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Cyclic thiosulfinates "click" couple with dithiols, enabling *in vivo* pharmacological chaperones, an alternative to di-ene-mediated crosslinking, and cargo transport across the cell membrane

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We present cyclic thiolsulfinates as the first tool to permanently modify thiol pairs while transiently binding lone thiols. This tool can be tuned to enable "click" coupling of cyclic thiosulfinates and dithiols, *in vivo* thiol-pair selective probes and pharmacological chaperones, a less toxic alternative to current di-ene crosslinkers for creating biopolymers, active transport of cargo across the cell membrane. 1,2-dithiane-1-oxide was synthesized, administered in human blood, human cell lines, and to an ALS mouse model, and shown to selectively crosslink the dithiol pair (8 Å distance) of Cu/Zn-superoxide dismutase (SOD1) by our proposed mechanism, stabilizing its quaternary structure. Salient characteristics of cyclic thiosulfinate chemistry include: 1) binding one (lone) thiol reversibly, but crosslinking thiols indefinitely; 2) crosslinking is driven by the enthalpies of disulfide bond and water formation; 3) attributes of click chemistry including orthogonality with common protein functional groups, high reaction yields, compatibility with aqueous solvents, and much higher ring strain-dependence than molecules comprised only of period 2 elements.

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