

**Salicylate Metal-Binding Isosteres as Fragments for
Metalloenzyme Inhibition**

SUPPORTING INFORMATION

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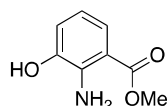
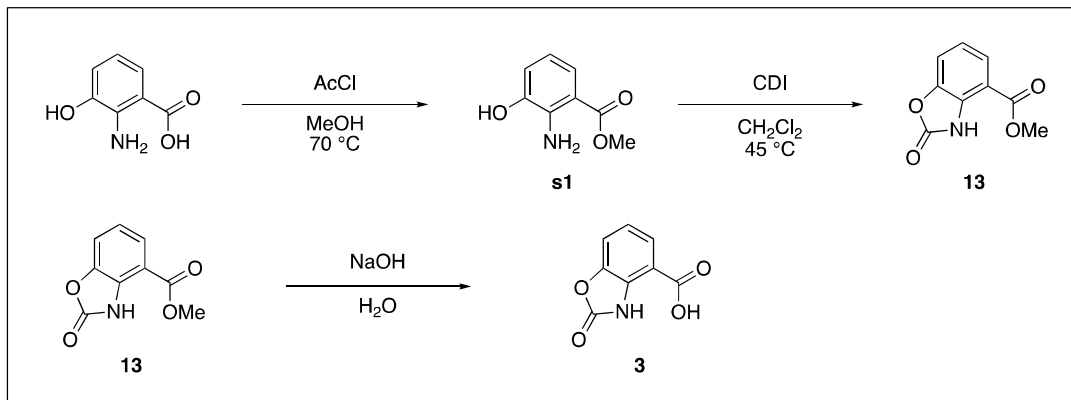
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1. General information

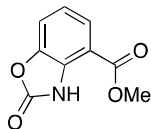
All solvents and reagents, unless otherwise noted, were obtained from commercial sources and used without further purification. Compounds **2**, **4**, **6**, and **11** were purchased from Combi-Blocks Inc. and used without further purification. All reactions, unless otherwise stated, were performed under a nitrogen atmosphere. Silica chromatography was performed using a CombiFlash Rf Teledyne ISCO system using hexane, ethyl acetate, methylene chloride, or methanol as eluents. C18 reverse-phase chromatography was performed using the same instrument using 0.1% formic acid in methanol, acetonitrile, or water as eluent. Separations were monitored by mass spectrometry via a Teledyne ISCO RF⁺ Purlon ESI-MS detector with 1 Da resolution. ¹H- and ¹³C-NMR spectra were obtained on a Varian (400 MHz) spectrometer or Jeol (500 MHz) spectrometer or a VX (500 MHz) equipped with an XSens cold probe (Varian) spectrometer in the Department of Chemistry and Biochemistry at U.C. San Diego. Standard resolution mass spectrometry (MS) was performed either at U.C. San Diego Molecular Mass Spectrometry Facility or on the aforementioned Teledyne ISCO RF⁺ Purlon MS. High resolution mass spectrometry (HRMS) analysis was performed using an Agilent 6230 accurate-mass liquid chromatography time-of-flight mass spectrometry LC-TOFMS located at the U.C. San Diego Molecular Mass Spectrometry Facility.

2. Preparation of Salicylate MBIs



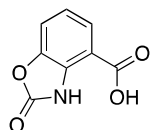
Methyl 2-amino-3-hydroxybenzoate (**s1**)

2-Amino-3-hydroxybenzoic acid (1.00 g, 7.00 mmol, 1.00 equiv) was dissolved in MeOH (15 mL) and acetyl chloride (0.90 mL, 14.0 mmol, 2.00 equiv) was added dropwise. The resulting dark-brown solution was refluxed for 14 h. All volatiles were removed under reduced pressure and the resulting solid was suspended in H₂O (5 mL). Sat. NaHCO₃ was added until a basic pH was reached, EtOAc (100 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (3x50 mL) and the combined organics were washed with brine (50 mL), dried and concentrated under reduced pressure to obtain the desired product, which was used for the next steps without any further purifications. **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 7.53 – 7.43 (m, 1 H), 6.86 – 6.77 (m, 1H), 6.56 – 6.44 (m, 1H), 5.53 (br s, 2H), 3.87 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 169.2, 143.7, 140.9, 123.5, 118.3, 115.6, 118.8, 52.0. These spectral characteristics were identical to those previously reported.¹



Methyl 2-oxo-2,3-dihydrobenzo[d]oxazole-4-carboxylate (**13**)

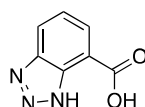
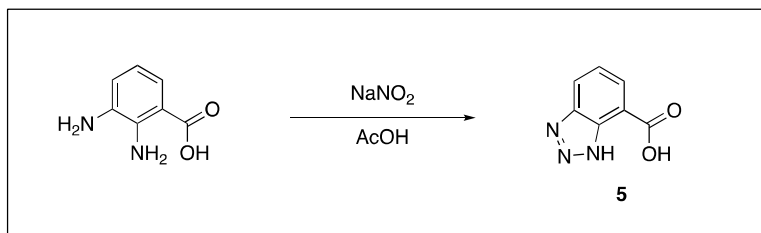
Compound **s1** (200 mg, 1.20 mmol, 1.00 equiv) was dissolved in CH₂Cl₂ (4 mL) and CDI (388 mg, 2.40 mmol, 2.00 equiv) was added as a solid. The resulting mixture was stirred for 14 h at 45 °C. Water (10 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The combined organics were washed with 1 M HCl (3x5 mL) and brine (10 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired compound as an off-white solid. Yield: 170 mg (74%). **¹H NMR** (400 MHz, DMSO-d₆): δ [ppm] = 11.82 (br s, 1H), 7.67 – 7.60 (m, 1H), 7.58 – 7.51 (m, 1H), 7.22 – 7.13 (m, 1H), 3.88 (s, 3H); **¹³C NMR** (100 MHz, DMSO-d₆): δ [ppm] = 164.5, 154.4, 143.9, 131.3, 124.3, 121.6, 113.9, 112.4, 52.2; **HRMS** (ESI): calculated for [C₉H₈NO₄]⁺: *m/z* = 194.0448, found: *m/z* = 194.0449.



2-Oxo-2,3-dihydrobenzo[d]oxazole-4-carboxylic acid (**3**)

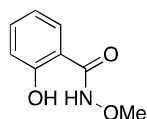
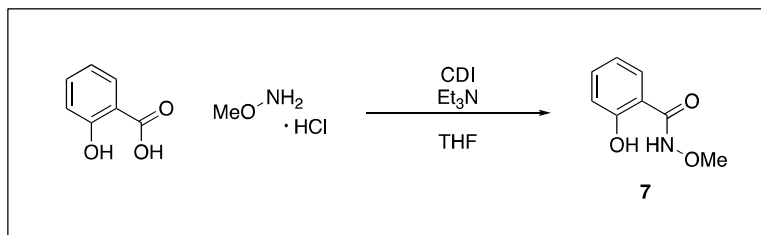
Compound **13** (80.0 mg, 0.41 mmol, 1.00 equiv) was suspended in 1 M NaOH (3 mL) and stirred for 3 h at room temperature. 1 M HCl was added until a pH <1 was reached and the mixture was extracted with EtOAc (3x10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by C18 column chromatography (MeOH:H₂O 1:10 to 10:1 + 0.1% HCO₂H) was used to obtain the desired product as a colorless solid. Yield: 50 mg (67%). **¹H NMR** (400 MHz, DMSO-d₆): δ [ppm] = 13.42 (br s, 1H), 11.68 (br s, 1H), 7.62 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.16 (t, *J* = 8.1 Hz, 1H); **¹³C NMR** (100 MHz, DMSO-d₆): δ [ppm] = 165.7, 154.3,

143.9, 131.5, 124.5, 121.4, 113.7, 113.5; **HRMS** (ESI): calculated for $[C_8H_4NO_4]^-$: $m/z = 178.0146$, found: $m/z = 178.0146$.



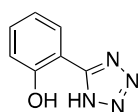
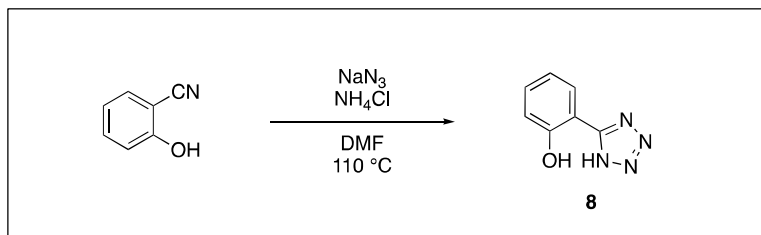
1H-Benzo[d][1,2,3]triazole-7-carboxylic acid (5)

2,3-Diaminobenzoic acid (300 mg, 1.97 mmol, 1.00 equiv) was dissolved in H_2O (2 mL) and $AcOH$ (1 mL) and stirred for 5 min. Afterwards, a solution of $NaNO_2$ (151 mg, 2.19 mmol, 1.11 equiv) in H_2O (2 mL) was added dropwise. The resulting suspension was stirred for 18 h at room temperature. The brown solid was filtered off, washed with H_2O (3x20 mL) and dried under high-vacuum. Purification by C18 column chromatography (MeOH: H_2O 1:10 to 10:1 + 0.1% HCO_2H) produced the desired product as an off-white solid. Yield: 190 mg (60%). **1H NMR** (400 MHz, $DMSO-d_6$): δ [ppm] = 13.71 (br s, 1H), 8.34 (dd, $J = 8.3, 1.0$ Hz, 1H), 8.10 (d, $J = 7.3$ Hz, 1H), 7.61 – 7.41 (m, 1H); **^{13}C NMR** (100 MHz, $DMSO-d_6$): δ [ppm] = 166.3, 145.8, 132.2, 129.9, 124.5, 124.0, 116.0; **HRMS** (ESI): calculated for $[C_7H_4N_3O_2]^-$: $m/z = 162.0309$, found: $m/z = 162.0310$.



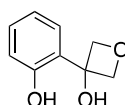
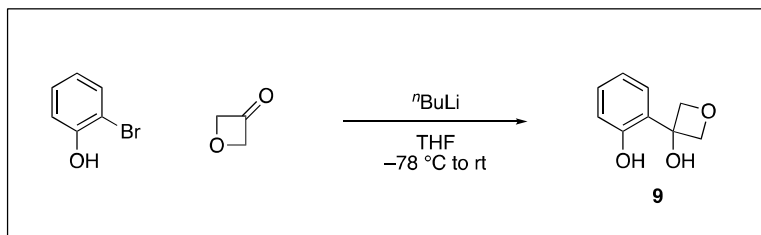
2-Hydroxy-N-methoxybenzamide (7)

Salicylic acid (150 mg, 1.09 mmol, 1.00 equiv) was suspended in anhydrous THF (3 mL). CDI (264 mg, 1.63 mmol, 1.50 equiv) was added as a solid and the resulting mixture was stirred for 0.5 h at room temperature. O-Methylhydroxylamine hydrochloride (181 mg, 2.17 mmol, 2.00 equiv) and Et₃N (0.30 mL, 2.17 mmol, 2.00 equiv) were added and the resulting suspension was stirred at room temperature for 14 h. All volatiles were removed and the resulting brownish oil was purified by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product as a colorless solid. Yield: 100 mg (55%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 11.5 (br s, 1H), 9.20 (br s, 1H), 7.46 – 7.20 (m, 2H), 7.06 – 6.94 (m, 1H), 6.90 – 6.77 (m, 1H), 3.89 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 169.1, 161.3, 135.0, 125.5, 119.2, 188.8, 112.2, 65.0; **HRMS** (ESI): calculated for [C₈H₁₀NO₃]⁺: *m/z* = 168.0655, found: *m/z* = 168.0657.



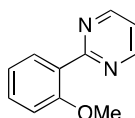
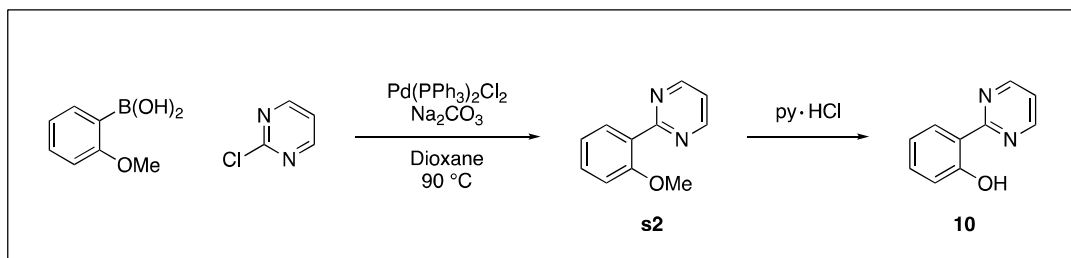
2-(1H-Tetrazol-5-yl)phenol (**8**)

2-Hydroxybenzonitrile (240 mg, 2.01 mmol, 1.00 equiv), NaN₃ (262 mg, 4.03 mmol, 2.00 equiv) and NH₄Cl (216 mg, 4.03 mmol, 2.00 equiv) were suspended in anhydrous DMF (3 mL) and the resulting mixture was stirred at 110 °C for 2 h (progress of the reaction monitored by TLC). H₂O (15 mL) was added to obtain a clear solution. 6 M HCl was added dropwise until a slightly acidic pH was reached and a colorless solid crushed out. The colorless solid was collected by filtration, washed with H₂O (3x30 mL) and dried under high-vacuum to obtain the desired product as a colorless solid. Yield: 150 mg (50%). **¹H NMR** (400 MHz, DMSO-d₆): δ [ppm] = 10.99 (br s, 1H), 7.99 (dd, J = 7.8, 1.7 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.07 (dd, J = 8.3, 1.1 Hz, 1H), 7.00 (td, J = 7.5, 1.1 Hz, 1H); **¹³C NMR** (100 MHz, DMSO-d₆): δ [ppm] = 155.4, 151.7, 132.2, 129.1, 120.2, 116.4, 111.0; **HRMS** (ESI): calculated for [C₇H₅N₄O]⁻: *m/z* = 161.0469, found: *m/z* = 161.0470.



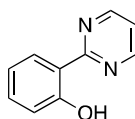
3-(2-Hydroxyphenyl)oxetan-3-ol (9)

2-Bromophenol (242 mg, 1.40 mmol, 1.00 equiv) was dissolved in anhydrous THF (4 mL) and $n\text{-BuLi}$ (1.6 M in hexanes, 3.08 mmol, 2.2 equiv) was added dropwise at $-78\text{ }^\circ\text{C}$. The mixture was allowed to warm to room temperature and stirred for 30 min. The suspension was cooled back to $-78\text{ }^\circ\text{C}$ and oxetane-3-one (121 mg, 1.68 mmol, 1.20 equiv) in THF (2 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 14 h. Sat. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The combined organics were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product as a colorless solid. Yield: 50 mg (22%). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ [ppm] = 7.34 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.26 – 7.21 (m, 1H), 6.96 (td, $J = 7.6, 1.2$ Hz, 1H), 6.87 (dd, $J = 8.1, 1.2$ Hz, 1H), 5.06 (dd, $J = 7.2, 1.0$ Hz, 2H), 4.91 (dd, $J = 7.2, 1.0$ Hz, 2H); **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ [ppm] = 154.6, 130.1, 126.0, 125.3, 120.7, 117.3, 84.2, 77.3; **HRMS** (ESI): calculated for $[\text{C}_9\text{H}_9\text{O}_3]^-$: $m/z = 165.0557$, found: $m/z = 165.0557$.



2-(2-Methoxyphenyl)pyrimidine (**s2**)

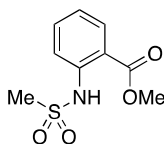
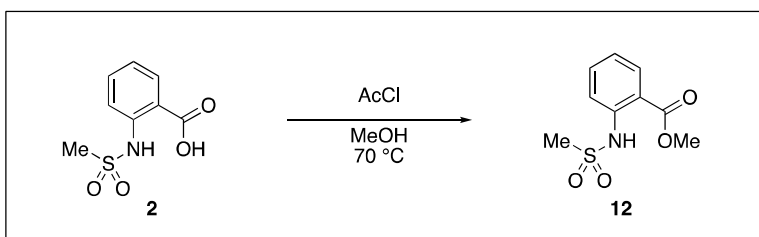
The compound was prepared according to a modified procedure from the literature.¹ (2-Methoxyphenyl)boronic acid (182 mg, 1.20 mmol, 1.20 equiv), 2-chloro-pyrimidine (115 mg, 1.00 mmol, 1.00 equiv), and Pd(PPh₃)₂Cl₂ were suspended in dioxane (2.5 mL). Afterwards, 2 M Na₂CO₃ (2.5 mL) was added and the resulting mixture was stirred at 90 °C for 5 h (progress of the reaction was monitored by TLC). H₂O (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product as a colourless solid. Yield: 140 mg (75%). ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 8.86 (d, J = 4.9 Hz, 2H), 7.77 – 7.66 (m, 1H), 7.48 – 7.37 (m, 1H), 7.22 (t, J = 4.9 Hz, 1H), 7.12 – 6.97 (m, 2H), 3.87 (s, 3H). These spectral characteristics matched those previously reported in the literature.²



2-(Pyrimidin-2-yl)phenol (**10**)

The compound was prepared according to a modified procedure from the literature.¹ Compound **s2** (140 mg, 0.75 mmol, 1.00 equiv) and pyridine hydrochloride (350 mg, 3.00 mmol, 4.00 equiv) were heated to 210 °C and the resulting solution was stirred for 1 h. After

cooling to room temperature, EtOAc (20 mL) and sat. NaHCO₃ (10 mL) were added the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product as a colourless solid. Yield: 60 mg (47%). ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 8.79 (d, *J* = 4.9 Hz, 2H), 8.52 – 8.45 (m, 1H), 7.43 – 7.36 (m, 1H), 7.23 (t, *J* = 4.9 Hz, 1H), 7.06 – 7.00 (m, 1H), 7.00 – 6.90 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = 165.4, 160.7, 156.2, 133.5, 129.3, 119.3, 118.8, 118.4, 118.1. These spectral characteristics matched those previously reported in the literature.²

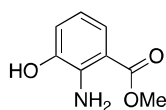
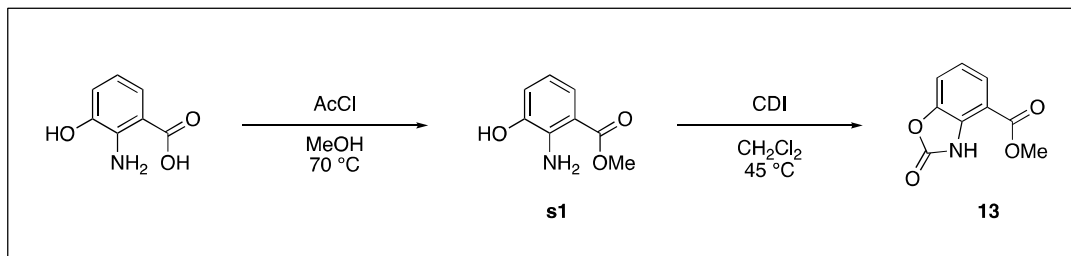


Methyl 2-(methylsulfonyl)benzoate (**12**)

Compound **2** (150 mg, 0.70 mmol, 1.00 equiv) was dissolved in anhydrous MeOH (2 mL) and acetyl chloride (0.15 mL, 2.10 mmol, 3.00 equiv) was added dropwise. The mixture was stirred at 70 °C for 14 h. All volatiles were removed under reduced pressure and sat. NaHCO₃ was added until a neutral pH was reached. The aqueous phase was extracted with EtOAc (3x10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 3:1) produced the desired product as a colorless solid. Yield: 30 mg (20%). ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 10.48 (br s, 1H), 8.10 – 8.00 (m, 1H), 7.80 – 7.68 (m, 1H), 7.60 – 7.50 (m, 1H), 7.18 – 7.06 (m, 1H), 3.94 (s, 3H), 3.06 (s, 3H); ¹³C NMR

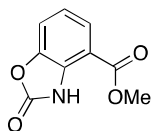
(100 MHz, CDCl₃): δ [ppm] = 168.5, 140.9, 135.1, 131.7, 123.0, 118.1, 115.4, 52.8, 40.1;

HRMS (ESI): calculated for [C₉H₁₁NO₄SNa]⁺: m/z = 252.0301, found: m/z = 252.0304.



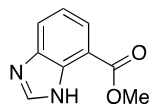
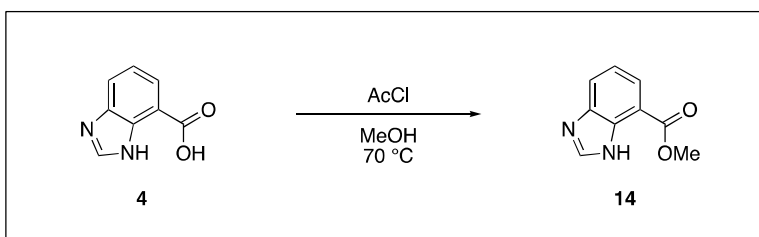
Methyl 2-amino-3-hydroxybenzoate (s1**)**

2-Amino-3-hydroxybenzoic acid (1.00 g, 7.00 mmol, 1.00 equiv) was dissolved in MeOH (15 mL) and acetyl chloride (0.90 mL, 14.0 mmol, 2.00 equiv) was added dropwise. The resulting dark-brown solution was refluxed for 14 h. All volatiles were removed under reduced pressure and the resulting solid was suspended in H₂O (5 mL). Sat. NaHCO₃ was added until a basic pH was reached, EtOAc (100 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (3x50 mL) and the combined organics were washed with brine (50 mL), dried and concentrated under reduced pressure to obtain the desired product, which was used for the next steps without any further purifications. **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 7.53 – 7.43 (m, 1 H), 6.86 – 6.77 (m, 1H), 6.56 – 6.44 (m, 1H), 5.53 (br s, 2H), 3.87 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 169.2, 143.7, 140.9, 123.5, 118.3, 115.6, 118.8, 52.0. These spectral characteristics were identical to those previously reported.¹



Methyl 2-oxo-2,3-dihydrobenzo[d]oxazole-4-carboxylate (13)

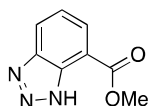
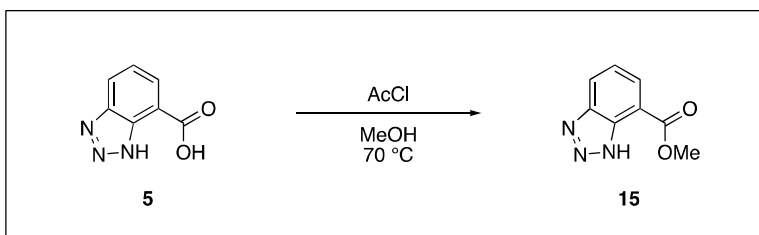
Methyl 2-amino-3-hydroxybenzoate (200 mg, 1.20 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (4 mL) and CDI (388 mg, 2.40 mmol, 2.00 equiv) was added as a solid. The resulting mixture was stirred for 14 h at 45 °C. Water (10 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The combined organics were washed with 1 M HCl (3x5 mL) and brine (10 mL), dried over MgSO_4 , and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired compound as an off-white solid. Yield: 170 mg (74%). $^1\text{H NMR}$ (400 MHz, DMSO-d_6): δ [ppm] = 11.82 (br s, 1H), 7.67 – 7.60 (m, 1H), 7.58 – 7.51 (m, 1H), 7.22 – 7.13 (m, 1H), 3.88 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6): δ [ppm] = 164.5, 154.4, 143.9, 131.3, 124.3, 121.6, 113.9, 112.4, 52.2; **HRMS** (ESI): calculated for $[\text{C}_9\text{H}_8\text{NO}_4]^+$: m/z = 194.0448, found: m/z = 194.0449.



