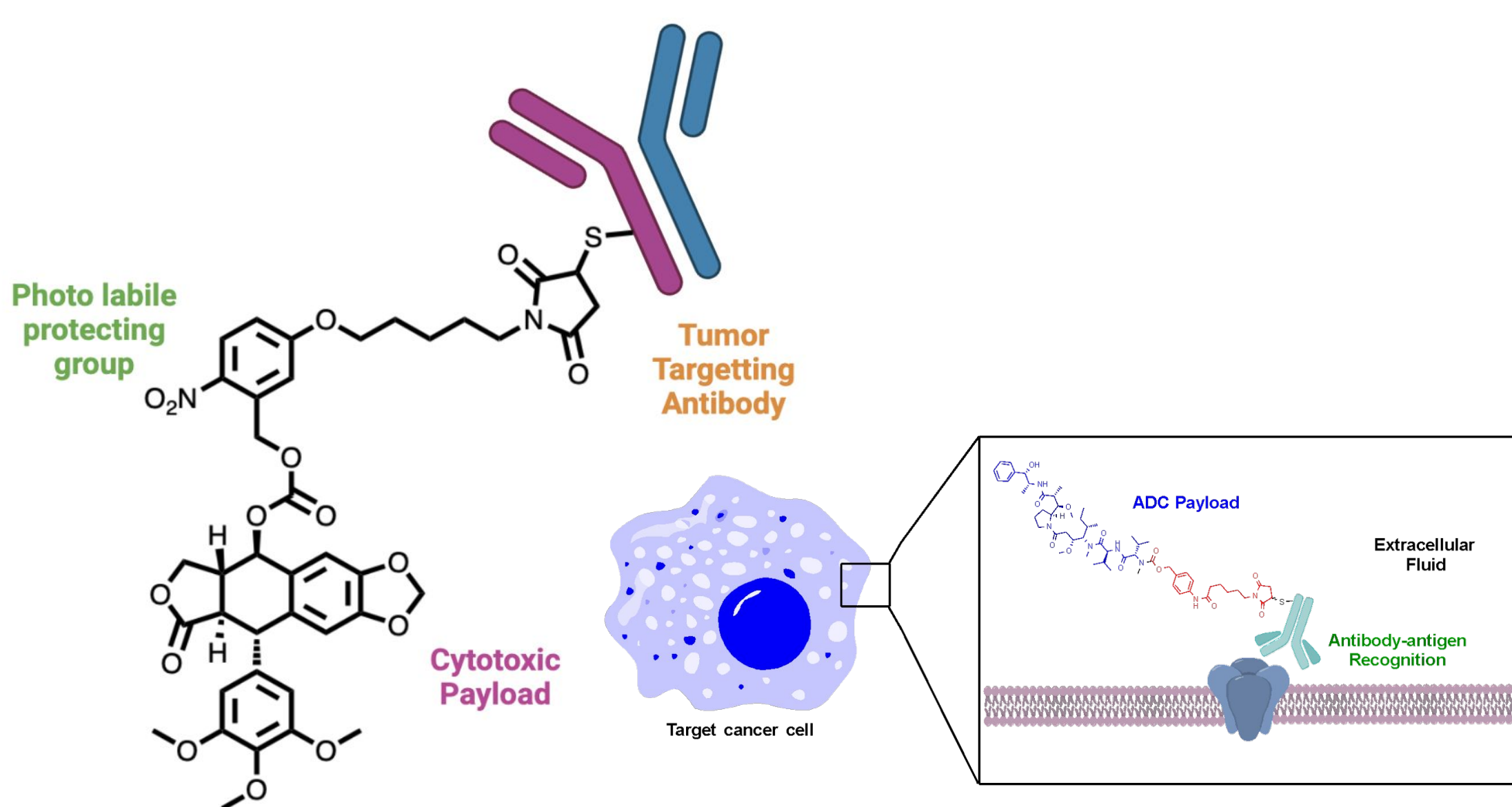
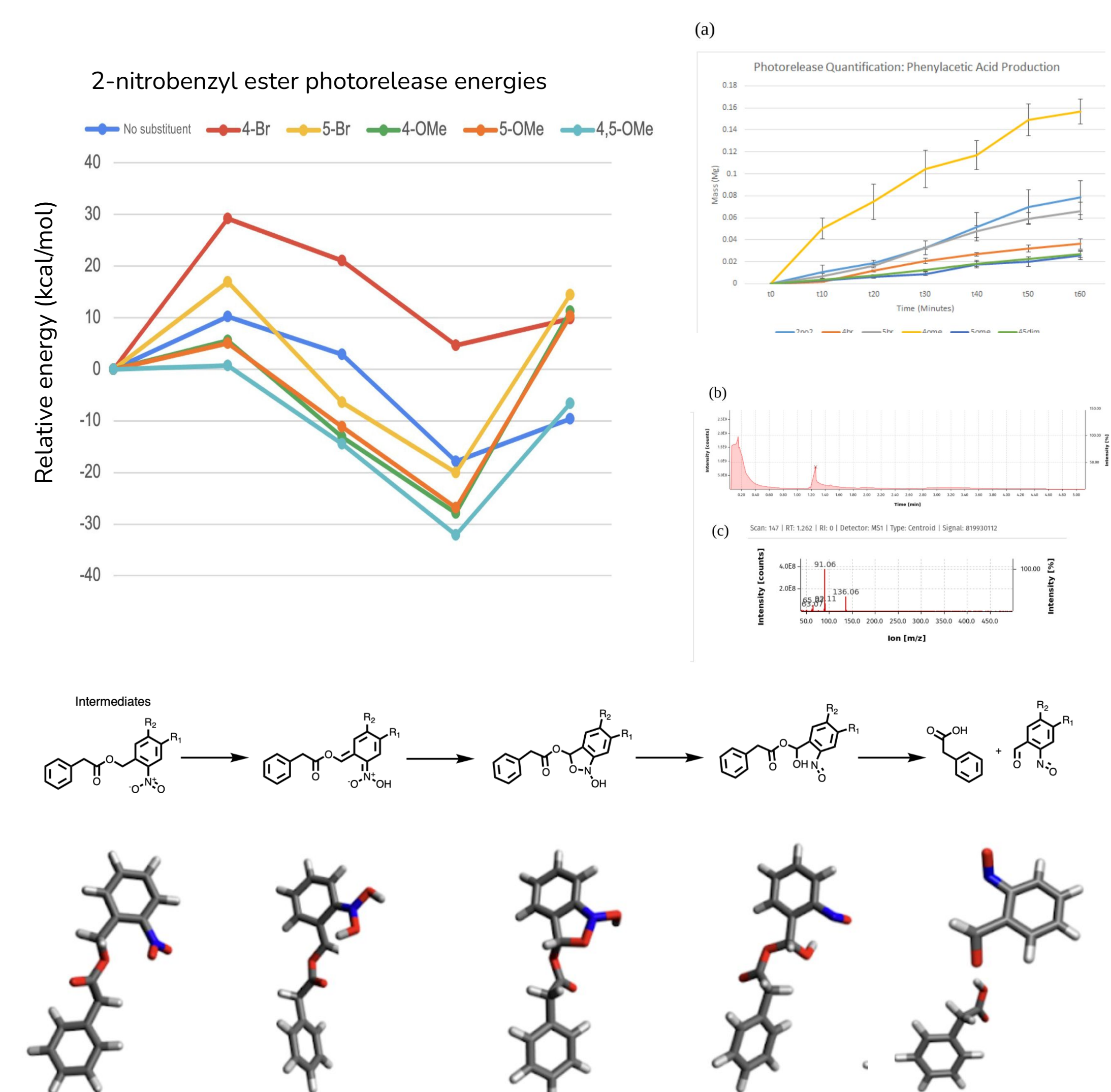


