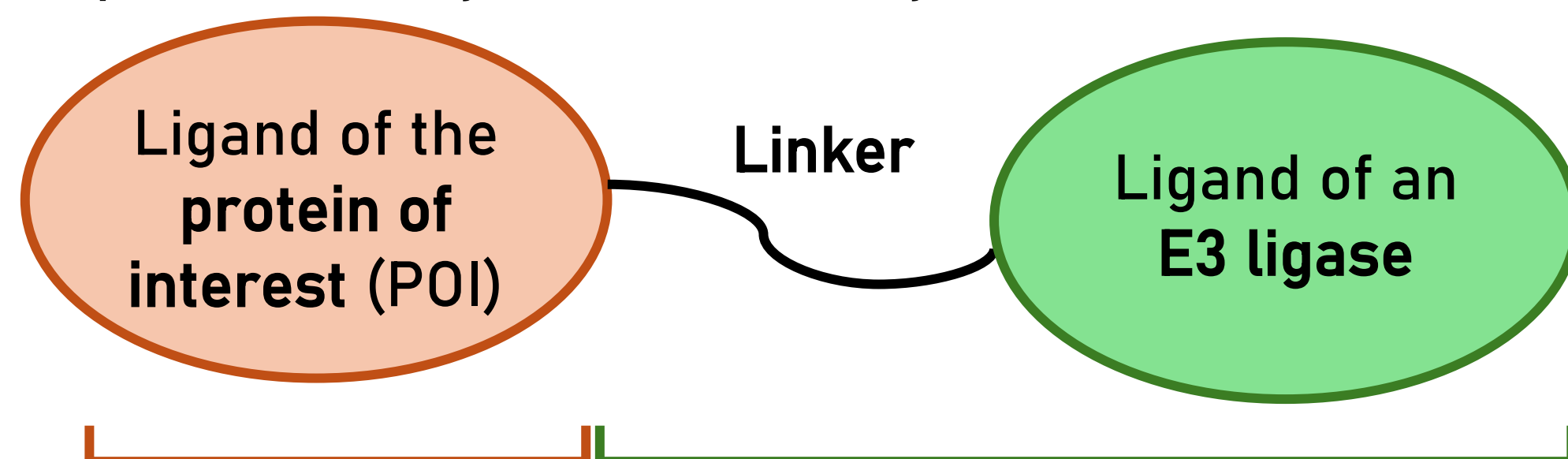


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Proteolysis targeting chimeras

Proteolysis targeting chimeras (PROTACs) are heterobifunctional compounds able to induce targeted protein degradation through the ubiquitin proteasome system (UPS). They are made of:

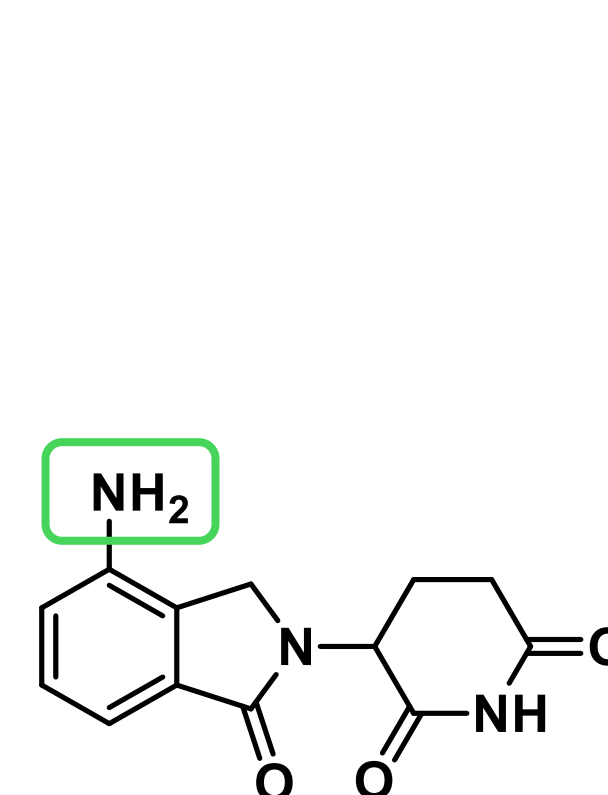


Target specific

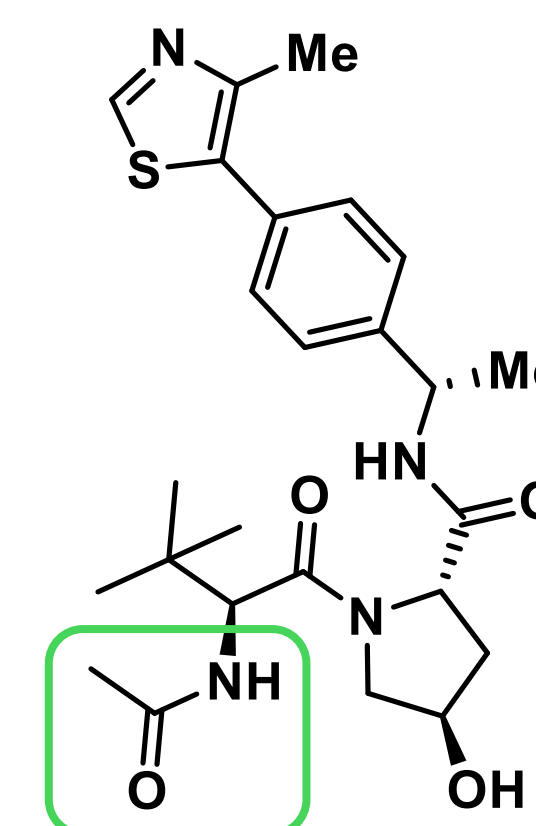
Found identical in structure across several PROTACs

→ *Green* functionalization strategies can be broadly applied

Common E3 ligase recruiters



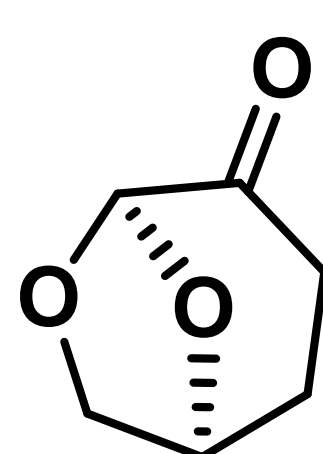
Lenalidomide
Cereblon (CRBN) recruiter



(VH-032)-Me
Von Hippel Lindau Protein (VHL) recruiter

Commonly functionalized through an amide coupling reaction, which requires toxic solvents as DCM or DMF