Methyl 1H-benzo[d]imidazole-7-carboxylate (14)

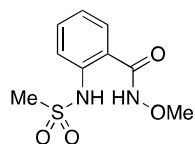
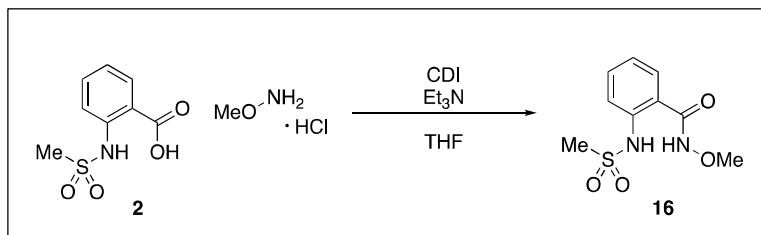
Compound **4** (200 mg, 1.23 mmol, 1.00 equiv) was dissolved in anhydrous MeOH (2.5 mL) and acetyl chloride (0.26 mL, 3.70 mmol, 3.00 equiv) was added dropwise. The mixture was stirred at 70 °C for 14 h. All volatiles were removed under reduced pressure and sat. NaHCO_3 was added until a neutral pH was reached. The aqueous phase was extracted with EtOAc (3x10 mL). The combined organics were washed with brine (10 mL), dried over MgSO_4 , and

concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product as a yellow solid. Yield: 120 mg (55%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 8.17 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.37 – 7.30 (m, 1H), 4.00 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 167.0, 143.7, 141.6, 133.4, 125.6, 125.4, 122.0, 113.9, 52.4; **HRMS** (ESI): calculated for [C₉H₉N₂O₂]⁺: *m/z* = 177.0659, found: *m/z* = 177.0660.



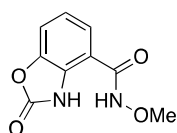
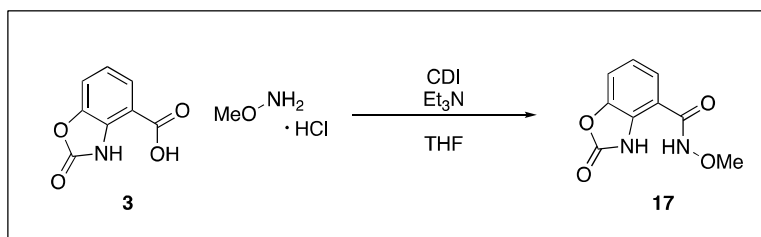
Methyl 1H-benzo[d][1,2,3]triazole-7-carboxylate (15)

Compound **5** (70.0 mg, 0.43 mmol, 1.00 equiv) was dissolved in anhydrous MeOH (1.00 mL) and acetyl chloride (0.09 mL, 1.30 mmol, 3.00 equiv) was added dropwise. The mixture was stirred at 70 °C for 14 h. All volatiles were removed under reduced pressure and sat. NaHCO₃ was added until a neutral pH was reached. The aqueous phase was extracted with EtOAc (3x10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product as a yellow solid. Yield: 30 mg (40%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 8.41 – 8.23 (m, 1H), 8.23 – 8.15 (m, 1H), 7.54 – 7.44 (m, 1H), 4.10 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 166.0, 145.5, 132.4, 130.1, 125.4, 124.0, 114.0, 53.0; **HRMS** (ESI): calculated for [C₈H₈N₃O₂]⁺: *m/z* = 178.0611, found: *m/z* = 178.0612.



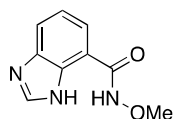
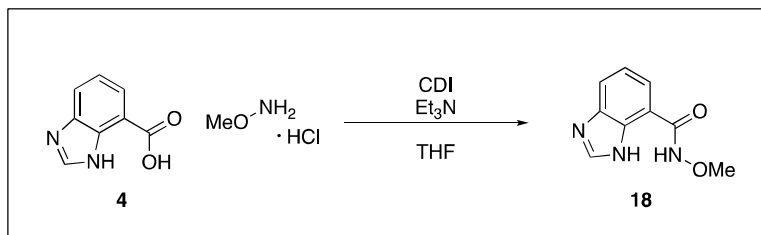
N-Methoxy-2-(methylsulfonylamido)benzamide (16)

Compound **2** (220 mg, 1.02 mmol, 1.00 equiv) was suspended in anhydrous THF (3 mL). CDI (249 mg, 1.53 mmol, 1.50 equiv) was added as a solid and the resulting mixture was stirred for 0.5 h at room temperature. *O*-methylhydroxylamine hydrochloride (142 mg, 2.04 mmol, 2.00 equiv) and Et₃N (0.30 mL, 2.04 mmol, 2.00 equiv) were added and the resulting suspension was stirred at room temperature for 14 h. All volatiles were removed and the resulting brownish oil was purified by column chromatography (hexanes:EtOAc 10:1 to 1:10) to obtain the desired product as a colorless solid. Yield: 120 mg (50%). **¹H NMR** (400 MHz, CD₃OD): δ [ppm] = 7.70 – 7.65 (m, 1 H), 7.63 – 7.59 (m, 1H), 7.58 – 7.52 (m, 1H), 7.23 – 7.16 (m, 1H), 3.82 (s, 3H), 3.03 (s, 3H); **¹³C NMR** (100 MHz, CD₃OD): δ [ppm] = 167.8, 139.8, 134.1, 129.2, 125.0, 122.0, 121.1 64.5, 39.8; **HRMS** (ESI): calculated for [C₉H₁₂N₂O₄SNa]⁺: *m/z* = 267.0410, found: *m/z* = 267.0408.



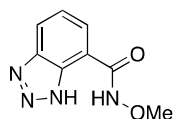
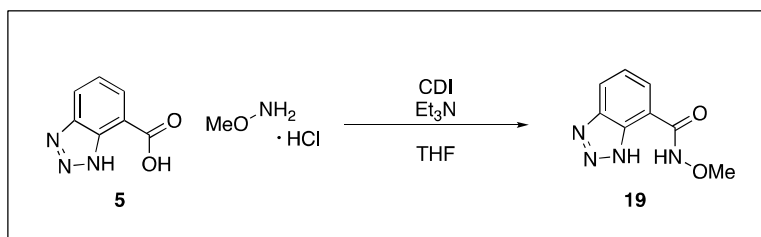
N-Methoxy-2-oxo-2,3-dihydrobenzo[d]oxazole-4-carboxamide (17)

Compound **3** (150 mg, 0.84 mmol, 1.00 equiv) was suspended in anhydrous THF (3 mL). CDI (163 mg, 1.00 mmol, 1.20 equiv) was added as a solid and the resulting mixture was stirred for 0.5 h at room temperature. *O*-methylhydroxylamine hydrochloride (116 mg, 1.68 mmol, 2.00 equiv) and Et₃N (0.23 mL, 1.68 mmol, 2.00 equiv) were added and the resulting suspension was stirred at room temperature for 14 h. All volatiles were removed and the resulting brownish oil was purified by column chromatography (CH₂Cl₂:MeOH 30:1 to 10:1) to obtain the desired product as a yellow solid. Yield: 60 mg (34%). **¹H NMR** (400 MHz, CD₃OD): δ [ppm] = 7.59 – 7.43 (m, 1H), 7.16 – 7.00 (m, 2H), 3.98 (s, 3H); **¹³C NMR** (100 MHz, CD₃OD): δ [ppm] = 161.3, 149.9, 146.0, 129.4, 124.5, 120.0, 118.4, 116.7, 64.4; **HRMS** (ESI): calculated for [C₉H₉N₂O₄]⁺: *m/z* = 209.0557, found: *m/z* = 209.0559.



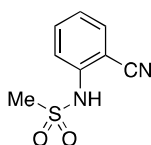
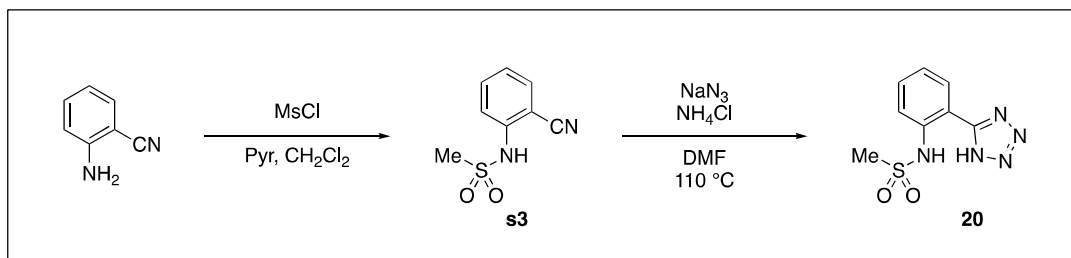
***N*-methoxy-1*H*-benzo[*d*]imidazole-7-carboxamide (18)**

Compound **4** (170 mg, 1.05 mmol, 1.00 equiv) was suspended in anhydrous THF (3 mL). CDI (255 mg, 1.57 mmol, 1.50 equiv) was added as a solid and the resulting mixture was stirred for 0.5 h at room temperature. *O*-methylhydroxylamine hydrochloride (146 mg, 2.10 mmol, 2.00 equiv) and Et₃N (0.29 mL, 2.10 mmol, 2.10 equiv) were added and the resulting suspension was stirred at room temperature for 14 h. All volatiles were removed and the resulting brownish oil was purified by column chromatography (CH₂Cl₂:MeOH 30:1 to 10:1) to obtain the desired product as an orange solid. Yield: 110 mg (55%). **¹H NMR** (400 MHz, Acetone-*d*₆): δ [ppm] = 12.35 (br s, 1H), 8.43 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.88 – 7.77 (m, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 3.88 (s, 3H); **¹³C NMR** (100 MHz, Acetone-*d*₆): δ [ppm] = 163.9, 143.1, 140.9, 134.3, 123.7, 123.6, 122.3, 116.4, 64.4; **HRMS** (ESI): calculated for [C₉H₁₀N₃O₂]⁺: *m/z* = 192.0768, found: *m/z* = 192.0767.



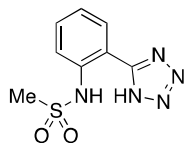
***N*-methoxy-1*H*-benzo[*d*][1,2,3]triazole-7-carboxamide (19)**

Compound **5** (180 mg, 1.10 mmol, 1.00 equiv) was suspended in anhydrous THF (3 mL). CDI (268 mg, 1.65 mmol, 1.50 equiv) was added as a solid and the resulting mixture was stirred for 0.5 h at room temperature. *O*-methylhydroxylamine hydrochloride (153 mg, 2.21 mmol, 2.00 equiv) and Et₃N (0.31 mL, 2.21 mmol, 2.00 equiv) were added and the resulting suspension was stirred at room temperature for 14 h. All volatiles were removed and the resulting brownish oil was purified by column chromatography (CH₂Cl₂:MeOH 30:1 to 10:1) to obtain the desired product as a yellow solid. Yield: 125 mg (60%). **¹H NMR** (400 MHz, Acetone-d₆): δ [ppm] = 8.15 – 8.13 (m, 1H), 8.07 – 8.05 (m, 1H), 7.62 – 7.58 (m, 1H), 3.91 (s, 3H); **¹³C NMR** (100 MHz, Acetone-d₆): δ [ppm] = 162.4, 140.2, 137.8, 126.4, 126.1, 119.9, 119.5, 64.3, **HRMS** (ESI): calculated for [C₈H₈N₄O₂Na]⁺: *m/z* = 215.0539, found: *m/z* = 215.0540.



***N*-(2-cyanophenyl)methanesulfonamide (**s3**)**

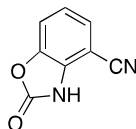
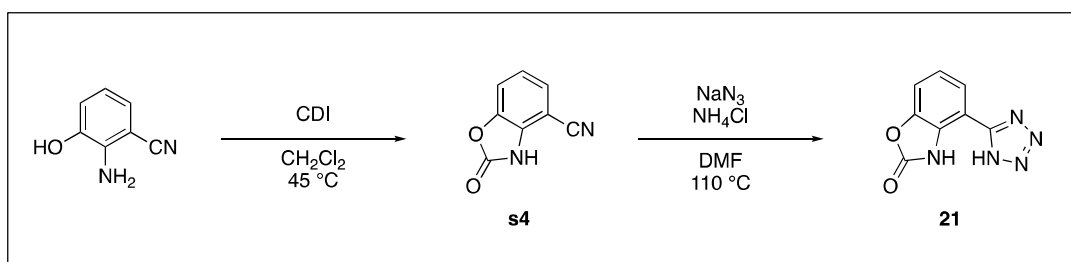
2-aminobenzonitrile (300 mg, 2.50 mmol, 1.00 equiv) was dissolved in anhydrous CH₂Cl₂ (5 mL) and pyridine (0.30 mL, 3.80 mmol, 1.50 equiv) was added. The resulting solution was cooled to –78 °C and MsCl (0.21 mL, 2.80 mmol, 1.10 equiv) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 14 h. H₂O (10 mL) and CH₂Cl₂ were added, the phases separated and the aqueous phase extracted with CH₂Cl₂ (3x20 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 3:1) to obtain the desired product, which was directly used for the next step. ¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.77 – 7.69 (m, 1H), 7.68 – 7.59 (m, 2H), 7.34 – 7.20 (m, 1H), 7.00 (br s, 1H), 3.13 (s, 3H); These spectral characteristics were identical to those previously reported.³



***N*-(2-(1*H*-tetrazol-5-yl)phenyl)methanesulfonamide (**20**)**

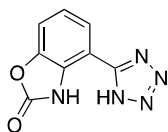
Compound **s3** (200 mg, 1.02 mmol, 1.00 equiv), NaN₃ (133 mg, 2.04 mmol, 2.00 equiv) and NH₄Cl (109 mg, 2.04 mmol, 2.00 equiv) were suspended in anhydrous DMF (3 mL) and the resulting mixture was stirred at 110 °C for 2 h (progress of the reaction monitored by TLC).

H₂O (15 mL) was added to obtain a clear solution. 6 M HCl was added dropwise until a slightly acidic pH was reached and a colorless solid crushed out. The colorless solid was collected by filtration, washed with H₂O (3x30 mL) and dried under high-vacuum to obtain the desired product as a colorless solid. Yield: 180 mg (74%). **¹H NMR** (400 MHz, DMSO-d₆): δ [ppm] = 10.25 (br s, 1H), 7.98 – 7.95 (m, 1H), 7.70 – 7.65 (m, 1H), 7.64 – 7.60 (m, 1H), 7.38 – 7.35 (m, 1H), 3.16 (s, 3H); **¹³C NMR** (100 MHz, DMSO-d₆): δ [ppm] = 154.3, 136.6, 132.4, 129.3, 124.4, 120.5, 113.9; **HRMS** (ESI): calculated for [C₈H₁₀N₅O₂S]⁺: *m/z* = 240.0550, found: *m/z* = 240.0551.



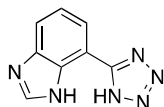
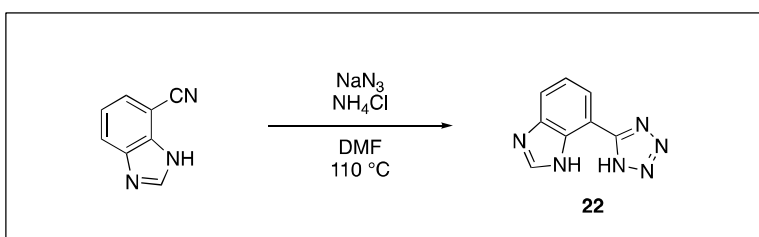
2-oxo-2,3-dihydrobenzo[d]oxazole-4-carbonitrile (s4)

2-amino-3-hydroxybenzonitrile (250 mg, 1.86 mmol, 1.00 equiv) was dissolved in CH₂Cl₂ (4 mL) and CDI (604 mg, 3.73 mmol, 2.00 equiv) was added as a solid. The resulting mixture was stirred for 14 h at 45 °C. Water (10 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The combined organics were washed with 1 M HCl (3x5 mL) and brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product, which was used directly for the next step. **¹H NMR** (400 MHz, DMSO-d₆): δ [ppm] = 12.83 (br s, 1H), 7.63 – 7.59 (m, 1H), 7.57 – 7.53 (m, 1H), 7.24 – 7.18 (m, 1H); **¹³C NMR** (100 MHz, DMSO-d₆): δ [ppm] = 153.9, 143.6, 133.9, 126.9, 122.4, 115.5, 114.2, 92.5; **HRMS** (ESI): calculated for [C₈H₃N₂O₂]⁻: *m/z* = 159.0200, found: *m/z* = 159.0199.



4-(1H-tetrazol-5-yl)benzo[d]oxazol-2(3H)-one (21)

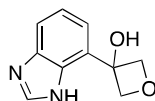
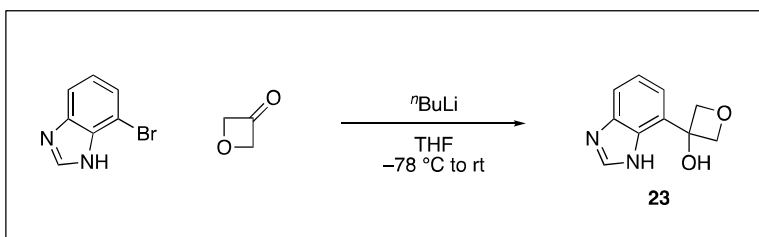
Compound **s4** (90.0 mg, 0.56 mmol, 1.00 equiv), NaN₃ (73.0 mg, 1.10 mmol, 2.00 equiv) and NH₄Cl (60.0 mg, 1.10 mmol, 2.00 equiv) were suspended in anhydrous DMF (2 mL) and the resulting mixture was stirred at 110 °C for 2 h (progress of the reaction monitored by TLC). H₂O (10 mL) was added to obtain a clear solution. 6 M HCl was added dropwise until a slightly acidic pH was reached and a colorless solid crushed out. The colorless solid was collected by filtration, washed with H₂O (3 x 20 mL) and dried under high-vacuum. Purification by column chromatography to obtain the desired product as a yellow solid (EtOAc:MeOH 100:1 to 10:1). Yield: 40 mg (35%). **¹H NMR** (400 MHz, CD₃OD): δ [ppm] = 7.76 (dd, J = 8.0, 1.1 Hz, 1H), 7.34 (dd, J = 8.0, 1.1 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H); **¹³C NMR** (100 MHz, CD₃OD): δ [ppm] = 156.1, 155.2, 144.5, 128.4, 122.2, 121.3, 110.6, 109.5; **HRMS** (ESI): calculated for [C₈H₆N₅O₂]⁺: *m/z* = 204.0516, found: *m/z* = 204.0518.



7-(1H-tetrazol-5-yl)-1H-benzo[d]imidazole (22)

1H-benzo[d]imidazole-7-carbonitrile (110 mg, 0.77 mmol, 1.00 equiv), NaN₃ (99.9 mg, 1.54 mmol, 2.00 equiv) and NH₄Cl (82.2 mg, 1.54 mmol, 2.00 equiv) were suspended in anhydrous DMF (2.5 mL) and the resulting mixture was stirred at 110 °C for 24 h (progress of the reaction

monitored by TLC). The mixture was concentrated under reduced pressure and H₂O (10 mL) was added. A solid crushed out which was collected by filtration, washed with H₂O (3x20 mL) and dried under high-vacuum. Purification by C18 column chromatography (H₂O:MeOH 10:1 to 1:10) to obtain the desired product as a greyish solid. Yield: 45 mg (31%). **¹H NMR** (400 MHz, DMSO-d₆): δ [ppm] = 8.42 (s, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H); **¹³C NMR** (100 MHz, DMSO-d₆): δ [ppm] = 153.4, 145.0, 137.7, 134.4, 122.5, 121.4, 118.3, 111.2; **HRMS** (ESI): calculated for [C₈H₇N₆]⁺: *m/z* = 187.0727, found: *m/z* = 187.0728.

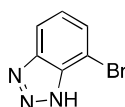
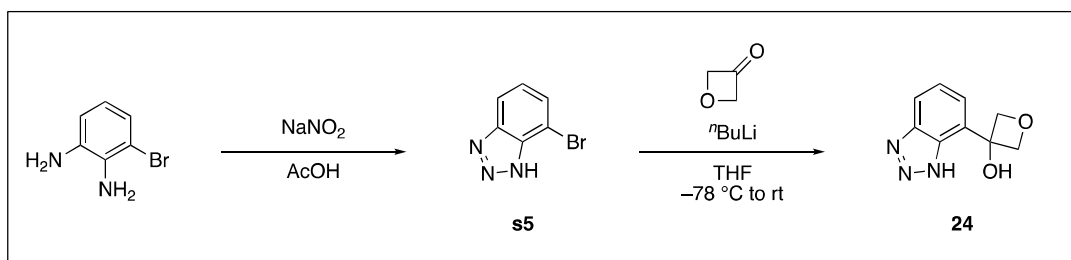


3-(1H-Benzo[d]imidazol-7-yl)oxetan-3-ol (23)

7-bromo-1H-benzimidazole (242 mg, 1.23 mmol, 1.00 equiv) was dissolved in anhydrous THF (6 mL) and ⁿBuLi (1.6 M in hexanes, 2.70 mmol, 2.20 equiv) was added dropwise at -78 °C. The resulting mixture was stirred at this temperature for 2 h. Oxetane-3-one (121 mg, 1.68 mmol, 1.20 equiv) in THF (2 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. Sat. NH₄Cl (10 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The combined organics were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (CH₂Cl₂:MeOH 100:1 to 10:1) to obtain the desired product as a colorless solid. Yield: 70 mg (30%). **¹H NMR** (400 MHz, CD₃OD): δ [ppm] = 8.14 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.31 (t, J = 7.8 Hz, 1H), 5.10 – 5.00 (m, 4H); **¹³C NMR** (100

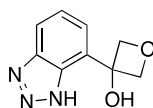
MHz, CD₃OD): δ [ppm] = 142.6, 141.6, 134.0, 130.3, 123.5, 120.2, 117.3, 86.7, 76.6;

HRMS (ESI): calculated for [C₁₀H₁₁N₂O₂]⁺: m/z = 191.0815, found: m/z = 191.0815.



7-bromo-1H-benzo[d][1,2,3]triazole (**s5**)

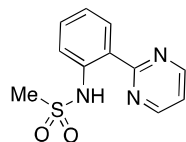
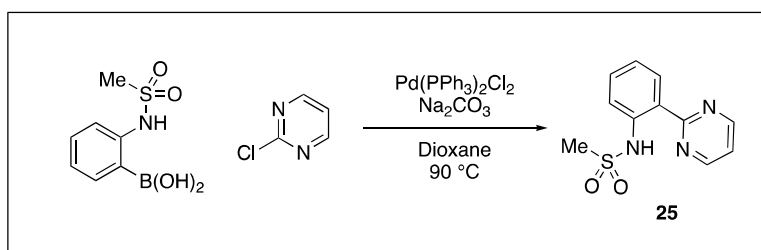
3-bromobenzene-1,2-diamine (500 mg, 2.67 mmol, 1.00 equiv) was dissolved in H₂O (5 mL) and AcOH (2 mL) and stirred for 5 min. There to, a solution of NaNO₂ (211 mg, 3.06 mmol, 1.11 equiv) in H₂O (2 mL) was added dropwise. The resulting suspension was stirred for 18 h at room temperature. The brown solid was filtered off, washed with H₂O (3 x 20 mL) and dried under high-vacuum to obtain the desired product, which was used without any further purifications for the next step. **¹H NMR** (400 MHz, Acetone-d₆): δ [ppm] = 7.91 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 7.4 Hz, 1H), 7.42 (dd, J = 8.3, 7.4 Hz, 1H); **¹³C NMR** (100 MHz, Acetone-d₆): δ [ppm] = 140.9, 139.3, 128.7, 128.1, 114.3, 109.5; **HRMS** (ESI): calculated for [C₆H₅BrN₃]⁺: m/z = 197.9661, found: m/z = 197.9659.



