SUPPORTING INFORMATION

Novel Analogues of the Chikungunya Virus Protease Inhibitor: Molecular Design, Synthesis, and Biological Evaluation

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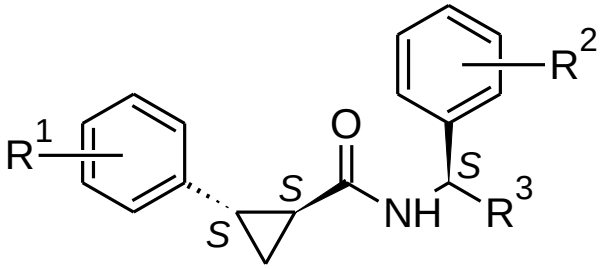
Table S1. Calculated Binding Energies of Small-Molecule Ligands to the Receptor CHIKV nsP2 at Potential Binding Sites 1 (ΔG1) and 2 (ΔG2). Letter *S* Denote the Absolute Configuration of the Stereocenters of Compounds



Code	R^1	R^2	R^3	ΔG1 (kcal/mol)	ΔG2 (kcal/mol)
1c	**3,4-CH_3**	**H**	**NH_2**	**-7.6**	**-7.6**
D1	H	H	NH_2	-5.9	-7.6
D2	H	H	H	-6.8	-7.3
D3	4,5-CH_3	3,4-CH_3	H	-6.4	-7.9
D4	H	H	SO_3H	-8.1	-7.0
D5	3,4-CH_3	3,4-CH_3	SO_3H	-8.8	-8.0
D6	3,4-CH_3	3,4-CH_3	SO_2NH_2	-7.2	-7.7
D7	3-CH_3	H	NH_2	-8.4	-7.2
D8	H	3-CH_3	NH_2	-8.4	-7.3
D9	3-CH_3	3-CH_3	NH_2	-8.6	-7.2
D10	4-CH_3	H	NH_2	-8.4	-7.3
D11	4-CH_3	3-CH_3	NH_2	-8.5	-7.4
D12	H	4-CH_3	NH_2	-8.5	-7.1
D13	4-CH_3	4-CH_3	NH_2	-8.7	-7.2
D14	5-CH_3	H	NH_2	-8.5	-7.5
D15	5-CH_3	4-CH_3	NH_2	-8.8	-7.4
D16	5-CH_3	3-CH_3	NH_2	-8.6	-7.6
D17	3,4-CH_3	H	NH_2	-8.6	-7.6
D18	3,5-CH_3	H	NH_2	-8.7	-7.7
D19	2,5-CH_3	H	NH_2	-8.1	-7.2
D20	3,4-CH_3	3-CH_3	NH_2	-8.7	-7.2
D21	3,5-CH_3	3-CH_3	NH_2	-8.9	-7.2
D22	3,6-CH_3	3-CH_3	NH_2	-8.3	-7.3
D23	3,4-CH_3	4-CH_3	NH_2	-8.9	-7.5
D24	3,5-CH_3	4-CH_3	NH_2	-9.0	-7.6
D25	2,5-CH_3	4-CH_3	NH_2	-8.5	-7.8
D26	3,4-CH_3	3,4-CH_3	NH_2	-9.0	-7.6
D27	3,5-CH_3	3,4-CH_3	NH_2	-9.1	-8.0
D28	2,5-CH_3	3,4-CH_3	NH_2	-8.6	-7.7
D29	3,4-CH_3	3,5-CH_3	NH_2	-8.4	-7.6
D30	3,5-CH_3	3,5-CH_3	NH_2	-8.5	-7.0
D31	2,5-CH_3	3,5-CH_3	NH_2	-7.5	-7.4
D32	3-CH_3	3,4-CH_3	NH_2	-8.9	-7.8
D33	4-CH_3	3,4-CH_3	NH_2	-8.8	-7.5

D34	5-CH_3	3,4-CH_3	NH_2	-8.9	-7.7
D35	2-CH_3	3,4-CH_3	NH_2	-7.9	-7.3
D36	3-CH_3	3,5-CH_3	NH_2	-8.2	-7.6
D37	4-CH_3	3,5-CH_3	NH_2	-8.3	-7.7
D38	5-CH_3	3,5-CH_3	NH_2	-7.5	-7.3
D39	4,5-CH_3	3,4-CH_3	NH_2	-9.1	-7.5
D40	2,3-CH_3	3,4-CH_3	NH_2	-8.5	-7.7
D41	3,4-CH_3	3,4-CH_3	NH_2	-9.0	-7.6
D42	4,5-CH_3	4,5-CH_3	NH_2	-9.1	-7.6
D43	3,4-CH_3	3,5-CH_3	NH_2	-8.5	-7.5
D44	2,3-CH_3	3,5-CH_3	NH_2	-8.1	-7.8
D45	3,5-CH_3	H	OCH_3	-8.3	-6.7
D46	2,5-CH_3	4-CH_3	OCH_3	-8.0	-7.4
D47	3,5-CH_3	3,4-CH_3	OCH_3	-8.7	-7.7
D48	2,5-CH_3	3,4-CH_3	OCH_3	-8.2	-7.3
D49	3-CH_3	3,4-CH_3	OCH_3	-8.5	-7.3
D50	5-CH_3	3,4-CH_3	OCH_3	-8.5	-7.3
D51	4-CH_3	3,5-CH_3	OCH_3	-7.7	-7.3
D52	2,3-CH_3	3,4-CH_3	OCH_3	-8.1	-7.5
D53	2,3-CH_3	3,5-CH_3	OCH_3	-7.3	-7.4
D54	3-F 5-CH_3	H	NH_2	-8.7	-7.4
D55	3-CH_3 5-F	H	NH_2	-8.6	-7.8
D56	3,5-F	H	NH_2	-8.6	-7.9
D57	3-CF_3 5-CH_3	H	NH_2	-6.7	-7.0
D58	3-CH_3 5-CF_3	H	NH_2	-8.8	-7.6
D59	3-CF_3 5-F	H	NH_2	-7.1	-7.6
D60	3-F 5-CF_3	H	NH_2	-8.8	-7.7
D61	3-F 5-CH_3	H	OCH_3	-8.2	-7.7
D62	3-CH_3 5-F	H	OCH_3	-8.2	-7.2
D63	3,5-F	H	OCH_3	-8.1	-7.6
D64	3-CF_3 5-CH_3	H	OCH_3	-6.2	-6.9
D65	3-CH_3 5-CF_3	H	OCH_3	-8.4	-6.9
D66	3-CF_3 5-F	H	OCH_3	-6.3	-7.6
D67	3-F 5-CF_3	H	OCH_3	-7.7	-7.5
D68	2-CH_3 5-F	4-CH_3	NH_2	-8.4	-7.5

D69	2-F 5-CH_3	4-CH_3	NH_2	-8.6	-7.6
D70	2,5-CH_3	4-F	NH_2	-8.2	-7.5
D71	2-CH_3 5-CF_3	4-CH_3	NH_2	-8.4	-8.4
D72	2-CF_3 5-CH_3	4-CH_3	NH_2	-8.0	-7.6
D73	2,5-CH_3	4-CF_3	NH_2	-6.9	-8.1
D74	2,5-F	4CH_3	NH_2	-8.6	-7.8
D75	2-F 5-CH_3	4-F	NH_2	-8.3	-7.6
D76	2-CH_3 5-F	4-F	NH_2	-8.1	-7.4
D77	2-F 5-CF_3	4-CH_3	NH_2	-7.3	-7.7
D78	2-CH_3 5-CF_3	4-F	NH_2	-7.6	-7.8
D79	2-F 5-CF_3	4-F	NH_2	-6.8	-8.1
D80	2-CF_3 5-F	4-CH_3	NH_2	-8.0	-7.5
D81	2-CF_3 5-CH_3	4-F	NH_2	-7.4	-7.5
D82	2-CF_3 5-F	4-F	NH_2	-7.4	-7.4
D83	2-CH_3 5-F	4-CF_3	NH_2	-8.7	-8.0
D84	2-F 5-CH_3	4-CF_3	NH_2	-8.8	-7.8
D85	2,5-F	4-CF_3	NH_2	-8.8	-7.8
D86	2,5-F	4-F	NH_2	-8.3	-8.0
D87	2-CH_3 5-F	4-CH_3	OCH_3	-8.1	-7.3
D88	2-F 2-CH_3	4-CH_3	OCH_3	-8.3	-7.6
D89	2,5-CH_3	4-F	OCH_3	-7.8	-7.4
D90	2-CH_3 5-CF_3	4-CH_3	OCH_3	-6.5	-8.2
D91	2-CF_3 5-CH_3	4-CH_3	OCH_3	-7.2	-7.4
D92	2,5-CH_3	4-CF_3	OCH_3	-8.3	-7.9
D93	2,5-F	4-CH_3	OCH_3	-8.1	-7.5
D94	2-F 5-CH_3	4-F	OCH_3	-6.9	-7.4
D95	2-CH_3 5-F	4-F	OCH_3	-8.0	-7.4
D96	2-F 5-CF_3	4-CH_3	OCH_3	-8.4	-8.2

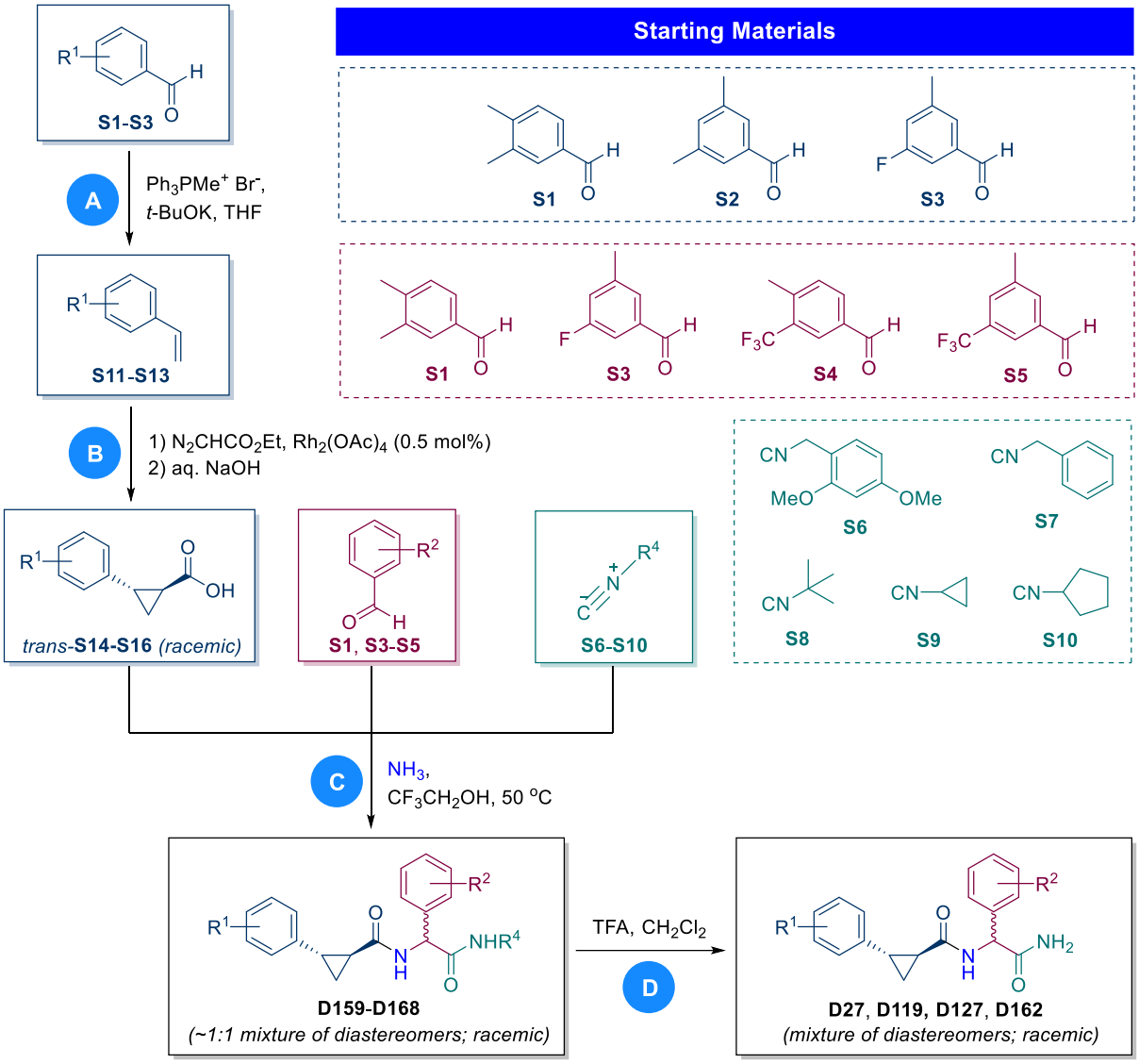
D97	2-F 5-CF_3	4-F	OCH_3	-8.1	-7.9
D98	2-CF_3 5-F	4-F	OCH_3	-6.5	-7.2
D99	2-CF_3 5-CH_3	4-F	OCH_3	-7.3	-7.2
D100	2-CH_3 5-F	4-CF_3	OCH_3	-8.3	-7.8
D101	2-F 5-CH_3	4-CF_3	OCH_3	-8.6	-7.6
D102	2,5-F	4-CF_3	OCH_3	-8.4	-7.6
D103	2,5-F	4-F	OCH_3	-7.8	-7.6
D104	3-F 5-CH_3	3,4-CH_3	NH_2	-9.1	-8.0
D105	3,5-F	3,4-CH_3	NH_2	-9.1	-7.7
D106	3-CH_3 5-F	3,4-CH_3	NH_2	-9.1	-7.7
D107	3,5-CH_3	3-F 4-CH_3	NH_2	-9.0	-7.7
D108	3,5-CH_3	3-CH_3 4-F	NH_2	-8.9	-7.8
D109	3-F 5-CH_3	3-F 4-CH_3	NH_2	-9.0	-7.8
D110	3-F 5-CH_3	3-CH_3 4-F	NH_2	-8.9	-7.7
D111	3-CH_3 5-F	3-F 4-CH_3	NH_2	-9.0	-7.8
D112	3-CH_3 5-F	3-CH_3 4-F	NH_2	-8.8	-7.8
D113	3,5-F	3-F 4-CH_3	NH_2	-8.8	-7.5
D114	3,5-F	3-CH_3 4-F	NH_2	-8.9	-7.6
D115	3-F 5-CH_3	3,4-F	NH_2	-8.8	-7.6
D116	3-CH_3 5-F	3,4-F	NH_2	-8.7	-7.6
D117	3-CF_3 5-CH_3	3,4-CH_3	NH_2	-9.2	-8.5
D118	3-CH_3 5-CF_3	3,4-CH_3	NH_2	-9.3	-7.7
D119	3,5-CH_3	3-CF_3 4-CH_3	NH_2	-9.0	-6.9
D120	3,5-CH_3	3-CH_3 4-CF_3	NH_2	-9.2	-8.7
D121	3-CF_3 5-F	3,4-CH_3	NH_2	-7.7	-8.4
D122	3-CF_3 5-CH_3	3-F 4-CH_3	NH_2	-9.2	-7.5

