ESI for

EDC-promoted one-step synthesis of *Teriflunomide* at industrial scale

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1. Experimental details

General methods

Reagents and solvents were purchased from the reagent companies. They were analytical pure and were directly used after receiving without any additional treatment. NMR spectra were recorded on a Bruker AVENCE 400 MHz instrument using DMSO-d_6 as the solvent and Me_4Si as the internal standard. Chemical shifts for ^1H NMR were referred to internal Me_4Si (0 ppm) and *J*-values were shown in Hz. Melting-point of the product was determined by WRS-2A digital instrument. HRMS (ESI) analysis was measured on a Bruker micro TOF-Q II instrument.

Synthetic procedures:

*Synthesis of Teriflunomide in the reaction scale using 31 mmol of **3***: 31 mmol of 4-aminobenzotrifluoride (**3**, 5.0 g), 93 mmol of 5-methylisoxazole-4-carboxylic acid (**1**, 11.8 g) and 46.5 mmol of EDC (7.1 g) were initially dissolved in 100 mL of DCM. The mixture was then added into a 250 mL three-necked round bottom flask equipped with a piece of magnetic stirring bar and condenser. The system was heated to 35 ^oC and magnetically stirred for 4 hours. After reaction, it was cooled to -5−5 ^oC, and poured into a 500 mL beaker containing 100 mL of aqueous HCl (0.6 mol/L) and a piece of magnetic bar. The mixture was magnetically stirred for about 3−4 hours at -5−5 ^oC. The precipitated crystal was separated by filtration. It was washed by water, ethanol absolute, and then dried in a vacuum oven to obtain the white solid as final product *Teriflunomide* (7.6 g, yielding 91%).

Semi-industrial production of Teriflunomide: To a 250 L reactor, 5.0 kg of 4-aminobenzotrifluoride (**3**), 11.8 kg of 5-methylisoxazole-4-carboxylic acid (**1**) and 7.1 kg of EDC were added. 100 L of DCM was then pumped into the kettle and the mixture was mechanically stirred for 0.5 h to well dissolve the reactants. The kettle was gradually heated to 35 ^{o}C, and was stirred at this temperature for 4 hours. After then, it was cooled to -5−5 ^{o}C. The mixture was then removed into a 500 L tank containing 100 L of aqueous HCl (0.6 mol/L) and cooling by ice water. The mixture was stirred for about 5 hours at -5−5 ^{o}C. The precipitated crystal was separated by filtration. It was washed by water, ethanol absolute, and then dried in a vacuum oven to obtain the white solid as final product *Teriflunomide* (7.5 kg, yielding 90%).

Characterization Data of the Products

Teriflunomide (**5**). 7.5 kg, yielding 90%. White solid, m.p. 230.2−232.1 ^{o}C (*lit.* 229−232 ^{o}C).[1]HNMR (400 MHz, DMSO-d_6, TMS, ppm): δ 10.35 (s, 1H), 9.10 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, ppm): δ 173.82, 160.06, 149.49, 142.70, 126.33 ($J_{C\text{-}F}$ = 34 Hz), 125.29 ($J_{C\text{-}F}$ = 235 Hz), 124.42, 120.45, 112.22, 12.65; ^{13}C NMR (376 MHz, $CDCl_3$, TMS, ppm): δ 62.39; HRMS (ESI-TOF) m/z $[M\text{-}H]^-$ calcd for $C_{12}H_8F_3N_2O_2^-$ 269.0543, found 269.0557; Known Compound.[1]