3-(1H-Benzo[d][1,2,3]triazol-7-yl)oxetan-3-ol (**24**)

Compound **s6** (242 mg, 1.22 mmol, 1.00 equiv) was dissolved in anhydrous THF (4 mL) and ⁿBuLi (1.6 M in hexanes, 3.67 mmol, 3.00 equiv) was added dropwise at -78 °C. The resulting mixture was stirred at this temperature for 2 h. Oxetane-3-one (264 mg, 3.67 mmol, 3.00 equiv) in THF (2 mL) was added dropwise. The resulting mixture was allowed to warm to

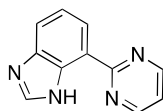
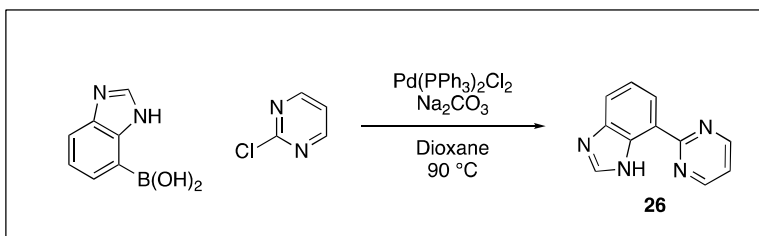
room temperature and stirred for 24 h. Sat. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3x20 mL). The combined organics were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2 :MeOH 100:1 to 10:1) to obtain the desired product as a colorless solid. Yield: 130 mg (56%). $^1\text{H NMR}$ (400 MHz, CD_3OD): δ [ppm] = 7.90 – 7.82 (m, 1H), 7.70 – 7.64 (m, 1H), 7.55 – 7.44 (m, 1H), 5.19 – 5.00 (m, 4H); $^{13}\text{C NMR}$ (100 MHz, CD_3OD): δ [ppm] = 142.9, 135.4, 131.1, 126.5, 123.3, 116.5, 86.2, 76.0; **HRMS** (ESI): calculated for $[\text{C}_9\text{H}_{10}\text{N}_3\text{O}_2]^+$: m/z = 192.0768, found: m/z = 192.0771.



N-(2-(Pyrimidin-2-yl)phenyl)methanesulfonamide (25)

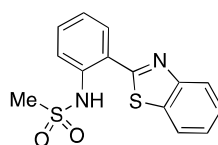
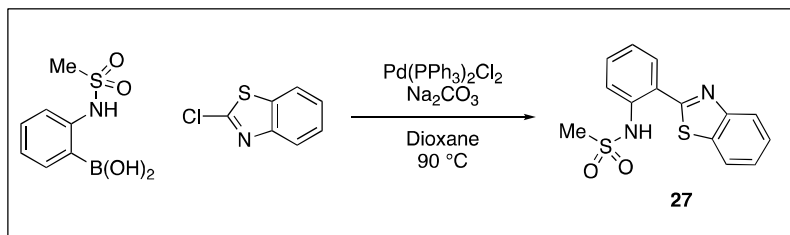
(2-(Methylsulfonylamido)phenyl)boronic acid (258 mg, 1.20 mmol, 1.20 equiv), 2-chloropyrimidine (115 mg, 1.00 mmol, 1.00 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.5 mol%) were suspended in Dioxane (2.5 mL). Thereto, 2 M Na_2CO_3 (2.5 mL) was added and the resulting mixture was stirred at $90\text{ }^\circ\text{C}$ for 5 h (progress of the reaction monitored by TLC). H_2O (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) followed by C18 column chromatography (H_2O :MeOH 10:1 to 1:10 + 0.1 % HCO_2H) to obtain the desired product as a colourless solid. Yield: 180 mg (32%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] = 12.51 (br s, 1H), 8.86 (d, J = 4.9 Hz, 2H), 8.70

– 8.63 (m, 1H), 7.82 – 7.71 (m, 1H), 7.54 – 7.43 (m, 1H), 7.28 (t, $J = 4.9$ Hz, 1H), 7.26 – 7.18 (m, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ [ppm] = 164.4, 156.7, 139.4, 132.8, 131.2, 123.5, 122.7, 119.1, 118.9, 39.8; HRMS (ESI): calculated for $[\text{C}_{11}\text{H}_{12}\text{N}_3\text{O}_2\text{S}]^+$: $m/z = 250.0645$, found: $m/z = 250.0647$.



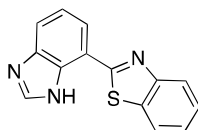
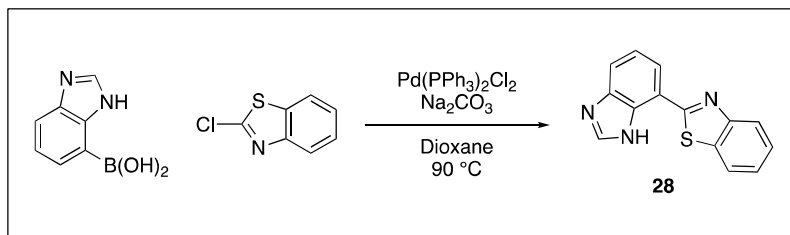
N-(2-(Pyrimidin-2-yl)phenyl)methanesulfonamide (26)

(1H-Benzo[d]imidazol-7-yl)boronic acid (150 mg, 0.93 mmol, 1.20 equiv), 2-chloro-pyrimidine (90.0 mg, 0.78 mmol, 1.00 equiv) and Pd(PPh₃)₂Cl₂ (1.5 mol%) were suspended in Dioxane (2 mL). There to, 2 M Na₂CO₃ (2 mL) was added and the resulting mixture was stirred at 90 °C for 5 h (progress of the reaction monitored by TLC). H₂O (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) followed by C18 column chromatography (H₂O:MeOH 10:1 to 1:10 + 0.1% HCO₂H) to obtain the desired product as a colourless solid. Yield: 30 mg (20%). ^1H NMR (400 MHz, Acetone-d₆): δ [ppm] = 12.36 (br s, 1H), 8.94 (d, $J = 4.8$ Hz, 2H), 8.50 – 8.44 (m, 1H), 8.29 (s, 1H), 7.92 – 7.86 (m, 1H), 7.43 – 7.36 (m, 2H); ^{13}C NMR (100 MHz, Acetone-d₆): δ [ppm] = 164.8, 158.3, 145.5, 143.1, 133.5, 123.5, 123.4, 122.4, 122.3, 119.9; HRMS (ESI): calculated for $[\text{C}_{11}\text{H}_9\text{N}_4]^+$: $m/z = 197.0822$, found: $m/z = 197.0820$.



N-(2-(Benzo[d]thiazol-2-yl)phenyl)methanesulfonamide (27)

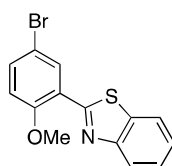
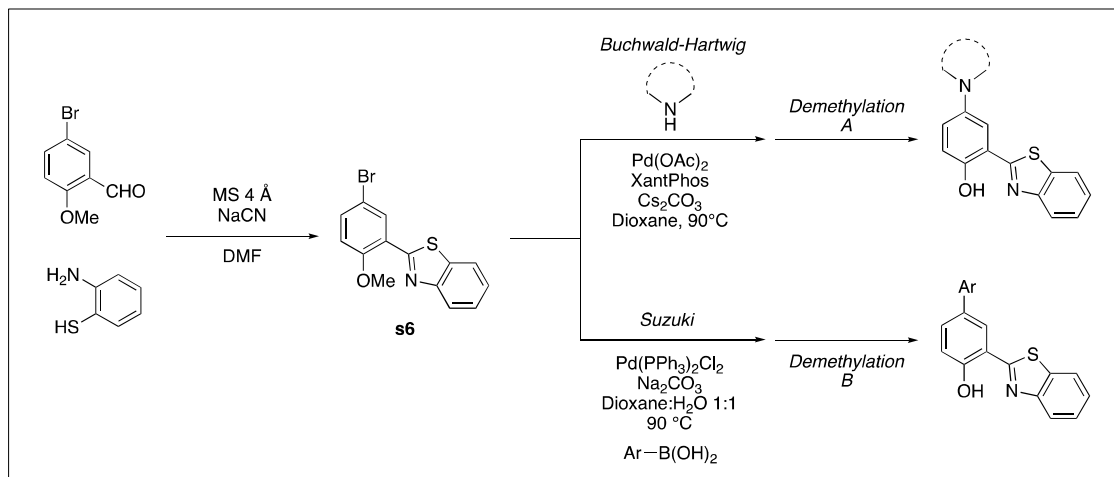
(2-(Methylsulfonylamino)phenyl)boronic acid (258 mg, 1.20 mmol, 1.20 equiv), 2-chlorobenzo[d]thiazole (170 mg, 1.00 mmol, 1.00 equiv) and Pd(PPh₃)₂Cl₂ (1.5 mol%) were suspended in Dioxane (2.5 mL). There to, 2 M Na₂CO₃ (2.5 mL) was added and the resulting mixture was stirred at 90 °C for 5 h (progress of the reaction monitored by TLC). H₂O (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) followed by C18 column chromatography (H₂O:MeOH 10:1 to 1:10 + 0.1% HCO₂H) to obtain the desired product as a colourless solid. Yield: 100 mg (33%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 12.17 (br s, 1H), 8.11 – 8.04 (m, 1H), 7.96 – 7.80 (m, 3H), 7.58 – 7.40 (m, 3H), 7.25 – 7.18 (m, 1H), 3.07 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 168.2, 152.6, 137.5, 133.2, 132.3, 130.5, 127.0, 126.2, 123.7, 123.3, 121.5, 119.7, 119.0, 40.0; **HRMS** (ESI): calculated for [C₁₄H₁₃N₂O₂S₂]⁺: *m/z* = 305.0413, found: *m/z* = 305.0416.



2-(1*H*-Benzo[*d*]imidazol-7-yl)benzo[*d*]thiazole (**28**)

(1*H*-Benzo[*d*]imidazol-7-yl)boronic acid (150 mg, 0.93 mmol, 1.20 equiv), 2-chlorobenzo[*d*]thiazole (133 mg, 0.78 mmol, 1.00 equiv) and Pd(PPh₃)₂Cl₂ (1.5 mol%) were suspended in Dioxane (2 mL). Thereto, 2 M Na₂CO₃ (2 mL) was added and the resulting mixture was stirred at 90 °C for 5 h (progress of the reaction monitored by TLC). H₂O (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) followed by C18 column chromatography (H₂O:MeOH 10:1 to 1:10 + 0.1% HCO₂H) to obtain the desired product as a colourless solid. Yield: 80 mg (40%). **¹H NMR** (400 MHz, benzene-*d*₆): δ [ppm] = 10.75 (br s, 1H), 8.05 – 7.99 (m, 2H), 7.58 – 7.53 (m, 1H), 7.45 – 7.41 (m, 1H), 7.40 (s, 1H), 7.26 – 7.21 (m, 1H), 7.07 – 6.97 (m, 2H); **¹³C NMR** (100 MHz, benzene-*d*₆): δ [ppm] = 167.4, 154.3, 144.8, 141.8, 134.3, 131.5, 126.6, 125.5, 123.9, 122.9, 122.8, 122.4, 122.0, 117.6; **HRMS** (ESI): calculated for [C₁₄H₁₀N₃S]⁺: *m/z* = 252.0590, found: *m/z* = 252.0592.

3. Preparation of MBI 11 derivatives



2-(5-bromo-2-methoxyphenyl)benzo[d]thiazole (**s6**)

5-Bromo-2-methoxybenzaldehyde (2.00 g, 8.00 mmol, 1.00 equiv) and 2-aminothiophenol (1.00 g, 8.00 mmol, 1.00 equiv) were dissolved in DMF (15 mL) and MS 4Å was added. The resulting mixture was stirred at 60 °C for 14 h. The mixture was allowed to cool to room temperature and NaCN (40.0 mg, 0.80 mmol, 0.10 equiv) was added as a solid. The resulting mixture was stirred for 14 h (open flask). All volatiles were removed under reduced pressure and the resulting oil was purified by column chromatography (hexanes:EtOAc 10:1) to obtain the desired product as a colourless solid. Yield: 2.2 g (90%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 8.70 – 8.65 (m, 1H), 8.12 – 8.07 (m, 1H), 7.96 – 7.88 (m, 1H), 7.56 – 7.46 (m, 2H), 7.43 – 7.33 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.03 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 161.6, 156.3, 152.0, 136.2, 134.4, 131.9, 126.3, 125.1, 124.0, 123.0, 121.4, 113.9, 113.5, 56.1; **HRMS** (ESI): calculated for [C₁₄H₁₁BrNOS]⁺: *m/z* = 319.9739, found: *m/z* = 319.9735.

General conditions for Buchwald-Hartwig cross-coupling:

Compound **s6** (100 mg, 0.31 mmol, 1.00 equiv), amine (0.31 mmol, 1.00 equiv), Pd(OAc)₂ (5.60 mg, 25.0 μmol, 0.08 equiv), XantPhos (22.0 mg, 37.5 μmol, 0.12 equiv) and Cs₂CO₃ (204 mg, 0.62 mmol, 2.00 equiv) were mixed in dioxane (1.0 mL). The resulting mixture was degassed (Argon bubbling) for 15 min and stirred at 90 °C for 14 h. The mixture was allowed to cool to room temperature, H₂O (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography.

General conditions for Suzuki cross-coupling:

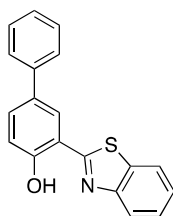
Compound **s6** (50.0 mg, 0.16 mmol, 1.00 equiv) and boronic acid (0.19 mmol, 1.20 equiv) were mixed in dioxane (0.5 mL) and aq. Na₂CO₃ (2 M, 0.5 mL) was added. The resulting mixture was degassed (Argon bubbling) for 15 min and stirred at 90 °C for 14 h. The mixture was allowed to cool to room temperature, H₂O (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography.

General conditions for demethylation A:

Phenol ether (1.00 equiv) was dissolved in CH₂Cl₂ (1.0 mL) and BBr₃ (1 M in heptane, 4.00 equiv) was added dropwise at 0 °C. The resulting mixture was stirred for 14 h at room temperature. Sat. aq. Na₂CO₃ (5 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography.

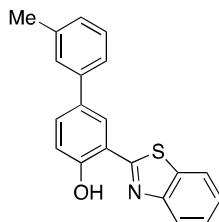
General conditions for demethylation B:

Phenol ether (1.00 equiv) and pyridine hydrochloride (4.00 equiv) were heated to 200 °C and stirred at this temperature for 2 h. The mixture was allowed to cool to room temperature and the residue was dissolved in EtOAc (15 mL), washed with sat. NaHCO₃ (5 mL), brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography.



3-(benzo[d]thiazol-2-yl)-[1,1'-biphenyl]-4-ol (11a)

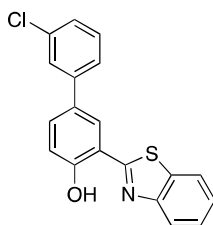
Prepared according to the *general conditions for Suzuki cross-coupling* and *general conditions for demethylation B*. Yield (over two steps): 30 mg (71%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 12.58 (br s, 1H), 8.05 – 7.97 (m, 1H), 7.95 – 7.91 (m, 1H), 7.90 – 7.87 (m, 1H), 7.65 – 7.59 (m, 3H), 7.55 – 7.50 (m, 1H), 7.50 – 7.40 (m, 3H), 7.40 – 7.35 (m, 1H), 7.19 (d, J = 8.6 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 169.4, 157.6, 153.9, 151.9, 140.2, 133.0, 132.7, 131.8, 129.1, 127.3, 126.9, 126.8, 125.8, 122.4, 121.7, 118.5, 117.0; **HRMS** (ESI): calculated for [C₁₉H₁₄NOS]⁺: m/z = 304.0791, found: m/z = 304.0790.



3-(benzo[d]thiazol-2-yl)-3'-methyl-[1,1'-biphenyl]-4-ol (11b)

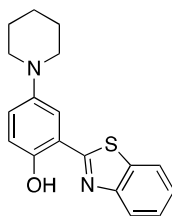
Prepared according to the *general conditions for Suzuki cross-coupling* and *general conditions for demethylation B*. Yield (over two steps): 30 mg (67%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 8.04 – 8.00 (m, 1H), 7.95 – 7.90 (m, 1H), 7.90 – 7.86 (m, 1H), 7.64 – 7.59 (m, 1H),

7.56 – 7.50 (m, 1H), 7.46 – 7.39 (m, 3H), 7.38 – 7.34 (m, 1H), 7.18 (d, $J = 8.5$ Hz, 2H), 2.45 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ [ppm] = 169.5, 157.5, 151.8, 140.2, 138.7, 133.2, 132.9, 132.7, 131.9, 129.0, 128.0, 127.7, 126.9, 125.8, 124.0, 122.3, 121.7, 118.4, 117.0, 21.7; **HRMS** (ESI): calculated for $[\text{C}_{20}\text{H}_{16}\text{NOS}]^-$: $m/z = 304.0791$, found: $m/z = 304.0790$.



3-(benzo[d]thiazol-2-yl)-3'-chloro-[1,1'-biphenyl]-4-ol (11c)

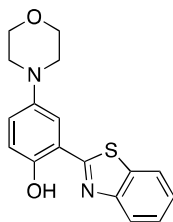
Prepared according to the *General conditions for Suzuki cross-coupling* and *General conditions for demethylation B*. Yield (over two steps): 30 mg (57%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] = 8.03 – 7.99 (m, 1H), 7.95 – 7.90 (m, 1H), 7.85 – 7.82 (m, 1H), 7.61 – 7.44 (m, 2H), 7.55 – 7.50 (m, 1H), 7.48 – 7.36 (m, 3H), 7.34 – 7.29 (m, 1H), 7.18 (d, $J = 8.6$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ [ppm] = 169.1, 158.0, 151.9, 142.0, 134.9, 132.7, 131.6, 131.5, 130.3, 127.2, 127.0, 126.9, 126.8, 125.9, 125.0, 122.4, 121.7, 118.7, 117.1; **HRMS** (ESI): calculated for $[\text{C}_{19}\text{H}_{11}\text{ClNOS}]^-$: $m/z = 336.0255$, found: $m/z = 336.0253$.



2-(benzo[d]thiazol-2-yl)-4-(piperidin-1-yl)phenol (11d)

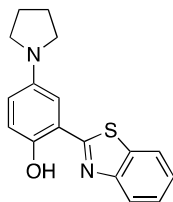
Prepared according to the *General conditions for Buchwald-Hartwig cross-coupling* and *General conditions for demethylation A*. Yield (over two steps): 40 mg (41%). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] = 12.13 (br s, 1H), 8.00 – 7.95 (m, 1H), 7.93 – 7.86 (m, 1H), 7.52 – 7.45 (m, 1H), 7.43 – 7.37 (m, 1H), 7.27 – 7.17 (m, 1H), 7.13 – 7.07 (m, 1H), 7.03 (d, $J = 9.0$ Hz, 1H), 3.16 – 2.99 (m, 4H), 1.88 – 1.68 (m, 4H), 1.67 – 1.51 (m, 2H); $^{13}\text{C NMR}$ (100 MHz,

CDCl₃): δ [ppm] = 169.7, 152.4, 152.1, 145.9, 132.7, 126.8, 125.5, 124.3, 122.3, 121.6, 118.4, 116.5, 52.6, 26.2, 24.2; **HRMS** (ESI): calculated for [C₁₈H₁₉N₂OS]⁺: m/z = 311.1213, found: m/z = 311.1214.



2-(benzo[d]thiazol-2-yl)-4-morpholinophenol (11e)

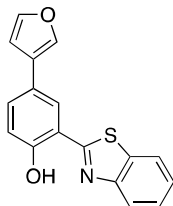
Prepared according to the *General conditions for Buchwald-Hartwig cross-coupling* and *General conditions for demethylation A*. Yield (over two steps): 25 mg (28%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 12.16 (br s, 1H), 8.02 – 7.96 (m, 1H), 7.93 – 7.88 (m, 1H), 7.54 – 7.48 (m, 1H), 7.44 – 7.39 (m, 1H), 7.21 – 7.13 (m, 1H), 7.12 – 7.03 (m, 2H), 4.01 – 3.74 (m, 4H), 3.26 – 2.90 (m, 4H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 169.4, 152.7, 152.1, 144.7, 132.7, 126.9, 125.7, 123.2, 122.3, 121.7, 118.7, 116.6, 115.6, 67.1, 51.1; **HRMS** (ESI): calculated for [C₁₇H₁₇N₂O₂S]⁺: m/z = 313.1005, found: m/z = 313.1002.



2-(benzo[d]thiazol-2-yl)-4-(pyrrolidin-1-yl)phenol (11f)

Prepared according to the *General conditions for Buchwald-Hartwig cross-coupling* and *General conditions for demethylation A*. Yield (over two steps): 35 mg (39%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 11.81 (br s, 1H), 8.00 – 7.96 (m, 1H), 7.91 – 7.86 (m, 1H), 7.52 – 7.46 (m, 1H), 7.42 – 7.36 (m, 1H), 7.06 – 7.00 (m, 1H), 6.84 – 6.70 (m, 2H), 3.48 – 3.13 (m, 4H), 2.18 – 1.90 (m, 4H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 170.00, 152.3, 149.3, 142.1,

132.8, 126.7, 125.4, 122.3, 121.6, 118.6, 118.1, 116.7, 109.4, 48.4, 25.5; **HRMS** (ESI):
calculated for $[C_{17}H_{17}N_2OS]^+$: $m/z = 297.1056$, found: $m/z = 297.1055$.



2-(benzo[d]thiazol-2-yl)-4-(furan-3-yl)phenol (11g)

Prepared according to the *General conditions for Suzuki cross-coupling* and *General conditions for demethylation A*. Yield (over two steps): 15 mg (33%). **¹H NMR** (400 MHz, CDCl₃): δ [ppm] = 12.56 (br s, 1H), 8.03 – 7.99 (m, 1H), 7.95 – 7.89 (m, 1H), 7.78 – 7.71 (m, 2H), 7.56 – 7.48 (m, 3H), 7.46 – 7.41 (m, 1H), 7.16 – 7.10 (m, 1H), 6.74 – 6.69 (m, 1H); **¹³C NMR** (100 MHz, CDCl₃): δ [ppm] = 169.2, 157.2, 151.9, 143.9, 138.1, 132.7, 130.7, 126.9, 125.8, 125.6, 125.5, 124.3, 122.4, 121.7, 118.5, 117.0, 109.0; **HRMS** (ESI): calculated for $[C_{17}H_{12}NO_2S]^+$: $m/z = 294.0583$, found: $m/z = 294.0582$.

