19949
C	0.87594	1.90462	-0.73025
C	1.01629	0.60428	0.06722
H	1.63857	2.62302	-0.39121
H	0.60820	0.80263	1.06685

H	1.04747	1.76229	-1.80810
C	3.30495	0.04516	-0.87192
C	2.46889	0.21300	0.25486
C	2.97461	0.00658	1.53835
C	4.31364	-0.36761	1.76190
H	2.93462	0.18965	-1.88878
H	2.31364	0.14342	2.39758
H	4.70253	-0.53104	2.76756
C	5.10960	-0.51712	0.64845
C	4.61280	-0.31448	-0.63933
O	5.60470	-0.56130	-1.54421
C	6.80199	-0.69003	-0.78693
O	6.41993	-0.89428	0.56763
H	7.37519	-1.55497	-1.14489
H	7.39316	0.23897	-0.86920



M6 – Hydrate

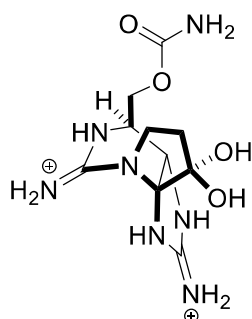
computed as single diastereomer

Energy: -952642.6505291

C	3.30689	-0.81648	-1.22672
N	3.99401	-0.93600	0.04938
C	3.31879	-0.73001	1.18444
C	2.39080	-2.00743	-1.49878
H	4.06718	-0.81901	-2.01814
N	3.72622	-1.27730	2.31928
H	4.48763	-1.94790	2.31569
H	3.35857	-0.96748	3.21201

H	4.85047	-1.47937	0.09606
N	2.21809	0.03602	1.16031
C	0.27726	0.80062	-0.01142
C	-0.15203	0.14136	1.33000
C	1.13689	-0.08037	2.13431
O	-0.30809	2.06324	-0.05936
H	1.17357	-1.06723	2.61303
H	1.24519	0.68032	2.92066
H	1.79006	-1.83404	-2.40122
H	2.99567	-2.91379	-1.64188
O	1.55374	-2.19396	-0.36496
C	0.27407	-2.53693	-0.51385
O	-0.18142	-2.92708	-1.56521
C	2.60261	0.53730	-1.27686
C	1.86034	0.89320	0.04152
N	2.29404	2.25806	0.26731
C	3.26982	2.62363	-0.56804
N	3.54723	1.63464	-1.41514
H	1.89097	0.54383	-2.11069
N	3.86764	3.79703	-0.55013
H	1.91178	2.85156	0.99613
H	4.12699	1.75795	-2.23881
H	4.58304	4.01840	-1.23437
H	3.60413	4.49568	0.13624
H	-0.72974	0.91171	1.85092
C	-0.46437	-2.44318	0.79921
C	-1.08581	-1.09474	1.24097
H	0.24815	-2.75586	1.57469
H	-1.34852	-1.28514	2.29401
H	-1.26628	-3.19291	0.77654
C	-3.19807	0.27606	1.17114
C	-2.40907	-0.73204	0.56537
C	-2.86843	-1.34918	-0.60063
C	-4.09043	-0.99646	-1.20861

H	-2.89197	0.76792	2.09606
H	-2.27170	-2.12778	-1.07663
H	-4.43531	-1.49224	-2.11655
O	-0.03913	0.07313	-1.15372
H	-0.05225	2.48707	-0.89206
H	-1.00341	-0.00167	-1.21778
C	-4.82699	-0.00598	-0.60313
C	-4.38563	0.61288	0.56625
O	-5.32242	1.51851	0.97227
C	-6.25447	1.62546	-0.09732
O	-6.04429	0.50572	-0.94891
H	-7.27756	1.60230	0.29952
H	-6.06763	2.55780	-0.65840



(+)-STX

Energy: -675524.0900058

C	-0.63622	-1.37319	-0.61820
N	-0.92744	-1.25405	0.80484
C	-0.68965	-0.09382	1.43263
C	-1.60489	-0.55955	-1.48010
H	-0.74998	-2.43333	-0.87551
N	-1.37835	0.25402	2.50593
H	-2.22463	-0.25106	2.74798
H	-1.12361	1.06682	3.05510
H	-1.66405	-1.84363	1.18173
N	0.27950	0.69188	0.94839
C	1.65107	1.53090	-0.74036

C	1.58077	2.56782	0.37548
C	0.38456	2.13537	1.21676
O	2.91497	1.50360	-1.30927
O	0.65063	1.71016	-1.69555
H	2.51041	2.52925	0.95976
H	1.46699	3.58116	-0.02992
H	-0.54950	2.62203	0.90109
H	0.54821	2.33432	2.28452
H	-1.43719	0.51733	-1.35963
H	-1.45692	-0.82579	-2.53446
O	-2.94019	-0.89101	-1.14274
C	-3.62618	-0.02715	-0.36011
O	-3.19429	1.06017	-0.01335
H	-5.46520	0.05460	0.49629
N	-4.82205	-0.52811	-0.02469
H	-5.13728	-1.41406	-0.40041
C	0.81075	-0.96677	-0.89290
C	1.28126	0.21134	0.00860
N	2.43186	-0.35369	0.68798
C	2.68227	-1.60725	0.29527
N	1.75702	-2.01743	-0.56514
H	0.91100	-0.68730	-1.95075
N	3.70146	-2.32945	0.71215
H	3.09466	0.20708	1.21489
H	1.74131	-2.94024	-0.98595
H	3.82956	-3.27657	0.37312
H	4.35591	-1.95222	1.38858
H	2.89830	0.88525	-2.05415
H	0.70657	2.61458	-2.03363

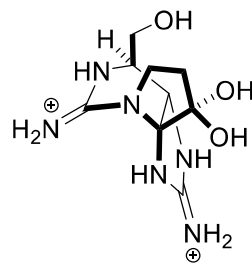
(+)-STX Ketone

Energy: -627544.9373161

C	0.10694	-1.64760	-0.99852
N	-0.02212	-2.02813	0.40190

C	-0.28560	-1.12104	1.34479
C	-1.21836	-1.39909	-1.71055
H	0.56523	-2.50051	-1.51491
N	-0.81651	-1.47128	2.50246
H	-1.19155	-2.40606	2.62660
H	-0.87267	-0.81832	3.27607
H	-0.22692	-3.00050	0.61282
N	0.01782	0.16476	1.09376
C	0.27426	1.92393	-0.39209
C	-0.48192	2.46437	0.78953
C	-0.58896	1.31195	1.79079
O	0.41912	2.42063	-1.47573
H	0.08606	3.31825	1.18879
H	-1.45875	2.84035	0.45908
H	-1.63320	1.07188	2.02947
H	-0.05256	1.52487	2.72623
H	-1.02779	-1.38053	-2.79110
H	-1.92269	-2.20948	-1.48392
O	-1.79454	-0.13584	-1.39727
C	-2.80363	-0.09080	-0.49825
O	-3.12485	-1.04045	0.19530
H	-4.10314	1.30643	0.20028
N	-3.38002	1.11775	-0.48248
H	-3.04543	1.86034	-1.08428
C	1.06693	-0.46520	-1.12150
C	0.89661	0.56740	0.01753
N	2.26799	0.77930	0.45483
C	3.10515	-0.10959	-0.09913
N	2.45537	-0.86684	-0.97672
H	0.91443	0.03931	-2.08716
N	4.38547	-0.20270	0.18703
H	2.51265	1.36293	1.25002
H	2.90783	-1.53278	-1.59452
H	4.96539	-0.89474	-0.27555

H	4.80069	0.40785	0.88244
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dc-STX

Energy: -569641.2639026

C	-1.36546	-1.26213	-0.58489
N	-1.66011	-1.04667	0.83152
C	-1.38582	0.15950	1.35492
C	-2.29610	-0.45059	-1.47843
H	-1.54264	-2.32630	-0.78853
N	-2.13079	0.67456	2.31864
H	-2.98279	0.20445	2.60607
H	-1.83401	1.49441	2.83644
H	-2.49921	-1.50220	1.18110
N	-0.33182	0.82570	0.87152
C	1.20533	1.42698	-0.77165
C	1.19530	2.52057	0.29100
C	-0.08244	2.26032	1.08240
O	2.48442	1.23502	-1.27154
O	0.27501	1.66314	-1.78410
H	2.08540	2.41299	0.92592
H	1.21246	3.51855	-0.16474
H	-0.93819	2.83309	0.69687
H	0.04624	2.48837	2.14947
H	-2.12392	0.62845	-1.31979
H	-2.04642	-0.67473	-2.53081
O	-3.61623	-0.81960	-1.15864

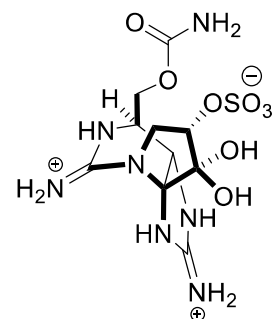
C	0.10670	-0.96616	-0.86139
C	0.65792	0.19499	0.01489
N	1.69966	-0.45690	0.78673
C	1.87477	-1.72965	0.41266
N	0.97706	-2.07226	-0.50363
H	0.23014	-0.71981	-1.92403
N	2.80476	-2.52645	0.89698
H	2.39066	0.05862	1.32383
H	0.88142	-3.00815	-0.88276
H	2.88059	-3.48300	0.56880
H	3.44994	-2.19153	1.60391
H	2.43559	0.58823	-1.99047
H	0.45062	2.53534	-2.16397
H	-4.21407	-0.19407	-1.58240

dc-STX Ketone

Energy: -521662.9158589

C	-0.43024	-1.60820	-1.06907
N	-0.77084	-1.95343	0.30521
C	-1.04215	-1.00526	1.20454
C	-1.64352	-1.17404	-1.87749
H	-0.02213	-2.50948	-1.54328
N	-1.79485	-1.27799	2.25907
H	-2.25511	-2.17928	2.33232
H	-1.83179	-0.65162	3.05548
H	-1.12807	-2.88664	0.48639
N	-0.53167	0.22861	1.04130
C	-0.14716	1.87521	-0.57458
C	-1.13021	2.44014	0.40963
C	-1.17793	1.44448	1.56828
O	0.20185	2.33669	-1.62754
H	-0.80686	3.44557	0.71271
H	-2.10068	2.53754	-0.09729
H	-2.20633	1.21242	1.86785