Reference

1. M. Kurz, D. Gretzke, R. Hörlein, S. Turpault, J. Atzrodt and V. Derdau, *J. Labelled Compd. Rad*., 2021, **64**, 82.

2. NMR spectra of *Teriflunomide*

Teriflunomide , ^{1}H NMR, DMSO, 400 MHz

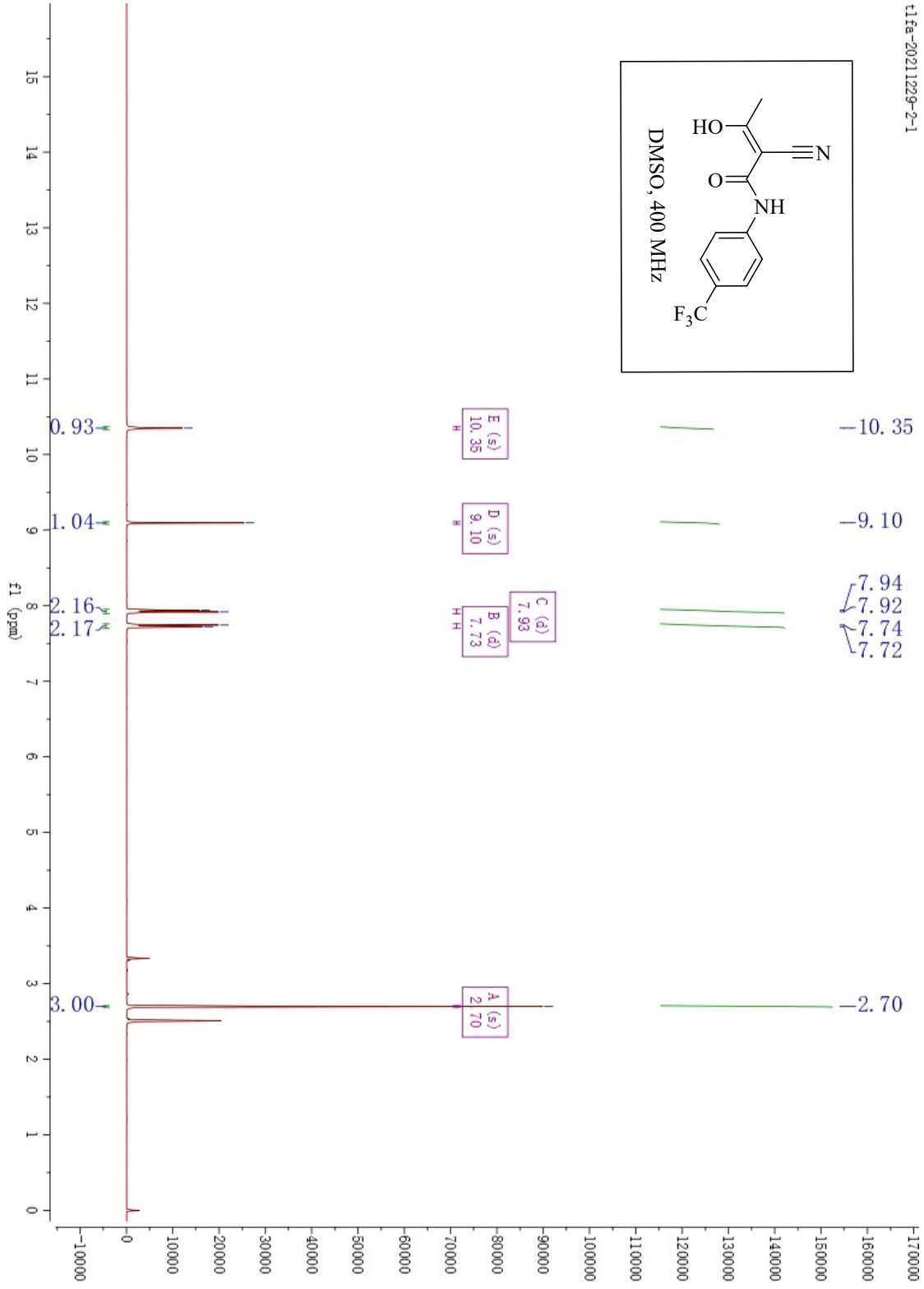


Figure S1. ^{1}H NMR spectrum of *Teriflunomide*.

