Salicylate Metal-Binding Isosteres as Fragments for Metalloenzyme Inhibition

SUPPORTING INFORMATION

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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 CH$_2$Cl$_2$ (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%).  $^1$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); $^{13}$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 [C$_9$H$_8$NO$_4$]: 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 MgSO$_4$, and concentrated under reduced pressure. Purification by C18 column chromatography (MeOH:H$_2$O 1:10 to 10:1 + 0.1% HCO$_2$H) was used to obtain the desired product as a colorless solid. Yield: 50 mg (67%). $^1$H NMR (400 MHz, DMSO-d$_6$): 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); $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ [ppm] = 165.7, 154.3,
143.9, 131.5, 124.5, 121.4, 113.7, 113.5; HRMS (ESI): calculated for [C₈H₄NO₄]⁻: 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 H₂O (2 mL) and AcOH (1 mL) and stirred for 5 min. Afterwards, a solution of NaNO₂ (151 mg, 2.19 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 (3x20 mL) and dried under high-vacuum. Purification by C18 column chromatography (MeOH:H₂O 1:10 to 10:1 + 0.1% HCO₂H) produced the desired product as an off-white solid. Yield: 190 mg (60%). ¹H NMR (400 MHz, DMSO-d₆): 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); ¹³C NMR (100 MHz, DMSO-d₆): δ [ppm] = 166.3, 145.8, 132.2, 129.9, 124.5, 124.0, 116.0; HRMS (ESI): calculated for [C₇H₄N₃O₂]⁻: 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-BuLi (1.6 M in hexanes, 3.08 mmol, 2.2 equiv) was added dropwise at –78 °C. The mixture was allowed to warm to room temperature and stirred for 30 min. The suspension was cooled back to –78 °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. 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 (hexanes:EtOAc 10:1 to 1:1) to obtain the desired product as a colorless solid. Yield: 50 mg (22%).

1H NMR (400 MHz, CDCl₃): 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); 13C NMR (100 MHz, CDCl₃): δ [ppm] = 154.6, 130.1, 126.0, 125.3, 120.7, 117.3, 84.2, 77.3; HRMS (ESI): calculated for [C₉H₉O₃]⁺: 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(PPh\(_3\))\(_2\)Cl\(_2\) were suspended in dioxane (2.5 mL). Afterwards, 2 M Na\(_2\)CO\(_3\) (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). H\(_2\)O (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) to obtain the desired product as a colourless solid. Yield: 140 mg (75%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) [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-(methylsulfonamido)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, CDCl$_3$): \( \delta \) [ppm] = 168.5, 140.9, 135.1, 131.7, 123.0, 118.1, 115.4, 52.8, 40.1;

HRMS (ESI): calculated for [C$_9$H$_{11}$NO$_4$SNa]$^+$: \( m/z = 252.0301 \), 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 H$_2$O (5 mL). Sat. NaHCO$_3$ 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. $^1$H NMR (400 MHz, CDCl$_3$): \( \delta \) [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); $^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta \) [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 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.