4. Computational docking

The geometry of the molecule was determined using density-functional theory (DFT) calculations with the Gaussian software package (Gaussian, Inc., Wallingford CT, 2016). The calculations were performed using the Pople double-zeta basis set with a single set of polarization functions on non-hydrogen atoms (6-31G(d)). Solvent effects were included using a polarizable continuum model (PCM). The structures of all calculated molecules correspond to minima on the ground state potential energy surfaces with no imaginary frequencies present. The protein structure (PDB: 3VW9)⁴ was downloaded from the Protein Data Bank (<https://www.rcsb.org/>) and prepared for the docking experiment using the Molecular Operating Environment (MOE, Chemical Computing Group ULC, Montreal, QC, Canada, 2019) software package. Water molecules, other small molecules, inhibitors, and ions were removed. Hydrogen atoms were added and the side chains protonated at physiological pH. The structurally optimized molecules were docked using the Genetic Optimization for Ligand Docking (GOLD, Cambridge Crystallographic Data Centre, Cambridge, United Kingdom, 2019) software package. The protein structure was considered rigid. The binding pose of the compounds was predicted using a genetic algorithm with a population size of 200, selection pressure of 1.2, number of operations of 500000, number of islands of 5, niche size of 2, crossover frequency of 95, mutation frequency of 95, and a migration frequency of 10. The genetic algorithm was set to 100 runs. During the docking procedure the binding poses were evaluated using the ChemPLP scoring function. After docking, the obtained solutions were re-scored using the GoldScore fitness function.

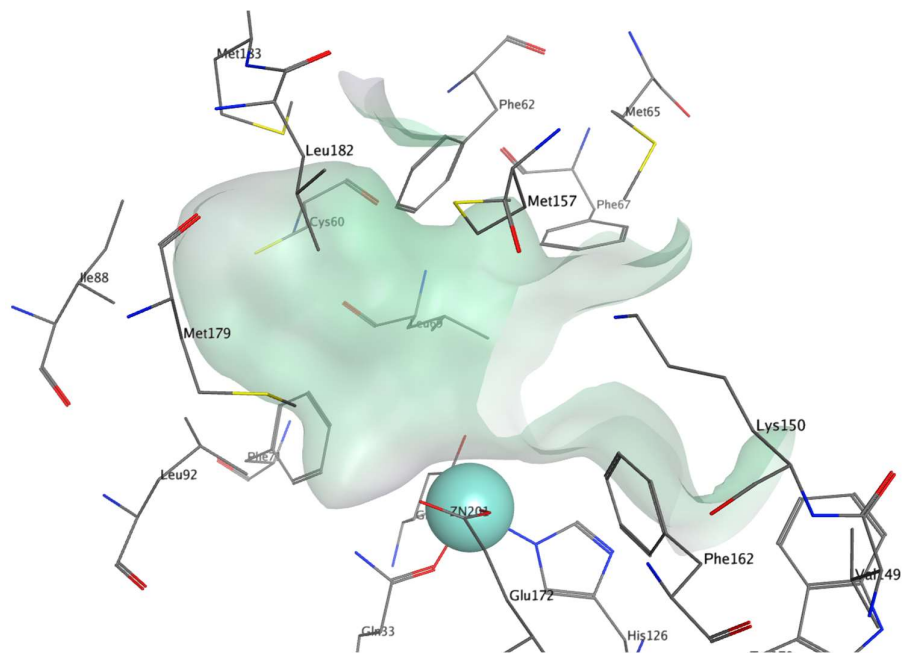


Figure S1. GLO1 active site without inhibitor bound.

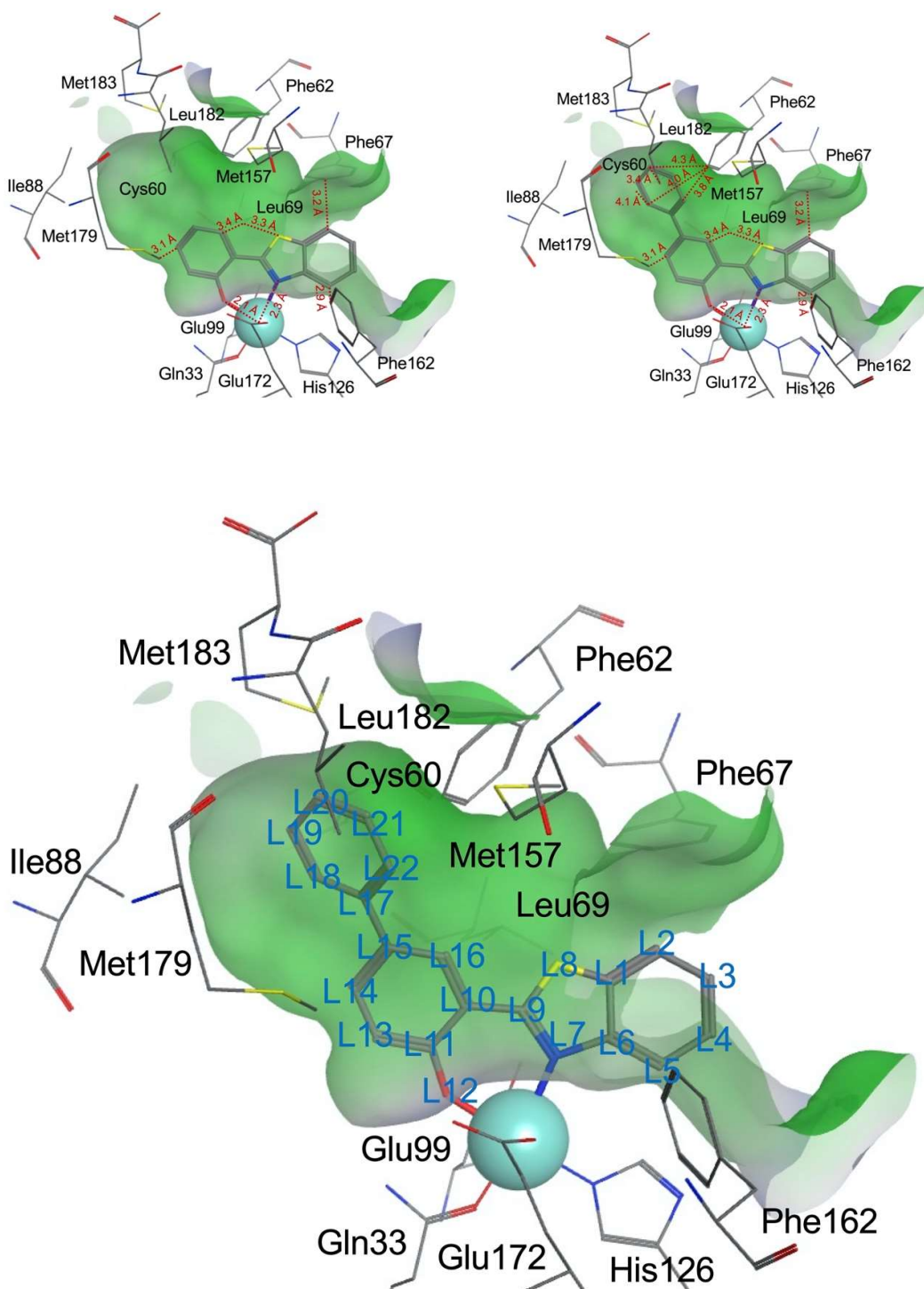


Figure S2. GLO1 active site with inhibitors **11** (*top left*) and **11a** (*top right*) bound and contacts shown; with atom labeling (*bottom*) (see Table S4).

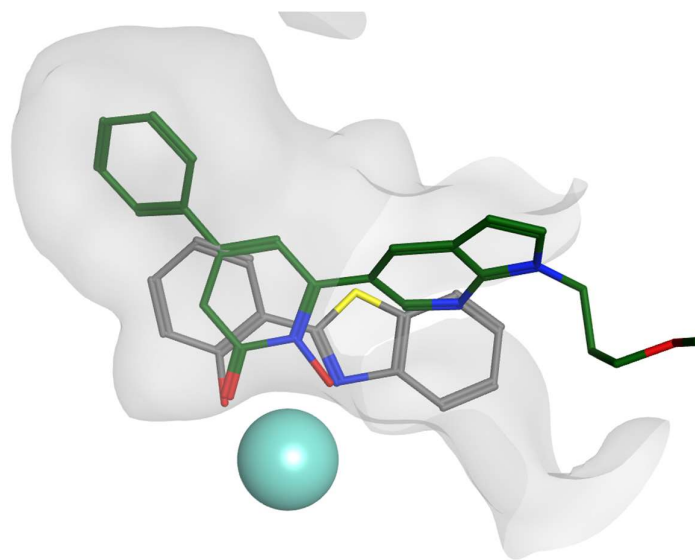


Figure S3. GLO1 active site with inhibitor **11** and literature known inhibitor **Chugai-3d⁴** show similar binding mode to the Zn²⁺ cation.

5. Single Point screening

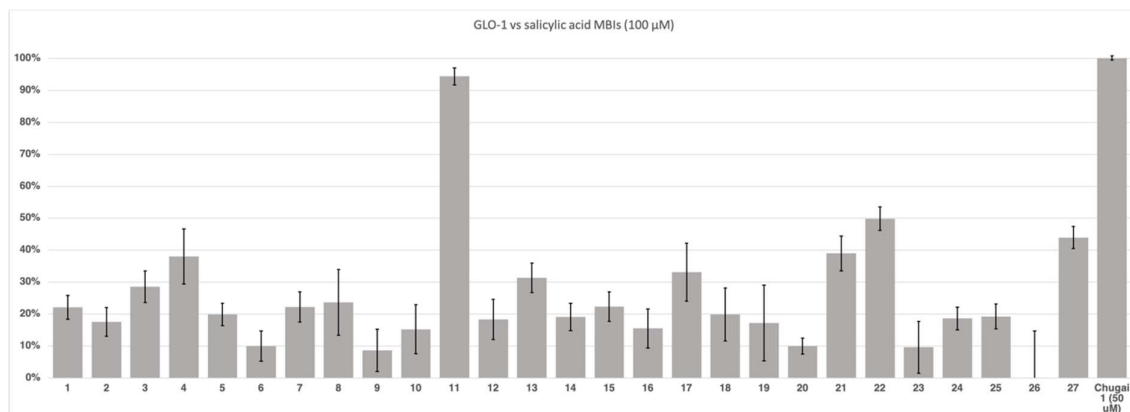


Figure S4. Single point screening of salicylate MBI library against GLO1 at 100 μM inhibitor concentration. **Chugai 1** (4,6-diphenyl-N-hydroxypyridone)⁴ as positive control.

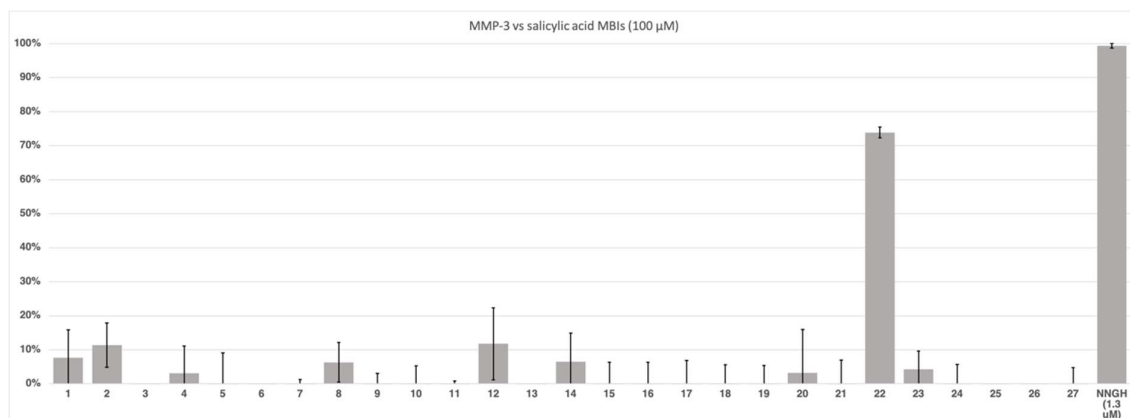


Figure S5. Single point screening of salicylate MBI library against MMP-3 at 100 μM inhibitor concentration. NNGH as positive control.

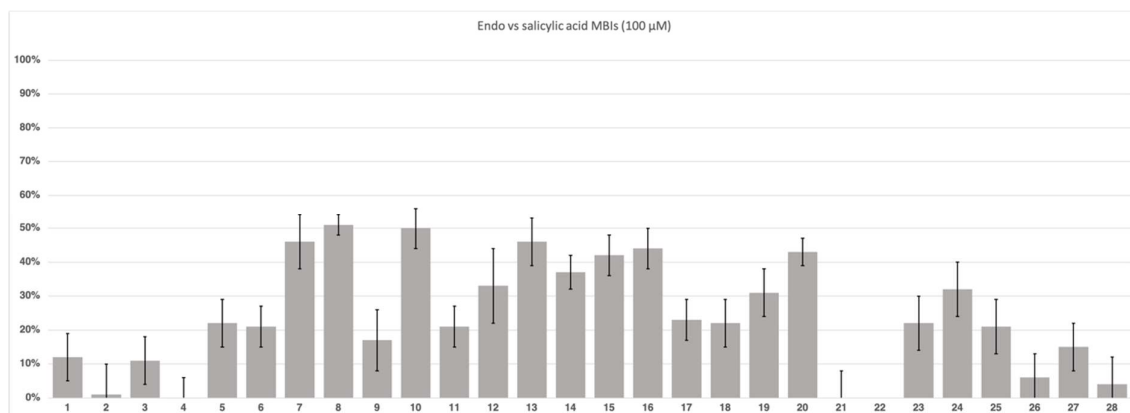


Figure S6. Single point screening of salicylate MBI library against Endo at 100 μ M inhibitor concentration.

6. Dose-response curves against GLO1

The raw data from the GLO1 assay was background corrected and normalized from 0 to 100 with 100 being the largest mean of each dataset. A variable slope log-logistic model was chosen for curve fitting. Some compounds did not dissolve well at higher concentrations (>50 μM). The corresponding datapoints are shown as empty bullets and were not included in the curve-fitting. The resulting restricted datasets were fitted according to a literature procedure setting the lower limit of the dose-response curve to zero. This compensates for the loss of information caused by trimming of the dataset.^{5,6}

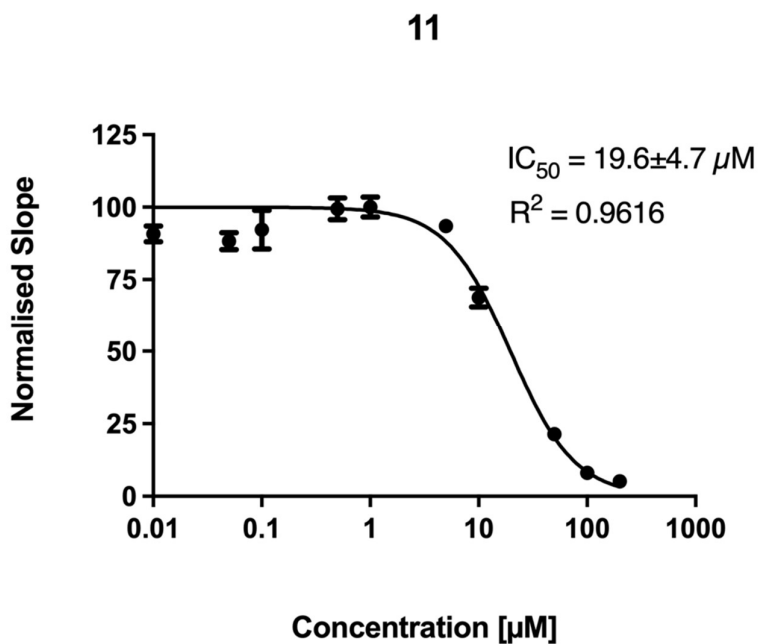


Figure S7. Dose-response curve of **11** against GLO1.

11a

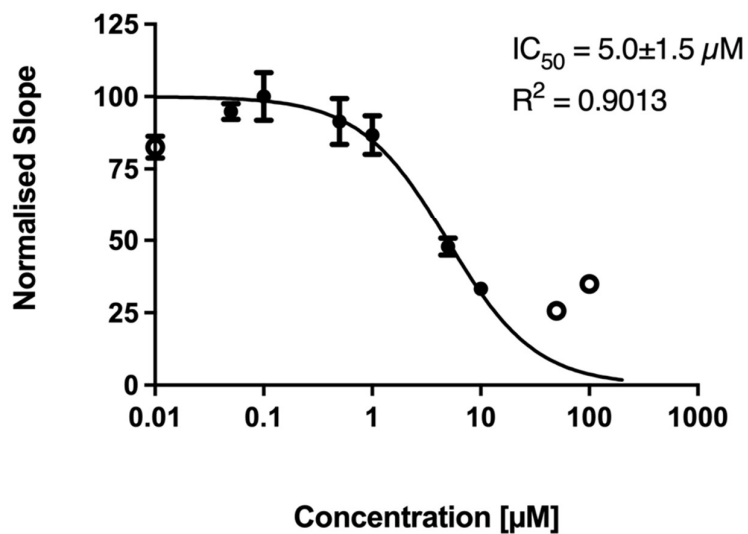


Figure S8. Dose-response curve of 11a against GLO1.

11b

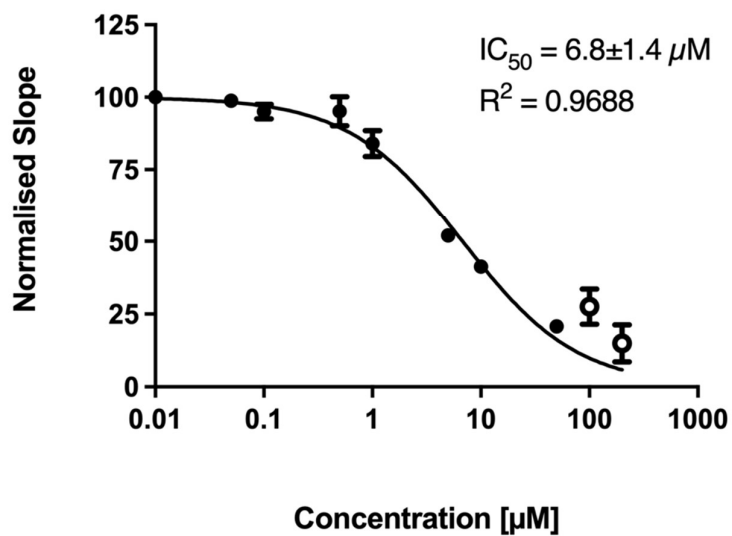


Figure S9. Dose-response curve of 11b against GLO1.

11c

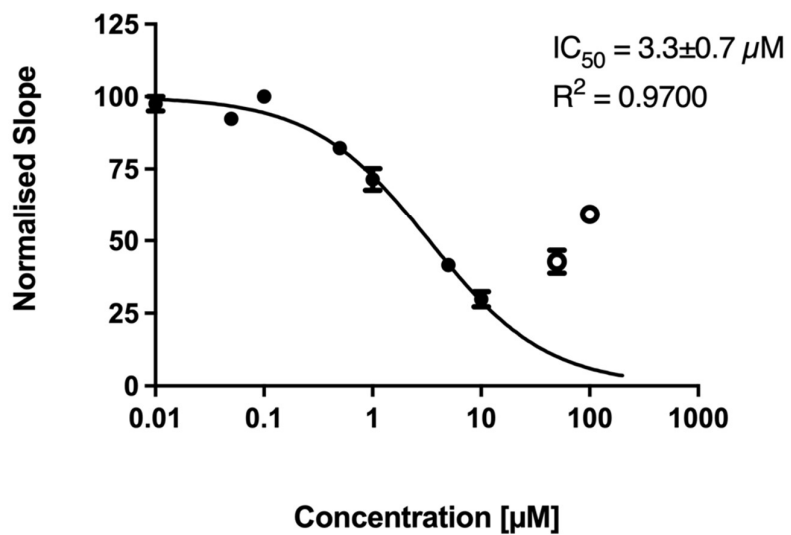


Figure S10. Dose-response curve of 11c against GLO1.

11f

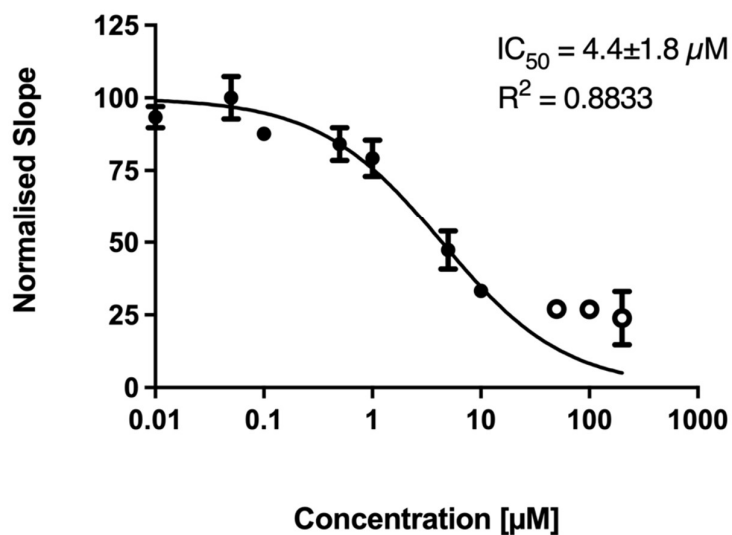


Figure S11. Dose-response curve of 11f against GLO1.

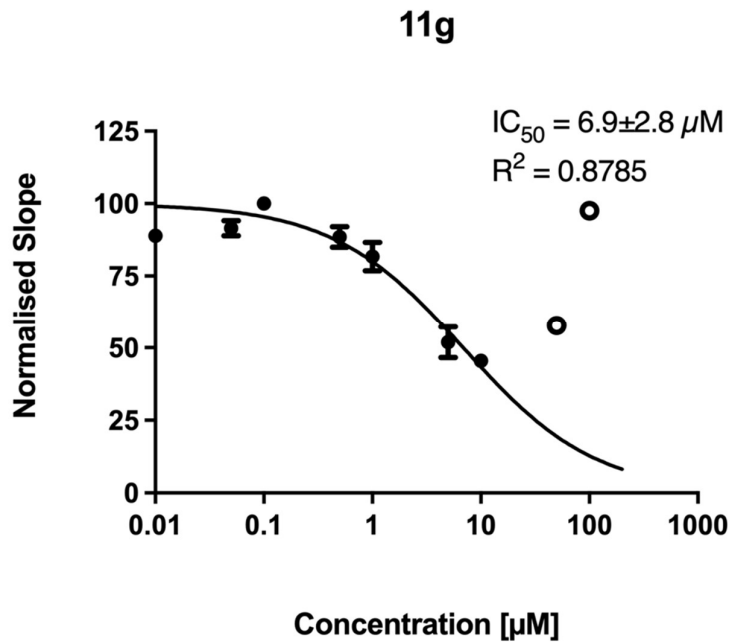


Figure S12. Dose-response curve of 11g against GLO1.

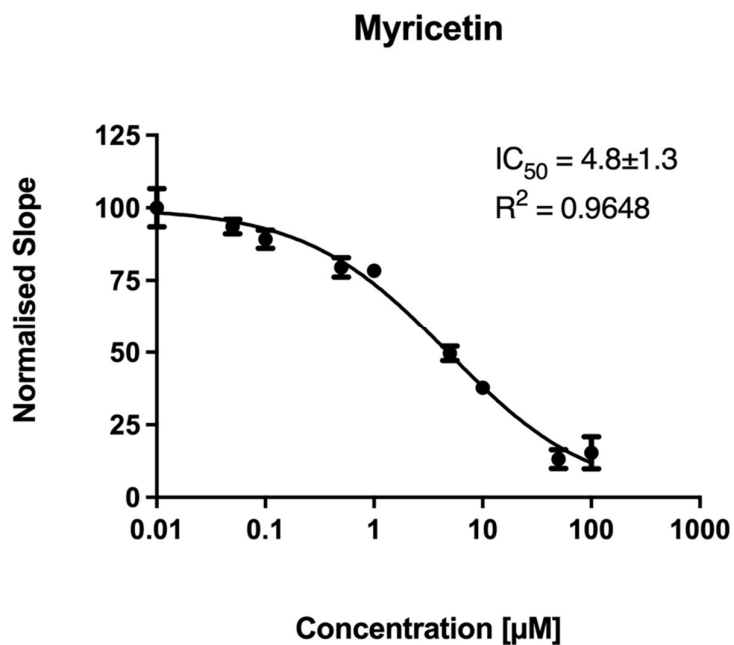


Figure S13. Dose-response curve of Myricetin against GLO1.

