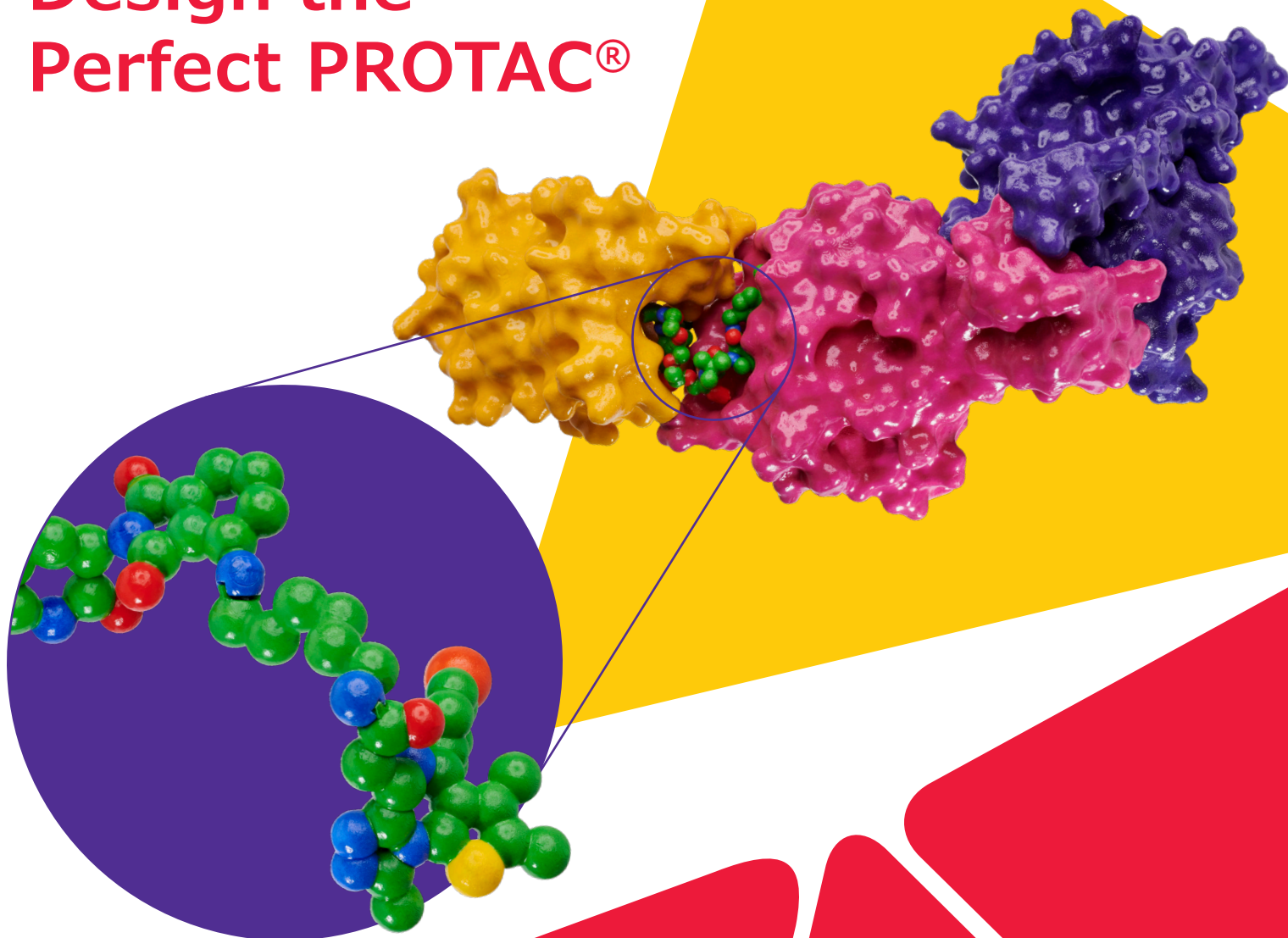


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Our protein degrader building blocks are the easiest way to generate libraries of protein degraders that can be screened for effective degradation of your target from cells.

