Supporting Information

X-ray Crystal Structure of Human Heme Oxygenase-1 with (2*R*, 4*S*)-2-[2-(4-Chlorophenyl)ethyl]-2-[(1*H*- imidazol-1-yl)methyl]-4[((5-trifluoromethylpyridin-2- yl)thio)methyl]-1,3-dioxolane: A Novel, Inducible Binding Mode.

Mona N. Rahman,¹ Jason Z. Vlahakis,³ Dragic Vukomanovic,² Walter A. Szarek,³ Kanji Nakatsu,² and
Zongchao Jia¹

¹ Departments of Biochemistry, ² Pharmacology & Toxicology, and ³ Chemistry, Queen's University,
Kingston, ON K7L 3N6, Canada

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Figure S1. The oxidative degradation of heme in the carbon monoxide/heme oxygenase (CO/HO) pathway.

Figure S2. Spectral analysis of **4** binding to hHO-1. Heme-conjugated hHO-1 (412 μ M in 20 mM potassium phosphate, pH 7.4) was mixed with **4** at a molar ratio of 1:3 and incubated for ~1 h at room temperature. The absorbance of an aliquot (1 μ L diluted 1:50 in 20 mM potassium phosphate, pH 7.4) was measured over a range of 300 nm to 700 nm at intervals of 1 nm, and the values were corrected for buffer. The wavelength corresponding to the Soret peak for each spectrum is indicated.

Figure S3. Structural alignment. Plot of the RMS deviation of main chain backbone atoms of hHO-1 in complex with **4** with the native holoenzyme (PDB code 1N45, Chain-A, magenta) and hHO-1 in complex with **2** (PDB code 3CZY, Chain-A cyan). Positions of the proximal and distal helices are indicated. Structural alignments were performed using “Superpose” in CCP4.¹

A **B**

Figure S4. Thermal factor analysis. (A) Plot of normalized B-factor (B_i) values for hHO-1 in complex with **4**, and the A-chain of the native holoenzyme (PDB code 1N45). (B) Difference plot of normalized B-factors of hHO-1 in complex with **4** relative to the native holoenzyme. See Experimental Methods section for details of normalization formula. Positions of the proximal and distal helices are indicated.

Table S1. Contacts between heme-conjugated hHO-1 and (2*R*, 4*S*)-2-[2-(4-chlorophenyl)ethyl]-2-[(1*H*-imidazol-1-yl)methyl]-4[((5-trifluoromethylpyridin-2-yl)thio)methyl]-1,3-dioxolane (**4**).^{a,b}

Inhibitor 4	Heme-hHO-1	Distance (Å)
CLBF	Phe47	CD1 3.73
		CE1 3.71
CAB	Val50	CG1 3.57
CAC	Val50	CG1 3.74
	Leu147	CD1 3.98
	Phe167	CZ 3.59
CAD	Leu147	CD1 3.7
		CE1 3.96
		CZ 3.73
CAA	Val50	CG1 3.71
	Water	O 3.88
CAG	Asp140	OD1 3.96
CAH	Asp140	OD1 3.31
	Leu147	CD1 3.7
CAI	Leu147	CD1 3.9
OAP	Water	O 3.97
CAJ	Water	O 3.81
	Leu147	CD1 3.07
NAK	Gly139	O 3.41
	Gly143	CA 3.8
	Leu147	CD1 3.87
CAO	Water	O 3.73
		CA 3.98
		C 3.59
		O 3.25
	Heme	N_C 3.76
		FE 3.96
NAN	Heme	C4C 3.5
		CHD 3.92
		C1D 3.84
		C4B 3.88
		N_B 3.33
		CHC 3.93
		C1C 3.51
		N_C 2.91
		N_A 3.82
		N_D 3.4
		FE 2.66

	Gly139	CA	3.99
		C	3.94
		O	3.47
CAM	Heme	C4B	3.86
		N_B	3.07
		N_C	3.77
		CHB	3.8
		C1B	3.58
		FE	2.83
		C1A	3.98
		C4A	3.59
		N_A	3.28
		N_D	3.9
	Gly139	O	3.75
CAL	Gly139	O	3.73
	Gly143	N	3.63
		CA	3.25
OAS	Water	O	3.48
	Asp140	OD1	3.66
CAR	Heme	C3C	3.71
		CHC	3.63
		C1C	3.32
		C2C	3.16
		CMC	3.37
		N_C	3.94
	Water	O	3.99
CAQ	Heme	CHC	3.66
		C1C	3.9
		C2C	3.98
		CMC	3.85
CAT	Phe214	CE2	2.98
		CD2	3.47
		CZ	3.74
	Heme	CMC	3.41
SAU	Phe214	CE2	3.72
		CD2	3.71
	Heme	CHC	3.18
		C1C	3.67
		C2C	3.45
		CMC	2.51
CAV	Phe214	CE2	3.87
		CD2	3.25
	Heme	CMC	3.85

References

1. Collaborative Computational Project, N. 4. The CCP4 suite: programs for protein crystallography. *Acta Crystallogr. D. Biol. Crystallogr.* **1994**, 50, 760-763.