7. X-Ray crystallography data

Single Crystal X-ray Diffraction

Suitable crystals of $[(\text{Tp}^{\text{Ph,Me}})\text{Zn}(\text{MBI})]$ complexes were selected and data was collected at 100 K on a Bruker APEX-II Ultra diffractometer with a Mo-K α Microfocus Rotating Anode and a APEX-II CCD area detector or a Bruker Kappa diffractometer equipped with a Bruker X8 APEX II Mo sealed tube and a Bruker APEX-II CCD. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. The structure was solved with the ShelXT⁷ structure solution program using direct methods and refined with the XL⁸ refinement package using least squares minimization using Olex2.⁹ The crystal data files were deposited into the Cambridge Crystallographic Data Centre (CCDC). Crystallographic data collection and refinement information is listed in Table S1. Disordered solvent was treated with the PLATON SQUEEZE¹⁰ function in $[(\text{Tp}^{\text{Ph,Me}})\text{Zn}(\mathbf{2})]$, $[(\text{Tp}^{\text{Ph,Me}})\text{Zn}(\mathbf{11})]$, and $[(\text{Tp}^{\text{Ph,Me}})\text{Zn}(\mathbf{15})]$. A pentane solvent molecule is positionally disordered in $[(\text{Tp}^{\text{Ph,Me}})\text{Zn}(\mathbf{3})]$.

Table S1. Crystal data and structure refinement for [(Tp^{Ph,Me})Zn(MBI)] complexes.

Compound	[(Tp ^{Ph,Me})Zn(2)]	[(Tp ^{Ph,Me})Zn(3)]	[(Tp ^{Ph,Me})Zn(10)]
Identification code	2117775	2117778	2117773
Empirical formula	C ₃₈ H ₃₆ BN ₇ O ₄ SZn	C _{40.62} H _{37.25} BN ₇ O ₄ Zn	C ₄₀ H ₃₅ BN ₈ OZn
Formula weight	762.98	763.7	719.94
Temperature/K	100	100	100
Crystal system	triclinic	monoclinic	monoclinic
Space group	P-1	P21/n	P21/n
a/Å	9.780(2)	11.6546(9)	11.4421(7)
b/Å	17.966(4)	14.6697(11)	22.4577(12)
c/Å	23.194(5)	21.3858(17)	13.4441(9)
α/°	87.678(3)	90	90
β/°	87.319(3)	97.912(3)	96.516(2)
γ/°	84.581(3)	90	90
Volume/Å ³	4050.0(16)	3621.5(5)	3432.3(4)
Z	4	4	4
ρ _{calc} /cm ³	1.251	1.401	1.393
μ/mm ⁻¹	0.704	1.373	0.762
F(000)	1584	1588	1496
Crystal size/mm ³	0.1 × 0.1 × 0.1	0.24 × 0.22 × 0.19	0.1 × 0.1 × 0.1
Radiation	MoKα (λ = 0.71073)	CuKα (λ = 1.54178)	MoKα (λ = 0.71073)
2θ range for data collection/°	2.828 to 52.91	7.33 to 141.156	4.434 to 52.296
Index ranges	-12 ≤ h ≤ 12, -22 ≤ k ≤ 22, -28 ≤ l ≤ 27	-13 ≤ h ≤ 14, -17 ≤ k ≤ 17, -19 ≤ l ≤ 26	-14 ≤ h ≤ 14, -27 ≤ k ≤ 27, -16 ≤ l ≤ 16
Reflections collected	82013	22461	51774
Independent reflections	16482 [R _{int} = 0.0905, R _{sigma} = 0.0776]	6808 [R _{int} = 0.0401, R _{sigma} = 0.0518]	6846 [R _{int} = 0.1286, R _{sigma} = 0.0706]
Data/restraints/parameters	16482/0/945	6808/33/526	6846/0/463
Goodness-of-fit on F ²	1.097	1.087	1.038
Final R indexes [I >= 2σ (I)]	R ₁ = 0.0760, wR ₂ = 0.1697	R ₁ = 0.0418, wR ₂ = 0.1122	R ₁ = 0.0409, wR ₂ = 0.0878
Final R indexes [all data]	R ₁ = 0.1103, wR ₂ = 0.1829	R ₁ = 0.0478, wR ₂ = 0.1168	R ₁ = 0.0608, wR ₂ = 0.0954
Largest diff. peak/hole / e Å ⁻³	3.29/-0.89	0.25/-0.62	0.42/-0.76

Table S1 (continued). Crystal data and structure refinement for [(Tp^{Ph,Me})Zn(MBI)] complexes.

Compound	[(Tp ^{Ph,Me})Zn(11)]	[(Tp ^{Ph,Me})Zn(12)]	[(Tp ^{Ph,Me})Zn(13)]
Identification code	2117776	2117770	2117767
Empirical formula	C ₄₃ H ₃₆ BN ₇ OSZn	C ₃₉ H ₃₈ BN ₇ O ₄ SZn	C ₃₉ H ₃₄ BN ₇ O ₄ Zn
Formula weight	775.03	777	740.91
Temperature/K	100	100	100
Crystal system	orthorhombic	orthorhombic	triclinic
Space group	Pbca	Pna21	P-1
a/Å	16.4658(6)	11.9864(16)	11.8862(8)
b/Å	22.9868(10)	16.941(2)	12.1596(8)
c/Å	23.1548(9)	18.040(2)	13.5975(9)
α/°	90	90	115.6050(10)
β/°	90	90	90.7810(10)
γ/°	90	90	98.5870(10)
Volume/Å ³	8764.0(6)	3663.3(8)	1745.7(2)
Z	8	4	2
ρ _{calc} /cm ³	1.175	1.409	1.41
μ/mm ⁻¹	0.647	0.779	0.757
F(000)	3216	1616	768
Crystal size/mm ³	0.1 × 0.1 × 0.1	0.2 × 0.1 × 0.1	0.1 × 0.1 × 0.1
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	4.652 to 50.848	3.298 to 52.256	3.334 to 52.876
Index ranges	-19 ≤ h ≤ 19, -27 ≤ k ≤ 27, -27 ≤ l ≤ 27	-11 ≤ h ≤ 14, -20 ≤ k ≤ 20, -22 ≤ l ≤ 21	-14 ≤ h ≤ 14, -15 ≤ k ≤ 15, -17 ≤ l ≤ 17
Reflections collected	208770	20238	22366
Independent reflections	8053 [R _{int} = 0.1453, R _{sigma} = 0.0348]	6978 [R _{int} = 0.0703, R _{sigma} = 0.0973]	7180 [R _{int} = 0.0391, R _{sigma} = 0.0353]
Data/restraints/parameters	8053/0/490	6978/1/483	7180/491/473
Goodness-of-fit on F ²	1.06	0.76	1.06
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0389, wR ₂ = 0.0906	R ₁ = 0.0431, wR ₂ = 0.1068	R ₁ = 0.0279, wR ₂ = 0.0724
Final R indexes [all data]	R ₁ = 0.0620, wR ₂ = 0.1076	R ₁ = 0.0681, wR ₂ = 0.1278	R ₁ = 0.0295, wR ₂ = 0.0735
Largest diff. peak/hole / e Å ⁻³	0.41/-0.46	0.43/-0.65	0.35/-0.29

Table S1 (continued). Crystal data and structure refinement for [(Tp^{Ph,Me})Zn(MBI)] complexes.

Compound	[(Tp ^{Ph,Me})Zn(14)]	[(Tp ^{Ph,Me})Zn(15)]	[(Tp ^{Ph,Me})Zn(16)]
Identification code	2117768	2117769	2117774
Empirical formula	C ₃₉ H ₃₅ BN ₈ O ₂ Zn	C ₃₈ H ₃₄ BN ₉ O ₂ Zn	C _{44.58} H _{43.62} BN ₈ O ₄ SZn
Formula weight	723.93	724.92	863.69
Temperature/K	100	100	100
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	Pbca	C2/c	P21/c
a/Å	17.7615(5)	24.7054(13)	24.9170(10)
b/Å	17.8877(6)	12.3535(7)	12.6257(7)
c/Å	21.4370(7)	25.1484(14)	27.9346(11)
α/°	90	90	90
β/°	90	107.2460(10)	100.3670(10)
γ/°	90	90	90
Volume/Å ³	6810.8(4)	7330.2(7)	8644.6(7)
Z	8	8	8
ρ _{calc} /cm ³	1.412	1.314	1.327
μ/mm ⁻¹	0.77	0.717	0.669
F(000)	3008	3008	3601
Crystal size/mm ³	0.1 × 0.1 × 0.1	0.1 × 0.1 × 0.1	0.1 × 0.1 × 0.1
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	3.748 to 52.77	3.392 to 52.828	4.032 to 52.122
Index ranges	-22 ≤ h ≤ 13, -17 ≤ k ≤ 22, -26 ≤ l ≤ 19	-30 ≤ h ≤ 30, -15 ≤ k ≤ 15, -31 ≤ l ≤ 29	-30 ≤ h ≤ 30, -15 ≤ k ≤ 15, -34 ≤ l ≤ 34
Reflections collected	29933	45312	170610
Independent reflections	6969 [R _{int} = 0.0536, R _{sigma} = 0.0430]	7531 [R _{int} = 0.0526, R _{sigma} = 0.0323]	17087 [R _{int} = 0.0922, R _{sigma} = 0.0448]
Data/restraints/parameters	6969/0/464	7531/84/434	17087/0/1109
Goodness-of-fit on F ²	1.045	1.037	1.023
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0314, wR ₂ = 0.0807	R ₁ = 0.0393, wR ₂ = 0.0915	R ₁ = 0.0449, wR ₂ = 0.0958
Final R indexes [all data]	R ₁ = 0.0377, wR ₂ = 0.0848	R ₁ = 0.0480, wR ₂ = 0.0971	R ₁ = 0.0717, wR ₂ = 0.1089
Largest diff. peak/hole / e Å ⁻³	0.36/-0.45	1.01/-0.84	0.98/-0.71

Table S1 (continued). Crystal data and structure refinement for [(Tp^{Ph,Me})Zn(MBI)] complexes.

Compound	[(Tp ^{Ph,Me})Zn(19)]	[(Tp ^{Ph,Me})Zn(23)]	[(Tp ^{Ph,Me})Zn(24)]
Identification code	2117772	2117777	2117771
Empirical formula	C ₄₄ H ₄₂ BN ₁₀ O ₂ Zn	C ₄₀ H ₃₇ BN ₈ O _{2.29} Zn	C ₃₉ H ₃₆ BN ₉ O ₂ Zn
Formula weight	819.05	742.63	738.95
Temperature/K	100	100	100
Crystal system	triclinic	monoclinic	triclinic
Space group	P-1	P21/c	P-1
a/Å	12.4046(17)	12.7201(5)	11.4528(7)
b/Å	12.5836(17)	22.4184(9)	11.6697(6)
c/Å	14.653(2)	13.4325(5)	13.8501(7)
α/°	88.179(5)	90	80.236(2)
β/°	66.003(4)	110.4160(10)	88.814(2)
γ/°	74.862(4)	90	73.751(2)
Volume/Å ³	2009.8(5)	3589.9(2)	1750.69(17)
Z	2	4	2
ρ _{calc} /cm ³	1.353	1.374	1.402
μ/mm ⁻¹	0.663	0.733	0.752
F(000)	854	1545	768
Crystal size/mm ³	0.1 × 0.1 × 0.1	0.2 × 0.1 × 0.1	0.2 × 0.04 × 0.03
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	4.732 to 52.01	4.866 to 52.82	3.69 to 51.368
Index ranges	-15 ≤ h ≤ 15, -15 ≤ k ≤ 15, -18 ≤ l ≤ 18	-15 ≤ h ≤ 15, -26 ≤ k ≤ 28, -16 ≤ l ≤ 16	-13 ≤ h ≤ 13, -14 ≤ k ≤ 14, -16 ≤ l ≤ 16
Reflections collected	48102	55492	54561
Independent reflections	7869 [R _{int} = 0.0683, R _{sigma} = 0.0402]	7360 [R _{int} = 0.0628, R _{sigma} = 0.0342]	6643 [R _{int} = 0.0783, R _{sigma} = 0.0392]
Data/restraints/parameters	7869/0/527	7360/0/486	6643/0/475
Goodness-of-fit on F ²	1.046	1.084	1.034
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0314, wR ₂ = 0.0810	R ₁ = 0.0462, wR ₂ = 0.0941	R ₁ = 0.0354, wR ₂ = 0.0725
Final R indexes [all data]	R ₁ = 0.0396, wR ₂ = 0.0854	R ₁ = 0.0611, wR ₂ = 0.1011	R ₁ = 0.0503, wR ₂ = 0.0803
Largest diff. peak/hole / e Å ⁻³	0.31/-0.35	0.97/-0.39	0.33/-0.33

8. Calculated physicochemical properties

Table S2. Calculated physicochemical properties of salicylic acid and salicylic acid MBIs. Calculator plugins were used for physicochemical property prediction and calculation, Marvin 21.11.2021, ChemAxon (<http://www.chemaxon.com>).

Compound	pK _a	logP	logD _{7.4}
1	2.79, 13.23	1.98	-1.52
2	3.55, 9.62	0.00	-3.34
3	2.96, 9.44	0.99	-2.49
4	2.00, 5.87, 12.64	0.92	-1.40
5	3.43, 9.24	0.96	-2.45
6	9.72	2.32	2.32
7	8.03, 13.54	1.55	1.45
8	5.72, 8.66	0.95	-0.66
9	9.82, 12.83	0.67	0.67
10	1.06, 7.32	2.12	1.78
11	1.79, 8.79	3.83	3.82
12	7.22	0.35	0.02
13	8.96	1.34	1.32
14	4.40, 10.45	1.26	1.26
15	8.32	1.30	0.82
16	4.99, 10.41	-0.43	-1.36
17	8.98, 12.01	0.56	0.55
18	4.79, 10.26, 13.18	0.48	0.48
19	8.48, 10.86	0.53	0.03
20	5.82, 7.24	-0.37	-2.02
21	5.72, 9.07	0.61	-1.00
22	4.73, 5.64, 11.81	0.54	-1.07
23	5.69, 11.69, 12.91	0.26	0.25
24	0.03, 9.01, 12.68	0.30	0.23
25	1.30, 7.71	0.96	0.81
26	0.70, 4.90, 11.85	1.69	1.69
27	7.88, 1.92	2.51	2.40
28	1.28, 4.98, 11.89	3.42	3.42

Table S3. Calculated physicochemical properties of MBI **11** derivatives. Calculator plugins were used for physicochemical property prediction and calculation, Marvin 21.11.2021, ChemAxon (<http://www.chemaxon.com>).

Compound	pK _a	logP	logD _{7.4}
11a	1.77, 8.69	5.48	5.46
11b	1.77, 8.69	6.00	5.97
11c	1.77, 8.67	6.09	6.06
11d	1.39, 9.12, 6.26	4.79	4.72
11e	1.53, 2.32, 9.06	3.72	3.71
11f	1.38, 5.86, 9.09	4.35	4.32
11g	1.77, 8.49	4.62	4.59

Table S4. Possible protein-ligand contacts for compounds **11** and **11a** upon docking with the active site of GLO1. Residue and atom labels can be found in Figure S2.

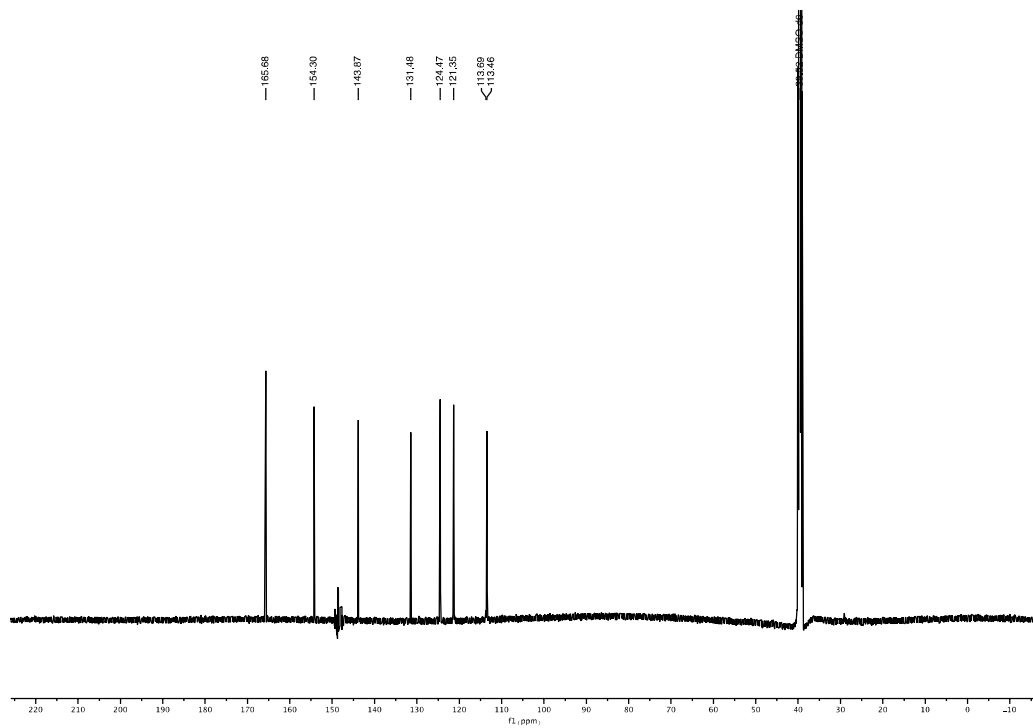
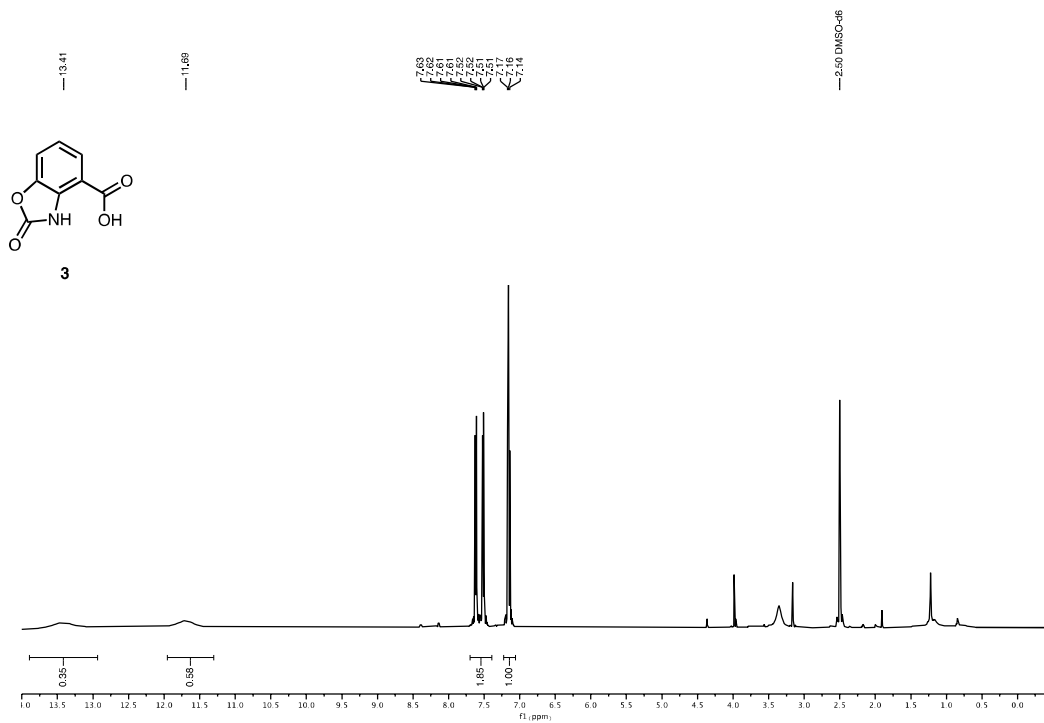
Inhibitor	Protein Residue – Atom of Ligand	Distance / Å	Type of Interaction
11	Phe67-L2	3.2	hydrophobic, π-π interaction
	Phe162-L5	2.9	hydrophobic, π-π interaction
	Zn-L7	2.3	metal-ligand
	Leu69-L8	3.3	hydrophobic
	Zn-L12	2.1	metal-ligand
	Met179-L14	3.1	hydrophobic
	Leu69-L16	3.4	hydrophobic
	11a	Phe67-L2	3.2
Phe162-L5		2.9	hydrophobic, π-π interaction
Zn-L7		2.3	metal-ligand
Leu69-L8		3.3	hydrophobic
Zn-L12		2.1	metal-ligand
Met179-L14		3.1	hydrophobic
Leu69-L16		3.4	hydrophobic
Phe62-L18		4.0	hydrophobic, π-π interaction
Cys60-L18		4.1	hydrophobic
Phe62-L20		4.3	hydrophobic, π-π interaction
Leu182-L20	3.4	hydrophobic	
Phe62-L22	3.8	hydrophobic, π-π interaction	

