

Strategies to Achieve Chemical Conjugation of Nicotinamide Mononucleotide into Poly (vinyl Alcohol) Hydrogel Reservoirs for Targeted Drug Delivery Applications

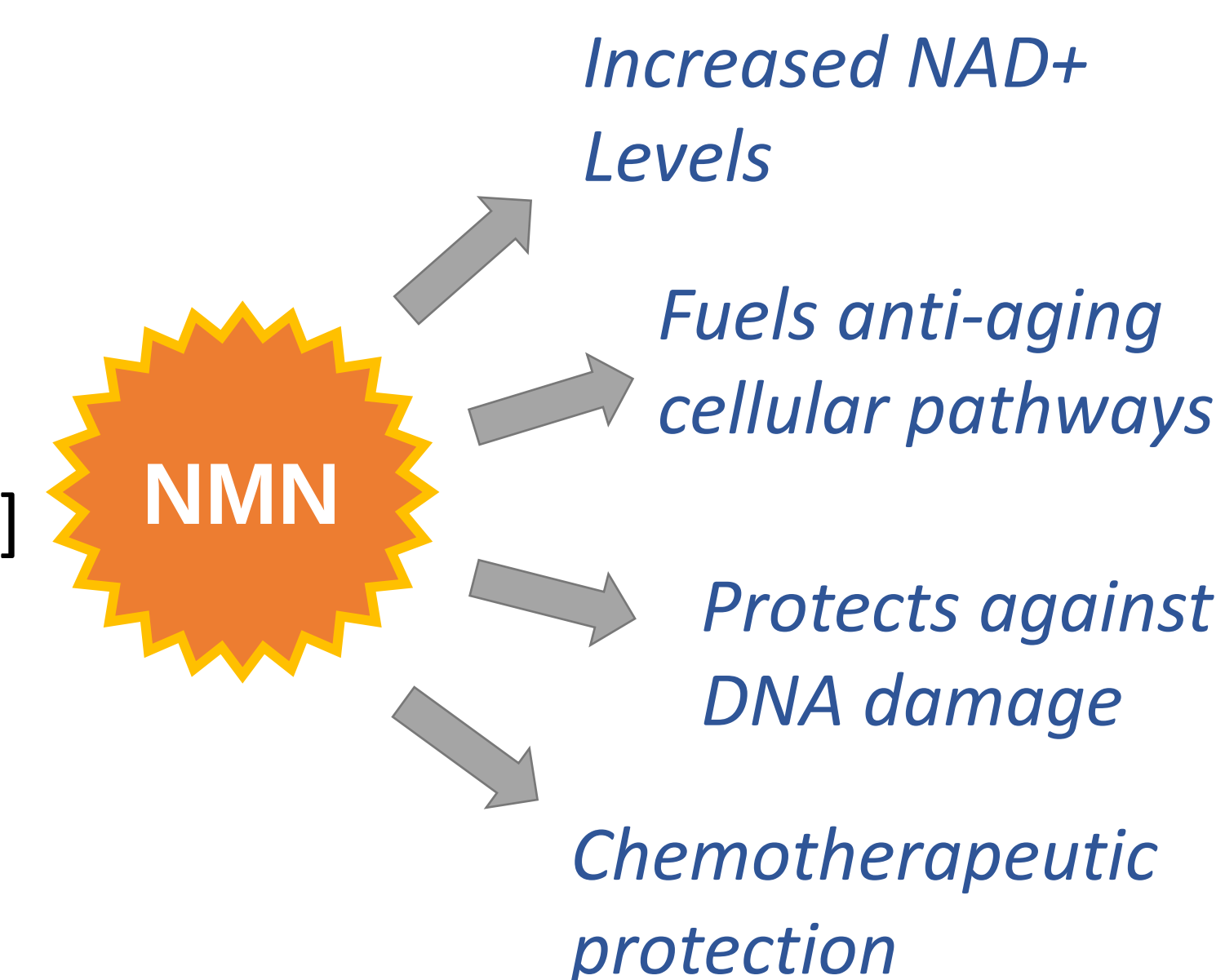
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Motivation:

- Administration of Nicotinamide Mononucleotide (NMN) is very beneficial to combat a wide range of diseases [1,2]
- NMN treatments may prevent fertility damage during chemotherapy



Problem:

