Electronic Supplementary Information

Theoretical evaluation of a bulky ortho-thioalkyl-azobenzene as an alternative to photocontrol structural cytotoxic effect of metal-free and disulfide oxidized hSOD1 in pathogenesis of ALS

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Table S1. Optimization energies for different functionals through studies of DFT for 1A and 2A molecules.

Functional	***trans* ortho-TIABP, 1A (Kcal)**	***trans* ortho-TMABP, 2A (Kcal)**
B3LYP	-4,1399e^{-18}	-3.8121e^{-18}
CAM-B3LYP	-4,1386e^{-18}	-3.8109e^{-18}
M06-2X	-4,1381e^{-18}	-3.8106e^{-18}
PBE	-4,1370e^{-18}	-3.8095e^{-18}

Table S2. Theoretical absorption wavelength (λ) and energy (E) for the calibration of functionals for ortho-S-alkyl substituents (*trans* ortho-TIABP (1A) and *trans* ortho-TMABP (2A), respectively). Theoretical values were calculated using the CPCM solvent model (Dimethyl sulfoxide) and the 6-31++G (d,p) basis set.

Molecule	Functional	Excited State	Transition (CI)	λ (nm)/E (eV)
1A	B3LYP	n → π* π → π*	H → L (0.63) H -1 → L (0.70)	529/2.36 444/2.79
	CAM-B3LYP	n → π* π → π*	H → L (0.50) H -1 → L (0.69)	467/2.65 347/3.57
	M06-2X	n → π* π → π*	H → L (0.61) H -1 → L (0.68)	540/2.29 420/2.95
	PBE	n → π* π → π*	H → L (0.61) H -1 → L (0.70)	511/2.42 421/2.95
2A	B3LYP	n → π* π → π*	H → L (0.64) H -1 → L (0.70)	533/2.32 449/2.76
	CAM-B3LYP	n → π* π → π*	H → L (0.63) H -1 → L (0.67)	454/2.72 353/3.44
	M06-2X	n → π* π → π*	H → L (0.66) H -1 → L (0.69)	523/2.37 461/2.69
	PBE	n → π* π → π*	H → L (0.67) H -1 → L (0.69)	499/2.49 450/2.76

Table S3. Absorption properties, including vertical transition energies (λ), oscillator strengths (f) and molecular orbitals involved in the excitation features of the ortho-O-alkyl azobenzenes (ortho-OABPs) and their respective hydrazobenzenes. All calculations were made on Gaussian09.

Azo compound	Isomer	Excited State	Transition (CI)	λ (nm)/E (eV)	*f*
3A	E	n → π*	H → L (0.66)	539/2.29	0.295
		π → π*	H -1 → L (0.69)	358/3.46	0.035
3B	E	n → π*	H → L (0.47)	339/3.66	0.464
		π → π*	H -1 → L (0.42)	331/3.74	0.083
3C	Z	n → π*	H → L (0.69)	498/2.49	0.014
		π → π*	H -1 → L (0.70)	382/3.18	0.003
3D	Z	n → π*	H → L (0.69)	378/3.28	0.113
		π → π*	H -1 → L (0.70)	365/3.40	0.047
4A	E	n → π*	H → L (0.65)	541/2.29	0.319
		π → π*	H -1 → L (0.56)	351/3.54	0.080
4B	E	π → π*	H → L (0.68)	333/3.73	0.060
		n→ π*	H -1 → L (0.52)	336/3.69	0.464
4C	Z	n → π*	H → L (0.69)	472/2.63	0.146
		π → π*	H -1 → L (0.70)	378/2.63	0.032
4D	Z	n → π*	H → L (0.70)	389/3.19	0.153
		π → π*	H -1 → L (0.70)	329/3.19	0.200

