SUPPLEMENTAL DATA

Structural and Enzymatic Insights into Species-specific Resistance to Schistosome Parasite Drug Therapy

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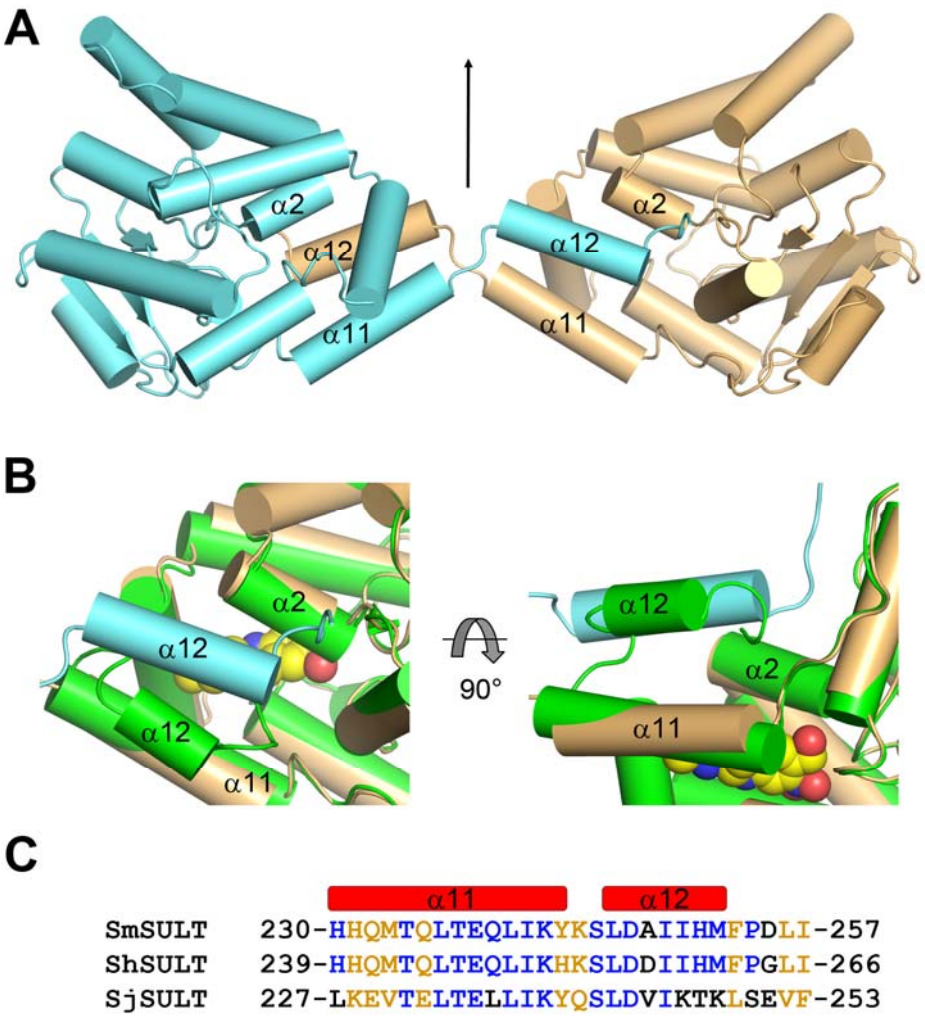
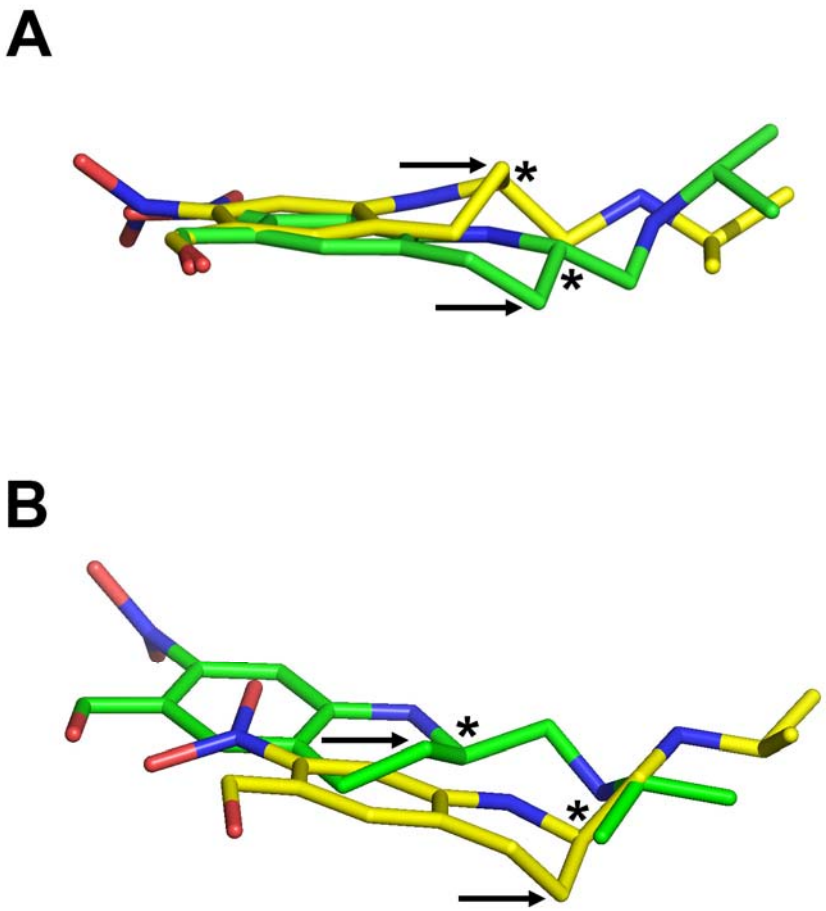
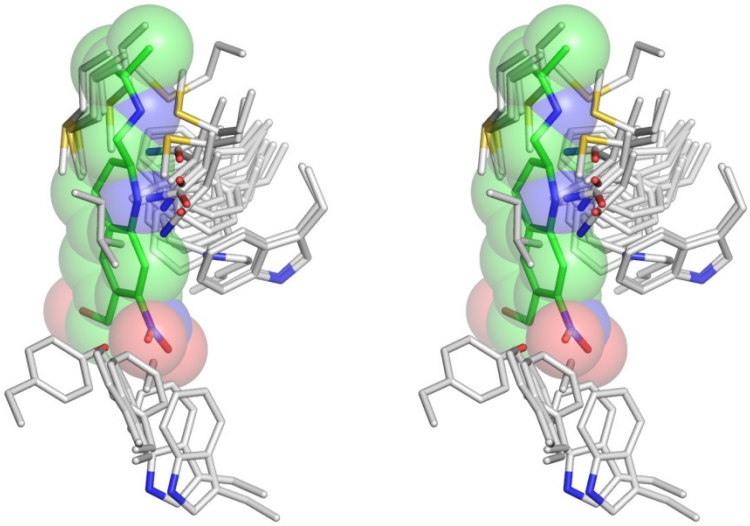


