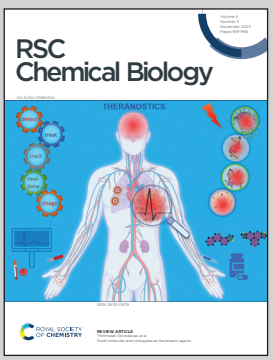
Showcasing research from Drs Jones and Nowak at Dana-Farber Cancer Institute, Boston, USA.

Development of a covalent cereblon-based PROTAC employing a fluorosulfate warhead

Cereblon-directed proteolysis targeting chimeras (PROTACs) have thus far utilized reversible binding ligands of the E3 adapter protein. A covalent degrader was developed for the first time that anchored the heterobifunctional molecule to a histidine residue in the cereblon sensor loop using a fluorosulfate latent electrophile. The BRD4 degrader FS-ARV-825 covalently engaged cereblon in cells and was insensitive to wash-out and competition by potent reversible ligands. This work establishes opportunities to enhance the pharmacodynamic properties of degraders, further expanding the scope of addressable targets using targeted protein degradation.

As featured in:



See Radosław P. Nowak, Lyn H. Jones *et al.*, *RSC Chem. Biol.*, 2023, **4**, 906.

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