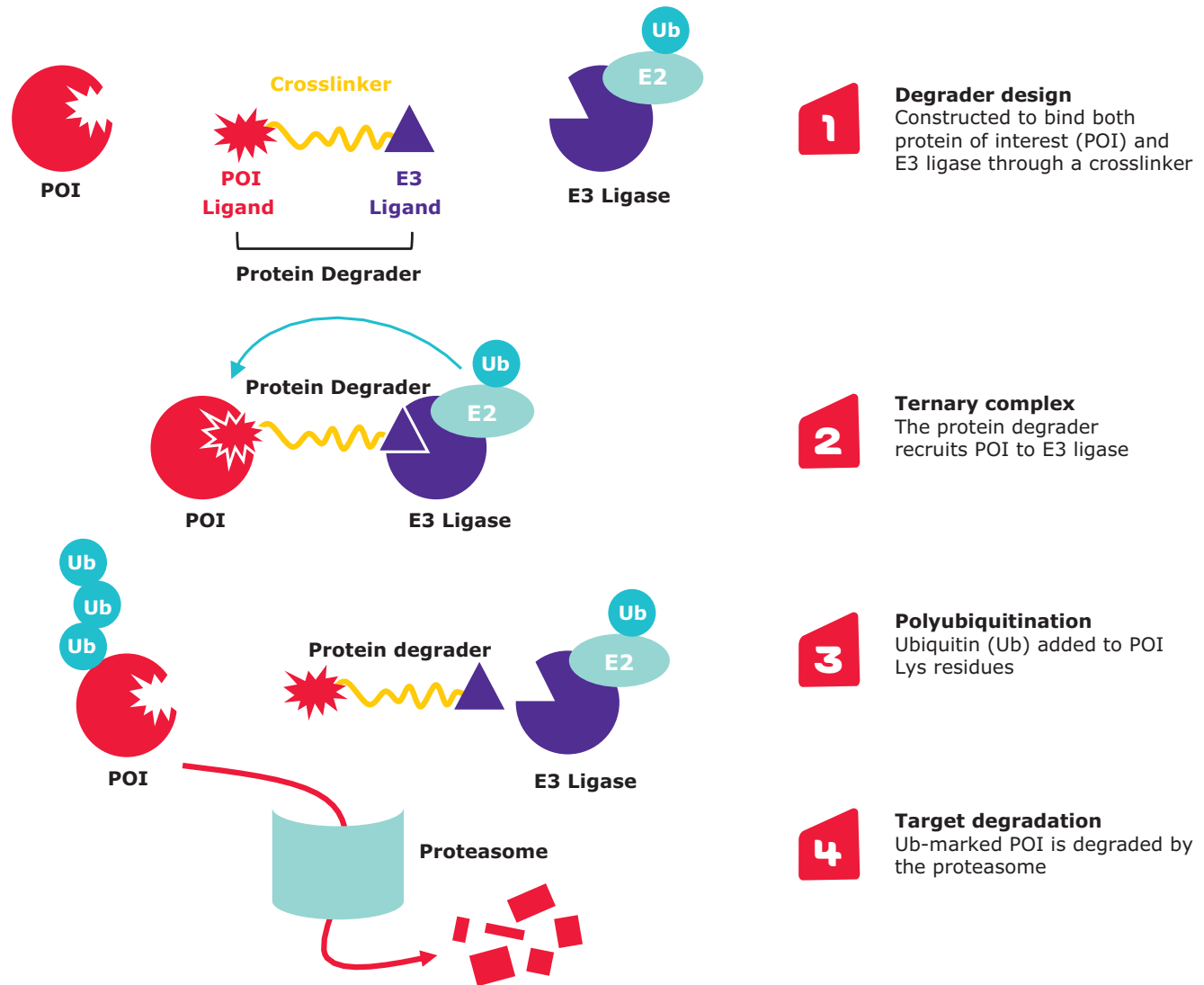
Targeted Protein Degradation

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

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

Figure 1.