H	-0.63150	1.81193	2.44780
H	-2.38461	-1.99159	-1.86748
H	-1.32333	-1.01784	-2.92161
O	-2.16749	0.00423	-1.31004
C	0.66270	-0.54781	-1.05599
C	0.42193	0.55193	-0.00241
N	1.76316	0.76661	0.51848
C	2.57755	-0.24550	0.17925
N	1.96057	-1.07263	-0.66124
H	0.73075	-0.07353	-2.04682
N	3.80962	-0.38474	0.61713
H	1.95392	1.38866	1.29947
H	2.44427	-1.79189	-1.18994
H	4.38382	-1.15771	0.29791
H	4.19812	0.28326	1.27418
H	-2.89301	0.32210	-1.85971



GTX

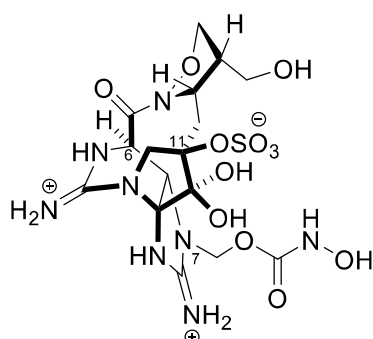
Energy: -1113935.5850828

C	-2.68979	1.06083	0.02900
N	-2.18282	2.23679	-0.66114
C	-1.04951	2.17018	-1.37504
C	-3.32685	0.08239	-0.96458
H	-3.48451	1.39868	0.70607
N	-0.84293	2.98440	-2.39776
H	-1.58698	3.59632	-2.71654
H	0.07264	3.07600	-2.82424

H	-2.86281	2.93674	-0.94471	O	3.43544	-2.05567	0.39251
N	-0.13145	1.26625	-1.02366	O	4.65429	-0.88641	-1.39107
C	0.48935	-0.81634	-0.20377				
C	1.63783	-0.29692	-1.10129				
C	0.99134	0.84900	-1.87367				
O	0.85014	-1.53160	0.91479	C	2.90880	0.83643	0.02188
O	-0.32743	-1.52504	-1.07580	N	2.55989	0.63686	1.42410
O	2.69957	0.21133	-0.30918	C	1.53782	-0.17098	1.73800
H	1.99089	-1.08829	-1.77626	C	3.68854	-0.36001	-0.53750
H	0.61459	0.51445	-2.84935	H	3.61055	1.67901	-0.01950
H	1.71594	1.66132	-2.02144	N	1.50500	-0.83187	2.87887
H	-3.95407	0.65252	-1.66079	H	2.32155	-0.84263	3.48223
H	-2.56760	-0.46774	-1.53650	H	0.66099	-1.29362	3.20142
O	-4.20257	-0.80974	-0.29072	H	3.31341	0.70682	2.10330
C	-3.81342	-2.06423	-0.01066	N	0.53139	-0.26508	0.85082
O	-2.68349	-2.49582	-0.21523	C	-0.62383	0.05241	-1.13981
H	-4.63216	-3.74021	0.78640	C	-1.13768	-1.23754	-0.49582
N	-4.80647	-2.77820	0.52320	C	-0.56548	-1.23224	0.92888
H	-5.72863	-2.37739	0.64392	O	-0.91550	0.48681	-2.21718
C	-1.58491	0.43632	0.88274	O	-2.52463	-1.42018	-0.62327
C	-0.17865	0.52762	0.22928	H	-0.68737	-2.05544	-1.07735
N	0.60368	1.19059	1.25785	H	-0.17262	-2.21797	1.20859
C	-0.12451	1.46800	2.34099	H	-1.31719	-0.92498	1.67013
N	-1.39708	1.13609	2.14163	H	3.77976	-0.27348	-1.62861
H	-1.83253	-0.61391	1.08585	H	4.69205	-0.34827	-0.09618
N	0.35540	2.00685	3.44284	O	3.15361	-1.62349	-0.16955
H	1.62063	1.18790	1.23392	C	2.17001	-2.14767	-0.92500
H	-2.11850	1.20790	2.85087	O	1.65864	-1.55002	-1.86101
H	-0.25101	2.17970	4.23699	H	2.29221	-3.79891	0.28620
H	1.33786	2.24983	3.50677	N	1.83154	-3.37248	-0.50863
H	1.75520	-1.89334	0.79407	H	1.07971	-3.86000	-0.98056
H	-1.14192	-1.85347	-0.63582	C	1.67030	1.27115	-0.78182
S	4.01899	-0.77805	-0.07785	C	0.34678	0.74883	-0.16219
O	4.75599	-0.02940	0.93318	N	-0.27954	1.95715	0.35230

Energy: -1065954.4688595

C	0.36029	3.04858	-0.09656
N	1.47297	2.71004	-0.73880
H	1.77023	0.93105	-1.81855
N	-0.06176	4.28075	0.08780
H	-1.28322	1.93745	0.55233
H	2.17182	3.37749	-1.04865
H	0.46988	5.06535	-0.27371
H	-0.92524	4.45573	0.59026
S	-3.56752	-0.39026	0.17946
O	-3.76956	-1.00281	1.49499
O	-2.83928	0.89421	0.23061
O	-4.73151	-0.40388	-0.69812



ZTX

Energy: -1483145.6066889

C	1.39107	1.22183	0.65608
N	1.48133	1.55127	-0.74541
C	0.83988	0.86163	-1.68682
C	0.28273	1.83624	1.53967
H	2.28759	1.63540	1.13023
N	0.78489	1.30590	-2.92888
H	1.12956	2.23342	-3.15773
H	2.07586	2.32650	-1.02441
N	0.19988	-0.27189	-1.33872
C	-0.90625	-1.46747	0.41025
C	-1.93490	-0.78483	-0.58862

C	-1.10353	-0.65511	-1.86615
O	-0.97276	-2.85082	0.32054
O	-1.03273	-1.01944	1.71545
H	-1.49776	0.10746	-2.54898
H	-1.05719	-1.62079	-2.38856
O	0.58371	2.02553	2.71387
C	1.41589	-0.29206	0.85886
C	0.51222	-1.04586	-0.13695
N	1.33810	-2.18467	-0.46579
C	2.61135	-2.00145	-0.11474
N	2.73588	-0.87749	0.62321
H	1.09861	-0.52092	1.88420
N	3.60126	-2.80859	-0.41661
C	3.84431	-0.56631	1.48252
H	4.56307	-2.47823	-0.27881
H	-1.93181	-1.26434	2.00267
C	-2.52697	0.56698	-0.14114
O	4.70244	0.41697	0.93193
H	3.45027	-0.12641	2.40531
H	4.40793	-1.47520	1.72716
C	5.70477	-0.00831	0.14122
O	5.89947	-1.17098	-0.16267
N	6.48207	1.03222	-0.22103
H	6.14341	1.98661	-0.11615
O	7.37903	0.82871	-1.23060
H	8.24631	0.74116	-0.80662
H	-3.34187	0.72049	-0.85758
H	-2.99239	0.46259	0.84809
N	-0.94418	2.10925	1.06793
C	-1.70041	1.86136	-0.15810
C	-2.58209	3.13378	-0.13857
C	-2.84438	3.33043	1.35256
O	-1.83241	2.57248	2.03046
H	-1.04858	1.93777	-1.02792

