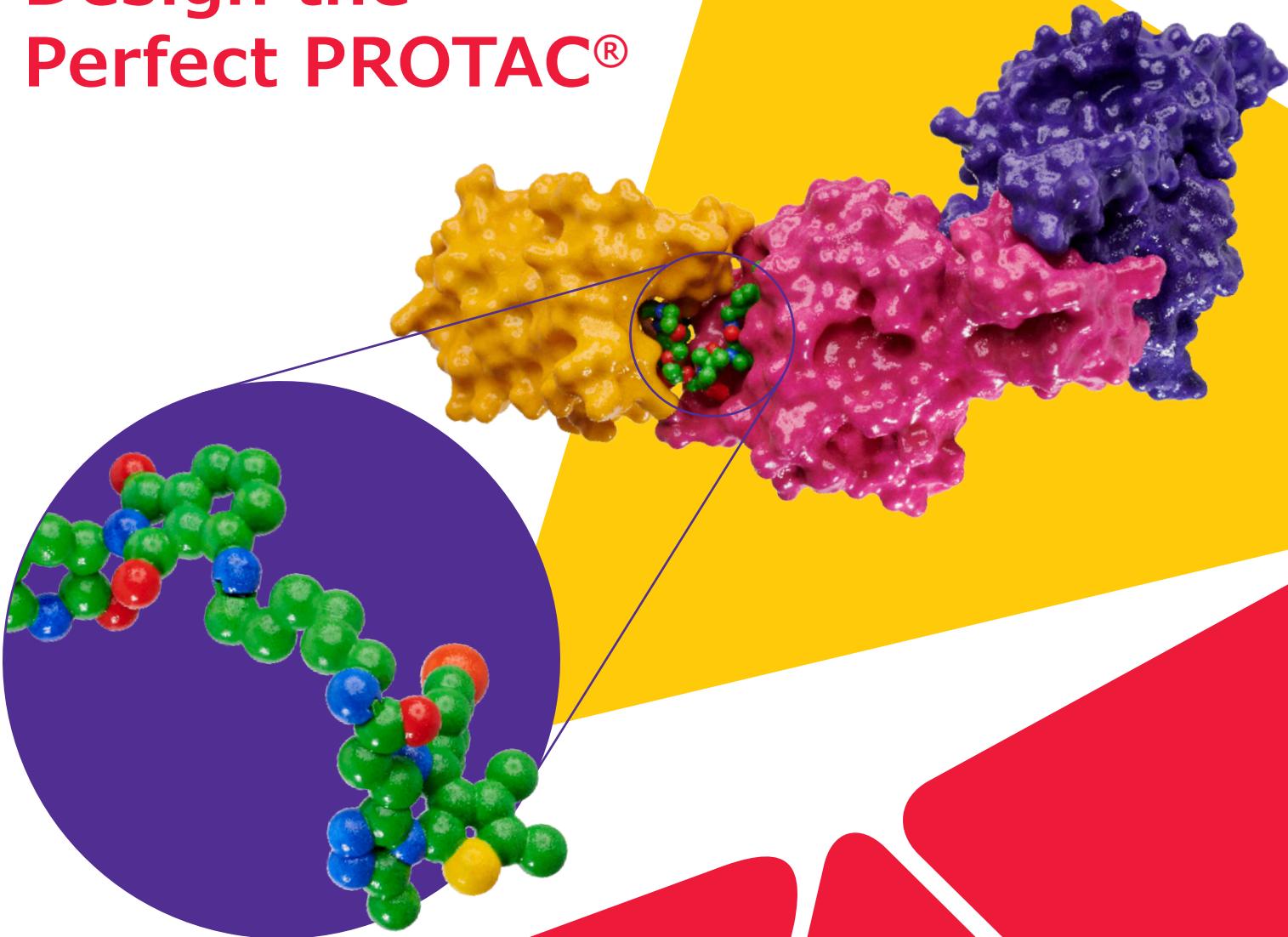
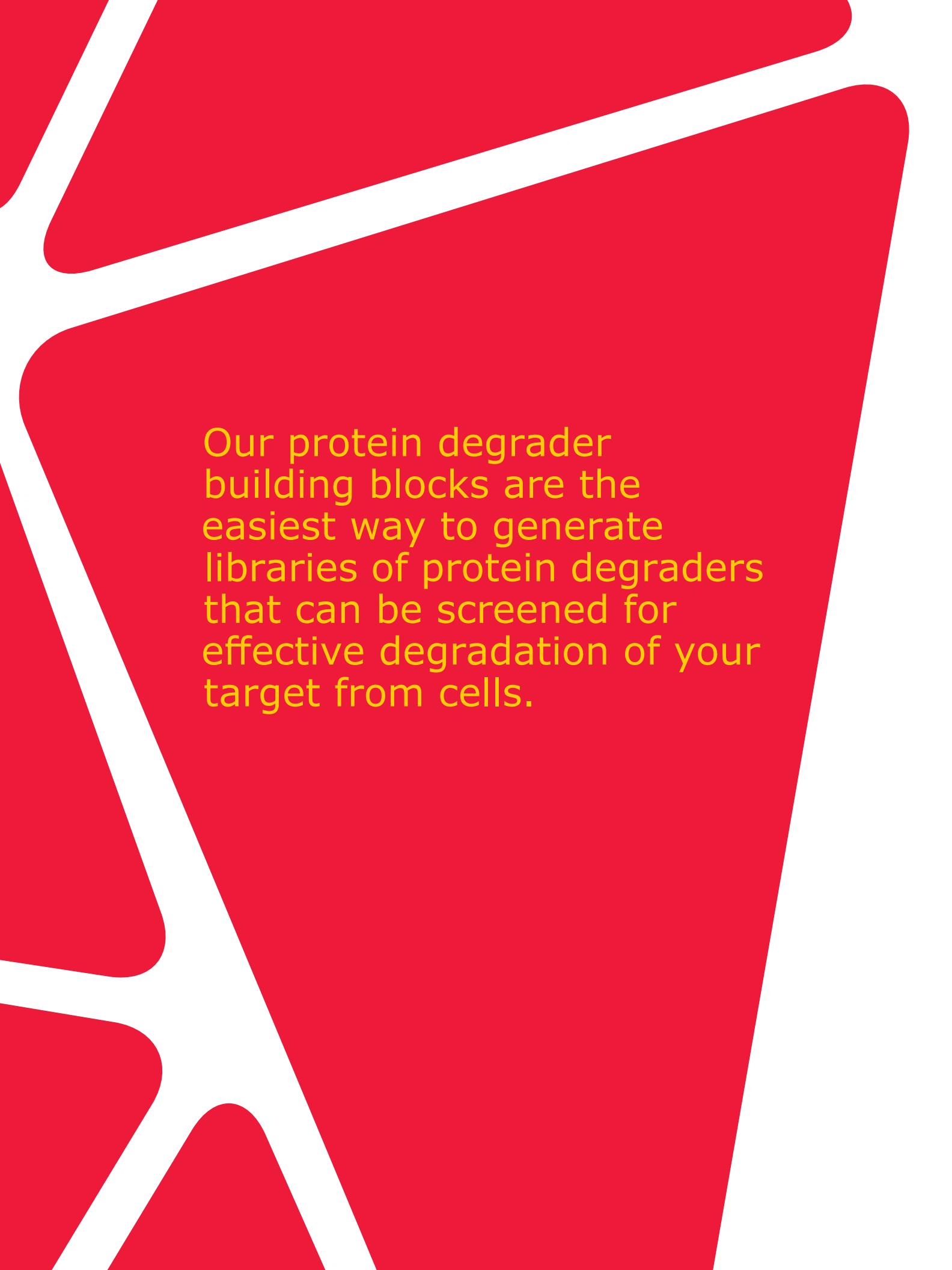