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

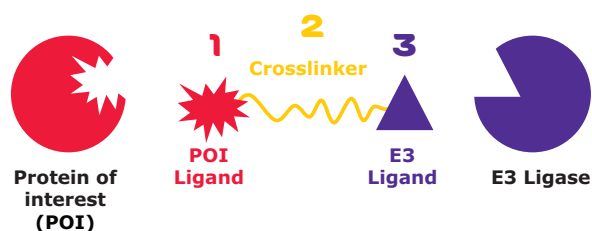


Protein Degradation Building Blocks for Target Degradation

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 Degradation



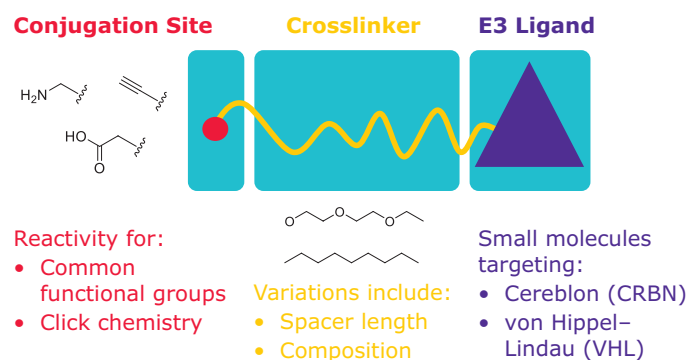
Degradation Building Blocks



Protein degradation 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

Degradation Building Block Components



Example

Pomalidomide-PEG₂-Alkyne

Conjugation site

- Alkyne



E3 ligand

- Pomalidomide

Crosslinker

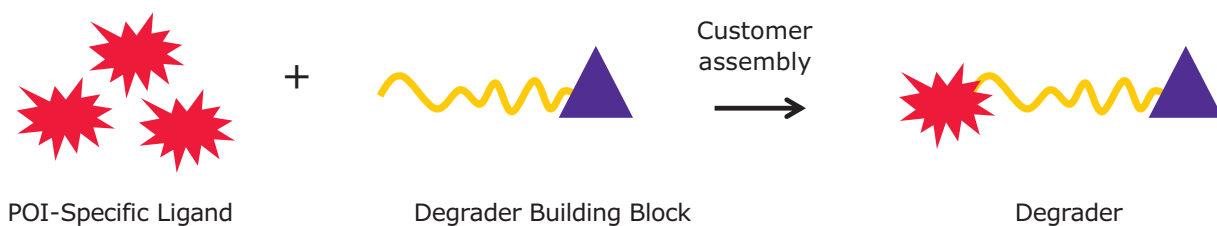
- Polyethylene glycol (PEG)

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.

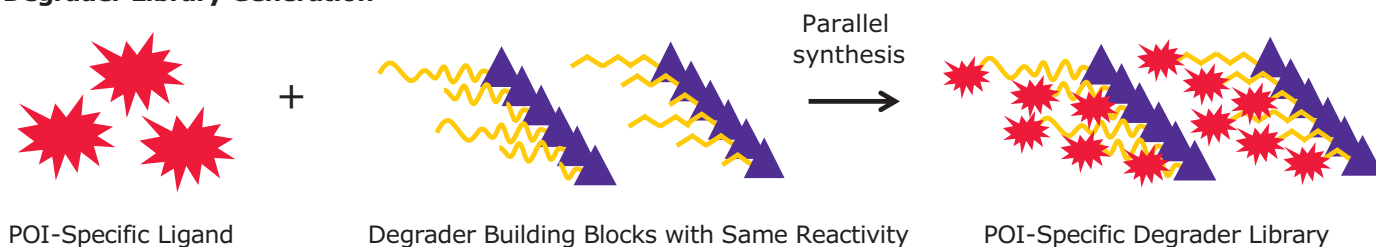
Figure 3.

Degrader Synthesis



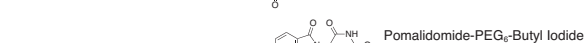
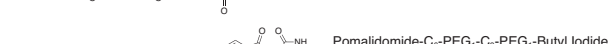
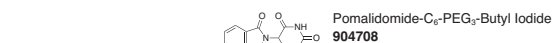
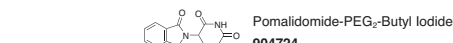
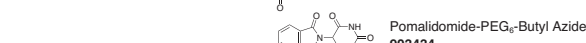
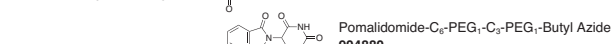
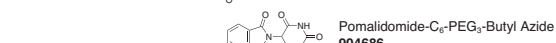
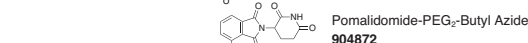
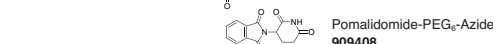
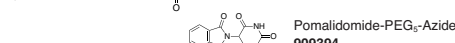
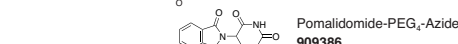
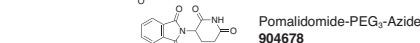
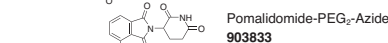
