Electronic Supporting Information for

Numbering-up Metal Microreactor for High-Throughput Production of Commercial Drug by Copper Catalysis

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1. Design of numbering-up metal microreactor system

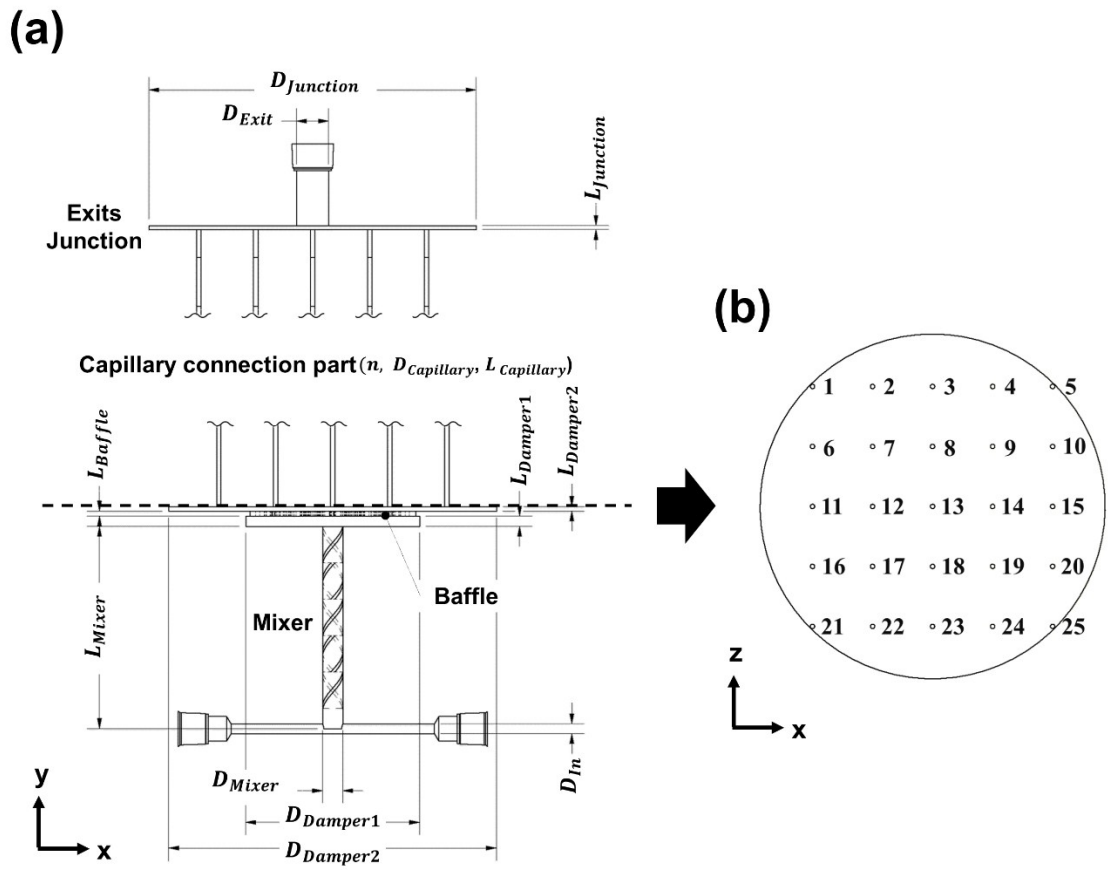


Fig. S1. Schematic of cross-sectional layout of the numbering-up system along **(a)** the *x*–*y* plane, **(b)** the *x*–*z* plane with 25 capillary exits at the top as numbered at the specific site.

Table S1. Detailed dimensions of the numbering-up system.

