Synthetic Approaches to Peptidomimetics

Sam Thompson

aSchool of Chemistry, University of Southampton, Southampton, SO17 1QT

[*https://www.southampton.ac.uk/chemistry/about/staff/st3a15.page*](https://www.southampton.ac.uk/chemistry/about/staff/st3a15.page)

The >650,000 protein-protein interactions (PPIs) that regulate human cellular processes represent a potential therapeutic goldmine, however the large and apparently featureless interfacial protein surfaces of these interactions make them highly demanding targets for small molecule inhibitor design.1 From a synthetic chemistry perspective, the rational design of conformationally pre-organised scaffolds that mimic protein secondary structure is appealing.2 These peptidomimetics are promising but, in common with many non–covalent protein inhibition strategies, they frequently suffer from low potency.

Here we describe a synthetic strategy to dramatically increase the affinity of mimetics for their target protein by forming a covalent bond between the two. Whilst such a covalent approach has been used to great effect for the inhibition of enzymes3 it has not been explored widely with PPIs.4 We focus on boronic acids, and their derivatives, as they have the potential to mediate covalent protein modification with a strong preference for (pairs of) *N*– and *O*–centered Lewis basic amino acid side-chains.

Diagram

Description automatically generated

1 M. R. Arkin, Y. Tang and J. A. Wells, *Chem. Biol.*, 2014, **21**, 1102–1114.

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3 E. E. Manasanch and R. Z. Orlowski, *Nat. Rev. Clin. Oncol.*, 2017, **14**, 417–433.

4 G. Akçay, M. A. Belmonte, B. Aquila, C. Chuaqui, A. W. Hird, M. L. Lamb, P. B. Rawlins, N. Su, S. Tentarelli, N. P. Grimster and Q. Su, *Nat. Chem. Biol.*, 2016, **12**, 931–936.