# Continuous Flow Total Synthesis of Rufinamide

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# Supporting Information

## General Information.

Parts for the construction of flow reactors are purchased from IDEX Health & Science Technologies, unless otherwise stated. Regular flow reactors were constructed from high purity PFA tubing with 1/16" o.d. and 0.03" i.d. and PEEK ¼-28 nut. Copper flow reactors were constructed from copper C122 seamless tubing with 1/16" o.d. and 0.03" i.d., purchased from Amazon.com (supplier: Small Parts) and stainless steel 1/16" female nut purchased from Swagelok. Stainless steel flow reactors were constructed from stainless steel 316 tubing with 1/16" o.d. and 0.03" i.d. and stainless steel 1/16" female nut purchased from Swagelok. The metal reactors were linked with PFA tubing through 1/16" stainless steel unions purchased from Swagelok. The reagents and reaction streams were mixed with Tefzel T-mixers with 0.02" thru. The reaction pressure was controlled

by back-pressure regulators (BPRs). Reagents were delivered by either PhD Ultra syringe pumps purchased from Harvard Apparatus equipped with high-pressure stainless steel syringes and SGE air-tight glass syringes purchased from VWR or Asia syringe pumps from Syrris.

Chemicals and solvents were purchased from Sigma-Aldrich and used without further purification unless otherwise stated. 2,6-Difluorobenzyl bromide was purchased from Oakwood Chemical.