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. 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: 120 mg (55%). \[^1H\text{NMR}\] (400 MHz, CDCl$_3$): $\delta$ [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); \[^{13}C\text{NMR}\] (100 MHz, CDCl$_3$): $\delta$ [ppm] = 167.0, 143.7, 141.6, 133.4, 125.6, 125.4, 122.0, 113.9, 52.4; HRMS (ESI): calculated for [C$_{9}$H$_{9}$N$_{2}$O$_{2}$]$^+$: $m/z$ = 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. 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: 30 mg (40%). \[^1H\text{NMR}\] (400 MHz, CDCl$_3$): $\delta$ [ppm] = 8.41 – 8.23 (m, 1H), 8.23 – 8.15 (m, 1H), 7.54 – 7.44 (m, 1H), 4.10 (s, 3H); \[^{13}C\text{NMR}\] (100 MHz, CDCl$_3$): $\delta$ [ppm] = 166.0, 145.5, 132.4, 130.1, 125.4, 124.0, 114.0, 53.0; HRMS (ESI): calculated for [C$_{8}$H$_{8}$N$_{3}$O$_{2}$]$^+$: $m/z$ = 178.0611, found: $m/z$ = 178.0612.
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.
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 [C₉H₇N₂O₄]⁺: m/z = 209.0557, found: m/z = 209.0559.
**N-methoxy-1H-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-d₆): 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-d₆): 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-1H-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.
2-aminobenzonitrile (300 mg, 2.50 mmol, 1.00 equiv) was dissolved in anhydrous CH$_2$Cl$_2$ (5 mL) and pyridine (0.30 mL, 3.80 mmol, 1.50 equiv) was added. The resulting solution was cooled to $-78 \, ^\circ\text{C}$ 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. H$_2$O (10 mL) and CH$_2$Cl$_2$ were added, the phases separated and the aqueous phase extracted with CH$_2$Cl$_2$ (3x20 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 3:1) to obtain the desired product, which was directly used for the next step. \textit{^1H NMR} (400 MHz, CDCl$_3$): $\delta$ [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.$^3$

\textbf{N-(2-(1H-tetrazol-5-yl)phenyl)methanesulfonamide (20)}

Compound s3 (200 mg, 1.02 mmol, 1.00 equiv), NaN$_3$ (133 mg, 2.04 mmol, 2.00 equiv) and NH$_4$Cl (109 mg, 2.04 mmol, 2.00 equiv) were suspended in anhydrous DMF (3 mL) and the resulting mixture was stirred at 110 $^\circ\text{C}$ 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 \([C₈H₁₀N₂O₂S]⁺\): m/z = 240.0550, found: m/z = 240.0551.

\[
\begin{array}{c}
\text{HO} \quad \text{CN} \\
\text{NH₂} \quad \text{CH₂Cl₂} \quad \text{CDI} \quad 45 \degree C \\
\text{O} \quad \text{HN} \quad \text{NN} \\
\text{CN} \quad \text{DMF} \quad 110 \degree C
\end{array}
\]

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 H$_2$O (10 mL) was added. A solid crushed out which was collected by filtration, washed with H$_2$O (3x20 mL) and dried under high-vacuum. Purification by C18 column chromatography (H$_2$O:MeOH 10:1 to 1:10) to obtain the desired product as a greyish solid. Yield: 45 mg (31%). $\text{^1H NMR (400 MHz, DMSO-d$_6$): } \delta$ [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); $\text{^{13C NMR (100 MHz, DMSO-d$_6$): } \delta$ [ppm] = 153.4, 145.0, 137.7, 134.4, 122.5, 121.4, 118.3, 111.2; $\text{HRMS (ESI): calculated for [C}_8\text{H}_7\text{N}_6\text{]^+ m/z = 187.0727, found: m/z = 187.0728.}$

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

7-bromo-1H-benzof[d]imidazole (242 mg, 1.23 mmol, 1.00 equiv) was dissolved in anhydrous THF (6 mL) and $^{n}$BuLi (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. NH$_4$Cl (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$_2$Cl$_2$:MeOH 100:1 to 10:1) to obtain the desired product as a colorless solid. Yield: 70 mg (30%). $\text{^1H NMR (400 MHz, CD$_3$OD): } \delta$ [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); $\text{^{13C NMR (100}$
MHz, CD$_3$OD): $\delta$ [ppm] = 142.6, 141.6, 134.0, 130.3, 123.5, 120.2, 117.3, 86.7, 76.6;

HRMS (ESI): calculated for $[\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2]^+$: $m/z = 191.0815$, found: $m/z = 191.0815$.

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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 H$_2$O (5 mL) and AcOH (2 mL) and stirred for 5 min. Thereto, a solution of NaNO$_2$ (211 mg, 3.06 mmol, 1.11 equiv) in H$_2$O (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$_2$O (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. $^1$H NMR (400 MHz, Acetone-$d_6$): $\delta$ [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); $^{13}$C NMR (100 MHz, Acetone-$d_6$): $\delta$ [ppm] = 140.9, 139.3, 128.7, 128.1, 114.3, 109.5; HRMS (ESI): calculated for $[\text{C}_6\text{H}_5\text{BrN}_3]^+$: $m/z = 197.9661$, found: $m/z = 197.9659$.

