Supplementary Information

Structural Basis of Inhibitor Selectivity in Human Indoleamine 2,3-Dioxygenase 1 and Tryptophan Dioxygenase

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Table S1. Crystallographic data collection and refinement statistics. Values in parenthesis are for highest resolution shell.

	hIDO1-IPD / hIDO1-IPD$_2$	**hTDO-IPD[a]**	**hTDO-IPD$_2$**
PDB Code	**6PZ1**	**6PYZ**	**6PYY**
Data collection			
X-ray source	APS 31-ID-D	APS 31-ID-D	APS 31-ID-D
Wavelength (Å)	0.97931	0.97931	0.97931
Space group	$P2_12_12_1$	$P2_12_12$	$P2_12_12$
Unit cell dimensions			
a, b, c (Å)	87.5, 97.8, 132.0	143.6, 154.2, 87.9	144.2, 154.0, 88.0
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å)	78.61-2.65	29.86-2.02	29.90-2.40
No of unique reflections	33561 (4816)	127544 (18361)	77243 (11127)
R_{merge} (%)	13.3 (179)	10.9 (213)	14.8 (127)
R_{pim} (%)	8.0 (107)	4.2 (82.9)	8.9 (78.1)
I/σ(I)	7.4 (1.0)	11.3 (1.1)	7.8 (1.4)
$CC_{1/2}$	0.99 (0.54)	1.00 (0.39)	1.00 (0.39)
Completeness (%)	99.8 (100.0)	99.5 (99.1)	99.9 (99.9)
Redundancy	7.1 (7.2)	7.5 (7.5)	7.2 (7.0)
Refinement			
Resolution (Å)	40.00-2.65	29.86-2.02	29.90-2.40
No of reflections	31777	121109	73360
R_{work}/R_{free}	0.2201/0.2698	0.1893/0.2428	0.1911/0.2374
No of atoms			
Protein	5963	11593	11436
Ligand/Ions	167	304	308
Water	188	1074	412
B factor (mean) (Å^2)	83.5	50.4	53.3
R.m.s. deviations			
Bond lengths (Å)	0.003	0.005	0.008
Bond angles (°)	1.416	1.355	1.692

[a.] The S_{exo} site is occupied by α-methyl tryptophan that is present in the crystallization solution.

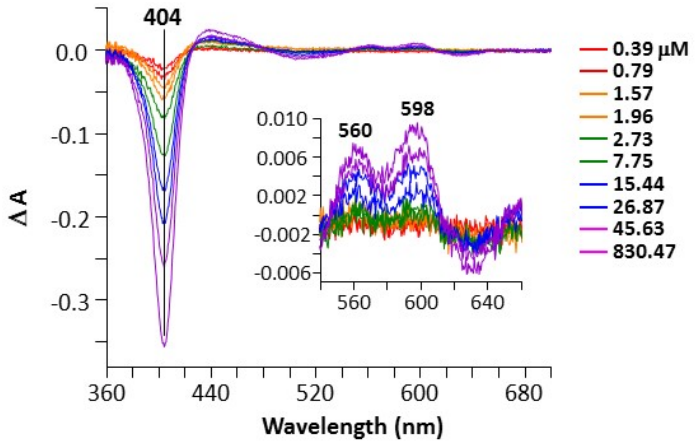

Figure S1. Difference spectra obtained following the titration of ferric hIDO1 with 0-1.2 mM IPD. The spectra were calculated by using the IPD-free spectrum as a reference; only representative spectra are shown here for clarity. The expanded view of the visible bands are shown in the inset.

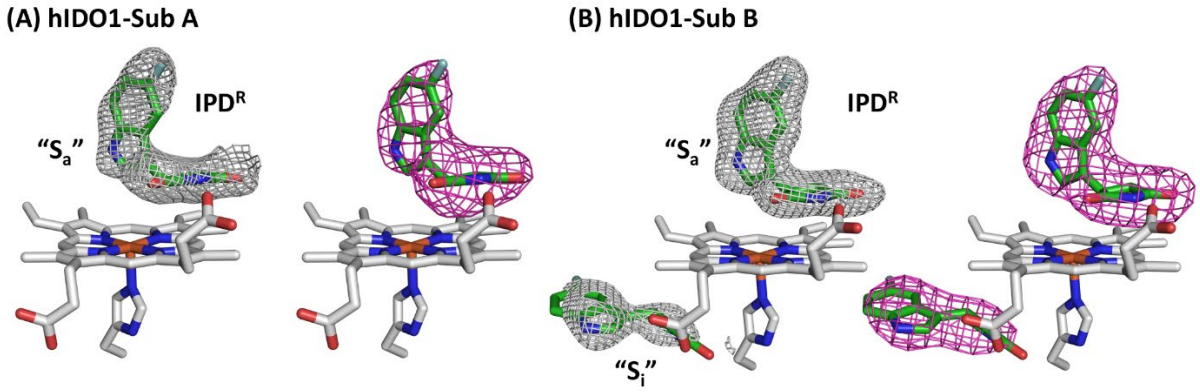

Figure S2. 2Fo-Fc maps (grey) and Polder maps (magenta) of IPD bound in the S_a and S_i sites in hIDO1. The structure is based on the hIDO1-IPD complex (PDB code: 6PZ1), where only the S_a site is occupied by IPD in subunit A (A), while both the S_a and S_i sites are occupied by IPD in subunit B (B). The electron density maps of IPD bound in the S_a site in both subunits are best modeled with the R enantiomer (see the main text), while that in the S_i site in subunit B can be fitted with either the R or S enantiomer due to the weaker electron density. Here only the R enantiomer is shown. The 2Fo-Fc maps and Polder maps are contoured at 1.0 σ and 5.0 σ, respectively.