D123	3-CF_3 5-CH_3	3-CH_3 4-F	NH_2	-9.0	-7.7
D124	3-F 5-CF_3	3,4-CH_3	NH_2	-9.4	-8.4
D125	3-CH_3 5-CF_3	3-F 4-CH_3	NH_2	-9.3	-7.5
D126	3-CH_3 5-CF_3	3-CH_3 4-F	NH_2	-9.1	-8.3
D127	3-F 5-CH_3	3-CF_3 4-CH_3	NH_2	-9.0	-8.5
D128	3-CH_3 5-F	3-CF_3 4-CH_3	NH_2	-9.0	-8.4
D129	3,5-CH_3	3-CF_3 4-F	NH_2	-7.8	-8.4
D130	3-F 5-CH_3	3,4-CH_3	OCH_3	-8.6	-7.7
D131	3,5-F	3,4-CH_3	OCH_3	-8.5	-7.8
D132	3-CH_3 5-F	3,4-CH_3	OCH_3	-8.7	-7.6
D133	3,5-CH_3	3-F 4-CH_3	OCH_3	-6.9	-7.3
D134	3,5-CH_3	3-CH_3 4-F	OCH_3	-8.5	-7.4
D135	3-F 5-CH_3	3-F 4-CH_3	OCH_3	-8.5	-7.5
D136	3-F 5-CH_3	3-CH_3 4-F	OCH_3	-8.4	-7.5
D137	3-CH_3 5-F	3-F 4-CH_3	OCH_3	-8.6	-7.4
D138	3-CH_3 5-F	3-CH_3 4-F	OCH_3	-8.4	-7.4
D139	3,5-F	3-F 4-CH_3	OCH_3	-8.4	-7.3
D140	3,5-F	3-CH_3 4-F	OCH_3	-8.3	-7.2
D141	3-F 5-CH_3	3,4-F	OCH_3	-8.3	-7.4
D142	3-CH_3 5-F	3,4-F	OCH_3	-8.3	-7.3
D143	3-CF_3 5-CH_3	3,4-CH_3	OCH_3	-7.2	-8.2
D144	3-CH_3 5-CF_3	3,4-CH_3	OCH_3	-6.5	-8.2
D145	3,5-CH_3	3-CF_3 4-CH_3	OCH_3	-8.6	-7.9
D146	3,5-CH_3	3-CH_3 4-CF_3	OCH_3	-8.9	-7.6
D147	3-CF_3 5-F	3,4-CH_3	OCH_3	-8.7	-8.1

D148	3-CF_3 5-CH_3	3-F 4-CH_3	OCH_3	-7.0	-7.5
D149	3-CF_3 5-CH_3	3-CH_3 4-F	OCH_3	-8.6	-7.8
D150	3-F 5-CF_3	3,4-CH_3	OCH_3	-8.9	-8.1
D151	3-CH_3 5-CF_3	3-F 4-CH_3	OCH_3	-8.7	-8.0
D152	3-CH_3 5-CF_3	3-CH_3 4-F	OCH_3	-7.2	-7.5
D153	3-F 5-CH_3	3-CF_3 4-CH_3	OCH_3	-7.1	-8.1
D154	3-CH_3 5-F	3-CF_3 4-CH_3	OCH_3	-7.6	-8.2
D155	3,5-CH_3	3-CF_3 4-F	OCH_3	-7.3	-8.1
D156	3-F 5-CH_3	3-F 4-CF_3	OCH_3	-8.9	-7.9
D157	3-CH_3 5-F	3-CH_3 4-CF_3	OCH_3	-8.8	-8.5
D158	3,5-CH_3	3-F 4-CF_3	OCH_3	-8.7	-8.2

Chemical Synthesis of New Inhibitors

Scheme S1. Block Diagram Representing Chemical Synthesis of New Inhibitors and Structures of the Starting Materials



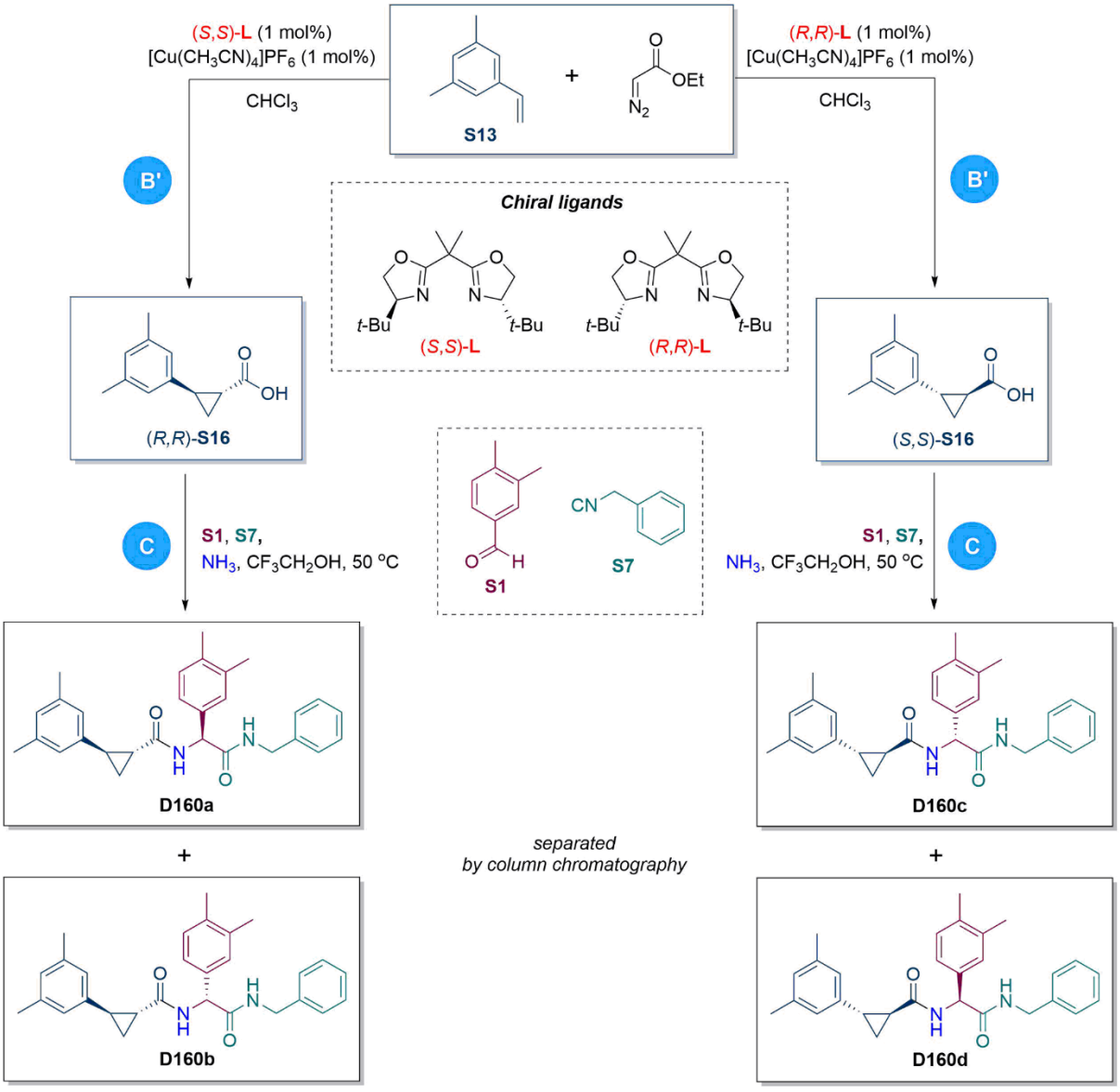
Starting materials: aldehydes **S1-S5** and isonitriles **S7-S10** are commercially available and were purchased from Fluorochem, AlfaAesar or Sigma-Aldrich. Synthesis of isonitrile **S6** is described below.

Chemical synthesis of the novel compounds with CHIKV inhibitory activity consists of four main steps (Scheme S1): **A**) Wittig olefination to produce styrenes **S11-S13**; **B**) Rhodium-catalyzed cyclopropanation with ethyldiazocetate, alkaline hydrolysis of the intermediate ethyl esters, and isolation of *trans*-2-arylcyclopropane-1-carboxylic acids

S14-S16;[1] **C**) Ugi multi-component reaction with ammonia;[2] **D**) Removal of amide protecting group (R^4 = 2,4-dimethoxybenzyl) with trifluoroacetic acid (TFA) in dichloromethane.

Compounds **D159-D166** were obtained as racemic mixtures of two diastereoisomers (mostly in ~1:1 ratio). After initial assessment of bioactivity, synthesis of individual stereoisomers was implemented for the most successful candidate **D160**, as shown below (Scheme S2).

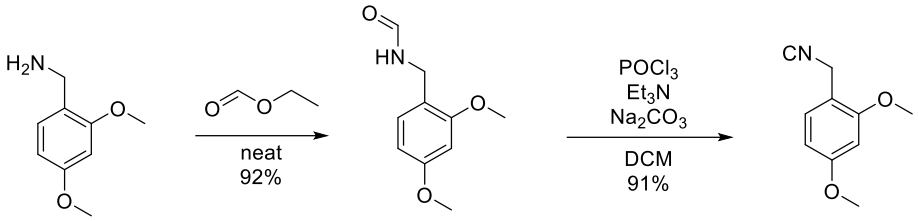
Scheme S2. Asymmetric Synthesis of Individual Stereoisomers for Compound D160

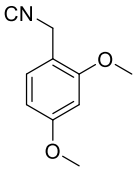


Synthesis of enantiomerically pure acids (*R*,*R*)- and (*S*,*S*)-**S16** (>94% *ee*) have been performed by using asymmetric copper-catalyzed cyclopropanation reaction (**B'**)[3] followed by alkaline hydrolysis. After the Ugi reaction (**C**), optically pure stereoisomers have been separated by

column chromatography. Experimental procedures, characterization of products, and intermediate compounds are described below.

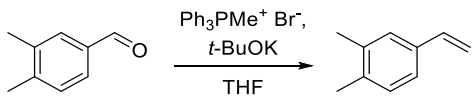
Preparation of isonitrile S6.[4]





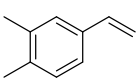
2,4-Dimethoxybenzyl isonitrile (S6). A mixture of ethyl formate (1.00 mL, 0.92 g, 12 mmol) and 2,4-dimethoxybenzylamine (1.50 mL, 1.67 g, 10 mmol) was stirred at 40 ºC overnight. The precipitate was collected by filtration, washed several times with hexane, and then dried to give crude *N*-(2,4-dimethoxybenzyl)formamide (1.79 g, 92%), which was used in the next step without further purification. The formamide (1.75 g, 8.96 mmol) was dissolved in dry DCM (23 mL) under Ar, triethylamine (3.75 mL, 2.72 g, 26.9 mmol) was added, and the solution was cooled to 0 ºC. Phosphorus oxychloride (1.04 mL, 1.72 g, 11.2 mmol) was introduced to the reaction mixture dropwise over 10 min, and then stirring was continued for 1 h, at which point 1 M Na_2CO_3 (9 mL) was added. The mixture was stirred vigorously for an additional 1 h and then transferred to a separating funnel. The organic layer was separated, and the aqueous phase extracted with DCM (3 x 20 mL). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by flash column chromatography on silica, eluted with petroleum ether/EtOAc (EtOAc 2% → 20%), yielding 2,4-dimethoxybenzyl isonitrile as an off-white solid (1.44 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.3 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 5.08–4.32 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H). NMR data correspond to those reported.