Design parameter	Design condition	Design parameter	Design condition
D_{In}	2.4 mm	$L_{Damper2}$	1.15 mm
D_{Exit}	8 mm	$L_{Junction}$	1 mm
D_{Mixer}	5 mm	n	25
$D_{Damper1}$	81 mm	$D_{Capillary}$	1 mm
$D_{Damper2}$	43 mm	$L_{Capillary}$	2,000 mm
$D_{Junction}$	81 mm	V_{Mixer}	0.77 mL
L_{Mixer}	50.11 mm	V_{Damper}	9.6 mL
L_{Baffle}	1.25 mm	$V_{Junction}$	5.2 mL
$L_{Damper1}$	2.5 mm	$V_{Capillary}$	39.3 mL

2. Numerical analysis of flow behavior in the numbering-up reactor system

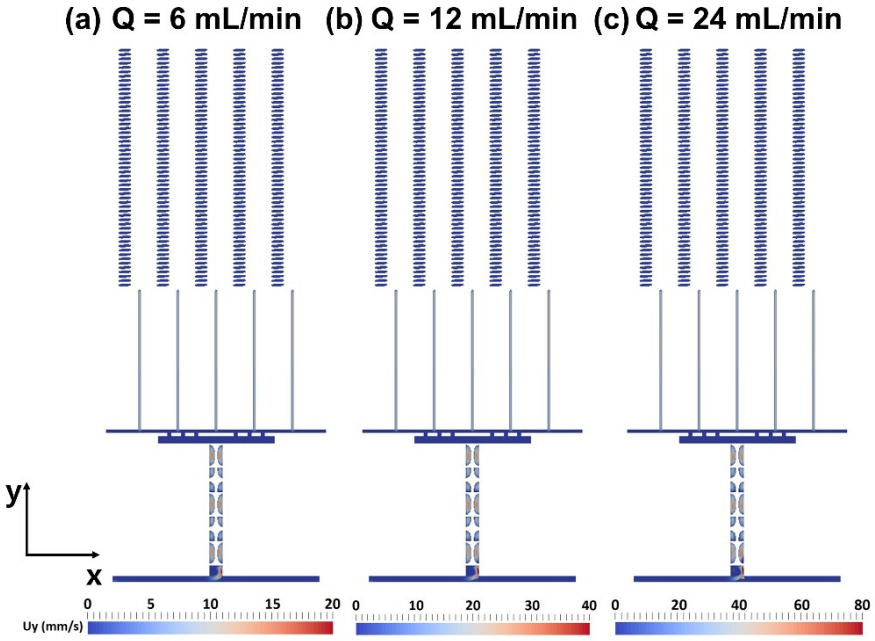


Fig. S2. Cross-sectional views of contour of *y*-directional velocity field at flow rates of (a) 6 mL/min, (b) 12 mL/min, and (c) 24 mL/min.

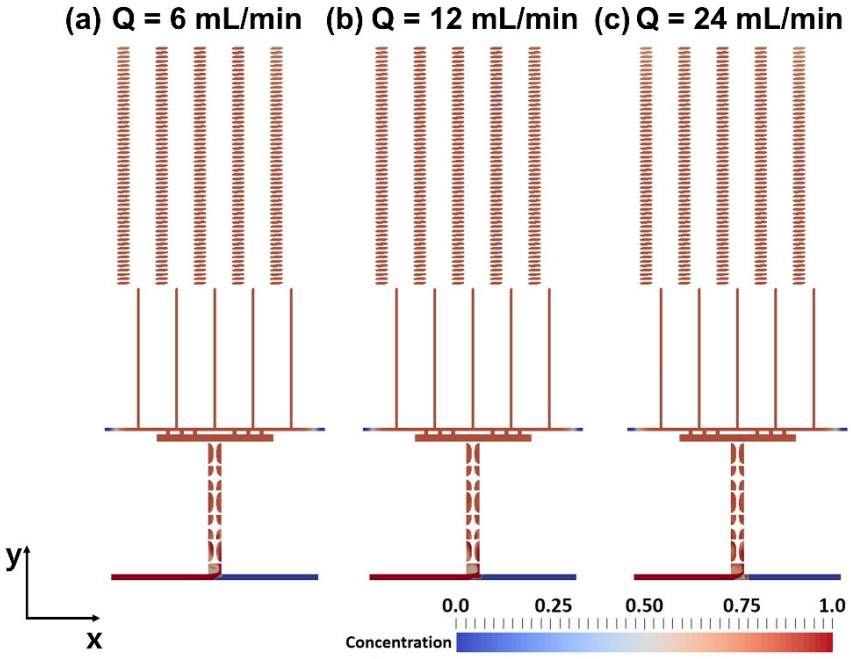


Fig. S3. Cross-sectional views of contour of concentration field at flow rates of (a) 6 mL/min, (b) 12 mL/min, and (c) 24 mL/min.