Background

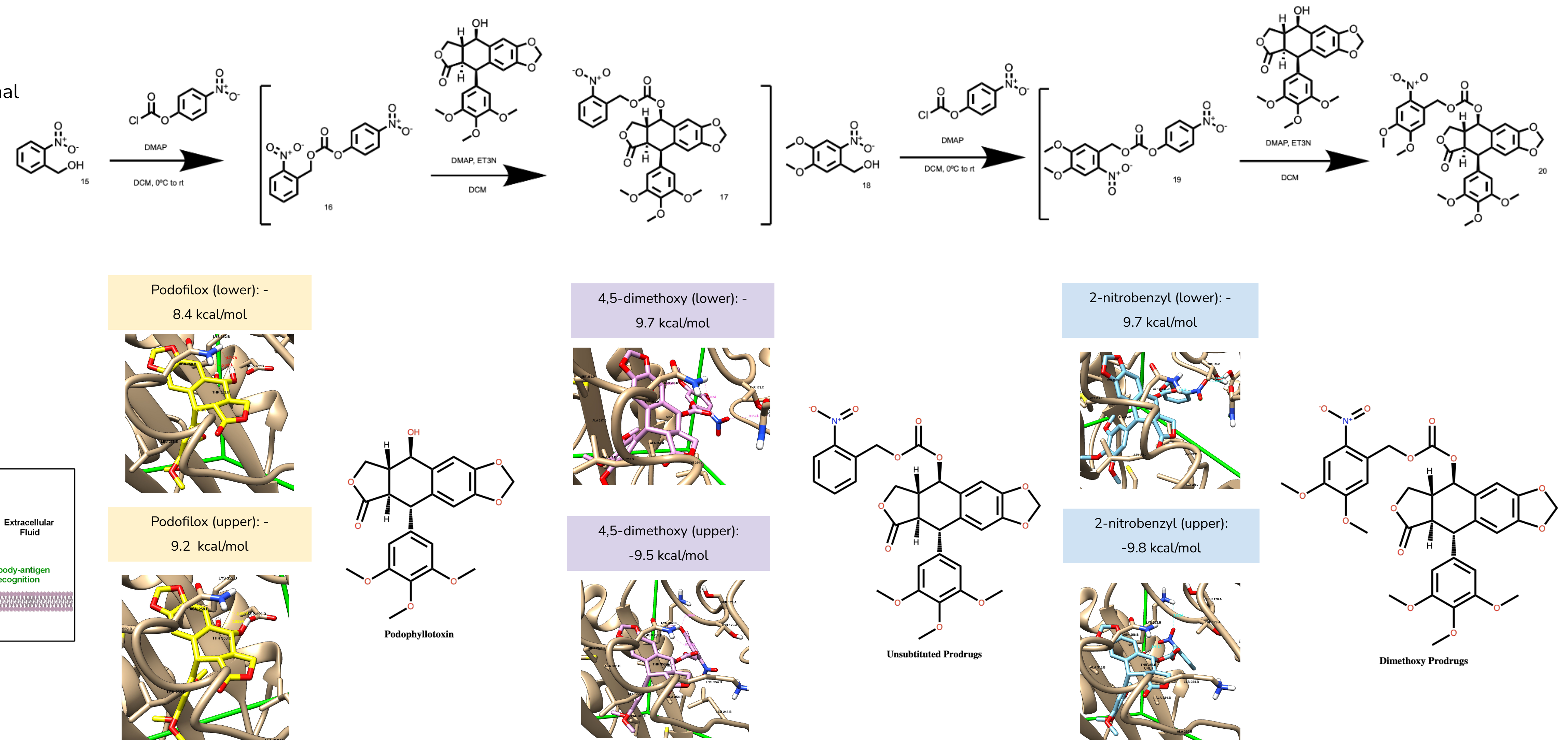
Photoreleasable protecting groups allow for the controlled release of a molecule at will. The *o*-nitrobenzyl group has been previously studied for its electronic properties and photorelease kinetics. Due to its bio-orthogonal release mechanism and ease of control, we have found optimizing *o*-nitrobenzyl linkers as a promising prodrugging strategy. By using a small-molecule cytotoxic payload, podophyllotoxin, we aim to create a synthetic workflow for the creation of antibody-drug conjugate (ADC) photoreleasable linkers for targeted cancer therapeutics.



