Expanding 3D Space in Medicinal Chemistry: Metallofragments as 3D Scaffolds for Fragment-Based Drug Discovery

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Supporting Information

General Experimental Details

All reagents and solvents were obtained from commercial sources and used without further purification. Microwave reactions were performed in 10 mL or 35 mL microwave vials using a CEM Discover S reactor. Silica gel column chromatography was performed on a CombiFlash Rf Teledyne ISCO system with prepacked silica cartridges or High Performance Gold C18 columns. Reverse phase column chromatography (C18 column) was performed on 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^+ PurIon ESI-MS or APCI-MS detector with 1 Da resolution. ^1H NMR spectra were recorded at ambient temperature on a 400 or 500 MHz Varian FT-NMR instrument located in the Department of Chemistry and Biochemistry at the University of California, San Diego. Some ^1H NMR spectra were recorded at ambient temperature on a 200, 250, 300, or 400 Bruker FT-NMR instrument located in the Department of Chemistry at the Ruhr University in Bochum, Germany. ^1H NMR data is expressed in parts per million (ppm) relative to the residual non-deuterated solvent signals, and spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), m (multiplet), and bs (broad singlet). Available coupling constants (*J*) are reported in hertz (Hz). Mass spectra were obtained at the Molecular Mass Spectrometry Facility (MMSF) in the Department of Chemistry and Biochemistry at the University of California, San Diego. Some mass spectra were obtained in the Department of Chemistry and Biochemistry at the Ruhr University in Bochum, Germany. Further details on synthesis may be found in the following sections of the Supporting Information. The purity of all compounds used in assays was determined to be ≥95% by ^1H NMR spectroscopy and confirmed by mass spectrometry.

Dose response data, collected with PA_N, NDM-1 and Hsp90, were analyzed using a four-parameter logistic model in the mathematics program MATLAB. The uncertainty of the determined IC_{50} values are reported as the 95% confidence interval from the linear regression. To determine the principal moments of inertia (PMI) values for 3D analysis, and to examine possible interactions of mFs with the active sites of the target proteins, PMI calculations and docking studies were carried out using the Molecular Operating Environment (MOE) program (version 2019.0101).[1] Docking calculations were carried out using the triangle matcher method, with 30 poses scored by London dG. Refinement was carried out using the rigid receptor method, with 5 poses scored by GBVI/WSA dG. Ligand efficiency (LE) values were calculated using Equation 1: LE = ΔG/heavy atom count (HAC), approximated as $-RT\ln(IC_{50})/HAC$, or $1.4(pIC_{50})/HAC$.[2]

Synthesis and characterization of metallofragment library

Class A compounds

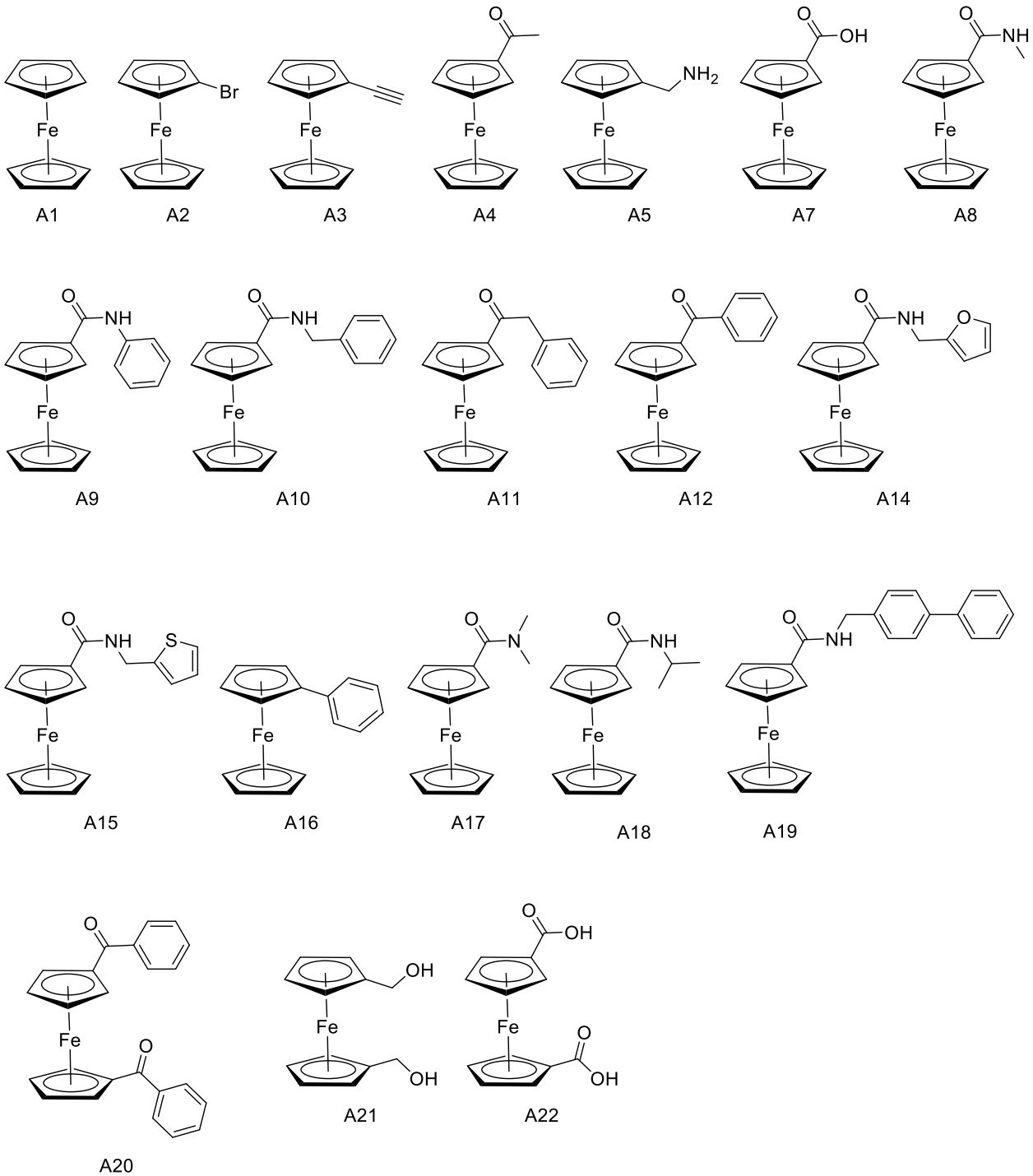


Figure S1. Ferrocene derivatives that comprise the Class **A** metallofragments.

$Fe(\eta^5\text{-}C_5H_5)_2]$ (ferrocene; A1). Compound A1 was purchased from Sigma Aldrich and used without further purification.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4Br)]$ (bromoferrocene; A2). Compound A2 was purchased from Sigma Aldrich and used without further purification.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CCH)]$ (ethynylferrocene; A3). Compound A3 was purchased from Sigma Aldrich and used without further purification.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4COCH_3)]$ (acetylferrocene; A4). Compound A4 was purchased from Sigma Aldrich and used without further purification.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CH_3NH_2)]$ (ferrocenemethylamine; A5). Ferroceneoxime was made from ferrocenecarboxaldehyde following a previously reported procedure.[3] To a solution of ferroceneoxime (214 mg; 0.93 mmol) in 12 mL dry THF in a N_2-flooded Schlenk flask, $LiAlH_4$ (2.4 M in THF; 2.06 mL) was added slowly. The reaction mixture was stirred for 72 h at room temperature, then poured onto ice. Et_2O was added and the resulting gray solid was collected via filtration. The aqueous layer was washed with Et_2O, and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to yield A5. Yield: 174 mg (87%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 4.24 – 4.06 (m, 9H), 3.55 (s, 2H). ESI-MS(+): *m/z* 224.7 $[M+H]^+$.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4COOH)]$ (ferrocenecarboxylic acid; A7). Compound A7 was purchased from Sigma Aldrich and used without further purification.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CONHCH_3)]$ (A8). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydroxybenzotriazole (HOBt) were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and methylamine was added. The reaction mixture was allowed to warm and stir at room temperature for 1 h before the solvent was removed. The product was purified with silica-based column chromatography and then recrystallized from DCM/EtOAc (5:1), yielding orange crystals. Yield: 55%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.74 (bs, 1H), 4.74 (t, J = 1.96 Hz, 2H), 4.32 (t, J = 1.83 Hz, 2H), 4.14 (s, 5H), 2.69 (d, J = 4.65 Hz, 3H). ESI-MS(+): *m/z* 244.22 $[M+H]^+$.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CONHC_6H_5)]$ (A9). EDC and HOBt were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and aniline was added. The reaction mixture was allowed to warm and stir at room temperature for 1 h before the solvent was removed. The product was purified with silica-based column chromatography and then recrystallized from DCM/EtOAc (5:1), yielding orange crystals. Yield: 15%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.44 (s, 1H), 7.68-7.72 (m, 2H), 7.29 - 7.36 (m, 2H), 7.06 (m, 1H), 5.01 (t, J = 1.9 Hz, 2H), 4.45 (t, J = 1.9 Hz, 2H), 4.22 (s, 5H). ESI-MS(+): *m/z* 306.43 $[M+H]^+$.

[Fe(η^5-C_5H_5)(η^5-$C_5H_4CONHCH_2C_6H_5$)] (A10). EDC and HOBt were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and benzylamine was added. The reaction mixture was allowed to warm and stir at room temperature for 1 h before the solvent was removed. The product was purified with silica-based column chromatography and then recrystallized from DCM/EtOAc (5:1), yielding orange crystals. Yield: 65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (t, J = 6.05 Hz, 1H), 7.30 - 7.36 (m, 4H), 7.20 - 7.26 (m, 1H), 4.82 (t, J = 1.9 Hz, 2H), 4.34 - 4.39 (m, 4H), 4.12 (s, 5H). ESI-MS(+): *m/z* 320.29 $[M+H]^+$.

[Fe(η^5-C_5H_5)(η^5-$C_5H_4COCH_2C_6H_5$)] (A11). To a stirred solution of ferrocene in DCM (5 mL) at 0 °C was added $AlCl_3$ in portions. A solution of 2-phenylacetyl chloride in DCM (5 mL) was added dropwise over 1 min while keeping the temperature at 0 °C. After addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated under reduced pressure and purified with silica-based column chromatography using a gradient of 0-100% Hex/EtOAc. Yield: 90%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.28 - 7.38 (m, 4H), 7.20 - 7.27 (m, 1H), 4.88 (t, J = 1.8 Hz, 2H), 4.60 (t, J = 1.8 Hz, 2H), 4.19 (s, 5H), 4.04 (s, 2H). ESI-TOFMS(+): *m/z* 305.0622 $[M+H]^+$.

[Fe(η^5-C_5H_5)(η^5-$C_5H_4COC_6H_5$)] (A12). To a stirred solution of ferrocene in DCM (5 mL) at 0 °C was added $AlCl_3$ in portions. A solution of benzoyl chloride in dichloromethane (5 mL) was added dropwise over 1 min while maintaining the temperature at 0 °C. After addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated under reduced pressure and purified with silica-based column chromatography using a gradient of 0-100% Hex/EtOAc. Yield: 58%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.87 (m, 2H), 7.51-7.64 (m, 3H), 4.83 (m, 2H), 4.70 (m, 2H), 4.25 (s, 5H). ESI-TOFMS(+): *m/z* 291.0467 $[M+H]^+$.

[Fe(η^5-C_5H_5)(η^5-$C_5H_4CONHCH_2C_4OH_3$)] (A14). EDC and HOBt were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and furanylmethylamine was added. The mixture was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. The product was purified with silica-based column chromatography and then recrystallized from DCM/EtOAc (5:1), yielding orange crystals. Yield: 65%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.24 (t, J = 5.87 Hz, 1H), 7.58 (dd, J = 0.86, 1.83 Hz, 1H), 6.41 (dd, J = 1.71, 3.18 Hz, 1H), 6.26 (dd, J = 0.73, 3.18 Hz, 1H), 4.81 (t, J = 1.96 Hz, 2H), 4.37 (d, J = 5.87 Hz, 2H), 4.34 (t, J = 1.96 Hz, 2H), 4.12 (s, 5H). ESI-TOFMS(+): *m/z* 310.0523 $[M+H]^+$. To the best of our knowledge, compound **A14** has not been reported previously in the literature.

[Fe(η^5-C_5H_5)(η^5-$C_5H_4CONHCH_2C_4SH_3$)] (A15). EDC and HOBt were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and thiophenylmethylamine was added. The mixture was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. The product was purified with silica-based column chromatography and then recrystallized from DCM/EtOAc (5:1), yielding orange crystals. Yield: 71%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.44 (t, J = 5.99 Hz, 1H), 7.40 (dd, J = 1.34, 5.01 Hz, 1H), 7.02 (dd, J = 1.22, 3.42 Hz, 1H), 6.97

(dd, J = 3.55, 5.01 Hz, 1H), 4.81 (t, J = 1.96 Hz, 2H), 4.53 (d, J = 5.62 Hz, 2H), 4.35 (t, J = 1.96 Hz, 2H), 4.12 (s, 5H). ESI-TOFMS(+): *m/z* 326.0295 $[M+H]^+$.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4C_6H_5)]$ (phenylferrocene; A16). Aniline (1.2 mmol), H_2O (2 ml) and concentrated HCl (2 ml) were combined in a round-bottom flask and cooled to 0 – 5 °C. While maintaining the temperature of the solution below 5 °C, 0.1 g $NaNO_2$ in 2 ml H_2O was added dropwise. After the addition, the mixture was stirred for 1–1.5 h at 5 °C. Adequate urea was added to decompose the surplus HNO_2. Then, again keeping the temperature below 5 °C, a solution of ferrocene (in 5 ml ether) and 0.1 g cetrimonium bromide (CTAB, $C_{16}H_{33}N(CH_3)_3Br$) was added dropwise over 5 mins with stirring. The solution was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure, and the product was purified with silica-based column chromatography using EtOAc/Hex (gradient 0-10%). Yield: 18%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.53 (m, 2H), 7.29 (m, 2H), 7.18 (m, 1H), 4.78 (m, 2H), 4.34 (m, 2H), 4.01 (s, 5H). ESI-MS(+): *m/z* 262.46 $[M+H]^+$.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CON(CH_3)_2)]$ (A17). EDC and HOBt were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and dimethylamine was added. The mixture was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. The product was purified with silica-based column chromatography and then recrystallized from DCM/EtOAc (5:1), yielding orange crystals. Yield: 76%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.60 (t, J = 1.83 Hz, 2H), 4.36 (t, J = 1.96 Hz, 2H), 4.22 (s, 5H), 2.7-3.25 (bd, 6H). ESI-MS(+): *m/z* 258.20 $[M+H]^+$.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CONCH(CH_3)_2)]$ (A18). EDC and HOBt were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and isopropylamine was added. The mixture was stirred for 1 h at room temperature before the solvent was removed under reduced pressure. The product was purified with silica-based column chromatography and then recrystallized from DCM/EtOAc (5:1), yielding orange crystals. Yield: 72%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.47 (d, J = 7.83 Hz, 1H), 4.80 (m, 2H), 4.31 (m, 2H), 4.13 (s, 5H), 3.98 - 4.08 (m, 1H), 1.13 (d, J = 6.60 Hz, 6H). ESI-MS(+): *m/z* 272.17 $[M+H]^+$.