Green solvent Cyrene

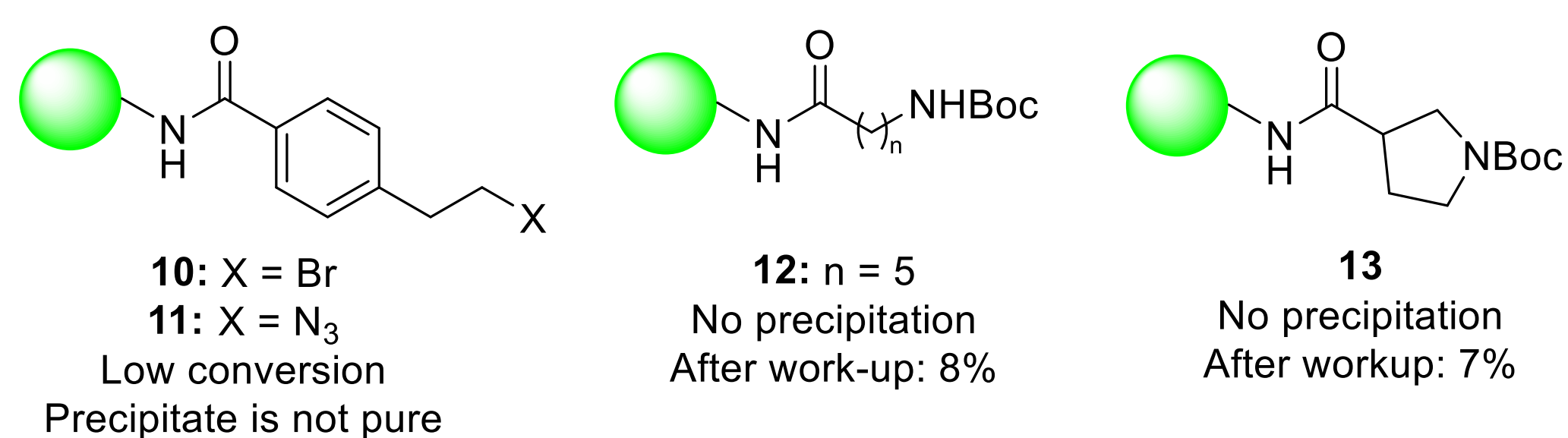
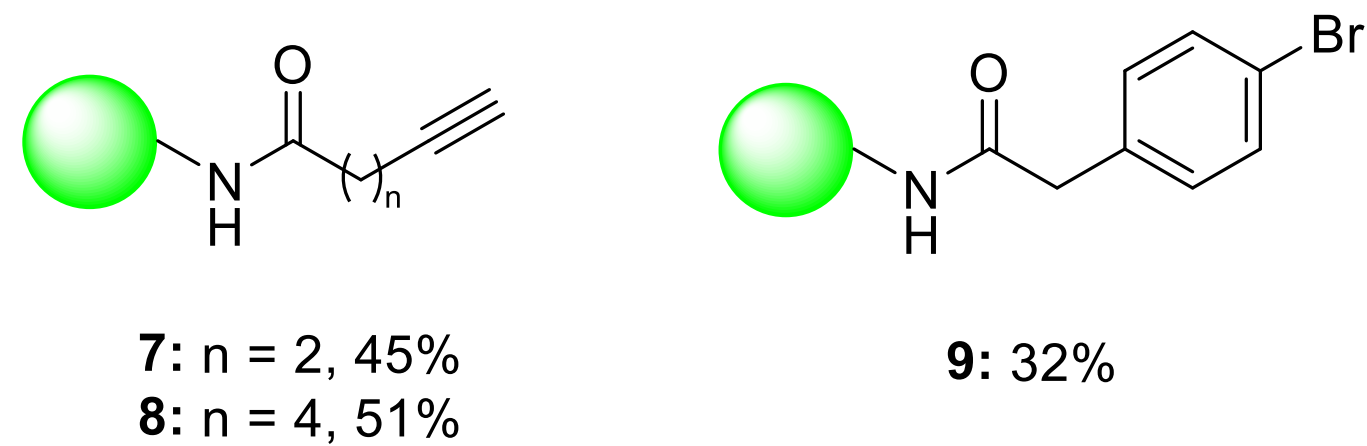
