

Targeting the conserved active site of splicing machines with specific and selective small molecule modulators

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The self-splicing group II introns are bacterial and organellar ancestors of the nuclear spliceosome and retro-transposable elements of pharmacological and biotechnological importance. Integrating enzymatic, crystallographic, and simulation studies, we demonstrate how these introns recognize small molecules through their conserved active site. These RNA-binding small molecules selectively inhibit the two steps of splicing by adopting distinctive poses at different stages of catalysis, and by preventing crucial active site conformational changes that are essential for splicing progression. Our data exemplify the enormous power of RNA binders to mechanistically probe vital cellular pathways. Most importantly, by proving that the evolutionarily-conserved RNA core of splicing machines can recognize small molecules specifically, our work provides a solid basis for the rational design of splicing modulators not only against bacterial and organellar introns, but also against the human spliceosome, which is a validated drug target for the treatment of congenital diseases and cancers.