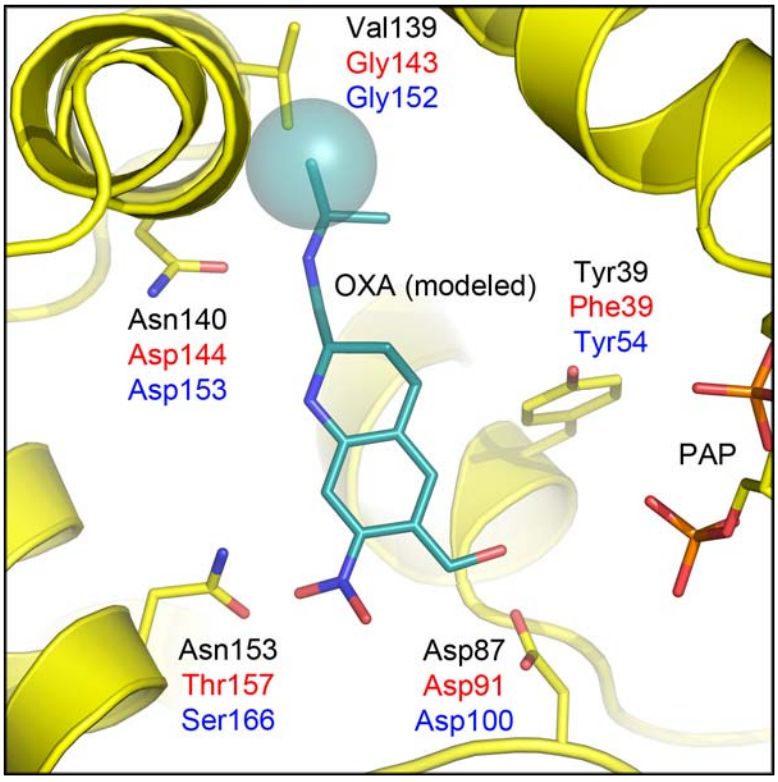
SUPPLEMENTAL FIGURE 1: *A*, structure of the domain swap of the SjSULT C-terminal helix α12 into the neighboring molecule about a crystallographic two-fold axis (shown as an arrow). Individual molecules are shown in cyan and orange. *B*, illustration of the divergent positions adopted by the α12 helices in SjSULT (orange) and the SmSULT:PAP:oxamniquine complex (green). The left and right panels are rotated 90° with respect to each other. Oxamniquine in the SmSULT structure is shown in sphere representation and colored by atom. The α12 helices in both structures do not interact with oxamniquine (see right panel). *C*, sequence alignment of schistosome SULT C-termini. Identities are shown in blue and conservative substitutions are shown in orange. SmSULT and ShSULT secondary structures are depicted above the sequence elements.