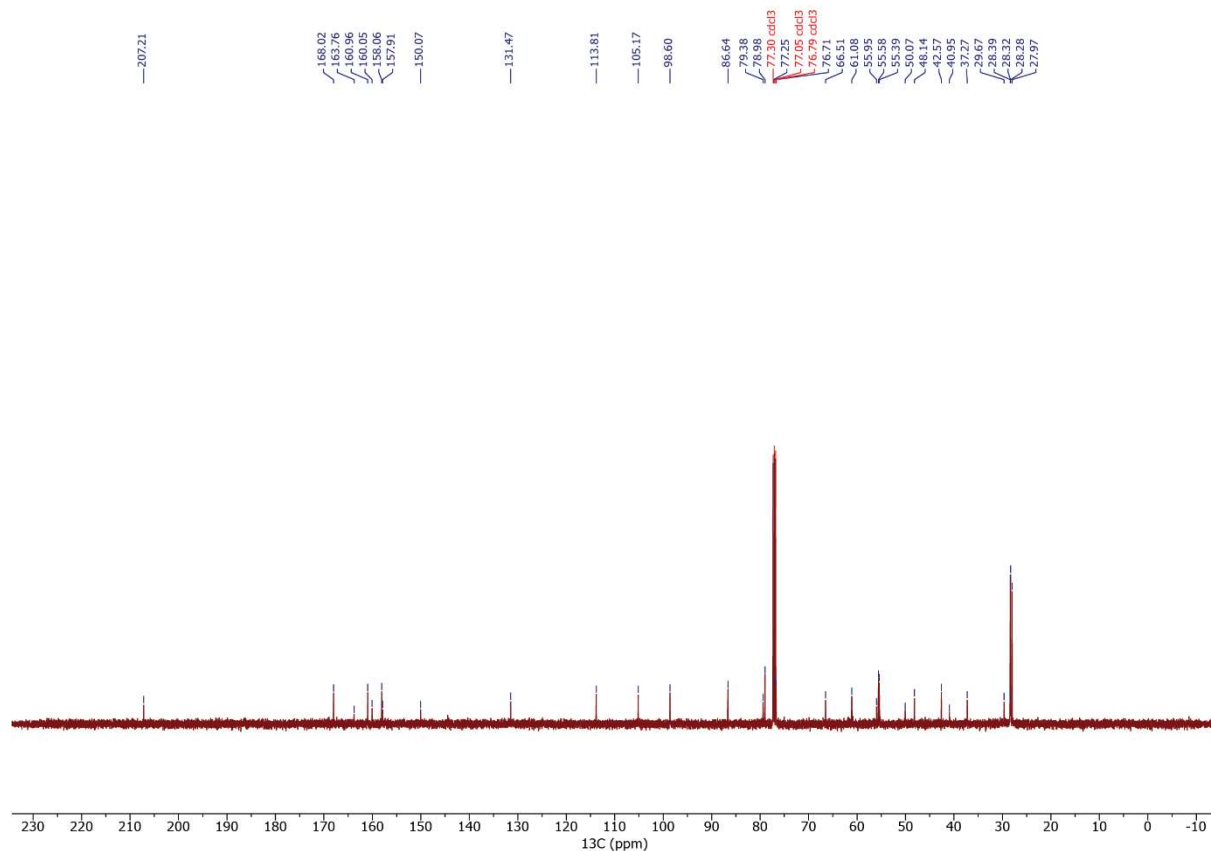
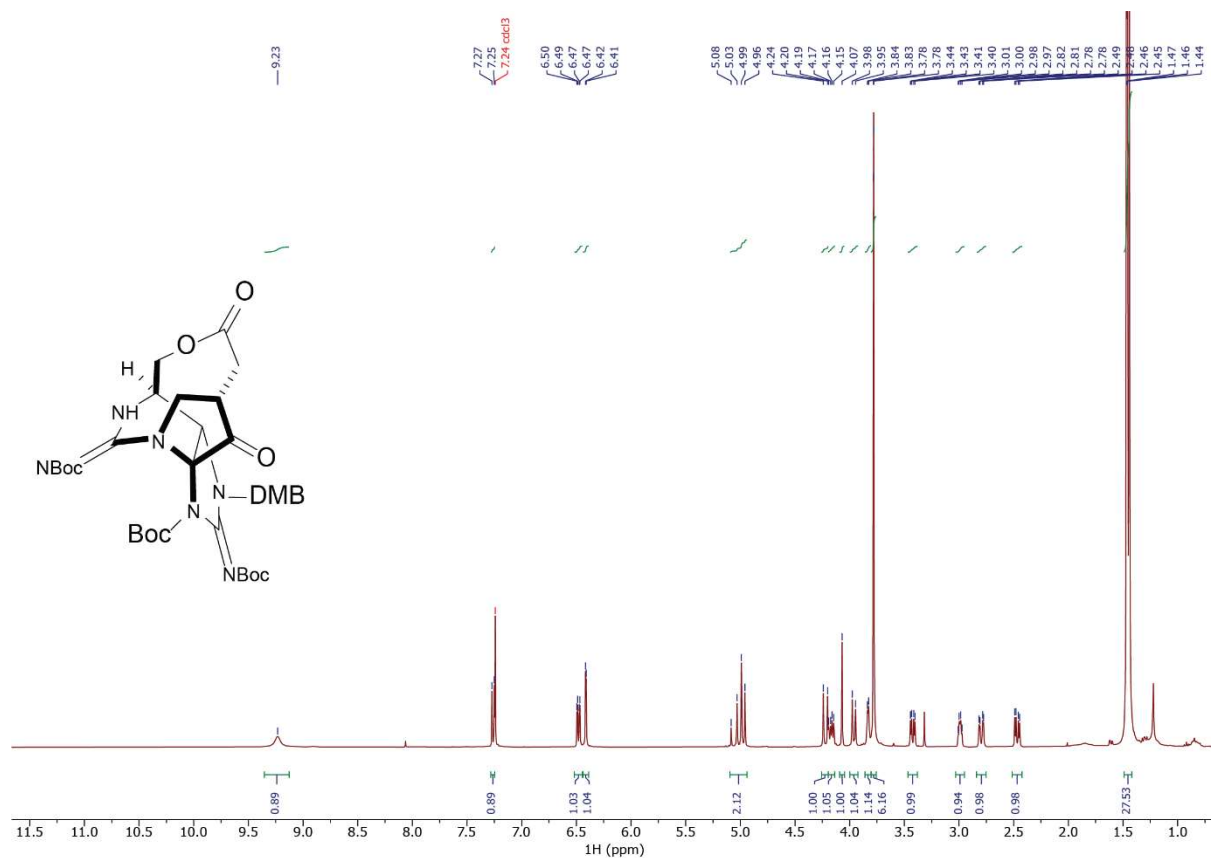
C	-3.83514	3.10580	-0.98720	H	-1.34298	1.94650	1.75129
H	-1.94130	3.95179	-0.50005	O	0.45664	-3.32689	-1.85043
H	-2.77420	4.38396	1.65733	C	1.19276	-0.23938	-1.02653
H	-3.81727	2.92280	1.66447	C	0.22310	0.73250	-0.33910
O	-3.45856	2.81972	-2.31750	N	0.95284	1.97545	-0.41470
H	-4.54563	2.35496	-0.59848	C	2.25694	1.75993	-0.61344
H	-4.33329	4.08898	-0.91083	N	2.47364	0.46074	-0.91907
H	-4.26140	2.71382	-2.84023	H	0.92134	-0.33147	-2.09096
O	-3.00047	-1.66533	-0.92988	N	3.19137	2.67641	-0.54721
S	-4.20035	-2.07139	0.14378	H	0.53670	2.85184	-0.10088
O	-5.12850	-0.94233	0.20505	C	3.66521	-0.05633	-1.53643
O	-4.72963	-3.28083	-0.47410	H	4.17162	2.37620	-0.50933
O	-3.46739	-2.30681	1.41528	C	-2.94223	-0.61368	0.04980
H	3.42429	-3.61469	-1.00763	O	4.48317	-0.76866	-0.62803
H	0.42317	0.72101	-3.67482	H	3.37494	-0.78334	-2.30272
H	1.02439	-2.92437	-1.08665	H	4.22981	0.75731	-2.00836
H	-1.82977	-3.10867	0.70286	C	5.35853	-0.05407	0.10419