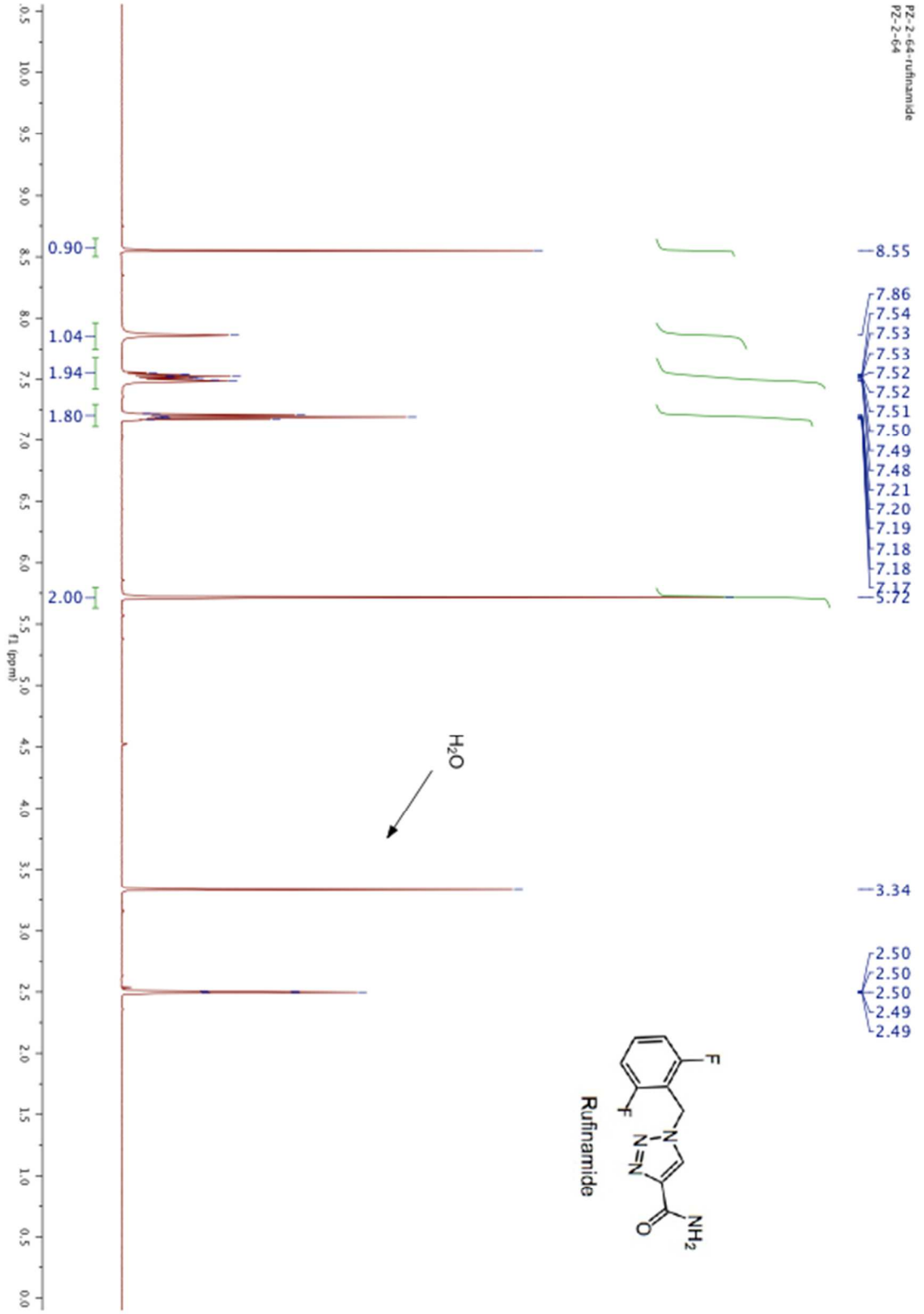
## Experimental Procedure

**Fully Continuous Synthesis of Rufinamide (6)**. A DMSO solution of 2,6-Difluorobenzyl bromide [1 M] and biphenyl (internal standard) [0.1 M] was loaded in an 8-mL stainless steel syringe (feed A). A [0.5 M] DMSO solution of sodium azide was loaded in a second 8-mL stainless steel syringe (feed B). Neat methyl propiolate (feed C) and ammonium hydroxide (~28% ammonia, feed D) were loaded in 2-mL SGE glass syringes, respectively. All the four syringes were pumped with Harvard Apparatus syringe pumps. Feed C was pumped at 2.2 μL/min and feed D was pumped at 6.6 μL/min. The two feeds were mixed and passed through a 40 μL PFA reactor; both mixer and reactor were cooled in a ice-water bath. At the meanwhile, feed A was pumped at 16.5 μL/min and feed B was pumped at 41.3 μL/min and stream upon mixing was passed through a 57 μL PFA reactor at room temperature. The two outlets were jointed with a T-mixer and passed through a 431 μL copper tubing reactor. The reactor was heated at 110 ºC and equipped with a 100 psi back-pressure regulator (BPR). The overall residence time for the continuous-flow reaction sequence was 11 minutes. Allowed 44 minutes to

stabilize, the reaction was collected for 60 minutes and afforded brown/red solution. Two drops of the solution was diluted with methanol to 1 mL, which was then analyzed by LCMS to give 98% yield. To the left reaction mixture was added 2V water while stirring and the resulting slurry was set for 15 minutes. Upon filtration, washing with water, the off-white sticky cake was dried in vacuum oven for 24 hours. The dried off-white solid afforded 215 mg rufinamide (92% yield). NMR in DMSO-d6 was in accordance with literature.[1] HRMS (ESI+) for $C_{10}H_8F_2N_4ONa$ [M+Na]: calculated: 261.0558, found: 261.0559.

## Spectrum Data

(1) Cherynyak, S.; Cyjon, R.; Ozer, I. (Taro Pharmaceutical Industries Limited, Haifa Bay, Italy) US patent 2014/0155619 A1, 2014.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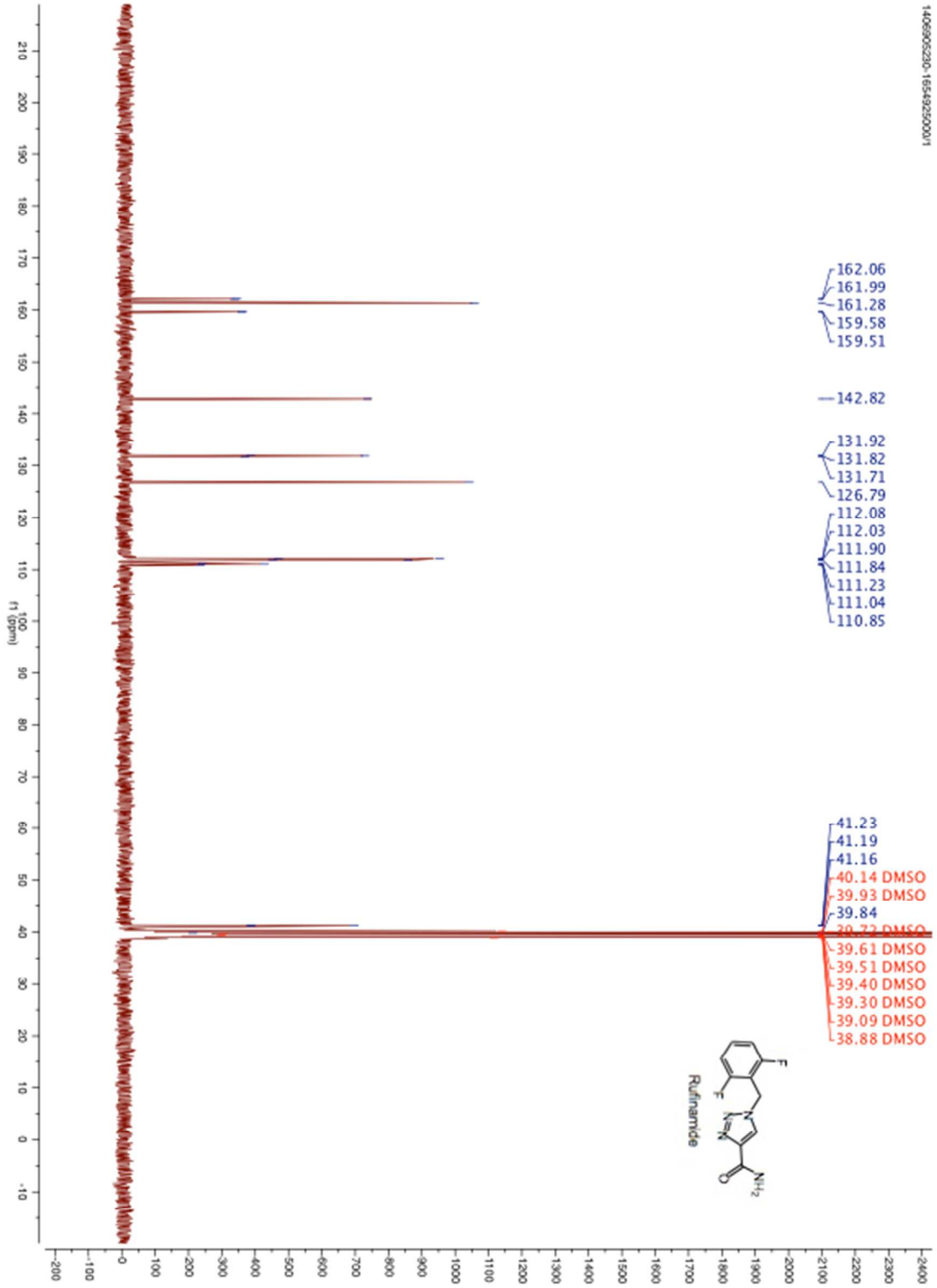
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Rufinamide
f1 (ppm)