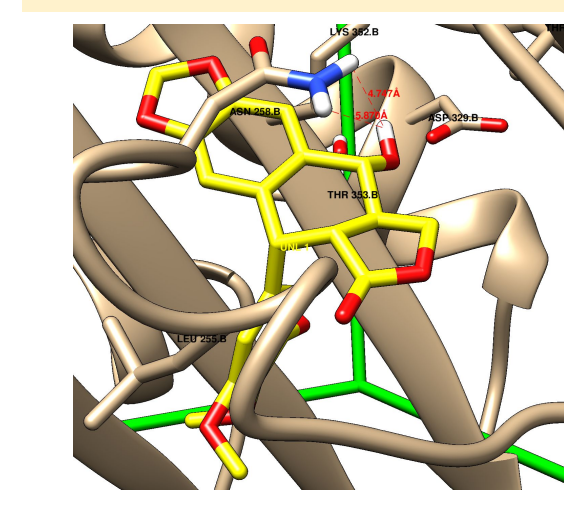
Photorelease Kinetics - Aromatic Substitutions



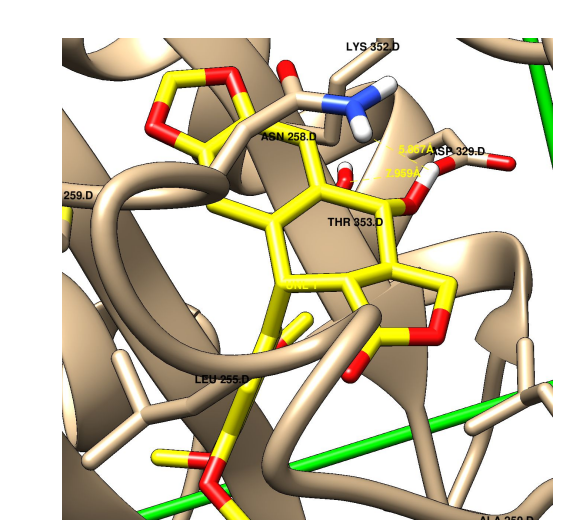
UV Photocaged Prodrugs of Podophyllotoxin



