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Assessing Green Chemistry Routes to ALC-0315

Comparative Green Chemistry and Scale-Up Assessment of Reductive Amination and Amine Alkylation Routes to ALC-0315

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Introduction

ALC-0315 is an **ionizable lipid** central to the lipid nanoparticle (LNP) delivery system of the Pfizer-BioNTech **COVID-19 vaccine**. Manufacturing this component at sufficient scale and purity was identified as a significant bottleneck during the pandemic.

Several **synthesis routes** to ALC-0315 have since been published, but each is reported and optimised in isolation. This study develops a s**tandardised computational framework** to directly compare material efficiency and waste across four reported routes.

Objectives

- Compare **four** reported ALC-0315 **synthesis** routes on a standardised, process-level basis
- Determine whether reaction **yield** reliably predicts overall material efficiency
- Establish whether **continuous-flow** operation offers a genuine material-efficiency advantage over **batch synthesis**

Methodology

1. Extracted **reaction-level data** (reagents, equivalents, solvents, yields) for four synthesis routes from the primary literature
2. Developed a **reproducible Python framework** calculating material and solvent requirements per kg of isolated product
3. Applied **standard green chemistry metrics**, including atom economy, reaction mass efficiency and process mass intensity
4. Where solvent volumes were not reported, applied a **standardised 0.30 M reference concentration** for all steps in Routes 1-3 and two of three steps in Route 4 (its esterification step is reported directly at 0.45 M), and tested this assumption's influence via sensitivity analysis

Route 1
Original method
Batch

Route 2
Improved method
Batch

Route 3
Alkylation method
Batch

Route 4
Alkylation method
Continuous flow

Results

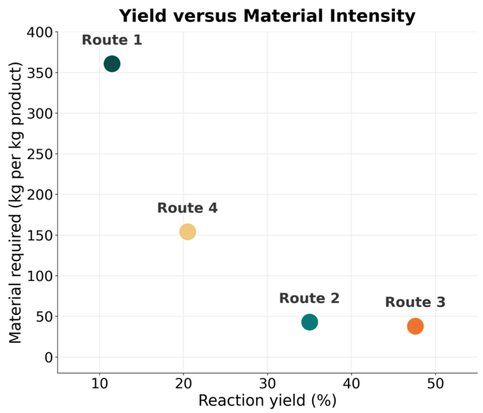

Figure 1: Yield vs. material intensity across all four routes. Intensity falls sharply as yield rises from Route 1, with diminishing returns beyond Route 2. The ranking is consistent across all four routes, but the relationship is not linear.

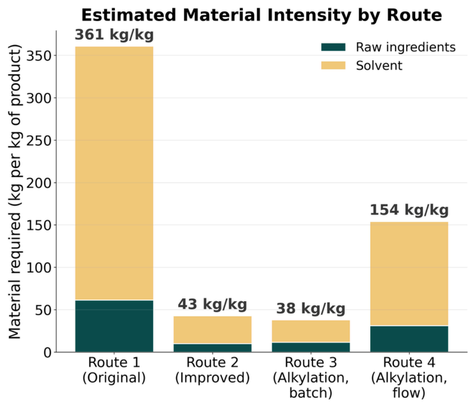

Figure 2: Estimated material intensity per kg of product, decomposed into reagent and solvent contributions. Solvent dominates in every route (69-83% of total mass).

Results (continued)

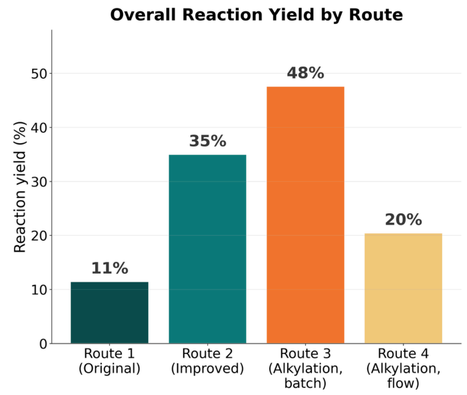

Figure 1: Overall reaction yield across the four routes, ranging from 11.5% to 47.6%.

Key Numbers

Route	Yield	Material needed
Route 1	11.5%	361 kg
Route 2	35.0%	43 kg
Route 3	**47.6%**	**38 kg (lowest)**
Route 4	20.5%	154 kg

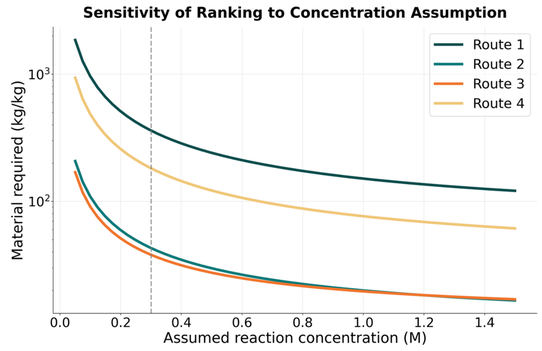

Figure 4: Sensitivity of material intensity to the assumed reaction concentration (dashed line marks the reference value). Route ranking holds across the full range tested, confirming the result isn't an artefact of this assumption.

Discussion & Conclusion

The study indicates that ALC-0315 synthesis routes **cannot** be ranked on **reaction yield** alone. Yield, atom efficiency and material intensity identify different routes as "best" (see Key Numbers), confirming that a standardised, **multi-metric comparison is necessary** to assess true process performance.

Key findings include **Route 2** achieving the highest atom and **reaction-mass efficiency**, Route 3 achieving both the highest yield and the lowest material intensity, and Route 4 (continuous flow) recording a **higher material intensity** than Route 3 despite being the only route with a directly measured throughput (7 mmol/h, 5.4 g/h) rather than a modelled one.

Estimated reduction in material intensity, original route versus best-performing route

89%

Route 1 (original, 360.9 kg/kg) compared with Route 3 (lowest, 38.1 kg/kg)

**Assumptions were made during modelling for standardisation; see Methodology. Purification materials could not be quantified for any route due to insufficient published data.*

Future Research

Further work is required in several areas. Most notably, **experimental validation** of the standardised assumptions is needed, alongside **incorporation of energy demand, solvent hazard scoring,** and testing of the framework's generality across other ionizable lipids.

Acknowledgement & References

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