Teriflunomide , ^{13}C NMR, DMSO, 400 MHz

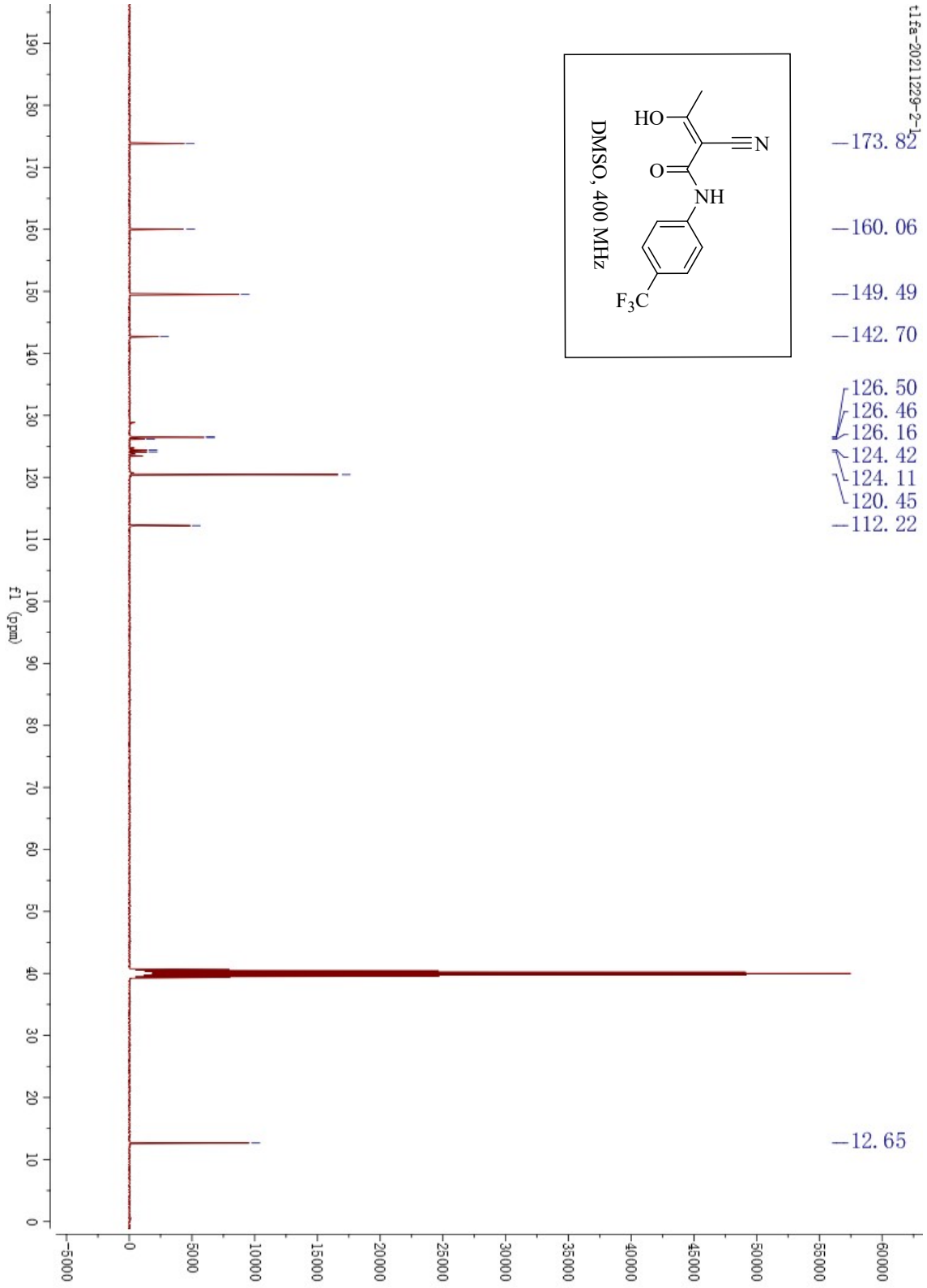


Figure S2. ^{13}C NMR spectra of *Teriflunomide*.