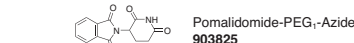
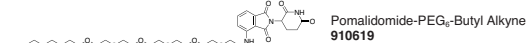
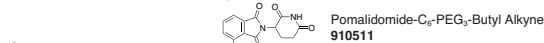
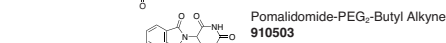
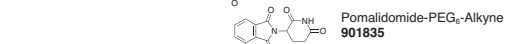
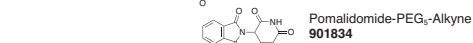
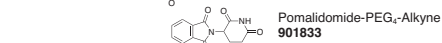
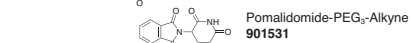
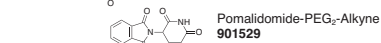
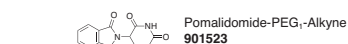
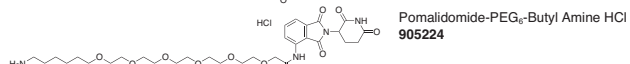
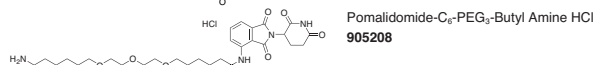
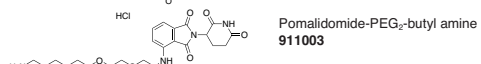
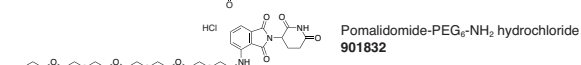
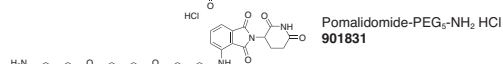
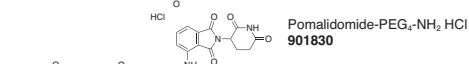
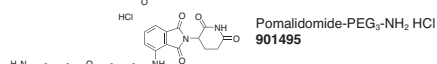
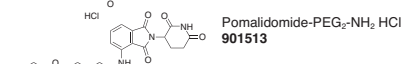
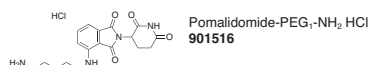
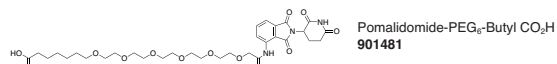
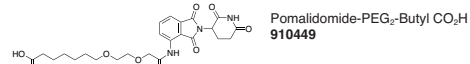
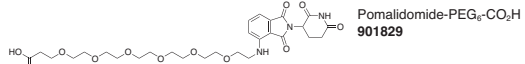
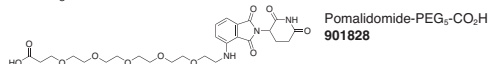
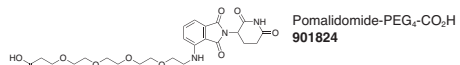
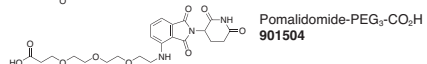
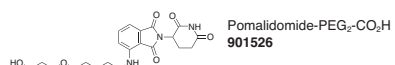
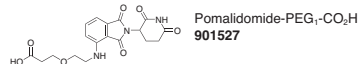
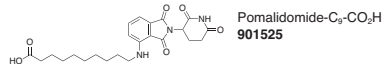
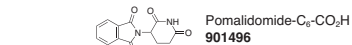
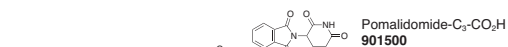
Degrader building blocks simplify the synthesis of PROTACs.