$[Fe(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CONHCH_2C_6H_4C_6H_5)]$ (A19). EDC and HOBt were added to a suspension of ferrocenecarboxylic acid in DCM (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to 0 °C and (biphenyl-4-yl)methylamine was added. The mixture was stirred for 72 h at room temperature before the solvent was removed under reduced pressure. The product was purified with silica-based column chromatography using a gradient of 0-100% Hex/EtOAc. Yield: 40 %. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.37 (t, J = 6.0 Hz, 1H), 7.62 (d, J = 8.1 Hz, 4H), 7.41 (t, J = 7.8 Hz, 4H), 7.31 (t, J = 7.4 Hz, 1H), 4.81 (t, J = 1.8 Hz, 2H), 4.39 (d, J = 6.0 Hz, 2H), 4.34 – 4.32 (m, 2H), 4.11 (s, 5H). *m/z* 396.24 $[M+H]^+$.

$[Fe(\eta^5\text{-}C_5H_4COC_6H_5)_2]$ (A20). To a stirred solution of ferrocene in DCM (5 mL) at 0 °C was added $AlCl_3$ in portions. A solution of benzoyl chloride in dichloromethane (5 mL) was added dropwise over 1 min while keeping the temperature at 0 °C. After addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated

under reduced pressure and purified with silica-based column chromatography using a gradient of 0-100% Hex/EtOAc. Yield: 26%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.69 - 7.81 (m, 4H), 7.56 - 7.64 (m, 2H), 7.42 - 7.54 (m, 4H), 4.78 - 4.94 (m, 4H), 4.62 - 4.77 (m, 4H). ESI-TOFMS(+): *m/z* 395.0727 $[M+H]^+$.

[Fe(η^5-$C_5H_4CH_2OH)_2$] (1,1'-ferrocenedimethanol; A21). Compound A21 was purchased from Sigma Aldrich and used without further purification.

[Fe(η^5-$C_5H_4COOH)_2$] (1,1'-ferrocenedicarboxylic acid; A22). Compound A22 was purchased from Sigma Aldrich and used without further purification.

Class B compounds

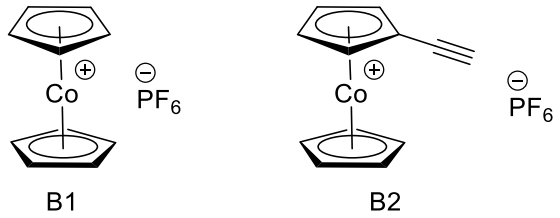


Figure S2. Cobaltocene scaffolds that comprise the Class **B** metallofragments.

$[Co(\eta^5\text{-}C_5H_5)_2]^+[PF_6]^-$ (cobaltocenium hexafluorophosphate; B1). Compound B1 was purchased from Sigma Aldrich and used without further purification.

$[Co(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4CCH)]^+[PF_6]^-$ (B2). Compound B2 was synthesized following a previously reported procedure.[4] ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.19 (t, J = 2.1 Hz, 2H), 5.91 (t, J = 2.0 Hz, 2H), 5.88 (s, 5H), 4.71 (s, 1H). ESI-MS(+): *m/z* 212.7 $[M+H]^+$.

Class C compounds

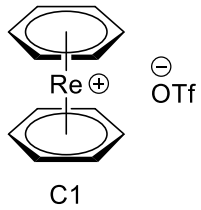


Figure S3. The rhenium sandwhich complex that comprises Class **C**.

$[Re(\eta^6\text{-}C_6H_6)_2]^+[OTf]^-$ (Bis(arene)rhenium triflate; C1). Compound C1 was synthesized following a previously reported procedure.[5] ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.04 (s, 12H). ESI-MS(+): *m/z* 342.5 $[M+H]^+$.

Class D compounds

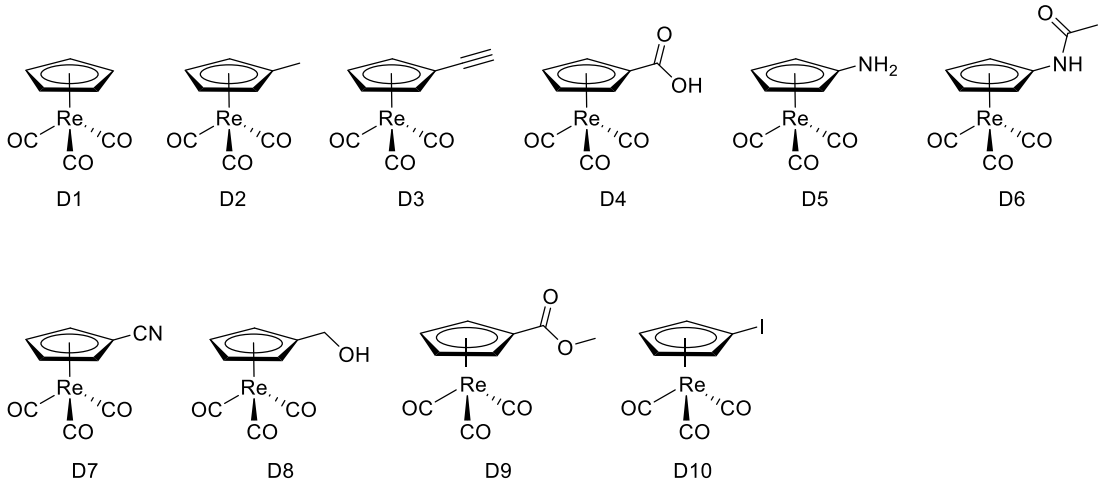


Figure S4. Rhenium piano-stool scaffolds that comprise the Class **D** metallofragments.

Note: Mass spectra could not be obtained for most Class D compounds.

[Re(η^5-C_5H_5)$(CO)_3$] (D1). Compound D1 was purchased from commercial sources and used without further purification.

[Re(η^5-$C_5H_4CH_3$)$(CO)_3$] (D2). Compound D2 was synthesized following a previously reported procedure.[6] ^{1}H NMR (200 MHz, Chloroform-d_1): δ 5.23 (s, 4H), 2.23 (s, 3H).

[Re(η^5-C_5H_4CCH)$(CO)_3$] (D3). To make the Re(Cp-acetylene-TMS)$(CO)_3$ precursor, compound D10 (121 mg; 0.26 mmol) and TMS-acetylene (0.05 mL; 0.38 mmol) were dissolved in 3.5 mL of a mixture of NEt_3/DMF/THF (0.5/1/2). The mixture was degassed by three freeze-pump-thaw cycles before $Pd(MeCN)_2Cl_2$ (5 mol%) and CuI (10 mol%) were added. The reaction mixture stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and Re(Cp-acetylene-TMS)$(CO)_3$ was purified with silica-based column chromatography using PE/EtOAc (20:1) as eluent. Yield: 84 mg (76%). To make compound D3, Re(Cp-acetylene-TMS)$(CO)_3$ (81 mg; 0.19 mmol) and K_2CO_3 (29 mg; 0.21 mmol) were diluted with 2 mL MeOH, and the white suspension stirred for 3 h at room temperature. After the addition of 4 mL H_2O, the product was extracted with Et_2O. Yield: 61 mg (90%). ^{1}H NMR (300 MHz, Chloroform-d_1): δ 5.66 (t, J = 2.2 Hz, 2H), 5.28 (t, J = 2.2 Hz, 2H), 2.82 (s, 1H).

[Re(η^5-C_5H_4COOH)$(CO)_3$] (D4). Compound D1 (110 mg; 0.33 mmol) was dissolved in 6 mL dry THF in a N_2-flooded Schlenk flask, and the solution was cooled to -78 °C. After the slow addition of n-BuLi (1.6 M in n-hexane; 0.31 mL), the reaction mixture was kept cooled and stirred for 1 h. CO_2 was bubbled through the mixture while it was allowed to warm up very slowly over several hours. The reaction was quenched with water, and the aqueous layer was washed with Et_2O. The pH of the aqueous layer was adjusted to 1 with 1 M HCl, and the product was extracted with Et_2O. Yield: 41 mg (33%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.22 (t, J = 1.9 Hz, 2H), 5.75 (t, J = 1.9 Hz, 2H). EI-MS(+): *m/z* 379.9 [M].

[Re(η⁵-$C_5H_4NH_2$)$(CO)_3$] (D5). Compound D5 was synthesized following a previously reported procedure.[6] After extraction, the product was purified with silica-based column chromatography using PE/EtOAc (10:1) as the eluent. Solvent was evaporated from the product under reduced pressure, and the product was recrystallized by slow evaporation of a mixture of DCM/n-hexane. ^{1}H NMR (200 MHz, Chloroform-d_1): δ 5.05 (t, J = 2.2 Hz, 2H), 4.92 (t, J = 2.2 Hz, 2H), 3.28 (s, 2H). EI-MS(+): *m/z* 350.9 [M].

Re(η⁵-$C_5H_4NCOCH_3$)$(CO)_3$ (D6). Compound D6 was synthesized following a previously reported procedure.[7] ^{1}H NMR (200 MHz, Chloroform-d_1): δ 6.90 (s, 1H), 5.69 (q, J = 2.0 Hz, 2H), 5.19 (q, J = 2.0, 2H), 2.07 (s, 3H). ESI-TOFMS(+): *m/z* 394.0081 $[M+H]^+$.

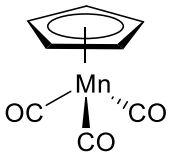
[Re(η⁵-C_5H_4CN)$(CO)_3$] (D7). Re(η⁵-C_5H_4COH)$(CO)_3$ was synthesized following a previously reported procedure with some modification.[8] To make the Re(η⁵-C_5H_4COH)$(CO)_3$ precursor, compound D1 (200 mg; 0.60 mmol) was dissolved in 12 mL dry THF in a N_2-flooded Schlenk flask, and the solution was cooled to -78 °C. After the slow addition of n-BuLi (1.6 M in n-hexane; 0.56 mL), the reaction mixture was kept cool and stirred for 35 min. Dry DMF (0.11 mL; 1.49 mmol) was added, and the mixture was stirred first for 1.5 h at -78 °C and then for 1 h at -5 °C. The reaction was quenched with saturated aqueous NH_4Cl (3 mL). The aqueous phase was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. Purification of Re(η⁵-C_5H_4COH)$(CO)_3$ was performed with silica-based column chromatography using DCM/PE (1:2) as eluent. Yield: 169 mg (78%). Compound D7 was synthesized following a previously reported procedure with some modification.[9] To Re(η⁵-C_5H_4COH)$(CO)_3$ (169 mg; 0.47 mmol) and $NH_2OH{\cdot}HCl$ (48 mg; 0.70 mmol) was added 6 mL of formic acid. The mixture was stirred for 30 min at 80 °C. After cooling to ambient temperature, it was poured onto ice. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure. The compound was dissolved in DCM, and the organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure, and the product was purified with silica-based column chromatography using DCM/n-hexane (1:1) as the eluent. Yield: 72 mg (41%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 5.91 (t, J = 2.3 Hz, 2H), 5.42 (t, J = 2.3 Hz, 2H).

[Re(η⁵-$C_5H_4CH_2OH$)$(CO)_3$] (D8). Re(η⁵-C_5H_4COH)$(CO)_3$ was synthesized following a previously reported procedure with some modification, as described for D7.[8] To make compound D8, Re(η⁵-C_5H_4COH)$(CO)_3$ (130 mg; 0.36 mmol) was dissolved in 6 mL dry Et_2O in a N_2-flooded Schlenk flask at 0 °C, and $LiAlH_4$ (7 mg; 0.18 mmol) was added. The reaction mixture stirred for 1 h at 0 °C and 1.5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (3 mL), and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure, and the product was purified with silica-based column chromatography using DCM as the eluent. Yield: 86 mg (66%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 5.31 (t, J = 2.2 Hz, 2H), 5.45 (t, J = 2.2 Hz, 2H), 4.44 (d, J = 5.2 Hz, 2H).

[Re(η^5-$C_5H_4COOCH_3$)$(CO)_3$] (D9). Compound D1 (100 mg; 0.30 mmol) was dissolved in 12 mL dry THF in a N_2-flooded Schlenk flask, and the solution was cooled to -78 °C. After the slow addition of n-BuLi (1.6 M in n-hexane; 0.22 mL), the reaction mixture was kept cooled and stirred for 30 min. Methyl chloroformate (0.03 mL; 0.43 mmol) was added, and the mixture stirred first for 1.5 h at -78 °C, then for 1 h at -5 °C. The reaction was quenched with saturated aqueous NH_4Cl (3 mL). The aqueous phase was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and purification of the product was done with silica-based column chromatography using DCM/n-hexane (1:3) as the eluent. Yield: 114 mg (98%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 6.10 – 5.91 (m, 2H), 5.43 – 5.30 (m, 2H), 3.81 (s, 3H).

[Re(η^5-C_5H_4I)$(CO)_3$] (D10). $ReCp(CO)_3$ (125 mg; 0.37 mmol) was dissolved in 10 mL dry THF in a N_2-flooded Schlenk flask, and the solution was cooled to -78 °C. After the addition of n-BuLi (1.6 M in n-hexane; 0.35 mL), the reaction mixture was kept cooled and stirred for 1 h. I_2 (142 mg; 0.56 mmol) was dissolved in 3 mL dry THF and slowly added to the reaction mixture. The mixture was allowed to warm gradually to reach room temperature and then continued to stir overnight. The reaction was quenched with 3 mL of a saturated aqueous NH_4Cl solution, extracted with Et_2O, and washed with brine. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Purification was performed with silica-based column chromatography using n-hexane/EtOAc (20:1) as the eluent. Yield: 121 mg (70%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 5.61 (t, J = 2.2 Hz, 2H), 5.27 (t, J = 2.2 Hz, 2H).

Class E compounds



E1

Figure S5. The manganese tricarbonyl complex is the Class **E** metallofragment.

[Mn(η^5-C_5H_5)$(CO)_3$] (E1). Compound E1 was purchased from commercial sources and used without further purification.

Class F compounds

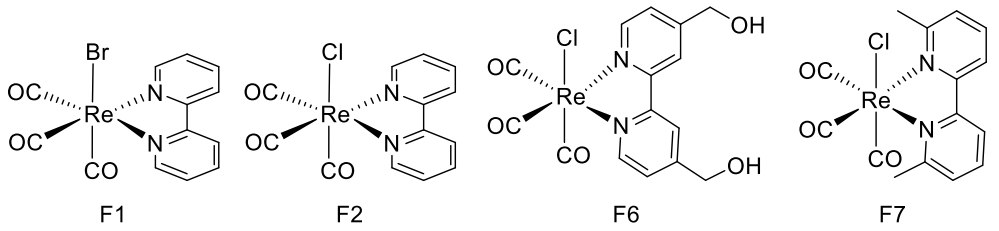


Figure S6. Rhenium tricarbonyl scaffolds that comprise the Class **F** metallofragments.