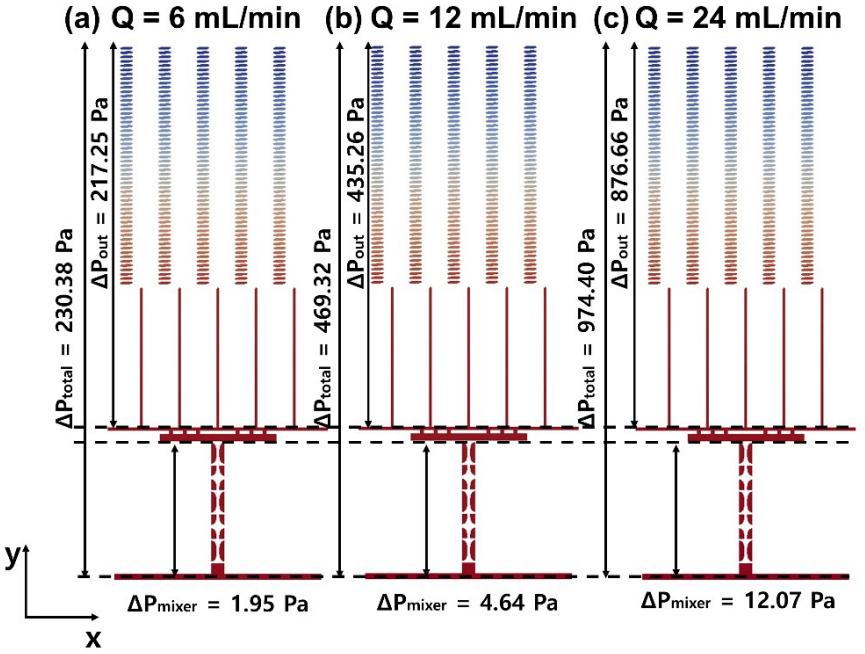


Fig. S4. Cross-sectional views of contour of pressure field at flow rates of (a) 6 mL/min, (b) 12 mL/min, and (c) 24 mL/min.

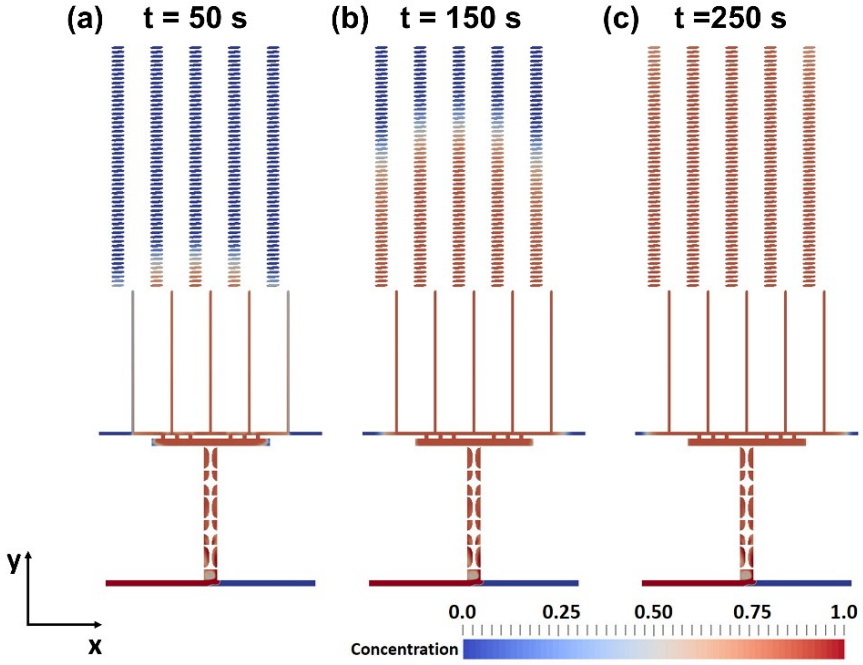


Fig. S5. Cross-sectional views of temporal changes for concentration field in the system at flow rate of 12 mL/min: concentration field at (a) t = 50 s, (b) t = 150 s, and (c) t = 250 s.

