Advanced Toolbox for PROTACs synthesis

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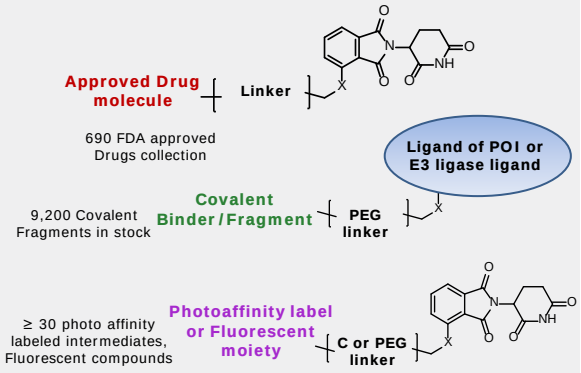
Introduction and Aim

Proteolysis targeting chimeras (PROTACs) is the most interesting emerging field in discovery of new medications. Absolutely new approach with great potential in the reducing of side effects, works through inducing of ubiquitin-proteasome system to remove disease-causing proteins. This new modality of therapeutic intervention requires new chemistry and new approaches to synthesize functional PROTAC molecules.

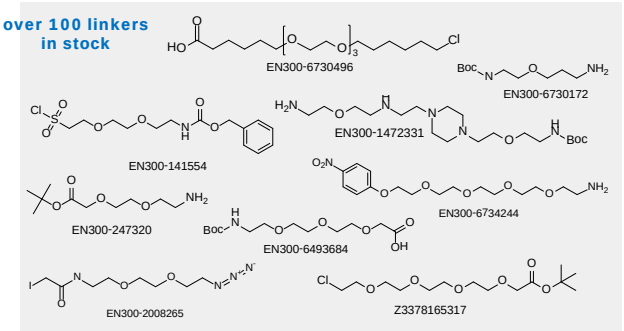
Several recent papers (Oprea et al. and Cravatt's paper) examined chemical space and ligandable proteome to evaluate a state of the targeted human genome. Functionalized and labeled PROTAC molecules are excellent tool to investigate yet undiscovered signaling pathways or new fractions of human proteome. Here in, we describe our first results in synthesis of bifunctional conjugate molecules and would like to show a great potential of this chemistry when combining with reference molecules and potent covalent binders.

Patterns of feasible heterobifunctional molecules



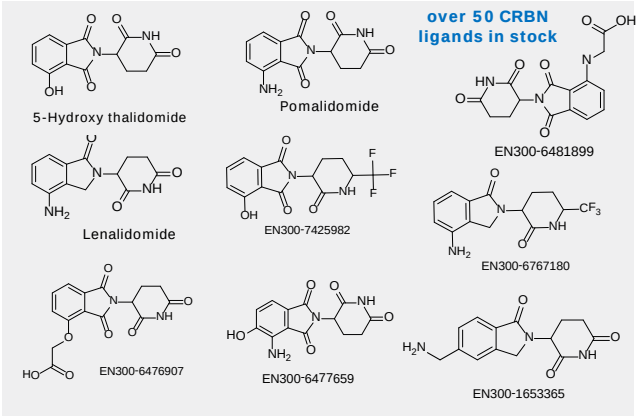
Advanced orthogonal linkers

To facilitate and accelerate synthesis of bifunctional conjugate molecules we created a toolbox, that consist of three distinct parts: high affinity E3 ligase binders, PEG and PEG-like linkers and set of Reference Compounds including FDA approved drugs. This customized library was created from only in-stock intermediates and verified in-house chemistry to facilitate further production of new heterobifunctional molecules.



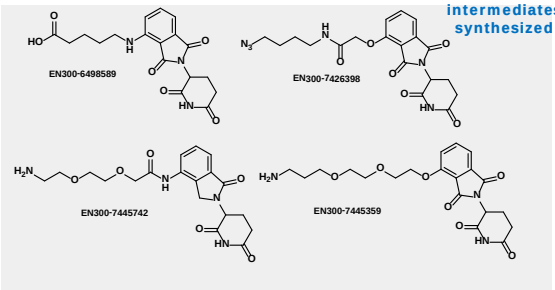
Glutarimide-scaffolds and VHL ligand

High affinity ligands of E3 ligase are key components in construction of new PROTACs. Glutarimides have proved their efficacy in construction of CRBN-recruiting PROTAC molecules. We synthesized a number of Thalidomide and Lenalidomide based intermediates which can be used for further derivatization.



CRBN ligands with linkers

The series of Thalidomide-like CRBN ligands with attached linkers of different length and lipophilicity have been synthesized and now available from stock.

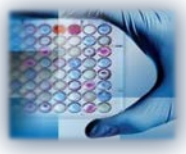


Reference compounds

Our scientific team can provide design and synthesis of functional derivative of reference compounds, that can be further used for synthesis of PROTACs. Collection of Bioreference compounds synthesized in house and their intermediates can be used for fast derivatization.

Bioreference plated compound sets

FDA approved drugs 687cmpds	**Ligase inhibitors** 163 cmpds
Clinical trails library 197cmpds	**CNS library** 85 approved drugs
GPCRs Inhibitors 160cmpds	**Kinase Inhibitors** 240 cmpds



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