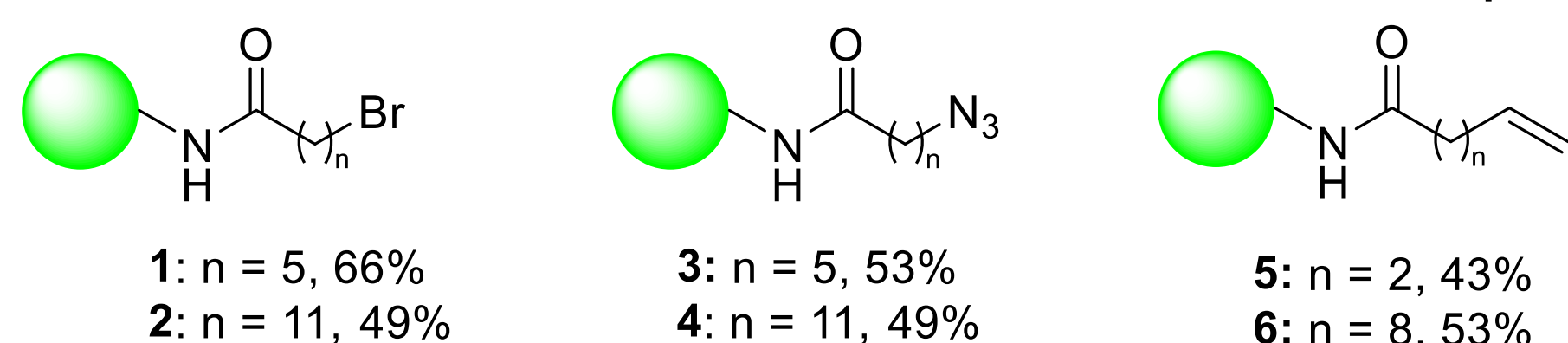
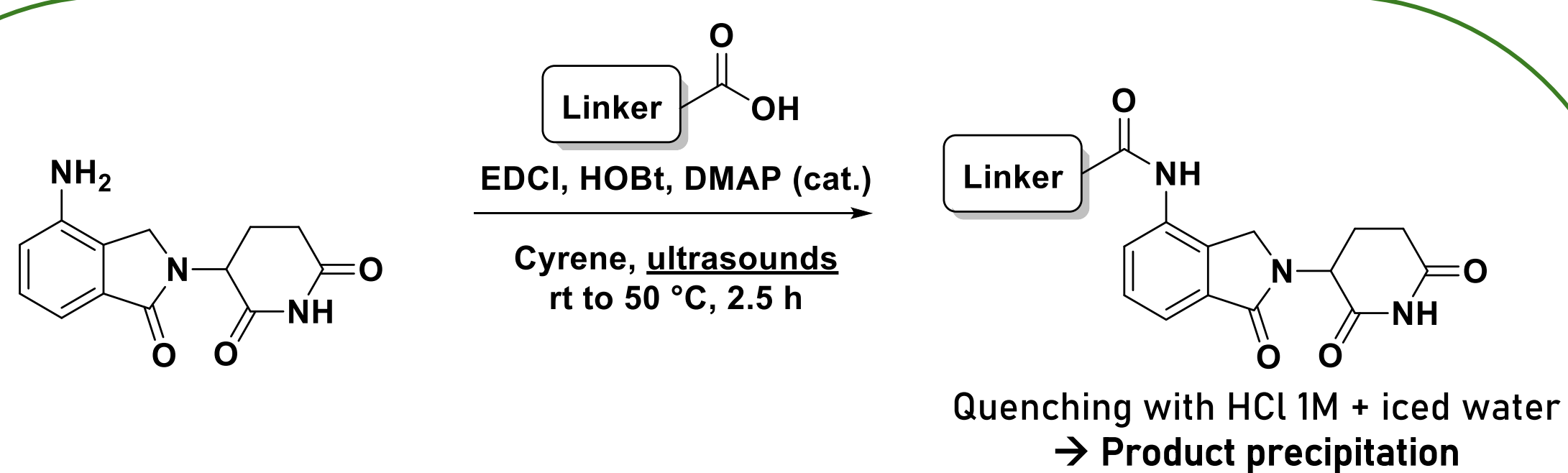