Table S2. Summary of maldistribution factors MF (%), mixing efficiency η (%) and pressure drops ΔP (Pa) regarding to change of the total flow rates Q (mL/min).

Q	MF	η	ΔP_{mixer}	$\Delta P_{reactor}$	ΔP_{total}
6	0.347	98.27	1.95	217.25	230.38
12	0.348	98.40	4.64	435.26	469.32
24	0.347	98.54	12.07	876.66	974.40

3. Numerical analysis of flow distributor performance in the numbering-up system

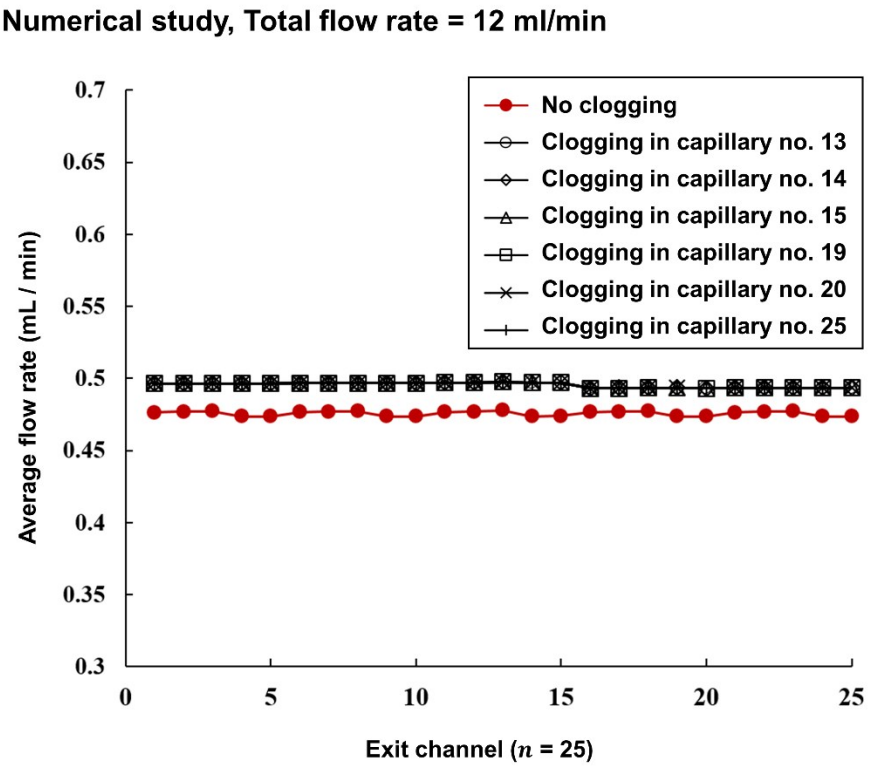


Fig. S6. Average flow rate of 25 capillaries in two cases under total flow rate of 12 mL/min: normal, single capillary clogging at different site.

Table S3. Maldistribution factors MF (%) and pressure drops ΔP (Pa) at two cases under total flow rate of 12 mL/min: under normal operation, single-capillary clogging at different sites.

Clogged capillary no.	MF	ΔP_{mixer}	$\Delta P_{reactor}$	ΔP_{total}
13	0.341	4.64	435.26	487.61
14	0.347	4.64	453.64	487.54
15	0.348	4.64	453.47	487.53
19	0.342	4.64	453.46	487.53
20	0.341	4.64	453.46	487.53
25	0.344	4.64	453.45	487.53

4. Numerical analysis of mixer performance

Table S4. Maldistribution factors MF (%), mixing efficiency η (%), and pressure drops ΔP (Pa) for two cases: T mixer only, both T-mixer and static mixer.