[Re(2,2'-bipyridine)Br(CO)$_3$] (F1). $Re(CO)_5Br$ (50 mg; 0.14 mmol) and 2,2'-bipyridine (27 mg; 0.15 mmol) were suspended in 5 mL toluene (stored over molecular sieves). The suspension was saturated with N_2 and stirred overnight at 60 °C before the solvent was evaporated under reduced pressure. The residue was dissolved in DCM, and MeOH was added to the solution. The DCM was slowly evaporated under reduced pressure until the product started to precipitate. The yellow crystalline product was collected via filtration. Yield: 66 mg (97%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (d, J = 5.3 Hz, 2H), 8.77 (d, J = 8.1 Hz, 2H), 8.33 (td, J = 8.0 Hz, 1.6 Hz, 2H), 7.83 – 7.70 (m, 2H). ESI-TOFMS(+): *m/z* 523.9589 $[M+NH_4]^+$, 528.9142 $[M+Na]^+$.

[Re(2,2'-bipyridine)Cl(CO)$_3$] (F2). $Re(CO)_5Cl$ (50 mg; 0.14 mmol) and 2,2'-bipyridine (27 mg; 0.15 mmol) were suspended in 5 mL toluene (stored over molecular sieves). The suspension was saturated with N_2 and stirred overnight at 60 °C before the solvent was evaporated under reduced pressure. The residue was dissolved in DCM, and MeOH was added to the solution. The DCM was slowly evaporated under reduced pressure until the product started to precipitate. The yellow crystalline product was collected via filtration. Yield: 66 mg (97%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 9.02 (d, J = 5.2 Hz, 2H), 8.77 (d, J = 8.1 Hz, 2H), 8.34 (td, J = 7.9 Hz, 1.3 Hz, 2H), 7.76 (m, 2H). ESI-TOFMS(+): *m/z* 427.0084 $[M-Cl]^+$.

[Re([2,2'-bipyridine]-4,4'-diyldimethanol)Cl(CO)$_3$] (F6). $Re(CO)_5Cl$ (50 mg; 0.14 mmol) and [2,2'-bipyridine]-4,4'-diyldimethanol (31 mg; 0.15 mmol) were suspended in 5 mL toluene (stored over molecular sieves). The suspension was saturated with N_2 and stirred overnight at 60 °C before the solvent was evaporated under reduced pressure. The resulting residue was suspended in a mixture of DCM and MeOH and was sonicated for 0.5 h. The yellow powdery product was collected via filtration. Yield: 48 mg (67%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.94 (d, J = 5.7 Hz, 2H), 8.61 (d, J = 1.6 Hz, 2H), 7.69 (dd, J = 5.7, 1.6 Hz, 2H), 5.81 (t, J = 5.7 Hz, 2H), 4.77 (d, J = 5.7 Hz, 4H). ESI-MS(+): *m/z* 544.93 $[M+Na]^+$. ESI-MS(-): *m/z* 520.95 $[M-H]^-$.

[Re(6,6'-dimethyl-2,2'-bipyridine)Cl(CO)$_3$] (F7). $Re(CO)_5Cl$ (50 mg; 0.14 mmol) and 6,6'-dimethyl-2,2'-bipyridine (27 mg; 0.15 mmol) were suspended in 5 mL toluene (stored over molecular sieves). The suspension was saturated with N_2 and stirred overnight at 60 °C before the solvent was evaporated under reduced pressure. The residue was dissolved in DCM, and

MeOH was added to the solution. The DCM was slowly evaporated under reduced pressure until the product started to precipitate. The yellow crystalline product was collected via filtration. Yield: 66 mg (97%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.99 (dd, J = 7.7, 1.0 Hz, 2H), 7.89 (t, J = 7.9 Hz, 2H), 7.45 (dd, J = 7.7, 1.2 Hz, 2H), 3.13 (s, 6H). ESI-MS(+): m/z 513.00 $[M+Na]^+$, 455.17 $[M-Cl]^+$.

Class G compounds

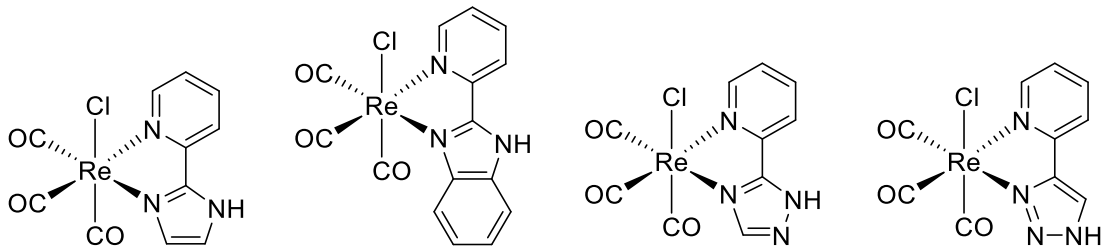


Figure S7. Rhenium tricarbonyl scaffolds that comprise the Class **G** metallofragments.

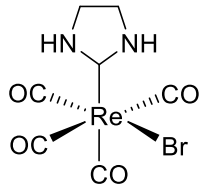
[Re(2-(1*H*-imidazol-2-yl)pyridine)Cl(CO)$_3$] (G1). $Re(CO)_5Cl$ (50 mg; 0.14 mmol) and 2-(1*H*-imidazol-2-yl)pyridine (21 mg; 0.15 mmol) were suspended in 5 mL toluene (stored over molecular sieves). The suspension was saturated with N_2 and stirred overnight at 60 °C. The solvent was evaporated under reduced pressure, and the yellow residue was washed with pentane and dried in vacuo. Recrystallization from hot acetone gave the product as yellow crystals. Yield: 61 mg (98%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.90 (d, J = 5.4 Hz, 1H), 8.34 – 8.21 (m, 2H), 7.69 (d, J = 1.3 Hz, 1H), 7.62 (ddd, J = 7.3, 5.4, 1.8 Hz, 1H), 7.50 (d, J = 1.4 Hz, 1H). ESI-MS(+): m/z 416.04 $[M\text{-}Cl]^-$, 433.66 $[M\text{-}Cl+NH_3]$.

[Re(2-(1*H*-benzimidazol-2-yl)pyridine)Cl(CO)$_3$] (G2). $Re(CO)_5Cl$ (50 mg; 0.14 mmol) and 2-(1*H*-benzimidazol-2-yl)pyridine (28 mg; 0.15 mmol) were suspended in 5 mL toluene (stored over molecular sieves). The suspension was saturated with N_2 and stirred overnight at 60 °C. The solvent was evaporated under reduced pressure, and the yellow residue was washed with pentane and dried in vacuo. Recrystallization from hot acetone gave the product as yellow crystals. Yield: 62 mg (90%). ^{1}H NMR (500 MHz, Methanol-d_4): δ 9.10 (dt, J = 5.5, 1.2 Hz, 1H), 8.41 – 8.34 (m, 1H), 8.30 (td, J = 7.8, 1.5 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.76 – 7.68 (m, 2H), 7.57 – 7.50 (m, 2H). ESI-MS(+): m/z 466.04 $[M\text{-}Cl]^-$, 433.66 $[M\text{-}Cl+NH_3]$.

[Re(2-(1*H*-1,2,4-triazol-5-yl)pyridine)Cl(CO)$_3$] (G3). $Re(CO)_5Cl$ (50 mg; 0.14 mmol) and 2-(1*H*-1,2,4-triazol-5-yl)pyridine (21 mg; 0.15 mmol) were suspended in 5 mL toluene (stored over molecular sieves). The suspension was saturated with N_2 and stirred overnight at 60 °C. The solvent was evaporated under reduced pressure, and the residue was suspended in acetone. The suspension was filtered, and hexane was added slowly to the filtrate. The resulting precipitate was collected via filtration and was re-dissolved in a mixture of acetone and H_2O. The acetone was slowly evaporated under reduced pressure until a white solid started to precipitate. The precipitate was collected via filtration and evaporated to dryness. The product was recrystallized from acetone. Yield: 15 mg (24%). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.47 (s, 1H), 9.07 (ddd, J = 5.5, 1.5, 0.9 Hz, 1H), 8.39 (dt, J = 8.0, 1.2 Hz, 1H), 8.34 (td, J = 7.7, 1.5 Hz, 1H), 7.84 – 7.76 (m, 1H). ESI-MS(+): m/z 417.14 $[M\text{-}Cl]^+$ 434.70 $[M\text{-}Cl+H_2O]^+$. To the best of our knowledge, compound **G3** has not been reported previously in the literature

[Re(2-(1*H*-1,2,3-triazol-5-yl)pyridine)Cl(CO)$_3$] (G4). $Re(CO)_5Cl$ (50 mg; 0.14 mmol) and 2-(1*H*-1,2,3-triazol-5-yl)pyridine (21 mg; 0.15 mmol) were suspended in 3 mL acetone. The suspension was heated to 60 °C overnight. The solvent was evaporated under reduced pressure, and the residue was purified with silica-based column chromatography using DCM/MeOH as eluent (3 min 0% MeOH, 22 min 0-10.1% MeOH, 3.4 min 10.1% MeOH). Yield: 18 mg (29%). ^{1}H NMR (500 MHz, Acetone-d_6): δ 9.13 (s, 1H), 9.06 (dt, J = 5.6, 1.1 Hz, 1H), 8.33 (dt, J = 7.9, 1.2 Hz, 1H), 8.27 (td, J = 7.7, 1.4 Hz, 1H), 7.67 (ddd, J = 7.4, 5.6, 1.4 Hz, 1H). ESI-MS(+): m/z 417.02 $[M\text{-}Cl]^+$ 434.69 $[M\text{-}Cl+H_2O]^+$. ESI-MS(-): m/z 451.03 $[M\text{-}H]^-$. To the best of our knowledge, compound **G4** has not been reported previously in the literature.

Class H compounds



H1

Figure S8. Rhenium tricarbonyl scaffold that is the Class **H** metallofragment.

[Re(imidazolidine)Br(CO)$_3$] (H1). Compound H1 was synthesized following a previously reported procedure.[10] ^{1}H NMR (200 MHz, Chloroform-d_1): δ 6.87 (bs, 2H), 3.78 (s, 4H). ESI-TOFMS(+): *m/z* 465.9398 $[M+NH_4]^+$, 470.8937 $[M+Na]^+$.

Class I compounds

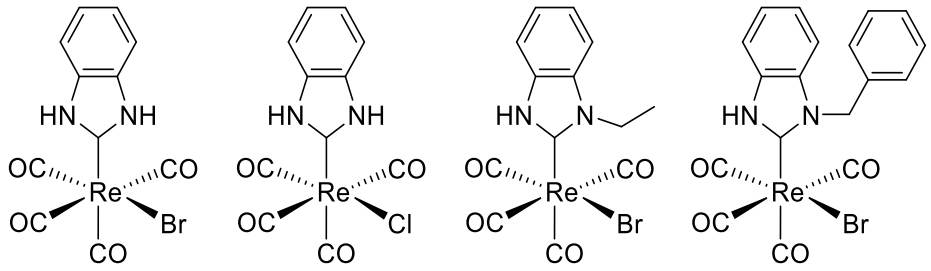


Figure S9. Rhenium tricarbonyl scaffolds that comprise the Class **I** metallofragments.

[Re(2,3-dihydro-1*H*-benzo[d]imidazole)Br(CO)$_3$] (I1). To make the 2-((triphenyl-λ^5-phosphaneylidene)amino)aniline ligand, 2-azidoaniline (224 mg, 1.67 mmol, 1 eq.) was dissolved in toluene in a nitrogen atmosphere. After 10 minutes the reaction mixture was treated with a solution of triphenylphosphine (440 mg, 1.7 mmol, 1.02 eq.) in toluene. The solution was stirred for 20 h at room temperature before the solvent was removed under reduced pressure, and the crude foamy product was purified by silica-based column chromatography using hexanes/EtOAc (4:1 to 0:1) as the eluent. The ligand was obtained as an orange crystalline solid and dried under reduced pressure. Yield: 550 mg (89%). ^{1}H NMR (250 MHz, Chloroform-d_1): δ 7.82 – 7.72 (m, 6H), 7.56 – 7.42 (m, 9H), 6.75 – 6.70 (m, 1H), 6.60 – 6.52 (m, 1H), 6.41 – 6.31 (m, 2H), 4.36 (bs, 2H). ESI-MS(+): *m/z* 369.0 $[M+H]^+$.

The following synthetic procedure for compound I1 was originally published elsewhere.[11] Under a nitrogen atmosphere, bromopentacarbonylrhenium(I) (220 mg, 0.54 mmol, 1 eq.) and 2-((triphenyl-λ^5-phosphaneylidene)amino)aniline (200 mg, 0.54 mmol, 1 eq.) were dissolved in toluene and stirred for 24 h at ambient temperature. The solvent was removed under reduced pressure, and the crude product was purified by silica-based column chromatography using hexanes/EtOAc (9:1) as the eluent. The product was obtained as an off-white solid and dried under reduced pressure. Yield: 230 mg (86%). ^{1}H NMR (200 MHz, DCM-d_2): δ 10.54 (bs, 2H), 7.59 – 7.53 (m, 2H), 7.42 – 7.35 (m, 2H). EI-MS(+): *m/z* 495.8 $[M]^+$.

[Re(2,3-dihydro-1*H*-benzo[d]imidazole)Cl(CO)$_3$] (I2). Under a nitrogen atmosphere, pentacarbonylchlororhenium(I) (300 mg, 0.83 mmol, 1 eq.) and 2-((triphenyl-λ^5-phosphaneylidene)amino)aniline (305 mg, 0.83 mmol, 1 eq.) were dissolved in toluene and stirred for 18 h at ambient temperature. The solvent was removed under reduced pressure, and the crude product was purified by silica-based column chromatography using PE:EtOAc (4:1) as the eluent. The desired product was obtained as a beige solid and dried under reduced pressure. Yield: 282 mg (75%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 10.58 (bs, 2H), 7.58 – 7.50 (m, 2H), 7.42 – 7.34 (m, 2H). ESI-TOFMS(+): *m/z* 469.9899 $[M+NH_4]^+$, 474.9452 $[M+Na]^+$.

[Re(1-ethyl-2,3-dihydro-1*H*-benzo[d]imidazole)Br(CO)$_3$] (I3). To make the *N*-ethyl-2-((triphenyl-λ^5-phosphaneylidene)amino)aniline ligand, 2-azido-N-ethylaniline (166 mg, 1 mmol, 1 eq.) was dissolved in toluene in a nitrogen atmosphere. The reaction mixture was treated with a solution of triphenylphosphine (268 mg, 1 mmol, 1 eq.) in toluene. The solution was stirred for 20 h at room temperature. Subsequently, the solvent was removed under reduced pressure, and the crude product was purified by silica-based column chromatography using DCM as the eluent. The product was obtained as an orange crystalline solid. Yield: 190 mg (48%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 7.81-7.72 (m, 6H), 7.56-7.41 (m, 9H), 6.70-6.64 (m, 1H), 6.59-6.54 (m, 1H), 6.42-6.38 (m, 1H), 6.33-6.27 (m, 1H), 4.99 (bs, 1H), 3.24 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ESI-MS(+): *m/z* 397.0 [M+H]$^+$.