Design the Perfect PROTAC®



The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

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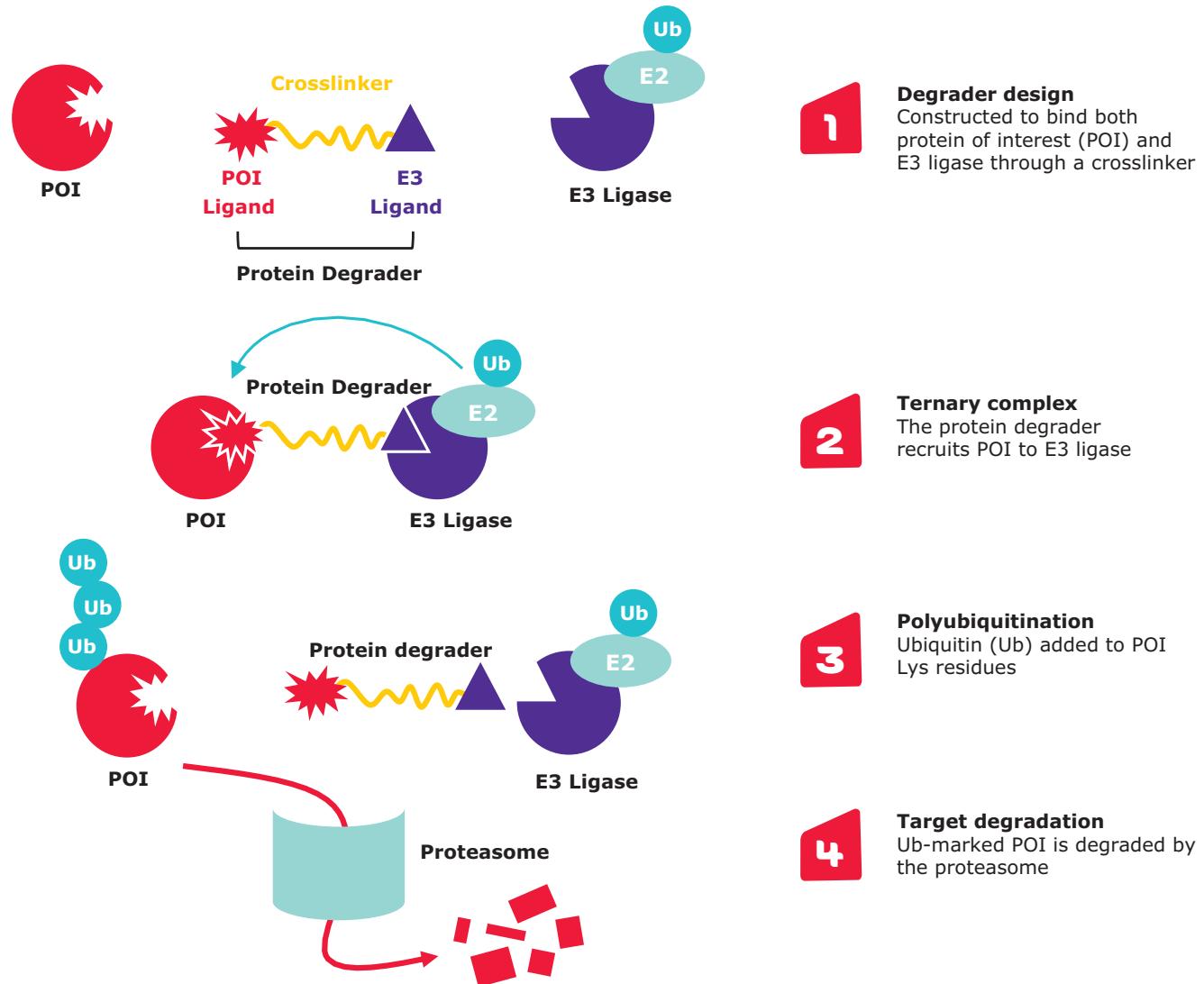
Our protein degrader building blocks are the easiest way to generate libraries of protein degraders that can be screened for effective degradation of your target from cells.

Targeted Protein Degradation

Targeted protein degradation is an emerging drug discovery strategy that allows access to difficult-to-treat diseases. While traditional small-molecule or antibody drugs may only allow access to ~20% of the proteome, degradation techniques may open the door to the other 80%.¹ The molecules used in these approaches are called protein degraders, such as proteolysis targeting chimeras (PROTACs), bifunctional molecules that eliminate target proteins from cells (Figure 1).¹⁻⁵

Figure 1.