Condition	MF	η	$\Delta P_{reactor}$	ΔP_{total}
T-mixer only	0.35	88.33	435.13	465.55
Both mixers	0.348	98.40	435.26	469.32

5. Experiments of flow distribution in the numbering-up system.

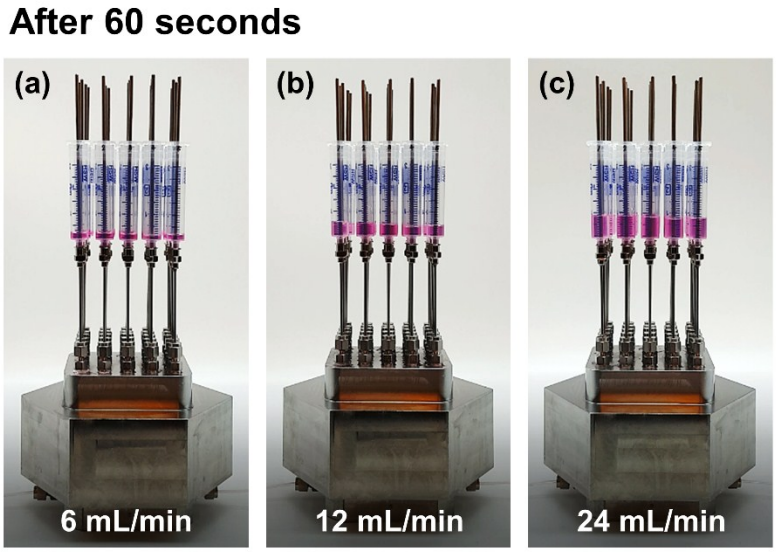


Fig. S7. Visual observation on red-dyed ethanol solutions collected for 1 min by 25 syringe barrels at total flow rates of (a) 6 mL/min, (b) 12 mL/min, (c) 24 mL/min. The experimental MF values are (a) 4.4 %, (b) 4.0 % and (c) 3.0 %.