The following synthetic procedure for compound I3 was originally published elsewhere.[11] Under a nitrogen atmosphere, *N*-ethyl-2-((triphenyl-λ^5-phosphaneylidene)amino)aniline (160 mg, 0.4 mmol, 1 eq.) was dissolved in dry toluene (8 ml) and treated with rheniumpentacarbonylbromide (166 mg, 0.4 mmol, 1 eq.). The orange solution was stirred for 18 h at room temperature. Subsequently, the solvent was removed under reduced pressure, and the beige crude product was purified by silica-based column chromatography using hexanes:EtOAc (4:1) as the eluent. The product was obtained as a beige crystalline solid. Yield: 127 mg (60%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 11.19 (bs, 1H), 7.55 – 7.47 (m, 2H), 7.41 – 7.35 (m, 2H), 4.52 (q, J = 7.2 Hz, 2H), 1.56 (t, J = 7.2 Hz, 3H). ESI-TOFMS(+): *m/z* 445.0199 [M-HBr]$^+$, 541.9690 [M+NH$_4$]$^+$.

[Re(1-benzyl-2,3-dihydro-1*H*-benzo[d]imidazole)Br(CO)$_3$] (I4). To make the *N*-benzyl-2-((triphenyl-λ^5-phosphaneylidene)amino)aniline ligand, 2-azido-N-benzylaniline (200 mg, 0.9 mmol, 1 eq.) was dissolved in toluene under a nitrogen atmosphere and treated with a solution of triphenylphosphine (239 mg, 0.91 mmol, 1.05 eq.) in toluene. The solution was stirred for 24 h at room temperature. Subsequently, the solvent was removed under reduced pressure, and the crude product was purified by silica-based column chromatography using hexanes/EtOAc (4:1) as the eluent. The product was obtained as an orange solid and dried under reduced pressure. Yield: 310 mg (75%). ^{1}H NMR (250 MHz, Chloroform-d_1): δ 7.91-7.80 (m, 6H), 7.65-7.48 (m, 11H), 7.45-7.28 (m, 3H), 6.67-6.57 (m, 2H), 6.50-6.44 (m, 1H), 6.37-6.29 (m, 1H), 5.50 (bs, 1H), 4.54 (s, 2H). ESI-MS(+): *m/z* 458.9 [M+H]$^+$.

The following synthetic procedure for compound I4 was originally published elsewhere.[11] Under a nitrogen atmosphere, bromopentacarbonylrhenium(I) (112 mg, 0.28 mmol, 1 eq.) and *N*-benzyl-2-((triphenyl-λ^5-phosphaneylidene)amino)aniline (126 mg, 0.28 mmol, 1 eq.) were dissolved in THF and stirred for 24 h at room temperature. The solvent was removed in vacuo and the crude product was purified by silica-based column chromatography using hexanes/EtOAc (4:1) as the eluent. The product was obtained as a grey solid and dried under reduced pressure. Yield: 137 mg (85%). ^{1}H NMR (200 MHz, Chloroform-d_1): δ 11.35 (s, 1H), 7.54 – 7.50 (m, 1H), 7.36 – 7.21 (m, 6H), 7.04 – 7.00 (m, 2H), 5.67 (s, 2H).

Class J compounds

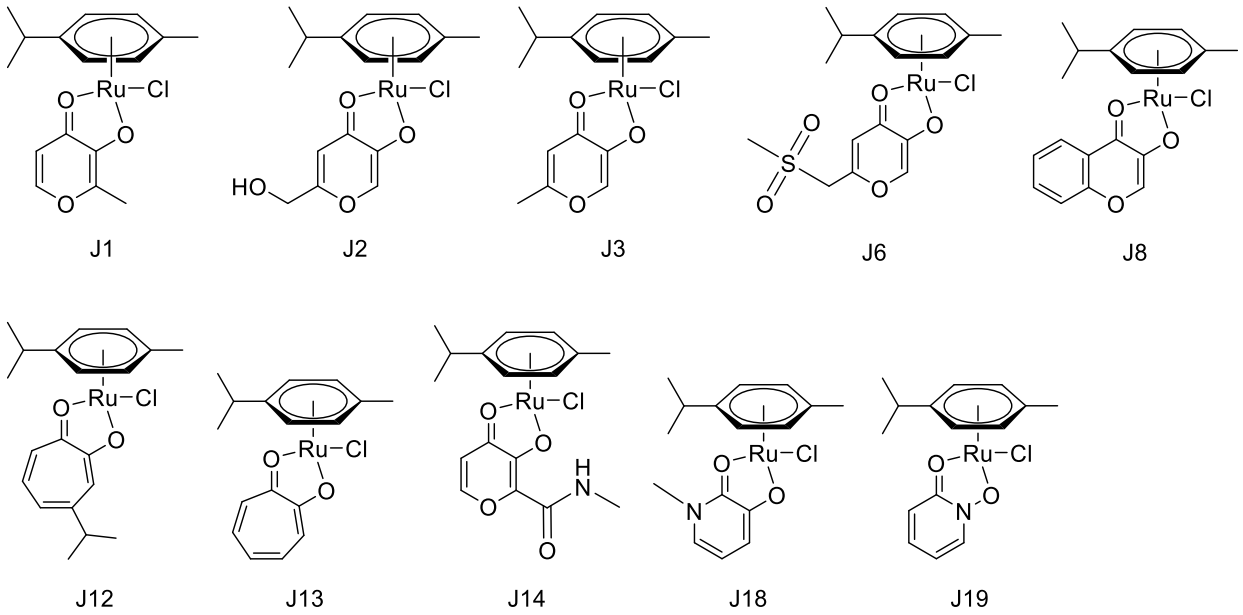


Figure S10. Ruthenium piano-stool scaffolds that comprise the Class **J** metallofragments.

[Ru(η^6-*p*-cymene)Cl(maltol)] (J1). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of maltol (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 56.0 mg (78%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.55 (d, J = 5.1 Hz, 1H), 6.50 (d, J = 5.1 Hz), 5.53 – 5.49 (m, 2H), 5.32 – 5.27 (m, 2H), 2.91 – 2.88 (m, 1H), 2.41 (s, 3H), 2.32 (s, 3H), 1.34 – 1.29 (m, 6H). ESI-MS(+): m/z = 361.23 [M-Cl]$^+$.

[Ru(η^6-*p*-cymene)Cl(6-(hydroxymethyl)-4-oxo-4*H*-pyran-3-olate)] (J2). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 47.8 mg (64%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.68 (s, 1H), 6.63 (s, 1H), 5.54 – 5.51 (m, 2H),

5.31 (s, 2H), 4.44 (s, 2H), 2.92 – 2.90 (m, 1H), 2.70 (s, 1H), 2.30 (s, 3H), 1.33 – 1.29 (m, 6H). ESI-MS(+): m/z = 377.23 $[M\text{-}Cl]^+$.

[Ru(η^6-*p*-cymene)Cl(allomaltol)] (J3). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of allomaltol (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 44.3 mg (62%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.62 (s, 1H), 6.30 (s, 1H), 5.49 (t, J = 6.6 Hz, 2H), 5.28 (d, J = 5.9 Hz, 2H), 2.91 – 2.85 (m, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 1.28 (dd, J = 6.6, 4.5 Hz, 6H). ESI-MS(+): m/z = 361.25 $[M\text{-}Cl]^+$.

[Ru(η^6-*p*-cymene)Cl(6-(methylsulfonyl)-4-oxo-4H-pyran-3-olate)] (J6). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of 5-hydroxy-2-(methylsulfonyl)-4*H*-pyran-4-one (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 18.4 mg (25%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.76 (s, 1H), 6.67 (s, 1H), 5.56 (t, J = 4.6 Hz, 2H), 5.34 (dd, J = 5.1, 3.9 Hz, 2H), 4.18 (d, J = 2.9 Hz, 2H), 2.96 (s, 2H), 2.31 (s, 3H), 1.35 – 1.33 (dd, J = 6.9, 0.8 Hz, 6H). ESI-MS(+): m/z = 439.00 $[M\text{-}Cl]^+$. To the best of our knowledge, compound **J6** has not been reported previously in the literature

[Ru(η^6-*p*-cymene)Cl(4-oxo-4*H*-chromen-3-olate)] (J8). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of 3-hydroxy-4*H*-chromen-4-one (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 18.8 mg (24%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 8.82 (dd, J = 8.2, 1.5 Hz, 1H), 7.93 (s, 1H), 7.60 (ddd, J = 8.6, 7.0, 1.6 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.34 (ddd, J = 8.1, 7.1, 0.9 Hz, 1H), 5.65 – 5.59 (m, 2H), 5.40 (t, J = 4.8 Hz, 2H), 2.99 – 2.94 (m, 1H), 2.36 (s, 3H), 1.37 – 1.33 (m, 6H). ESI-MS(+): m/z = 397.21

$[M\text{-}Cl]^+$. To the best of our knowledge, compound **J8** has not been reported previously in the literature

[Ru(η^6-*p*-cymene)Cl(3-isopropyl-7-oxocyclohepta-1,3,5-trien-1-olate)] (J12). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of 2-hydroxy-4-isopropylcyclohepta-2,4,6-trien-1-one (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 66.4 mg (84%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.21 (d, J = 1.5 Hz, 1H), 7.11 – 7.09 (m, 2H), 6.73 – 6.66 (m, 1H), 5.53 (t, J = 6.7 Hz, 2H), 5.32 (t, J = 5.9 Hz, 2H), 2.90 (dt, J = 13.8, 6.9 Hz, 1H), 2.73 (dt, J = 13.7, 6.9 Hz, 1H), 2.32 (d, J = 2.7 Hz, 3H), 1.32 – 1.30 (m, 6H), 1.19 – 1.17 (m, 6H). ESI-MS(+): m/z = 399.19 $[M\text{-}Cl]^+$. To the best of our knowledge, compound **J12** has not been reported previously in the literature

[Ru(η^6-*p*-cymene)Cl(7-oxocyclohepta-1,3,5-trien-1-olate)] (J13). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of 2-hydroxycyclohepta-2,4,6-trien-1-one (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 53.0 mg (75%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.24 – 7.14 (m, 4H), 6.81 – 6.73 (m, 1H), 5.54 (d, J = 6.1 Hz, 2H), 5.33 (d, J = 6.1 Hz, 2H), 2.90 (dt, J = 13.9, 6.9 Hz, 1H), 2.32 (s, 3H), 1.31 (d, J =7.0 Hz, 6H). ESI-MS(+): m/z = 357.13 $[M\text{-}Cl]^+$.

[Ru(η^6-*p*-cymene)Cl(2-(methylcarbamoyl)-4-oxo-4*H*-pyran-3-olate)] (J14). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of 3-hydroxy-N-methyl-4-oxo-4*H*-pyran-2-carboxamide (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 31.3 mg (39%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 9.08 (d, J = 4.4 Hz, 1H), 7.83 (d, J = 5.1 Hz, 1H), 6.59 (d, J = 5.1 Hz, 1H), 5.66 – 5.55 (m, 2H), 5.37 (dd, J = 5.2, 3.7 Hz, 2H), 2.99 (d, J = 4.9 Hz, 3H), 2.96 – 2.84 (m, 1H), 2.33 (s, 3H), 1.36 (t, J = 6.7 Hz, 6H). ESI-MS(+):

m/*z* = 404.07 $[M\text{-}Cl]^+$. To the best of our knowledge, compound **J14** has not been reported previously in the literature

[Ru(η^6-*p*-cymene)Cl(methyl-2-oxo-1,2-dihydropyridin-3-olate)] (J18). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of 3-hydroxymethylpyridin-2(1*H*)-one (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 40.2 mg (56%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 6.63 (dd, J = 7.7, 1.4 Hz, 1H), 6.43 (dd, J = 6.5, 1.4 Hz, 1H), 6.20 (dd, J = 7.7, 6.5 Hz, 1H), 5.55 – 5.51 (m, 2H), 5.32 (t, J = 5.5 Hz, 2H), 3.62 (s, 3H), 2.96 – 2.89 (m, 1H), 2.32 (s, 3H), 1.36 – 1.31 (m, 6H). ESI-MS(+): *m*/*z* = 360.24 $[M\text{-}Cl]^+$. To the best of our knowledge, compound **J18** has not been reported previously in the literature

[Ru(η^6-*p*-cymene)Cl(2-oxopyridin-1(2*H*)-olate)] (J19). A solution of 0.2 M sodium methoxide was made by dissolving sodium (230 mg, 10.0 mmol) into methanol (50 mL). The reaction was kept as dry as possible, and the sodium methoxide solution was kept under a nitrogen atmosphere. Bis[dichlorido(η^6-*p*-cymene)Ru(II)] (0.9 eq.) was added to a solution of hydroxypyridin-2(1*H*)-one (1 eq.) and sodium methoxide (1.1 eq.) in methanol (80 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4–8 h. Afterwards the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and filtered to remove NaCl. Solvent was evaporated from the filtrate under reduced pressure, and the resulting solid was purified with silica-based column chromatography using DCM/MeOH as eluent (gradient of 0-10% MeOH). Yield: 31.4 mg (45%). ^{1}H NMR (500 MHz, Chloroform-d_1): δ 7.82 (dd, J = 6.7, 1.7 Hz, 1H), 7.14 (ddd, J = 8.7, 7.1, 1.7 Hz, 1H), 6.75 (dd, J = 8.7, 1.6 Hz, 1H), 6.36 (td, J = 6.9, 1.6 Hz, 1H), 5.53 (dd, J = 9.7, 5.8 Hz, 2H), 5.30 (dd, J = 8.0, 5.9 Hz, 2H), 2.97 – 2.91 (m, 1H), 2.34 (s, 3H), 1.34 (dd, J = 6.9, 2.9 Hz, 6H). ESI-MS(+): *m*/*z* = 346.11 $[M\text{-}Cl]^+$. To the best of our knowledge, compound **J19** has not been reported previously in the literature.

Class K compounds

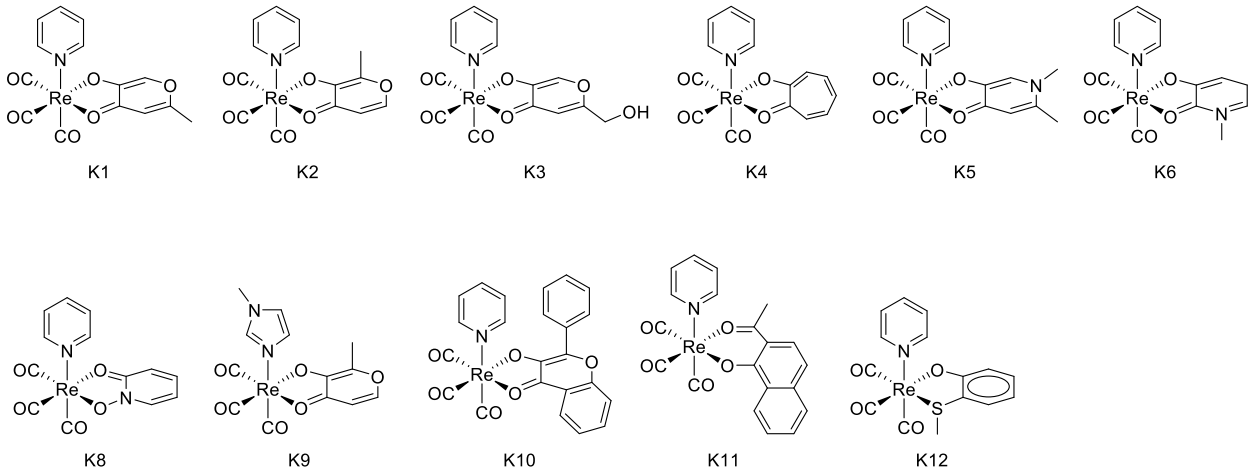


Figure S11. Rhenium tricarbonyl scaffolds that comprise the Class **K** metallofragments.