SUPPLEMENTAL FIGURE 2: *A*, conformations of *S*-oxamniquine shown in isolation from aligned SmSULT (yellow) and ShSULT (green) complexes. Arrows point to the C3 atoms defining opposite puckers in the piperidine rings and the chiral centers are marked with asterisks. *B*, conformations of *R*-oxamniquine from aligned SmSULT (yellow) and ShSULT (green) complexes marked as in *A*.

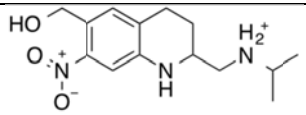
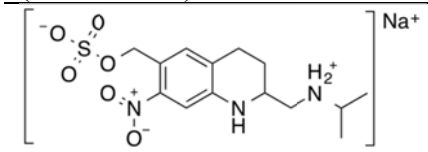
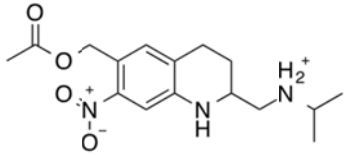
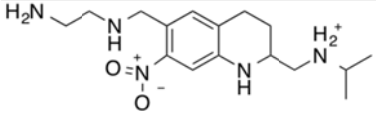


SUPPLEMENTAL FIGURE 3: Wall-eyed stereo view of predicted steric interference with oxamniquine in known human SULT active site structures shows that they likely prohibit interaction with oxamniquine. SmSULT (PDB entry 5BYK) was superimposed onto human SULT enzymes using PyMOL. Oxamniquine is shown in green stick representation with transparent spheres. Human SULT residues that would be in the equivalent position of the oxamniquine-binding site in SmSULT are shown in grey [SULT 1A1 (PDB 1LS6), SULT1A3 (PDB 1CJM), SULT1B1 (PDB 2Z5F), SULT1C1 (PDB 3BFX), SULT1C2 (PDB 2GWH), SULT1C3 (PDB 2H8K), SULT 4A1 (PDB 1ZD1), hydroxysteroid SULT (PDB 1EFH), estrogen SULT (PDB 1G3M), dehydroepiandrosterone SULT (PDB 1J99) and tyrosylprotein SULT (PDB 3AP3)]. All aligned examples have structural elements that impose upon the space that oxamniquine is predicted to occupy for productive turnover.



SUPPLEMENTAL FIGURE 4: Oxamniquine modeled into the SjSULT active site by superposition of the SmSULT:PAP:oxamniquine complex crystal structure (PDB entry 5BYK) onto the SjSULT structure (SmSULT residues in red, ShSULT residues in blue). The transparent sphere indicates a region for potential steric clash with oxamniquine and Val 139. Both SmSULT and ShSULT contain glycine at the equivalent position.

SUPPLEMENTAL TABLE 1. Products of the SULT reaction detected by continuous-flow mass spectrometry.

Enzyme	Buffer	Compound	Observed m/z	Predicted m/z	Relative ion intensities	
					1.2 s	6 s
SmSULT	50 mM 1,2-diamino ethane/acetate, 12.5 mM ammonium acetate, pH 8.0	 oxamniquine ($C_{14}H_{22}N_3O_3$)	280.1658	280.1656	100	65
		 oxamniquine sulfate + Na^+ ($C_{14}H_{21}N_3O_6SNa$)	382.1045	382.1043	0.16	0.042
		 acetyl-oxamniquine ($C_{16}H_{24}N_3O_4$)	322.1762	322.1761	6.0	13
		 oxamniquine-ethanediamine ($C_{16}H_{28}N_5O_2$)	322.2240	322.2238	42	100
	12.5 mM ammonium acetate, pH 7.0	oxamniquine	280.1658	280.1656	100	100
		oxamniquine sulfate + Na^+	382.1046	382.1043	0.99	0.53
		acetyl-oxamniquine	322.1762	322.1761	2.9	7.6
ShSULT	50 mM 1,2-diamino ethane/acetate, 12.5 mM ammonium acetate, pH 8.0	oxamniquine	280.1659	280.1656	100	100
		oxamniquine sulfate + Na^+	382.1047	382.1043	0.043	0.22
		acetyl-oxamniquine	322.1765	322.1761	2.7	19
		oxamniquine-ethanediamine	322.2241	322.2238	8.4	39