Current Application



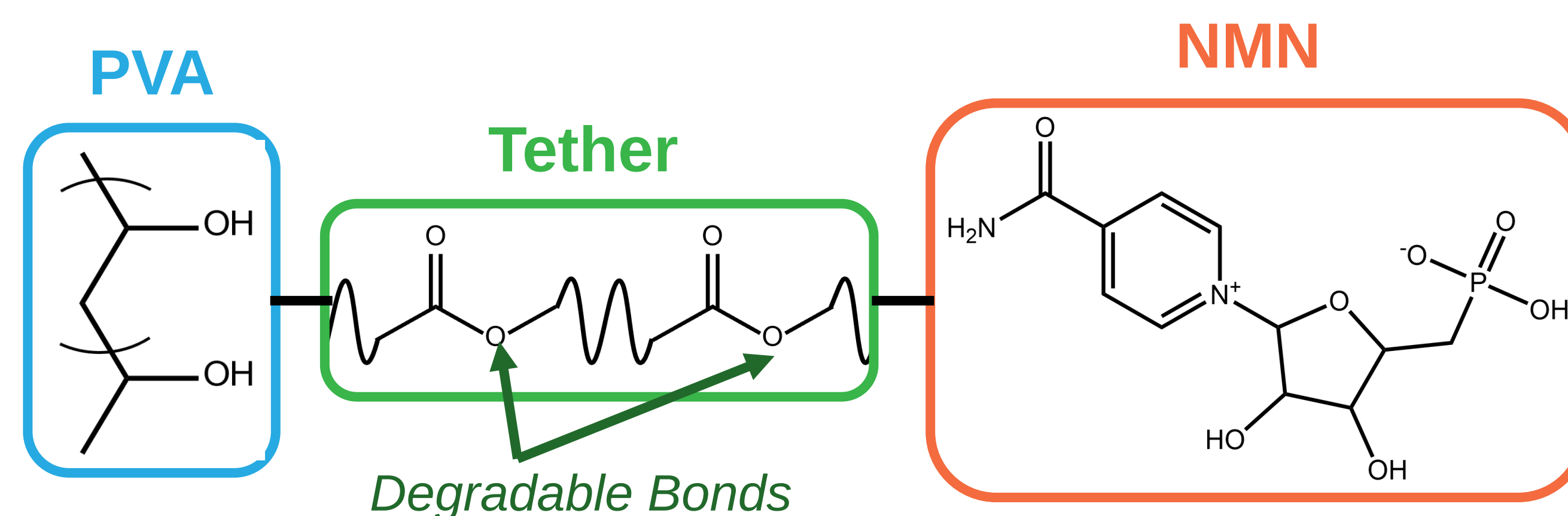
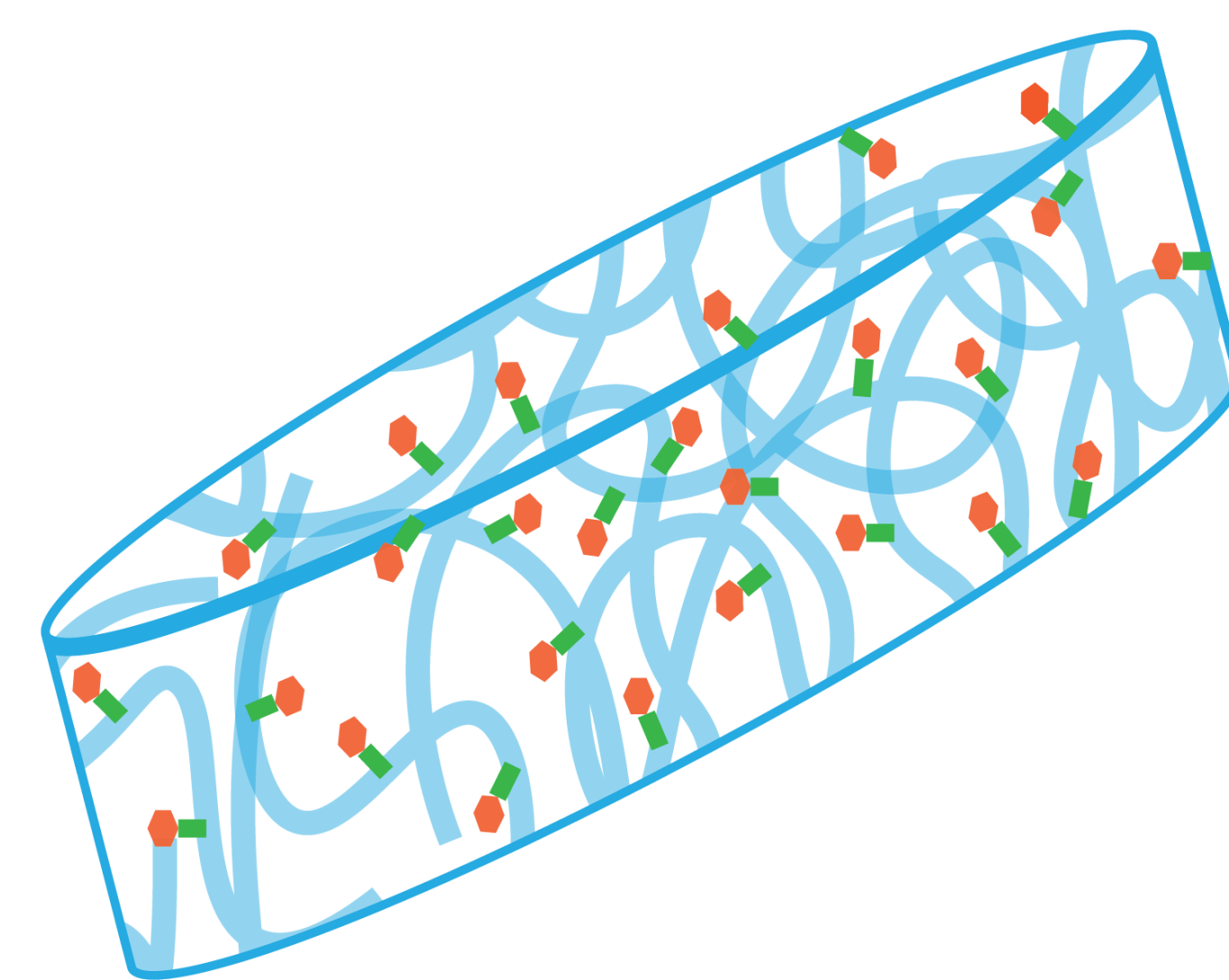
- Systemic only (oral or IV injection) can lead to side effects and requires high dosages