Targeted protein degradation via protein degraders (e.g. PROTACs)



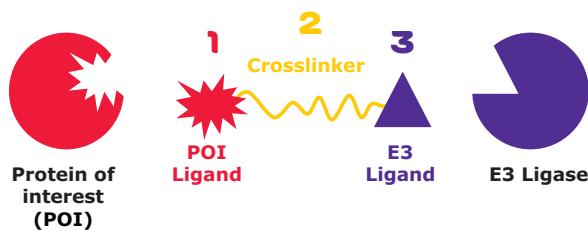
Protein degraders are designed with three primary components: 1) a ligand at one end that targets the protein of interest (POI); 2) a second ligand at the opposite end that binds an E3 ligase; and 3) a crosslinker in the middle that joins the two ends (Figure 2). The simultaneous degrader binding of two proteins brings the POI in close enough proximity for polyubiquitination by the E2 enzyme associated to the E3 ligase, which flags the POI for degradation through the proteasome.¹⁻⁵

Protein Degrader Building Blocks for Target Degradation

The design of small molecules for target degradation is not trivial since even slight alterations in ligands and crosslinkers can affect binding to the POI or E3 ligase.³⁻⁵ Thus, many analogs are synthesized – varying each structure slightly – and screened in cells to discover the optimal degrader for target degradation. To streamline this synthesis, our degrader building blocks are a collection of crosslinker-E3 ligand conjugates with a pendant functional group for covalent linkage to a target ligand (Figure 2). Furthermore, because the same functional group is present across a series, one target ligand can be conjugated to several degrader building blocks in parallel for facile library generation and subsequent screening (Figure 3).

Figure 2.

Full Protein Degrader



Degrader Building Blocks



Protein degrader building blocks are permutations of the following components:

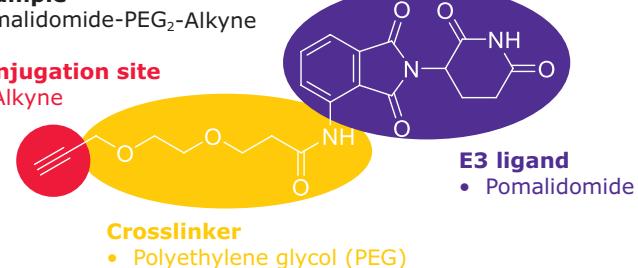
- Ligands targeting the E3 ligase Cereblon (CRBN) or von Hippel–Lindau (VHL)
- Crosslinkers with varied lengths and compositions
- Conjugation sites with reactivity for common functional groups

Degrader Building Block Components

Conjugation Site	Crosslinker	E3 Ligand
 H ₂ N—CH ₂ —CH ₂ —NH ₂ HO—CH ₂ —CH ₂ —COOH	 O—CH ₂ —CH ₂ —O— CH ₂ —CH=CH—CH ₂ — CH ₂ —C≡C—CH ₂ —	
Reactivity for: • Common functional groups • Click chemistry	Variations include: • Spacer length • Composition	Small molecules targeting: • Cereblon (CRBN) • von Hippel–Lindau (VHL)

Example

Pomalidomide-PEG₂-Alkyne

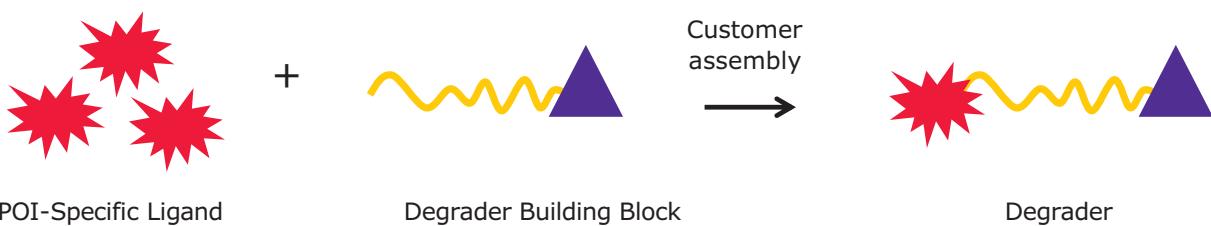


Advantages

- **Compatibility:** Linkers conjugate to common functional groups present on target ligands.
- **Molecule design:** Strategic variety encompassed in the combinations of linkers and ligands aids the design of target degraders.
- **Synthetic time-saver:** The E3 ligand-crosslinker conjugates decrease the amount of time spent on degrader synthesis.
- **Library generation:** Using degrader building blocks with the same conjugation site enables the simultaneous generation of several degraders via parallel synthesis.

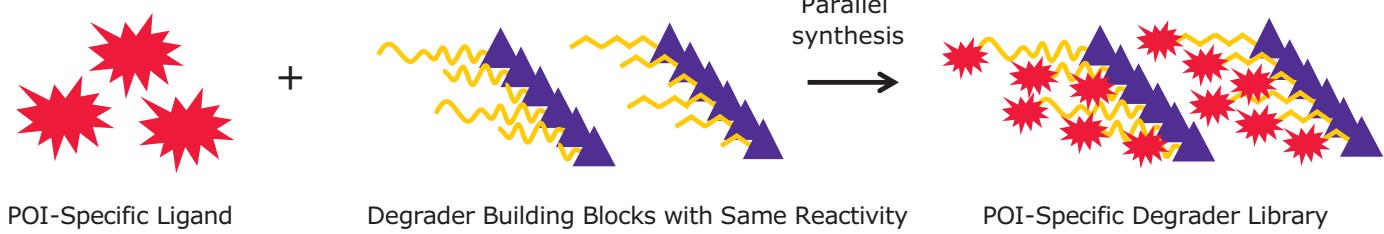
Figure 3.