A **Typical procedure for Wittig olefination. Preparation of 3,4-dimethylstyrene (S11).**[5]



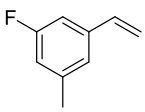
Solution of *t*-BuOK (3.59 g, 32 mmol) in anhydrous THF (30 mL) was added dropwise to suspension of [Ph_3PMe]Br (11.4 g, 32 mmol) in THF (30 mL) under argon atmosphere at 0 ºC.

The obtained yellow suspension was stirred at 0 ºC for 1 h, and then a solution of 3,4-dimethylbenzaldehyde (2.68 g, 20 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred for 1 h and TLC monitoring showed full conversion of the starting material. The reaction was stopped by addition of satd. aqueous NH_4Cl (40 mL), the organic phase was diluted with ether (50 mL) and separated. Aqueous phase was extracted with ether (2 x 30 mL). Combined organic phase was washed with satd. aqueous NaCl and dried (Na_2SO_4). After evaporation of the solvent, the residue was treated with small amount of hexane (~1 mL), precipitated PPh_3O was filtered out and washed with petroleum ether. The filtrate was evaporated, and the residue was purified by short column chromatography over silica gel (eluent – petroleum ether) to afford the title compound (2.19 g, 83%) as a colorless liquid.

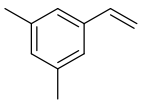


3,4-Dimethylstyrene (S11): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.66 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.69 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.16 (dd, *J* = 10.9, 1.0 Hz, 1H), 2.26 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 136.94, 136.73, 136.46, 135.40, 129.92, 127.62, 123.80, 112.74, 19.91, 19.67.

Other styrenes were prepared analogously from the corresponding aldehydes.

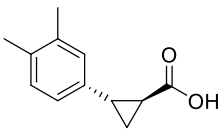


3-Fluoro-5-methylstyrene (S12): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.92 (d, *J* = 9.9 Hz, 1H), 6.78 (d, *J* = 9.4 Hz, 1H), 6.65 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 2.34 (s, 3H).



3,5-Dimethylstyrene (S13): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 2H), 6.91 (s, 1H), 6.67 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.73 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.21 (dd, *J* = 10.9, 1.0 Hz, 1H), 2.32 (s, 6H). NMR data correspond to those reported.[6]

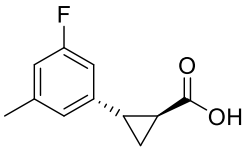
B **Typical procedure for the preparation of *trans*-cyclopropane carboxylic acids.**



S14

***trans*-2-(3,4-Dimethylphenyl)cyclopropane-1-carboxylic acid (S14).** Under argon atmosphere, a solution of ethyl diazoacetate (1.89 g, 16.6 mmol) in dichloromethane (15 mL) was slowly added (within 4 h) to a solution of 3,4-dimethylstyrene (2.19 g, 16.6 mmol) and $Rh_2(OAc)_4$ (37 mg, 0.083 mmol, 0.5 mol%) in dichloromethane (20 mL) at room temperature. After completion of the addition, the reaction mixture was stirred overnight and filtered through the layer of silica gel. The residue after solvent evaporation was purified by column

chromatography (eluent – petroleum ether / ethyl acetate) to recover unreacted starting olefin (0.466 g, 21%) and to afford a mixture of ethyl esters of *cis*- and *trans*-2-(3,4-dimethylphenyl)cyclopropane-1-carboxylic acid (2.33 g, 82% b.r.s.m., *cis*/*trans* = 35:65). *cis*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06–6.96 (m, 3H), 3.90 (q, *J* = 7.1 Hz, 2H), 2.52 (pseudo q, *J* = 8.7 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 2.03 (ddd, *J* = 9.2, 7.8, 5.6 Hz, 1H), 1.66 (ddd, *J* = 7.5, 5.6, 5.0 Hz, 1H), 1.28 (m, 1H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.31, 136.01, 134.88, 134.00, 130.80, 129.31, 126.70, 60.25, 25.34, 21.71, 19.85, 19.53, 14.22, 11.34. *trans*-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.83 (dd, *J* = 7.5, 2.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.46 (ddd, *J* = 9.3, 6.6, 4.2 Hz, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 1.85 (ddd, *J* = 8.4, 5.3, 4.2 Hz, 1H), 1.55 (ddd, *J* = 9.3, 5.3, 4.5 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.27 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.71, 137.63, 136.76, 134.87, 129.82, 127.74, 123.60, 60.74, 26.05, 24.13, 19.87, 19.44, 17.01, 14.41. The obtained mixture of stereoisomeric ethyl esters (0.50 g, 2.3 mmol) was dissolved in ethanol (2 mL) and THF (4 mL) mixture and treated with 2 M aq. NaOH (0.75 mL, 1.5 mmol, 0.65 equiv.). After stirring at room temperature overnight, the reaction mixture was evaporated, then diluted with water and extracted with dichloromethane (3 x 5 mL) to remove unreacted *cis*-ester and dried (Na_2SO_4). The aqueous layer was acidified with 10% aq. HCl and extracted with dichloromethane (3 x 5 mL). The combined extracts were washed with satd. NaCl solution and dried (Na_2SO_4). Evaporation of the solvent and recrystallization from hexane afforded pure *trans*-cyclopropane carboxylic acid (0.21 g, 48% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (br s, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.84 (dd, *J* = 7.8, 2.0 Hz, 1H), 2.55 (ddd, *J* = 9.3, 6.7, 4.1 Hz, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 1.85 (ddd, *J* = 8.3, 5.2, 4.1 Hz, 1H), 1.62 (ddd, *J* = 9.3, 5.2, 4.5 Hz, 1H), 1.37 (ddd, *J* = 8.3, 6.7, 4.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 180.13, 137.02, 136.86, 135.16, 129.89, 127.86, 123.74, 27.04, 23.96, 19.89, 19.46, 17.49. HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{12}H_{13}O_2$ 189.0921, found 189.0915.

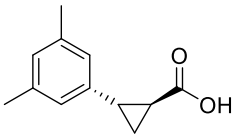


S15

***trans*-2-(3-Fluoro-5-methylphenyl)cyclopropane-1-carboxylic acid (S15).** White solid (0.36 g, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (br s, 1H), 6.73 (m, 1H), 6.72 (s, 1H), 6.59 (m, 1H), 2.54 (ddd, *J* = 9.2, 6.6, 4.1 Hz, 1H), 1.88 (ddd, *J* = 8.4, 5.3, 4.1 Hz, 1H), 2.31 (s, 3H), 1.65 (ddd, *J* = 9.2, 5.3, 4.7 Hz, 1H), 1.37 (ddd, *J* = 8.4, 6.6, 4.7 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.73, 163.10 (d, J_{CF} = 245.2 Hz), 141.88 (d, J_{CF} = 8.2 Hz), 140.64 (d, J_{CF} = 8.2 Hz), 123.05 (d, J_{CF} = 2.4 Hz), 114.43 (d, J_{CF} = 21.0 Hz), 110.24 (d, J_{CF} = 22.2 Hz), 26.80 (d,

J_{CF} = 2.3 Hz), 23.97, 21.45 (d, J_{CF} = 1.9 Hz), 17.61. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}FO_2$ 193.0670, found 193.0666.

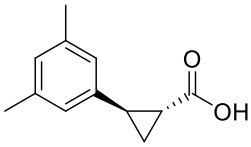
***trans*-2-(3,5-Dimethylphenyl)cyclopropane-1-carboxylic acid (S16).** White solid (0.56 g, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.5 (br s, 1H), 6.86 (s, 1H), 6.73 (s, 2H), 2.54 (ddd, *J* = 9.3, 6.7, 4.0 Hz, 1H), 2.29 (s, 6H), 1.88 (ddd, *J* = 8.3, 5.2, 4.1 Hz, 1H), 1.63 (dt, *J* = 9.3, 4.9 Hz, 1H), 1.39 (ddd, *J* = 8.3, 6.7, 4.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 179.72, 139.56, 138.25, 128.51, 124.26, 27.22, 23.92, 21.39, 17.56. HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{12}H_{13}O_2$ 189.0921, found 189.0914.



S16

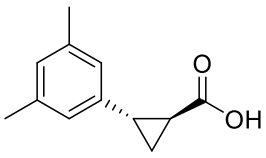
B' Asymmetric cyclopropanations.

Synthesis of (1*R*,2*R*)-2-(3,5-Dimethylphenyl)cyclopropane-1-carboxylic acid.[3] A 25 mL Schlenk flask with a stirring bar was charged with $[Cu(CH_3CN)_4]PF_6$ (22.4 mg, 0.06 mmol, 1 mol%), (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) (18.3 mg, 0.062 mmol), and evacuated-backfilled with argon three times. Anhydrous chloroform (7 mL) was added, and the resulted mixture was stirred for 1 h to get a colorless or pale-green solution of catalytically active copper complex. After cooling the reaction vessel down to 0 ºC with an ice bath, a solution of 3,5-dimethylstyrene (2.3 g, 17.4 mmol) in chloroform (6 mL) was added via a syringe, followed by slow (5 h) dropwise addition of ethyl diazoacetate (0.68 g, 6 mmol) in chloroform (5 mL) by using a syringe pump. After completion of the addition, the reaction mixture was allowed to stir overnight, and solvent was evaporated under reduced pressure. The residue was subjected to flash silica gel column chromatography using gradient of ethyl acetate (from 0 to 30%) in petroleum ether for elution, collecting the recovered styrene (1.25 g) followed by a mixture of ethyl esters of *cis*- and *trans*-2-(3,5-dimethylphenyl)cyclopropane-1-carboxylic acid (1.12 g, 85% yield, *cis*/*trans* = 30:70). ^{1}H NMR (400 MHz, $CDCl_3$, 30:70 d.r., asterisk denotes minor *cis*-isomer peaks) δ 6.88* (s, 0.6 H), 6.85-6.80 (m, 1H), 6.71 (s, 1.4H), 4.16 (q, *J* = 7.1 Hz, 1.4 H), 3.90* (dq, *J* = 7.1, 1.4 Hz, 0.6 H), 2.51* (q, *J* = 8.6 Hz, 0.3 H), 2.44 (ddd, *J* = 9.2, 6.5, 4.1 Hz, 0.7 H), 2.28 (s, 4.2 H), 2.27* (s, 1.8 H), 2.03* (ddd, *J* = 9.3, 7.6, 5.4 Hz, 0.3 H), 1.87 (ddd, *J* = 8.4, 5.3. 4.1 Hz, 0.7 H), 1.66* (dt, *J* = 7.6, 5.4 Hz, 0.3 H), 1.60-1.51 (m, 1H), 1.31-1.27 (m, 0.7 H), 1.27 (t, *J* = 7.1 Hz, 2.1 H), 1.00* (t, *J* = 7.1 Hz, 0.9 H).



(*R*,*R*)-**S16**

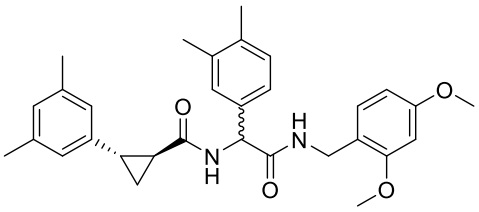
Enantiomeric purity of *trans*-ethyl ester was determined as not less than 94% *ee* by HPLC analysis with a chiral stationary phase: Chiralpak OD-H; hexane/*i*-PrOH (99:1), flow rate = 1.0 mL/min, λ = 210 nm, 25 °C; t_R = 4.9 min (major), t_R = 5.3 min (minor). The obtained mixture of diastereoisomeric ethyl esters (1.12 g, 5.1 mmol) was dissolved in ethanol (5 mL) and THF (10 mL) and treated with 2 M aq. NaOH (1.8 mL, 3.6 mmol, 0.70 equiv.). After stirring at room temperature overnight, the reaction mixture was evaporated, then diluted with water and extracted with dichloromethane (4 x 10 mL) to remove unreacted *cis*-ester and dried (Na_2SO_4). The aqueous layer was acidified with 10% aq. HCl and extracted with dichloromethane (3 x 7 mL). The combined extracts were washed with satd. NaCl solution and dried (Na_2SO_4). Evaporation of the solvent and afforded pure (1*R*,2*R*)-carboxylic acid (0.66 g, 97% yield) as a colorless oil. Analytical data correspond to those for the racemic compound, as reported above. $[\alpha]_D^{21}$ = -312 (*c* 0.41, $CHCl_3$).