Desired Application



- Administration to target tissue only
- Extended release

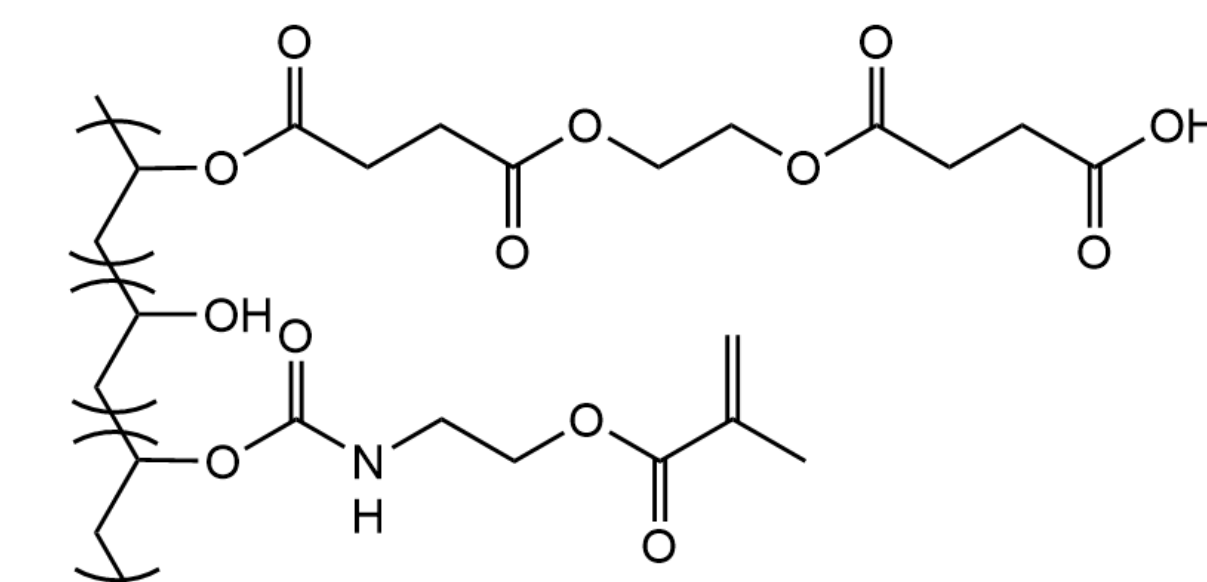
Approach:



- Chemically conjugate NMN into a PVA hydrogel via a tether containing biodegradable bonds (ester and amide)
- Hydrogel can be implanted at location of interest for targeted drug release
- Several chemical synthesis strategies are proposed

PVA modified with Ester and Methacrylate Moieties

- PVA polymer with methacrylate groups to allow for UV crosslinking [3]
- A pendant containing multiple ester groups was attached via a novel synthesis process.
- This is used as base polymer for subsequent strategies