Degrader Library Generation

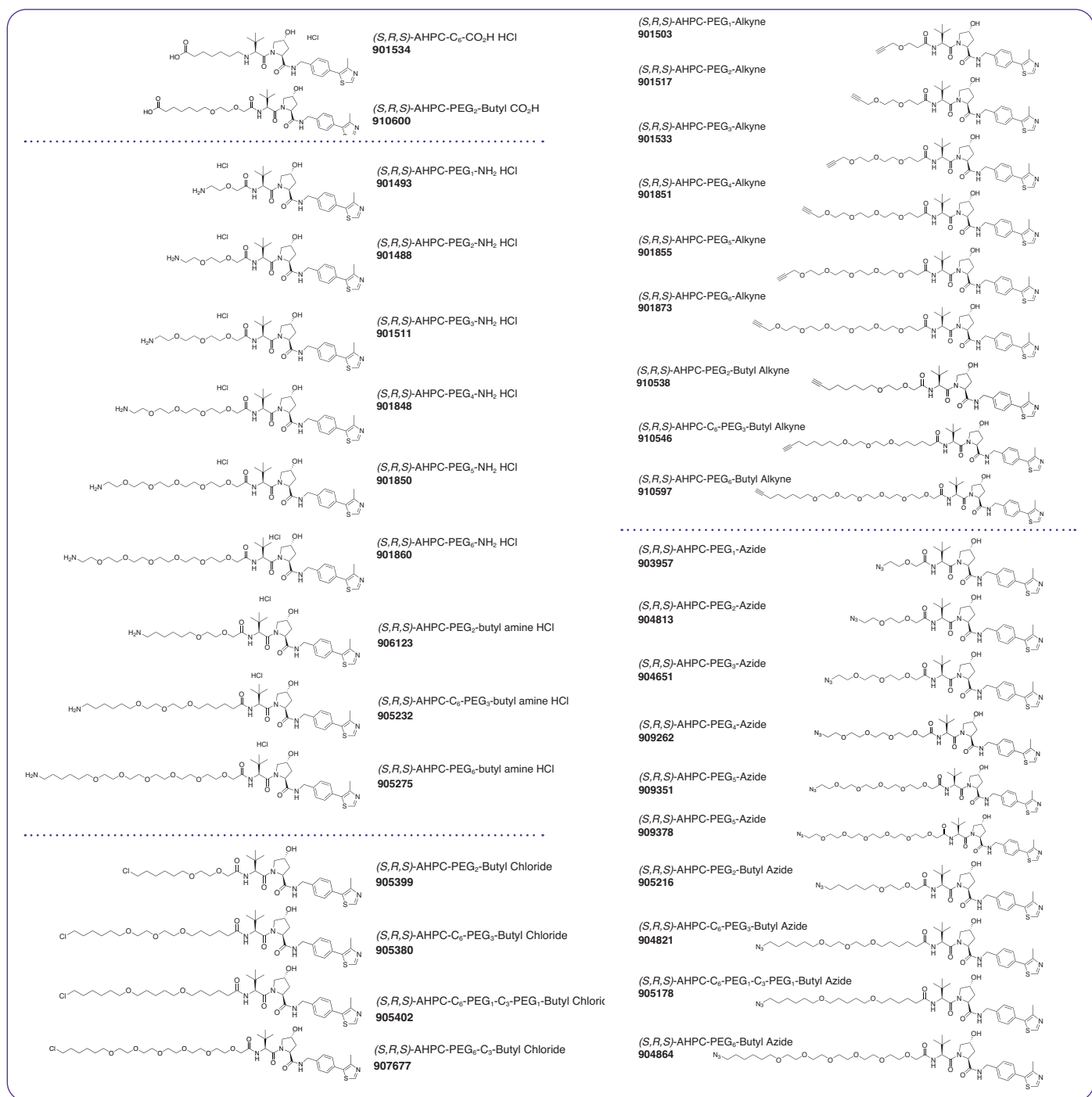


Use of a set of degrader building blocks with the same conjugation site streamlines the synthesis of libraries.

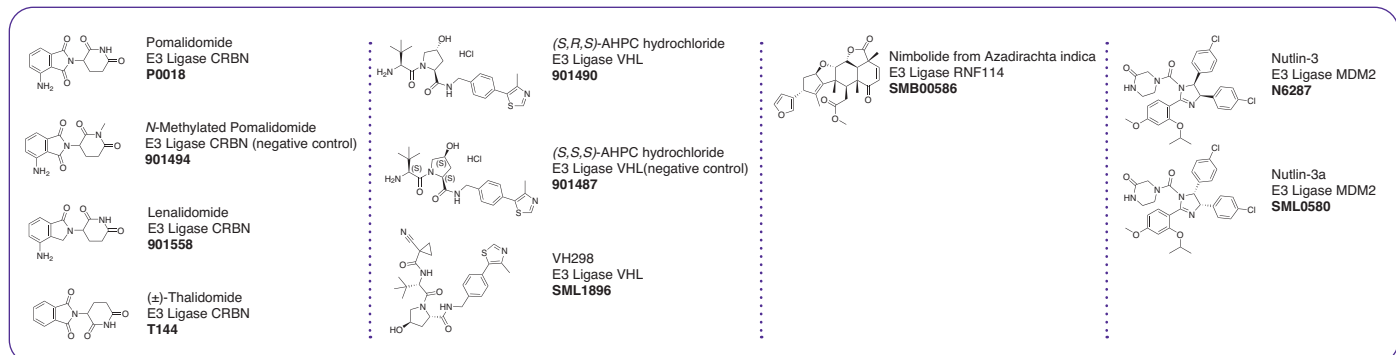
Protein Degradator Building Blocks for CRBN



Protein Degradator Building Blocks for VHL


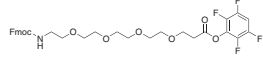

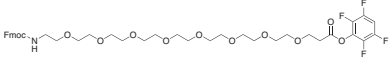

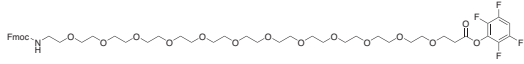

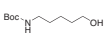
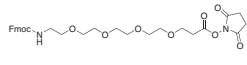

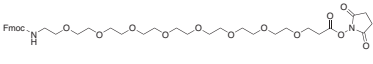

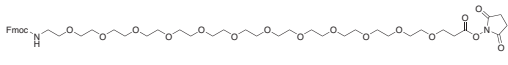

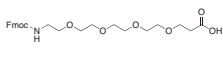

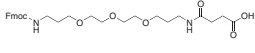
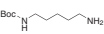
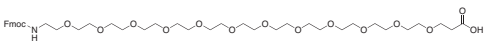




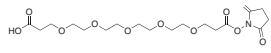

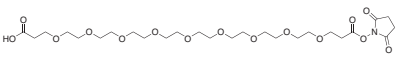

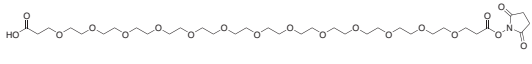


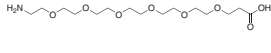
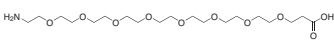
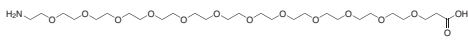
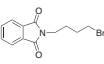
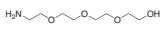

