

The Culinary Chemist

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Baking is a Science — *from the Lab to the Tent*

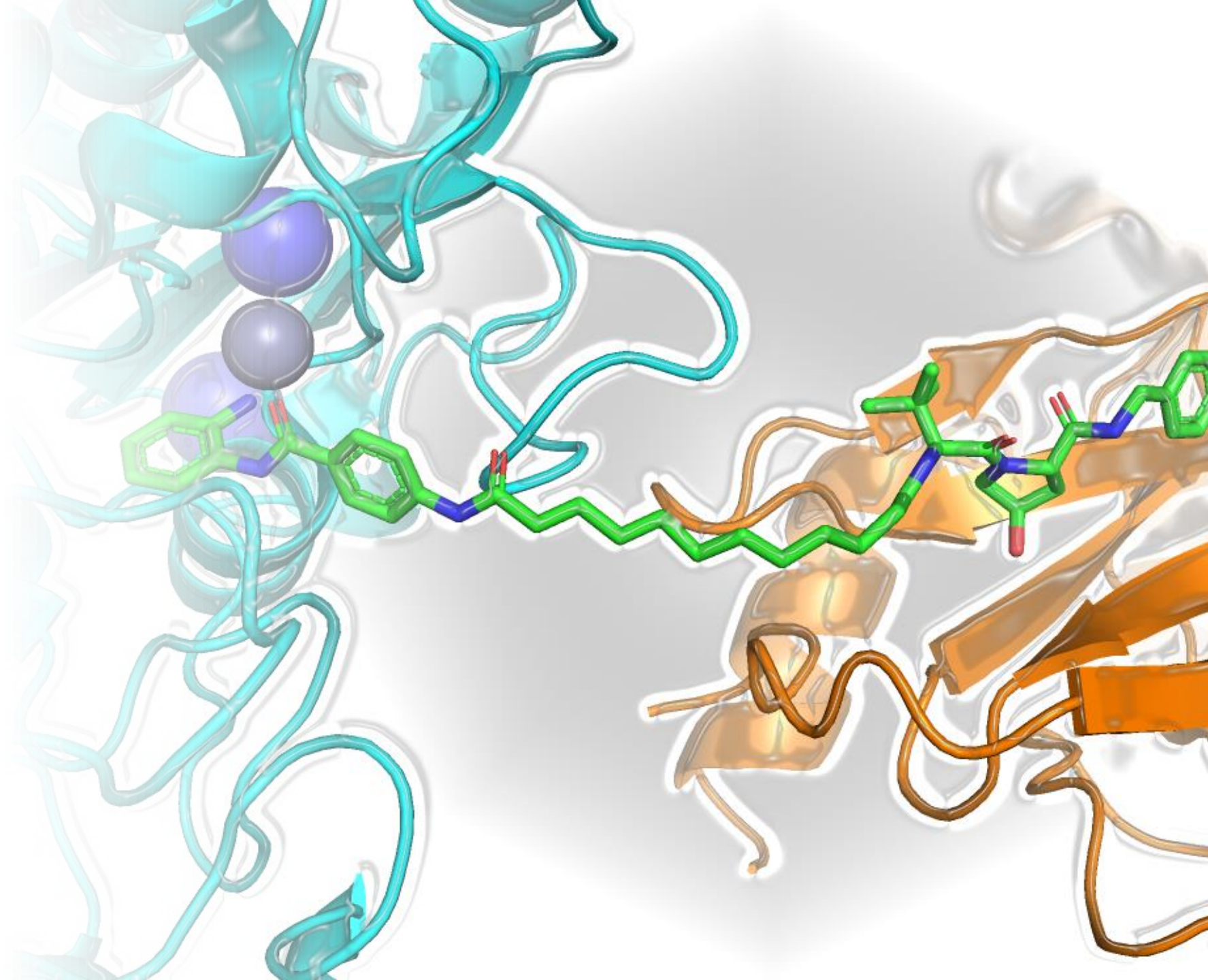


Chemical Biology Lab
University of Leicester



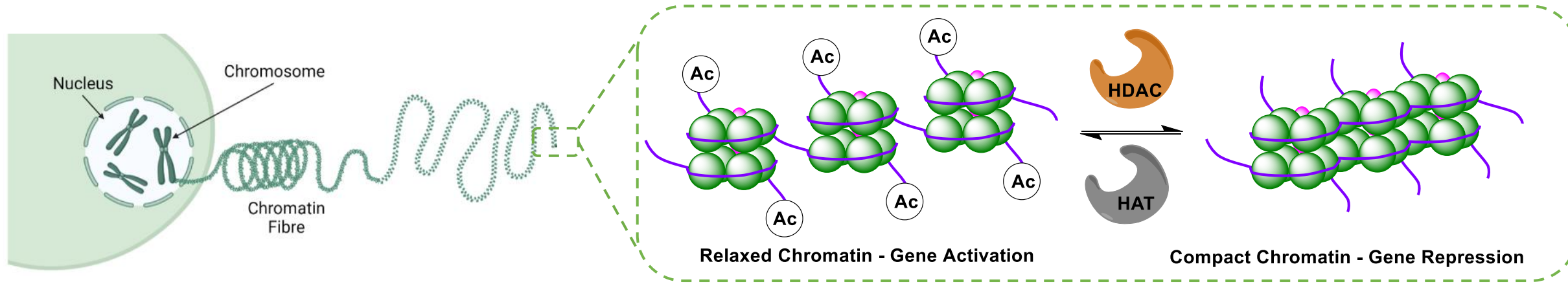
Great British Bake Off Tent!
The Final Three

Research
at Leicester

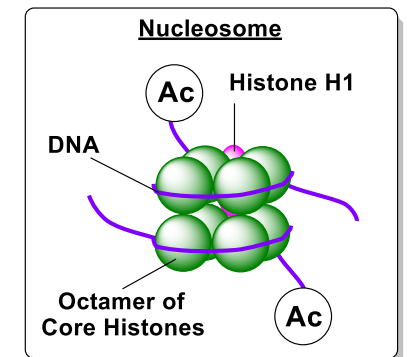
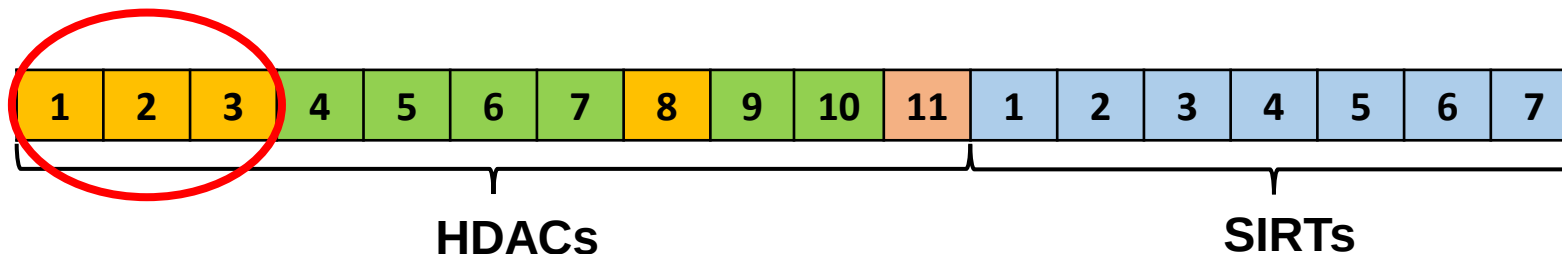


