GREEN AND SUSTAINABLE SOLVENTS FOR SOLID-PHASE PEPTOID SYNTHESIS

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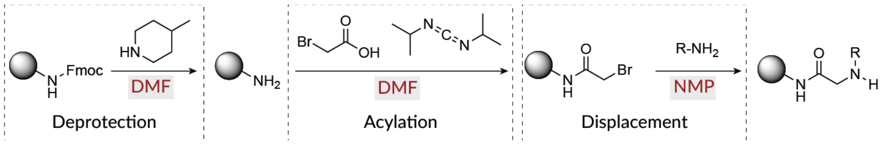
MOTIVATION: SUSTAINABLE PEPTOID SYNTHESIS

Peptoids, a class of **peptidomimetic polymers**, are an important platform for the development of new materials for therapeutics, cryopreservation, and biosensing. They can be readily synthesized using a **submonomer solid-phase synthesis strategy**.[1]



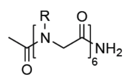
While this method has been widely adopted among peptoid researchers and optimized for unique applications, **limitations in the sustainability and safety** of these protocols remain.

Solid-phase peptoid synthesis is reliant on solvents that are[2]:

(1) hazardous (reprotoxic),

(2) increasingly restricted globally, and

(3) used in excess to wash the resin.



6-mer peptoid

Scale: 62 μmol

Solvent consumed: 225 mL

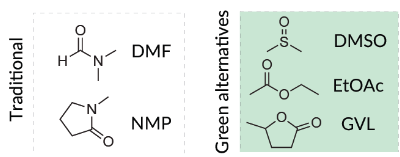
SELECTION OF ALTERNATIVE SOLVENTS

Alternative solvents for solid-phase peptoid synthesis were selected based upon their[3]:

(1) polarity,

(2) Environmental, Health, and Safety (EHS) assessment, and

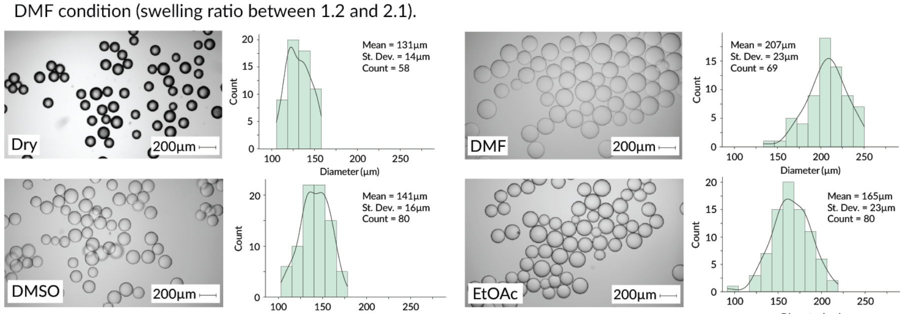
(3) cost compared with traditional peptoid solvents.

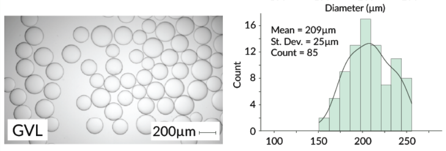


RESULTS: RESIN SWELLING

Resin swelling performance of traditional and green alternative solvents was investigated using light microscopy.

Acceptable solvents for solid-phase peptoid synthesis swell the resin to ±30% of the diameter observed in the DMF condition (swelling ratio between 1.2 and 2.1).



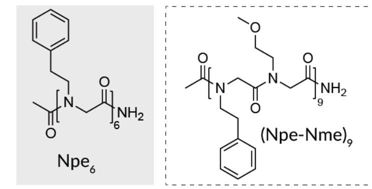


Solvent	Swelling Ratio	Solvent	Swelling Ratio	Solvent	Swelling Ratio
Dry	1.0	DMSO	1.1	1:1 DMSO:EtOAc	1.5
DMF	1.6	EtOAc	1.3	1:9 DMSO:EtOAc	1.5
NMP	1.7	GVL	1.6	DCM	1.8

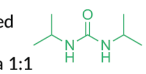
METHODS: SOLID-PHASE PEPTOID SYNTHESIS WITH GREEN SOLVENTS

	DMF/NMP	Method 1	Method 2	Method 3	Method 4	Method 5	Method 6
Swelling	DMF	GVL	DMSO	DMSO	1:9 DMSO:EtOAc	EtOAc	EtOAc
Deprotection	DMF	GVL	DMSO	DMSO	1:9 DMSO:EtOAc	EtOAc	EtOAc
Deprotection Wash	DMF	GVL	DMSO	DMSO	DMSO	DMSO	EtOAc
Acylation	DMF	GVL	DMSO	DMF	1:9 DMSO:EtOAc	EtOAc	EtOAc
Acylation Wash	DMF	GVL	DMSO	DMSO	DMSO	DMSO	1:1 DMSO:EtOAc
Displacement	NMP	GVL	DMSO	DMSO	1:9 DMSO:EtOAc	EtOAc	EtOAc
Displacement Wash	DMF	GVL	DMSO	DMSO	DMSO	DMSO	EtOAc

Target 6-mer and 18-mer peptoids:

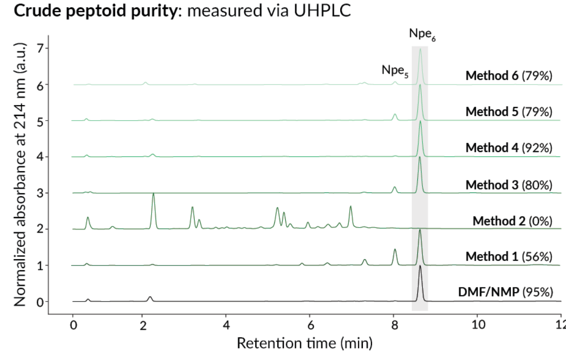


1,3-diisopropylurea is formed during acylation and is not soluble in EtOAc, requiring a 1:1 DMSO:EtOAc acylation wash in **Method 6.**

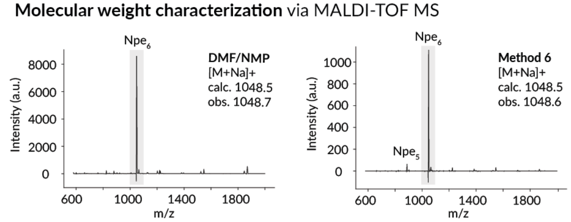


RESULTS: PEPTOID CHARACTERIZATION

Crude peptoid purity: measured via UHPLC

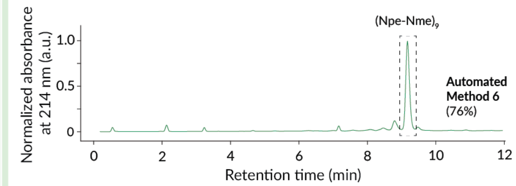


Molecular weight characterization via MALDI-TOF MS



RESULTS: AUTOMATION

New protocols were adapted to an **automated synthesizer** for the synthesis of 18-mer peptoids with excellent purities.



CONCLUSIONS

The **purities** and **yields** of the peptoids synthesized with green solvent mixtures (DMSO and EtOAc) are **comparable to traditional methods**, which use DMF and NMP.

FUTURE WORK

Additional solvent testing:

(1) Aqueous micellar media

(2) Bioderived DMF mimics

(3) Solvent-free approaches

Reducing solvent consumption:

Recycling washes (80-90% of total waste produced)

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