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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 $^n$BuLi (1.6 M in hexanes, 3.67 mmol, 3.00 equiv) was added dropwise at $-78 \degree$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. 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: 130 mg (56%). ¹H NMR (400 MHz, CD₃OD): 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); ¹³C NMR (100 MHz, CD₃OD): δ [ppm] = 142.9, 135.4, 131.1, 126.5, 123.3, 116.5, 86.2, 76.0; HRMS (ESI): calculated for [C₉H₁₀N₃O₂]⁺: m/z = 192.0768, found: m/z = 192.0771.

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

(2-(Methylsulfonamido)phenyl)boronic acid (258 mg, 1.20 mmol, 1.20 equiv), 2-chloropyrimidine (115 mg, 1.00 mmol, 1.00 equiv) and Pd(PPh₃)₂Cl₂ (1.5 mol%) were suspended in Dioxane (2.5 mL). Thereto, 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: 180 mg (32%). ¹H NMR (400 MHz, CDCl₃): 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}\text{C} \text{ NMR} \ (100 \text{ MHz, CDCl}_3): \ \delta \ [\text{ppm}] = \ 164.4, 156.7, 139.4, 132.8, 131.2, 123.5, 122.7, 119.1, 118.9, 39.8; \ \text{HRMS} \ (\text{ESI}): \ \text{calculated for} \ [\text{C}_{11}\text{H}_{12}\text{N}_3\text{O}_2\text{S}]^+: \ m/z = 250.0645, \ \text{found:} \ m/z = 250.0647.

\begin{center}
\[ 
\begin{array}{c}
\text{N-(2-(Pyrimidin-2-yl)phenyl)methanesulfonamide (26)}
\end{array}
\]
\end{center}

\(1H\text{-Benzo}[d]\text{imidazol-7-yl})\text{boronic acid (150 mg, 0.93 mmol, 1.20 equiv), 2-chloro-pyrimidine (90.0 mg, 0.78 mmol, 1.00 equiv) and Pd(PPh}_3\text{)}_2\text{Cl}_2 \ (1.5 \text{ mol%)} \text{ were suspended in Dioxane (2 mL). Thereto, 2 M Na}_2\text{CO}_3 \ (2 mL) \text{ was added and the resulting mixture was stirred at 90 °C for 5 h (progress of the reaction monitored by TLC). H}_2\text{O} \ (5 mL) \text{ and EtOAc} \ (15 mL) \text{ 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 \text{ and concentrated under reduced pressure. Purification by column chromatography (hexanes:EtOAc 10:1 to 1:1) followed by C18 column chromatography (H}_2\text{O:MeOH 10:1 to 1:10 + 0.1% HCO}_2\text{H}) to obtain the desired product as a colourless solid. Yield: 30 mg (20%).}

\(1H \text{ NMR} \ (400 \text{ MHz, Acetone-}d_6): \ \delta \ [\text{ppm}] = 12.36 \text{ (br s, 1H), 8.94 (d,} \ J = 4.8 \text{ 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}\text{C NMR} \ (100 \text{ MHz, Acetone-}d_6): \ \delta \ [\text{ppm}] = 164.8, 158.3, 145.5, 143.1, 133.5, 123.5, 123.4, 122.4, 122.3, 119.9; \ \text{HRMS} \ (\text{ESI}): \ \text{calculated for} \ [\text{C}_{11}\text{H}_{9}\text{N}_4]^+: \ m/z = 197.0822, \ \text{found:} \ m/z = 197.0820.
(2-(Methylsulfonamido)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(PPh$_3$)$_2$Cl$_2$ (1.5 mol%) were suspended in Dioxane (2.5 mL). Thereto, 2 M Na$_2$CO$_3$ (2.5 mL) was added and the resulting mixture was stirred at 90 °C for 5 h (progress of the reaction monitored by TLC). H$_2$O (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$_2$O:MeOH 10:1 to 1:10 + 0.1% HCO$_2$H) to obtain the desired product as a colourless solid.