(*S*,*S*)-**S16**

(1*S*,2*S*)-2-(3,5-Dimethylphenyl)cyclopropane-1-carboxylic acid.[3] Was prepared as described above for (*R*,*R*)-enantiomer, by using (4*R*,4'*R*)-2,2'-(propane-2,2-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) as a chiral ligand. Enantiomeric purity of intermediate *trans*-ethyl ester was determined as 97% *ee* by HPLC analysis with on a chiral stationary phase: Chiralpak OD-H; hexane/*i*-PrOH (99:1), flow rate = 1.0 mL/min, λ = 210 nm, 25 °C; t_R = 4.9 min (minor), t_R = 5.3 min (major). Colorless oil, $[\alpha]_D^{21}$ = +306 (*c* 0.39, $CHCl_3$).

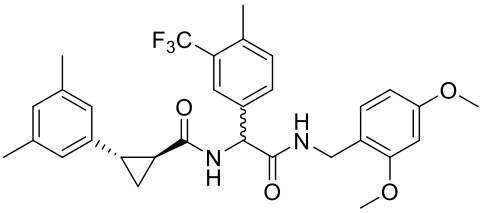
C **Typical procedure for Ugi multi-component reaction.**[2]



D165

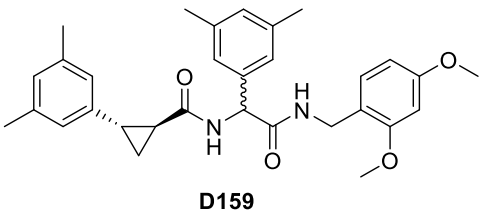
***trans*-*N*-(2-((2,4-Dimethoxybenzyl)amino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D165).** A stirred solution of 3,4-dimethylbenzaldehyde (39 mg, 0.287 mmol, 1 equiv.) in dry 2,2,2-trifluoroethanol (1.0 mL) was mixed with 9 M NH_3 in MeOH (0.10 mL, 0.860 mmol, 3 equiv.), NH_4Cl (17 mg, 0.315 mmol, 1.1 equiv.), *trans*-2-(3,5-dimethylphenyl)cyclopropane-1-carboxylic acid (60 mg, 0.315 mmol, 1.1 equiv.) and 2,4-dimethoxybenzyl isonitrile (56 mg, 0.315 mmol, 1.1 equiv.). The mixture was stirred at 50 °C in a sealed vial for 3-4 h. The precipitate was filtered off, washed with MeOH, dissolved in DCM (to filter ammonia chloride off), and concentrated. The product was purified by

suspending in boiling MeOH to provide the product as a fine white solid (74 mg, 52%, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.01 (m, 10H), 6.81 (d, *J* = 5.9 Hz, 2H), 6.68 (s, 2H), 6.65 (s, 2H), 6.43–6.35 (m, 4H), 6.08 (t, *J* = 5.9 Hz, 2H), 5.35 (d, *J* = 6.4 Hz, 1H), 5.34 (d, *J* = 6.6 Hz, 1H), 4.39–4.23 (m, 4H), 3.78 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.39–2.31 (m, 2H), 2.27 (s, 6H), 2.25 (s, 6H), 2.23 (s, 3H), 2.22 (s, 6H), 2.20 (s, 3H), 1.76–1.64 (m, 2H), 1.55–1.44 (m, 2H), 1.23–1.11 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.48, 171.45, 169.94, 169.84, 160.72, 158.58, 140.87, 140.69, 138.10, 138.06, 137.34, 136.77, 136.18, 136.06, 130.42, 130.39, 130.28, 128.63, 128.59, 128.07, 128.02, 124.95, 124.17, 123.94, 118.27, 103.92, 98.66, 57.27, 55.53, 55.26, 39.78, 39.74, 26.47, 26.31, 25.35, 25.08, 21.38, 19.95, 19.93, 19.61, 16.48, 16.05. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{36}N_2O_4Na$ 523.2567, found 523.2574.



D167

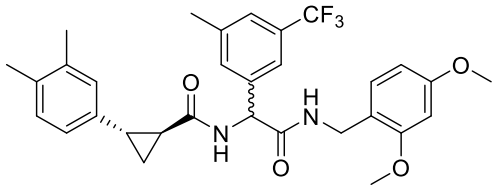
***trans*-*N*-(2-((2,4-Dimethoxybenzyl)amino)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D167).** White solid (60 mg, 43%, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2H), 7.45–7.34 (m, 2H), 7.24–7.19 (m, 2H), 7.19–7.13 (m, 2H), 7.09–7.02 (m, 2H), 6.86–6.80 (m, 2H), 6.69–6.66 (m, 2H), 6.66–6.64 (m, 2H), 6.37 (s, 4H), 6.21 (q, *J* = 5.1 Hz, 2H), 5.47–5.40 (m, 2H), 5.44 (d, *J* = 6.6 Hz, 1H), 5.44 (d, *J* = 6.1 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 2.45 (s, 6H), 2.37–2.29 (m, 2H), 2.27 (s, 6H), 2.26 (s, 6H), 1.76–1.68 (m, 2H), 1.52–1.41 (m, 2H), 1.24–1.15 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, selected peaks) δ 171.73, 171.70, 168.99, 168.92, 160.88, 158.57, 140.59, 140.47, 138.17, 138.13, 136.64, 136.55, 132.65, 130.67, 130.53, 130.50, 128.17, 128.15, 124.76, 124.14, 123.94, 117.88, 104.02, 98.71, 56.92, 55.53, 55.27, 39.96, 31.08, 26.37, 26.20, 25.52, 25.32, 21.38, 21.37, 19.15, 16.16. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{33}F_3N_2O_4Na$ 577.2285, found 577.2274.



D159

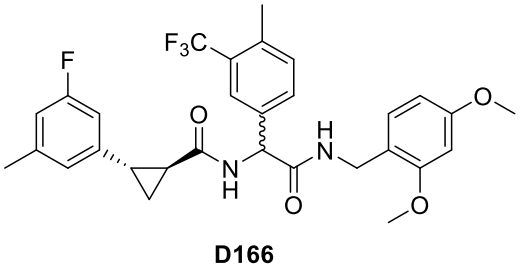
***trans*-*N*-(2-((2,4-Dimethoxybenzyl)amino)-1-(3,5-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D159).** White solid (58 mg, 40%, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, two diastereoisomers are integrated as one compound) δ 7.14–7.01 (m, 2H), 6.95–6.88 (m, 3H), 6.82 (d, *J* = 5.3 Hz, 1H), 6.67 (d, *J* = 13.1 Hz, 2H), 6.44–6.31 (m, 2H), 6.03 (t, *J* = 5.8 Hz, 1H), 5.32 (d, *J* = 6.5 Hz, 1H), 4.39–4.24 (m, 2H), 3.84–3.72 (m, 3H), 3.70–3.65 (m, 3H), 2.41–2.32 (m, 1H), 2.30–2.19 (m, 12H),

1.75-1.63 (m, 1H), 1.55–1.46 (m, 1H), 1.22–1.12 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.48, 171.45, 169.94, 169.84, 160.72, 158.58, 140.87, 140.69, 138.10, 138.06, 137.34, 136.77, 136.18, 136.06, 130.42, 130.39, 130.28, 128.63, 128.59, 128.07, 128.02, 124.95, 124.17, 123.94, 118.27, 103.92, 98.66, 57.27, 55.53, 55.26, 39.78, 39.74, 26.47, 26.31, 25.35, 25.08, 21.38, 19.95, 19.93, 19.61, 16.48, 16.05. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{37}N_2O_4$ 501.2748, found 501.2752.



D168

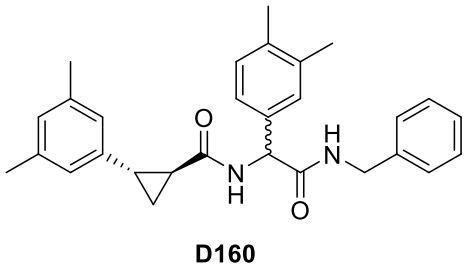
***trans*-*N*-(2-((2,4-Dimethoxybenzyl)amino)-1-(3-methyl-5-(trifluoromethyl)phenyl)-2-oxoethyl)-2-(3,4-dimethylphenyl)cyclopropane-1-carboxamide (D168).** White solid (104 mg, 39%, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 6H), 7.17–6.99 (m, 6H), 6.88–6.82 (m, 2H), 6.82–6.75 (m, 2H), 6.41–6.35 (m, 4H), 6.11–6.01 (m, 2H), 5.39 (d, *J* = 6.4 Hz, 1H), 5.39 (d, *J* = 6.2 Hz, 1H), 4.36–4.28 (m, 4H), 3.78 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.42–2.30 (m, 8H), 2.25–2.19 (m, 12H), 1.72–1.64 (m, 2H), 1.54–1.44 (m, 2H), 1.24–1.15 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, selected peaks) δ 170.94, 168.79, 160.90, 158.57, 137.92, 136.81, 134.78, 131.49, 130.53, 129.85, 127.76, 127.53, 123.59, 123.33, 117.87, 104.03, 98.72, 57.14, 55.54, 55.28, 40.06, 25.37, 25.15, 21.47, 19.88, 19.46, 19.43, 16.15. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{33}F_3N_2O_4Na$ 577.2285, found 577.2272.



D166

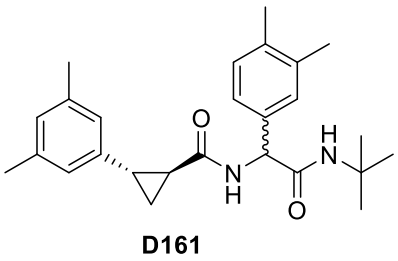
***trans*-*N*-(2-((2,4-Dimethoxybenzyl)amino)-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-oxoethyl)-2-(3-fluoro-5-methylphenyl)cyclopropane-1-carboxamide (D166).** White solid (167 mg, 30%, d.r. 1.4:1). ^{1}H NMR (400 MHz, $CDCl_3$, two diastereoisomers are integrated as single compound) δ 7.60–7.54 (m, 1H), 7.44–7.35 (m, 1H), 7.33–7.26 (m, 1H), 7.24–7.17 (m, 1H), 7.08–7.00 (m, 1H), 6.75–6.60 (m, 2H), 6.56–6.45 (m, 1H), 6.41–6.30 (m, 3H), 5.50 (d, *J* = 6.5 Hz, 1H), 4.37-4.22 (m, 2H), 3.76–3.74 (two singlets, 3H), 3.65–3.63 (two singlets, 3H), 2.46–2.43 (m, 3H), 2.29 (d, *J* = 6.4 Hz, 4H), 1.78–1.68 (m, 1H), 1.52–1.41 (m, 1H), 1.21–1.11 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.39, 171.33, 169.04, 168.98, 164.29, 161.86, 160.86, 158.56, 143.00, 142.89, 142.81, 140.48, 140.39, 136.81, 136.55, 136.48, 132.63, 132.61, 130.54, 130.49, 130.47, 129.62, 129.32, 125.73, 124.75, 124.70, 124.64, 124.59, 123.00, 122.89, 122.87, 122.80, 122.78, 117.85, 114.11, 113.90, 110.15, 110.05, 109.93, 109.82, 104.00, 98.69,

56.79, 55.49, 55.25, 39.87, 26.41, 26.35, 25.19, 25.01, 21.43, 21.41, 19.15, 19.13, 16.46, 16.31. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{30}F_4N_2O_4Na$ 581.2034, found 581.2034.



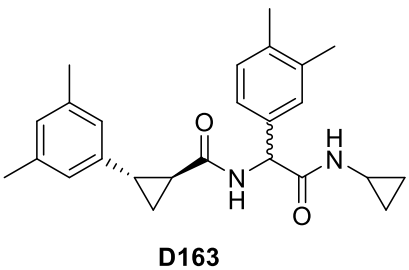
D160

***trans*-*N*-(2-(Benzylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D160).** White solid (48 mg, 38%, d.r. 1.35:1). ^{1}H NMR (400 MHz, $CDCl_3$, two diastereoisomers are integrated as single compound) δ 7.31–7.20 (m, 3H), 7.17–7.02 (m, 6H), 6.83 (s, ~0.5H), 6.81 (s, ~0.5H), 6.67 (s, 1H), 6.65 (s, 1 H), 6.17 (q, *J* = 6.5 Hz, 1H), 5.51–5.44 (m, 1H), 4.48–4.33 (m, 2H), 2.38-2.29 (m, 1H), 2.29–2.21 (m, 12H), 1.76–1.65 (m, 1H), 1.53–1.42 (m, 1H), 1.23–1.12 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 171.60, 170.43, 170.31, 140.74, 140.58, 138.11, 138.09, 137.79, 137.49, 137.03, 135.83, 135.69, 130.40, 128.78, 128.65, 128.62, 128.12, 128.07, 127.65, 127.63, 124.90, 124.12, 123.94, 57.28, 43.86, 26.44, 26.32, 25.46, 25.20, 21.39, 19.95, 19.93, 19.63, 16.50, 16.12. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{33}N_2O_2$ 441.2537, found 441.2539.