Teriflunomide , ^{19}F NMR, $CDCl_3$, 376 MHz

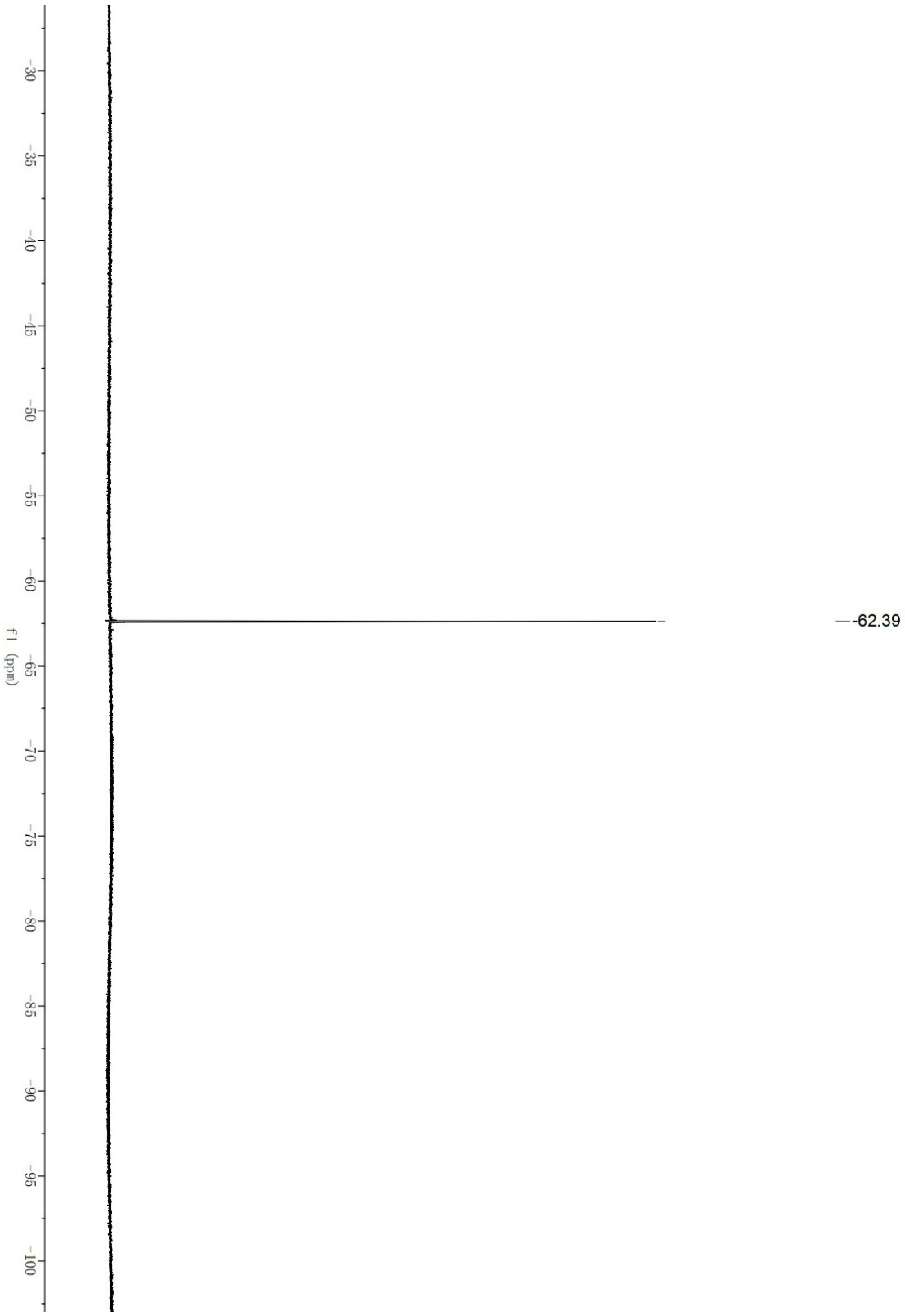
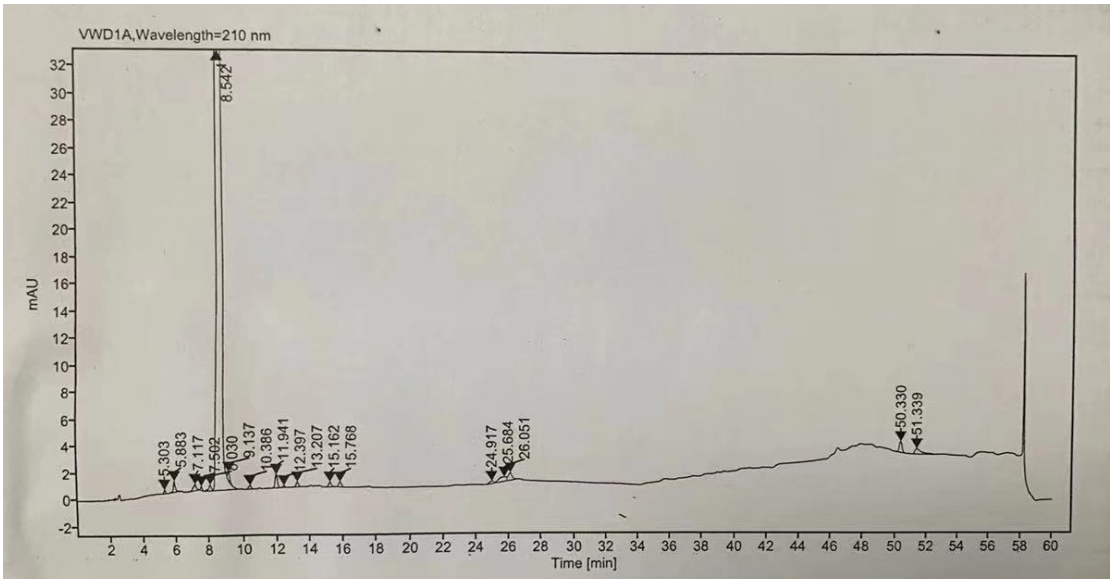


Figure S3. ^{19}F NMR spectrum of *Teriflunomide.*

3. HPLC spectrum of *Teriflunomide*



Signal: VWD1A,Wavelength=210 nm

Peak #	RT [min]	Type	Width [min]	Area	Height	Area%	Plates	Resolution	Tail Factor	Compound
1	5.303	BB	0.192	2.028	0.281	0.010	12214		1.34	
2	5.883	BB	0.186	6.933	0.824	0.034	15984	3.07	1.55	
3	7.117	BB	0.341	6.451	0.484	0.032	6982	4.68	1.11	
4	7.502	BB	0.188	2.138	0.309	0.010	25441	1.46	0.87	
5	8.030	BV	0.265	5.131	0.439	0.025	14733	2.33	0.78	
6	8.542	VV R	0.242	20297.551	2229.473	99.495	19932	2.03	1.29	
7	9.137	VB X	0.236	6.111	0.661	0.030	23987	2.48	0.99	
8	10.386	BB	0.272	3.023	0.299	0.015	23326	4.92	0.98	
9	11.941	BB	0.242	9.419	1.025	0.046	38816	6.05	1.03	
10	12.397	BB	0.245	1.312	0.146	0.006	40799	1.86	0.95	

Figure S4. HPLC spectrum of *Teriflunomide*.