Targeted Protein Degradation

Degraders (e.g., PROTACs, SNIPERs etc) are bifunctional small molecules that harness the Ubiquitin Proteasome System (UPS) to selectively degrade target proteins within cells. They represent an exciting new modality, repurposing small molecule ligands to achieve selective degradation (knockdown) of target proteins. Moreover, they have the potential to expand the ‘druggable proteome’, since they can be used to degrade proteins that, although bound, are not effectively inhibited by small molecules.

Degraders are modular in design and consist of three, covalently linked components:
- E3 ubiquitin ligase ligand
- Linker
- Warhead ligand for a target protein of interest

Currently, predictions regarding the optimal nature of each component cannot be done a priori and empirical effort is required to guide the development process.

Degrader Database

We have built a ‘Degrader Database’ containing 422 Degraders from 73 published articles published between 2014 and 2019. The database contains both fully optimized Degraders as well as all available published structures of Degraders tested during development, including first generation and poorly performing compounds.

The dataset includes 70 different warhead ligands for 39 different target proteins. The E3 ligase enzymes harnessed by Degraders in the dataset are: Cereblon (CRBN); DDB1 and CUL4-associated factor 15 (DCAF15); Inhibitor of Apoptosis (IAP) proteins; Murine double minute 2 (MDM2) and Von Hippel-Lindau (VHL).

All Degraders were profiled according to the constituent ligands used, linker type, linker length and physicochemical properties.

Beyond the Rule of 5 – Degrader Chemical Space

We compared physicochemical properties for Degraders (taking the average values from compounds in the 4th quartile (by Deg_S) with other published bR50 compound classes.

Properties such as hydrogen bond donor/acceptor count and TPSA are noticeably reduced compared to other bR50 compound classes with similar MW. Conversely, the number of rotatable bonds in Degrader molecules is significantly higher than all other classes considered. This property is conferred by the current predominant use of flexible linker groups.

An alternative, representative view (Figure 3) illustrates the chemical space occupied by Degraders in relation to published predictions of solubility⁶ and membrane permeability⁶. We anticipate that dynamically exposed polarity will be a better measure than TPSA for understanding and predicting Degrader membrane permeability. We plan to explore this in future work.

Developing Degraders

To probe any correlation between Degrader Score and physicochemical properties, data were subject to PCA. The correlation loadings for PC1 versus PC2 are shown in Figure 4. For both predominant classes of Degraders (CRBN- and VHL-based), increased Degrader Score is associated with increasing cLogP and decreasing TPSA and HBD count.

Based on this study we suggest that for new Degrader projects, the HBD count is kept ≤5. We observe that for the highest scoring (Deg_S) Degraders, the TPSA does not exceed 250 Å² and that the highest scoring Degraders have an average cLogP of 6.

Further, we observe that in most cases, simple alkyl and ethylene glycol (PEG) repeating units are sufficient to generate potent, proof of concept Degraders.

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5. Schrödinger, LLC., 2500 Olmstead Ave., Sunnyvale, CA 94086 (2010)