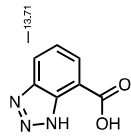
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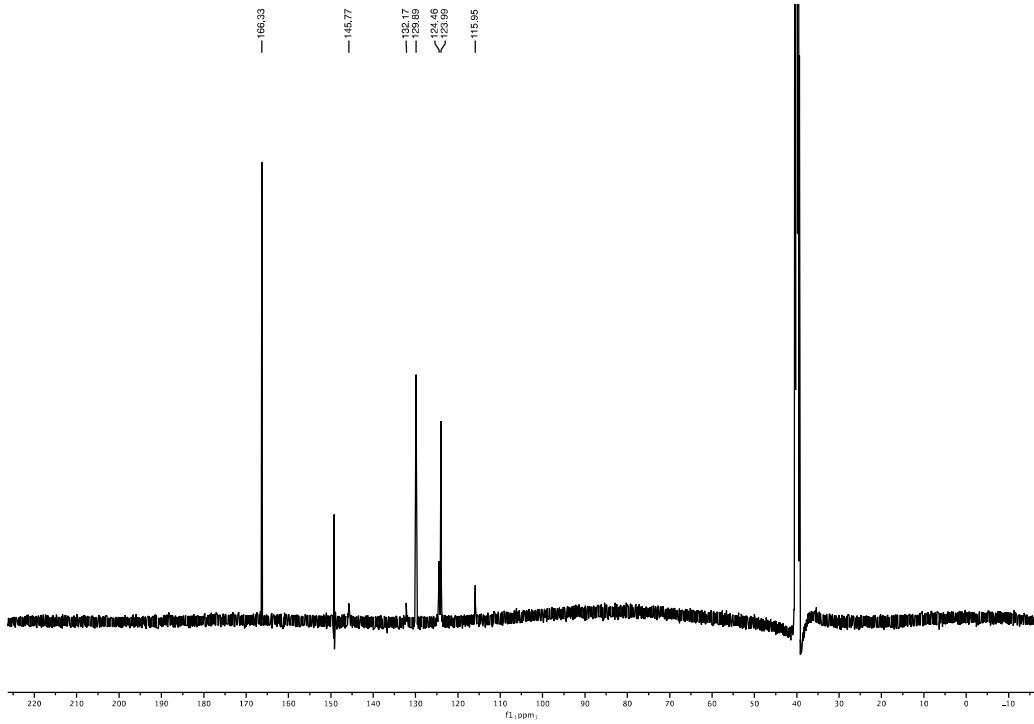
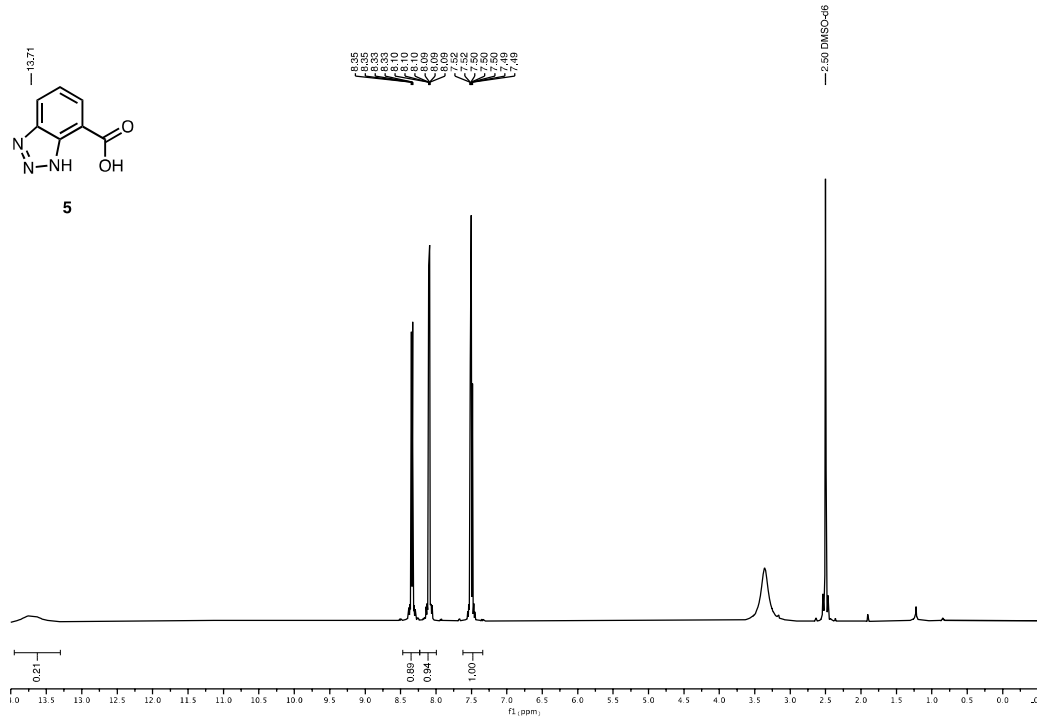
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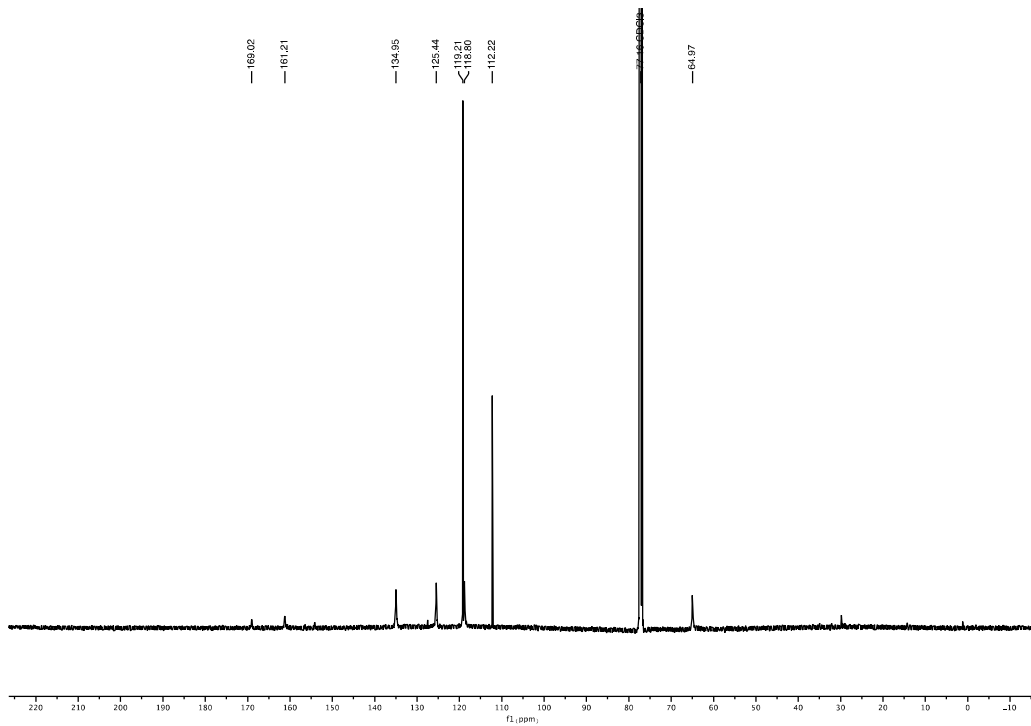
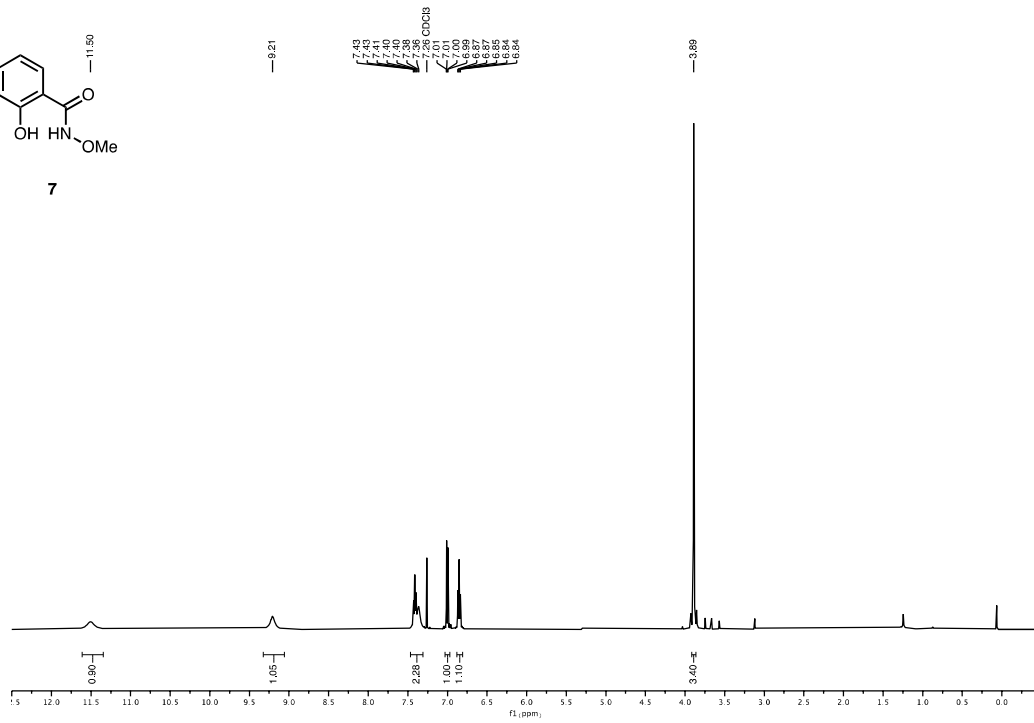
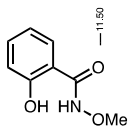
10. NMR Spectra

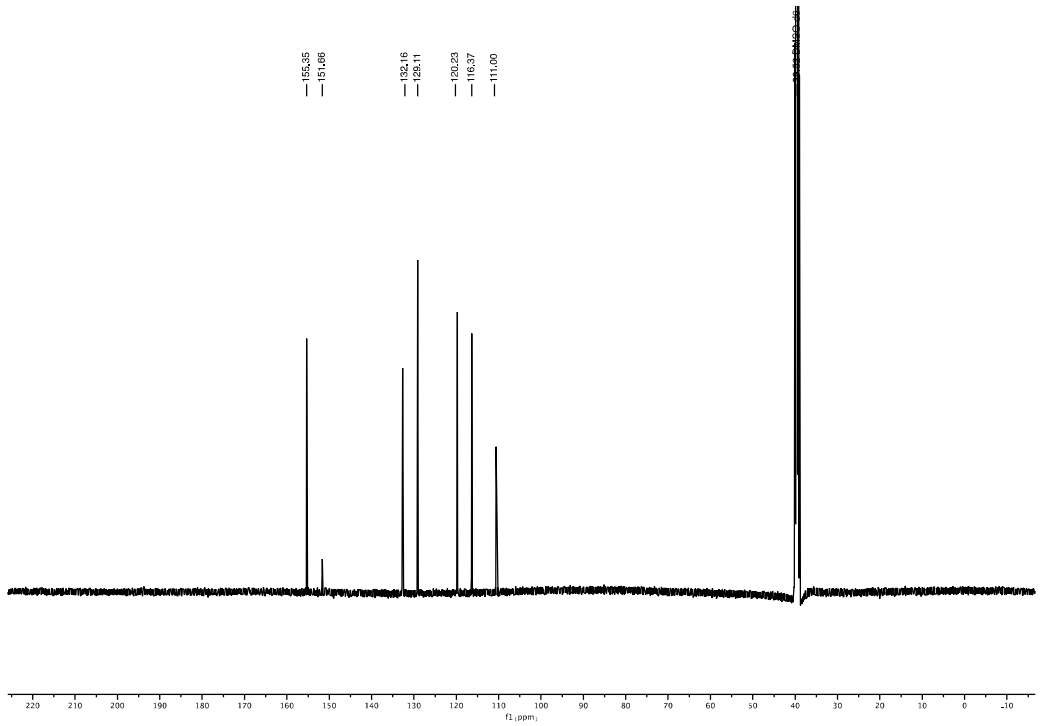
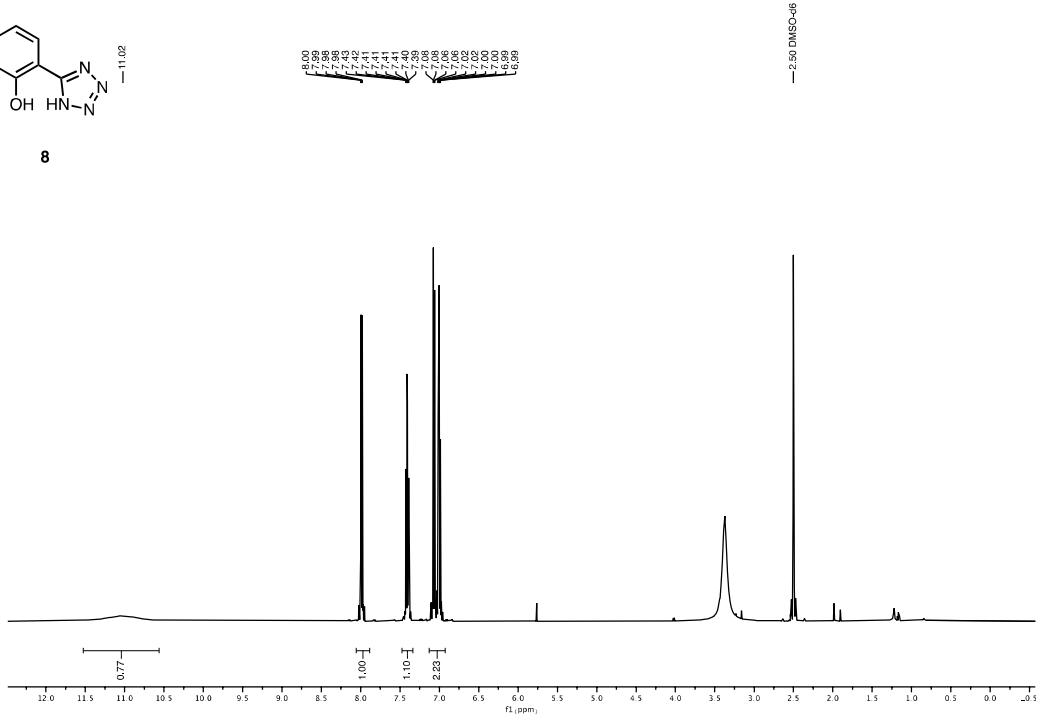
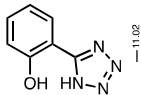


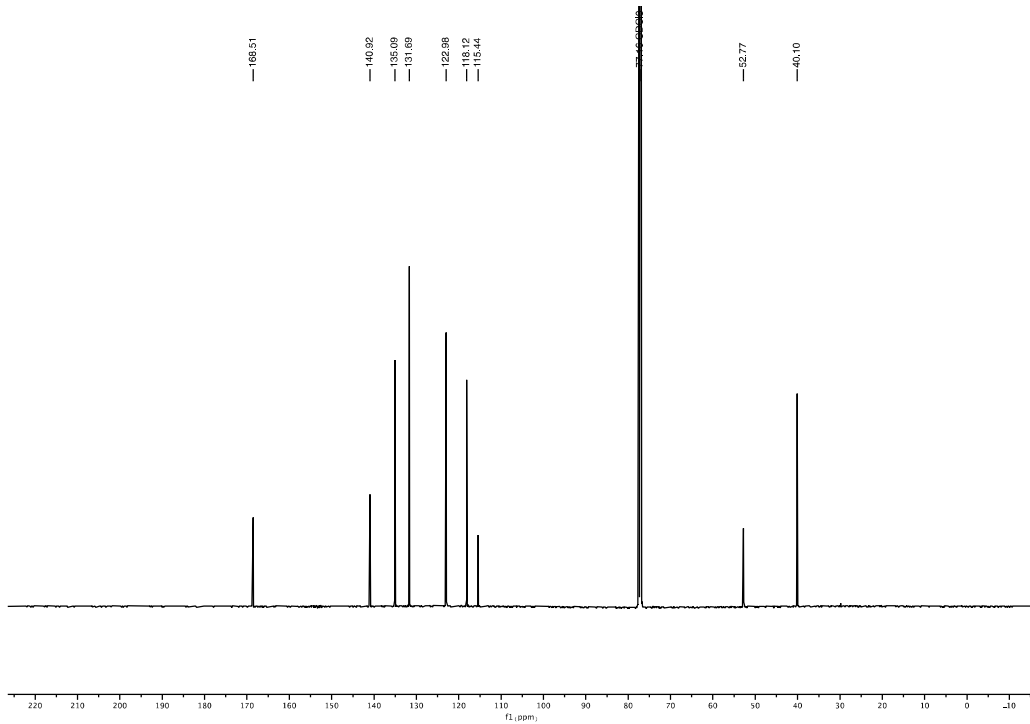
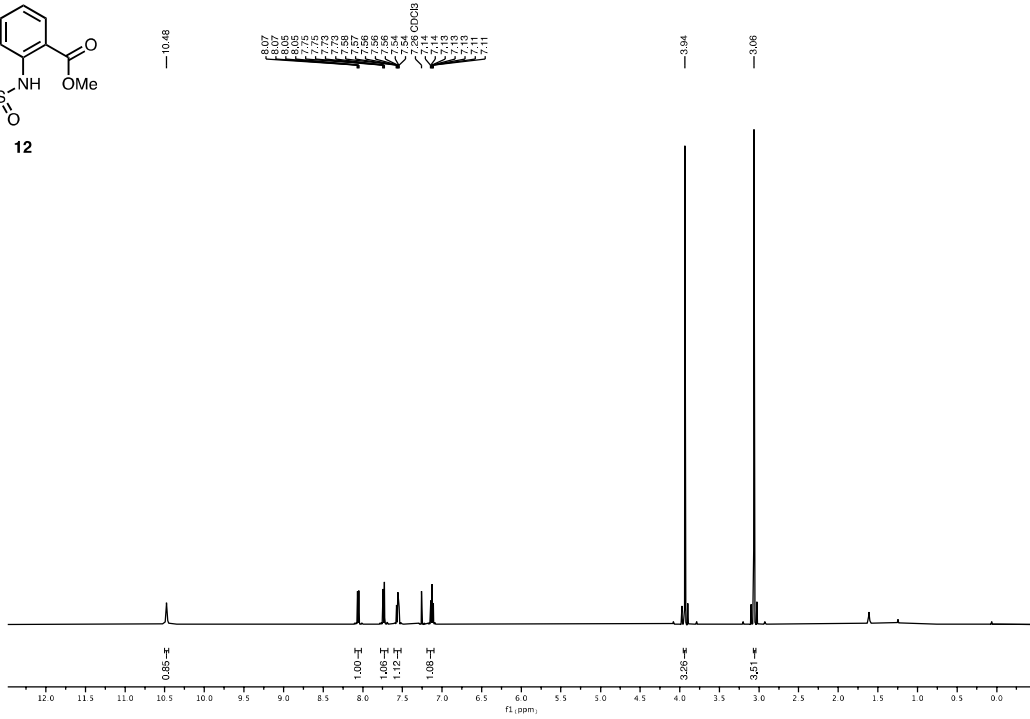
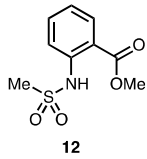


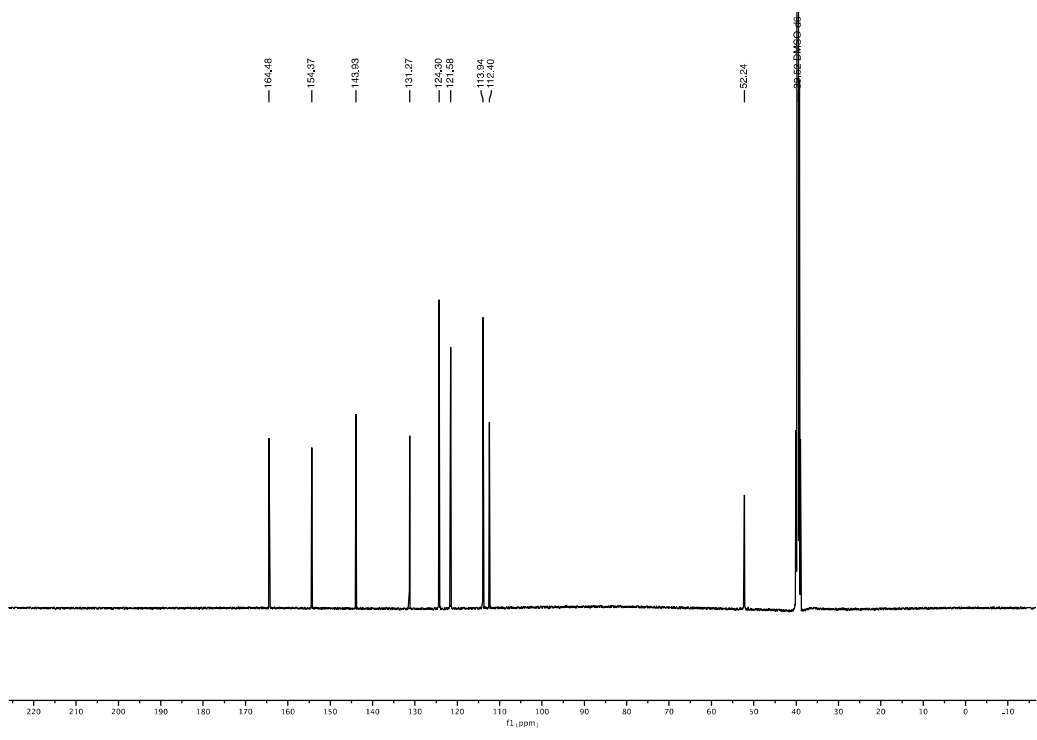
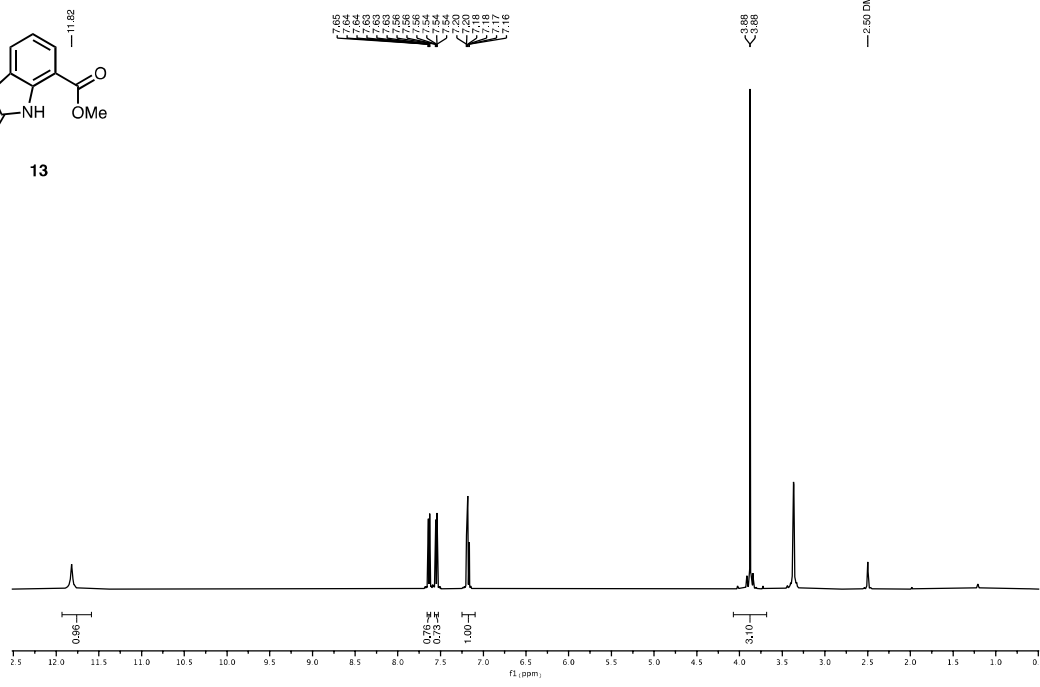
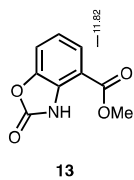
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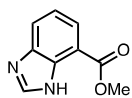