D161

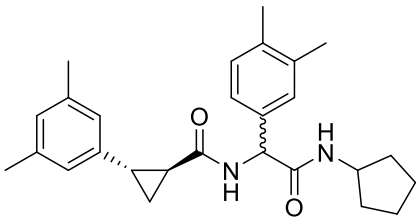
***trans*-*N*-(2-(*tert*-Butylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D161).** White solid (113 mg, 58%, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, two diastereoisomers are integrated as single compound) δ 7.18–7.07 (m, 3H), 7.00 (dd, *J* = 16.4, 6.7 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 15.5 Hz, 2H), 5.37 (d, *J* = 3.8 Hz, 1H), 5.28 (d, *J* = 6.7 Hz, 1H), 2.42–2.33 (m, 1H), 2.31–2.19 (m, 12H), 1.75–1.65 (m, 1H), 1.56–1.46 (m, 1H), 1.35–1.26 (two singlets, 9H), 1.23–1.11 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, selected peaks) δ 171.43, 171.38, 169.44, 169.33, 140.87, 140.72, 138.11, 138.09, 136.84, 130.38, 128.72, 128.68, 128.09, 128.03, 124.80, 124.13, 123.96, 57.39, 51.92, 28.72, 26.50, 26.36, 25.34, 25.10, 21.39, 21.38, 19.99, 19.96, 19.64, 16.50, 16.20. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{35}N_2O_2$ 407.2693, found 407.2696.



D163

***trans*-*N*-(2-(Cyclopropylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D163).** White solid (52 mg, 28%, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, two diastereoisomers are integrated as single compound) δ 7.16–7.03 (m, 4H), 6.82 (d, *J* = 7.3 Hz,

1H), 6.67 (d, *J* = 13.2 Hz, 2H), 6.06–5.99 (m, 1H), 5.40–5.33 (m, 1H), 2.70–2.60 (m, 1H), 2.41–2.32 (m, 1H), 2.29–2.20 (m, 12H), 1.77–1.67 (m, 1H), 1.56-1.46 (m, 1H), 1.24–1.13 (m, 1H), 0.81–0.64 (m, 2H), 0.53–0.34 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.75, 171.63, 171.57, 171.53, 140.74, 140.58, 138.13, 138.11, 137.48, 136.98, 135.86, 135.71, 130.39, 128.61, 128.59, 128.14, 128.08, 124.83, 124.80, 124.15, 123.94, 57.00, 56.99, 26.46, 26.30, 25.43, 25.19, 22.95, 22.93, 21.39, 21.38, 19.98, 19.95, 19.63, 16.49, 16.11, 6.88, 6.47. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{30}N_2O_2Na$ 413.2199, found 413.2195.



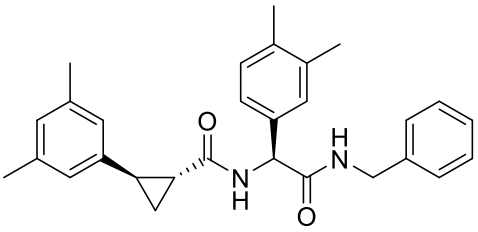
D164

***trans*-*N*-(2-(Cyclopentylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D164).** White solid (71 mg, 36%, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, two diastereoisomers are integrated as single compound) δ 7.13 (d, *J* = 10.4 Hz, 1H), 7.11–7.05 (m, 3H), 6.82 (d, *J* = 6.9 Hz, 1H), 6.67 (d, *J* = 11.9 Hz, 2H), 5.96–5.82 (m, 1H), 5.45–5.39 (m, 1H), 4.21–4.08 (m, 1H), 2.41–2.32 (m, 1H), 2.30–2.17 (m, 12H), 2.01–1.79 (m, 2H), 1.78–1.68 (m, 1H), 1.61–1.46 (m, 5H), 1.42–1.29 (m, 1H), 1.29–1.11 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.41, 171.36, 169.77, 169.65, 140.67, 140.50, 138.00, 137.98, 137.21, 136.67, 135.99, 135.84, 130.18, 128.46, 128.43, 128.00, 127.94, 124.64, 124.62, 124.01, 123.82, 56.94, 51.61, 51.57, 32.89, 32.87, 32.78, 32.77, 26.35, 26.23, 25.28, 25.02, 23.71, 23.66, 21.27, 19.87, 19.84, 19.50, 16.36, 16.00. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{34}N_2O_2Na$ 441.2512, found 441.2508.

Synthesis of individual stereoisomers of compound D160 via Ugi reaction.

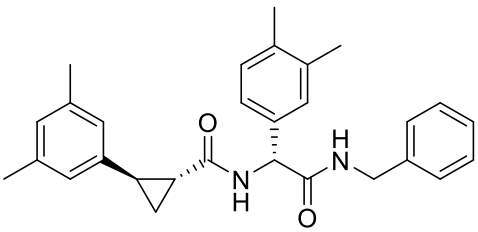
3,4-Dimethylbenzaldehyde (80 mg, 0.60 mmol), ammonium chloride (35 mg, 0.65 mmol), (1*R*,2*R*)- or (1*S*,2*S*)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxylic acid **S16** (124 mg, 0.65 mmol), 9 M ammonia in MeOH (0.20 mL, 2 mmol) and benzyl isonitrile (76 mg, 0.65 mmol) were combined together in dry 2,2,2-trifluoroethanol (2 mL). The mixture was stirred at 50 °C in a sealed vial for 5 h, then cooled to room temperature and transferred to a separating funnel with water (10 mL) and CH_2Cl_2 (15 mL). Organic phase was washed with aq. Na_2CO_3, water, and dried ($MgSO_4$). The crude reaction mixture after evaporation of the solvent was subjected to flash silica gel column chromatography using gradient of ethyl acetate (from 2 to 40%) in CH_2Cl_2 for elution, collecting the first diastereoisomer (51 mg, 19% yield), then mixed fraction (41 mg, 16% yield) and finally the second diastereoisomer (54 mg, 20% yield). After

evaporation of solvent, the products were additionally purified by suspending in boiling MeOH to provide the product as fine white solids.



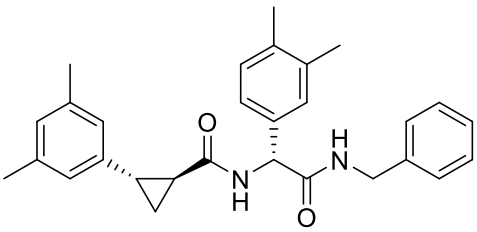
D160a

(1*R*,2*R*)-*N*-((*S*)-2-(Benzylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D160a): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.22 (m, 3H), 7.18–7.08 (m, 5H), 7.05 (d, *J* = 6.6 Hz, 1H, NH), 6.83 (s, 1H), 6.67 (s, 2H), 6.19 (t, *J* = 5.9 Hz, 1H, NH), 5.49 (d, *J* = 6.6 Hz, 1H), 4.45 (dd, *J* = 15.0, 5.9 Hz, 1H), 4.37 (dd, *J* = 15.0, 5.9 Hz, 1H), 2.34 (ddd, *J* = 9.4, 6.4, 4.1 Hz, 1H), 2.28 (s, 6H), 2.23 (s, 3H), 2.22 (s, 3H), 1.69 (ddd, *J* = 8.2, 5.2, 4.1 Hz, 1H), 1.47 (ddd, *J* = 9.4, 5.2, 4.4 Hz, 1H), 1.16 (ddd, *J* = 8.2, 6.4, 4.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 171.58, 170.29, 140.58, 138.09, 137.80, 137.49, 137.03, 135.78, 130.40, 128.80, 128.66, 128.12, 127.67, 127.65, 124.92, 124.12, 57.32, 43.87, 26.37, 25.46, 21.39, 19.94, 19.64, 16.12. First eluted diastereoisomer, R_f = 0.60 (CH_2Cl_2/EtOAc 10:1). $[\alpha]_D^{21}$ = -250 (*c* 0.29, $CHCl_3$, d.r.~95:5).



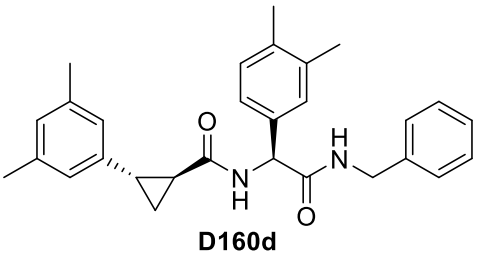
D160b

(1*R*,2*R*)-*N*-((*R*)-2-(Benzylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D160b): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.22 (m, 3H), 7.18–7.08 (m, 5H), 7.02 (d, *J* = 6.6 Hz, 1H, NH), 6.81 (s, 1H), 6.65 (s, 2H), 6.09 (t, *J* = 5.9 Hz, 1H, NH), 5.45 (d, *J* = 6.6 Hz, 1H), 4.47 (dd, *J* = 15.0, 5.9 Hz, 1H), 4.38 (dd, *J* = 15.0, 5.9 Hz, 1H), 2.34 (ddd, *J* = 9.4, 6.4, 4.1 Hz, 1H), 2.26 (s, 6H), 2.23 (s, 3H), 2.21 (s, 3H), 1.71 (ddd, *J* = 8.2, 5.2, 4.1 Hz, 1H), 1.50 (ddd, *J* = 9.4, 5.2, 4.4 Hz, 1H), 1.20 (ddd, *J* = 8.2, 6.4, 4.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 171.63, 170.38, 140.76, 138.12, 137.78, 137.54, 137.08, 135.64, 130.43, 128.81, 128.66, 128.07, 127.69, 127.63, 124.96, 123.93, 57.38, 43.89, 26.49, 25.21, 21.39, 19.93, 19.64, 16.53. Second eluted diastereoisomer, R_f = 0.40 (CH_2Cl_2/EtOAc 10:1). $[\alpha]_D^{21}$ = -71.3 (*c* 0.61, $CHCl_3$, d.r.~95:5).



D160c

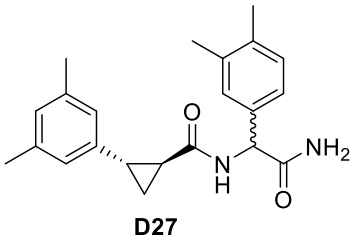
(1*S*,2*S*)-*N*-((*R*)-2-(Benzylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D160c): NMR data and R_f value correspond to those of its enantiomer **D160a**. $[\alpha]_D^{21}$ = +241 (*c* 0.39, $CHCl_3$, d.r.~98:2).



D160d

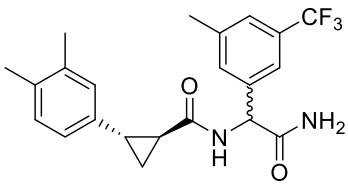
(1*S*,2*S*)-*N*-((*S*)-2-(Benzylamino)-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D160d): NMR data and R_f value correspond to those of its enantiomer **D160b**. $[\alpha]_D^{21}$ = +110 (*c* 0.38, $CHCl_3$, d.r.~93:7).

D Typical procedure for the removal of 2,4-dimetoxybenzyl protecting group.



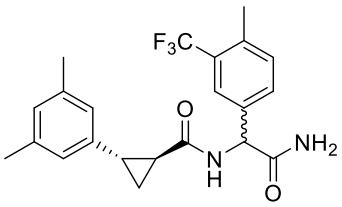
D27

***trans*-*N*-(2-Amino-1-(3,4-dimethylphenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D27).** Trifluoroacetic acid (0.5 mL) was added to the solution of Ugi reaction product **D165** (60 mg, 0.12 mmol) in DCM (2 mL). The mixture was stirred at 35 °C overnight, quenched with 1 M NaOH (6 mL), diluted with sat. $NaHCO_3$ (10 mL), and extracted with DCM (4 x 20 mL). The combined organic layers were dried over Na_2SO_4, concetrated, and the residue was purified by flash column chromatography on silica, eluted with petroleum DCM/MeOH (MeOH 2% → 10%). The resedue was repurified by suspending in boiling MeOH to provide the product as a fine white solid (25 mg, 60%, d.r. 1:1). ^{1}H NMR (400 MHz, DMSO-d_6, two diastereoisomers are integrated as single compound) δ 8.71–8.58 (m, 1H), 7.58 (d, *J* = 10.5 Hz, 1H), 7.23–7.16 (m, 1H), 7.16–7.00 (m, 3H), 6.79 (d, *J* = 10.7 Hz, 1H), 6.70 (d, *J* = 14.0 Hz, 2H), 5.41–5.32 (m, 1H), 2.28–2.06 (m, 14H), 1.32–1.20 (m, 1H), 1.17–1.02 (m, 1H). ^{13}C NMR (101 MHz, DMSO, selected peaks) δ 171.96, 170.63, 170.58, 140.93, 137.18, 137.16, 136.46, 135.85, 135.31, 135.27, 129.26, 128.27, 128.19, 127.36, 124.54, 123.70, 55.79, 24.65, 24.59, 24.01, 23.92, 20.91, 20.88, 19.52, 19.49, 19.02. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_2$ 351.2067, found 351.2071.