Yield: 100 mg (33%). $^1$H NMR (400 MHz, CDCl$_3$): 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); $^{13}$C NMR (100 MHz, CDCl$_3$): 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 [C$_{14}$H$_{13}$N$_2$O$_2$S$_2$]$^+$: m/z = 305.0413, found: m/z = 305.0416.
2-(1H-Benzo[d]imidazol-7-yl)benzo[d]thiazole (28)

(1H-Benz[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-d₆): 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-d₆): 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%). \( ^{1}H \text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) [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, \( J = 8.8 \text{ Hz} \), 1H), 4.03 (s, 3H); \( ^{13}C \text{NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) [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; \( \text{HRMS} \) (ESI): calculated for [C\(_{14}\)H\(_{11}\)BrNOS]: \( m/z \) = 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 Cs$_2$CO$_3$ (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, H$_2$O (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.

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. Na$_2$CO$_3$ (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, H$_2$O (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.

General conditions for demethylation A:

Phenol ether (1.00 equiv) was dissolved in CH$_2$Cl$_2$ (1.0 mL) and BBr$_3$ (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. Na$_2$CO$_3$ (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.
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. NaHCO$_3$ (5 mL), brine (5 mL), dried over MgSO$_4$ 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%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ [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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ [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 [C$_{19}$H$_{14}$NOS]$^+$/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%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ [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\(_3\)): \(\delta \text{ [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; \(\text{HRMS (ESI)}\): 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\(_3\)): \(\delta \text{ [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\(_3\)): \(\delta \text{ [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; \(\text{HRMS (ESI)}\): 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\(_3\)): \(\delta \text{ [ppm]} = 12.13 \text{ (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,
CDCl$_3$): $\delta$ [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 [C$_{18}$H$_{19}$N$_2$O$^+$]: m/z = 311.1213, found: m/z = 311.1214.

![](image)

**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%). **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ [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); **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ [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 [C$_{17}$H$_{17}$N$_2$O$_2$S$^+$]: m/z = 313.1005, found: m/z = 313.1002.

![](image)

**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%). **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ [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); **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ [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 \([\text{C}_{17}\text{H}_{17}\text{N}_2\text{OS}]^+\): \(m/z = 297.1056\), found: \(m/z = 297.1055\).

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

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%). **\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \(\delta [\text{ppm}] = 12.56 (\text{br s}, 1\text{H}), 8.03 - 7.99 (\text{m}, 1\text{H}), 7.95 - 7.89 (\text{m}, 1\text{H}), 7.78 - 7.71 (\text{m}, 2\text{H}), 7.56 - 7.48 (\text{m}, 3\text{H}), 7.46 - 7.41 (\text{m}, 1\text{H}), 7.16 - 7.10 (\text{m}, 1\text{H}), 6.74 - 6.69 (\text{m}, 1\text{H}); **\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): \(\delta [\text{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 \([\text{C}_{17}\text{H}_{12}\text{NO}_2\text{S}]^+\): \(m/z = 294.0583\), 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) 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-3d\textsuperscript{4} show similar binding mode to the Zn\textsuperscript{2+} 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 µM 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.\textsuperscript{5,6}

![Dose-response curve of 11 against GLO1.](image)

**Figure S7.** Dose-response curve of 11 against GLO1.
Figure S8. Dose-response curve of 11a against GLO1.

Figure S9. Dose-response curve of 11b against GLO1.
Figure S10. Dose-response curve of 11c against GLO1.