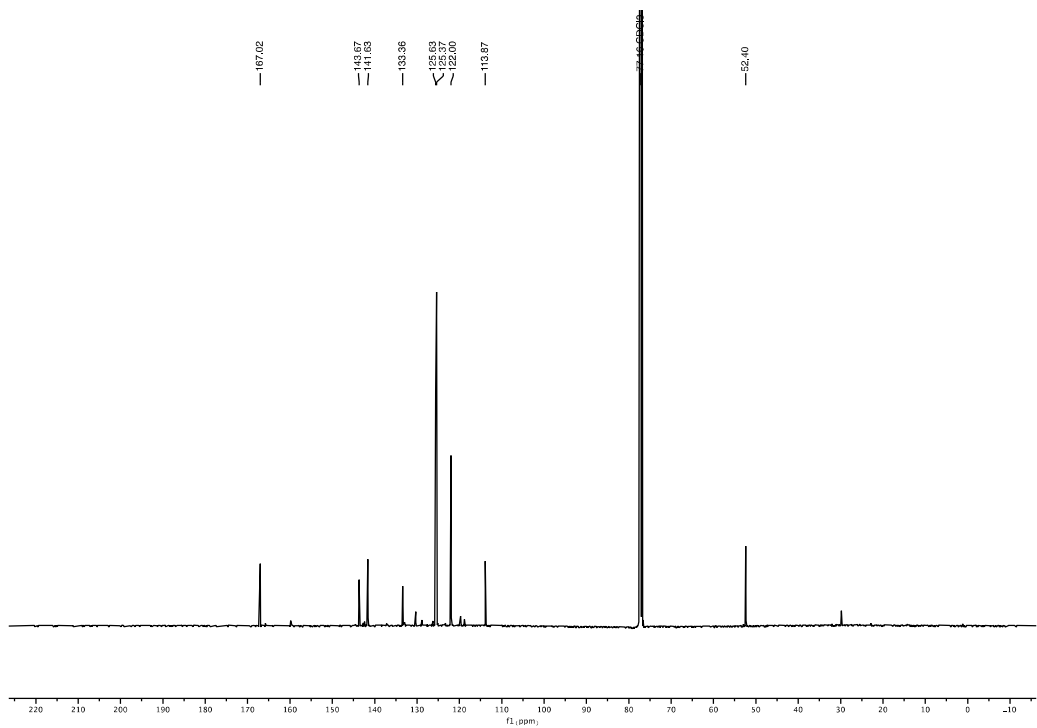
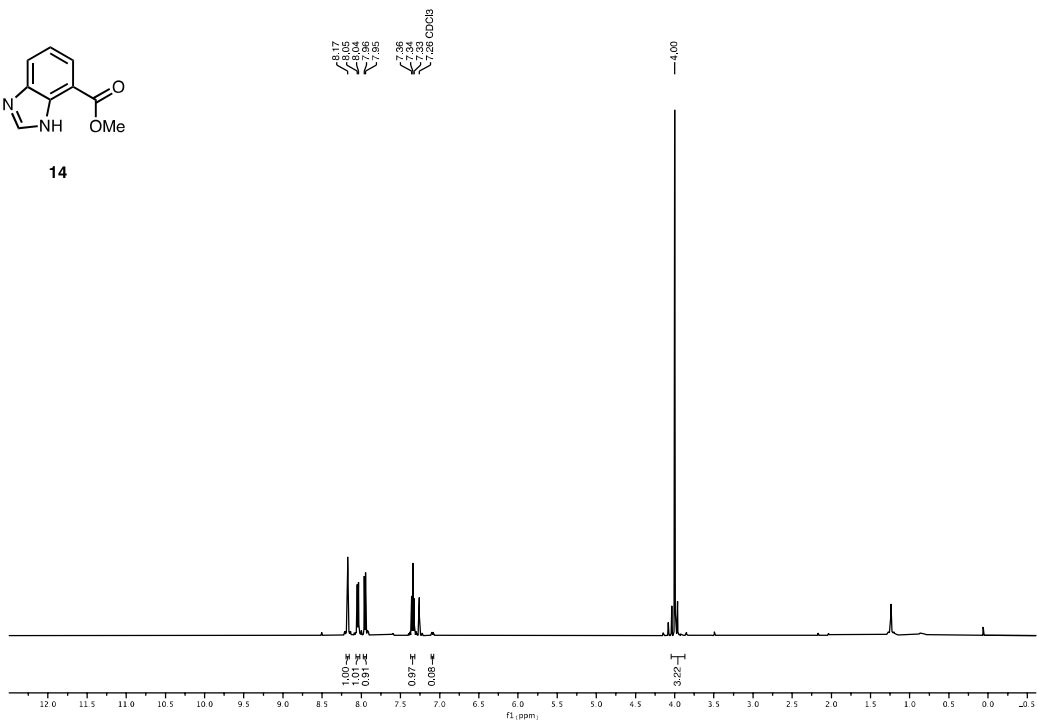


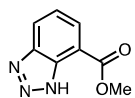




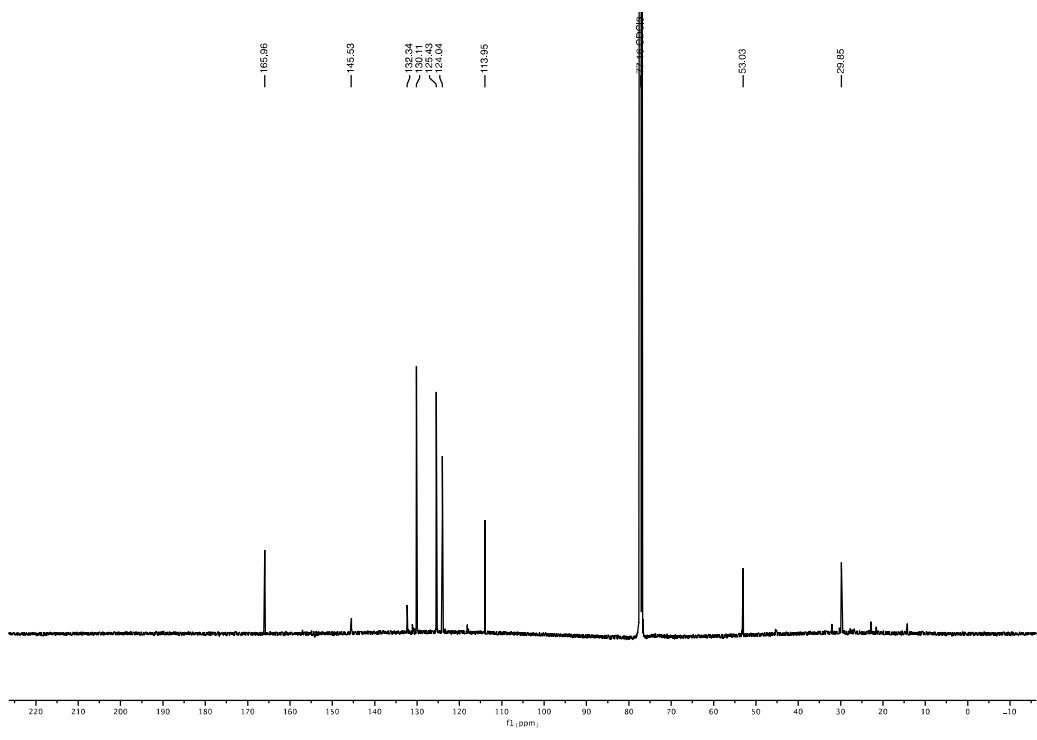
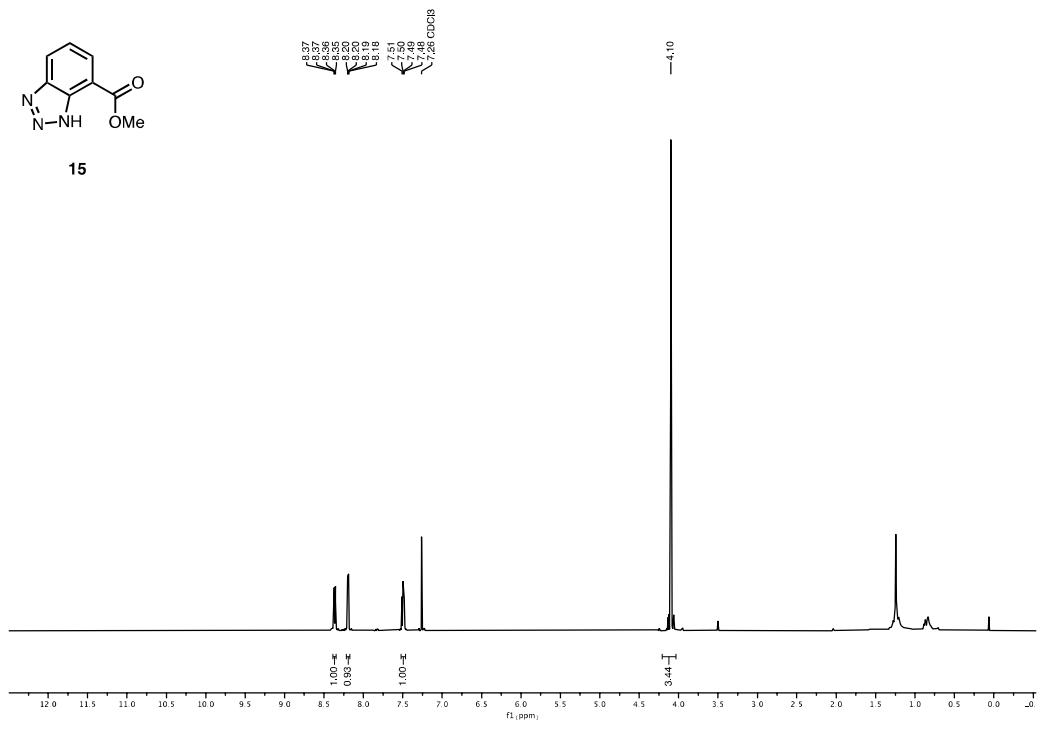


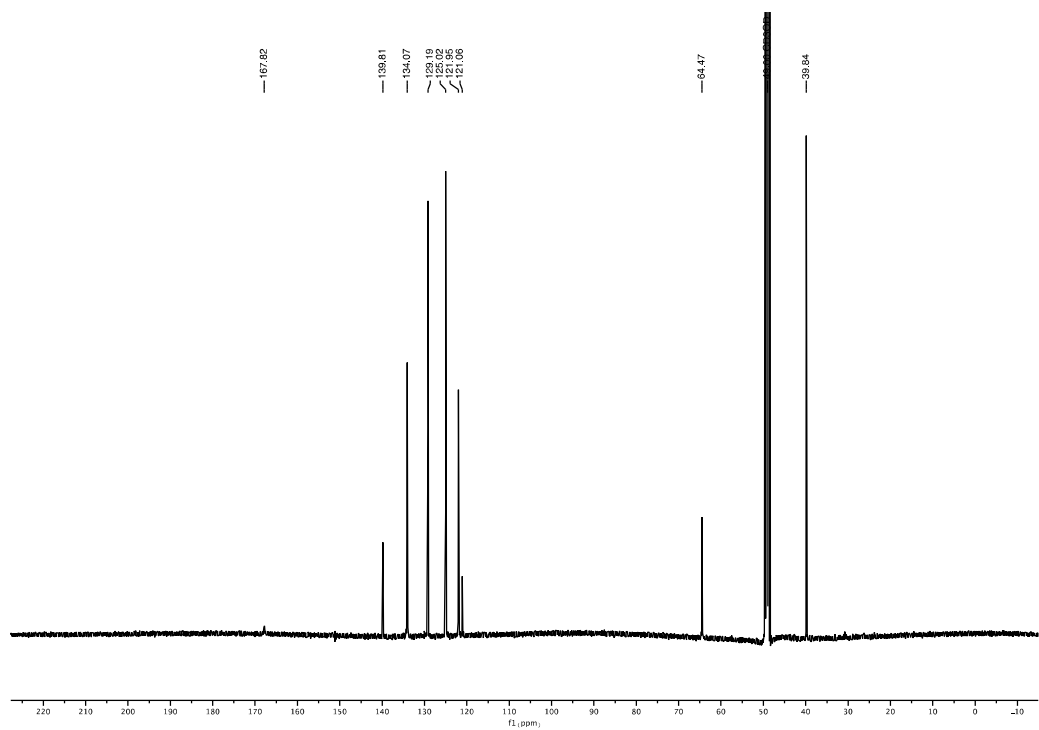
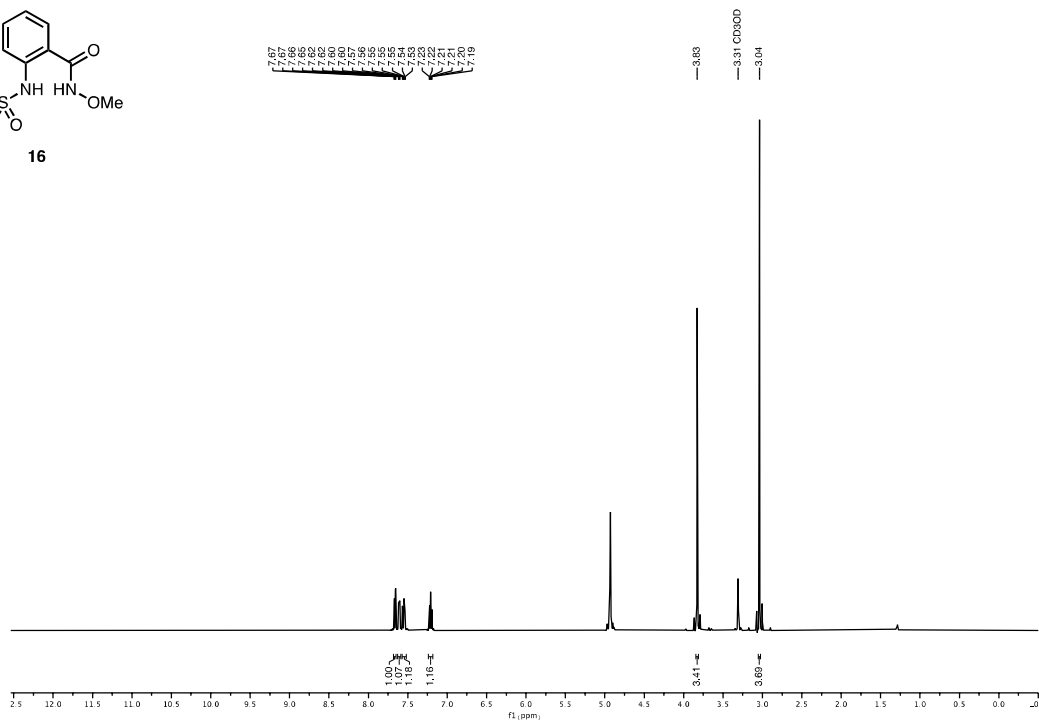
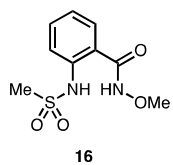
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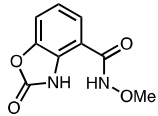




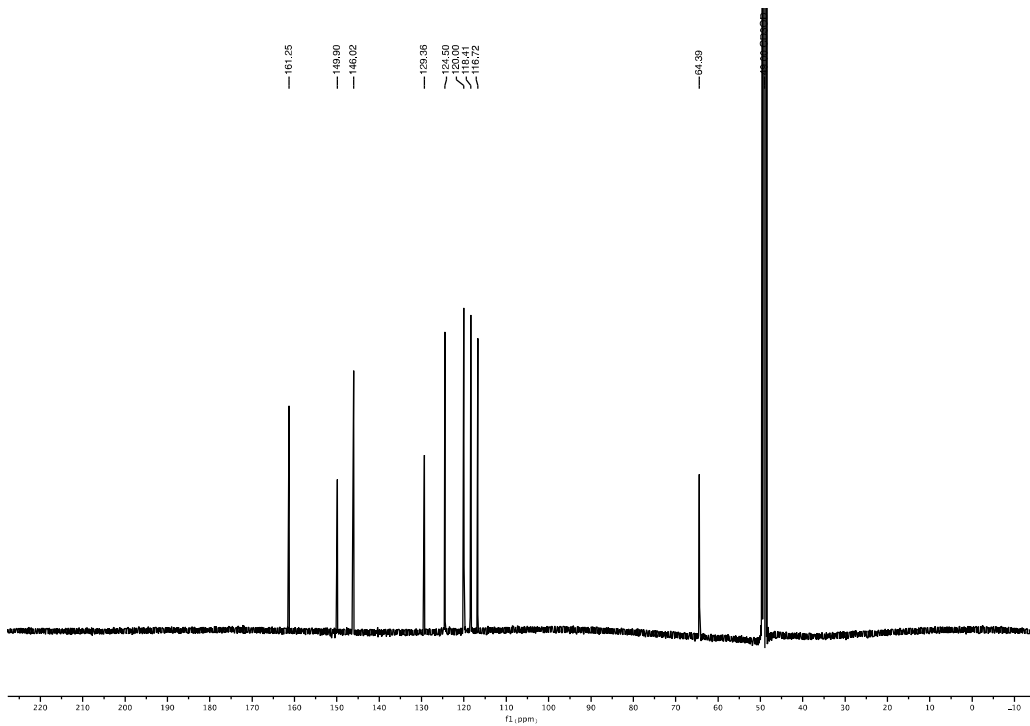
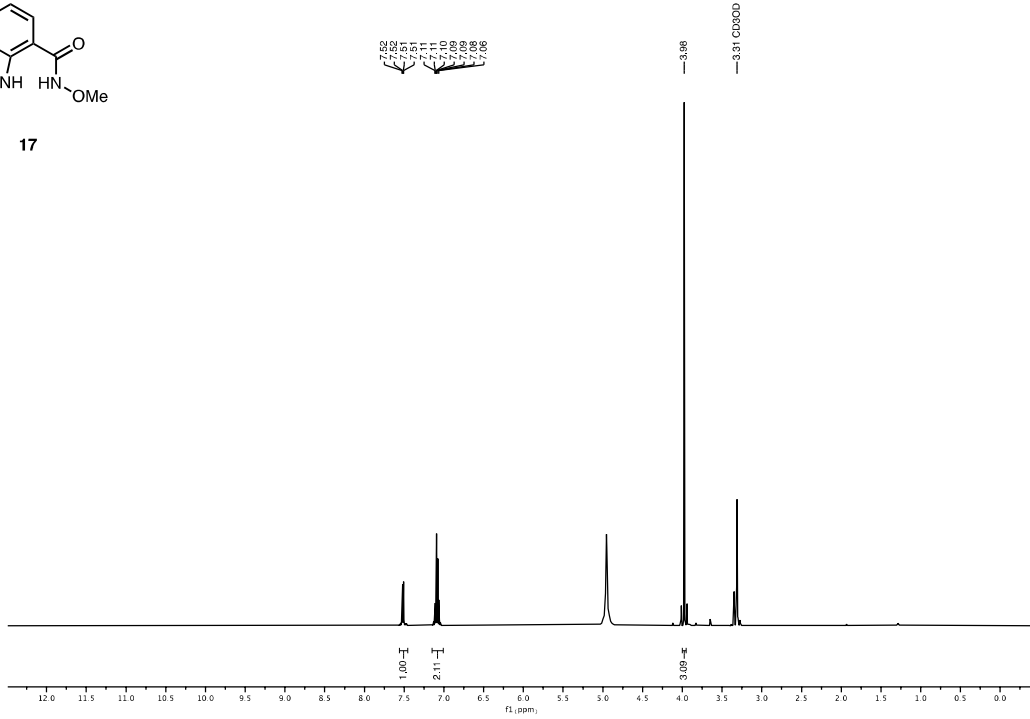
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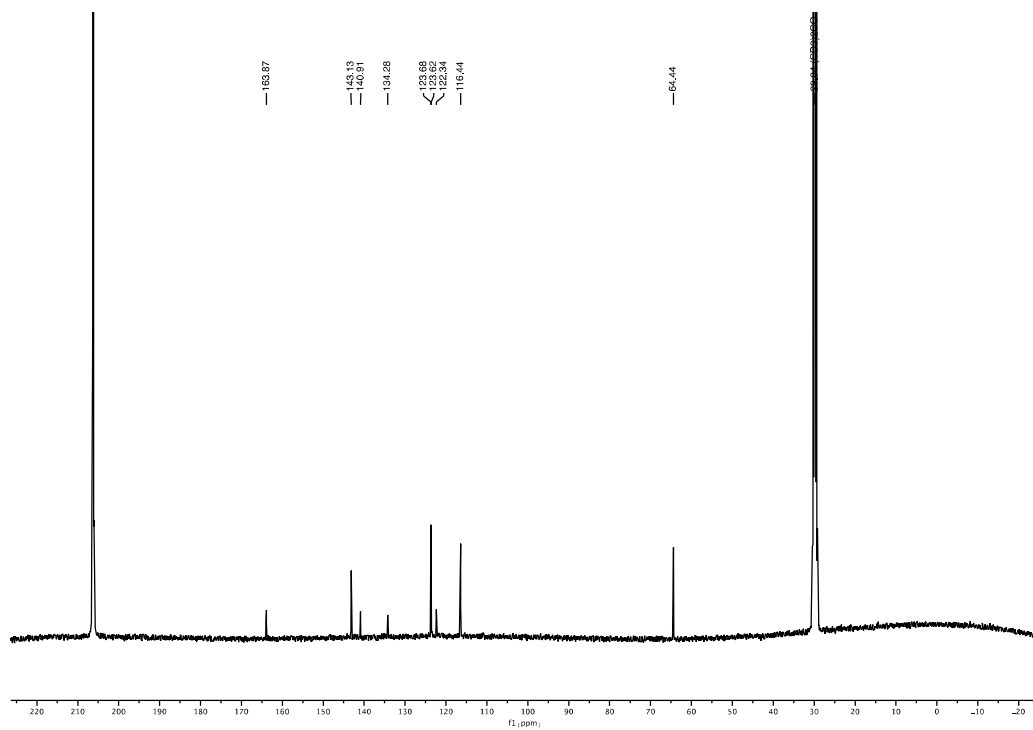
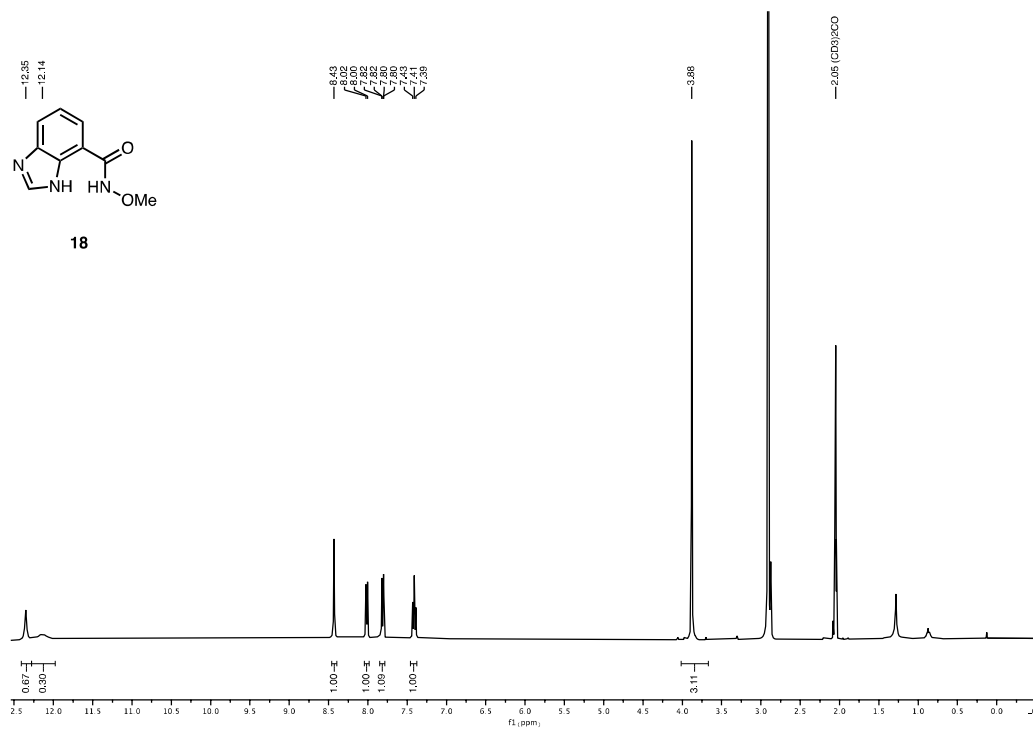
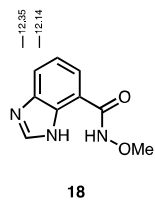