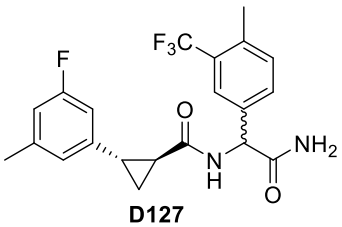
D162

***trans*-*N*-(2-Amino-1-(3-methyl-5-(trifluoromethyl)phenyl)-2-oxoethyl)-2-(3,4-dimethylphenyl)cyclopropane-1-carboxamide (D162).** Prepared from **D168**. White solid (19 mg, 52%, d.r. 2.75:1). ^{1}H NMR (400 MHz, DMSO-d_6, two diastereoisomers are integrated as single compound) δ 8.94–8.82 (m, 1H), 7.83–7.72 (m, 1H), 7.63–7.45 (m, 3H), 7.19 (s, 1H), 7.07–6.95 (m, 1H), 6.95–6.74 (m, 2H), 5.57–5.47 (m, 1H), 2.44–2.34 (m, 3H), 2.24–2.10 (m, 8H), 1.33–1.20 (m, 1H), 1.19–1.04 (m, 1H). ^{13}C NMR (101 MHz, DMSO, selected peaks) δ 171.18, 171.04, 170.93, 140.59, 140.45, 139.20, 138.23, 136.01, 135.99, 133.69, 131.85, 131.77, 129.40, 129.22, 127.12, 127.08, 123.29, 123.26, 120.77, 55.60, 24.67, 24.00, 23.90, 20.84, 20.82, 19.41, 19.38, 18.96, 15.51. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{23}F_3N_2O_2Na$ 427.1604, found 427.1606.



D119

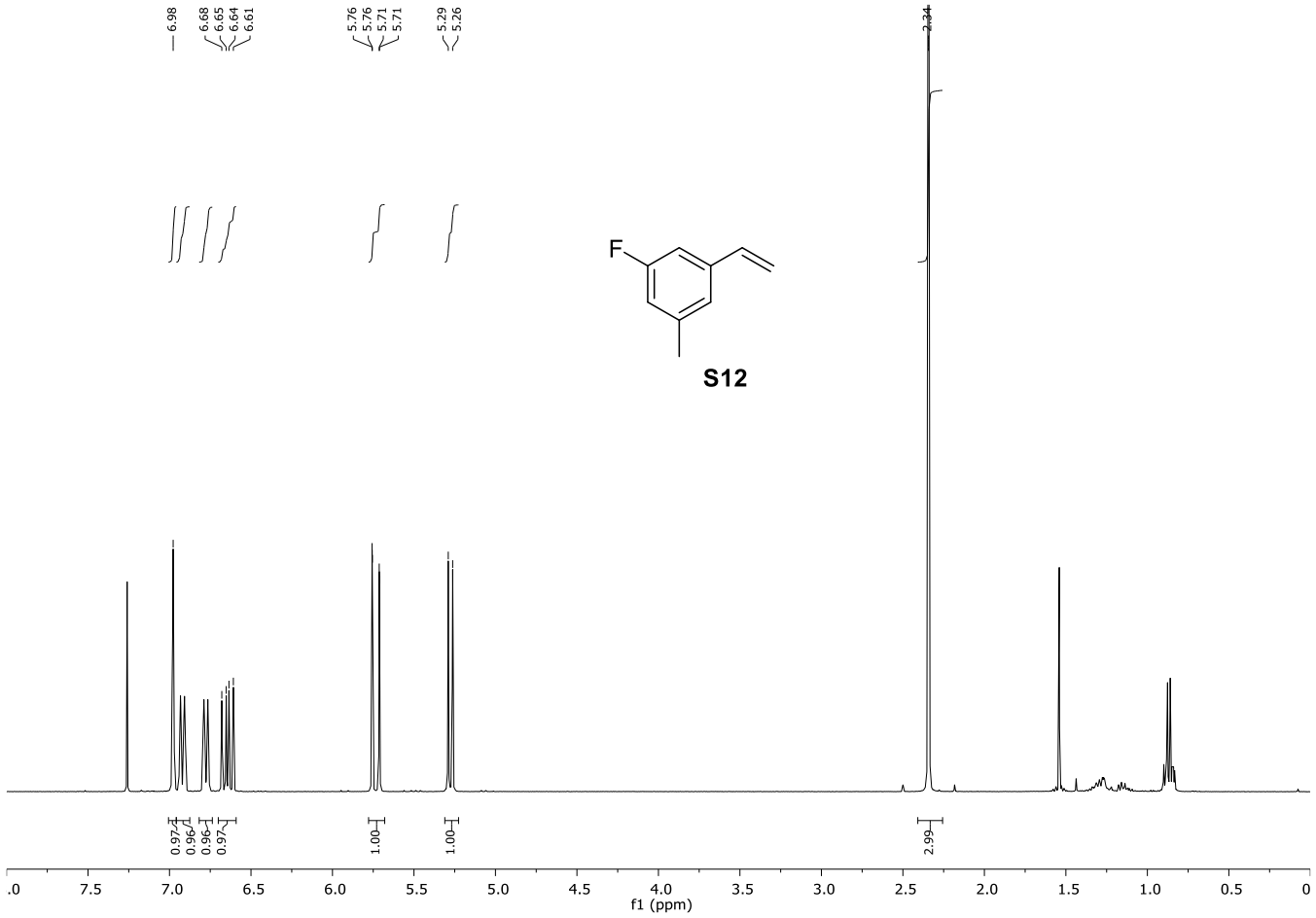
***trans*-*N*-(2-Amino-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-oxoethyl)-2-(3,5-dimethylphenyl)cyclopropane-1-carboxamide (D119).** Prepared from **D167**. White solid (19 mg, 52%, d.r. 1:1). ^{1}H NMR (400 MHz, DMSO-d_6, two diastereoisomers are integrated as single compound) δ 8.90–8.81 (m, 1H), 7.84–7.67 (m, 2H), 7.66–7.49 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.18 (s, 1H), 6.79 (d, *J* = 9.7 Hz, 1H), 6.70 (d, *J* = 14.5 Hz, 2H), 5.57–5.45 (m, 1H), 2.45–2.38 (m, 3H), 2.28–2.06 (m, 8H), 1.31–1.22 (m, 1H), 1.19–1.07 (m, 1H). ^{13}C NMR (101 MHz, DMSO, selected peaks) δ 171.26, 170.91, 170.82, 140.83, 140.76, 137.62, 137.51, 137.20, 137.17, 132.23, 127.39, 123.73, 123.69, 24.66, 24.56, 24.14, 20.90, 20.87, 18.41, 15.44. HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{23}F_3N_2O_2Na$ 427.1604, found 427.1595.



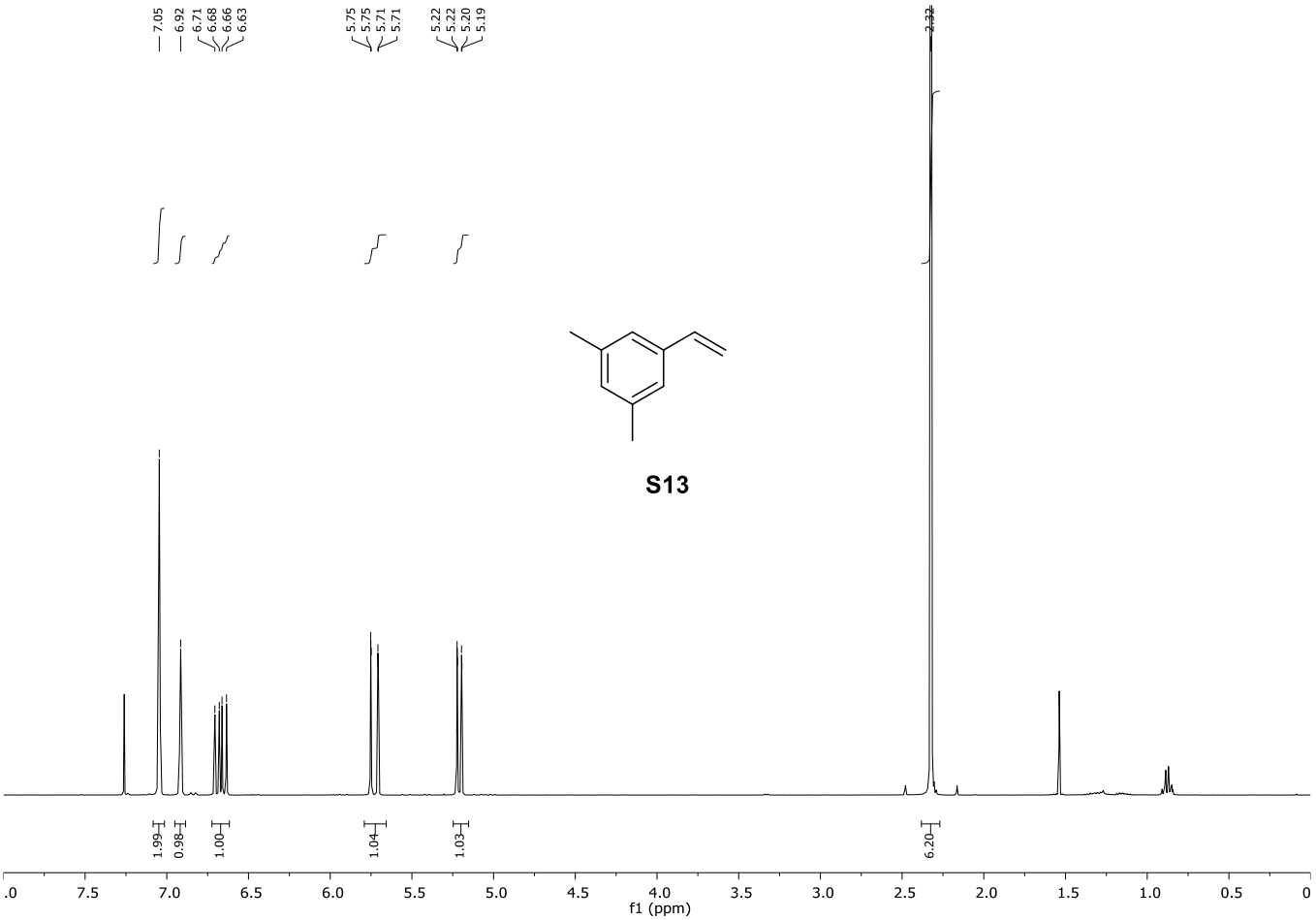
D127

***trans*-*N*-(2-Amino-1-(4-methyl-3-(trifluoromethyl)phenyl)-2-oxoethyl)-2-(3-fluoro-5-methylphenyl)cyclopropane-1-carboxamide (D127).** Prepared from **D166**. White solid (30 mg, 27%, d.r. 1:1). ^{1}H NMR (400 MHz, DMSO-d_6, two diastereoisomers are integrated as single compound) δ 8.96–8.82 (m, 1H), 7.81–7.68 (m, 2H), 7.66–7.54 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.19 (s, 1H), 6.90-6.68 (m, 3H), 5.54–5.46 (m, 1H), 2.46–2.36 (m, 3H), 2.30–2.12 (m, 5H), 1.36–1.26 (m, 1H), 1.25-1.13 (m, 1H). ^{13}C NMR (101 MHz, DMSO, selected peaks) δ 171.21, 170.57, 170.48, 143.83, 140.13, 137.59, 137.46, 135.30, 132.24, 131.04, 122.87, 122.77, 113.27, 113.05, 109.70, 109.51, 55.49, 55.35, 25.08, 24.94, 23.90, 23.78, 20.79, 18.41. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{21}F_4N_2O_2$ 409.1534, found 409.1526.