Degrader Synthesis



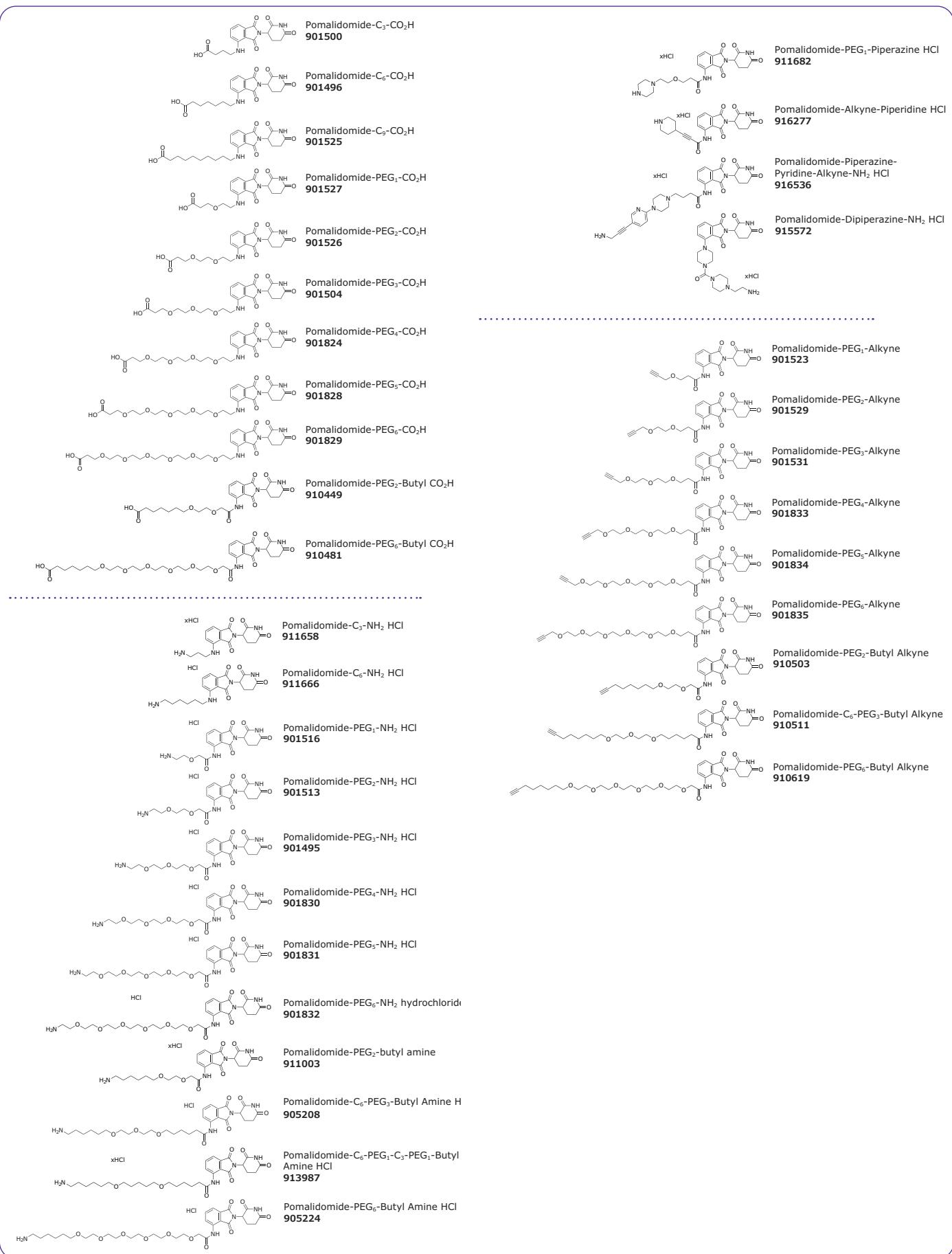
Degrader building blocks simplify the synthesis of PROTACs.

Degrader Library Generation

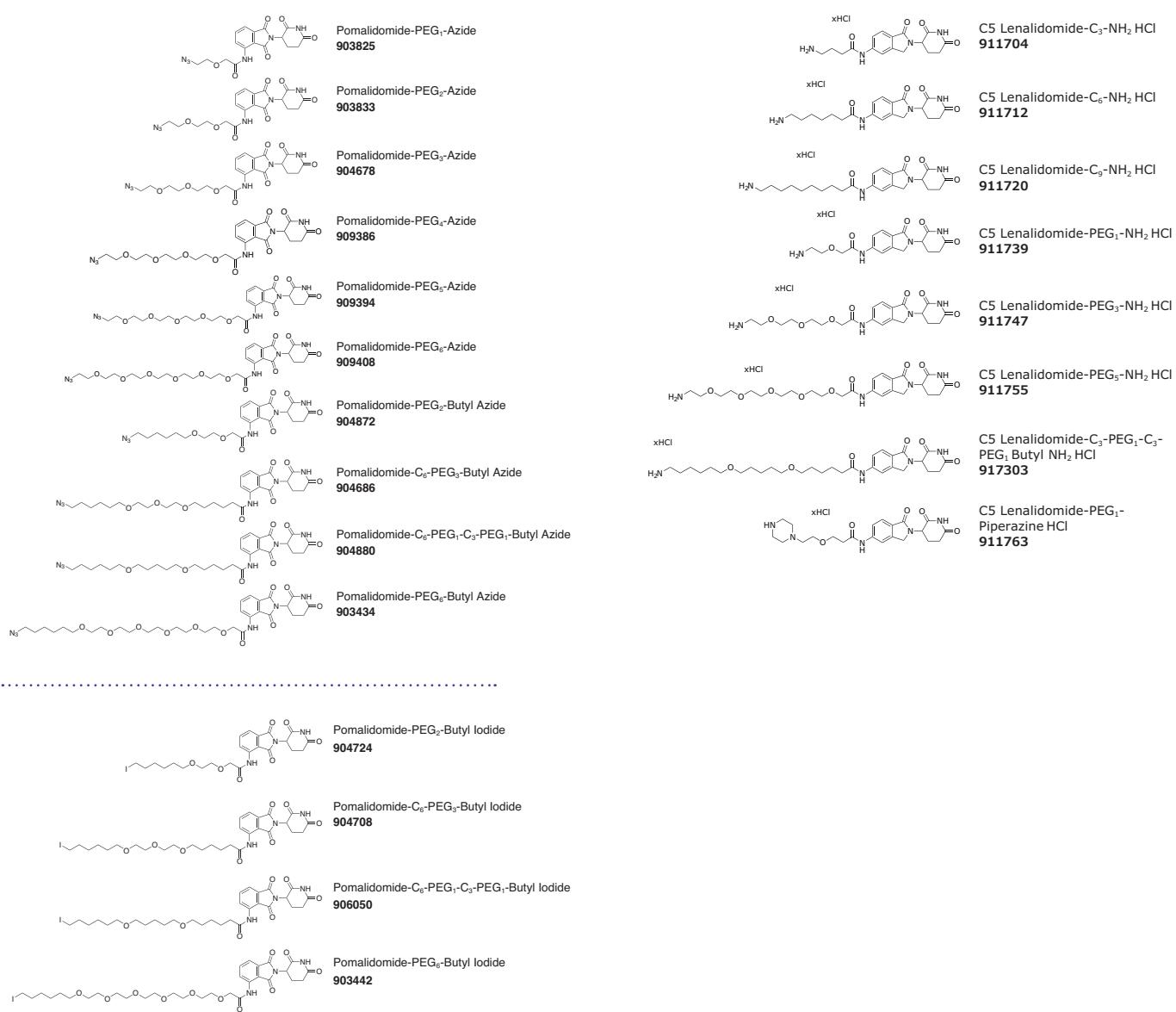


Use of a set of degrader building blocks with the same conjugation site streamlines the synthesis of libraries.