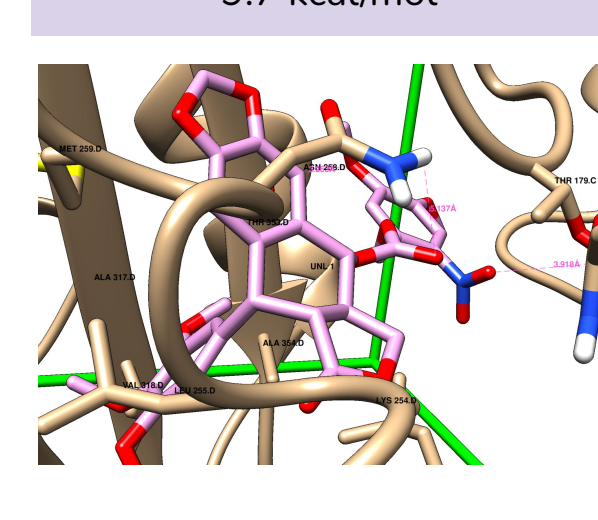
Podofitox (lower): - 8.4 kcal/mol



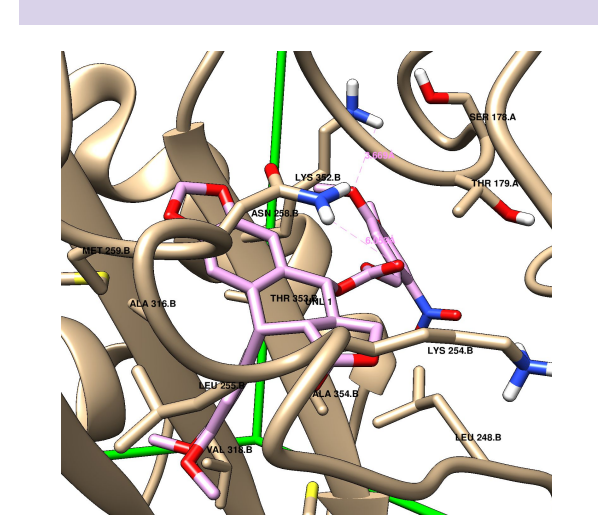
Podofitox (upper): - 9.2 kcal/mol



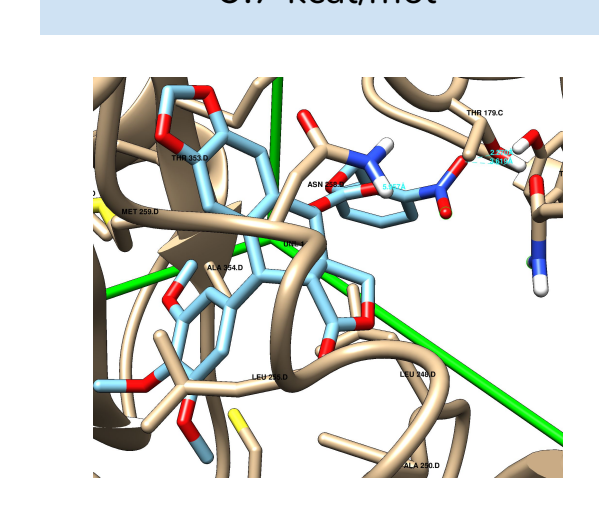
4,5-dimethoxy (lower): - 9.7 kcal/mol



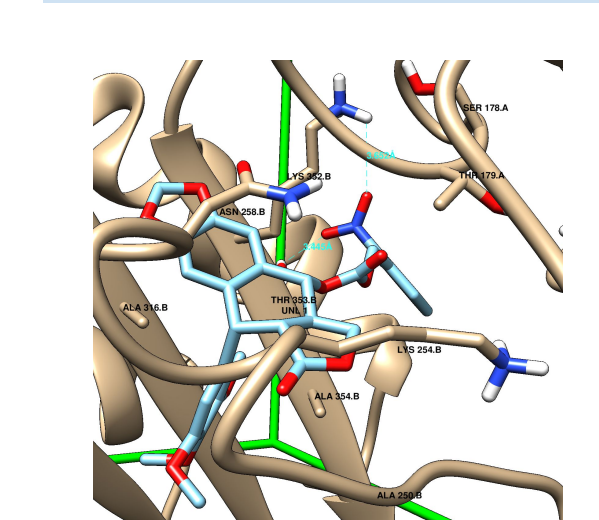
4,5-dimethoxy (upper): -9.5 kcal/mol