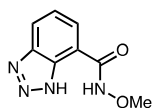




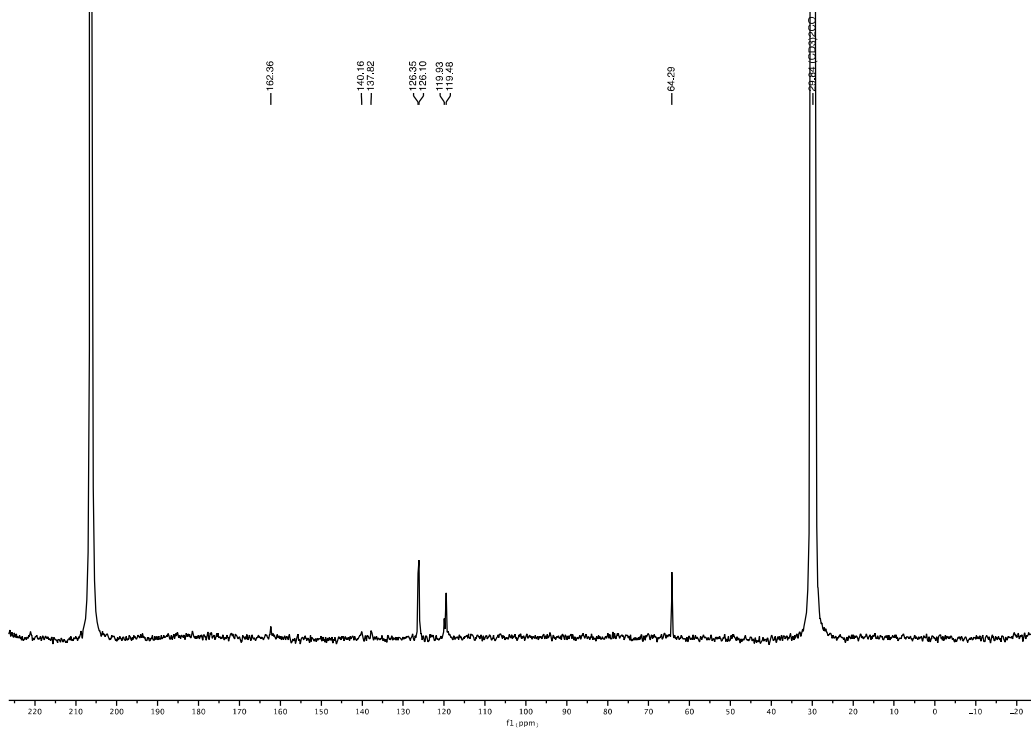
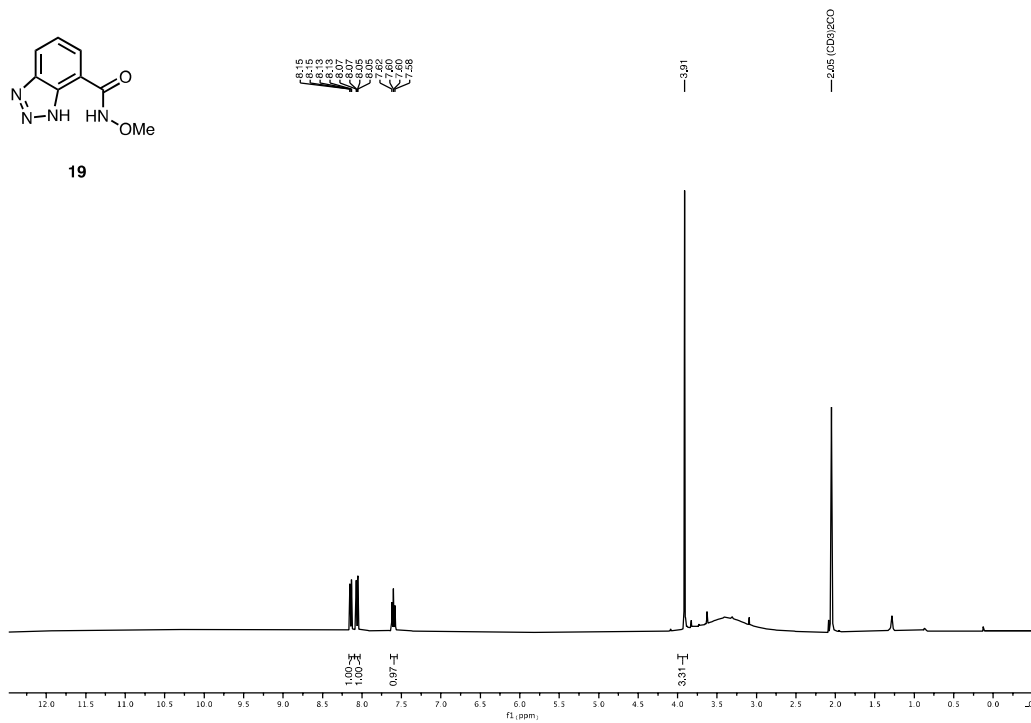
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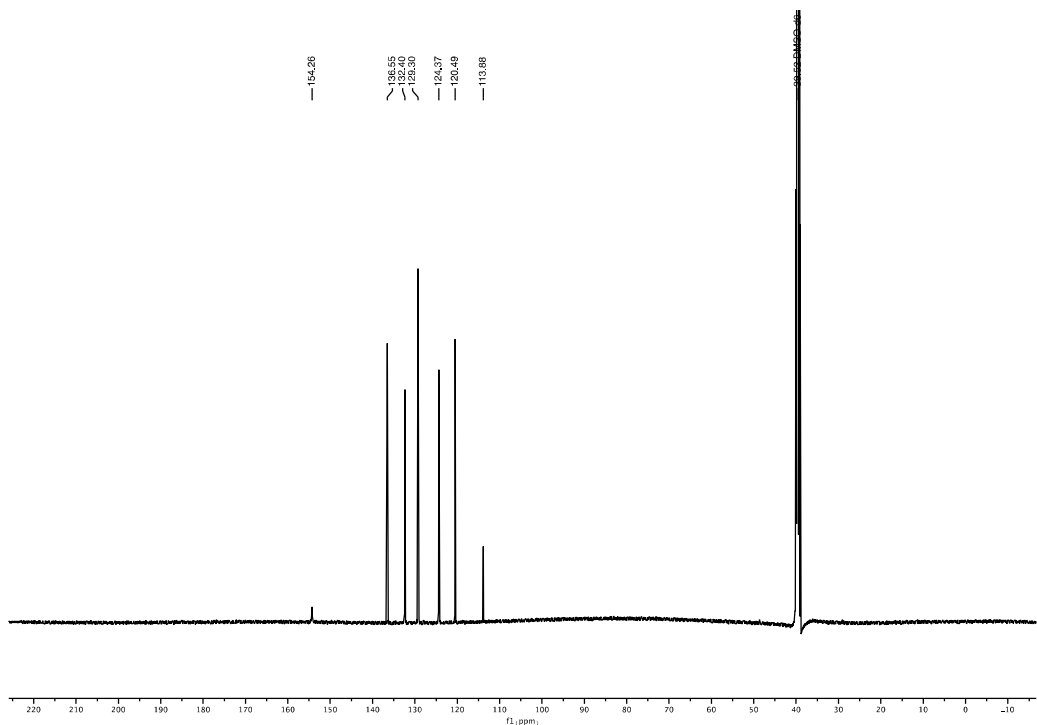
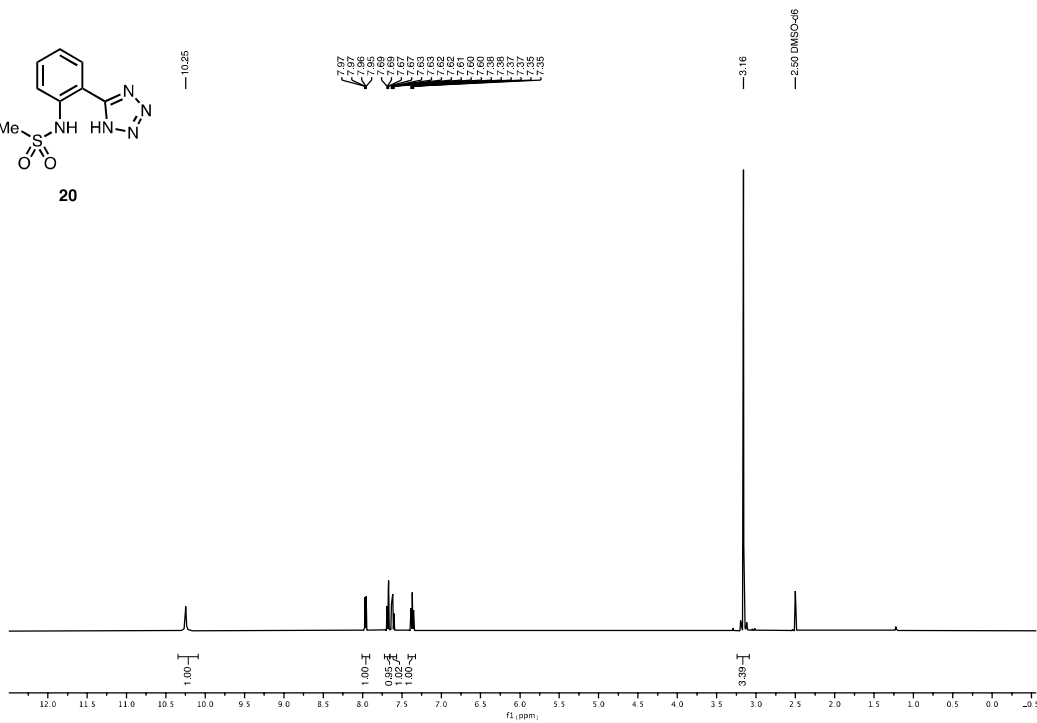
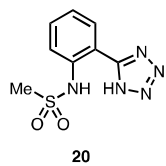


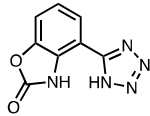




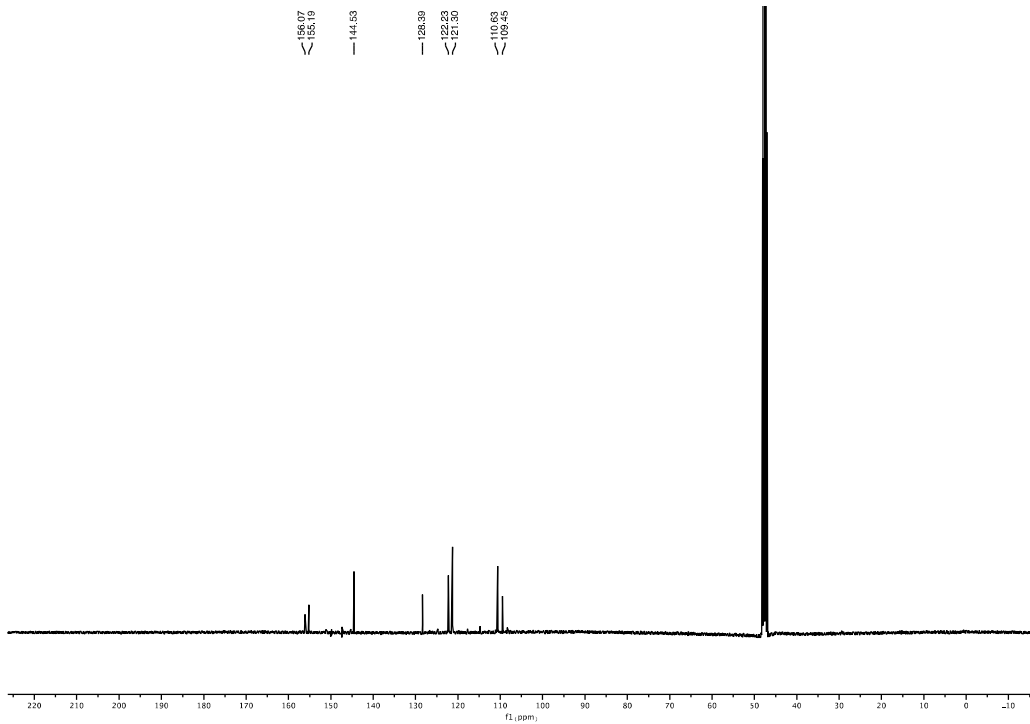
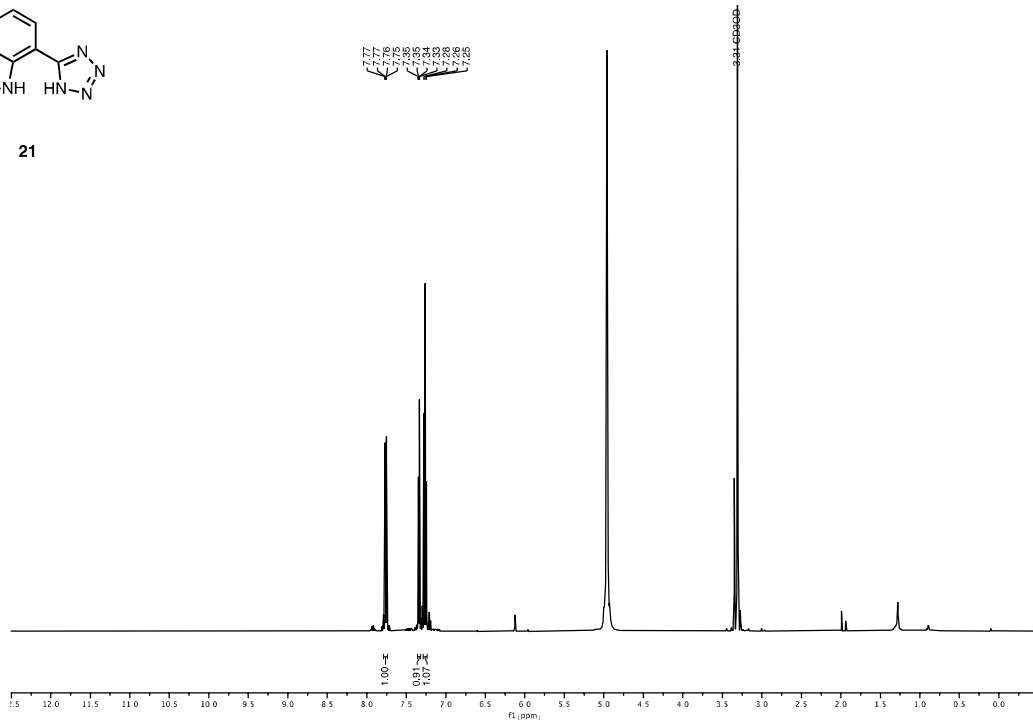
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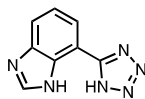




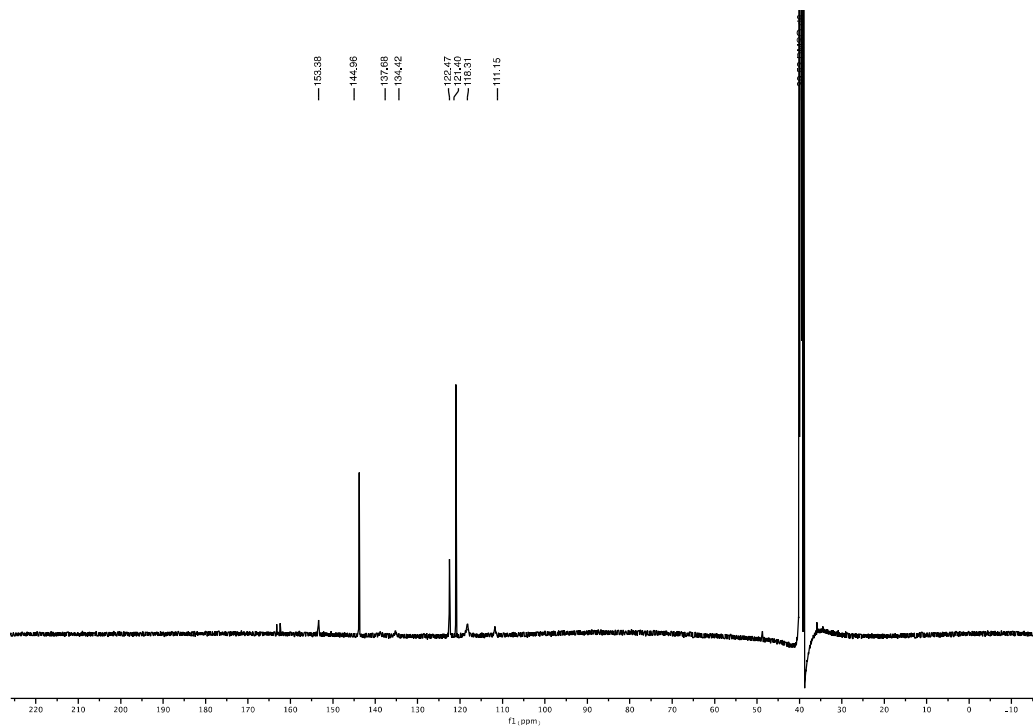
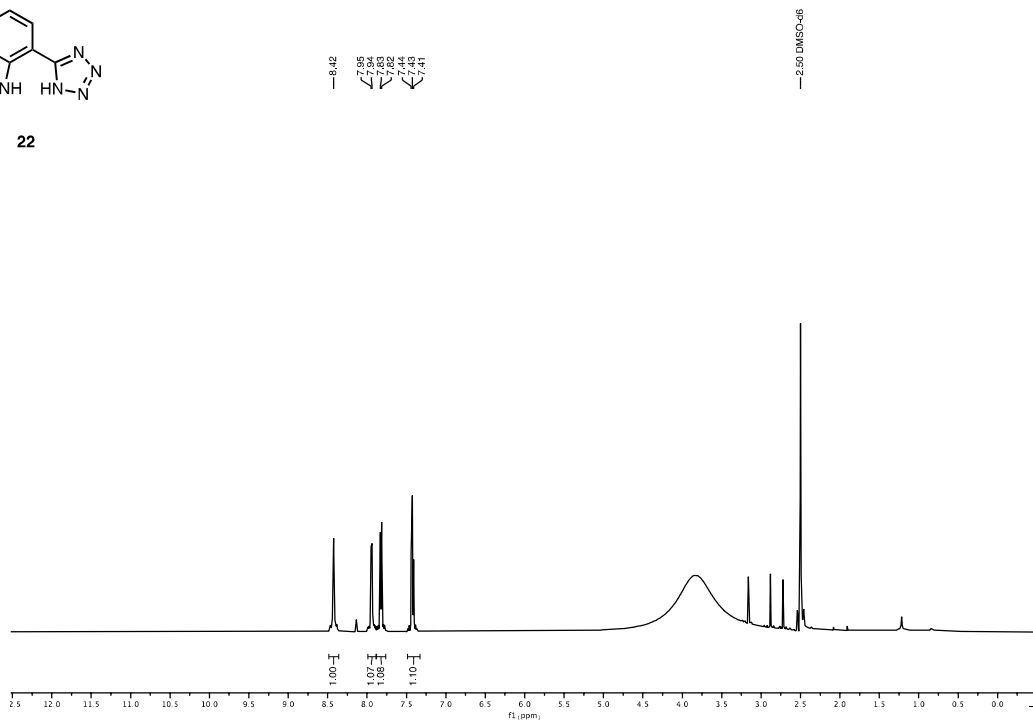


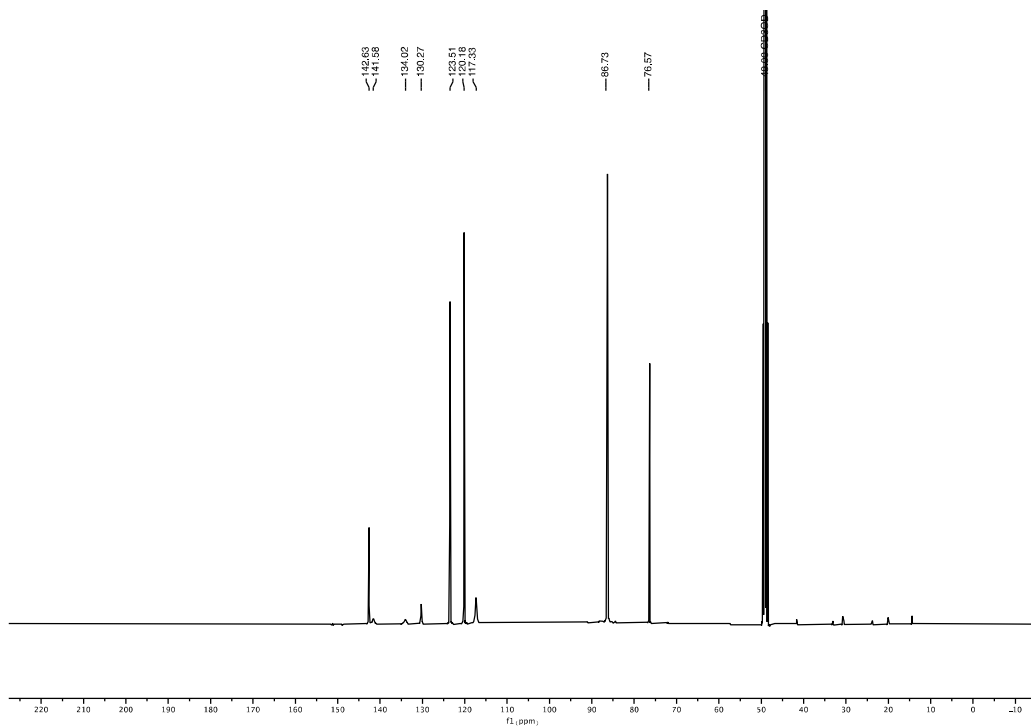
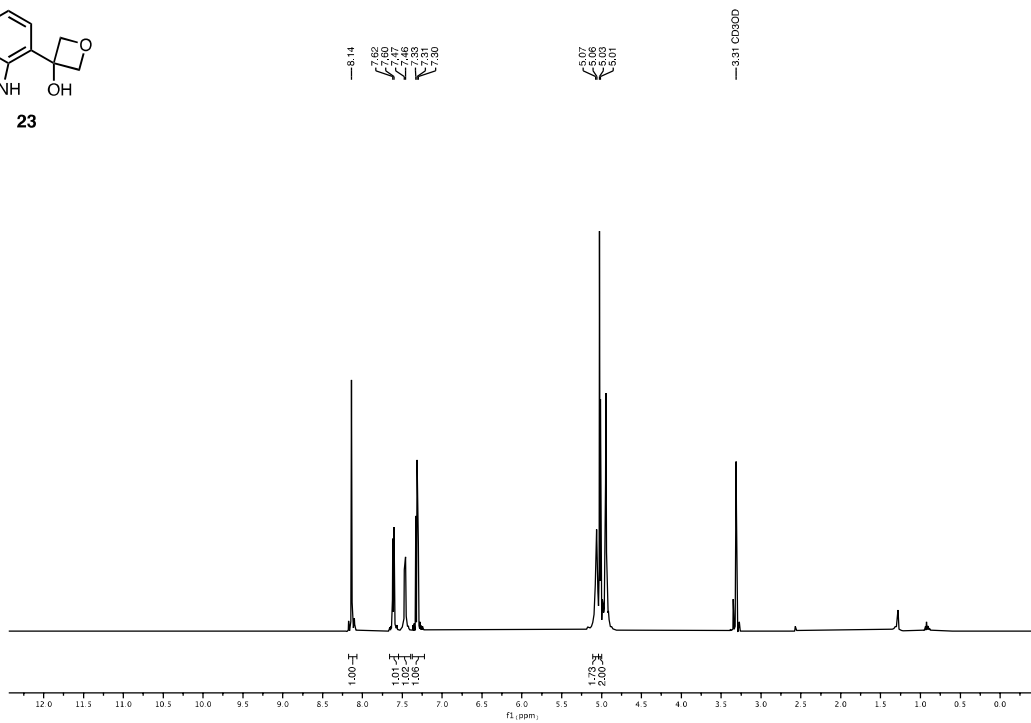
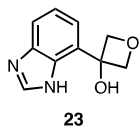
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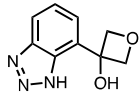




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