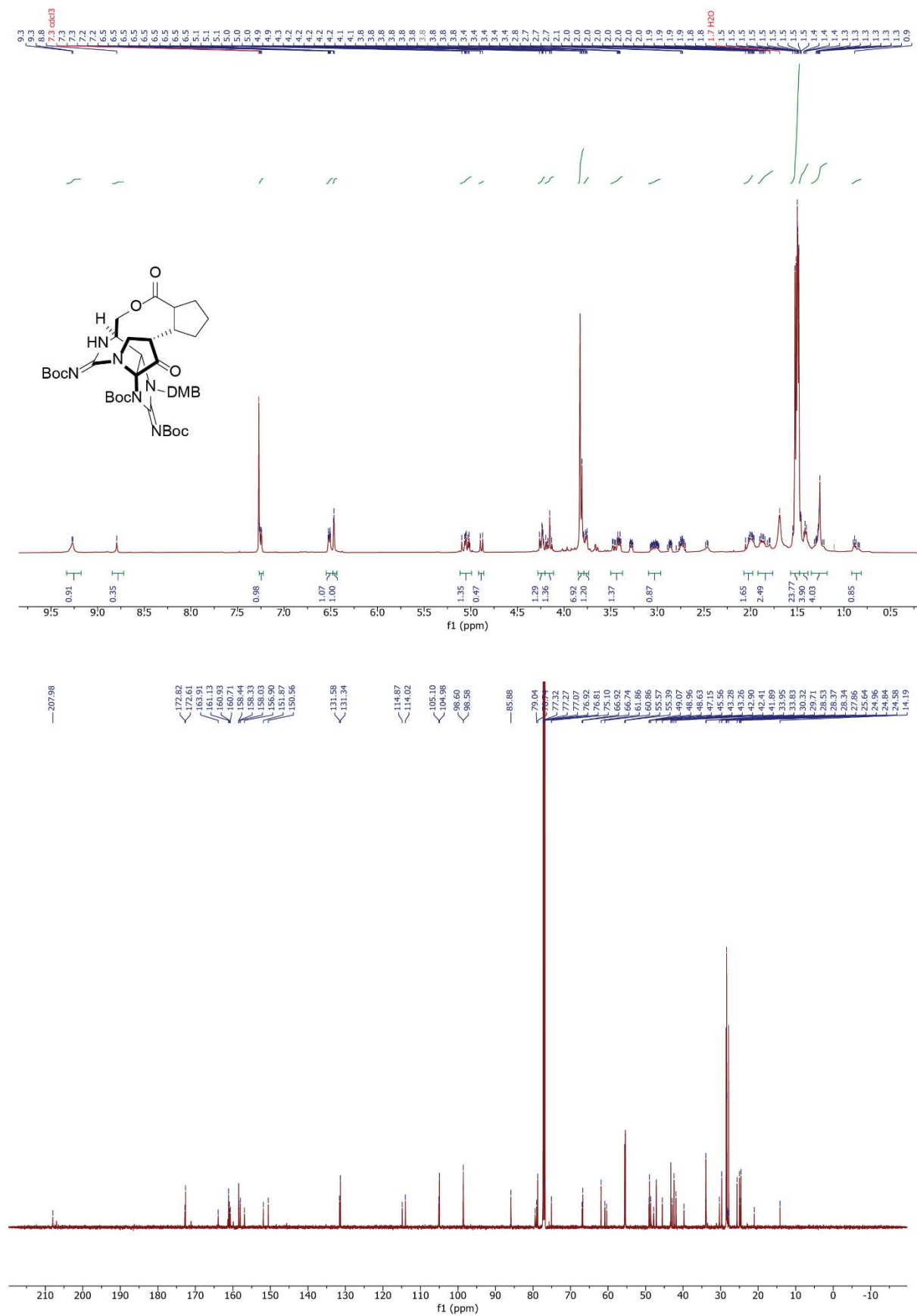
ZTX Ketone

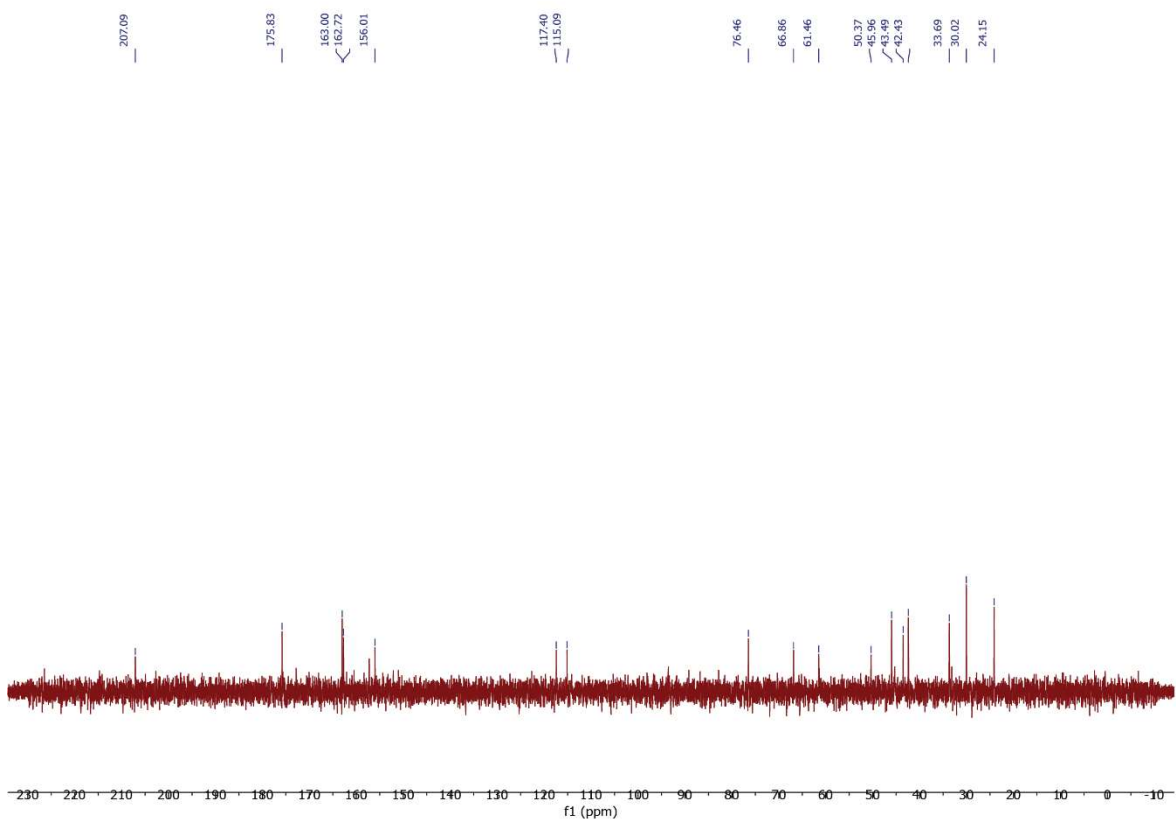
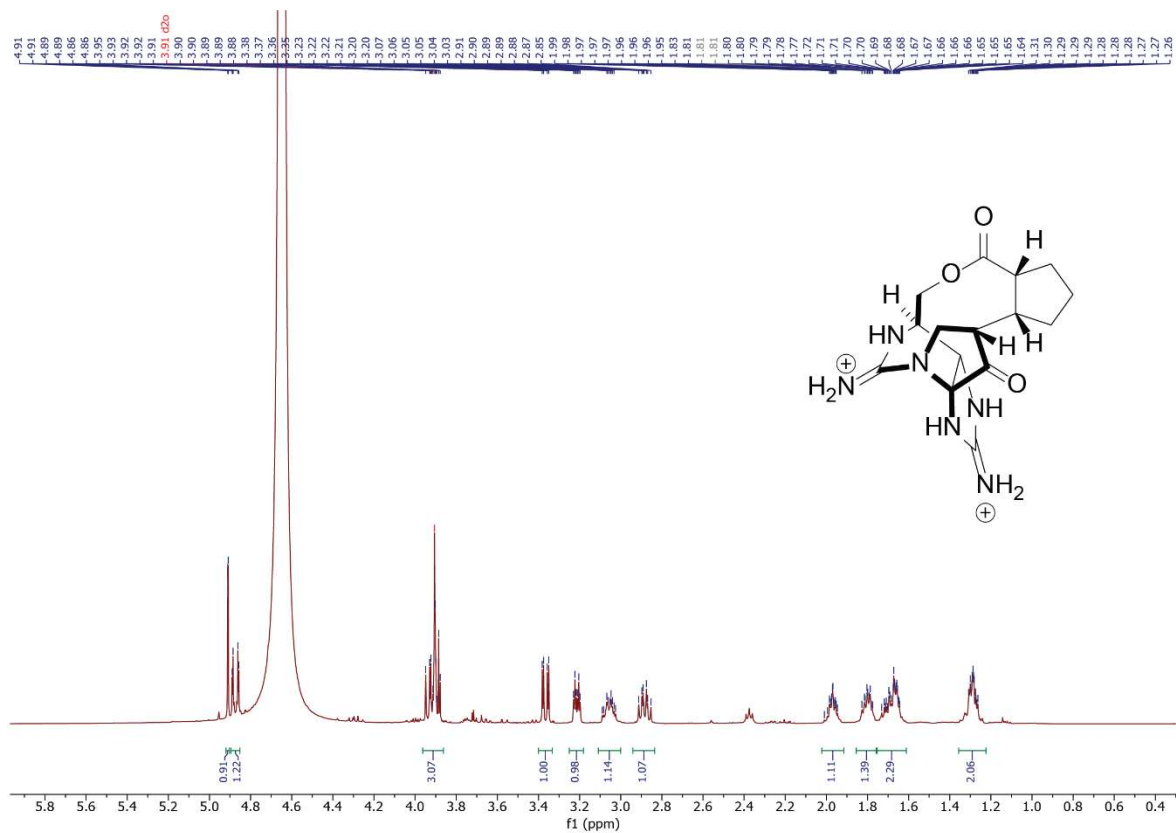
Energy: -1435170.4188048

C	1.19470	-1.62325	-0.37651	H	6.00692	-1.86955	0.81507
N	1.21793	-1.51449	1.06165	O	7.11077	-0.36034	1.59247
C	0.51931	-0.59828	1.72842	H	6.84229	-0.16551	2.50301
C	0.09905	-2.47557	-1.06153	H	-3.68019	-0.61324	0.86299
H	2.11332	-2.14232	-0.66906	H	-3.48418	-0.65736	-0.90654
N	0.40310	-0.65964	3.04069	N	-1.21247	-2.05265	-0.98810
H	0.76058	-1.46192	3.55097	C	-2.05523	-1.84929	0.20009
H	1.79810	-2.16450	1.58513	C	-2.82989	-3.18852	0.22043
N	-0.11242	0.37130	1.03407	C	-2.92948	-3.54382	-1.26389
C	-1.17480	0.85549	-0.98801	O	-2.02985	-2.64713	-1.93711
C	-2.23524	0.75052	0.12259	H	-1.44326	-1.80522	1.10363
C	-1.42007	0.90396	1.42223	C	-4.16264	-3.17221	0.93891
O	-1.37164	0.98093	-2.16133	H	-2.17622	-3.91629	0.72373
H	-1.84796	0.31130	2.23954	H	-2.63414	-4.58321	-1.46592
				H	-3.92950	-3.35850	-1.68132

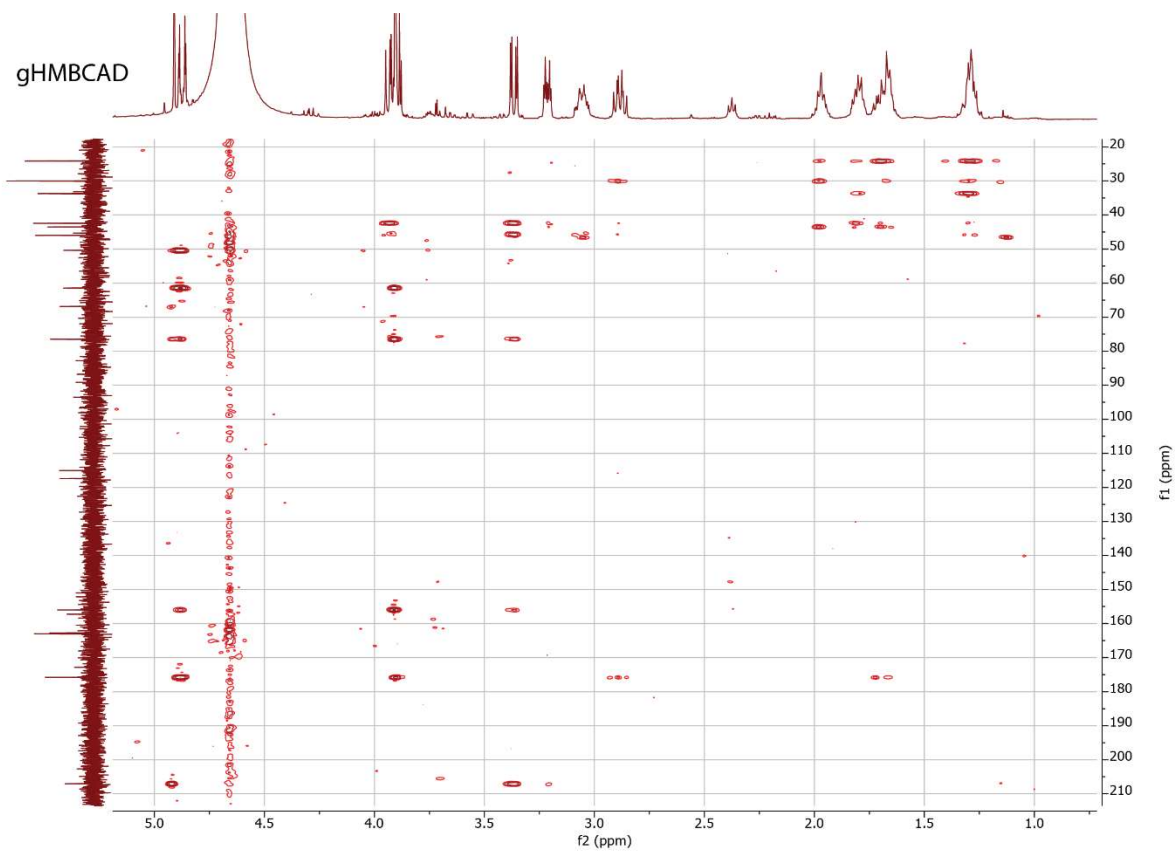
O	-3.93616	-2.78970	2.27863
H	-4.85946	-2.48039	0.43288
H	-4.60846	-4.18138	0.87735
H	-4.79091	-2.70608	2.71634
O	-3.25490	1.70459	-0.05901
S	-2.88963	3.33595	0.06517
O	-3.11612	3.66047	1.47543
O	-1.47242	3.42112	-0.34372
O	-3.84091	3.92356	-0.87021
H	2.94362	3.62051	-0.26647
H	0.01412	0.11816	3.56399