Histone Deacetylase (HDAC) Enzymes

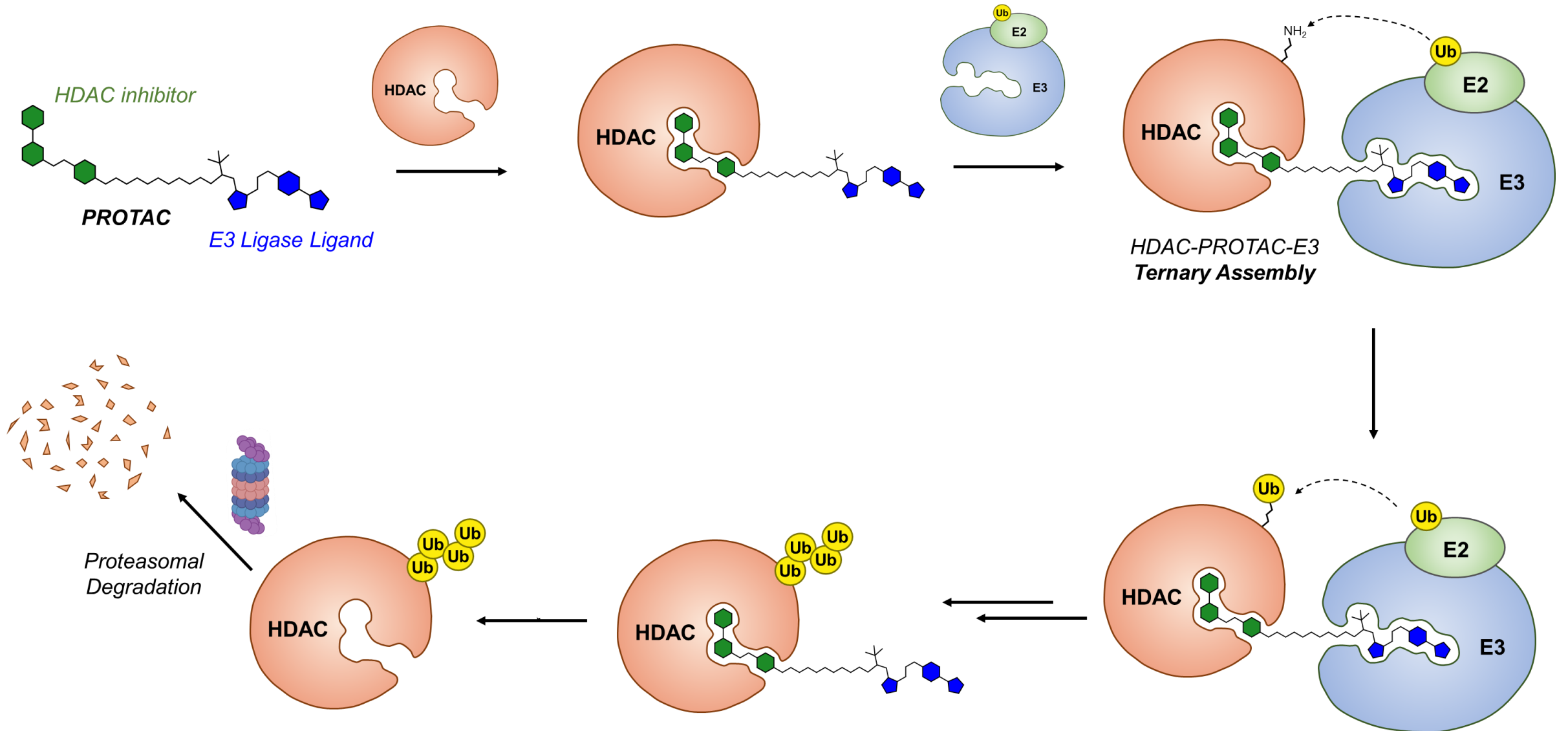
- Epigenetic regulators that catalyse hydrolysis of acetyl groups from lysine residues on histones



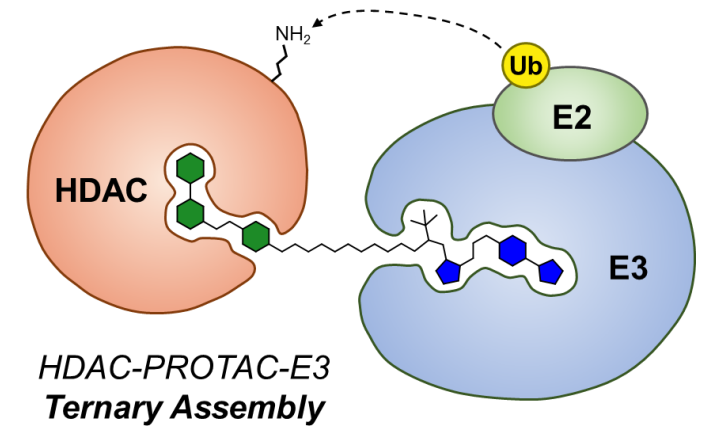
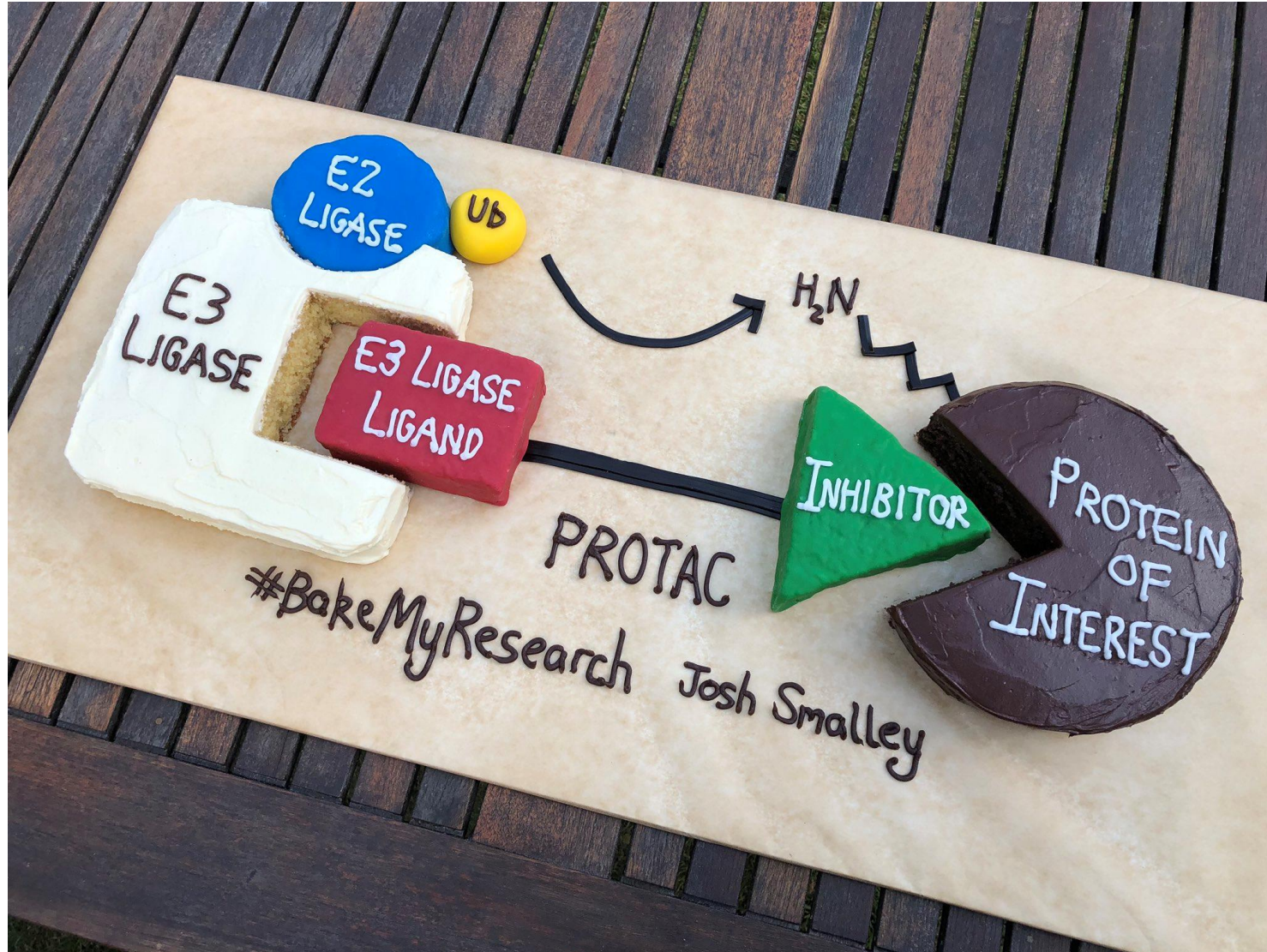
- 18 HDACs Identified in the human genome:
 - Zinc dependent (Class I, II and IV)
 - NAD^+ dependent (Class III) – aka Sirtuins (SIRT), homologues of yeast Sir2