Cyrene is a *green* solvent that can be obtained from cellulose, and is used as a sustainable replacement of DMF

- bp 227 °C
- Polar, good miscibility with water
- Non-mutagenic and non-toxic

→ functionalization of lenalidomide and (VH-032)-Me as PROTAC precursors using the *green* solvent Cyrene

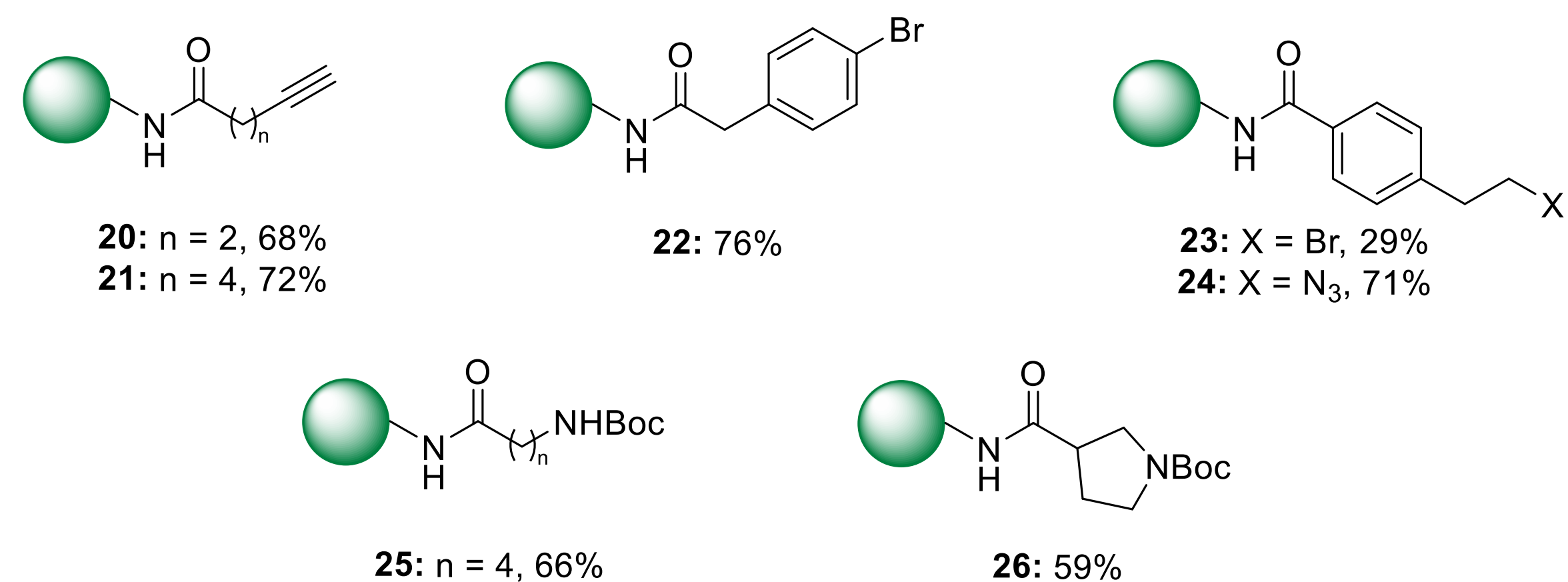
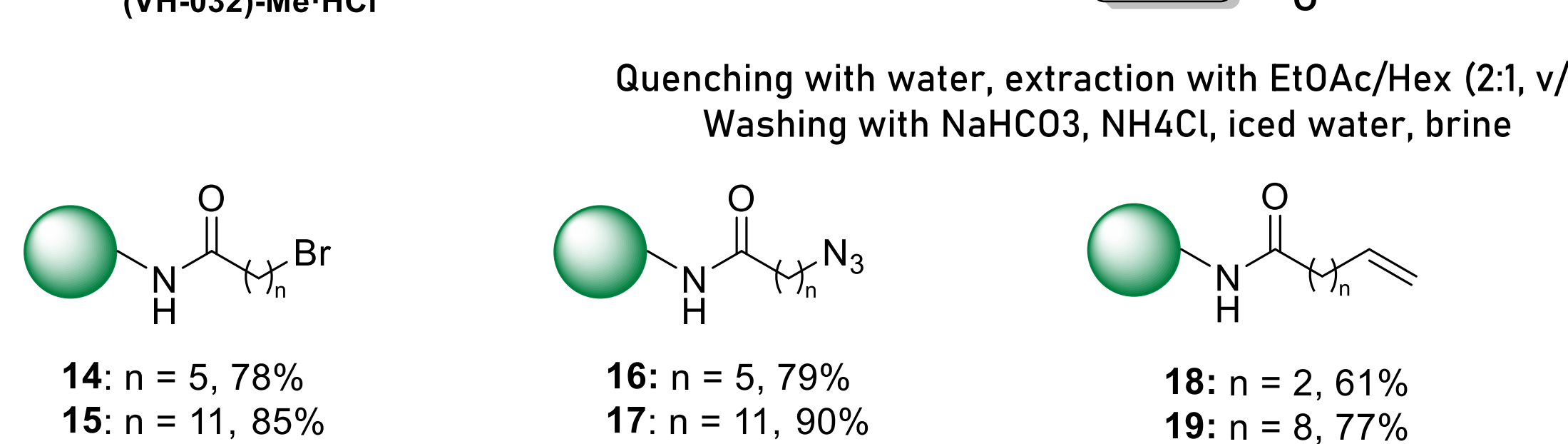
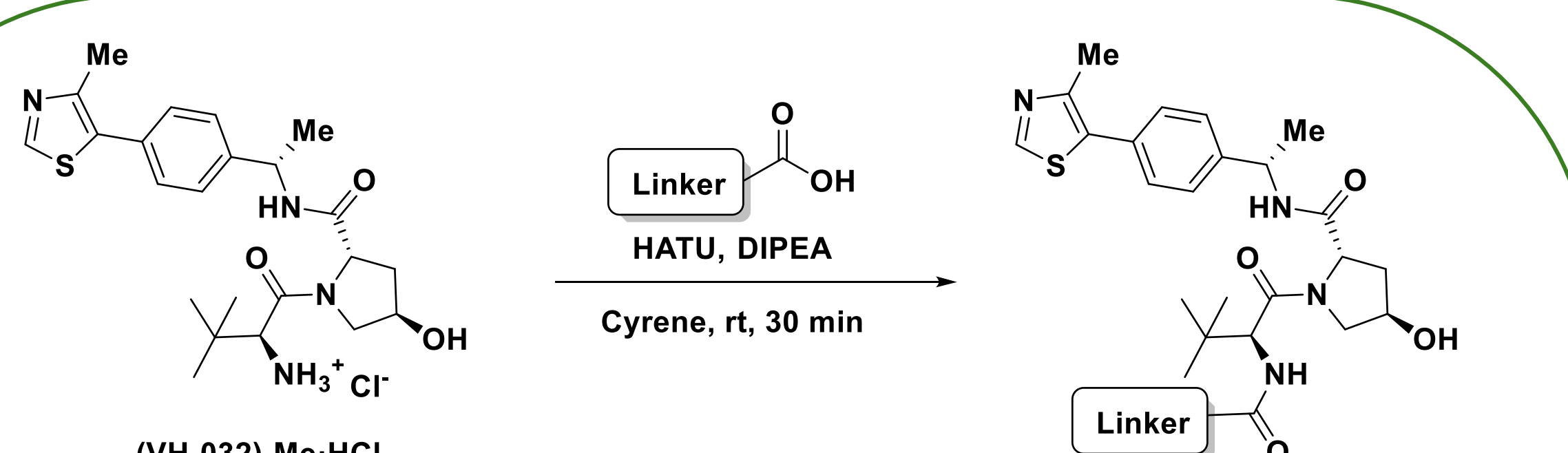
Functionalization of lenalidomide