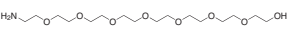


Ligands

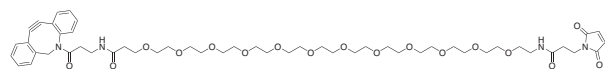


Heterobifunctional Crosslinkers

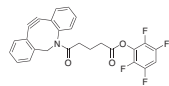
	Propargyl-PEG ₁ -Acid 901567		2-(Fmoc-amino)ethanol 445185
	Propargyl-PEG ₂ -Acid 901566		3-(Fmoc-amino)-1-propanol 47305
	Propargyl-PEG ₃ -Acid 901565		4-(Fmoc-amino)-1-butanol 47295
	Propargyl-PEG ₄ -Acid 902543		5-(Fmoc-amino)-1-pentanol 47299
	Alkyne-PEG ₅ -Acid 764167		6-(Fmoc-amino)-1-hexanol 47297
	Propargyl-PEG ₆ -Acid 902667		N-Fmoc-ethylenediamine hydrobromide 47542
	Amino-PEG ₂ -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)ethoxy)acetic acid 910058		N-Fmoc-cadaverine hydrobromide 47544
	3,6,9,12,15,18-Hexaoxahexacos-25-ynoic acid 910023		N-Fmoc-1,6-hexanediamine hydrobromide 47543
<hr/>			N-Fmoc-2-bromoethylamine 09767
	14-Azido-3,6,9,12-Tetraoxatetradecanoic Acid Solution 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		t-Boc-N-Amido-PEG ₁ -CH ₂ CO ₂ H 901579
	Azido-dPEG [®] ₂ -TFP ester QBD10567		t-Boc-N-Amido-PEG ₂ -CH ₂ CO ₂ H 901577
	Azido-dPEG [®] ₁₂ -TFP ester >90% QBD10569		t-Boc-N-Amido-PEG ₃ -CH ₂ CO ₂ H 901575
	Azido-dPEG [®] ₃ -amine QBD10522		BocNH-PEG ₄ -acid 902551
	Azido-dPEG [®] ₇ -amine QBD10523		BocNH-PEG ₅ -Acid 902683
	Azido-dPEG [®] ₁₁ -amine QBD10524		BocNH-PEG ₆ -Acid 902683
	Azido-dPEG [®] ₁ -NHS ester QBD10501		N-Boc-N-Succinyl-4,7,10-Trioxa-1,13-Tridecanediamine 671401
	Azido-dPEG [®] ₅ -NHS ester QBD10503		15-(Boc-amino)-4,7,10,13-tetraoxapentadecanoic acid 30953
	Azido-dPEG [®] ₁₂ -NHS ester QBD10505		21-(Boc-amino)-4,7,10,13,16,19-hexaoxaheneicosanoic acid 38263
	Azido-dPEG [®] ₄ -acid QBD10502		N-Boc-2,2'-(ethylenedioxy)diethylamine 89761
	20-17-Azido-3,6,9,12,15-pentaoxaheptadecanoic acid 910015		N-Boc-4,7,10-Trioxa-1,13-Tridecanediamine 93113
	Azido-3,6,9,12,15,18-hexaoxaicosanoic acid 910007		
	Azido-dPEG [®] ₈ -acid QBD10512		
	Azido-dPEG [®] ₁₂ -acid QBD10513		

	<i>N</i> -Boc-ethanolamine 382027		Fmoc-N-amido-dPEG ₄ -TFP ester QBD11000
	3-(Boc-amino)-1-propanol 416444		Fmoc-N-amido-dPEG ₈ -TFP ester QBD11005
	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 ₅ -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		Fmoc-N-amido-dPEG ₄ -acid QBD10213
	<i>N</i> -Boc-1,4-butanediamine 15404		<i>N</i> -Fmoc- <i>N</i> -Succinyl-4,7,10-Trioxa-1,13-Tridecanediamine 671517
	<i>N</i> -Boc-cadaverine 15406		Fmoc-N-amido-dPEG ₁₂ -acid QBD10283
	<i>N</i> -Boc-1,6-hexanediamine 79229		
	2-(Boc-amino)ethyl bromide 17354		
	3-(Boc-amino)propyl bromide 17356		
	4-(Boc-amino)butyl bromide 90303		Acid-dPEG ₅ -NHS ester QBD10109
	<i>N</i> -Boc-1,6-hexanediamine hydrochloride 437018		Acid-dPEG ₉ -NHS ester QBD10119
	<i>N</i> -Boc-2-isothiocyanatoethylamine 15524		Acid-dPEG ₁₃ -NHS ester QBD10127
	<i>N</i> -Boc-3-isothiocyanatopropylamine 15530		
	Benzyl <i>N</i> -(3-hydroxypropyl)carbamate 478709		Amino-dPEG ₉ -acid QBD10067
			Amino-dPEG ₈ -acid QBD10277
			Amino-dPEG ₁₂ -acid QBD10287
	<i>N</i> -(4-Bromobutyl)phthalimide 100919		Amino-dPEG ₄ -OH QBD10249
	<i>N</i> -(2-Bromoethyl)phthalimide B66302		Amino-dPEG ₈ -OH QBD10240