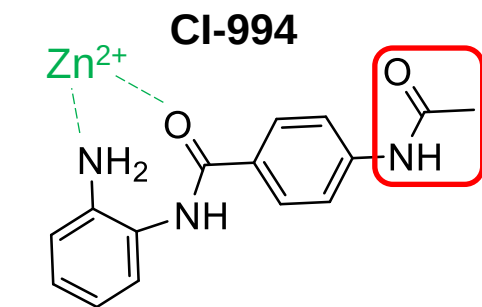
PROTACS – Proteolysis Targeting Chimeras



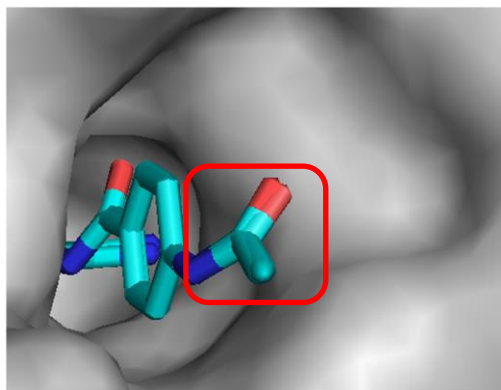
PROTACS – Proteolysis Targeting Chimeras



HDAC PROTAC Design

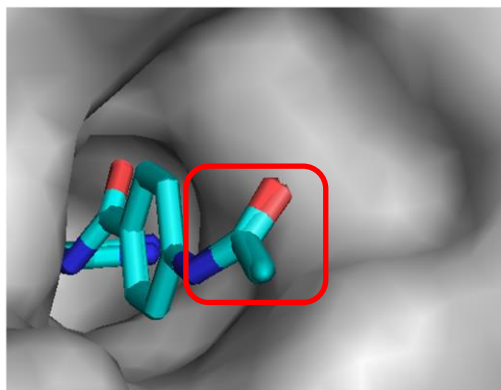
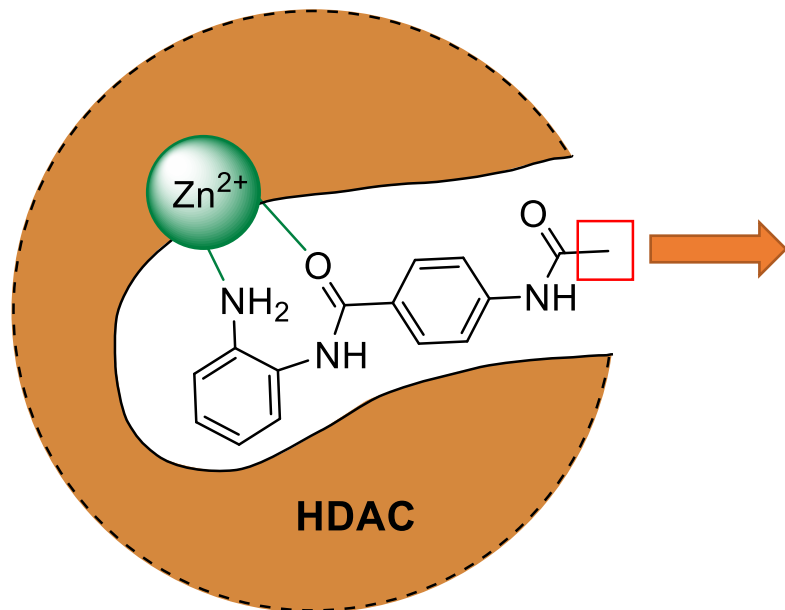


Class I HDAC Inhibitor
 $IC_{50} = 0.4-1.2 \mu M$ (HDACs 1-3)



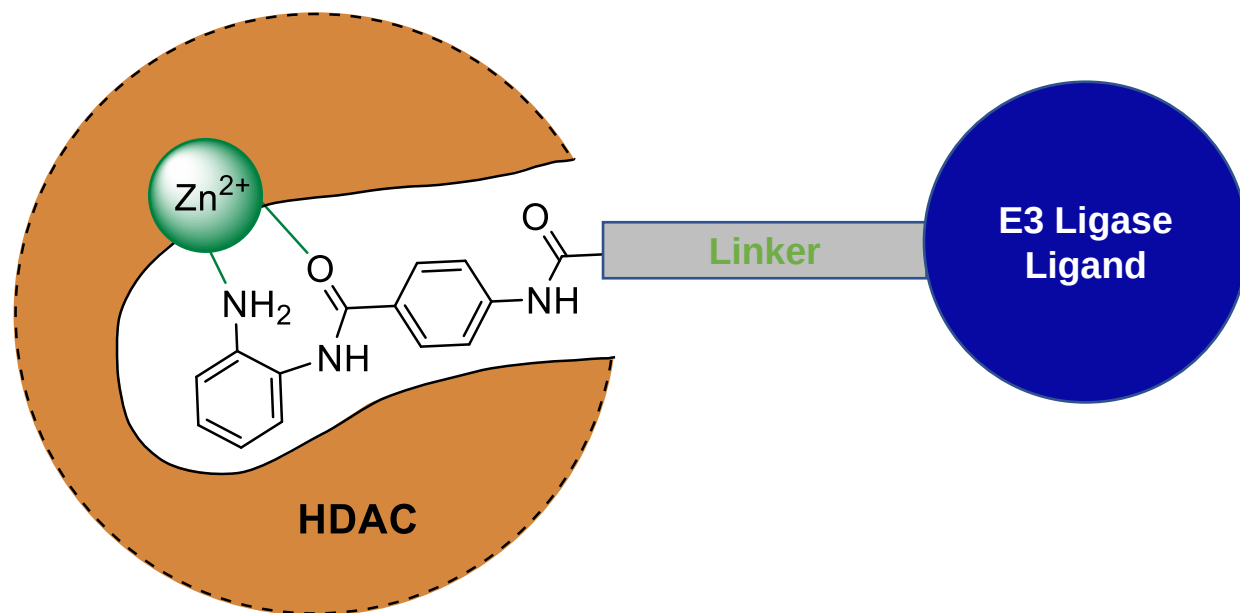
Benzamide HDAC inhibitor
bound to HDAC2 (PDB 4LY1)