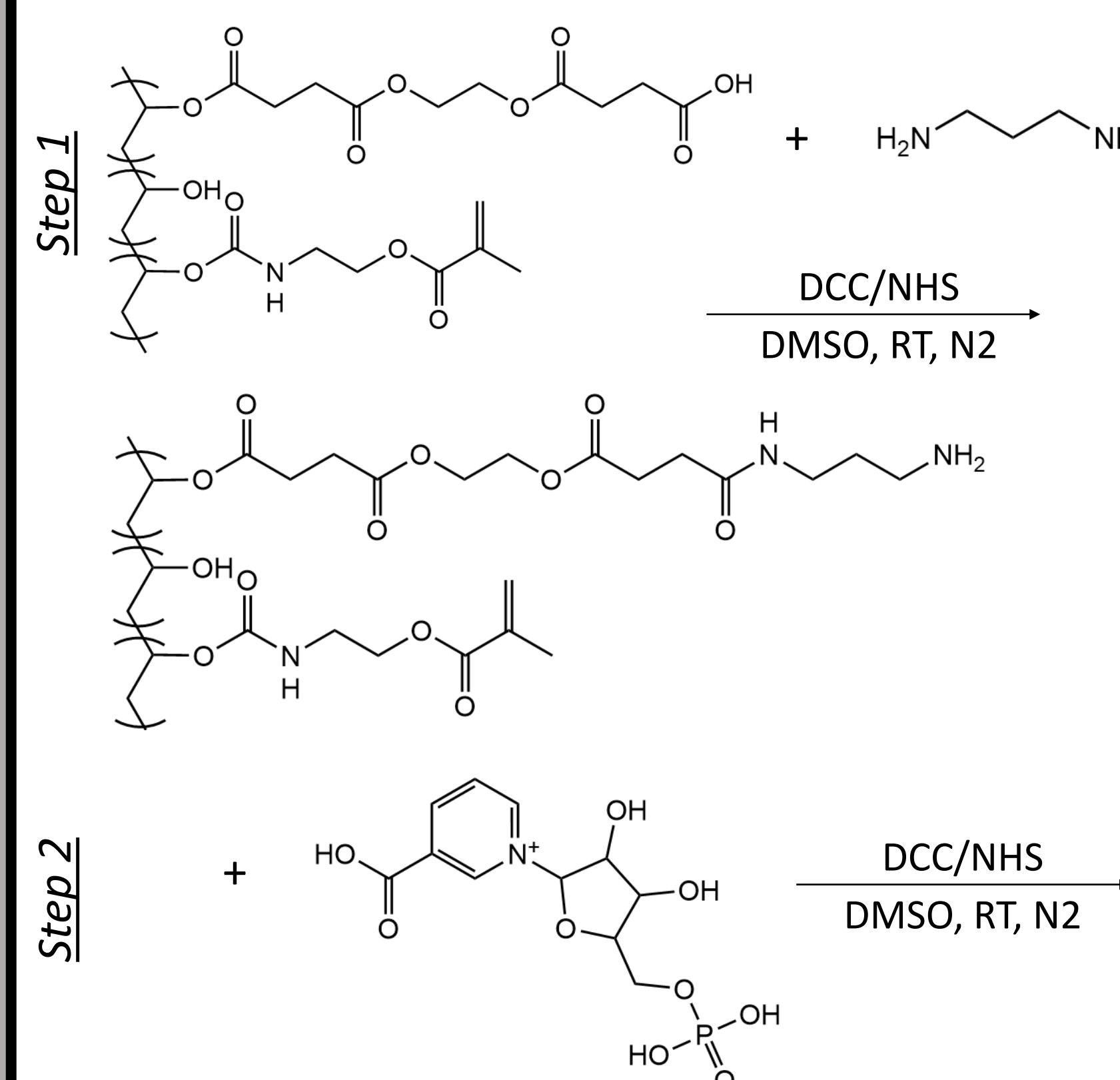
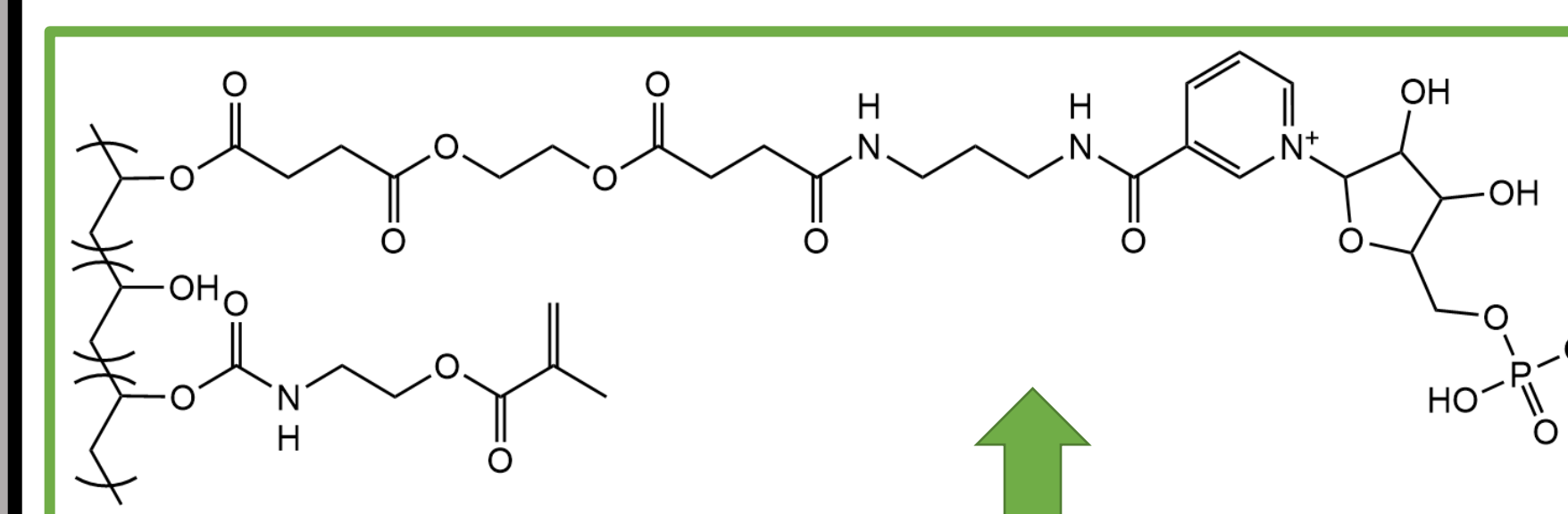