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 [(Tp^{Ph,Me})Zn(MBI)] complexes were selected and data was collected at 100 K on a Bruker APEX-II Ultra diffractometer with a Mo-Kα 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 ShelXT\textsuperscript{7} structure solution program using direct methods and refined with the XL\textsuperscript{8} refinement package using least squares minimization using Olex2.\textsuperscript{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 SQUEEZE\textsuperscript{10} function in [(Tp^{Ph,Me})Zn(2)], [(Tp^{Ph,Me})Zn(11)], and [(Tp^{Ph,Me})Zn(15)]. A pentane solvent molecule is positionally disordered in [(Tp^{Ph,Me})Zn(3)].
| Compound | [(Tp<sup>Ph</sup>Me)Zn(2)] | [(Tp<sup>Ph</sup>Me)Zn(3)] | [(Tp<sup>Ph</sup>Me)Zn(10)] |
|----------|-----------------|-----------------|-----------------|
| Identification code | 2117775 | 2117778 | 2117773 |
| Empirical formula | C<sub>38</sub>H<sub>36</sub>B<sub>7</sub>N<sub>3</sub>O<sub>4</sub>Zn | C<sub>40.62</sub>H<sub>37.25</sub>B<sub>7</sub>N<sub>3</sub>O<sub>4</sub>Zn | C<sub>40</sub>H<sub>38</sub>B<sub>8</sub>O<sub>4</sub> |
| 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<sup>3</sup> | 4050.0(16) | 3621.5(5) | 3432.3(4) |
| Z | 4 | 4 | 4 |
| ρ<sub>calc</sub>/g/cm<sup>3</sup> | 1.251 | 1.401 | 1.393 |
| μ/mm<sup>-1</sup> | 0.704 | 1.373 | 0.762 |
| F(000) | 1584 | 1588 | 1496 |
| Crystal size/mm<sup>3</sup> | 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<sub>int</sub> = 0.0905, R<sub>sigma</sub> = 0.0776] | 6808 [R<sub>int</sub> = 0.0401, R<sub>sigma</sub> = 0.0518] | 6846 [R<sub>int</sub> = 0.1286, R<sub>sigma</sub> = 0.0706] |
| Data/restraints/parameters | 16482/0/945 | 6808/33/526 | 6846/0/463 |
| Goodness-of-fit on F<sup>2</sup> | 1.097 | 1.087 | 1.038 |
| Final R indexes [I>2σ (I)] | R<sub>1</sub> = 0.0760, wR<sub>2</sub> = 0.1697 | R<sub>1</sub> = 0.0418, wR<sub>2</sub> = 0.1122 | R<sub>1</sub> = 0.0409, wR<sub>2</sub> = 0.0878 |
| Final R indexes [all data] | R<sub>1</sub> = 0.1103, wR<sub>2</sub> = 0.1829 | R<sub>1</sub> = 0.0478, wR<sub>2</sub> = 0.1168 | R<sub>1</sub> = 0.0608, wR<sub>2</sub> = 0.0954 |
| Largest diff. peak/hole / e Å<sup>-3</sup> | 3.29/-0.89 | 0.25/-0.62 | 0.42/-0.76 |
Table S1 (continued). Crystal data and structure refinement for \([(\text{Tp}^{\text{Ph,Me}})_2\text{Zn(MBI)}]\)
complexes.