HDAC PROTAC Design

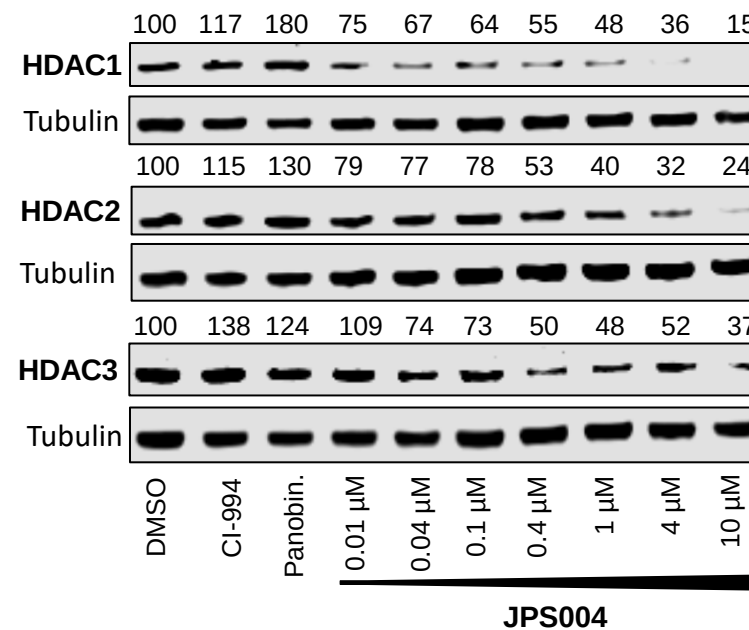
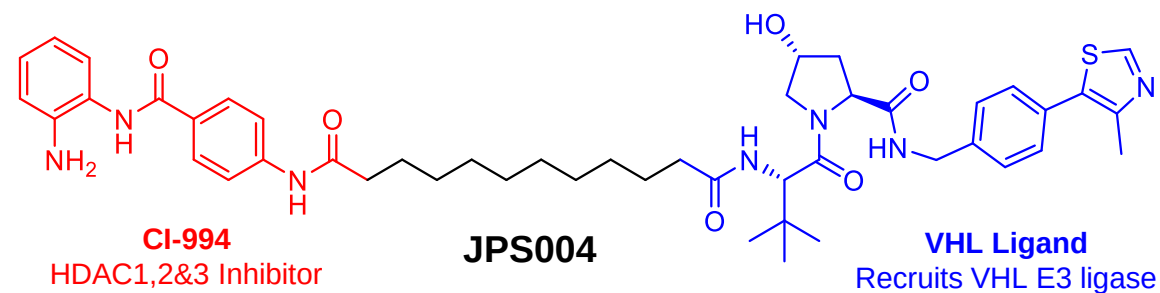
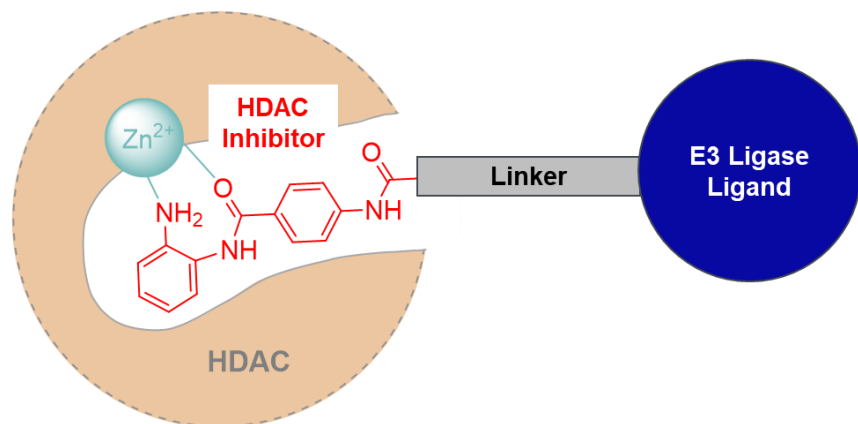


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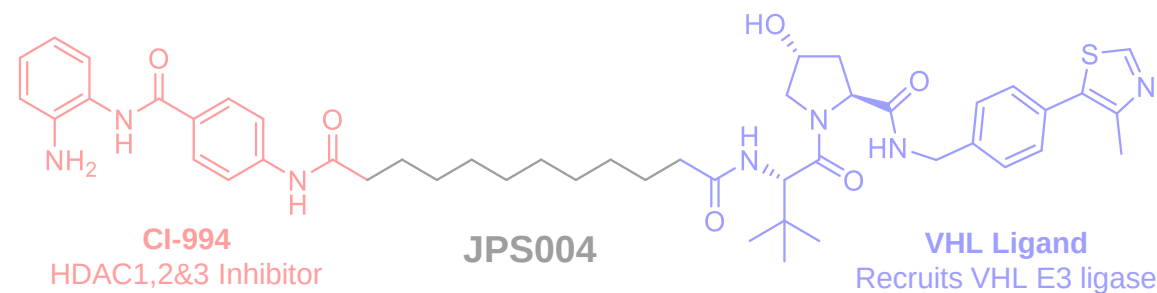
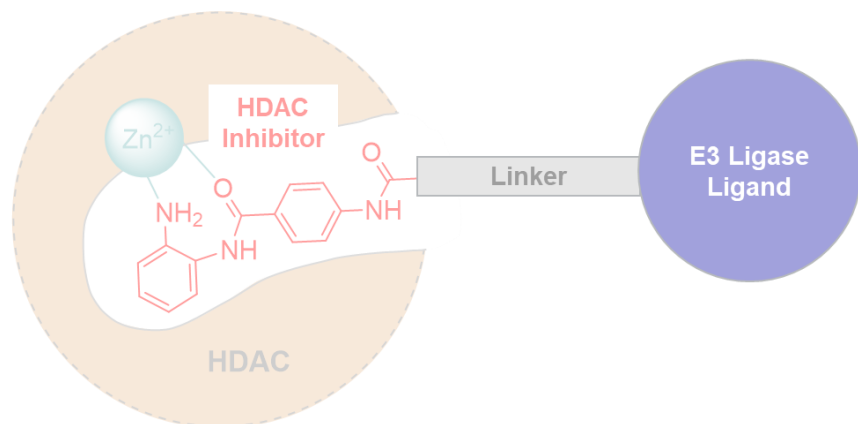