[Re(pyridine)(allomaltol)(CO)$_3$] (K1). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), allomaltol (22 mg; 0.18 mmol) and pyridine (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (3 min 0% EtOAc, 22.7 min 0-100% EtOAc, 4.3 min 100% EtOAc). Yield: 41 mg (57%). ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.60 (tq, J = 3.2, 1.7 Hz, 2H), 8.08 – 8.01 (m, 1H), 7.87 (t, J = 2.4 Hz, 1H), 7.58 (ddd, J = 7.1, 4.7, 2.4 Hz, 2H), 6.53 (t, J = 2.4 Hz, 1H), 2.34 (q, J = 2.0 Hz, 3H). ESI-MS(+): m/z = 497.80 [M+Na]$^+$; 446.71 [M-CO] $^+$; 350.08 [M-(O,O-Lig)]$^+$. To the best of our knowledge, compound **K1** has not been reported previously in the literature

[Re(pyridine)(maltol)(CO)$_3$] (K2). $Re_2(CO)_{10}$ (75 mg; 0.11 mmol), maltol (33 mg; 0.26 mmol) and pyridine (19 μL; 0.23 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (3 min 0% EtOAc, 22.7 min 0-100% EtOAc, 4.3 min 100% EtOAc). Yield: 64 mg (59%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.70 – 8.57 (m, 2H), 8.02 (dd, J = 9.5, 6.5 Hz, 2H), 7.57 (t, J = 6.9 Hz, 2H), 6.63 (d, J = 5.0 Hz, 1H), 2.39 (s, 3H). ESI-MS(+): m/z = 446.98 [M-CO] $^+$; 350.15 [M-(O,O-Lig)]$^+$. To the best of our knowledge, compound **K2** has not been reported previously in the literature

[Re(pyridine)(5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one)(CO)$_3$] (K3). $Re_2(CO)_{10}$ (80 mg; 0.12 mmol), 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one (40 mg; 0.28 mmol) and pyridine (20 μL; 0.25 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h.

The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (1.8 min 0% EtOAc, 2 min 0-40% EtOAc, 18 min 40-100% EtOAc, 3.7 min 100% EtOAc). Yield: 70 mg (58%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.61 (d, J = 5.6 Hz, 2H), 8.05 (t, J = 7.9 Hz, 1H), 7.92 (s, 1H), 7.59 (t, J = 6.9 Hz, 2H), 6.71 (s, 1H), 4.84 (d, J = 6.9 Hz, 1H), 4.49 (t, J = 5.8 Hz, 2H). ESI-MS(+): m/z = 529.67 $[M+K]^+$; 513.78 $[M+Na]^+$; 350.10 $[M-(O,O\text{-Lig})]^+$. To the best of our knowledge, compound **K3** has not been reported previously in the literature

[Re(pyridine)(tropolone)(CO)$_3$] (K4). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), tropolone (22 mg; 0.18 mmol) and pyridine (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (1.8 min 0% EtOAc, 20 min 0-100% EtOAc, 4 min 100% EtOAc). Yield: 24 mg (33%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.67 – 8.51 (m, 2H), 8.02 (t, J = 8.6, 6.7 Hz, 1H), 7.58 (t, J = 5.9 Hz, 2H), 7.54 (t, J = 9.2 Hz, 2H), 7.35 (d, J = 11.0 Hz, 2H), 7.13 (t, J = 9.6 Hz, 1H). APCI-MS: m/z = 392.96 $[M\text{-pyridine}+H]^+$; 382.87 $[M\text{-cycloheptatriene}+H]^+$. ESI-MS(+): m/z = 443.3 $[M\text{-CO}]^+$; 431.5 $[M\text{-pyridine}+K]^+$; 414.5 $[M\text{-pyridine}+Na]^+$.

[Re(pyridine)(5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one)(CO)$_3$] (K5). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), 5-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (25 mg; 0.18 mmol) and pyridine (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (1 min 0% EtOAc, 5 min 0-100% EtOAc, 15 min 100% EtOAc). Yield: 32 mg (43%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.66 – 8.56 (m, 2H), 7.99 (t, J = 7.9 Hz, 1H), 7.53 (t, J = 6.9 Hz, 2H), 7.16 (s, 1H), 6.33 (s, 1H), 3.71 (s, 3H), 2.31 (s, 3H). ESI-MS(+): m/z = 487.9 $[M]^+$; 460.0 $[M\text{-CO}]^+$. To the best of our knowledge, compound **K5** has not been reported previously in the literature

[Re(pyridine)(3-hydroxy-1-methylpyridin-2(1*H*)-one)(CO)$_3$] (K6). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), 3-hydroxy-1-methylpyridin-2(1*H*)-one (22 mg; 0.18 mmol) and pyridine (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (1 min 0% EtOAc, 20 min 0-100% EtOAc, 5 min 100% EtOAc). Yield: 40 mg (55%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.66 (dt, J = 5.1, 1.6 Hz, 2H), 8.01 (tt, J = 7.7, 1.6 Hz, 1H), 7.61 – 7.50 (m, 2H), 6.83 (dd, J = 6.5, 1.4 Hz, 1H), 6.59 (dd, J = 7.7, 1.4 Hz, 1H), 6.35 (dd, J = 7.7, 6.5 Hz, 1H), 3.71 (s, 3H). ESI-TOFMS(+): m/z 395.9890 $[M\text{-pyridine}]^+$. To the best of our knowledge, compound **K6** has not been reported previously in the literature

[Re(pyridine)(1-hydroxypyridin-2(1*H*)-one)(CO)$_3$] (K8). $Re_2(CO)_{10}$ (75 mg; 0.11 mmol), 1-hydroxypyridin-2(1*H*)-one (29 mg; 0.26 mmol) and pyridine (19 μL; 0.23 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (3.0 min 0% EtOAc, 22.7 min 0-100% EtOAc, 9.3 min 100% EtOAc). Yield: 41 mg (39%). Single crystals were obtained by layering a DCM solution of the compound with n-hexanes. ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.68 (d, J = 6.1 Hz, 2H), 8.04 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 6.7 Hz, 2H), 7.43 – 7.34 (m, 1H), 6.80 (d, J = 9.0 Hz, 1H), 6.63 (d, J = 7.4 Hz, 1H). ESI-MS(+): m/z = 444.7 [M-O]$^+$; 483.7 [M-O-pyridine+NH$_4$]$^+$; 365.8 [M-O-pyridine]$^+$; 337.8 [M-O-pyridine-CO]$^+$. To the best of our knowledge, compound **K8** has not been reported previously in the literature

[Re(1-methyl-1*H*-imidazole)(3-hydroxy-2-methyl-4*H*-pyran-4-one)(CO)$_3$] (K9). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), 3-hydroxy-2-methyl-4*H*-pyran-4-one (22 mg; 0.18 mmol) and 1-methyl-1*H*-imidazole (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (5 min 0% EtOAc, 25 min 0-100% EtOAc, 3 min 100% EtOAc). Yield: 50 mg (68%). Single crystals were obtained by layering a DCM solution of the compound with n-hexanes. ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.03 (d, J = 5.1 Hz, 1H), 7.83 (s, 1H), 7.13 (s, 1H), 6.98 (s, 1H), 6.59 (d, J = 5.1 Hz, 1H), 3.78 (s, 3H), 2.40 (s, 3H). ESI-MS(+): m/z = 516.8 [M+K]$^+$; 500.8 [M+Na]$^+$; 478.0 [M]$^+$; 450.3 [M-CO]$^+$. To the best of our knowledge, compound **K9** has not been reported previously in the literature

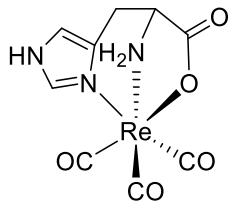
[Re(pyridine)(3-hydroxyflavone)(CO)$_3$] (K10). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), 3-hydroxyflavone (42 mg; 0.18 mmol) and pyridine (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. Orange powder and dark colored crystals were obtained, filtered, washed with hexane, and air-dried. Yield: 67 mg (74%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.78 – 8.70 (m, 4H), 8.23 (d, J = 8.1 Hz, 1H), 7.99 – 7.91 (m, 1H), 7.88 – 7.80 (m, 2H), 7.63 – 7.47 (m, 6H). ESI-MS(+): m/z = 587.8 [M]$^+$; 559.2 [M-CO]$^+$; 531.7 [M-pyridine+Na]$^+$.

[Re(pyridine)(2-acetyl-1-naphthol)(CO)$_3$] (K11). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), 2-acetyl-1-naphthol (33 mg; 0.18 mmol) and pyridine (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (5 min 0% EtOAc, 16 min 0-25%, 6 min 25-100% EtOAc, 3 min 100% EtOAc). Yield: 31 mg (38%). Single crystals were obtained by layering a DCM solution of the compound with n-hexanes. ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.75 (dt, J = 4.9, 1.6 Hz, 2H), 8.57 (d, J = 8.3 Hz, 1H), 8.07 – 7.98 (m, 1H), 7.69 – 7.60 (m, 2H), 7.57 (ddd, J = 7.7, 5.0, 1.5 Hz, 2H), 7.53 – 7.45 (m, 2H), 6.88 (d, J = 9.2 Hz, 1H), 2.63 (s,

3H). ESI-MS(+): m/z = 534.8 $[M]^+$; 506.9 $[M\text{-}CO]^+$. To the best of our knowledge, compound **K11** has not been reported previously in the literature

[Re(pyridine)(2-(methylthio)phenol)(CO)$_3$] (K12). $Re_2(CO)_{10}$ (50 mg; 0.08 mmol), 2-(methylthio)phenol (21 μL; 0.18 mmol) and pyridine (12 μL; 0.15 mmol) were suspended in 3 mL toluene (stored over molecular sieves) in a Teflon-lined steel vessel. The steel vessel was placed in an oven maintained at 140 °C for 48 h. The mixture was transferred to a round bottom flask, and the solvent was evaporated under reduced pressure. The residue was purified by silica-based column chromatography using n-hexane/EtOAc as eluent (5 min 0% EtOAc, 20 min 0-50% EtOAc, 5 min 50% EtOAc). Yield: 34 mg (45%). Single crystals were obtained by layering a DCM solution of the compound with n-hexanes. ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.79 (s, 2H), 8.02 (s, 1H), 7.56 (s, 2H), 7.33 (s, 1H), 7.02 (s, 1H), 6.78 (s, 1H), 6.46 (s, 1H), 3.08 (s, 3H). ESI-MS(+): m/z = 512.5 $[M+Na]^+$. To the best of our knowledge, compound **K12** has not been reported previously in the literature.

Class L compounds

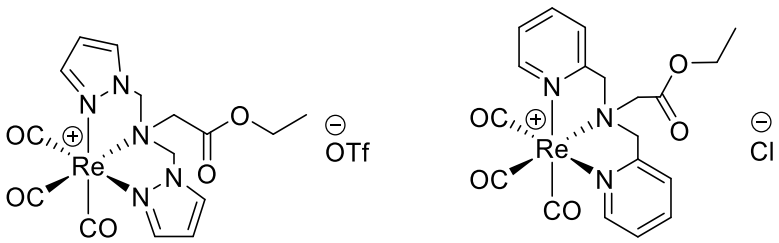


L1

Figure S12. Rhenium tricarbonyl scaffold that is the Class **L** metallofragment.

[Re(histidine)(CO)$_3$] (L1). $Re(CO)_5Cl$ (50 mg; 0.14 mmol), histidine (21 mg; 0.14 mmol), and NaOH (6 mg; 0.14 mmol) were dissolved in 3 mL H_2O. The reaction mixture stirred overnight at 60 °C. The mixture was concentrated under reduced pressure, and the white precipitate was collected via filtration, washed with H_2O, and dried in vacuo. The filtrate and washing solution were combined, concentrated, and stored at -18 °C overnight. The precipitate was collected via filtration, and both precipitation fractions were combined. The product was recrystallized from a MeOH/H_2O mixture. Yield: 17 mg (29%). ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.01 (d, J = 1.4 Hz, 1H), 7.02 (s, 1H), 5.74 (d, J = 6.7 Hz, 1H), 5.19 – 5.01 (m, 1H), 4.03 (ddd, J = 6.6, 4.3, 2.5 Hz, 2H), 3.18 (ddd, J = 17.1, 4.3, 1.5 Hz, 2H). ESI-MS(+): m/z 448.14 $[M+Na]^+$.

Class M compounds



M1 M2

Figure S13. Rhenium tricarbonyl scaffolds that comprise the Class **M** metallofragments.

[Re(ethyl-bis((1*H*-pyrazol-1-yl)methyl)glycinate)(CO)$_3$]$^+$[OTf]$^-$ (M1).
[Re(SO(CH$_3$)$_2$)$_3$(CO)$_3$]$^+$ triflate (75 mg; 0.11 mmol) was mixed with ethyl bis((1*H*-pyrazol-1-yl)methyl)glycinate (33 mg; 0.13 mmol), and the mixture was stirred for 1 h at 40 °C and for additional 0.5 h at 50 °C. MeOH was added, and the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved with MeCN, poured into cold Et_2O, and stored at -20 °C overnight. The obtained white solid was separated from the solution by decantation and air dried. Yield: 35 mg (45%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.19 (d, J = 2.8 Hz, 2H), 8.05 (d, J = 2.3 Hz, 2H), 6.54 (d, J = 12.1 Hz, 2H), 6.44 (t, J = 2.5 Hz, 2H), 5.79 (d, J = 12.1 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H). ESI-MS(+): m/z 534.17 [M$^+$]. To the best of our knowledge, compound **M1** has not been reported previously in the literature

To make the ligand ethyl bis((1*H*-pyrazol-1-yl)methyl)glycinate, glycine ethyl ester hydrochloride (203 mg; 1.46 mmol) was suspended in 20 mL DCM. Triethylamine (203 μL; 1.46 mmol) was added slowly, and the mixture was stirred for 10 min until most of the starting material was dissolved. (1*H*-pyrazol-1-yl)methanol (300 mg; 3.06 mmol) was added, and the mixture was stirred for 5 days at room temperature. H_2O and brine were used to wash the organic layer, which was then dried over $MgSO_4$ and evaporated to dryness. Residual (1*H*-pyrazol-1-yl)methanol was sublimed from the product in vacuo at 50 °C. The product was obtained as a colorless oil. Yield: 310 mg (81%). ^{1}H NMR (400 MHz, Chloroform-d_1): δ 7.56 (dd, J = 19.2, 2.1 Hz, 4H), 6.30 (t, J = 2.1 Hz, 2H), 5.11 (s, 4H), 4.11 (q, J = 7.1 Hz, 2H), 3.61 (s, 2H), 1.24 (t, J = 7.1 Hz, 3H). ESI-MS(+): m/z 286.16 [M+Na]$^+$.