| Compound | \([(\text{Tp}^{\text{Ph,Me}})_2\text{Zn(11)}]\) | \([(\text{Tp}^{\text{Ph,Me}})_2\text{Zn(12)}]\) | \([(\text{Tp}^{\text{Ph,Me}})_2\text{Zn(13)}]\) |
|----------|---------------------------------|---------------------------------|---------------------------------|
| Identification code | 2117776 | 2117770 | 2117767 |
| Empirical formula | \(\text{C}_{43}\text{H}_{36}\text{BN}_7\text{OSZn}\) | \(\text{C}_{39}\text{H}_{38}\text{BN}_7\text{O}_4\text{Zn}\) | \(\text{C}_{39}\text{H}_{38}\text{BN}_7\text{O}_4\text{Zn}\) |
| Formula weight | 775.03 | 777 | 740.91 |
| Temperature/K | 100 | 100 | 100 |
| Crystal system | orthorhombic | orthorhombic | triclinic |
| Space group | \(\text{Pbca}\) | \(\text{Pna21}\) | \(\text{P-1}\) |
| 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) |
| \(\alpha^\circ\) | 90 | 90 | 115.6050(10) |
| \(\beta^\circ\) | 90 | 90 | 90.7810(10) |
| \(\gamma^\circ\) | 90 | 90 | 98.5870(10) |
| Volume/Å\(^3\) | 8764.0(6) | 3663.3(8) | 1745.7(2) |
| Z | 8 | 4 | 2 |
| \(\rho_{\text{calc}}\)/g/cm\(^3\) | 1.175 | 1.409 | 1.41 |
| \(\mu\)/mm\(^-1\) | 0.647 | 0.779 | 0.757 |
| F(000) | 3216 | 1616 | 768 |
| Crystal size/mm\(^3\) | \(0.1 \times 0.1 \times 0.1\) | \(0.2 \times 0.1 \times 0.1\) | \(0.1 \times 0.1 \times 0.1\) |
| Radiation | \(\text{MoK\(\alpha\)} (\lambda = 0.71073)\) | \(\text{MoK\(\alpha\)} (\lambda = 0.71073)\) | \(\text{MoK\(\alpha\)} (\lambda = 0.71073)\) |
| 2\(\Theta\) range for data collection/\(^\circ\) | 4.652 to 50.848 | 3.298 to 52.256 | 3.334 to 52.876 |
| Index ranges | \(-19 \leq h \leq 19, -27 \leq k \leq 27, -27 \leq l \leq 27\) | \(-11 \leq h \leq 14, -20 \leq k \leq 20, -22 \leq l \leq 21\) | \(-14 \leq h \leq 14, -15 \leq k \leq 15, -17 \leq l \leq 17\) |
| Reflections collected | 208770 | 20238 | 22366 |
| Independent reflections | 8053 [\(R_{\text{int}} = 0.1453, R_{\text{sigma}} = 0.0348\)] | 6978 [\(R_{\text{int}} = 0.0703, R_{\text{sigma}} = 0.0973\)] | 7180 [\(R_{\text{int}} = 0.0391, R_{\text{sigma}} = 0.0353\)] |
| 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 [\(I \geq 2\sigma (I)\)] | \(R_1 = 0.0389, wR_2 = 0.0906\) | \(R_1 = 0.0431, wR_2 = 0.1068\) | \(R_1 = 0.0279, wR_2 = 0.0724\) |
| 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\textsubscript{Ph,Me}Zn(MBI)] complexes.