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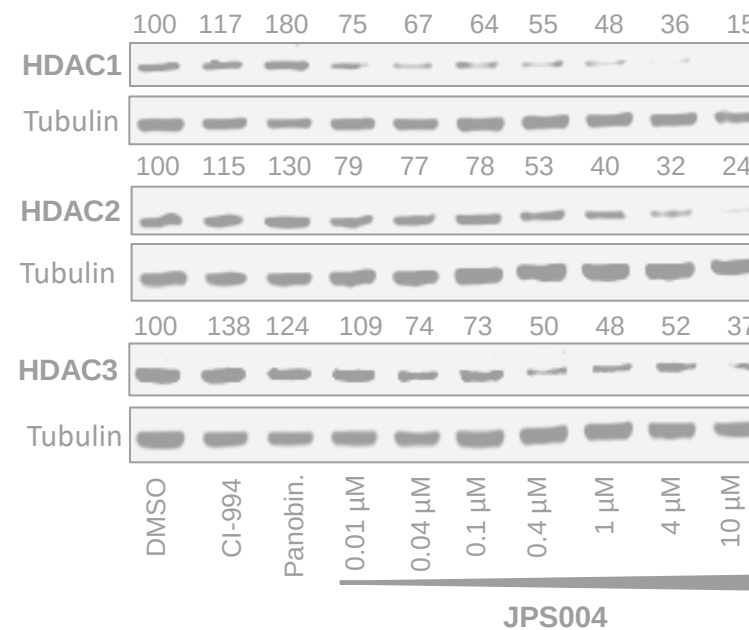
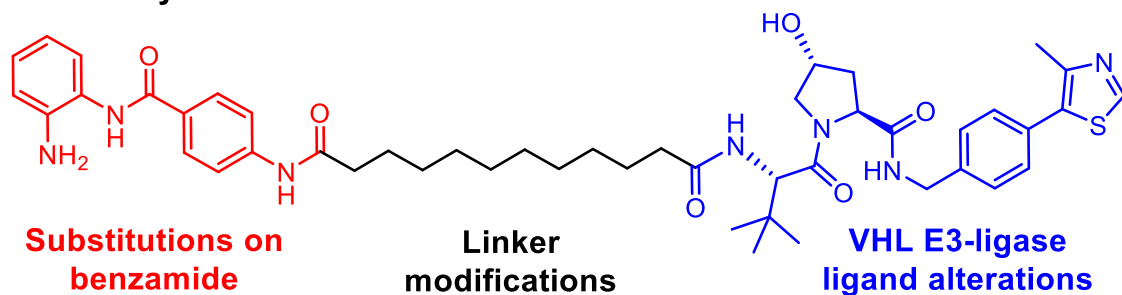


24h treatment
HCT116 cells

HDAC PROTAC Design

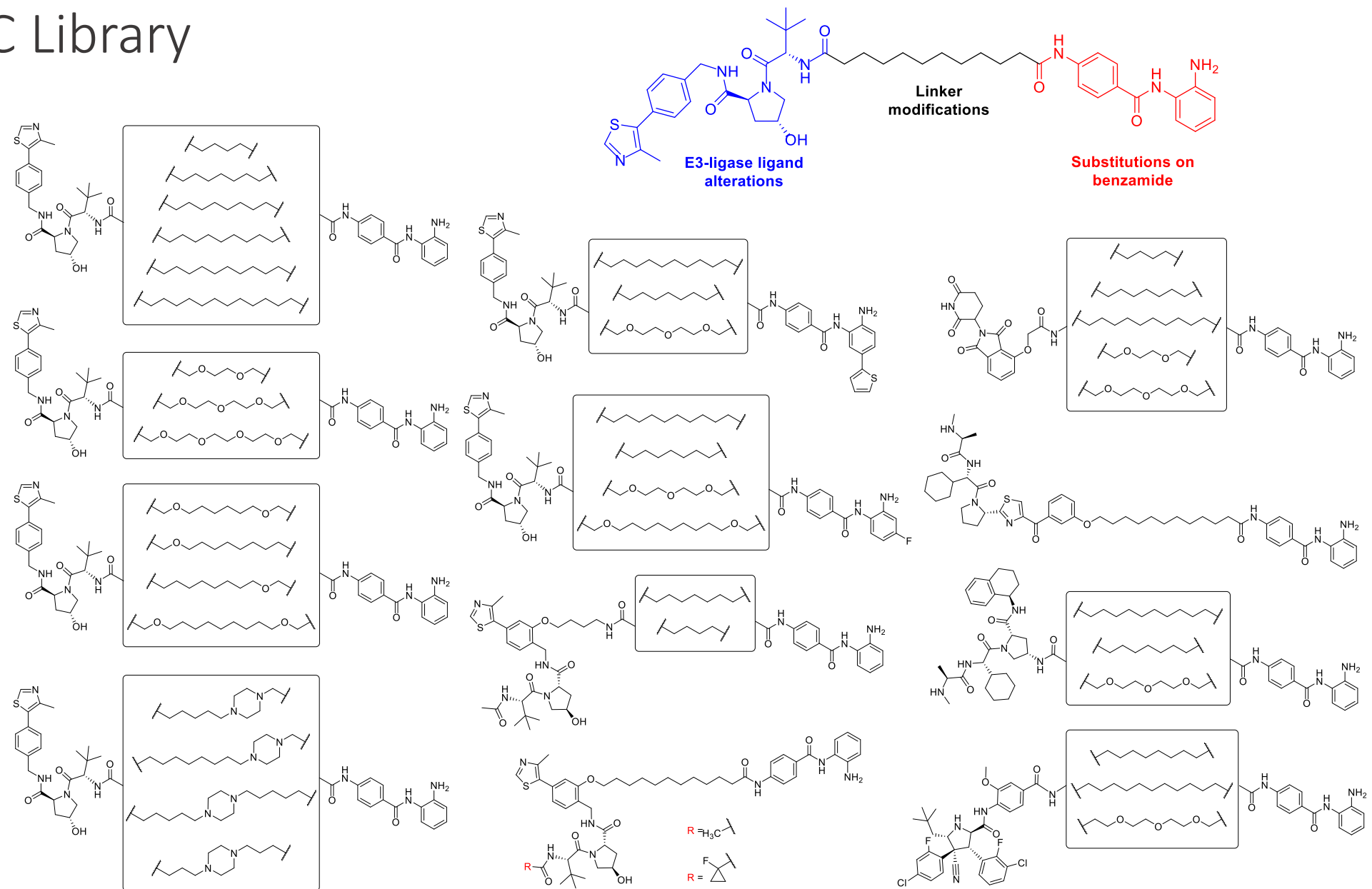


SAR study:

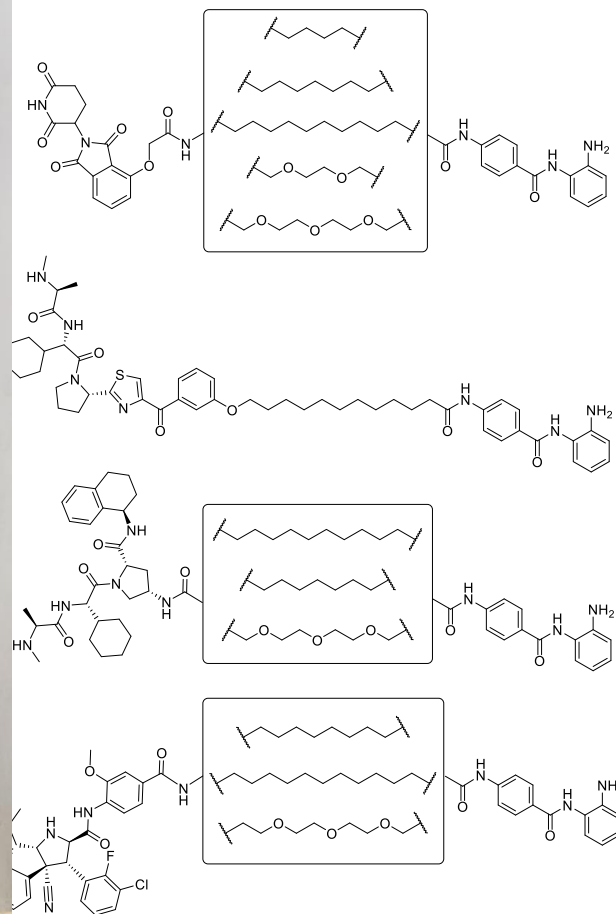
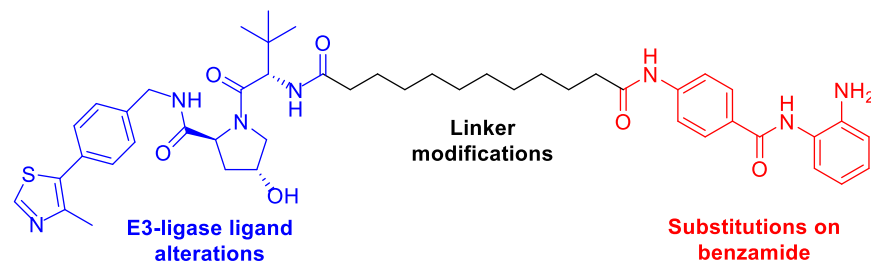
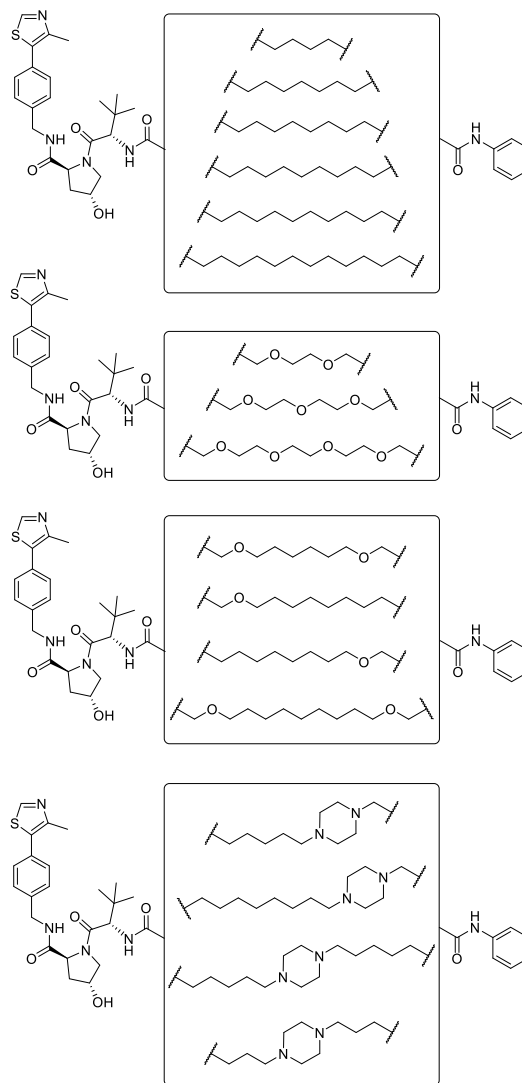


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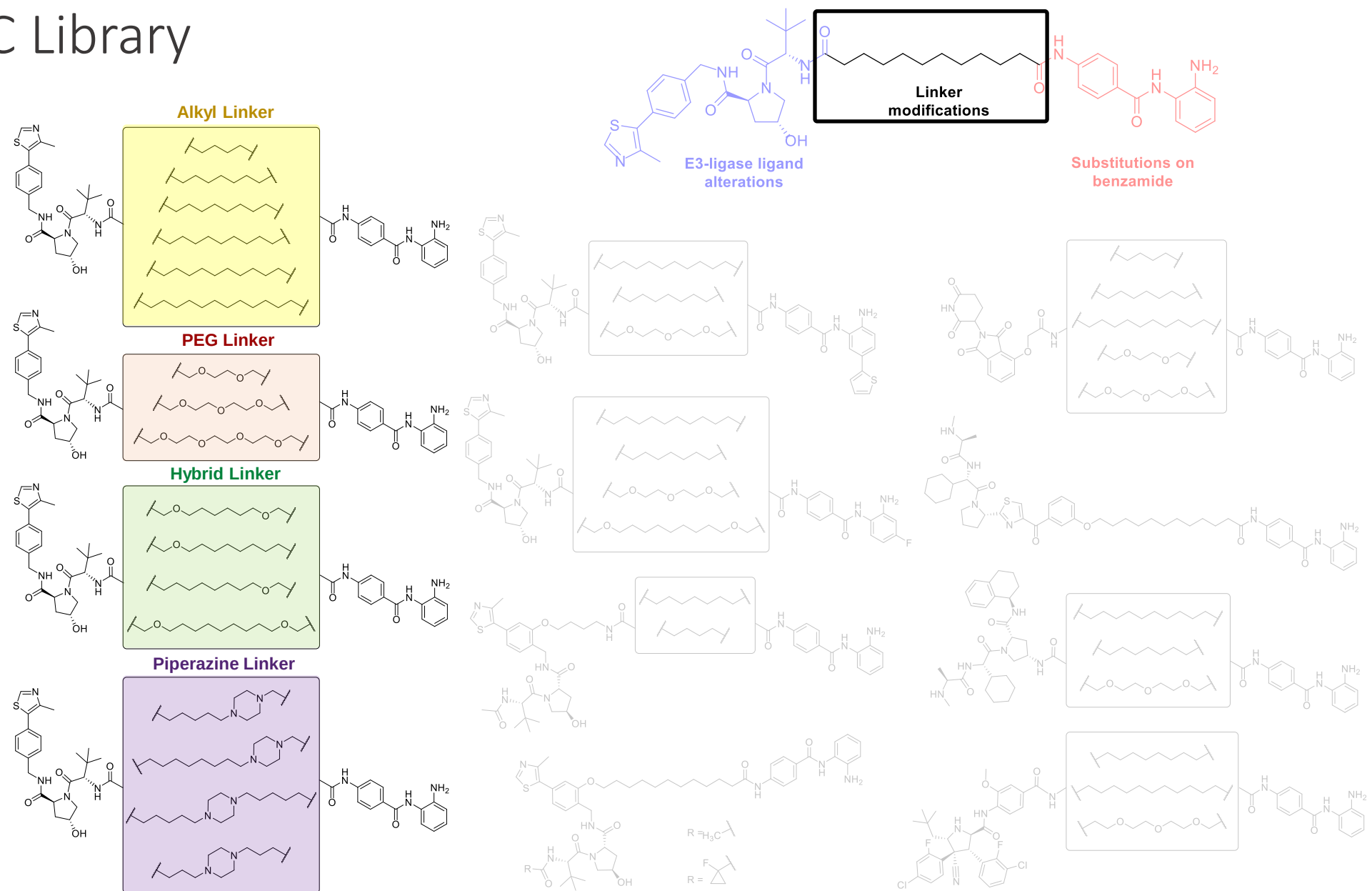
PROTAC Library