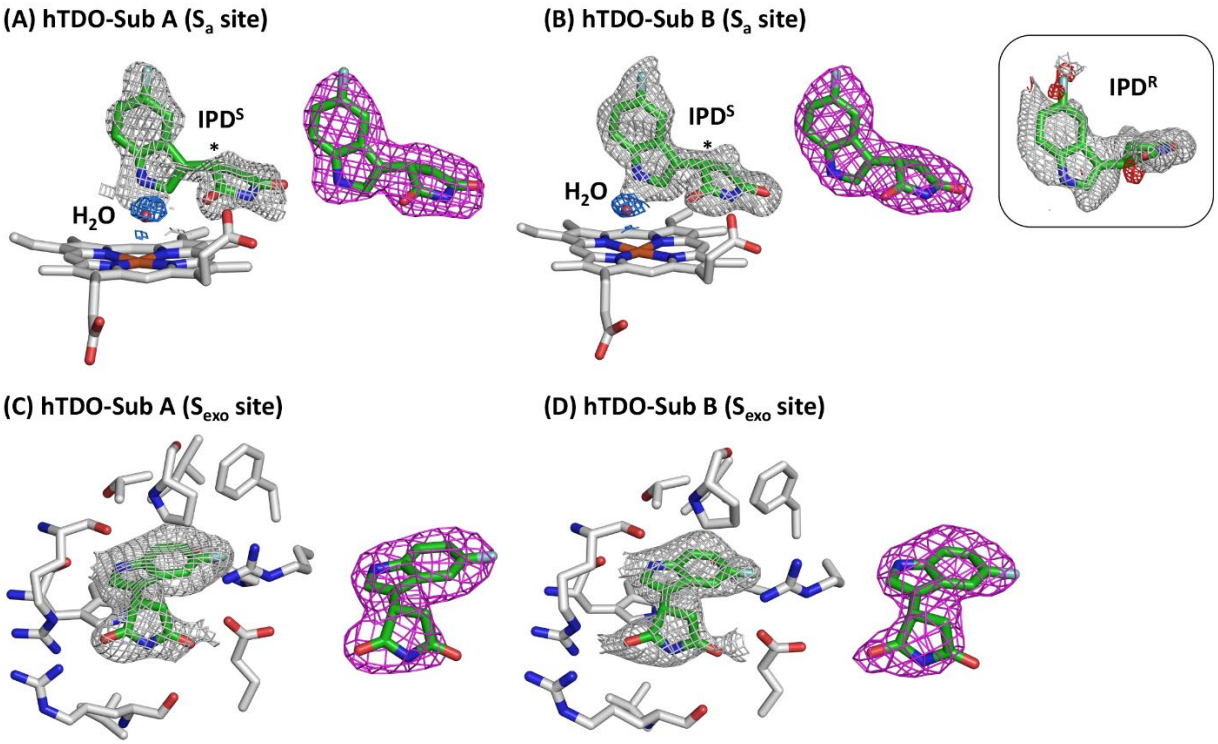

Figure S3. 2Fo-Fc maps (grey) and Polder maps (magenta) of IPD bound in the S_a site (A-B) and S_{exo} site (C-D) in hTDO. hTDO is a homo tetramer made up by a dimer of dimers. The electron density maps of IPD bound in the S_a sites (or S_{exo} sites) in all four subunits are comparable. Here we show the electron density maps of IPD bound in the subunit A and B as examples. The electron density maps of IPD bound in the S_a site in (A-B) are taken from the hTDO-IPD complex (PDB code: 6PYZ) with a resolution of 2.02 Å, where only the S_a site is occupied by IPD in each of the four subunits. They are best modeled with the S enantiomer. The right inset in (B) shows the improper fitting of the electron density with the R enantiomer, as highlighted by the presence of significant negative density in the Fo-Fc map (in red). The electron density maps associated with the distal water are shown in blue. The electron density maps of IPD bound in the S_{exo} site in (C-D) are taken from the hTDO-IPD_2 complex (PDB code: 6PYY), where both the S_a and S_{exo} sites are occupied by IPD in each of the four subunits. The electron density maps of IPD can be fitted with either the R or S enantiomer due to the limited resolution (2.40 Å). Here the density maps are modeled with the S enantiomer. The 2Fo-Fc maps and Polder maps are contoured at 1.0 σ and 5.0 σ, respectively, while the Fo-Fc map in (B) is contoured at 3.0 σ.