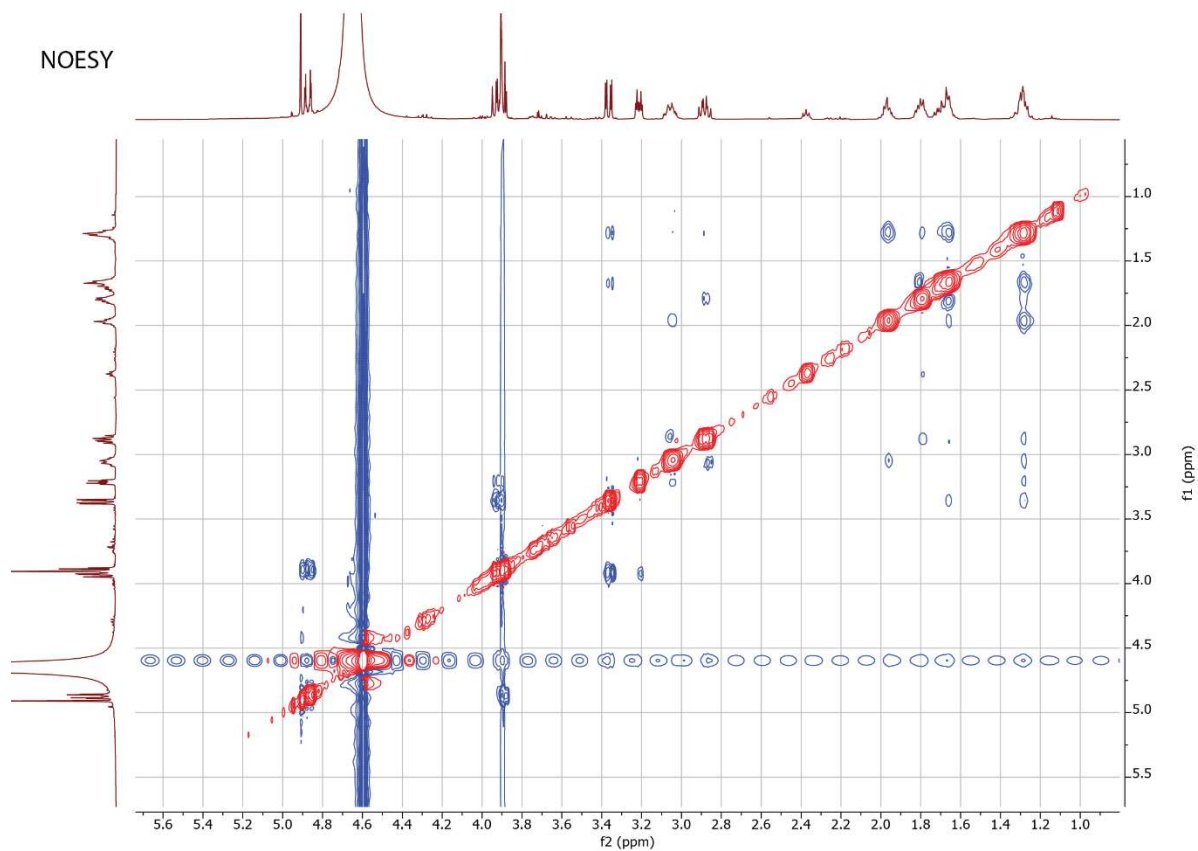


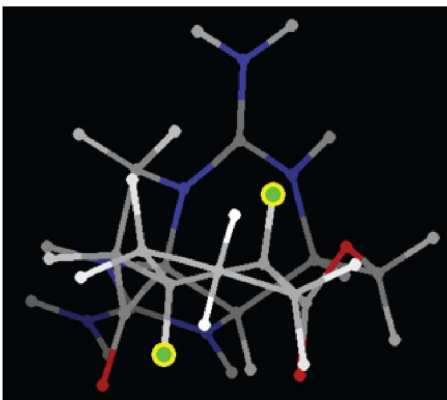


gHMBCAD

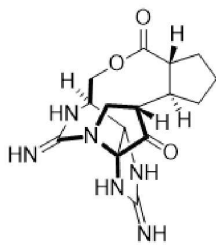


NOESY

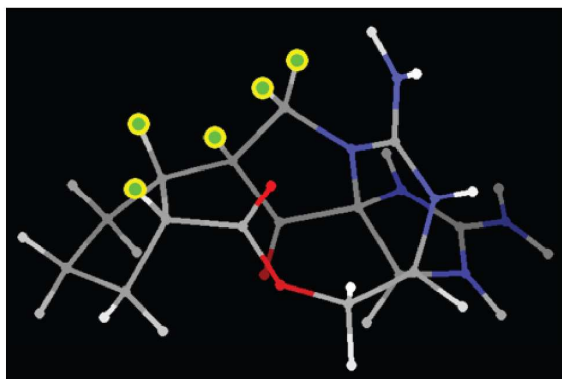




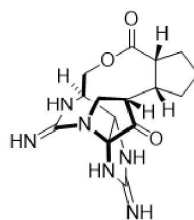
Trans-1



+3.32 kcal/mol

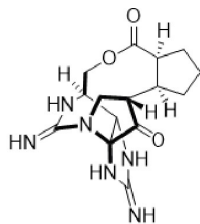


Cis-1

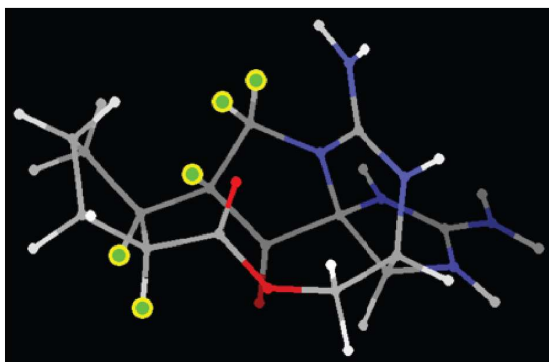