To make the precursor [Re(SO(CH$_3$)$_2$)$_3$(CO)$_3$]$^+$ triflate, Re(CO)$_5$Cl (100 mg; 0.28 mmol) in DMSO (60 μL; 0.84 mmol) was suspended in 8 mL acetone, and the flask was covered with aluminum foil before $AgCF_3SO_3$ (71 mg; 0.28 mmol) was added. The mixture was refluxed overnight under exclusion from light. The precipitation was collected via filtration, and the filtrate was concentrated under reduced pressure before it was poured into Et_2O and stored at -20 °C overnight. The obtained colorless crystals were separated from the solvent by decantation and air dried. Yield: 143 mg (87%).

[Re(ethyl-bis((1*H*-pyrazol-1-yl)methyl)glycinate)(CO)$_3$]$^+$[Cl]$^-$ (M2). Re(CO)$_5$Cl (52 mg; 0.14 mmol) and ethyl bis(pyridin-2-ylmethyl)glycinate (49 mg; 0.17 mmol) were suspended in 1 mL

MeOH, and the mixture was irradiated in a microwave at 110 °C for 10 min. The resulting solution was concentrated under reduced pressure and poured into cold Et_2O. The white precipitation was separated from the solution through centrifugation and dried in vacuo. Yield: 78 mg (86%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.82 (d, J = 5.5 Hz, 2H), 8.01 (td, J = 7.8, 1.5 Hz, 2H), 7.66 (d, J = 7.9 Hz, 2H), 7.43 (t, J = 6.8 Hz, 2H), 5.20 (d, J = 17.2 Hz, 2H), 5.10 (d, J = 17.1 Hz, 2H), 4.78 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). ESI-MS(+): m/z 556.10 [M^+].

To make ethyl (pyridin-2-ylmethyl)glycinate, glycine ethyl ester hydrochloride (474 mg; 3.39 mmol) was dissolved in 5 mL MeOH (stored over molecular sieves) under a N_2 atmosphere, and the solution was cooled to 0 °C. Picolinaldehyde (708 μL; 7.47 mmol) was added, followed by addition of $NaBH_4$ (206 mg; 5.43 mmol) in small portions. The reaction mixture was stirred overnight coming to room temperature during this time. H_2O (1 mL) was added slowly to quench the reaction, and the mixture was stirred for an additional 5 h. DCM was used to extract the product. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and evaporated to dryness. The product was purified by silica-based column chromatography using DCM/MeOH as eluent (5 min 0% MeOH, 32 min 0-8% MeOH, 10 min 8% MeOH). Yield: 522 mg (79%). ^{1}H NMR (400 MHz, Chloroform-d_1): δ 8.57 (s, 1H), 7.66 (d, J = 6.4 Hz, 1H), 7.35 (d, J = 6.4 Hz, 1H), 7.27 (d, J = 4.9 Hz, 1H), 7.18 (q, J = 6.2 Hz, 1H), 4.77 (d, J = 5.2 Hz, 1H), 4.20 (p, J = 6.9 Hz, 2H), 3.97 (d, J = 5.1 Hz, 2H), 3.49 (d, J = 5.6 Hz, 2H), 1.28 (q, J = 6.7 Hz, 3H).

To make ethyl bis(pyridin-2-ylmethyl)glycinate, ethyl (pyridin-2-ylmethyl)glycinate (522 mg; 2.69 mmol) and 2-(bromomethyl)pyridine hydrobromide (680 mg; 2.69 mmol) were dissolved in DMF (stored over molecular sieves), followed by addition of triethylamine (783 μL; 5.65 mmol). More DMF was added until most of the precipitation was gone. The reaction mixture stirred for 36 h at room temperature. H_2O was added, and the product was extracted with EtOAc. The combined organic layers were washed with H_2O and brine and evaporated to dryness. Yield: 582 mg (76%). ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.48 (d, J = 4.9 Hz, 2H), 7.74 (dt, J = 7.6, 3.8 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.22 (dd, J = 7.5, 4.9 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.98 (s, 4H), 3.46 (s, 2H), 1.22 (t, J = 7.1 Hz, 3H).

X-ray Crystallography

Class K compounds were crystallized as described in the synthesis and characterization section. All compounds crystallized as light-yellow blocks. The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å). Suitable crystals were mounted on a cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm and exposure time was 5 seconds per frame using a scan width of 0.75-2.0°. Data collection was 100% complete to 25.00° in θ. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.[12] All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. For compound K5, the absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.025(14). The crystal data file of all complexes was deposited into the Cambridge Crystallographic Data Centre (CCDC) with deposition numbers 1962326-1962330. Crystal structures are shown in Figure S14, and crystallographic data are summarized in Table S1.

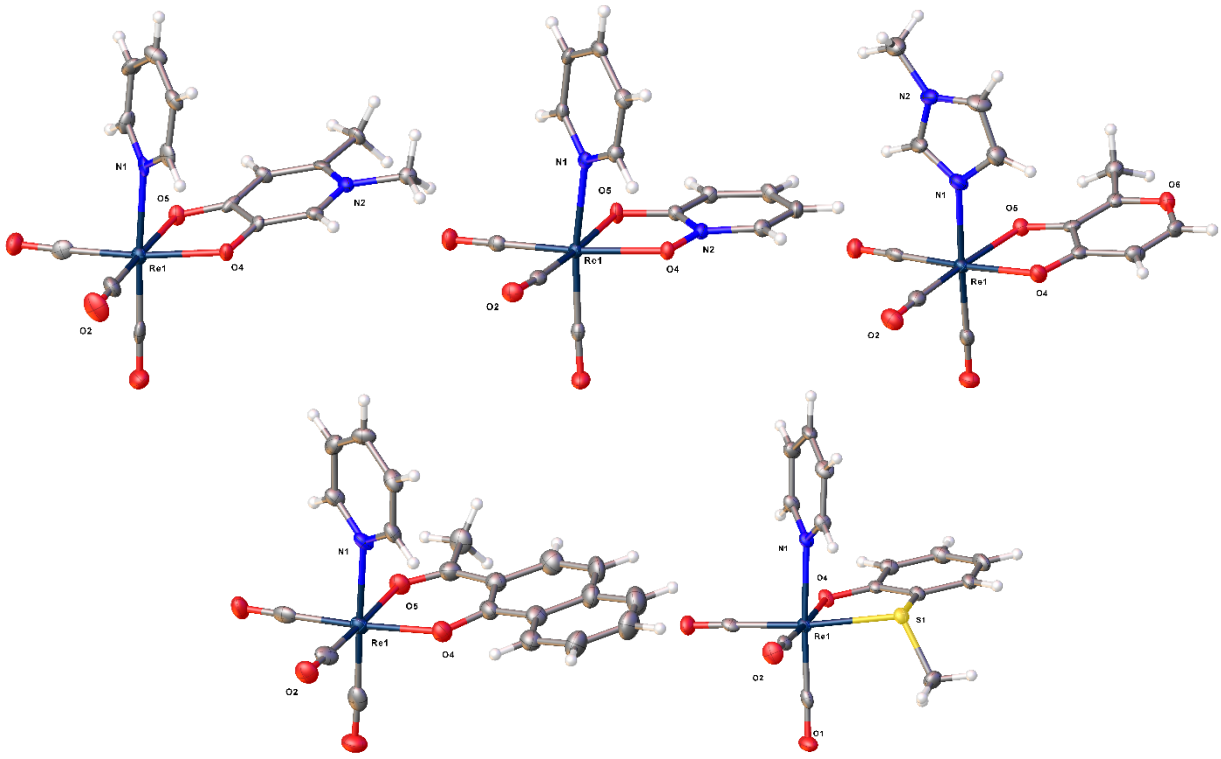


Figure S14. Structures of Class K compounds rendered as an ORTEP with atoms at 50% thermal probability ellipsoids. *Top row*: K5, K8, and K9; *bottom row*: K11 and K12. Only one molecule is shown for each metallofragment; however, all these compounds form in enantiomeric mixtures due to different binding orientations of the bidentate ligand, and both enantiomers are present in the unit cell. Color scheme: carbon = gray, hydrogen = white, oxygen = red, nitrogen = blue, sulfur = yellow, rhenium = navy blue.

Table S1. Crystal data and structure refinement for Class K compounds

Compound	K5	K8	K9
Identification code	1962326	1962327	1962328
Empirical formula	$C_{15}H_{13}N_2O_5Re$	$C_{13}H_9N_2O_5Re$	$C_{13}H_{11}N_2O_6Re$
Molecular formula	$C_{15}H_{13}N_2O_5Re$	$C_{13}H_9N_2O_5Re$	$C_{13}H_{11}N_2O_6Re$
Formula weight (g/mol)	487.47	459.42	477.44
Temperature (K)	100.0	100.0	100.0
Crystal system	Orthorhombic	Monoclinic	Triclinic
Space group	$P2_12_12_1$	$P\ 1\ 2_1/c\ 1$	P-1
a (Å)	6.3450(2)	9.1929(5)	9.1080(5)
b (Å)	14.5492(5)	13.3161(7)	9.5099(5)
c (Å)	16.7909(7)	11.3352(6)	9.7673(5)
α (°)	90	90	70.669(2)
β (°)	90	106.800(2)	80.012(2)
γ (°)	90	90	61.781(2)
Volume (Å^3)	1550.05(10)	1328.36(12)	703.28(7)
Z	4	4	2
ρ_{calc} (g/cm^3)	2.089	2.297	2.255
Absorption coefficient (mm^{-1})	7.866	9.171	8.671
F(000)	928	864	452
Crystal size (mm^3)	0.213 × 0.145 × 0.117	0.131 × 0.106 × 0.094	0.127 × 0.115 ×0.086
Theta range for data collection (°)	1.852 to 26.396	2.314 to 26.404	2.210 to 26.368
Index ranges	$-7 \le h \le 7$, $-18 \le k \le 18$, $-20 \le l \le 20$	$-11 \le h \le 11$, $-16 \le k \le 16$, $-14 \le l \le 13$	$-11 \le h \le 11$, $-11 \le k \le 8$, $-12 \le l \le 12$
Reflections collected	17683	25383	10244
Independent reflections	3161 [R_{int} = 0.0536, R_{sigma} = 0.0444]	2729 [R_{int} = 0.0373, R_{sigma} = 0.0197]	2866 [R_{int} = 0.0300, R_{sigma} = 0.0326]
Data / restraints / parameters	3161 / 0 / 211	2729 / 0 / 191	2866 / 37 / 245
Goodness-of-fit on F^2	1	1.068	1.047
Final R indices [$I \ge 2\sigma(I)$]	R_1 = 0.0239, wR_2 = 0.0424	R_1 = 0.0145, wR_2 = 0.0302	R_1 = 0.0200, wR_2 = 0.0378
R indices [all data]	R_1 = 0.0517, wR_2 = 0.0501	R_1 = 0.0175, wR_2 = 0.0309	R_1 = 0.0233, wR_2 = 0.0387
Absolute structure parameter	0.025(14)	n/a	n/a
Largest diff. peak and hole (e/Å^3)	0.494 and -0.533	0.404 and -0.587	0.563 and -0.513

Table S1 (continued). Crystal data and structure refinement for Class K compounds

Compound	K11	K12
Identification code	1962329	1962330
Empirical formula	$C_{20.50}H_{15}ClNO_5Re$	$C_{15}H_{12}NO_4ReS$
Molecular formula	$C_{20}H_{14}NO_5Re$, $0.5(CH_2Cl_2)$	$C_{15}H_{12}NO_4ReS$
Formula weight (g/mol)	576.98	488.52
Temperature (K)	100.0	100.0
Crystal system	Monoclinic	Monoclinic
Space group	*P* 1 2_1/c 1	*P* 1 2_1/n 1
a (Å)	20.753(2)	8.5304(5)
b (Å)	7.0352(8)	8.1560(5)
c (Å)	13.7941(18)	22.7941(15)
α (°)	90	90
β (°)	105.388(7)	96.365(2)
γ (°)	90	90
Volume (Å^3)	1941.8(4)	1576.10(17)
Z	4	4
ρ_{calc} (g/cm^3)	1.974	2.059
Absorption coefficient (mm^{-1})	6.428	7.858
F(000)	1108	928
Crystal size (mm^3)	0.153 × 0.147 × 0.136	0.087 × 0.065 × 0.063
Theta range for data collection (°)	2.036 to 25.381	2.470 to 26.379
Index ranges	$-24 \le h \le 24$, $-8 \le k \le 6$, $-16 \le l \le 16$	$-9 \le h \le 10$, $-10 \le k \le 10$, $-28 \le l \le 28$
Reflections collected	26253	21549
Independent reflections	3563 [R_{int} = 0.0959, R_{sigma} = 0.0639]	3228 [R_{int} = 0.0421, R_{sigma} = 0.0297]
Data / restraints / parameters	3563 / 1 / 267	3228 / 0 / 200
Goodness-of-fit on F^2	1.049	1.051
Final *R* indices [$I \ge 2\sigma(I)$]	R_1 = 0.0376, wR_2 = 0.0759	R_1 = 0.0207, wR_2 = 0.0355
R indices [all data]	R_1 = 0.0535, wR_2 = 0.0815	R_1 = 0.0285, wR_2 = 0.0372
Largest diff. peak and hole (e/Å^3)	0.923 and -1.342	0.465 and -0.821

Molecular volume analysis of metallofragment library

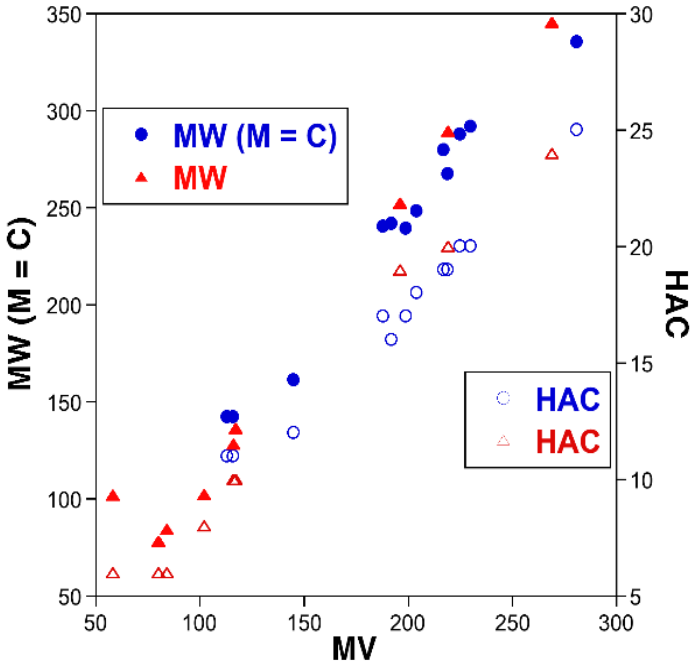


Figure S15. The size (molecular volume, MV in Å^3) of organic fragments (red triangles) versus metallofragments (blue circles) are indistinguishable when these molecules are compared using an apparent MW (filled symbols, where the metal ion is assigned the mass of a carbon atom, M = C) or when comparing heavy atom count (open symbols, HAC, e.g. the number of non-hydrogen atoms) in the fragment. In addition, the correlation of either MW or HAC vs. MV of organic and metallofragments is effectively the same; therefore, MV ≤300 Å^3 is proposed as a suitable 'rule' for metallofragment rule-of-3 compliance rather than MW ≤300 Da.