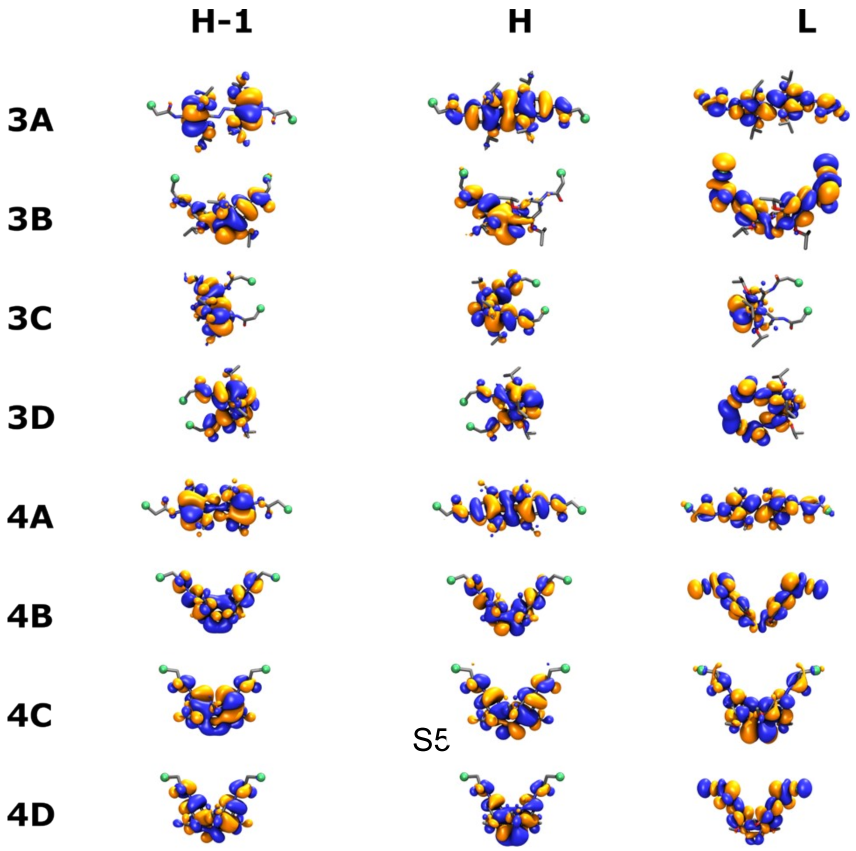


Figure S1. Molecular orbital surface for LUMO (L), HOMO (H) and HOMO-1(H-1) of ortho-O-alkyl azobenzenes (ortho-OABPs) and its corresponding hydrazobenzenes calculated with B3LYP/6-31G(d,p). Solvent was simulated with C-PCM model. 3A and 3B represent ortho-OIABP and their corresponding hydrazobenzenes in the *trans* conformation, while 3C and 3D represent ortho-OIABP and their corresponding hydrazobenzenes in the *cis* conformation. 4A and 4B represent ortho-OMABP and their corresponding hydrazobenzenes in the *trans* conformation, while 4C and 4D represent ortho-OMABP and their corresponding hydrazobenzenes in the *cis* conformation. Representations were obtained from VMD.

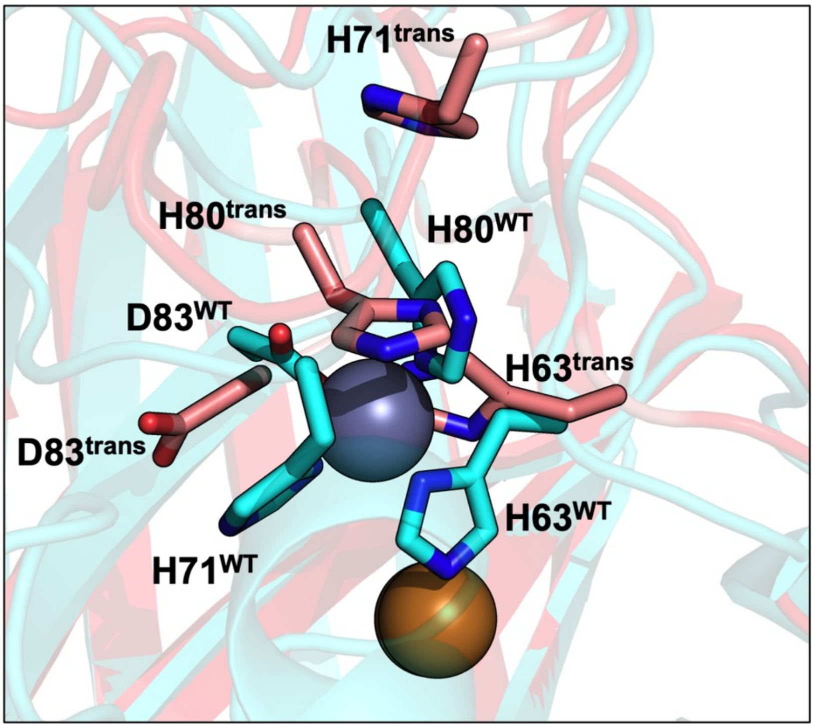
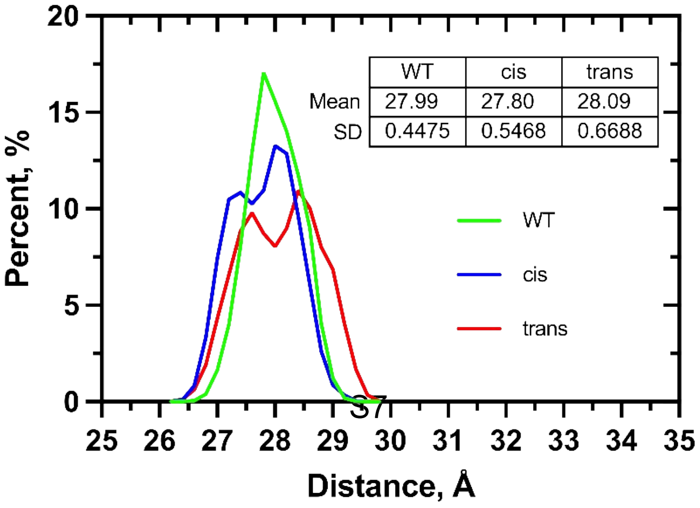


Figure S2. Metal-binding site of apo-hSOD1$^{S\text{-}S}$ and apo-hSOD1$^{S\text{-}S\mathit{trans}}$. The position of the amino acid residues that are part of the Zn(II) coordination site in the apo-hSOD1$^{S\text{-}S}$ and apo-hSOD1$^{S\text{-}S}$ derivatized with one ortho-TABP in *cis* conformation is shown in cyan. The position of the amino acid residues that are part of the Zn(II) coordination site after the transition of the ortho-TABP from *cis* to *trans* conformation is shown in red. Representation obtained from VMD.



	WT	cis	trans
Mean	27.99	27.80	28.09
SD	0.4475	0.5468	0.6688

Figure S3. Probability distribution of the distances between the centres of mass of each monomer in apo-hSOD1$^{S\text{-}S}$, apo-hSOD1$^{S\text{-}S\textit{cis}}$and apo-hSOD1$^{S\text{-}S\textit{trans}}$, calculated by the adaptive biasing force method (ABF).