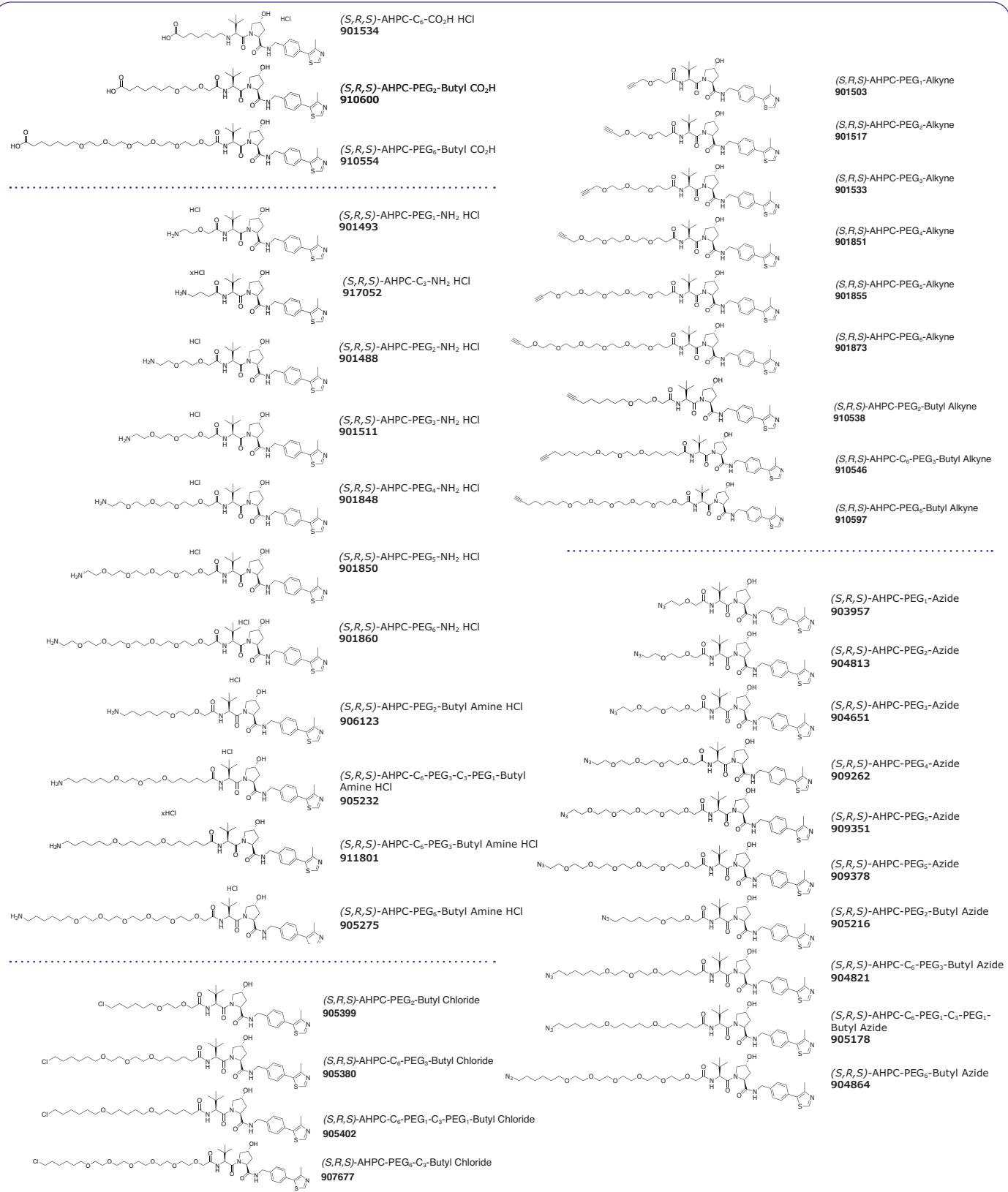
Protein Degrader Building Blocks for CRBN



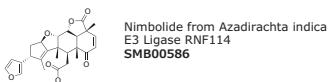
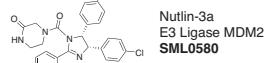
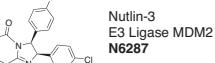
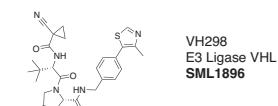
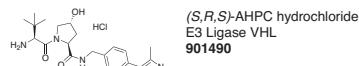
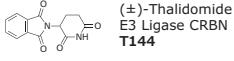
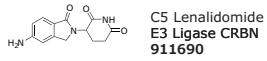
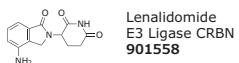
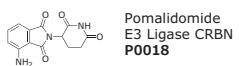
Protein Degrader Building Blocks for CRBN (continued)



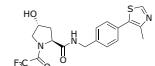
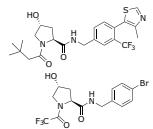
Protein Degrader Building Blocks for VHL



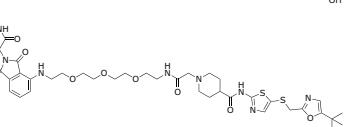
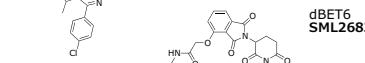
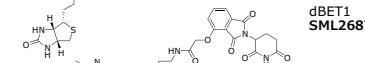
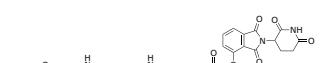
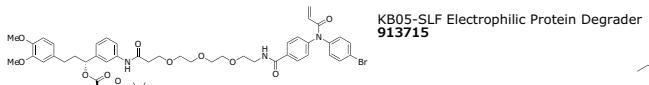
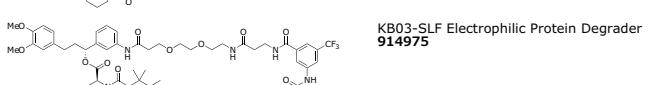
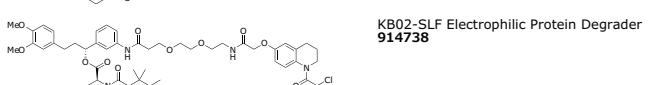
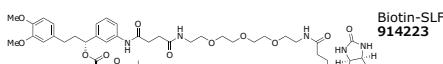
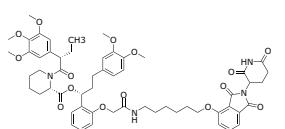
Ligands