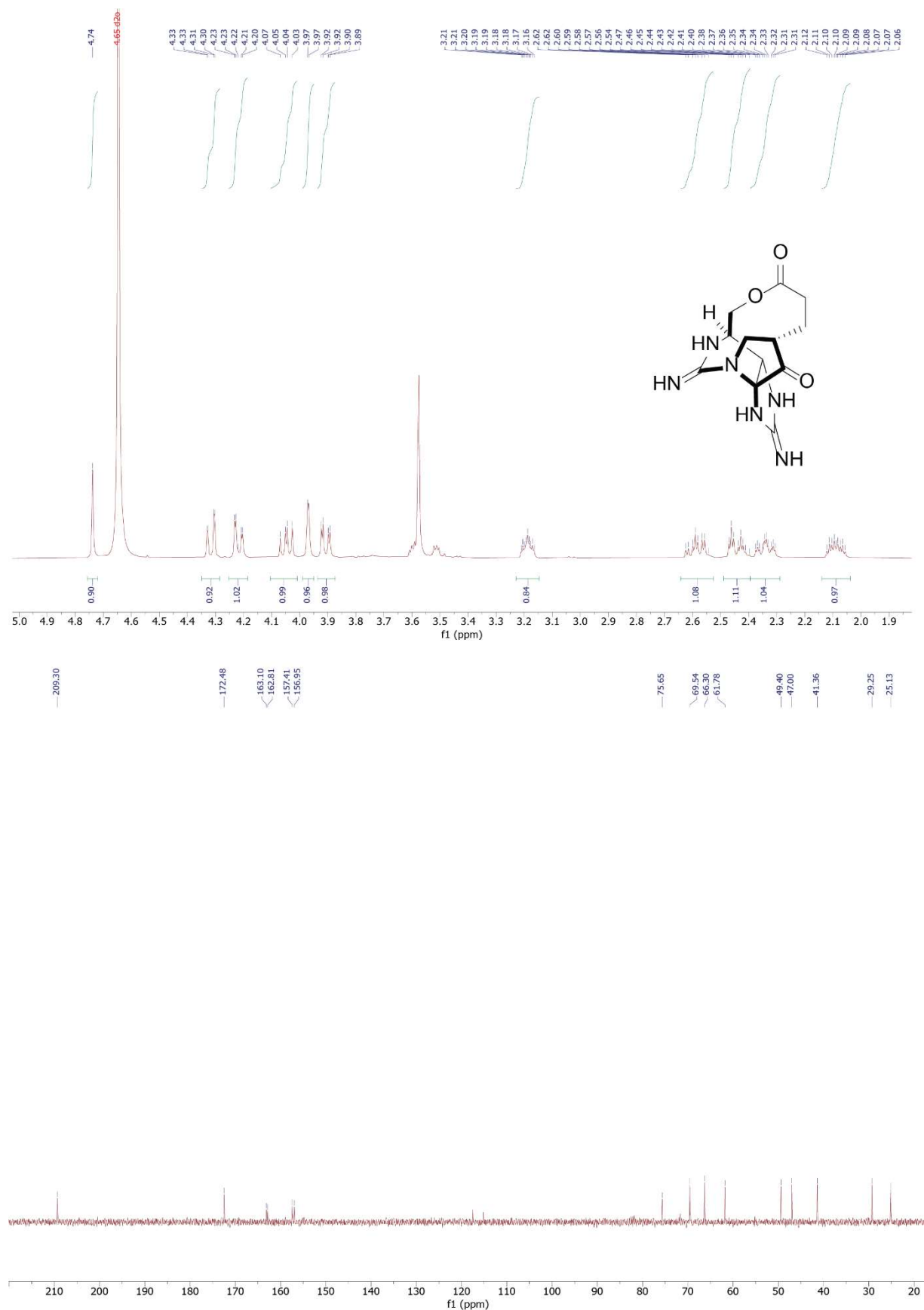
0 kcal/mol

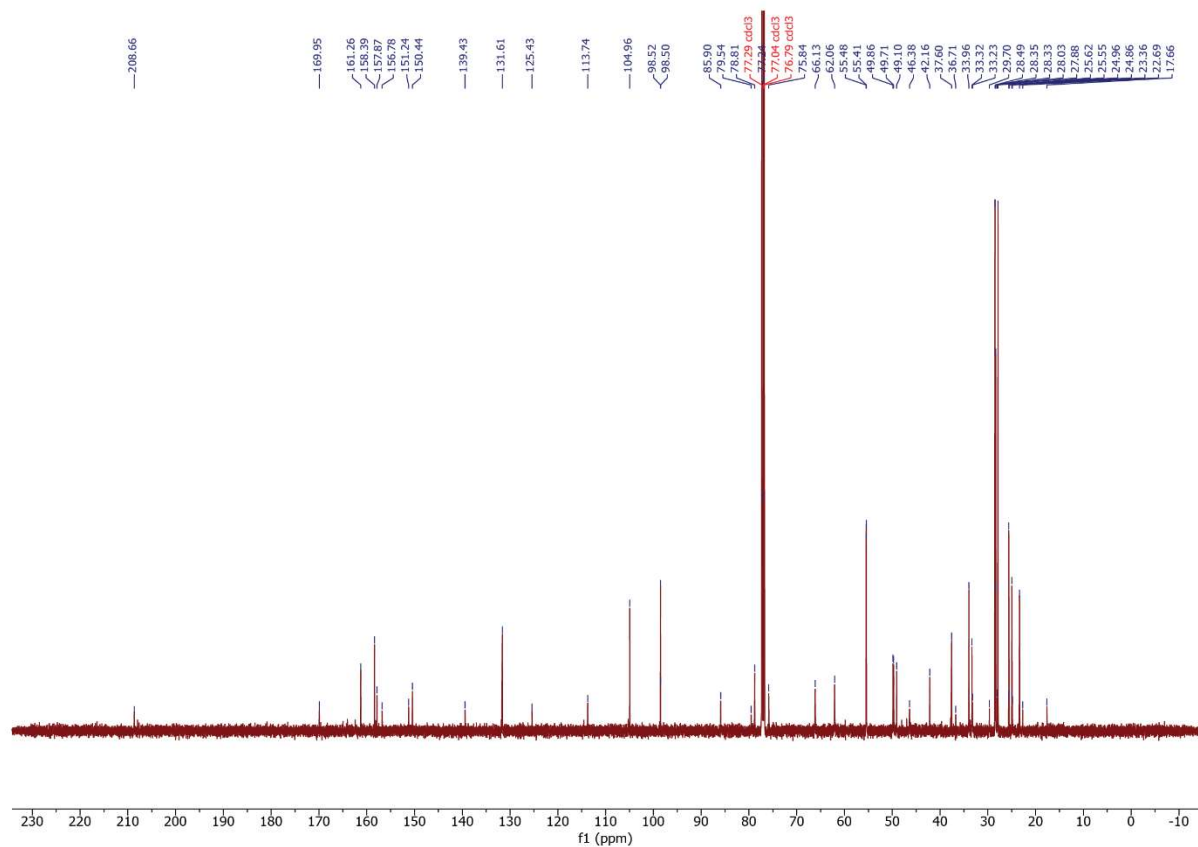
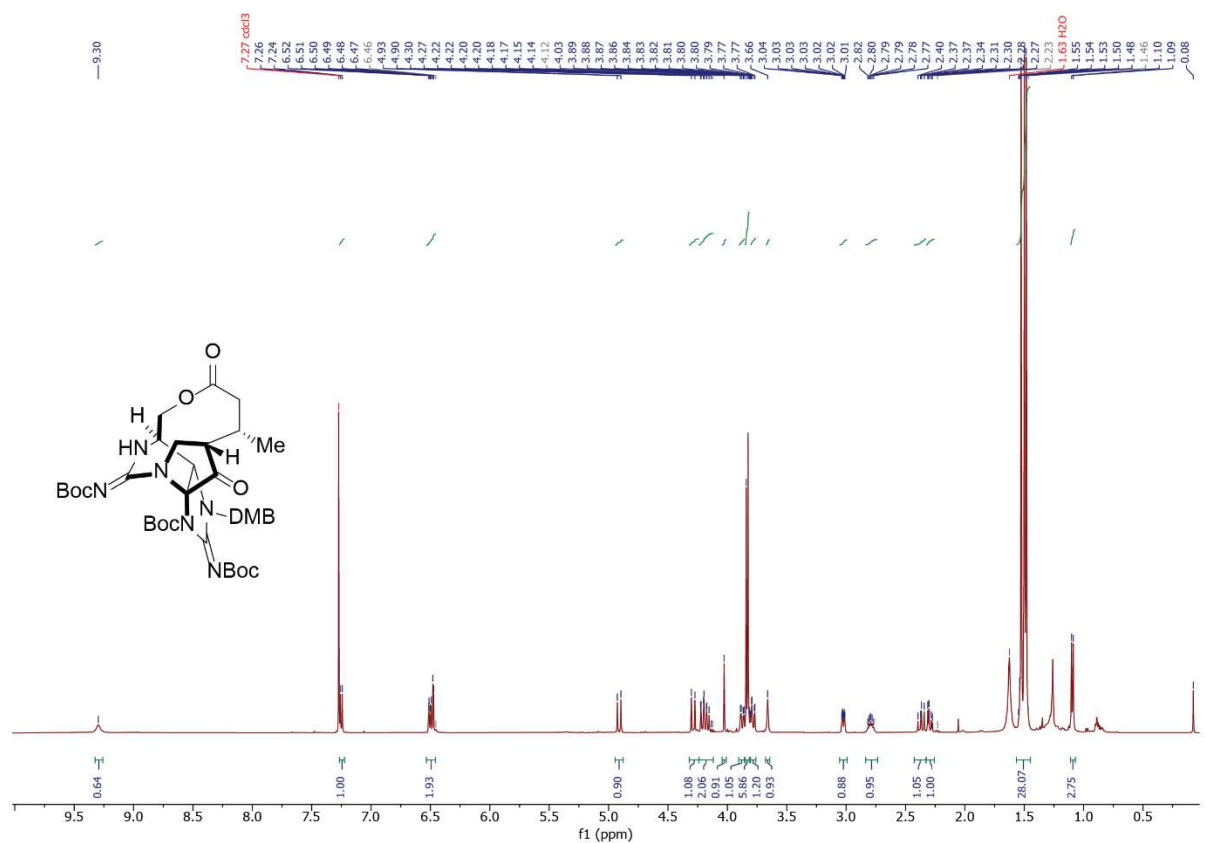
Cis-2

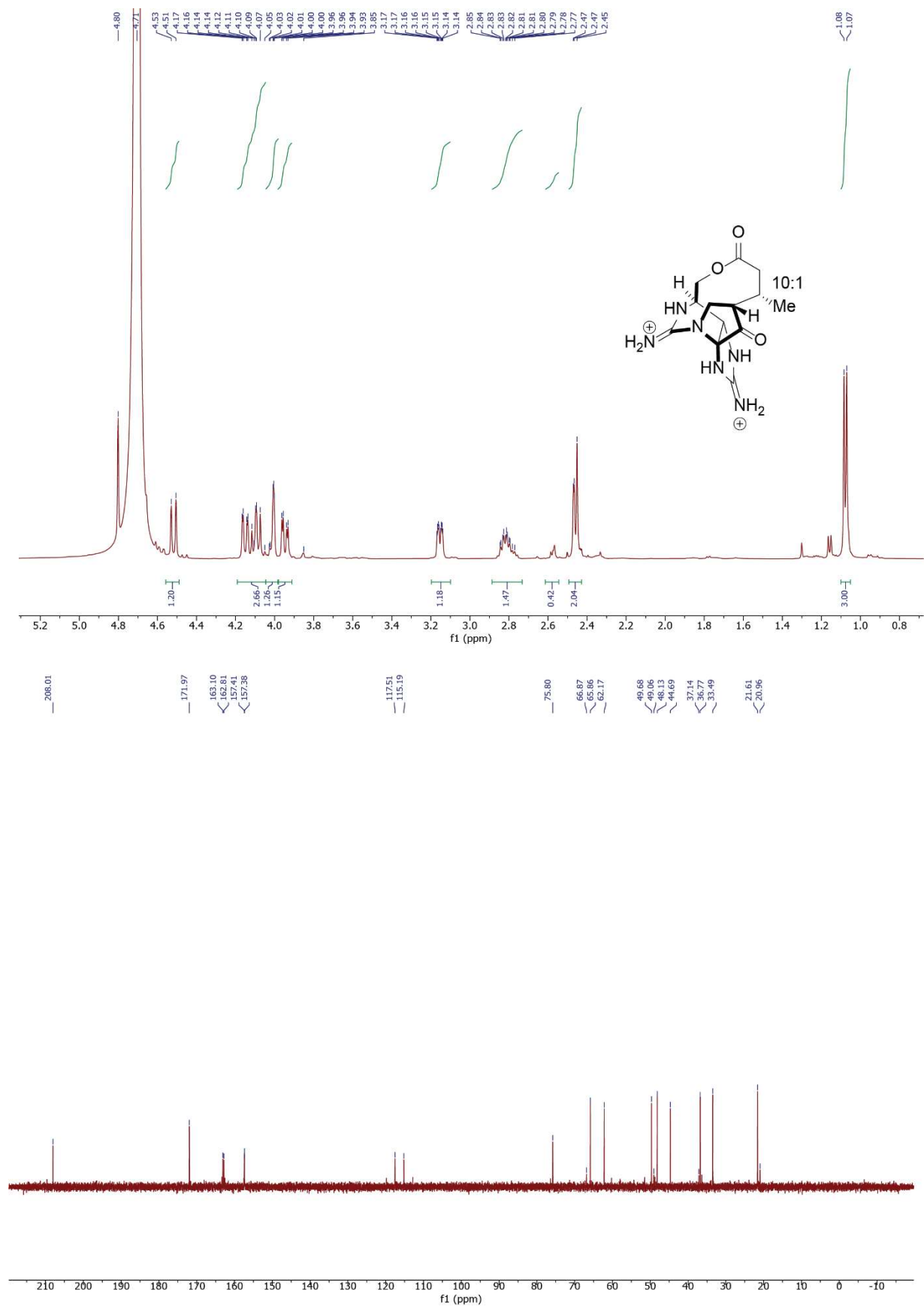


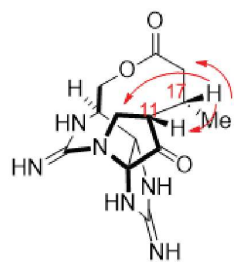
+2.34 kcal/mol



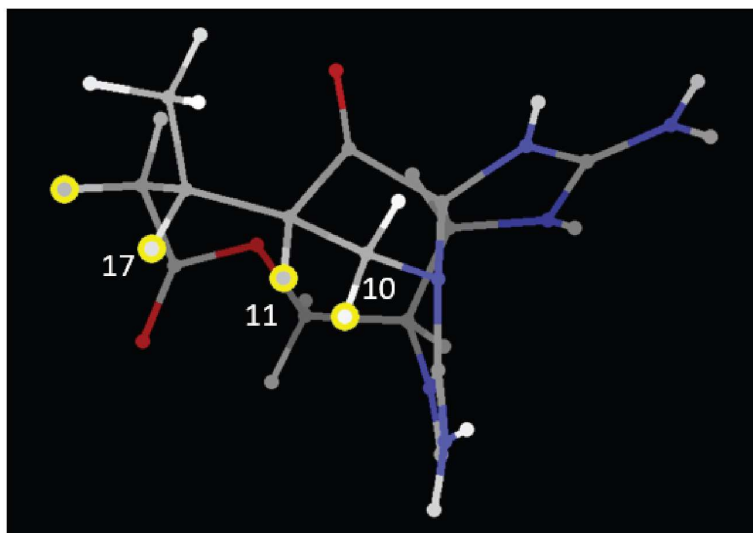






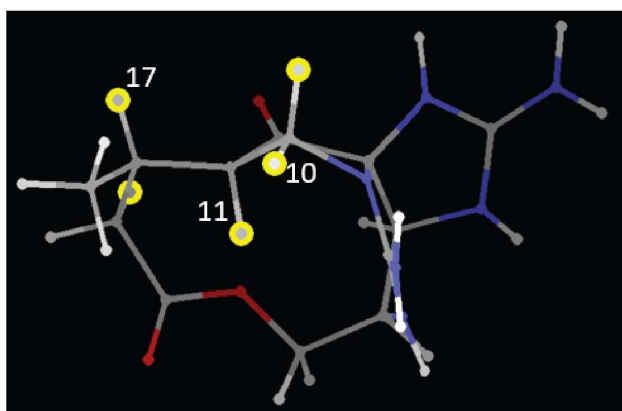
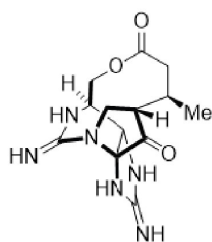