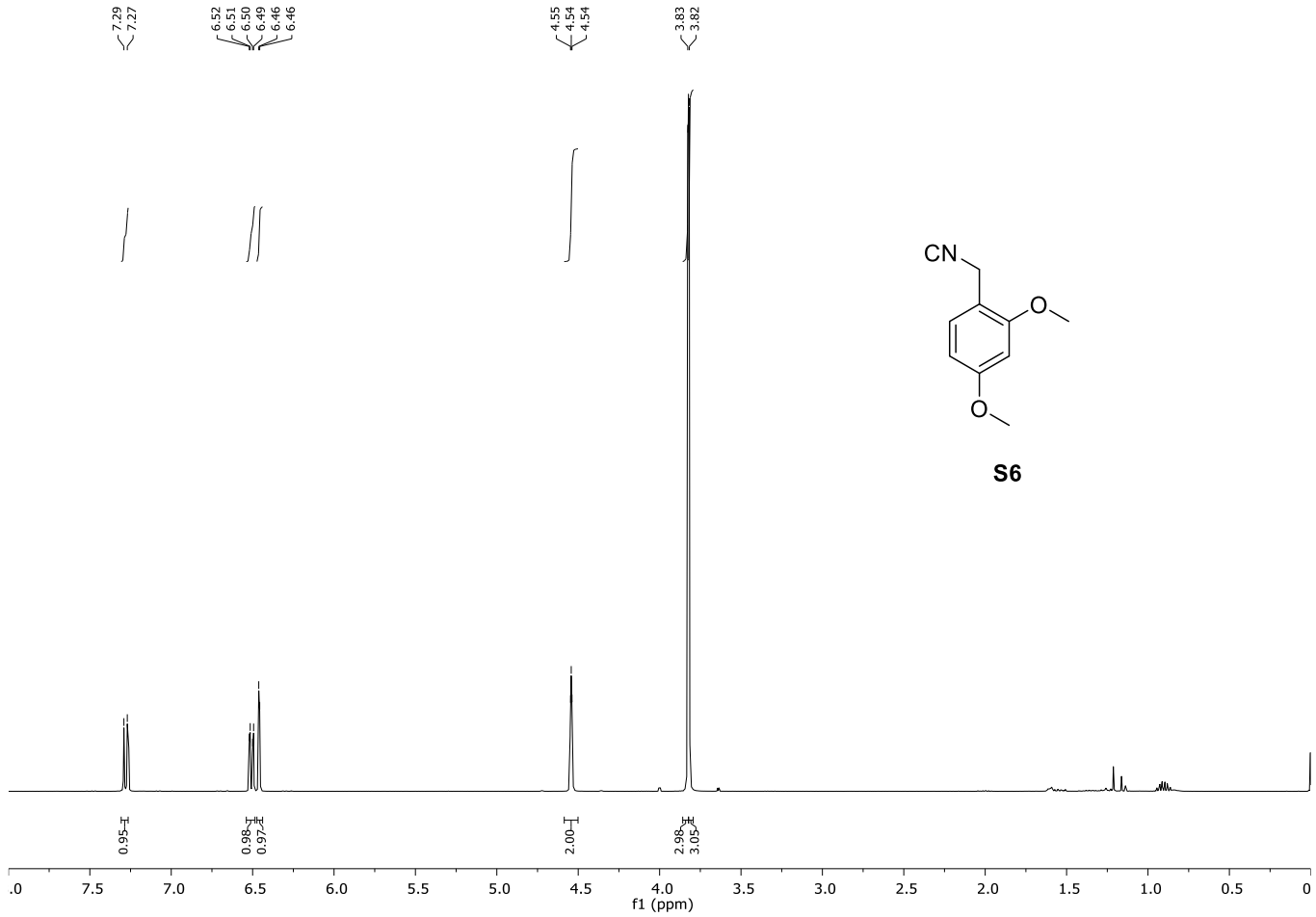
Copies of ^{1}H and ^{13}C NMR spectra



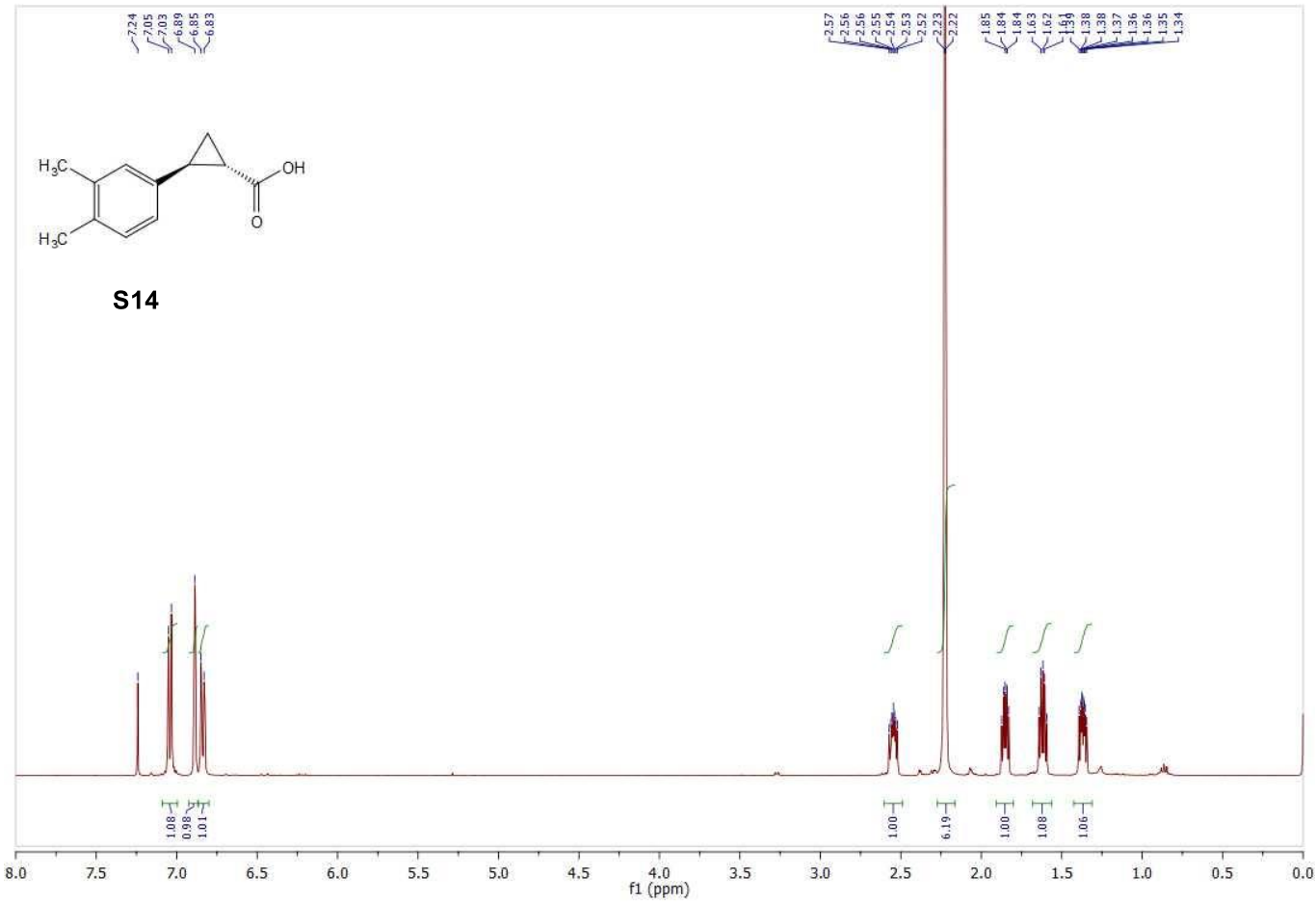
S12



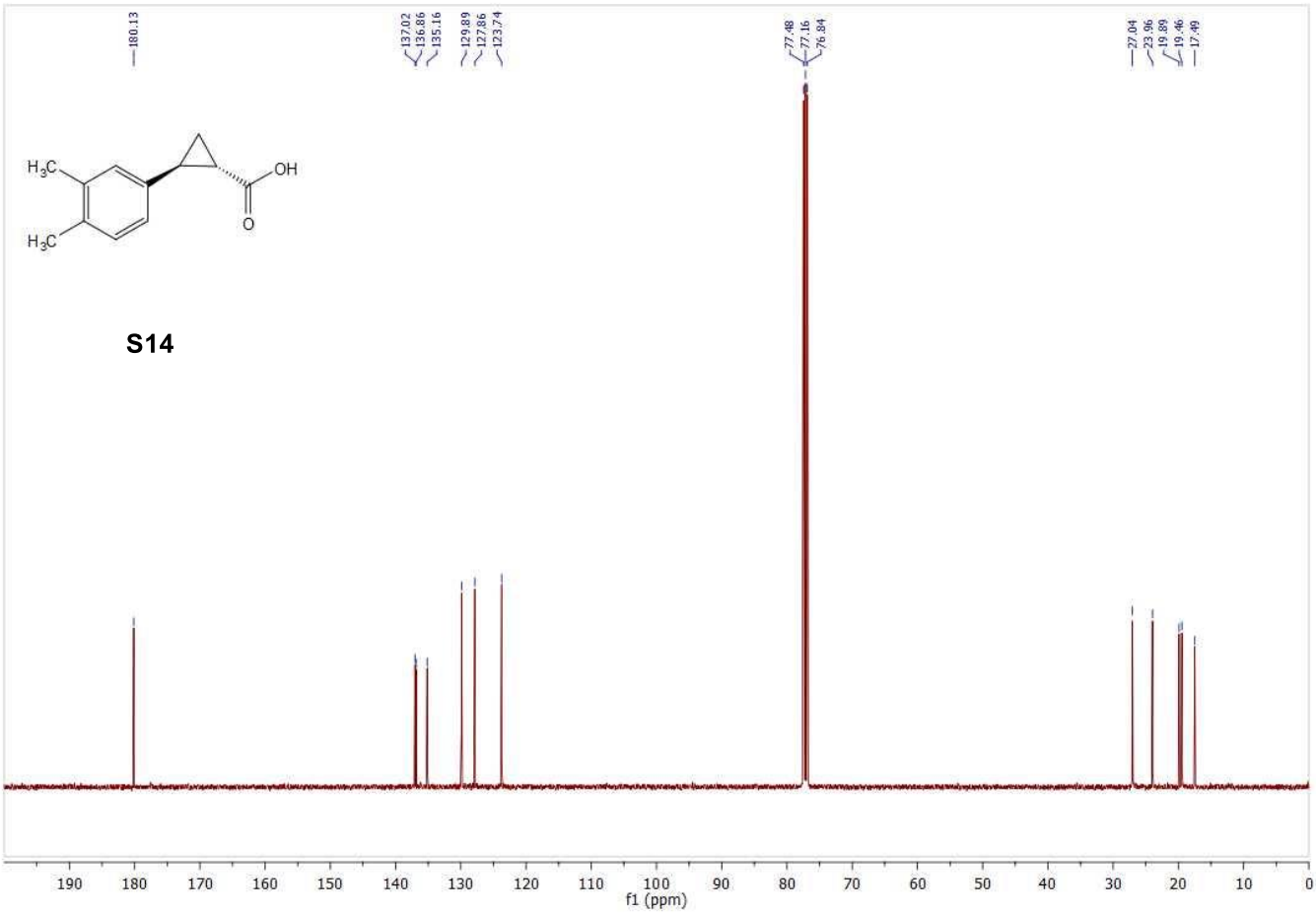
S13


7.29
7.27
6.52
6.51
6.50
6.49
6.46
6.46
4.55
4.54
4.54
3.83
3.82
CN
O
O
0.95
0.98
0.97
2.00
2.98
3.05
f1 (ppm)

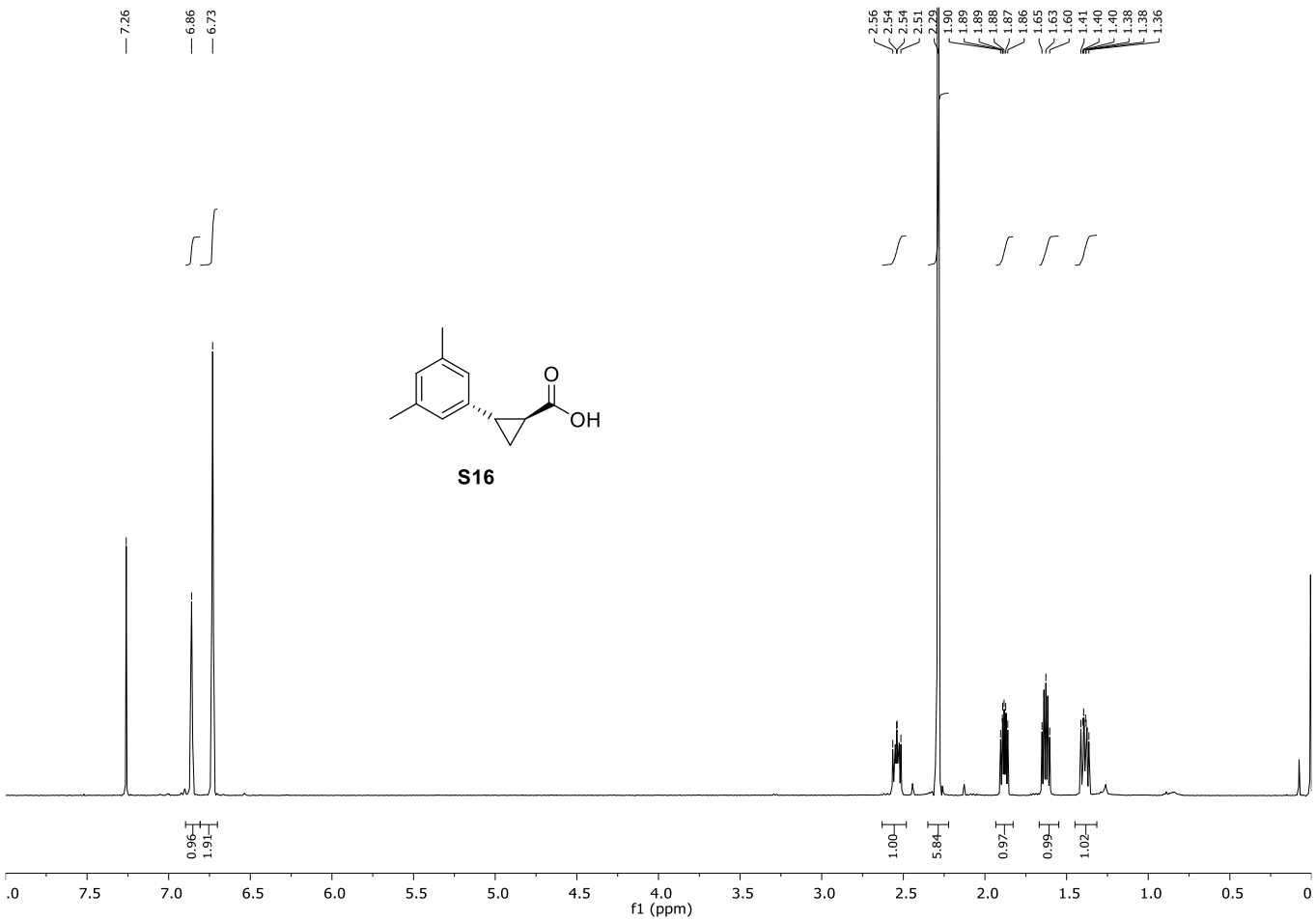
S6


7.24
7.05
7.03
6.89
6.85
6.83
2.57
2.56
2.56
2.55
2.54
2.53
2.52
2.23
2.22
1.85
1.84
1.84
1.63
1.62
1.38
1.38
1.37
1.36
1.36
1.35
1.34
H3C
H3C
OH
O
1.08
0.98
1.01
1.00
6.19
1.00
1.08
1.06
f1 (ppm)