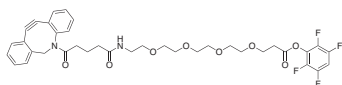
Heterobifunctional Crosslinkers (continued)



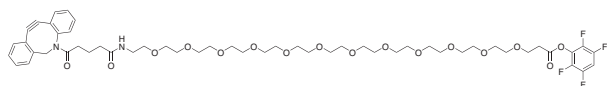
DBCO-dPEG[®]₁₂-MAL
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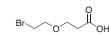
DBCO-TFP ester
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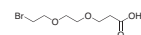
DBCO-dPEG[®]₄-TFP ester
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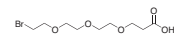
DBCO-dPEG[®]₁₂-TFP ester
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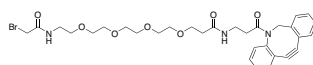
Bromo-PEG₇-Acid
901573



Bromo-PEG₂₇-Acid
901572



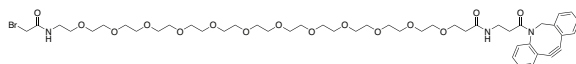
Bromo-PEG₃-Acid
901568



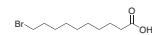
Bromoacetamido-dPEG[®]₄-amido-DBCO
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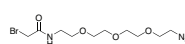
4-Bromobutyric acid
258083



Bromoacetamido-dPEG[®]₁₂-amido-DBCO
QBD11223



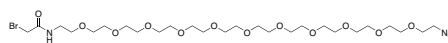
10-Bromodecanoic acid
541397



Bromoacetamido-dPEG[®]₃-azide
QBD11217



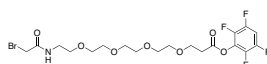
4-Bromobutryl chloride
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Bromoacetamido-dPEG[®]₁₁-azide
QBD11204



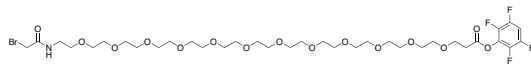
6-Bromo-1-hexanol
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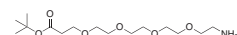
Bromoacetamido-dPEG[®]₄-TFP ester
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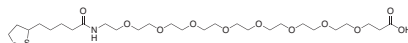
6-(Boc-amino)hexyl bromide
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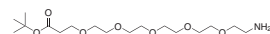
Bromoacetamido-dPEG[®]₁₂-TFP ester
QBD11202



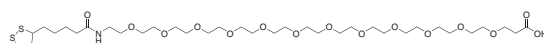
Amino-PEG₄-t-Butyl Ester
902535



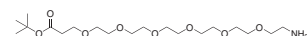
Lipoamido-dPEG[®]₉-acid
QBD10807



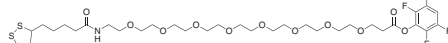
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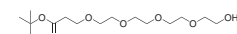
Lipoamido-dPEG[®]₁₂-acid
QBD10808



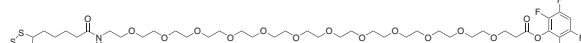
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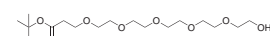
Lipoamido-dPEG[®]₉-TFP ester
QBD10642



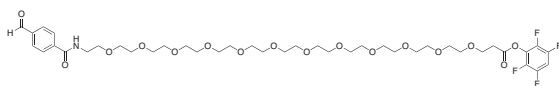
Hydroxy-PEG₂-t-Butyl Ester
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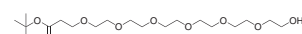
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QBD10814



Hydroxy-PEG₅-t-Butyl Ester
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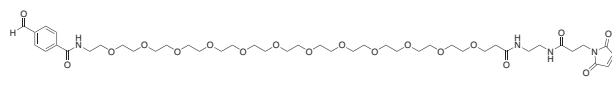
4-formyl-benzamido-dPEG[®]₁₂-TFP ester
QBD10081