- Ultrasound irradiation allows to **reduce the reaction time** (2.5 h)
- **Moderate yields** (32 - 66%)
- **Precipitation** of the pure product without the need of purification

- Slow conversion when aromatic carboxylic acids are used
- Presence of an amine functionality impedes precipitation

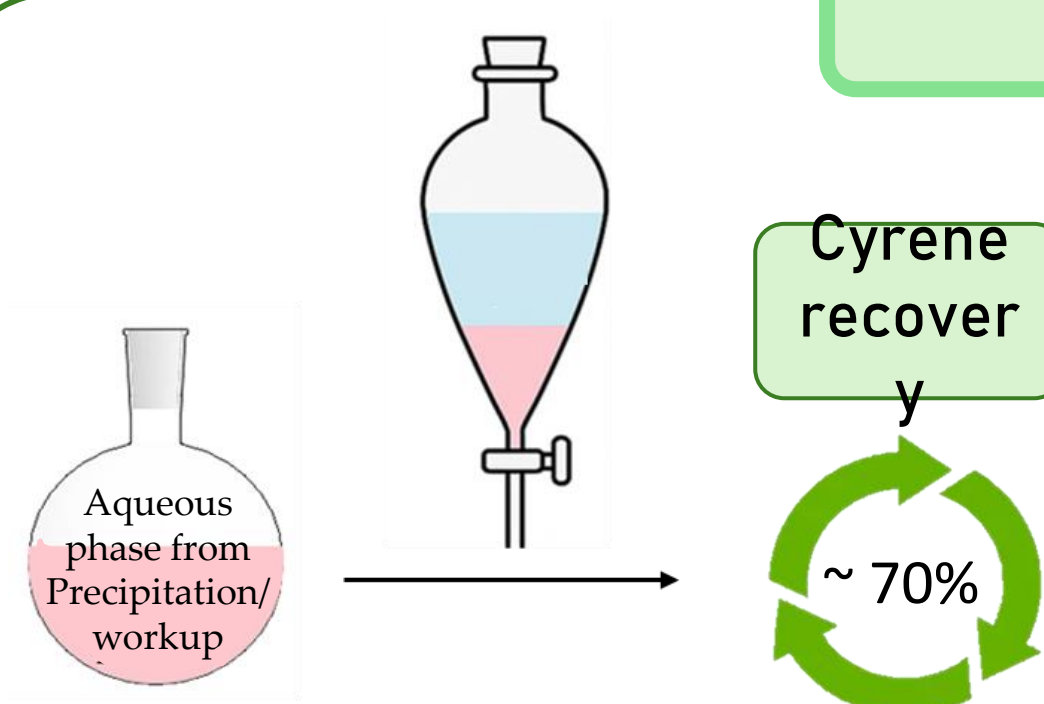
Functionalization of (VH-032)-Me



- **Reduced reaction time** (30 min)
- **Moderate to high yields** (29 - 90%)
- Product does **not** require further purification

- Aqueous workup is required due to the higher product solubility in water

Scalability and Cyrene recovery



compound 1

- Gram scale: **69%** yield
- Cyrene recovery: **71%**
- 2nd reaction cycle in recovered Cyrene: **67%**

compound 14

- Gram scale: **67%** yield
- Cyrene recovery: **67%**
- 2nd reaction cycle in recovered Cyrene: **71%**

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