| Compound | [(Tp\textsubscript{Ph,Me}Zn(14)] | [(Tp\textsubscript{Ph,Me}Zn(15)] | [(Tp\textsubscript{Ph,Me}Zn(16)] |
|----------|-------------------------------|-------------------------------|-------------------------------|
| Identification code | 2117768 | 2117769 | 2117774 |
| Empirical formula | C\textsubscript{39}H\textsubscript{35}B\textsubscript{9}N\textsubscript{8}O\textsubscript{2}Zn | C\textsubscript{38}H\textsubscript{34}B\textsubscript{9}N\textsubscript{9}O\textsubscript{2}Zn | C\textsubscript{44.58}H\textsubscript{43.62}B\textsubscript{9}N\textsubscript{8}O\textsubscript{4}Zn |
| Formula weight | 723.93 | 724.92 | 863.69 |
| Temperature/K | 100 | 100 | 100 |
| Crystal system | orthorhombic | monoclinic | monoclinic |
| Space group | Pbca | C\textsubscript{2}/c | P\textsubscript{2}1/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\textsuperscript{3} | 6810.8(4) | 7330.2(7) | 8644.6(7) |
| Z | 8 | 8 | 8 |
| ρ\textsubscript{calc}/g/cm\textsuperscript{3} | 1.412 | 1.314 | 1.327 |
| μ/mm\textsuperscript{-1} | 0.77 | 0.717 | 0.669 |
| F(000) | 3008 | 3008 | 3601 |
| Crystal size/mm\textsuperscript{3} | 0.1 x 0.1 x 0.1 | 0.1 x 0.1 x 0.1 | 0.1 x 0.1 x 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\textsubscript{int} = 0.0536, R\textsubscript{sigma} = 0.0430] | 7531 [R\textsubscript{int} = 0.0526, R\textsubscript{sigma} = 0.0323] | 17087 [R\textsubscript{int} = 0.0922, R\textsubscript{sigma} = 0.0448] |
| Data/restraints/parameters | 6969/0/464 | 7531/84/434 | 17087/0/1109 |
| Goodness-of-fit on F\textsuperscript{2} | 1.045 | 1.037 | 1.023 |
| Final R indexes [I>=2σ (I)] | R\textsubscript{1} = 0.0314, wR\textsubscript{2} = 0.0807 | R\textsubscript{1} = 0.0393, wR\textsubscript{2} = 0.0915 | R\textsubscript{1} = 0.0449, wR\textsubscript{2} = 0.0958 |
| Final R indexes [all data] | R\textsubscript{1} = 0.0377, wR\textsubscript{2} = 0.0848 | R\textsubscript{1} = 0.0480, wR\textsubscript{2} = 0.0971 | R\textsubscript{1} = 0.0717, wR\textsubscript{2} = 0.1089 |
| Largest diff. peak/hole / e Å\textsuperscript{-3} | 0.36/-0.45 | 1.01/-0.84 | 0.98/-0.71 |
| Compound | \([(\text{Tp}^{\text{Ph,Me}}\text{Zn}(19))]\) | \([(\text{Tp}^{\text{Ph,Me}}\text{Zn}(23))]\) | \([(\text{Tp}^{\text{Ph,Me}}\text{Zn}(24))]\) |
|----------|---------------------------------|---------------------------------|---------------------------------|
| Identification code | 2117772 | 2117777 | 2117771 |
| Empirical formula | C_{44}H_{42}BN_{10}O_{2}Zn | C_{40}H_{37}BN_{9}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/Å³ | 2009.8(5) | 3589.9(2) | 1750.69(17) |
| Z | 2 | 4 | 2 |
| \(\rho_{\text{calc}}/\text{g/cm}³\) | 1.353 | 1.374 | 1.402 |
| \(\mu/\text{mm}⁻¹\) | 0.663 | 0.733 | 0.752 |
| F(000) | 854 | 1545 | 768 |
| Crystal size/mm³ | 0.1 × 0.1 × 0.1 | 0.2 × 0.1 × 0.1 | 0.2 × 0.04 × 0.03 |
| Radiation | MoKα (\(\lambda = 0.71073\)) | MoKα (\(\lambda = 0.71073\)) | MoKα (\(\lambda = 0.71073\)) |
| 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 [\(R_{\text{int}} = 0.0683, R_{\text{sigma}} = 0.0402\)] | 7360 [\(R_{\text{int}} = 0.0628, R_{\text{sigma}} = 0.0342\)] | 6643 [\(R_{\text{int}} = 0.0783, R_{\text{sigma}} = 0.0392\)] |
| Data/restraints/parameters | 7869/0/527 | 7360/0/486 | 6643/0/475 |
| Goodness-of-fit on \(F²\) | 1.046 | 1.084 | 1.034 |
| Final R indexes \([l>2\sigma(l)]\) | \(R₁ = 0.0314, \ wR₂ = 0.0810\) | \(R₁ = 0.0462, \ wR₂ = 0.0941\) | \(R₁ = 0.0354, \ wR₂ = 0.0725\) |
| Final R indexes [all data] | \(R₁ = 0.0396, \ wR₂ = 0.0854\) | \(R₁ = 0.0611, \ wR₂ = 0.1011\) | \(R₁ = 0.0503, \ wR₂ = 0.0803\) |
| 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<sub>a</sub>   | logP | logD<sub>7.4</sub> |
|----------|------------------|------|-------------------|
| 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          | 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                       |
|           | 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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10. NMR Spectra
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