PA_N endonuclease protein expression and purification

Expression and purification of PA_N endonuclease was performed as reported previously.[13] Pandemic H1N1 N-terminal PA (PA_N) endonuclease Δ52-64:Gly truncated construct was expressed from a pET-28a parent vector containing a kanamycin-resistance reporter gene with expression inducible by the Lac 1 operon. PA_N endonuclease was expressed as an 8-histidine tagged fusion protein, cleavable by TEV protease. The transformation protocol was adapted from pET system manual (Novagen) using single competent BL21 cells. Briefly, 1 µL of 25 ng/µL recombinant plasmid was used for transformation. Cells were mixed by flicking with plasmid and were heat shocked at 42 ºC for 30 sec followed by incubation on ice for 5 minutes. Outgrowth was plated on LB agarose plates contain 50 µg/mL kanamycin and was incubated overnight at 37 ºC. One colony was scraped from the LB plate and added to 50 mL of SOC broth containing 50 µg/mL kanamycin and was incubated for 5 h at 37 ºC with shaking at 125 rpm. Glycerol stocks of this culture were prepared (0.9 mL cultured media + 0.1 mL 80% glycerol) and column frozen for future expressions. SOC media (100 mL) containing 50 µg/mL kanamycin was combined with 1 mL frozen cell glycerol stock and was incubated with shaking at 200 rpm at 37 ºC. When the OD_{600} of this starter culture reached >2 (~5-6 h), the culture was equally divided into 6 × 1 L batches of expression media (TB media with added 0.2% dextrose, 0.1 mM $MnCl_2$, and 0.1 mM $MgSO_4$) containing 50 µg/mL kanamycin. Cells were grown to the beginning of log phase (OD_{600} = between 0.4-0.6) at 37 ºC with shaking at 200 rpm. When the OD_{600} = 0.4-0.6, the cultures were cooled to room temperature over ice. Expression of PA_N endonuclease was then induced by the addition of IPTG to a final concentration of 0.1 mM. The cultures were grown with vigorous shaking (250 rpm) overnight at room temperature. The caps of the flasks were completely removed to increase aeration. After ~18 h, the cells were harvested by centrifuging at 2000g for 30 min at 4 ºC. The resulting cell paste was stored at -80 ºC prior to lysis.

The cell paste was thawed on ice for 2 h and re-suspended 1:1 (v/v) with lysis buffer (20 mM Na_2PO_4, 500 mM NaCl, 25 mM imidazole, 1 mM $MgCl_2$, 2 mM dithiothreitol, 0.2% Triton-X, pH=7.4) plus EDTA free protease inhibitor (1 pellet per ~50 mL lysis buffer), lysozyme (1 mg/mL), and DNAse-1 (10-100 µg/mL). Further lysis was performed using a probe sonicator over 10 min with cycles of 10 sec sonication and 20 sec rest. The cell suspension was kept in a water/ice bath during sonication. The lysates were free-flowing and homogenous. The lysates were shaken at 125 rpm for 30 min on ice. Cell debris was then pelleted by centrifugation at 10000 rpm for 45 min at 4 ºC. The supernatant was decanted from the pellet and was filtered through 0.45 µm syringe filters. The resulting lysate was loaded onto 2 × 5 mL HisTrap HP (Pharmacia) columns that had been previously charged with Ni ions. The columns were washed with binding buffer (20 mM Na_2PO_4, 500 mM NaCl, 25 mM imidazole, pH 7.4) until fraction absorbance reached a steady baseline. The protein was then eluted over a 45 min gradient at a flow rate of 4 mL/min, from 0-100% elution buffer (20 mM Na_2PO_4, 500 mM NaCl, 500 mM imidazole, pH 7.4). PA_N endonuclease eluted between 40-60% elution buffer. SDS-PAGE analysis showed a band corresponding to PA_N endonuclease running at ~23 kDa.

Fractions containing endonuclease protein were combined in a 10K MWCO dialysis bag with 2000 units of TEV protease and dithiothreitol final concentration of 1 mM. The solutions were dialyzed against dialysis buffer (100 mM NaCl, 1 mM dithiothreitol, 1 mM $MnCl_2$, 20 mM Tris, 5% glycerol, pH 8.0) overnight at 4 ºC with two buffer exchanges. A white precipitate

forms over time along the inside and outside walls of the dialysis tubing. After buffer exchange, the solution was filtered through a 0.45 μm filter and was concentrated to 5-10 mg/ml using a pressurized Amicon system. This protein was suitable for use in fluorescence quenching-based nuclease assays.

For thermal shift assays the concentrated protein was then purified on a gel-permeation size exclusion column (GE Superdex 75, 16/600) according to manufacturer recommendations in buffer (150 mM NaCl, 2 Mm $MgCl_2$, 2 mM $MnCl_2$, 20 mM HEPES, pH 7.5). A large peak corresponding to the cleaved PA_N endonuclease construct eluted at ~60 mL eluent. Fractions containing pure cleaved PA_N endonuclease were combined and concentrated to 5-7 mg/mL for storage. Stored protein was column-frozen in liquid nitrogen and kept at -80 ºC. Protein purity was determined using SDS PAGE. This protein was suitable for use in thermal shift assay experiments.

PA_N endonuclease fluorescence quenching-based nuclease activity assay

PA_N endonuclease activity assays were carried out as previously reported, with slight modification.[13] The only alteration made was to remove 2-mercaptoethanol from the assay buffer. Assays were performed using Black Costar 96-well plates. Each well contained a total volume of 100 μL comprised of buffer (20 mM Tris, 150 mM NaCl, 2 mM $MnCl_2$, 0.2% Triton-X100, pH 8.0), influenza PA_N endonuclease (25 nM), inhibitor (various concentrations), and fluorescent ssDNA-oligo substrate (200 nM). DMSO was present at a final concentration of 5% in each well. The presence of this concentration of DMSO was found to have a negligible effect on the assay. A single-stranded, 17-mer DNA substrate labeled with a 5′-FAM fluorophore and a 3′-TAMRA quencher ([6-FAM]AATCGCAGGCAGCACTC[TAM], Sigma-Aldrich) was employed as the substrate. All assay components were pipetted into the plate, and ultimately, the substrate was added using a multi-channel pipette, and the assay was immediately started. Samples were prepared in triplicates. Background wells consisting of all assay components except enzyme were prepared for each sample. Positive and negative controls were prepared on each plate to gauge the fluorescence signal of fully active protein and the absence of protein. Change in fluorescence of each well was measured by a Synergy H4 Hybrid Multi-Mode Microplate Reader (BioTek) at 39 second intervals over 45 min at 37 ºC (λ_{ex} = 485 nm; λ_{em} = 528 nm). The gain was set to 100. Typically, data collected between 20 and 35 minutes was used in the activity calculations, as this data range had a linear slope. The slope of the fluorescence signal for each sample was background corrected, and percent inhibition was determined by normalizing the slope of the sample to that of the positive and negative controls. For general library screening to identify hits, metallofragments were screened at a concentration of 200 μM. Dose response curves were generated for inhibitors by plotting percent inhibition versus log of the concentration for each inhibitor. An 8-point dose response curve was performed with concentrations of inhibitor between 500 μM and 0.64 μM. The data were fit with a sigmoidal curve to determine the IC_{50} value using a four parameter Matlab script.

Protein thermal shift assay (PA_N endonuclease, Hsp90 and NDM-1)

The same thermal shift assay was employed for PA_N endonuclease, NDM-1, and Hsp90. The buffer utilized for PA_N endonuclease was 150 mM NaCl, 2 mM $MnCl_2$, 20 mM HEPES at pH 7.5. The buffer utilized for NDM-1 and Hsp90 was 50 mM HEPES at pH 7.5.

To each well of a 96-well 0.2 mL optical MicroAmp (ThermoFisher) thermocycler plate was added 9.5 µL of buffer, 4 µL of protein in buffer, 4 µL of inhibitor in buffer (1 mM; 10% DMSO), and 2.5 µL of 20× sypro orange Thermal Shift® dye (ThermoFisher) in buffer. This results in a final well volume of 20 µL containing final concentrations of 0.5 – 2 µg protein, 200 µM inhibitor, and 6× dye in buffer with 2% DMSO. Thermocycler plate wells were sealed prior to analysis, and the plate was then heated in a thermocycler from 25 °C to 99 °C at a ramp rate of 0.1 °C/sec. Fluorescence was read using the ROX filter channel (λ_{ex} = 580 nm; λ_{em} = 623 nm), and the fluorescence signal was fitted to a first derivative curve to identify T_M.

In our experiments, native PA_N endonuclease unfolded at 58-60 °C, native NDM-1 unfolded at ~57 °C and Hsp90 n-terminus unfolded at ~51 °C.

NDM-1 meropenem activity assay

NDM-1 protein was expressed in purified in the laboratory of Dr. Michael W. Crowder according to previously published methods.[14] The NDM-1 activity assay was performed following a modified published procedure using meropenem as the substrate.[14] Briefly, the decrease in absorption of meropenem at 300 nm was monitored in UV-transparent 96-well plates (Corning product #3635). The buffer used was 50 mM HEPES and 2 mM CHAPS at pH 7. To each well, 1 μL of each compound (various concentrations) and 69 μL of NDM-1 (2.50 nM final concentration) was added. After incubating the plate at 25 ºC for 20 min, 30 μL of meropenem (180 μM final concentration) was added to each well to initiate the reaction. Positive control wells consisted of NDM-1 and meropenem (no inhibitor; fully active), and negative control wells consisted of meropenem (no enzyme; no reaction). Absorbance of each plate was measured using a Synergy H4 Hybrid Multi-Mode Microplate Reader (BioTek) at 300 nm over 5 min with 15 sec intervals.

Hsp90 fluorescence polarization activity assay

Hsp90α N-terminal domain (Hsp90) assay kits were purchased from BPS Bioscience (catalog #50293). The fluorescence polarization assays were carried out as described in the kit instruction with slight modification. The only alteration made was to replace the 2 mM dithiothreitol (final concentration) with 200 μM tris(2-carboxyethyl)phosphine (TCEP), which was validated using positive and negative controls, as well as geldanamycin dose response evaluation. Briefly, 5 μL FITC-labeled geldanamycin (100 nM final concentration) and 10 μL inhibitor (various concentrations) were added to each well of a 96-well, black, low binding, microtiter plate. Each well also contained 15 μL assay buffer, 5 μL TCEP (at 4 mM), 5 μL bovine serum albumin (at 2 mg/mL), and 40 μL H_2O. The reaction was initiated by adding 20 μL Hsp90 (at 17 ng/μL final concentration) to each well. Positive control wells consisted of FITC-labeled geldanamycin and Hsp90 (no inhibitor), and negative control wells consisted of FITC-labeled geldanamycin (no inhibitor or protein). Plates were incubated for 2 hours with slow shaking at room temperature prior to reading. After incubation, using a Synergy H4 Hybrid Multi-Mode Microplate Reader (BioTek), excitation was performed at 485 nm, and emission was measured at 530 nm. Fluorescence polarization was calculated according to the following equation: $mP = \left(\frac{I_{parallel} - I_{perpendicular}}{I_{parallel} + I_{perpendicular}}\right) x1000$. A G-factor correction was applied. Inhibition values were calculated by comparing the fluorescence polarization of sample wells versus control wells. Z-scores ranged from 0.82 – 0.93.

For general library screening to identify hits, metallofragments were screened at a concentration of 200 μM. Runs were performed in duplicate, and the error reported is the difference between the two inhibition values for each inhibitor. Dose response curves were generated for inhibitors by plotting percent inhibition versus log of the concentration for each inhibitor. An 8-point dose response curve was performed with concentrations of inhibitor between 500 μM and 0.64 μM. Dose response assays were performed in triplicate. The data was fit with a sigmoidal curve to determine the IC_{50} value using a four parameter Matlab script.

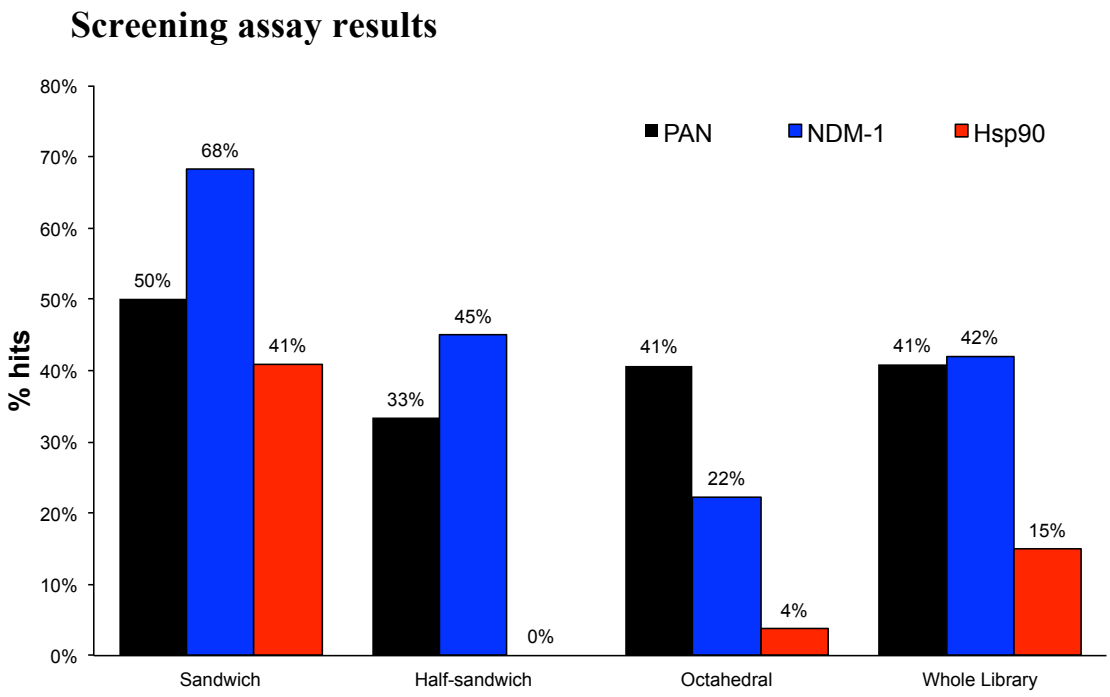


Figure S16. Analysis of the hit rates for the mF library and each of the respective subgroups against each of the three targets. Hits were considered to be any fragment that achieved a percent inhibition ≥ 50%.