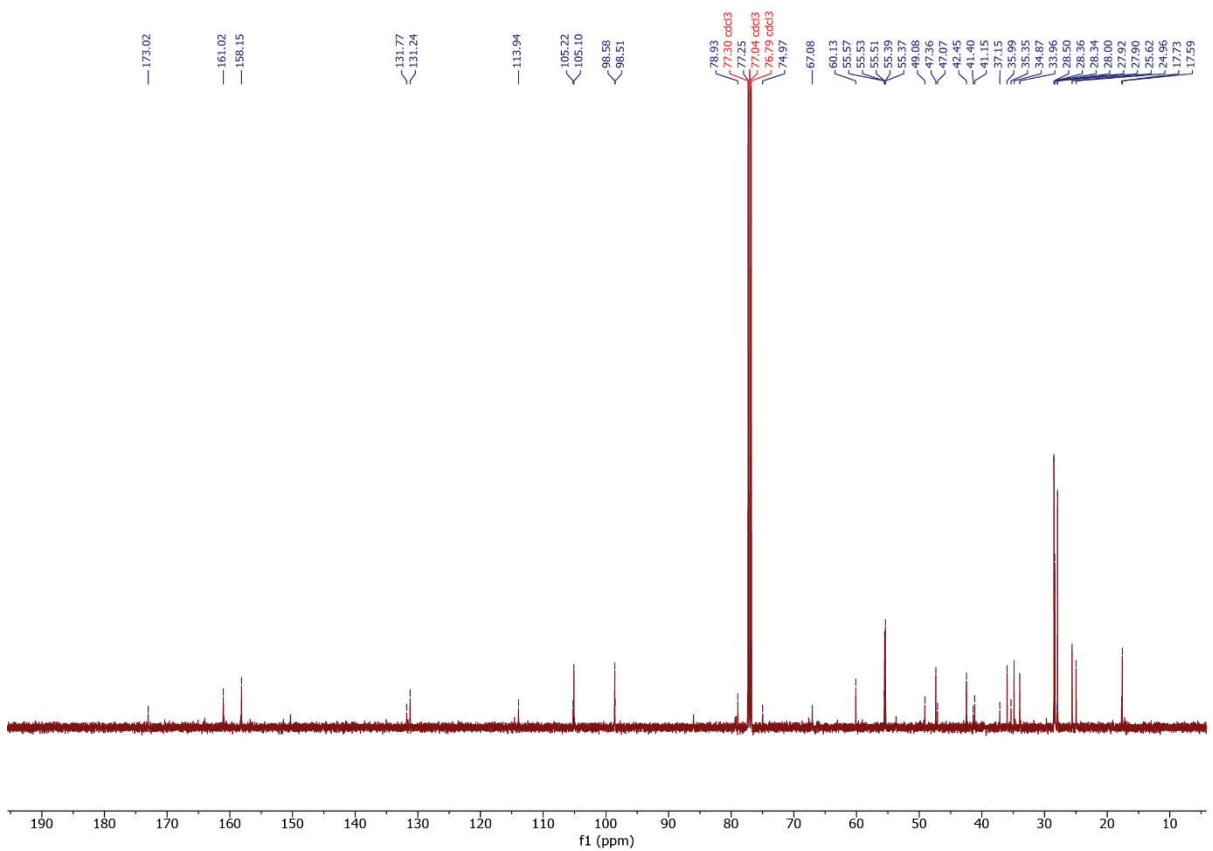
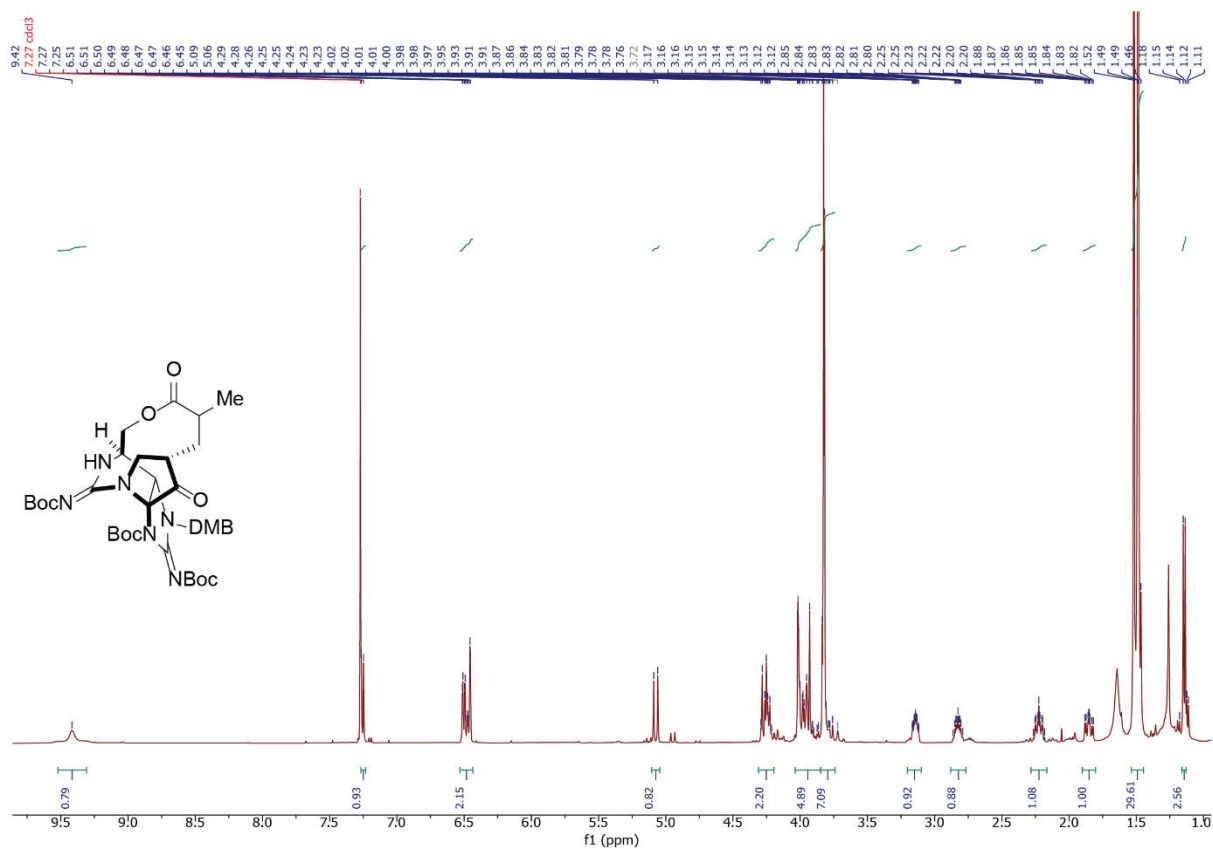
S-isomer
0 kcal/mol

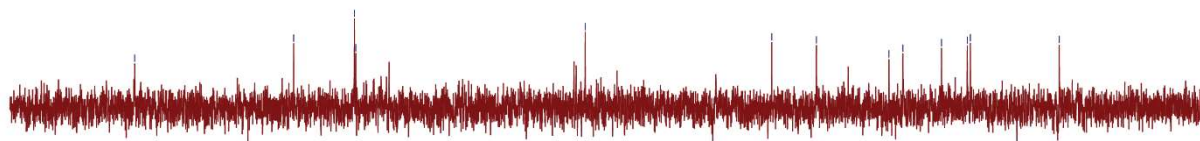
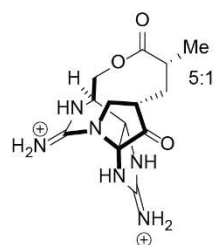


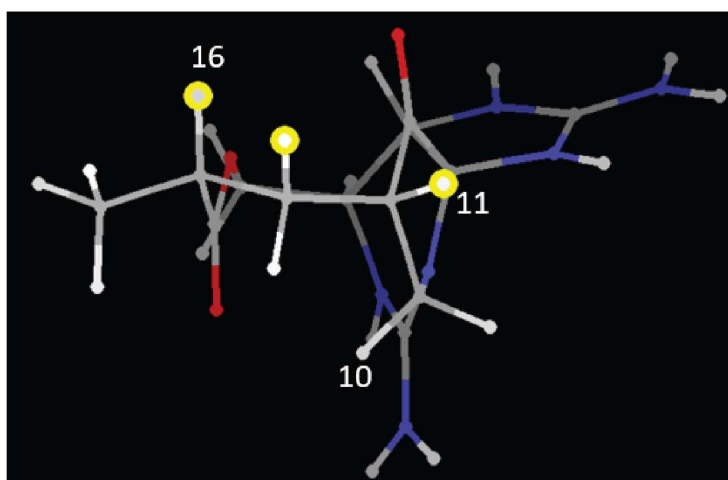
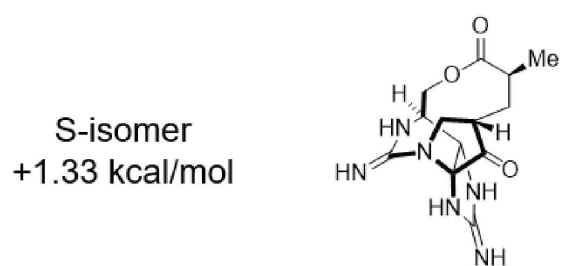
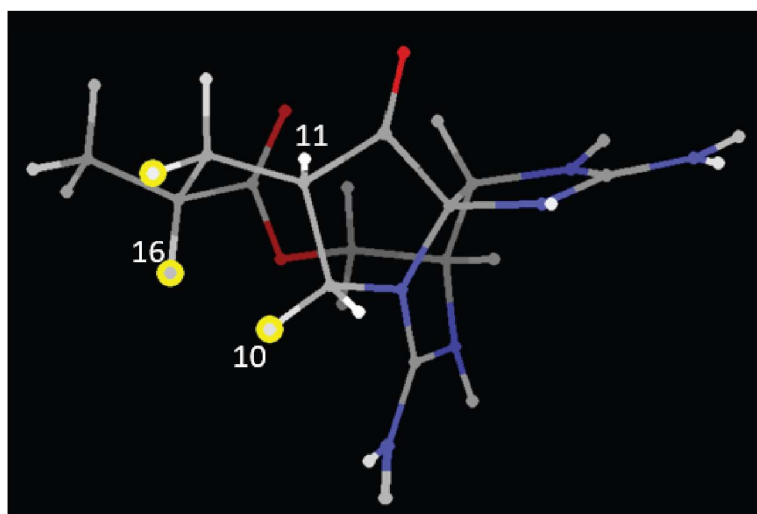
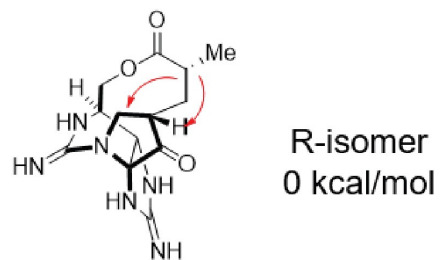
R-isomer
+1.3 kcal/mol