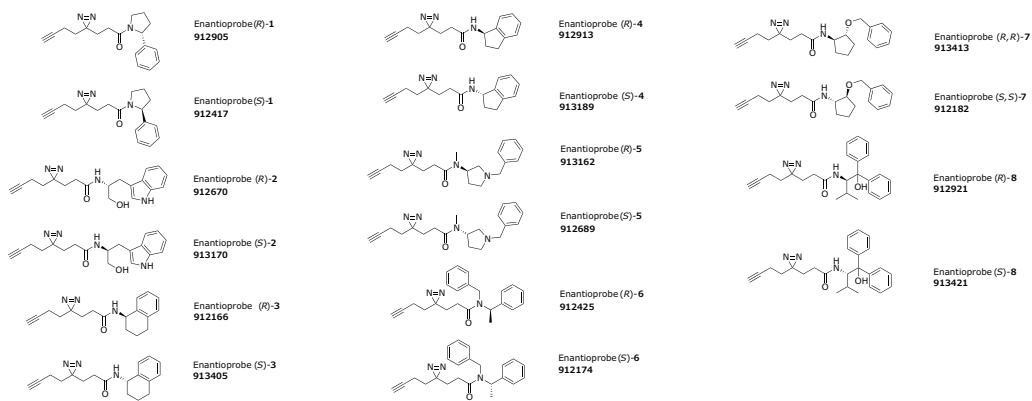
Spy Molecules for VHL Ligand Discovery



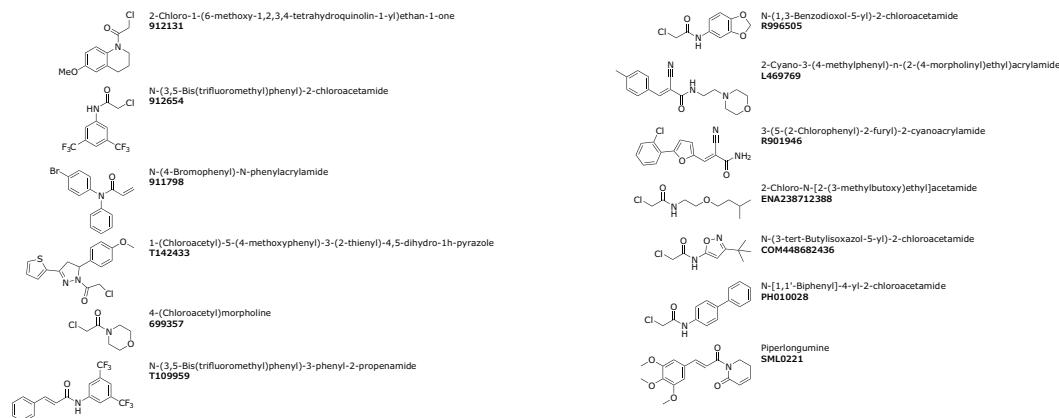
Protein Degraders and Lead Discovery Tools



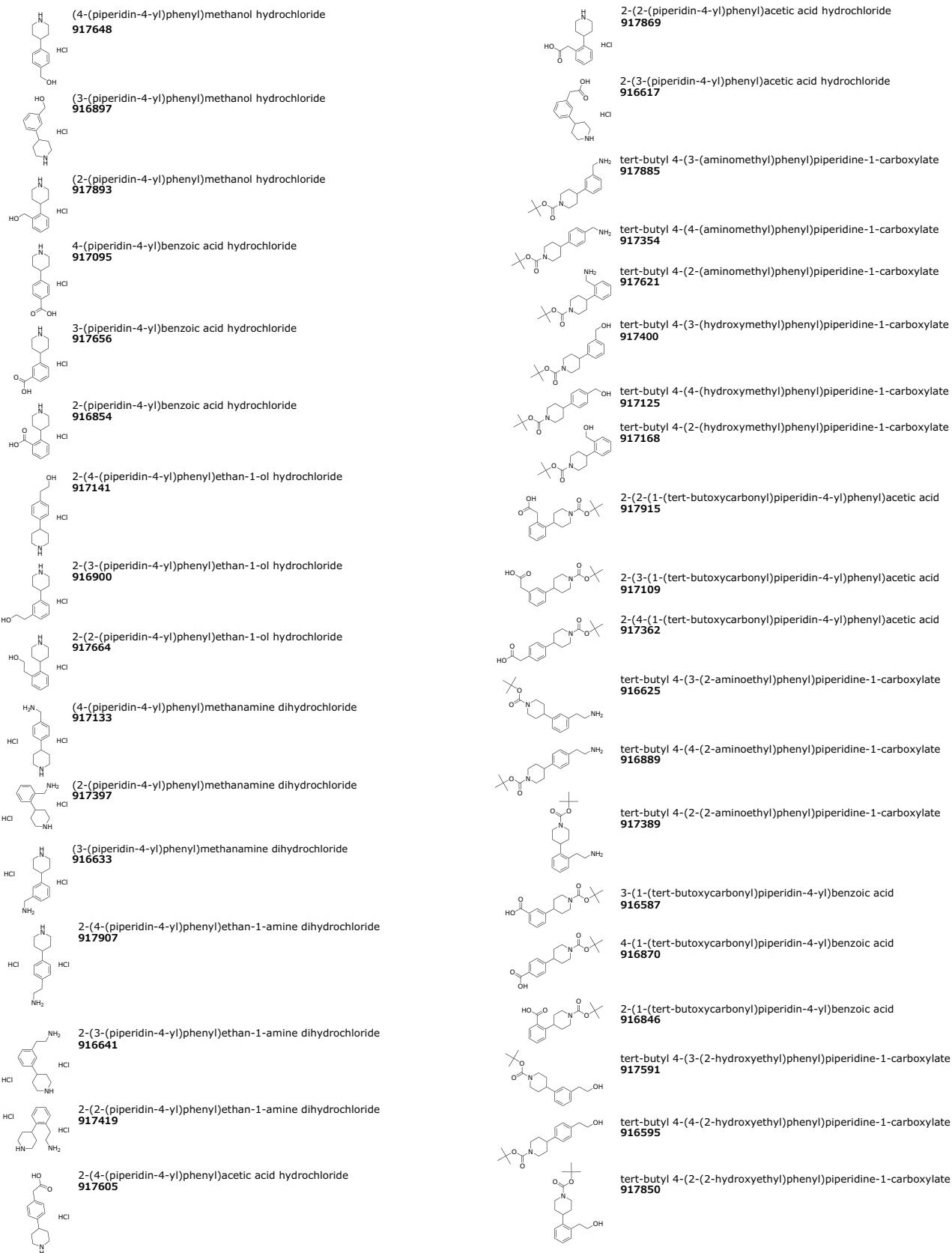
Fully Functionalized Enantiomeric Fragments for Proteome Ligandability Assessment