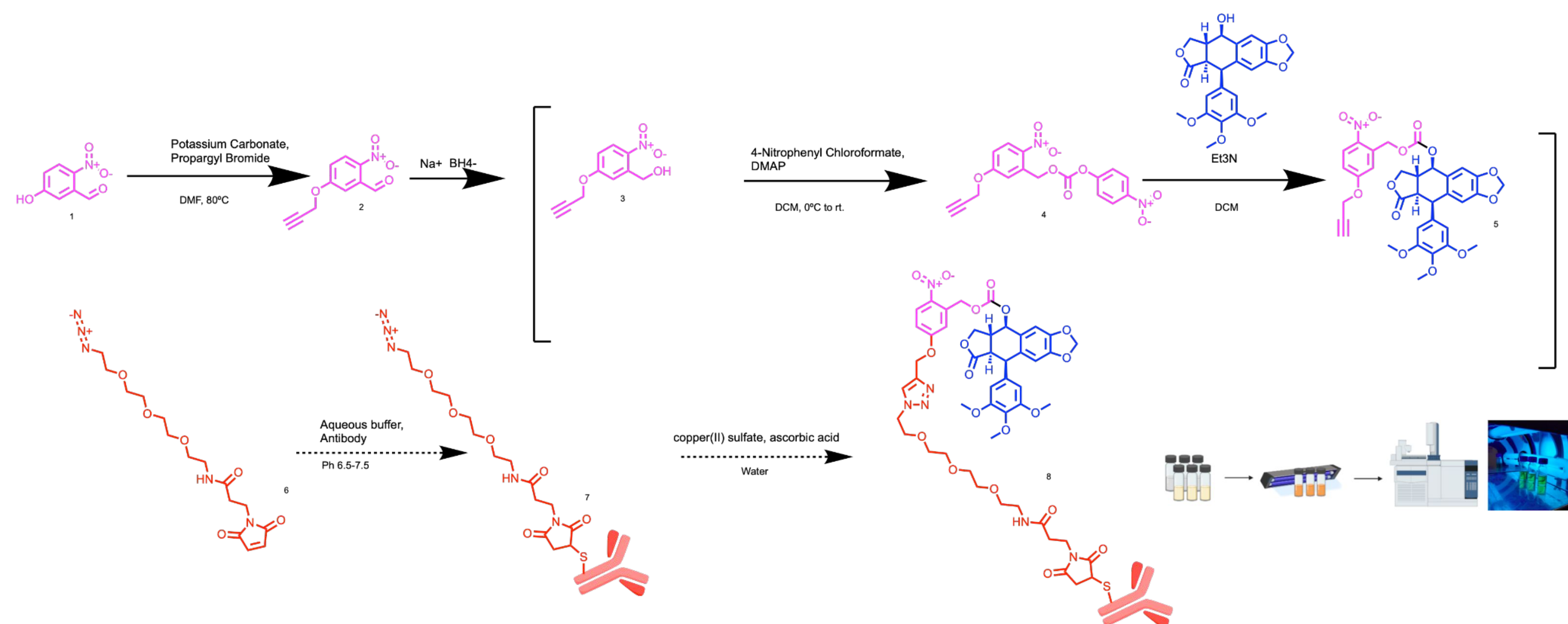
2-nitrobenzyl (lower): - 9.7 kcal/mol



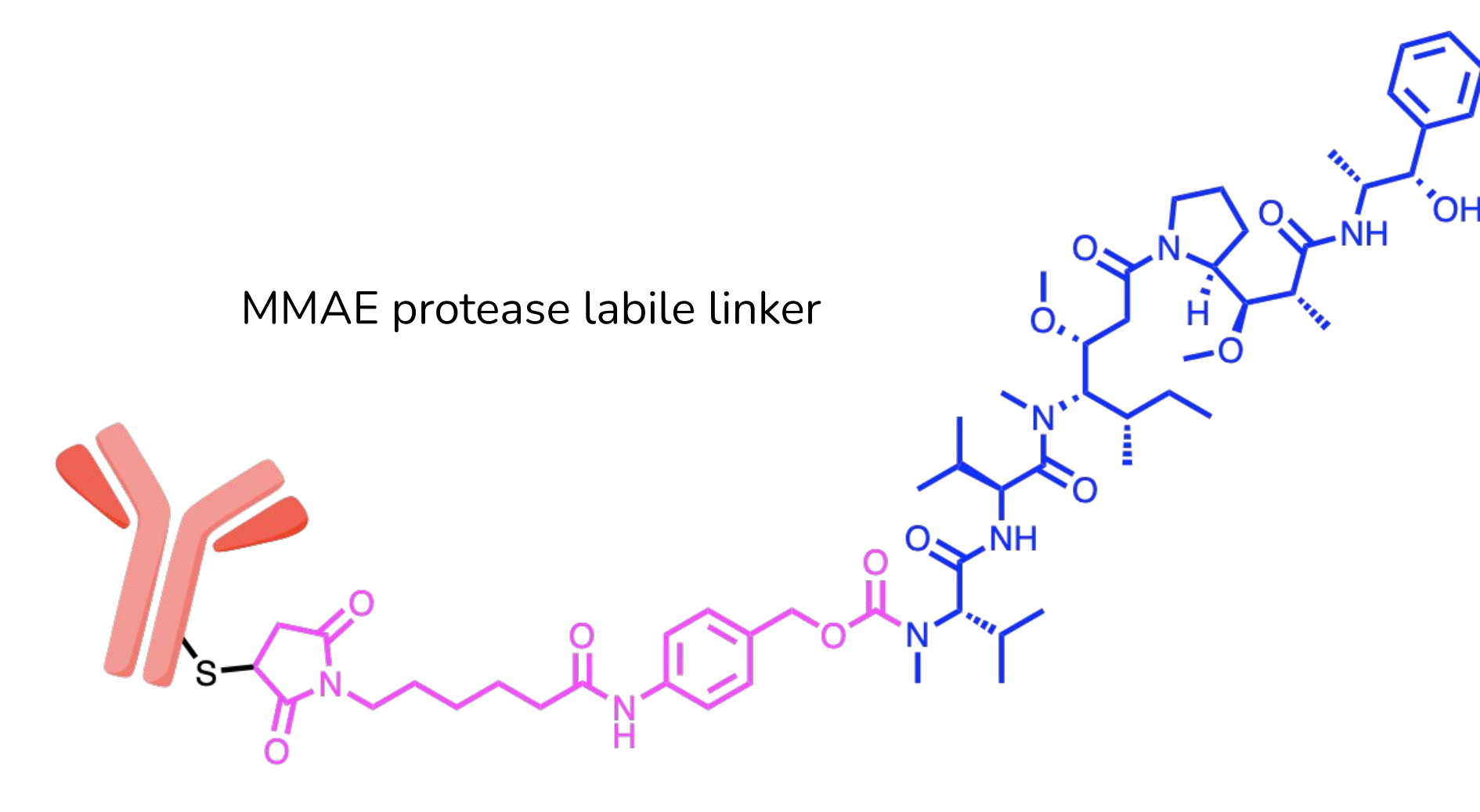
2-nitrobenzyl (upper): -9.8 kcal/mol



Photoreleasable ADC Linker

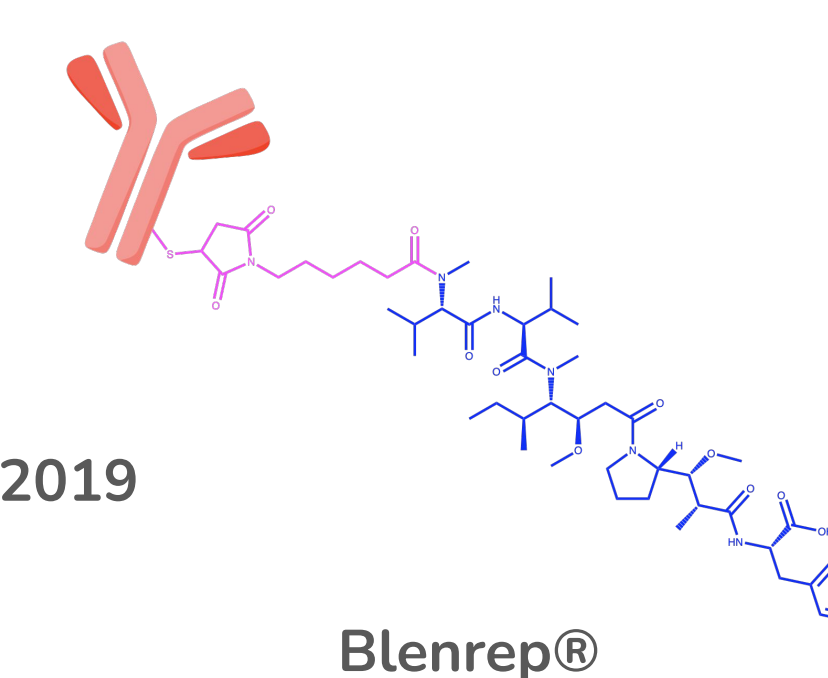


Non-Photoreleasable ADC Linkers