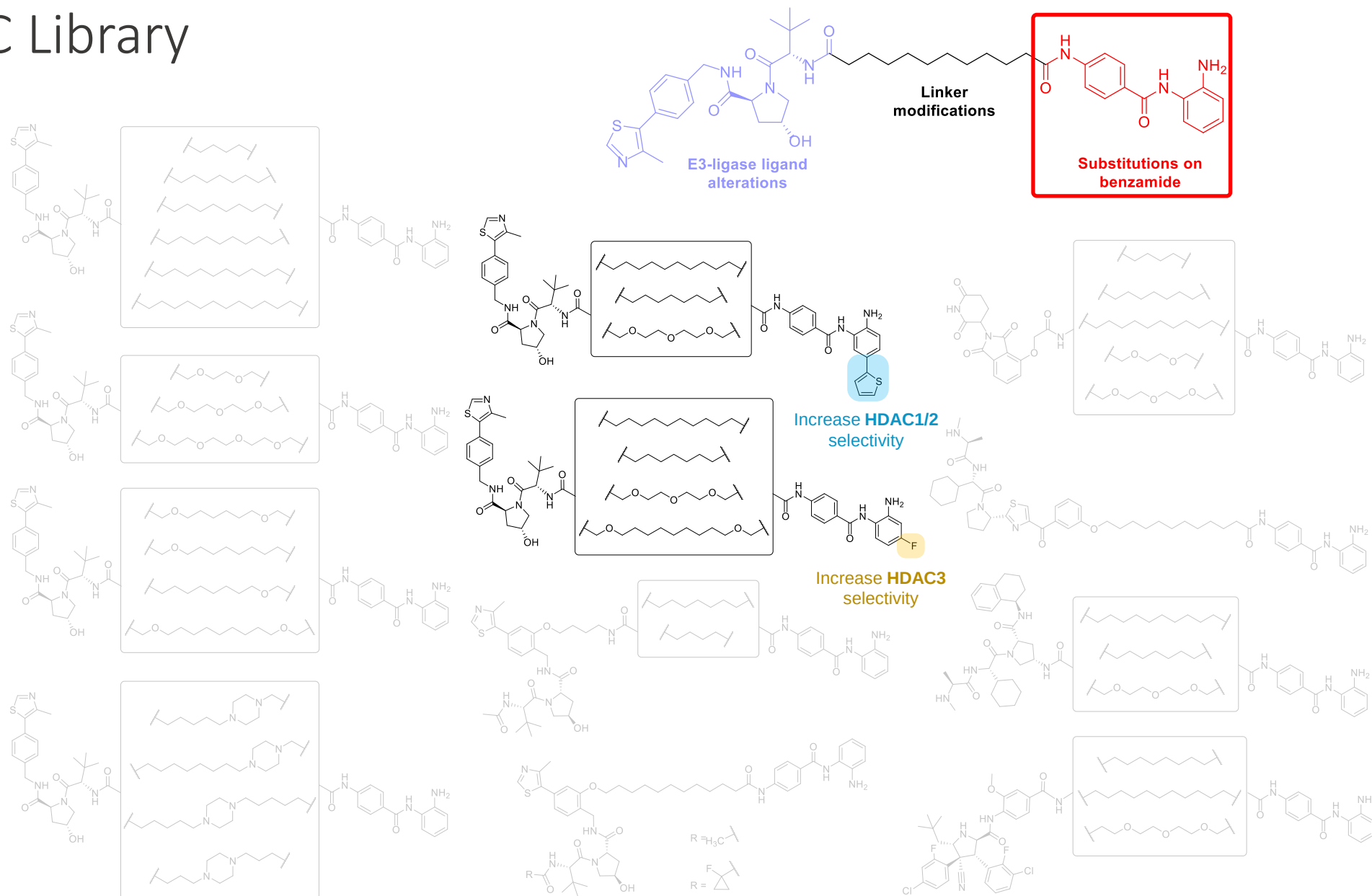
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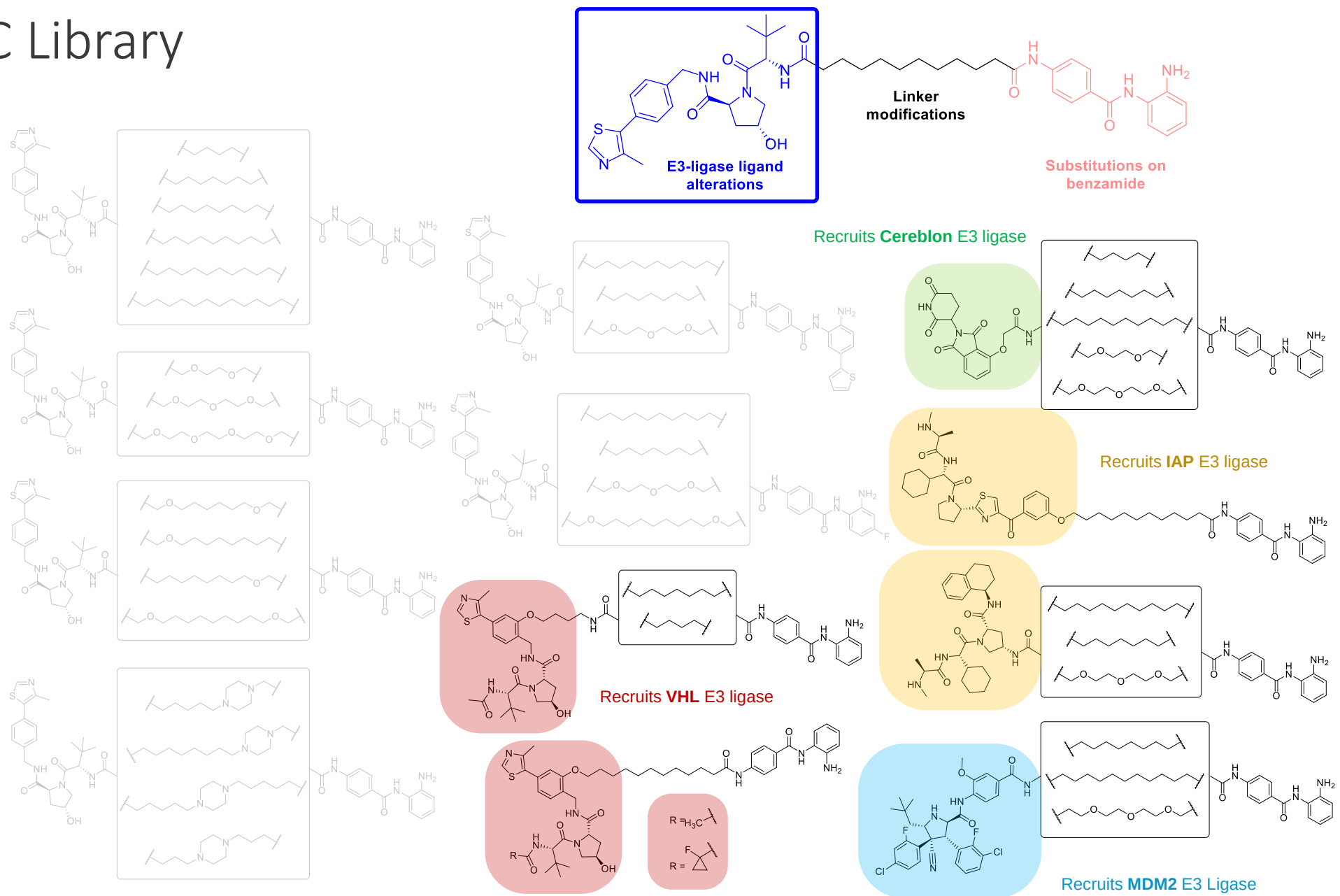
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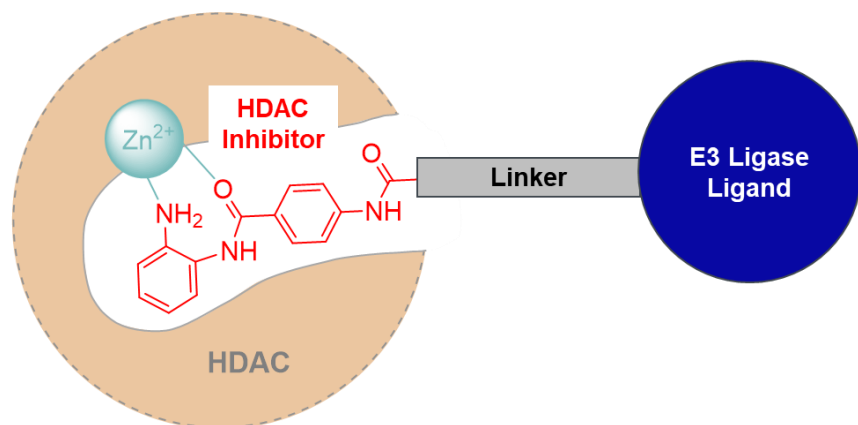
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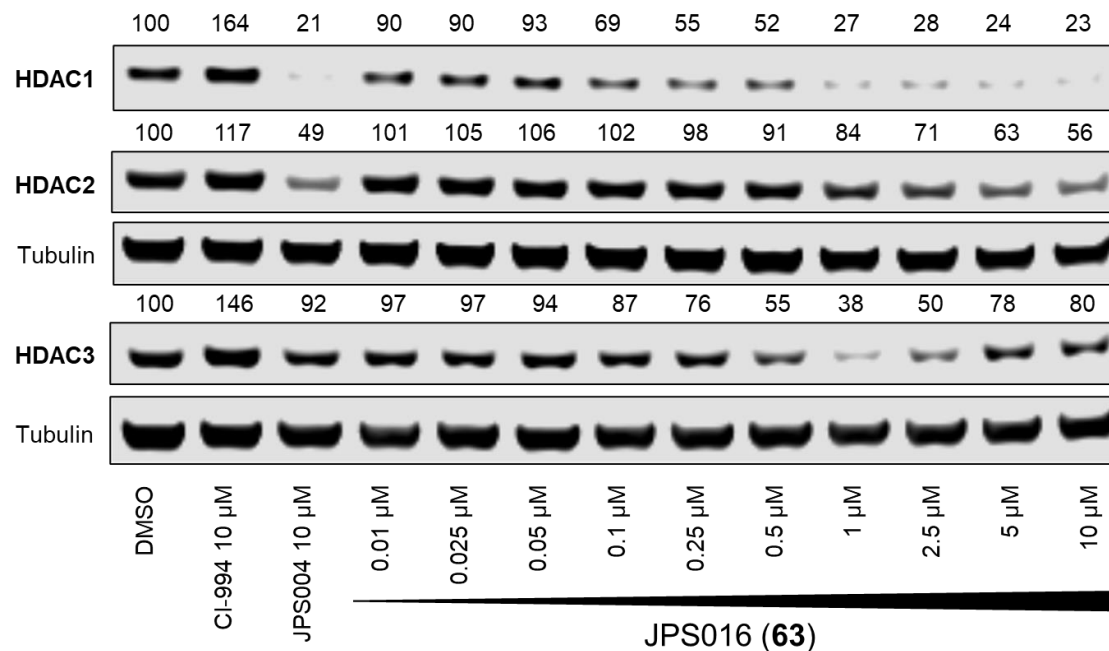
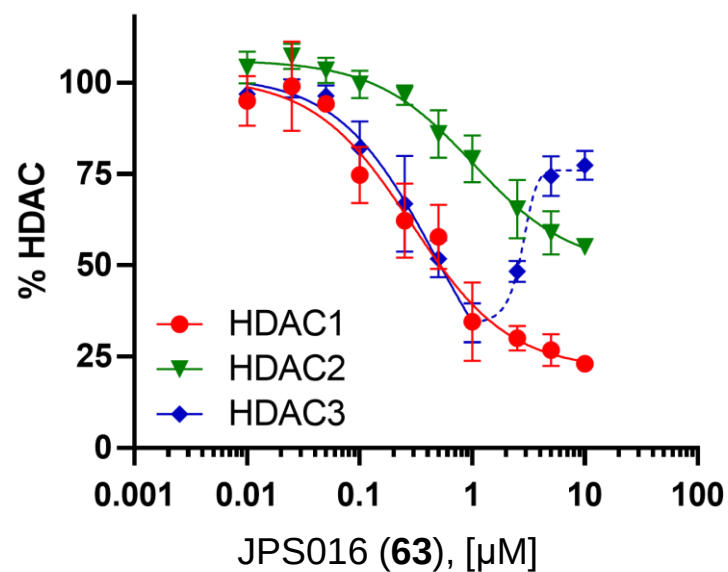
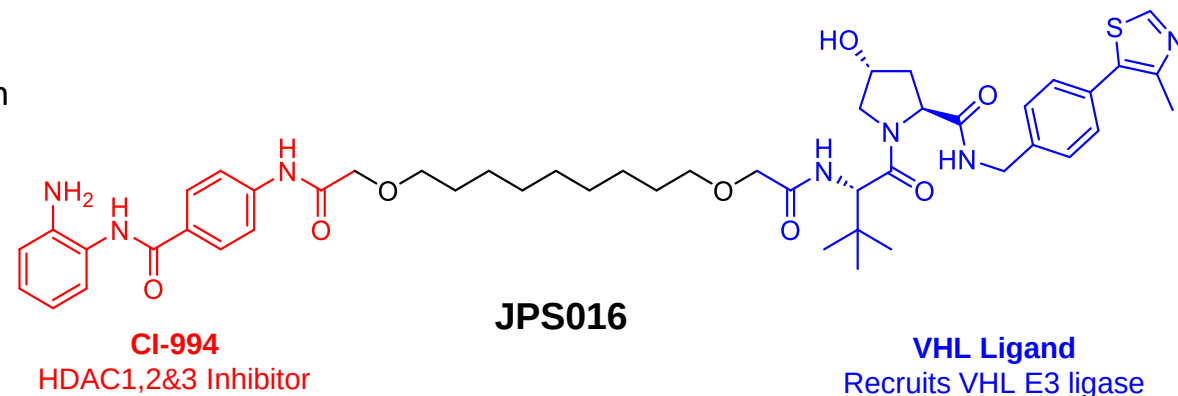
PROTAC Library



Potent HDAC Degraders JPS016



Extensive Modification
and Optimisation



J. P. Smalley et al., *Chem. Commun.* **2020**, 56, 4476.

J. P. Smalley et al., *J. Med. Chem.* **2022**, 65, 564

HDAC Degradar; **2021**, WO2021148811A1; **2023**, US2023-010211A1; **2023**, JP2023-510947

The Science Kitchen

- My big project going forwards – showcasing the science of baking and cooking
- Dedicated space for creating videos, preparing demonstrations and presentations, delivering webinars and hosting live events
- Watch this space!



Thank You For Listening

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