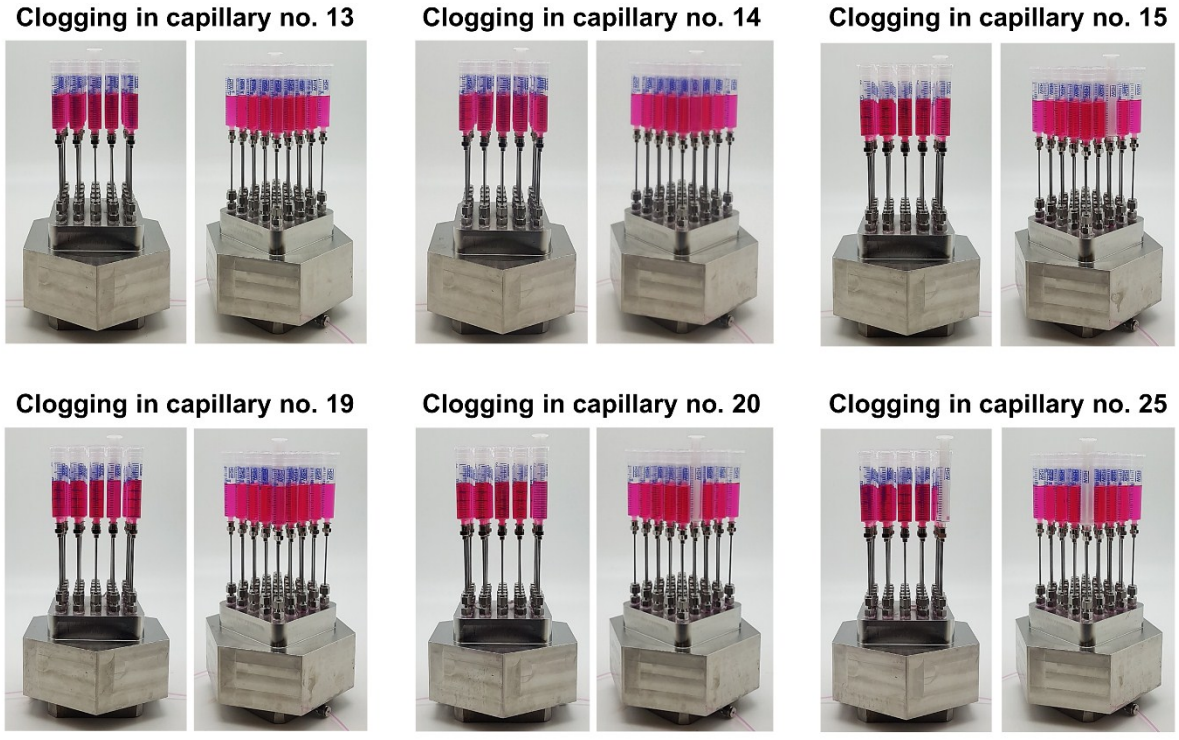


Fig. S8. Experimental verification of flow distribution during clogging. Distribution of dyed ethanol at a total flow rate of 12 mL/min was visually evaluated when clogging occurred in single capillary at different sites. The image was taken after 4 min at a total flow rate of 12 mL/min, so the total volume of fluid flow through the 24 capillaries was 48 mL, and each container contains 2 mL of fluid. The volume of fluid was confirmed using a balance.

6. Experiments for continuous-flow synthesis of drug “Rufinamide”

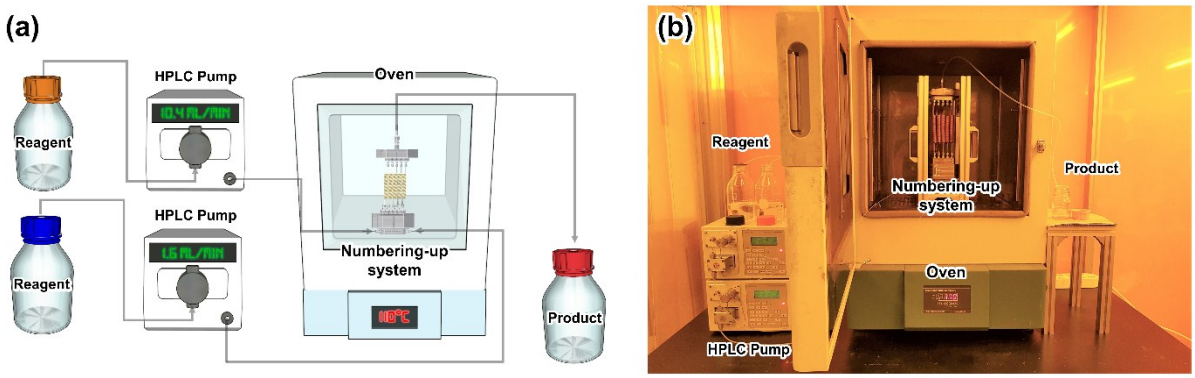


Fig. S9. (a) Illustration and (b) photograph of experimental setup for high-throughput production of Rufinamide by the numbering-up microreactor system. The reagents contained in each bottle are injected through two HPLC pumps into the reactor system placed in an oven at 110 °C, and the product from the reactor is collected in a prepared bottle.

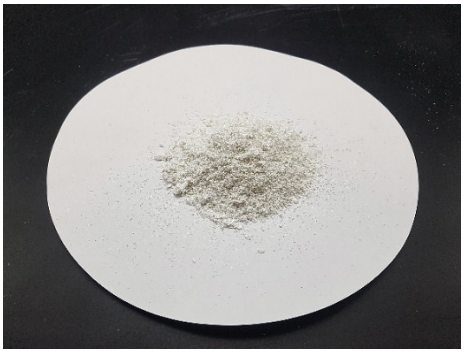


Fig. S10. Rufinamide as an isolated powdery product after continuous-flow synthesis for 10 min.