PVA with ester pendant (top) and methacrylate (bottom)

Discussion and Next Steps

- Goal of this project is to achieve a reliable synthesis method to achieve conjugation of NMN into the PVA-MA-ester polymer system
- Strategy 1 is complete and 2 is showing promising results in initial testing
- Hydrogel properties such as sol content, drug release, and cytocompatibility will be investigated
- The structure variation between the polymer products offers exciting opportunities to observe any variation in drug release and effectiveness

Strategy 1: "Amine Building Block"



3 ester, 2 amide bonds

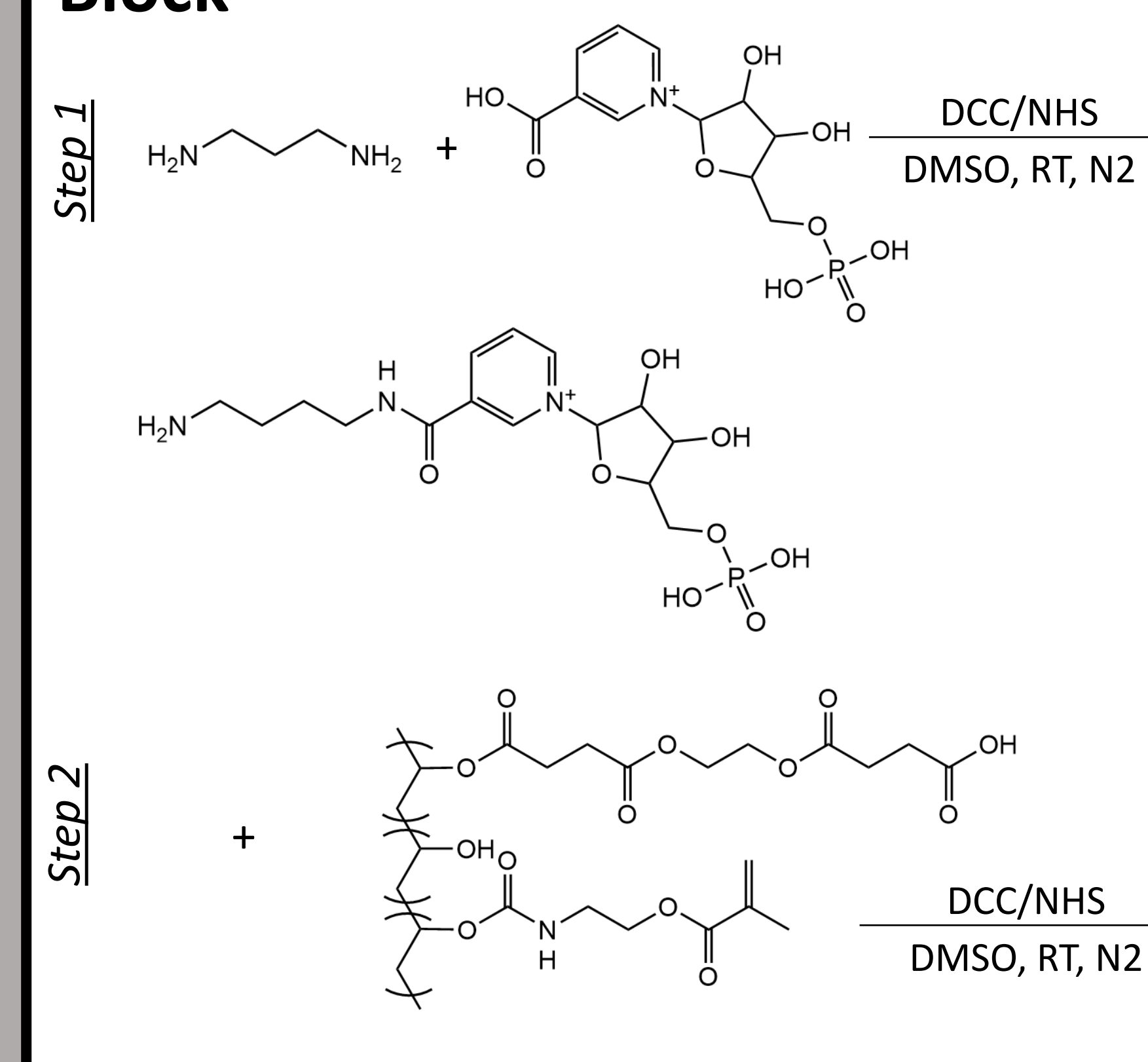
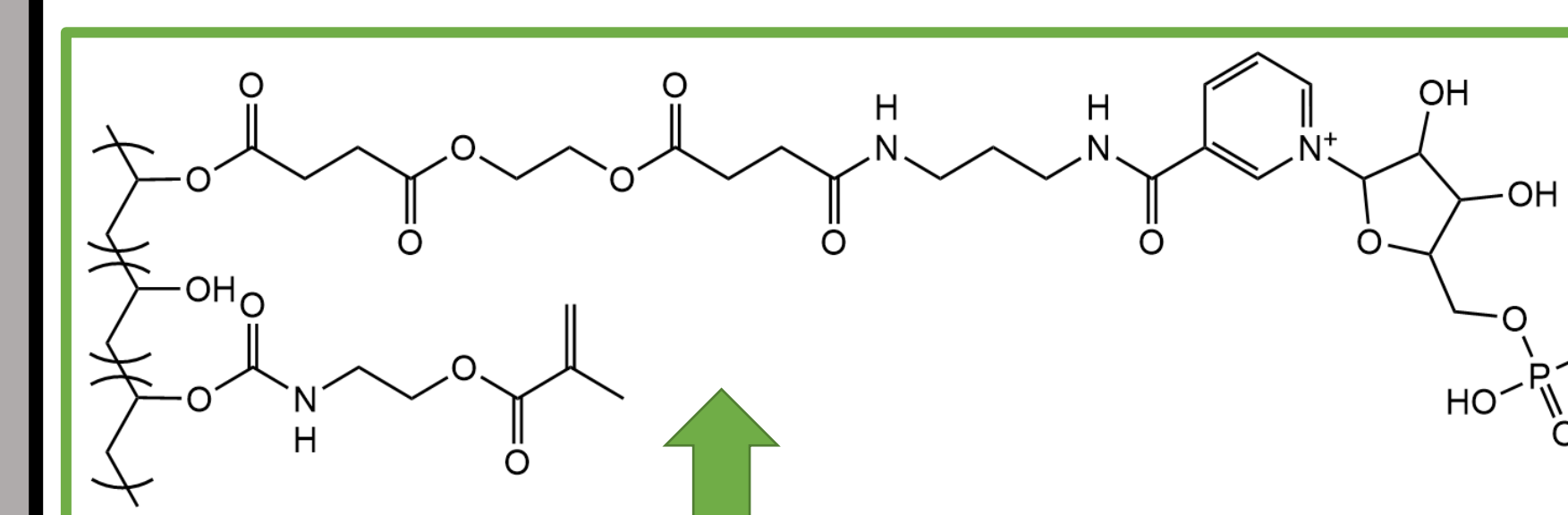
Pros