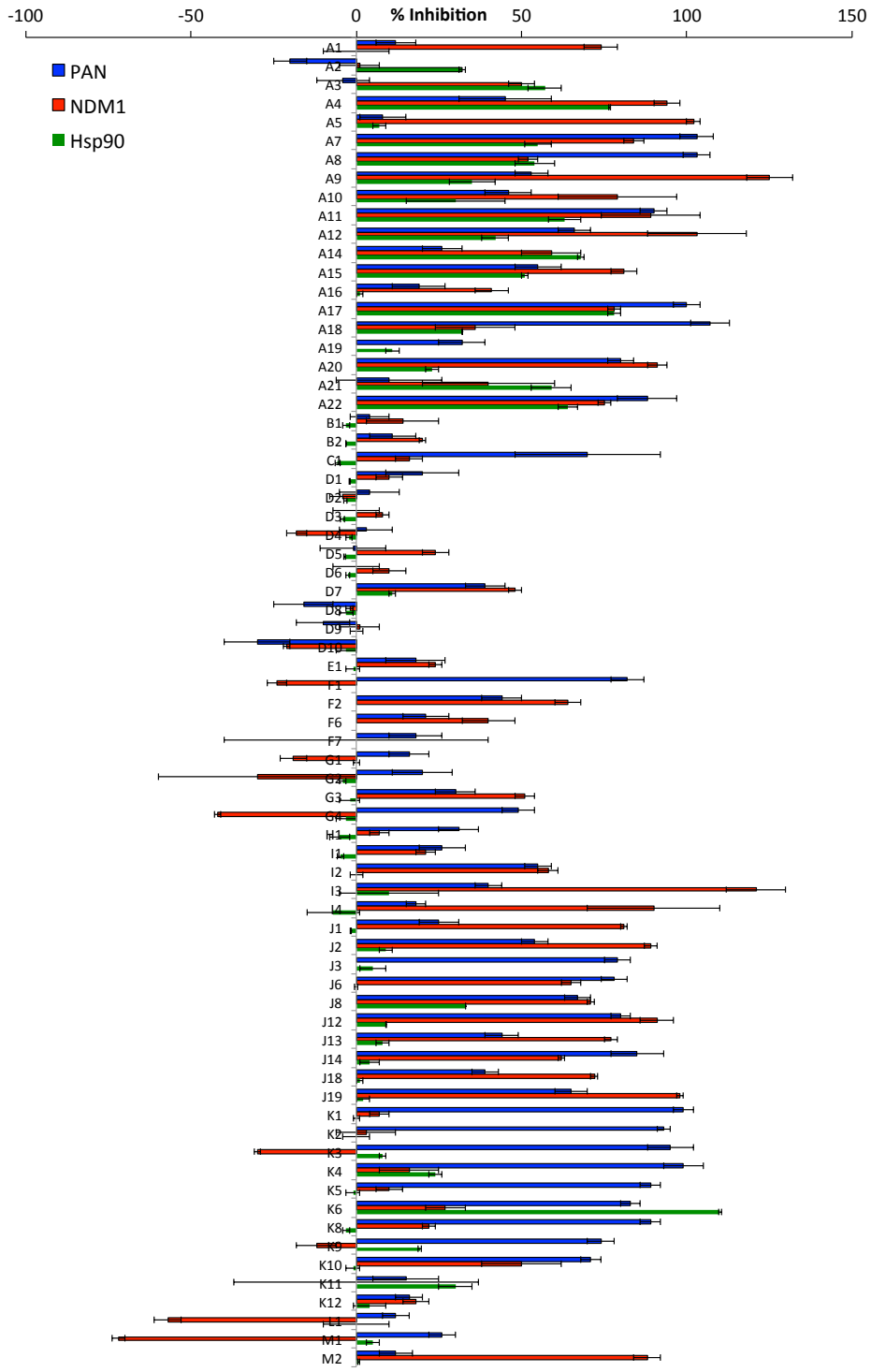


Figure S17. Results of the 200 μM mF screen against PA_N endonuclease, NDM-1 and Hsp90, presented as percent inhibition values.

Stability Analysis

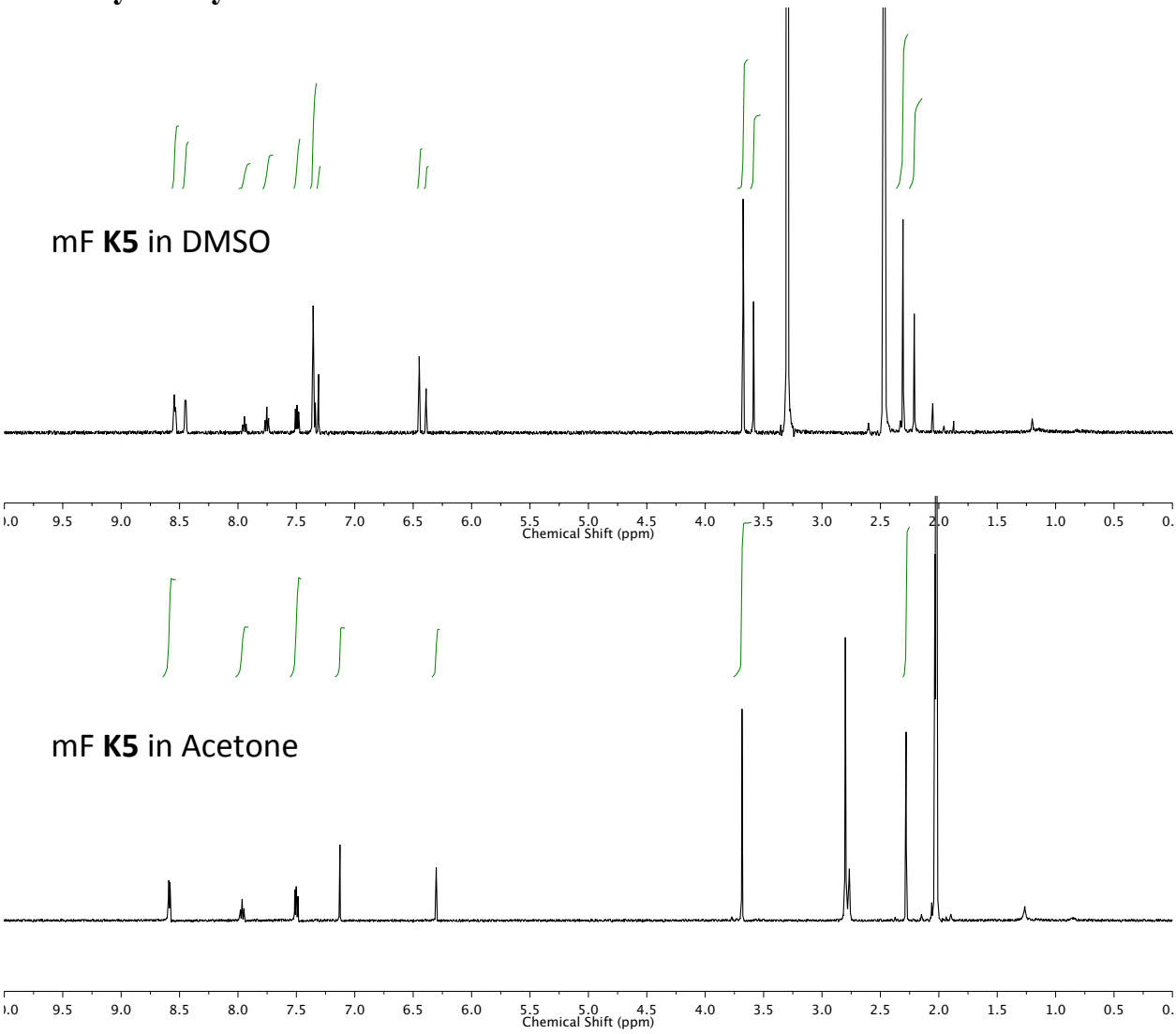


Figure S18. ^{1}H NMR analysis of a representative Class **K** mF in acetone (no loss of heterocycle) and in DMSO, in which the pyridine is lost to generate a second DMSO coordinated complex.

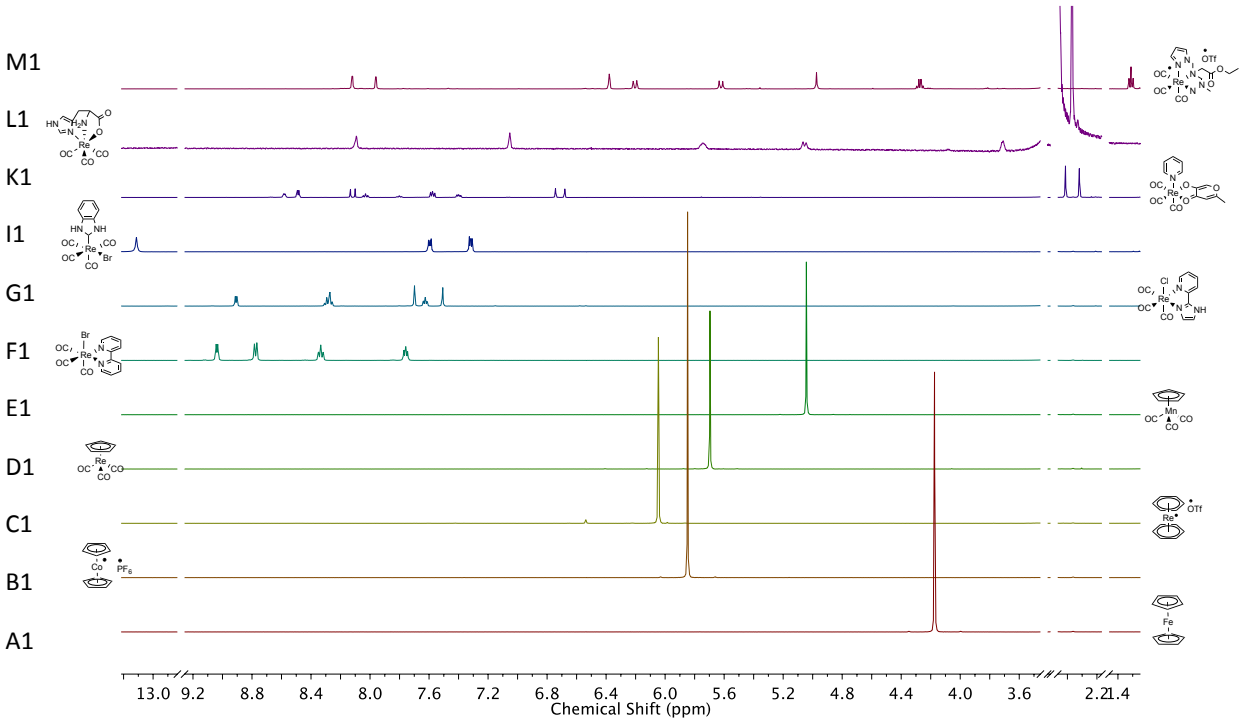


Figure S19. ^{1}H NMR analysis of the stability of a representative entry from each fragment class in d_6-DMSO.

PMI and 3D Structure Analysis

For each mF, a search was carried out in the Cambridge Structural Database (CSD) system (version 5.40, November 2018)[15] using the ConQuest platform (2.0.0)[16] for identical or the most analogous structure. The CIF file for each of the reported database identifiers or deposition numbers in Table S2 was downloaded and opened in MOE, and the PMI was calculated from the identical or minimally modified structure.

Table S2. The mFs and the corresponding CSD database identifiers for the X-ray crystallographic structures used for the PMI calculations, the two normalized PMI values, and their 3D score.

mF	CSD Identifier	I_1/I_3	I_2/I_3	3D Score
A1	FEHYAS	0.49	1.00	1.49
A2	DUKQOQ	0.34	0.86	1.20
A3	SURFIU	0.47	0.81	1.28
A4	BIWKEX	0.46	0.84	1.30
A5	DEQCAD	0.39	0.88	1.27
A7	CIZFAS	0.45	0.86	1.31
A8	DEXHOE	0.40	0.88	1.27
A9	UZOMEC	0.22	0.90	1.12
A10	BATLEO	0.28	0.86	1.14
A11	PACFER	0.24	0.87	1.11
A12	ZZZHCY01	0.31	0.88	1.20
A14	FAJVOE	0.31	0.88	1.19
A15	FAJVOE	0.30	0.90	1.20
A16	DICBIA	0.31	0.92	1.23
A17	XUXKOQ	0.34	0.88	1.22
A18	GAQQAQ	0.35	0.87	1.23
A19	BATLEO	0.26	0.85	1.10
A20	DBEFER01	0.17	0.96	1.13
A21	ZZDKO01	0.57	0.75	1.32
A22	FEROCA	0.61	0.69	1.31
B1	BEWBEM	0.47	0.99	1.47
B2	BOVQIM	0.46	0.82	1.28
C1	PEVDEB	0.55	1.00	1.55
D1	COCPRE	0.72	0.99	1.72
D2	KITCUL	0.68	0.91	1.58
D3	COXCOI	0.59	0.88	1.47
D4	KIXZOH	0.54	0.93	1.47
D5	UFAZUY	0.67	0.92	1.59
D6	QAYCIF	0.35	0.92	1.27
D7	COXCOI	0.58	0.88	1.46
D8	KIXZOH	0.59	0.89	1.48
D9	KIXZOH	0.44	0.94	1.38

mF	CSD Identifier	I_1/I_3	I_2/I_3	3D Score
D10	DUKREH	0.31	0.94	1.24
E1	CPMNCO	0.77	0.99	1.76
F1	ETUQAN	0.72	0.85	1.56
F2	XELXAO	0.60	0.73	1.34
F3	MUHTEQ	0.52	0.66	1.18
F4	SEPPAH	0.63	0.68	1.31
G1	DIYJAY	0.58	0.79	1.38
G2	DIYJAY	0.52	0.72	1.25
G3	DIYJAY	0.58	0.79	1.38
G4	DIYJAY	0.59	0.79	1.38
H1	WAPJOO	0.69	0.80	1.49
I1	PEHJEU	0.39	0.88	1.26
I2	PEHJEU	0.33	0.95	1.28
I3	PEHJEU	0.41	0.84	1.25
I4	PEHJEU	0.45	0.76	1.20
J1	YULJAR	0.34	0.88	1.21
J2	QUHNOX	0.32	0.82	1.14
J3	YULJIZ	0.35	0.89	1.23
J6	YULJIZ	0.20	0.93	1.13
J8	ODELAN	0.30	0.89	1.19
J12	OTIMOV	0.32	0.88	1.20
J13	OTIMOV	0.34	0.88	1.22
J14	YULJAR	0.32	0.92	1.24
J18	IJELAL	0.36	0.88	1.24
J19	KARYAF	0.44	0.74	1.18
K1	1962326	0.49	0.79	1.27
K2	1962326	0.55	0.80	1.34
K3	1962326	0.41	0.83	1.24
K4	1962326	0.53	0.77	1.30
K5	1962326	0.45	0.82	1.26
K6	1962326	0.55	0.80	1.36
K8	1962327	0.58	0.71	1.29
K9	1962328	0.57	0.73	1.29
K10	1962326	0.57	0.84	1.41
K11	1962329	0.50	0.94	1.43
K12	1962330	0.62	0.77	1.39
L1	EZATAA	0.55	0.80	1.35
M1	DISDEP	0.58	0.99	1.57
M2	BETDIO	0.61	0.90	1.51

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