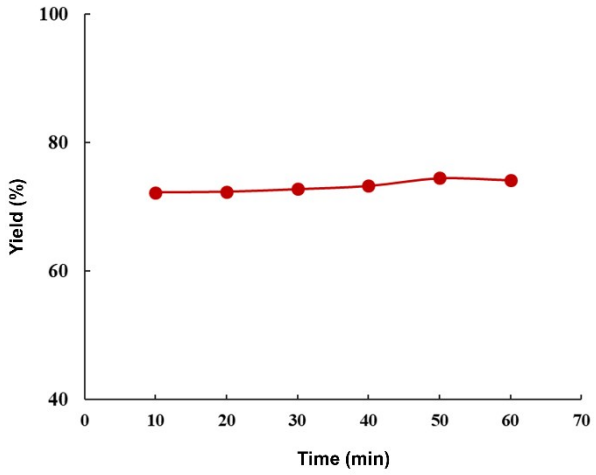
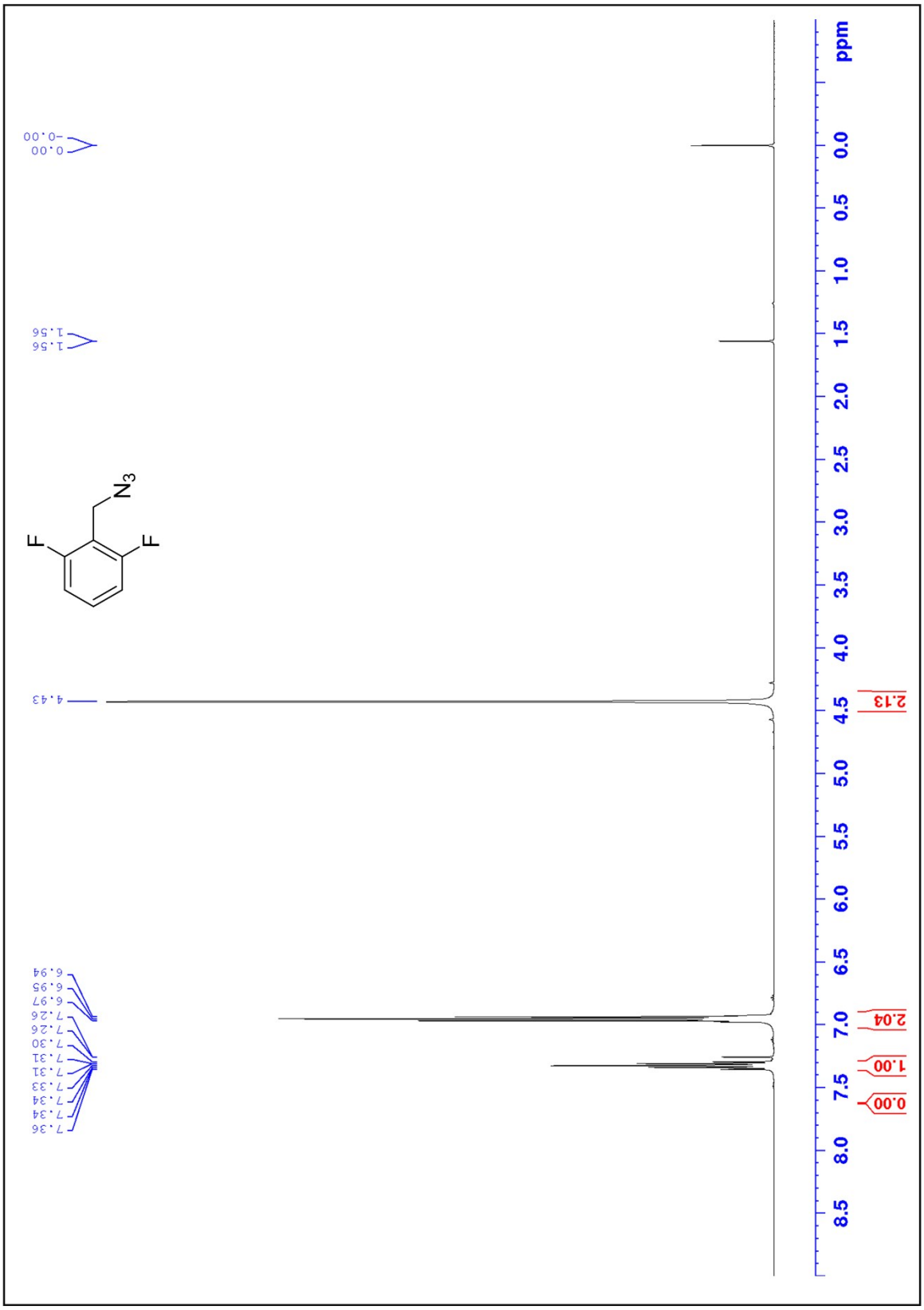