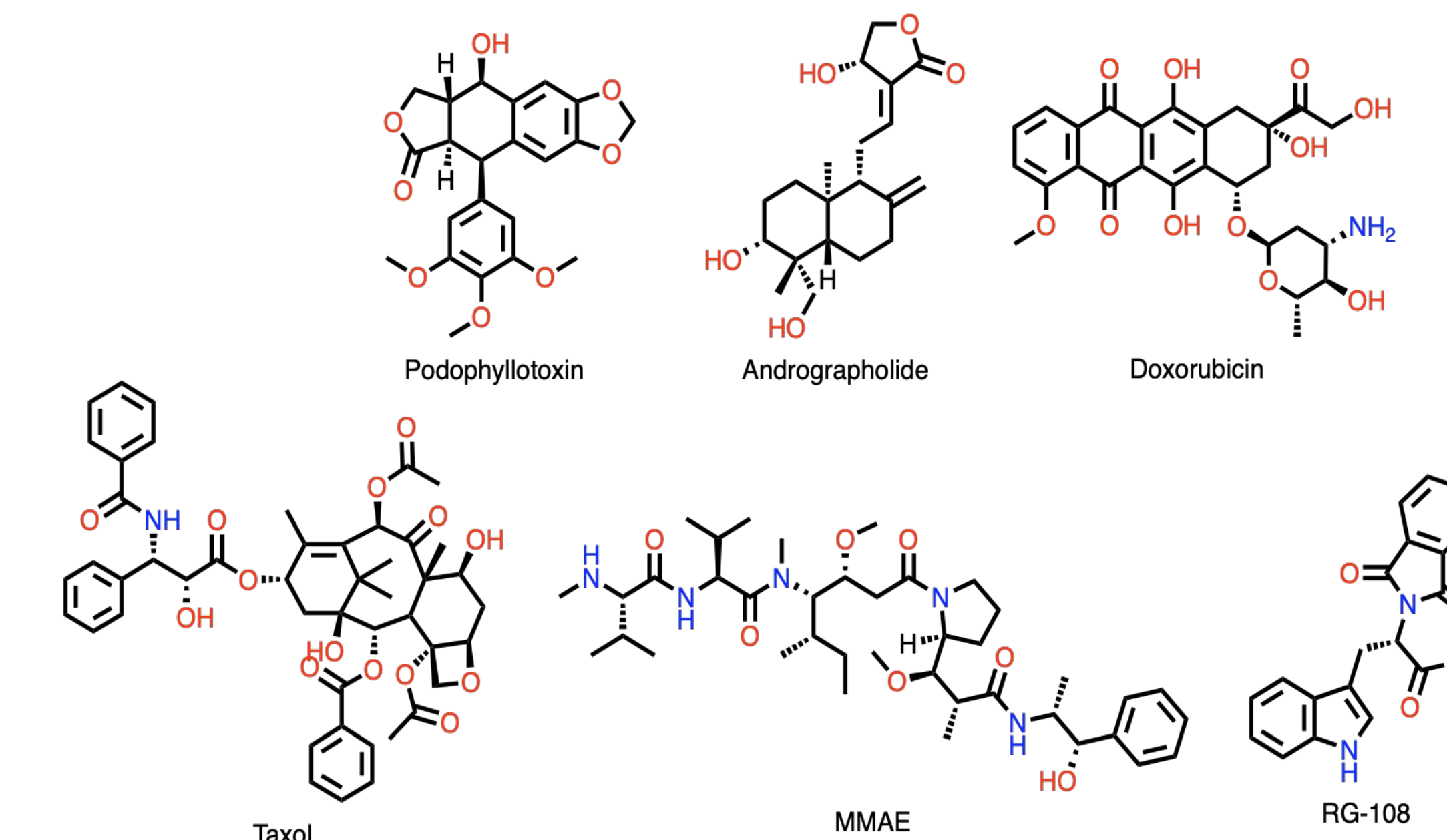


Currently FDA Approved ADCs

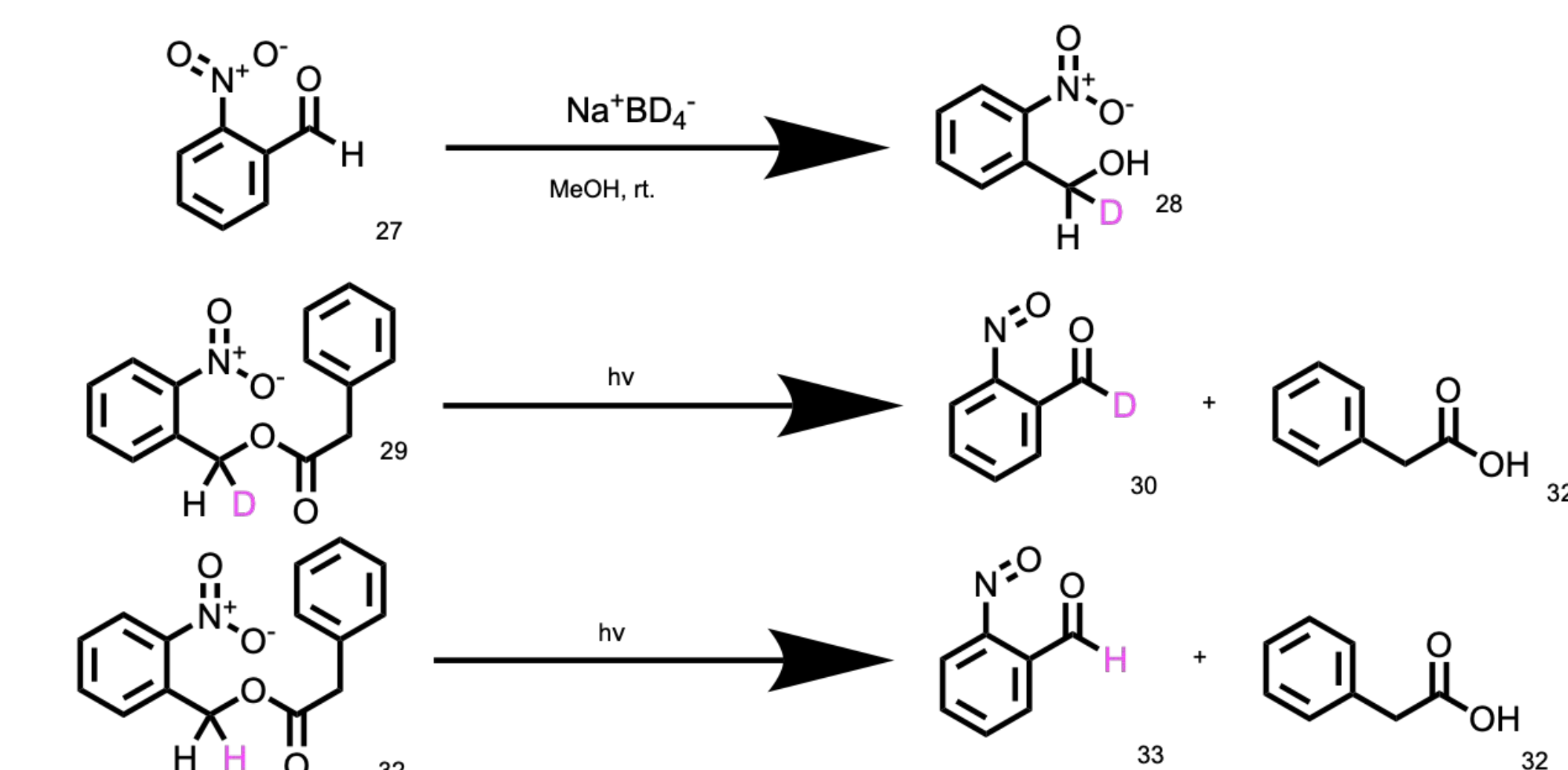
1. Mylotarg® (gemtuzumab ozogamicin) - 2000
2. Adcetris® (brentuximab vedotin) - 2011
3. Kadcyla® (ado-trastuzumab emtansine) - 2013
4. Besponsa® (inotuzumab ozogamicin) - 2017
5. Polivy® (polatuzumab vedotin-piiq) - 2019
6. Padcev® (enfortumab vedotin-ejfv) - 2019
7. Enhertu® (fam-trastuzumab deruxtecan-nxki) - 2019
8. Trodelvy® (sacituzumab govitecan-hziy) - 2020
9. Blenrep® (belantamab mafodotin-blmf) - 2020
10. Zynlonta® (loncastuximab tesirine-lpyl) - 2021
11. Tivdak® (tisotumab vedotin-tftv) - 2021