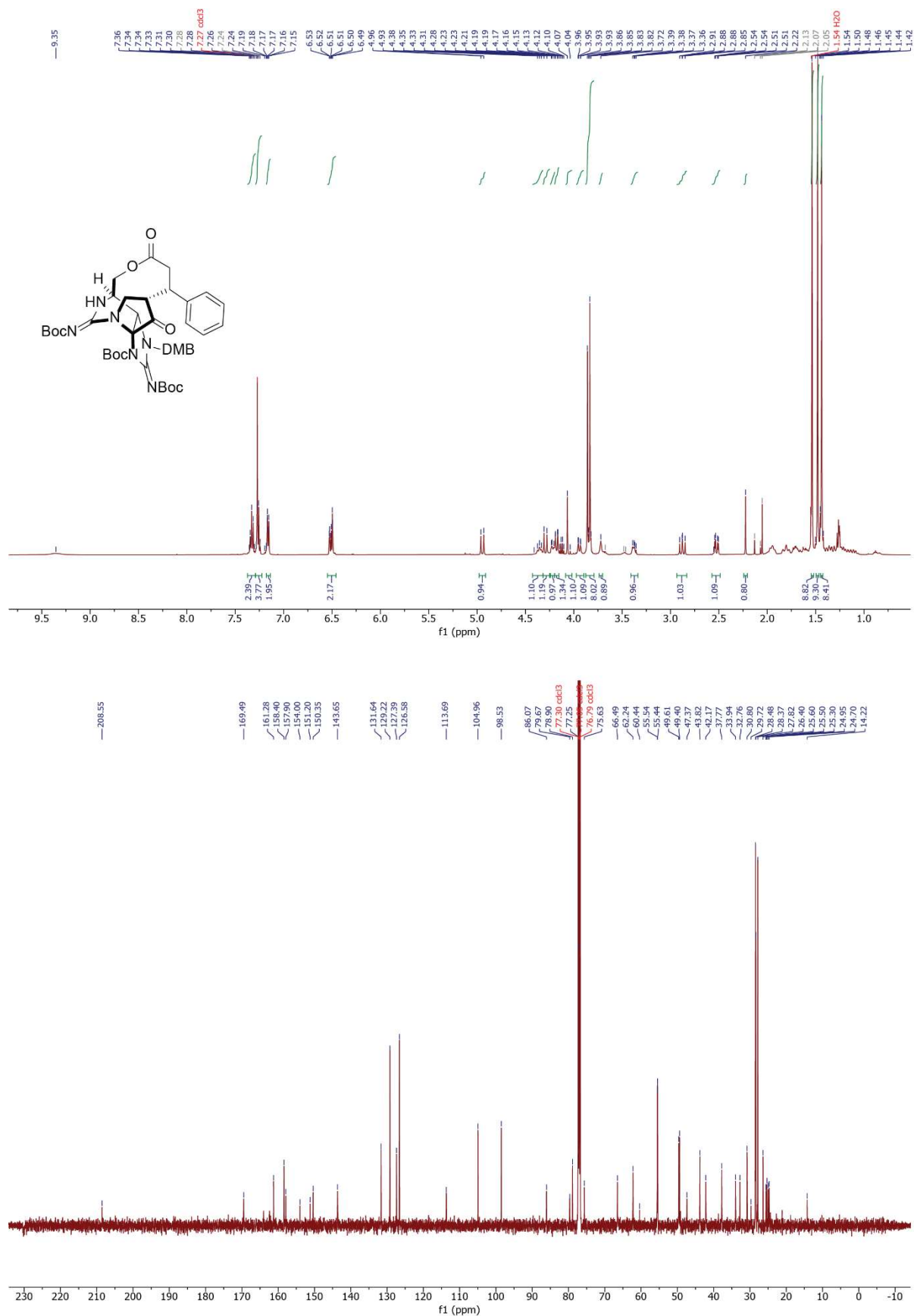
A^{1,3} strain with
C12 ketone

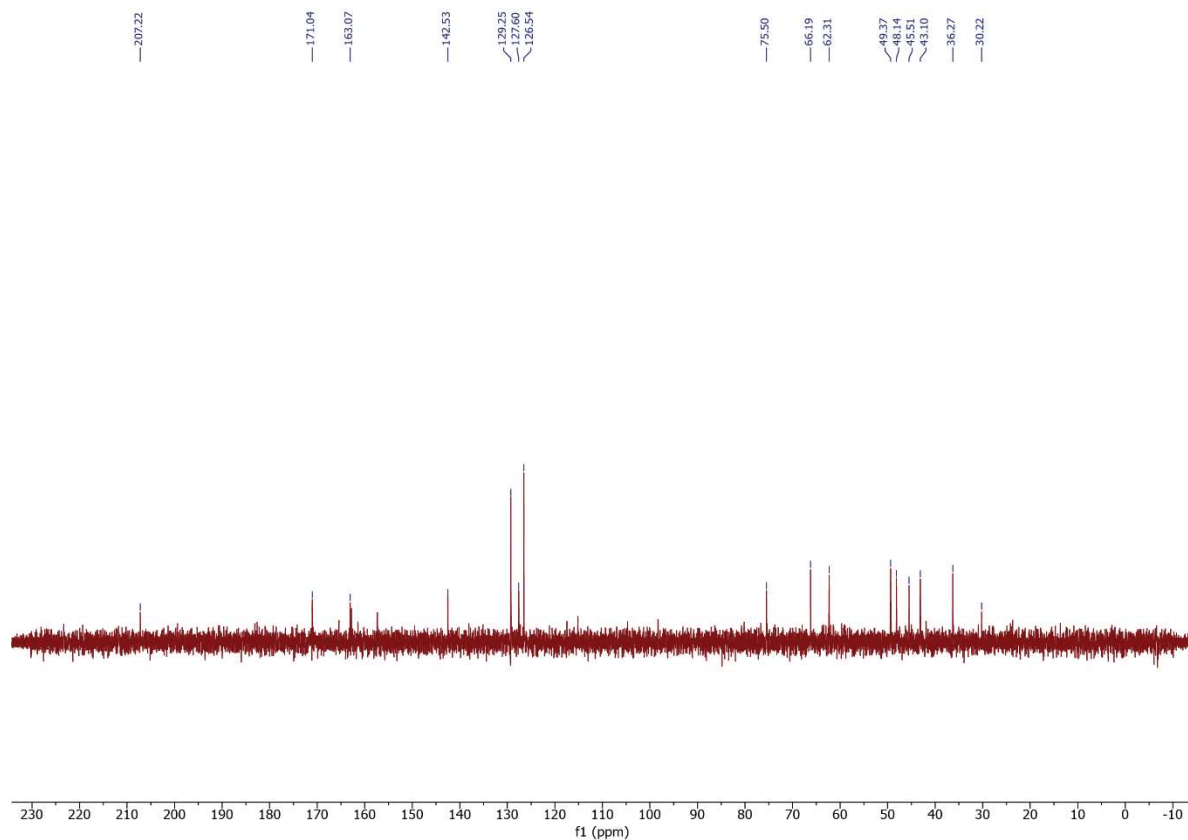
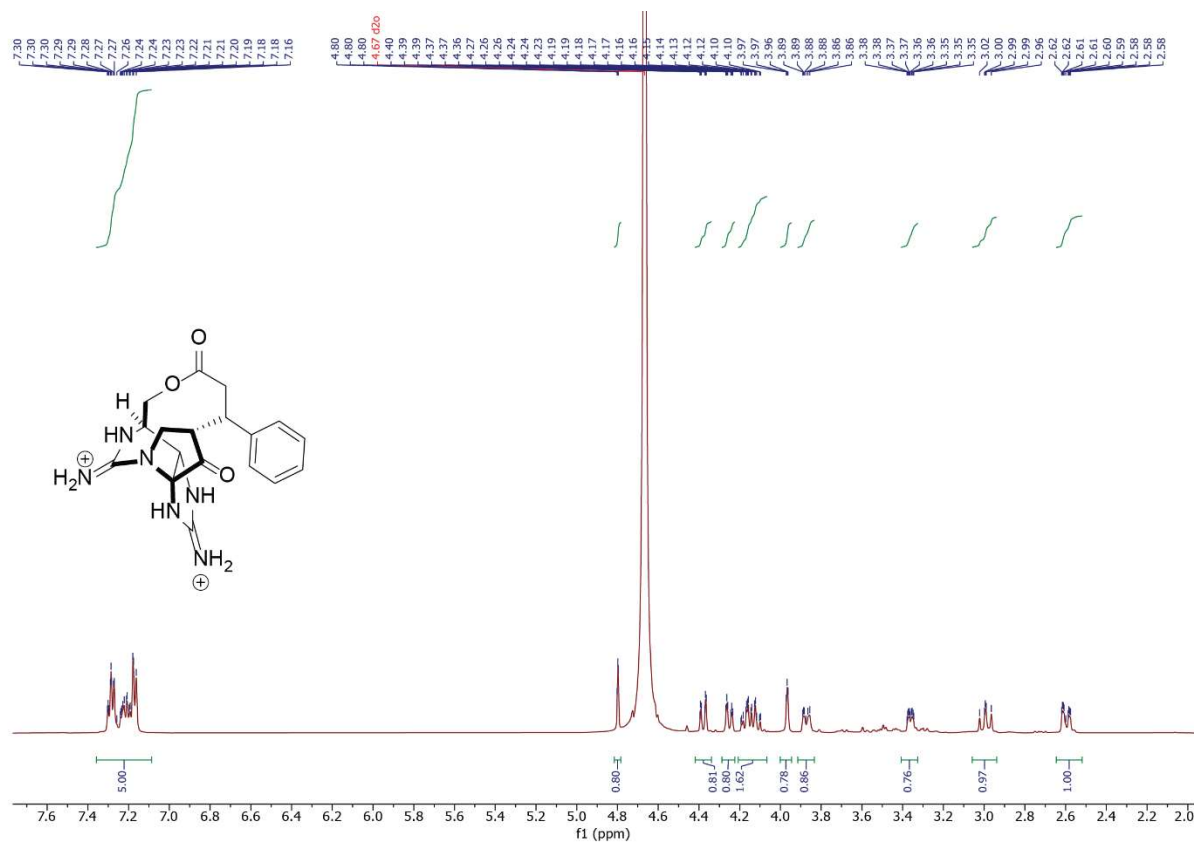














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