Electrophilic Scout Fragments for Cysteine Labeling



Semi-Flexible Crosslinkers

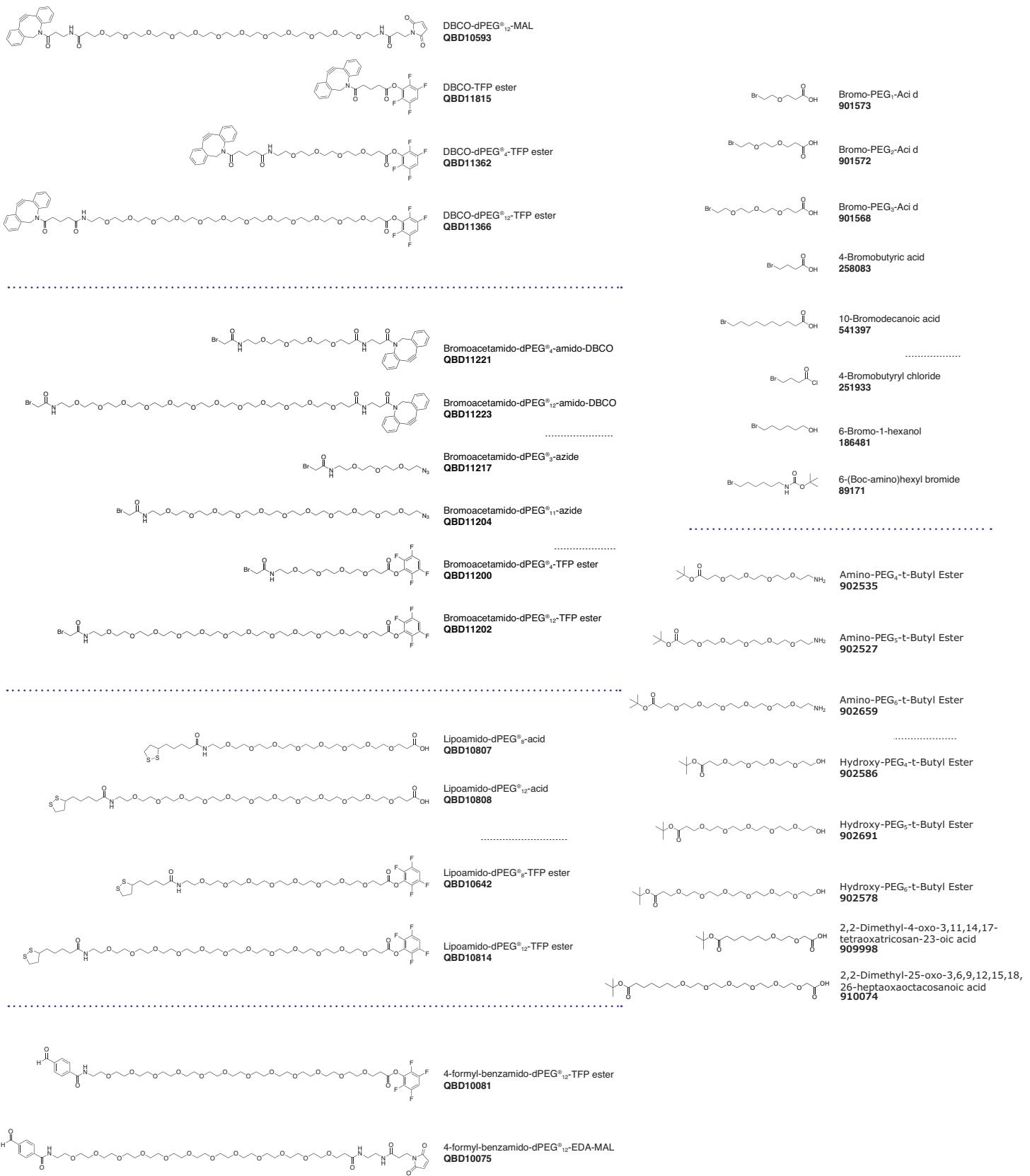


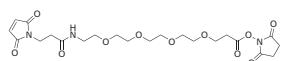
Heterobifunctional Crosslinkers

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	Propargyl-PEG ₃ -Acid 901565		4-(Fmoc-amino)-1-butanol 47295
	Propargyl-PEG ₄ -Acid 902543		5-(Fmoc-amino)-1-pentanol 47299
	Alkyne-PEG ₅ -Acid 764167		6-(Fmoc-amino)-1-hexanol 47297
	Propargyl-PEG ₆ -Acid 902667		N-Fmoc-ethylenediamine hydrobromide 47542
	Amino-PEG ₄ -Alkyne 764248		N-Fmoc-1,3-propanediamine hydrobromide 47556
	Propargyl-dPEG [®] ₁ -NHS ester QBD10511		N-Fmoc-1,4-butanediamine hydrobromide 47541
	2-(2-Oct-7-yn-1-yloxy)acetic acid 910058		N-Fmoc-cadaverine hydrobromide 47544
	6-(2-(2-Oct-7-yn-1-yloxy)ethoxy)hexanoic acid 910066		N-Fmoc-1,6-hexanediamine hydrobromide 47543
	3,6,9,12,15,18-Hexaoxahexacos-25-ynoic acid 910023		N-Fmoc-2-bromoethylamine 09767
	14-Azido-3,6,9,12-Tetraoxatetradecanoic Acid Soluti 744751		3-(Fmoc-amino)propyl bromide 76061
	14-Azido-3,6,9,12-Tetraoxatetradecan-1-Amine 901138		2-(Boc-amino)ethanethiol 458910
	17-Azido-3,6,9,12,15-Pentaoxaheptadecan-1-Amine 901155		
	Azido-dPEG [®] ₁₂ -TPF ester QBD10567		t-Boc-N-Amido-PEG ₁ -CH ₂ CO ₂ H 901579
	Azido-dPEG [®] ₁₂ -amine QBD10569		t-Boc-N-Amido-PEG ₂ -CH ₂ CO ₂ H 901577
	Azido-dPEG [®] ₃ -amine QBD10522		t-Boc-N-Amido-PEG ₃ -CH ₂ CO ₂ H 901575
	Azido-dPEG [®] ₁₁ -amine QBD10523		BocNH-PEG ₄ -acid 902551
	Azido-dPEG [®] ₁₁ -amine QBD10524		BocNH-PEG ₅ -Acid 902683
	Azido-dPEG [®] ₈ -NHS ester QBD10501		BocNH-PEG ₆ -Acid 902683
	Azido-dPEG [®] ₈ -NHS ester QBD10503		N-Boc-N-Succinyl-4,7,10-Trioxa-1,13-Tridecanediamine 671401
	Azido-dPEG [®] ₁₂ -NHS ester QBD10505		15-(Boc-amino)-4,7,10,13-tetraoxapentadecanoic acid 30953
	Azido-dPEG [®] ₈ -acid QBD10502		21-(Boc-amino)-4,7,10,13,16,19-hexaoxaheneicosanoic acid 38263
	20-17-Azido-3,6,9,12,15-pentaoxaheptadecanoic acid 910015		N-Boc-2,2'-(ethylenedioxy)diethylamin 89761
	Azido-3,6,9,12,15,18-hexaoxaicosanoic acid 910007		N-Boc-4,7,10-Trioxa-1,13-Tridecanediamine 93113
	Azido-dPEG [®] ₁₂ -acid QBD10513		