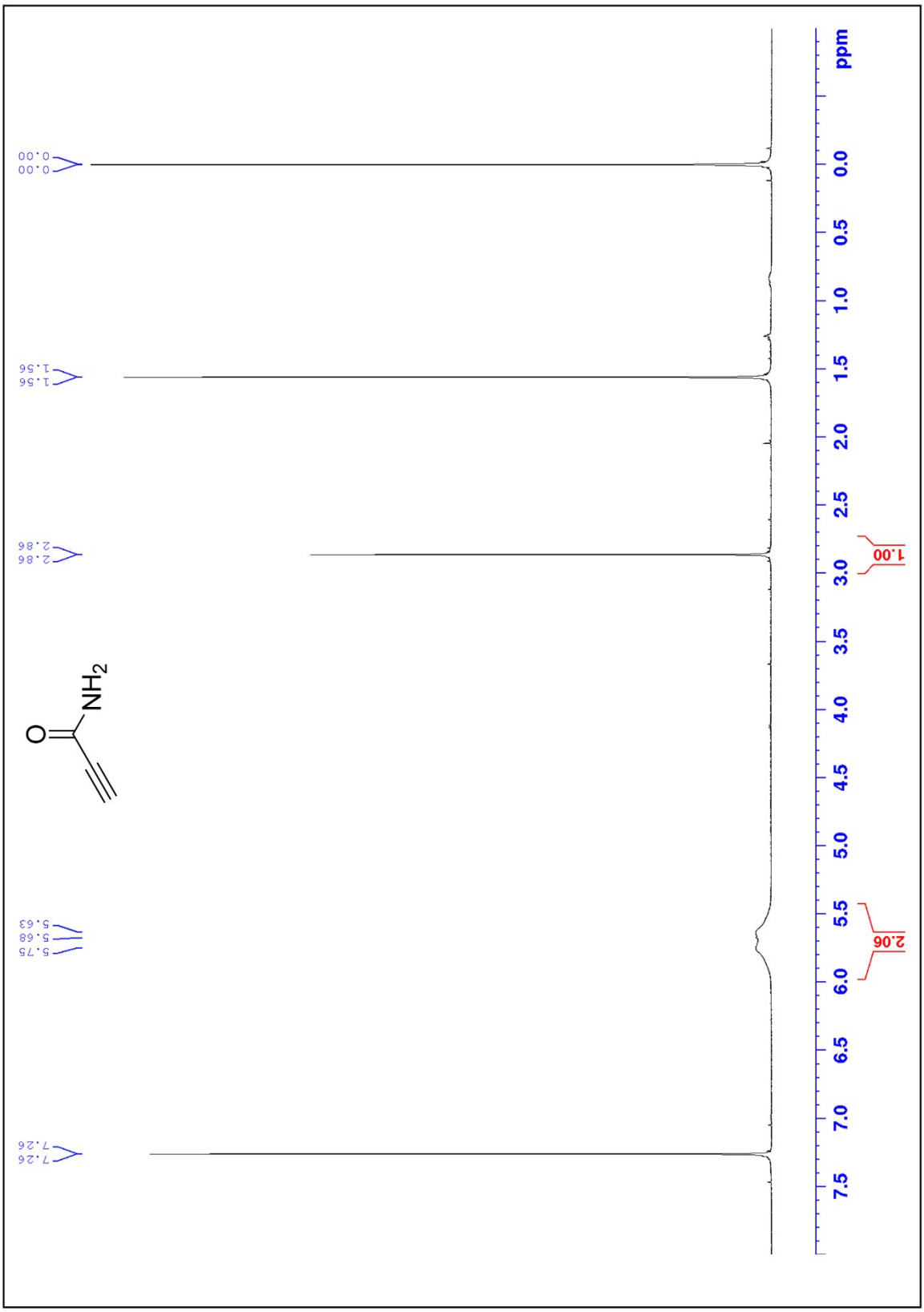
Fig. S11. Yield over time for the synthesis of rufinamide using the numbering-up microreactor system. The experiment lasted for one hour and the isolated yield was measured at every 10 min.

7. Spectrum Data

1H NMR spectrum of 2,6-difluorobenzyl bromide (1)



1H NMR spectrum of propiolamide (2)



1H NMR spectrum of Rufinamide (3)