- Successfully synthesized
- NMR/FTIR data supports each step of synthesis
- Cytocompatibility (I929 Fibroblast) exhibited no cell growth inhibition

Cons

- Competing imide bond formation side reactions, leading to unworkable crosslinked polymer
- Low % functionalization of tethered NMN, possibly leading to insufficient drug release

Strategy 2: "Reverse Amine Building Block"



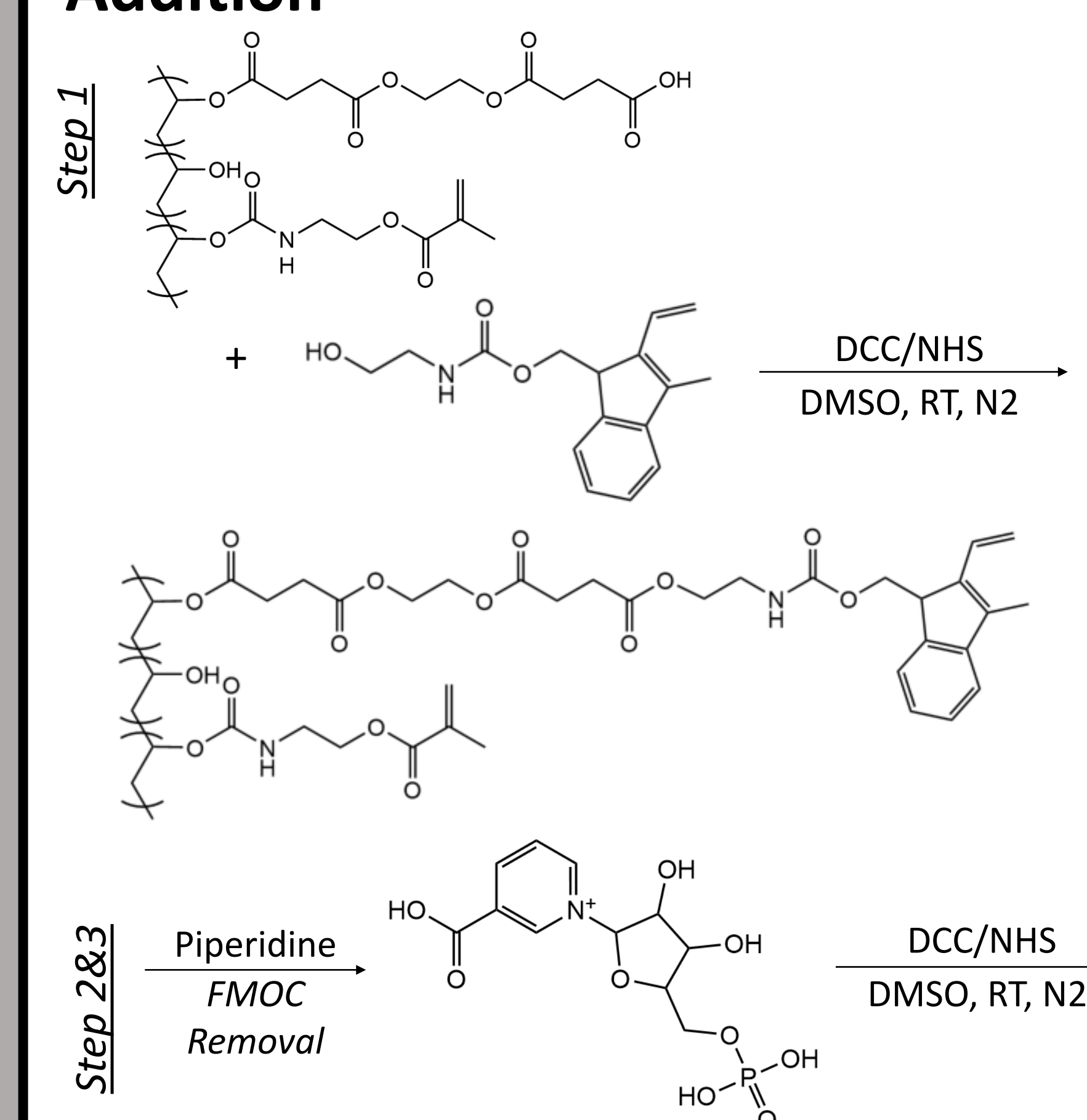
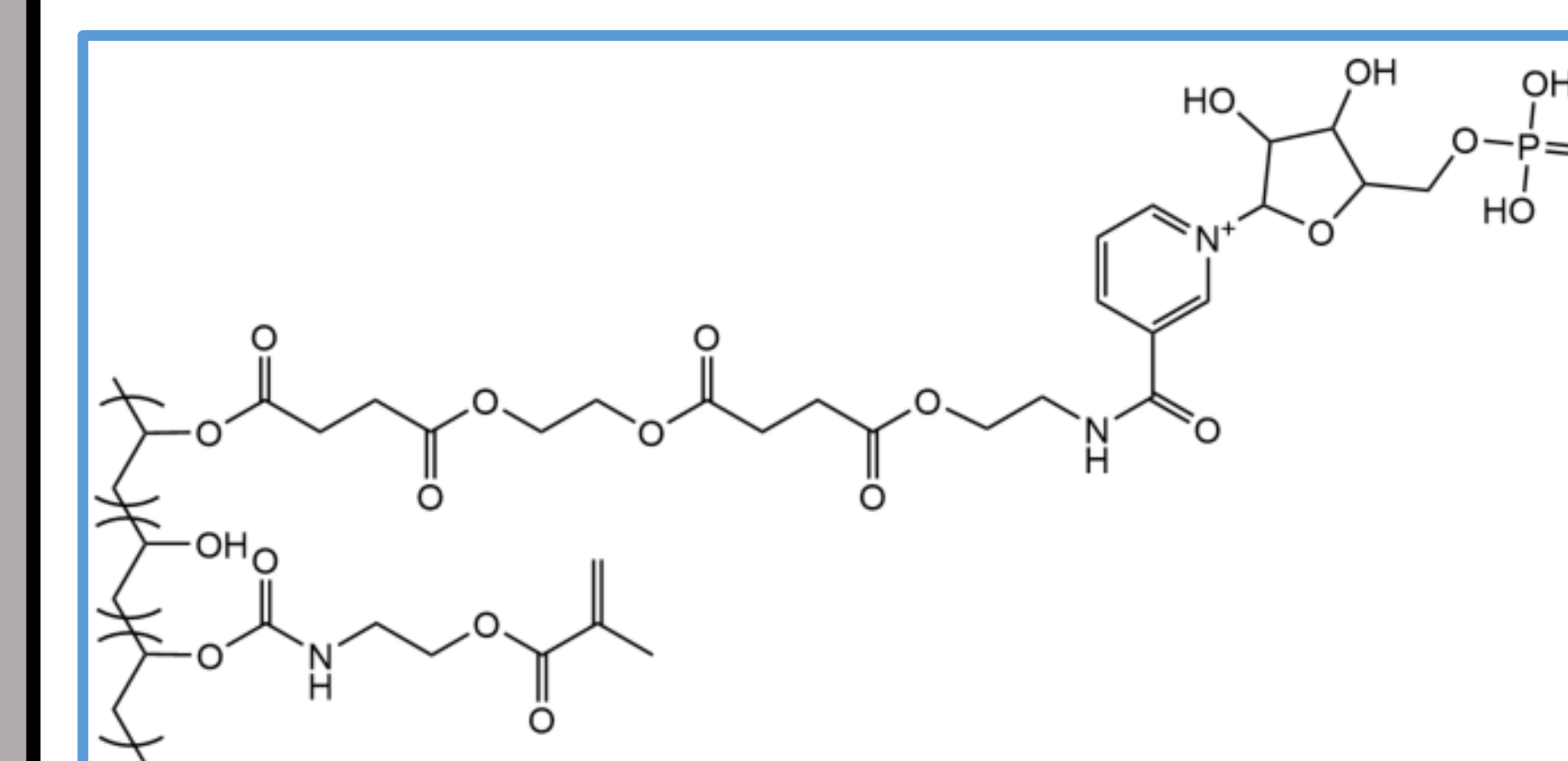
Pros

- Limits imide bond formation as DCC conjugation is favored and no free amine groups remain
- Yields same product
- Much higher percent functionalization

Cons

- Higher percent functionalization of NMN leads to intermolecular attractions between polymer chains, leading to upper limit of drug incorporation

Strategy 3: "Protecting Group Addition"



4 ester, 1 amide bonds

Pros

- More ester to amide bonds is desirable
- Imide formation will be prevented due to Fmoc

Cons

- More synthesis steps and purification needed

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References: [1] North BJ et al. EMBO J. 2014; 33: 1438-53 [2] Iami S, et al. Trends Cell Biol. 2014; 24(8) 464-71 [3] Nafea EH et al. J Biomater Sci Polym Ed, 2014; 25(16) 1771-90