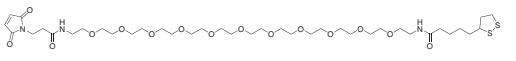
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	4-(Boc-amino)-1-butanol 15302		Fmoc-N-amido-dPEG ¹² -TFP ester QBD11006
	6-(Boc-amino)-1-hexanol 15304
	5-(Boc-amino)-1-pentanol 15307		Fmoc-N-amido-dPEG ⁴ -NHS ester QBD10994
	<i>N</i> -Boc-ethylenediamine 15369		Fmoc-N-amido-dPEG ⁸ -NHS ester QBD10995
	<i>N</i> -Boc- <i>N</i> -methylethylenediamine 15567		Fmoc-N-amido-dPEG ¹² -NHS ester QBD10996
	<i>N</i> -Boc-1,3-propanediamine 15408
	<i>N</i> -Boc-1,4-butanediamine 15404		Fmoc-N-amido-dPEG ⁴ -acid QBD10213
	<i>N</i> -Boc-cadaverine 15406		<i>N</i> -Fmoc- <i>N</i> -Succinyl-4,7,10-Trioxa-1,13-Tridecaned 671517
	<i>N</i> -Boc-1,6-hexanediamine 79229		Fmoc-N-amido-dPEG ⁸ -acid QBD10273
	2-(Boc-amino)ethyl bromide 17354
	3-(Boc-amino)propyl bromide 17356		Acid-dPEG ⁵ -NHS ester QBD10109
	4-(Boc-amino)butyl bromide 90303		Acid-dPEG ⁹ -NHS ester QBD10119
	<i>N</i> -Boc-1,6-hexanediamine hydrochloride 437018		Acid-dPEG ¹³ -NHS ester QBD10127
	<i>N</i> -Boc-2-isothiocyanatoethylamine 15524
	<i>N</i> -Boc-3-isothiocyanatopropylamine 15530
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	Benzyl <i>N</i> -(3-hydroxypropyl)carbamate 478709		Amino-dPEG ⁴ -acid QBD10244
			Amino-dPEG ⁶ -acid QBD10067
			Amino-dPEG ⁸ -acid QBD10277
	<i>N</i> -(4-Bromobutyl)phthalimide 100919		Amino-dPEG ¹² -acid QBD10287
	<i>N</i> -(2-Bromoethyl)phthalimide B66302		Amino-dPEG ⁴ -OH QBD10249

Heterobifunctional Crosslinkers (continued)

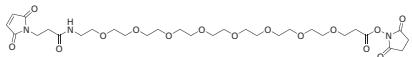




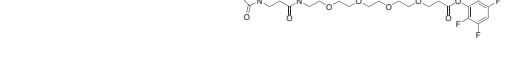
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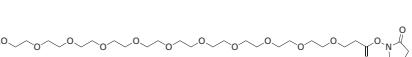
MAL-dPEG[®]₄-Lipoamide
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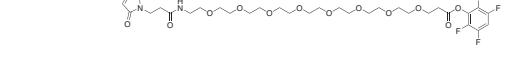
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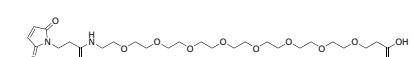
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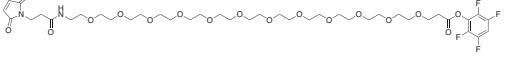
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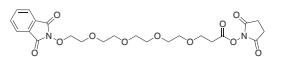
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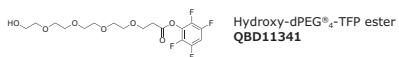
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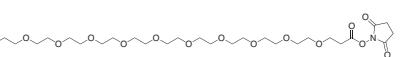
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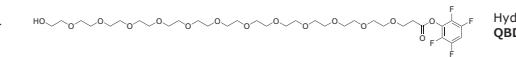
Phthalimidooxy-dPEG[®]₄-NHS ester
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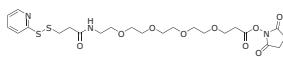
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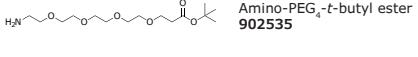
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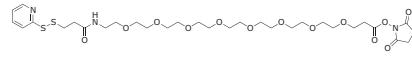
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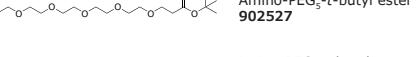
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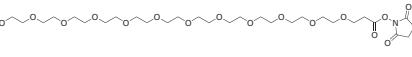
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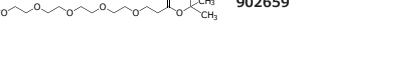
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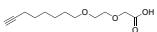
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902527



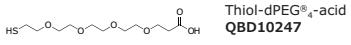
SPDP-dPEG[®]₁₂-NHS ester
QBD10378



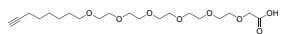
Amino-PEG₆-t-butyl ester
902659



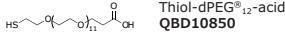
2-(2-(Oct-7-yn-1-yloxy)ethoxy)acetic acid
910058



Thiol-dPEG[®]₄-acid
QBD10247



3,6,9,12,15,18-Hexaoxahexacos-25-yonic acid
910023



Thiol-dPEG[®]₁₂-acid
QBD10850

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