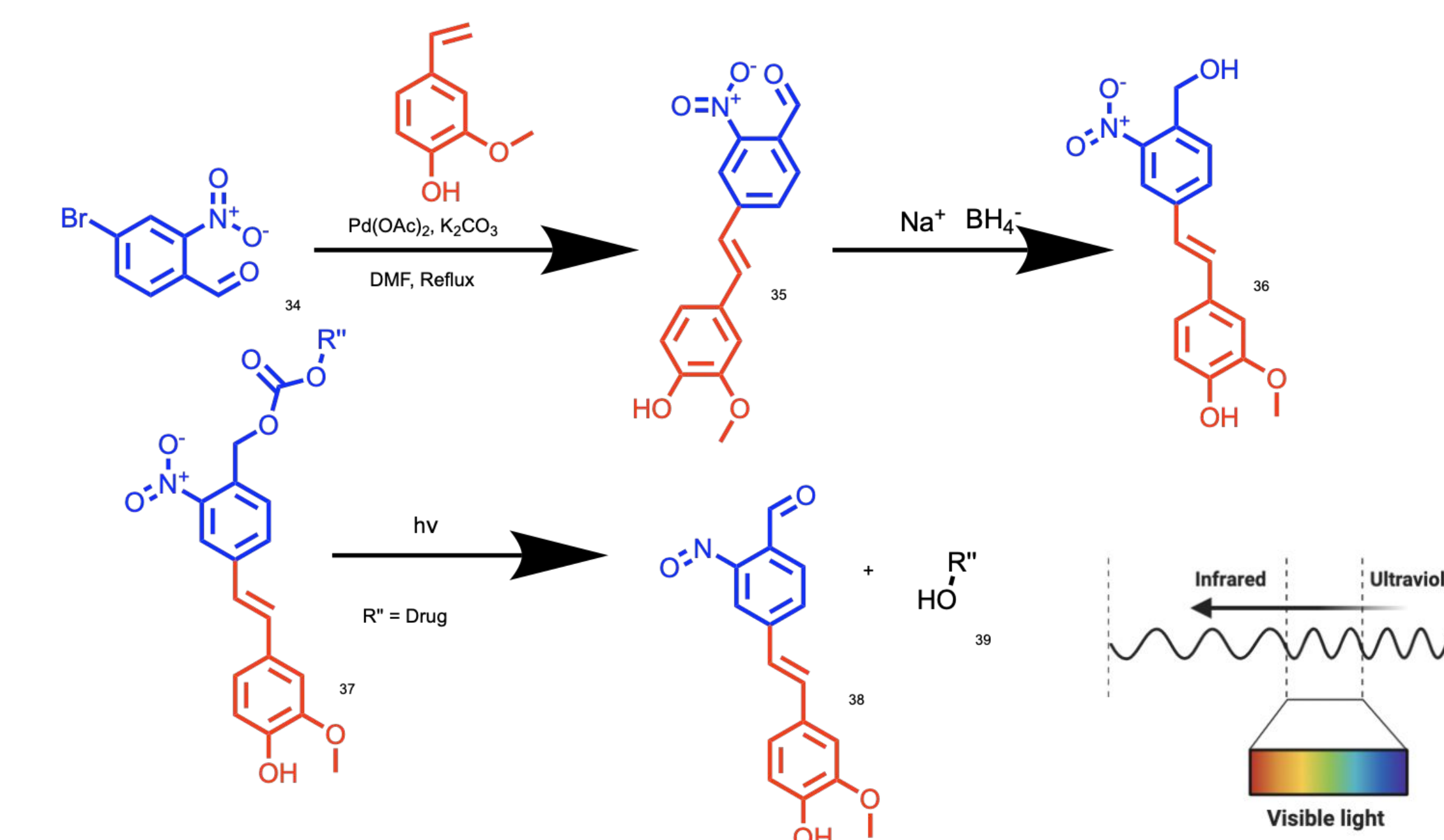
Future Payloads



KIE Photorelease Study



Redshifting Photorelease



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