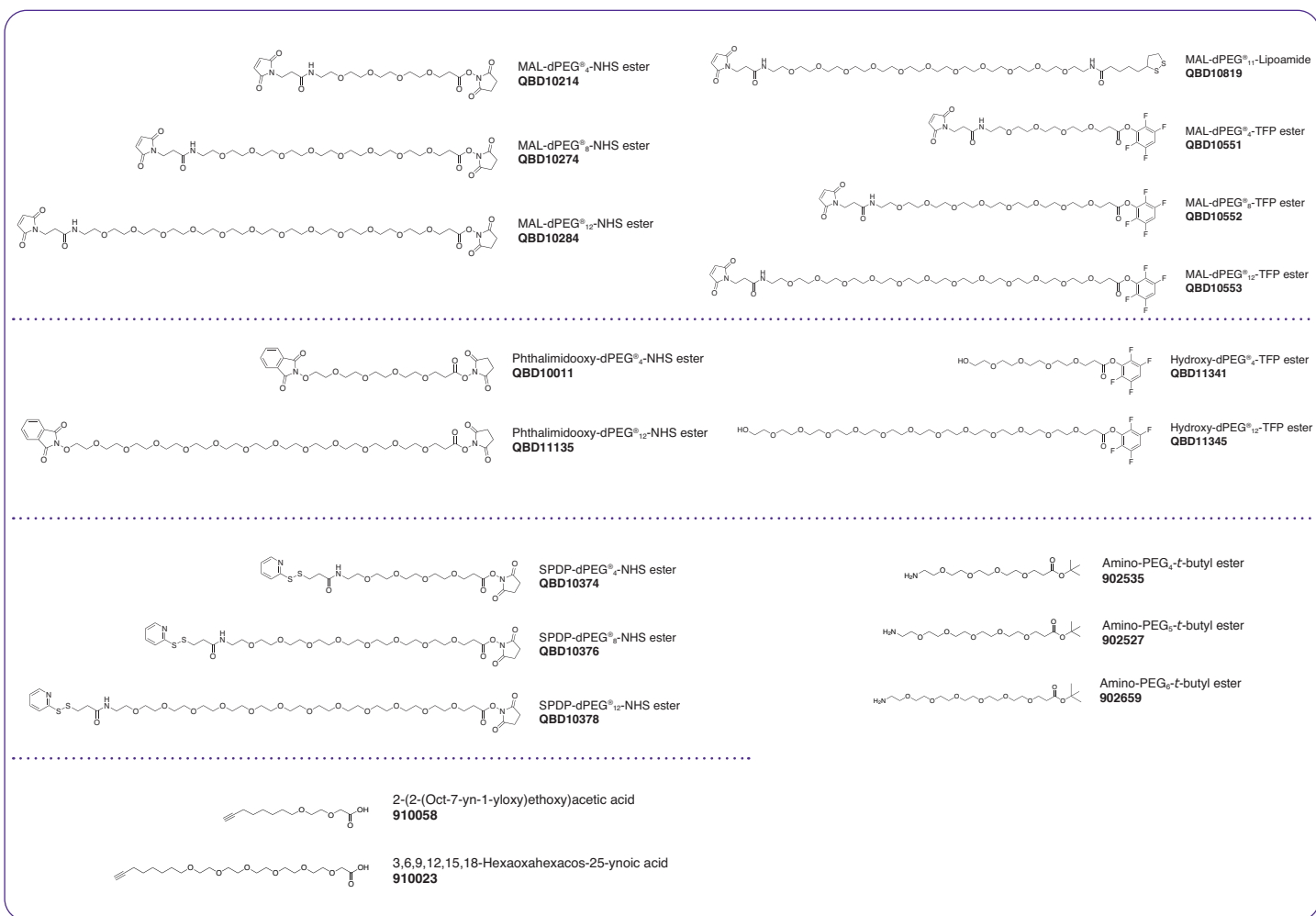
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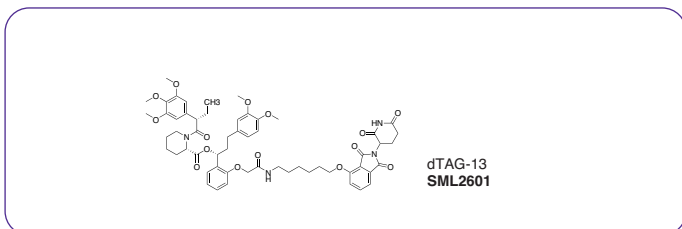
2,2-Dimethyl-4-oxo-3,11,14,17-tetraoxatricosan-23-oic acid
909998



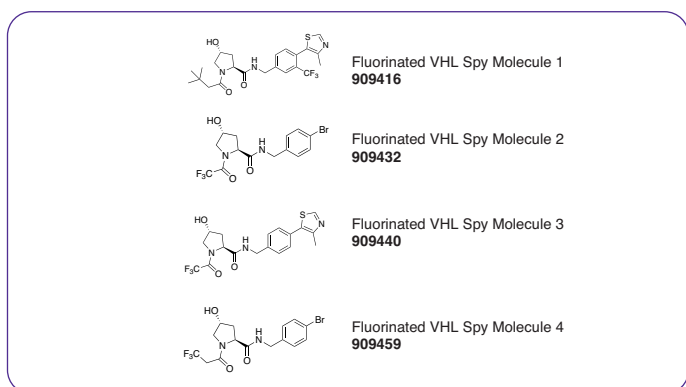
4-formyl-benzamido-dPEG[®]₁₂-EDA-MAL
QBD10075



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