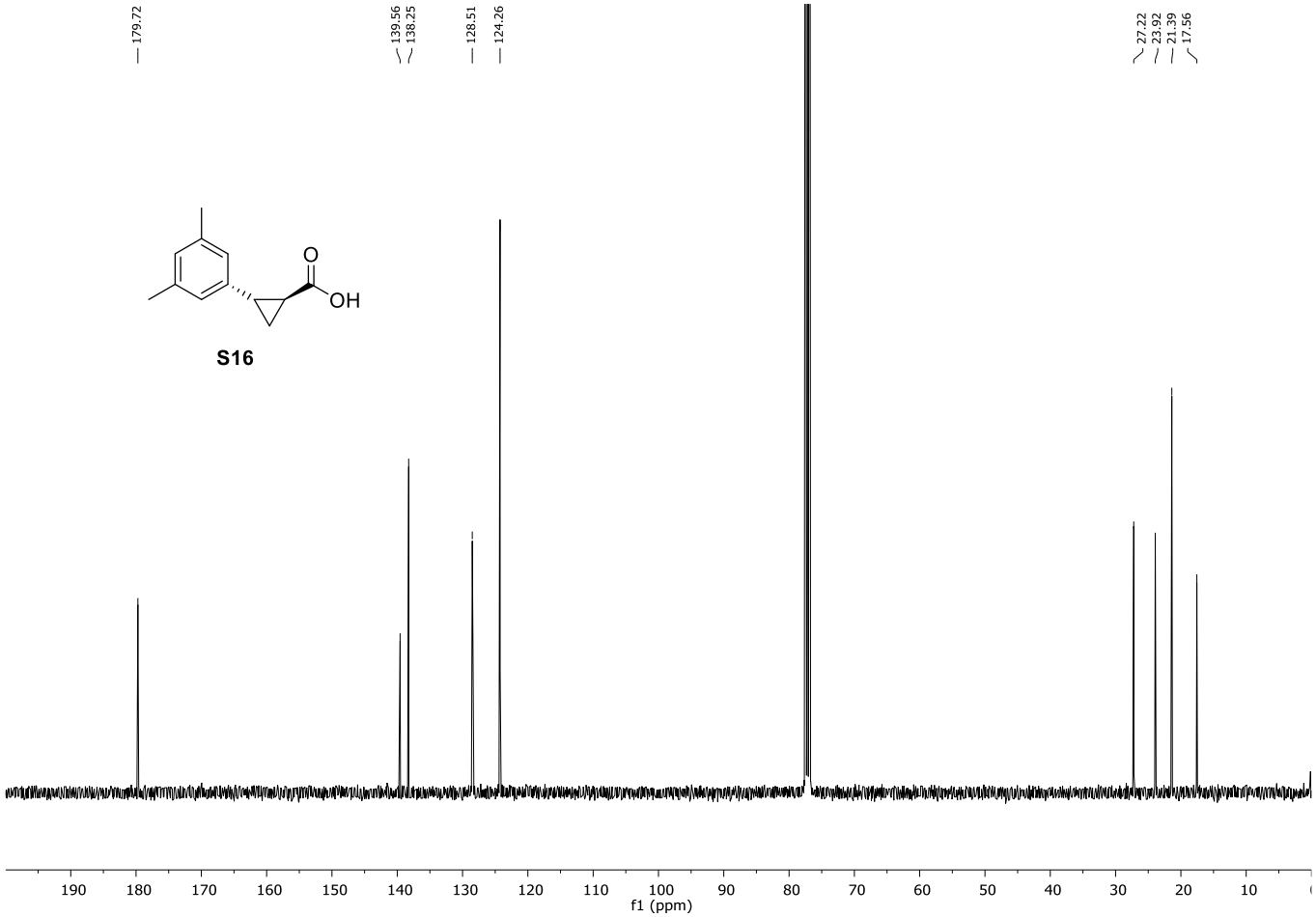
S14

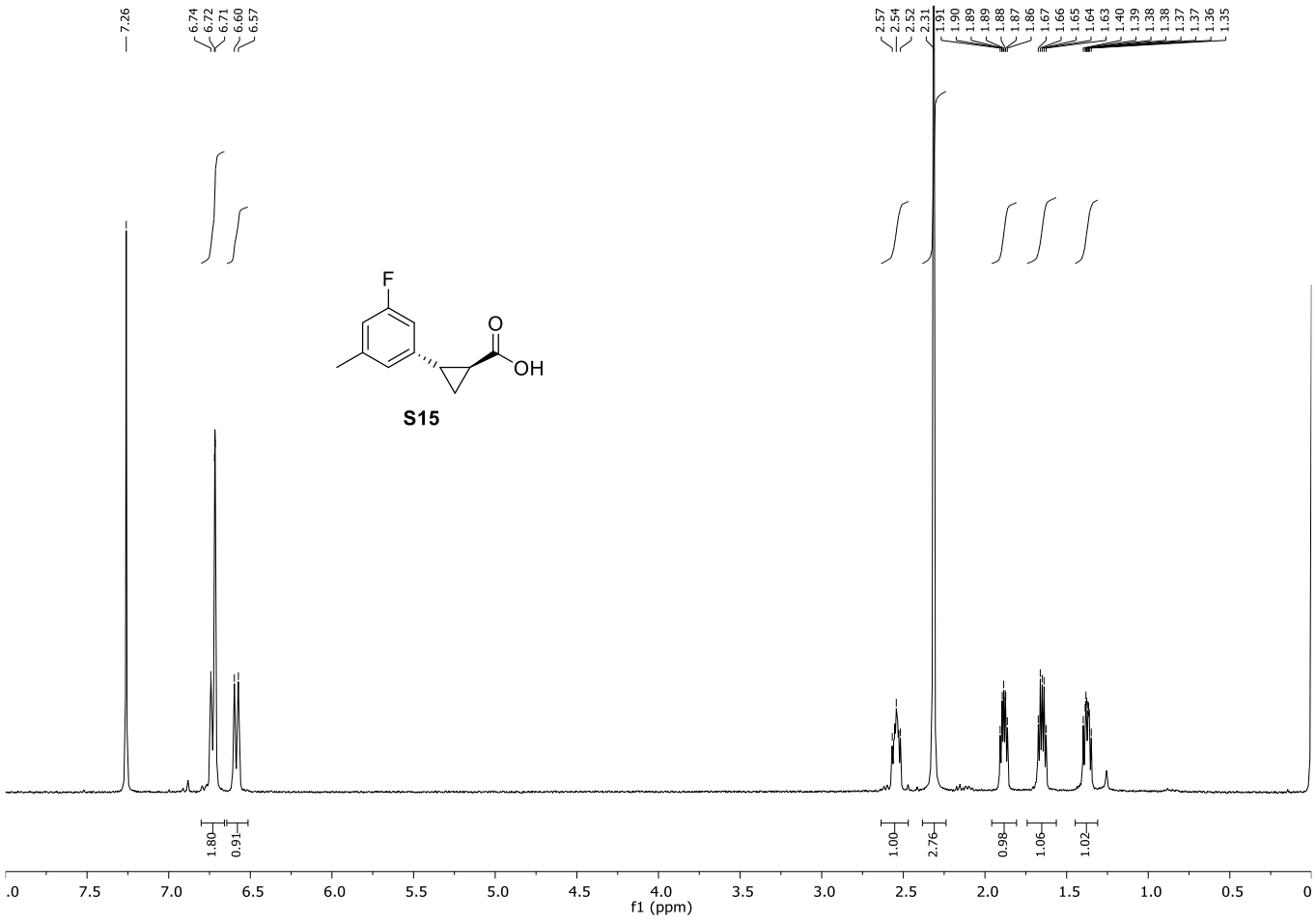

180.13
137.02
136.86
135.16
129.89
127.86
123.74
77.48
77.16
76.84
27.04
23.96
19.89
19.46
17.49
H3C
H3C
OH
O
f1 (ppm)

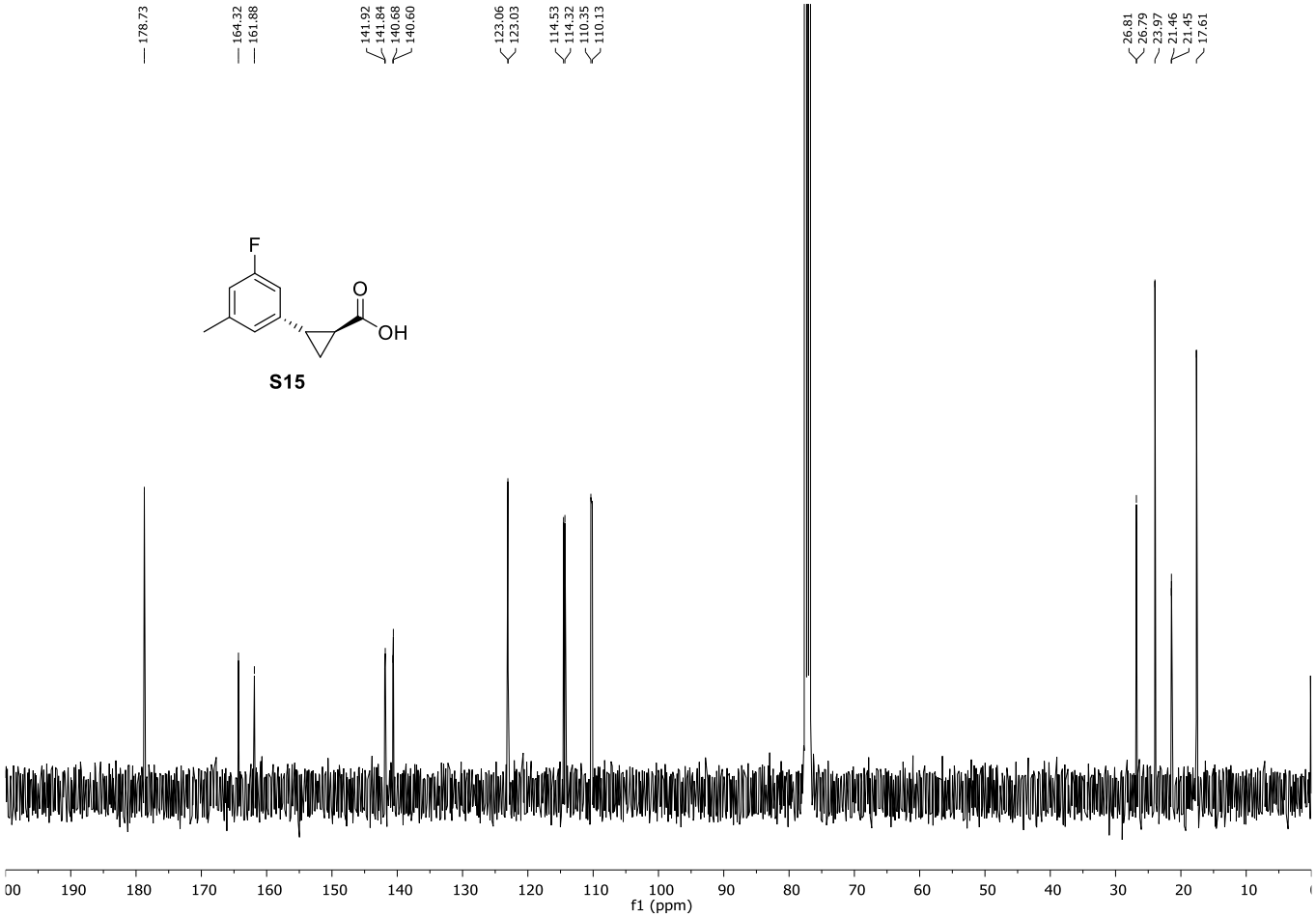
S14

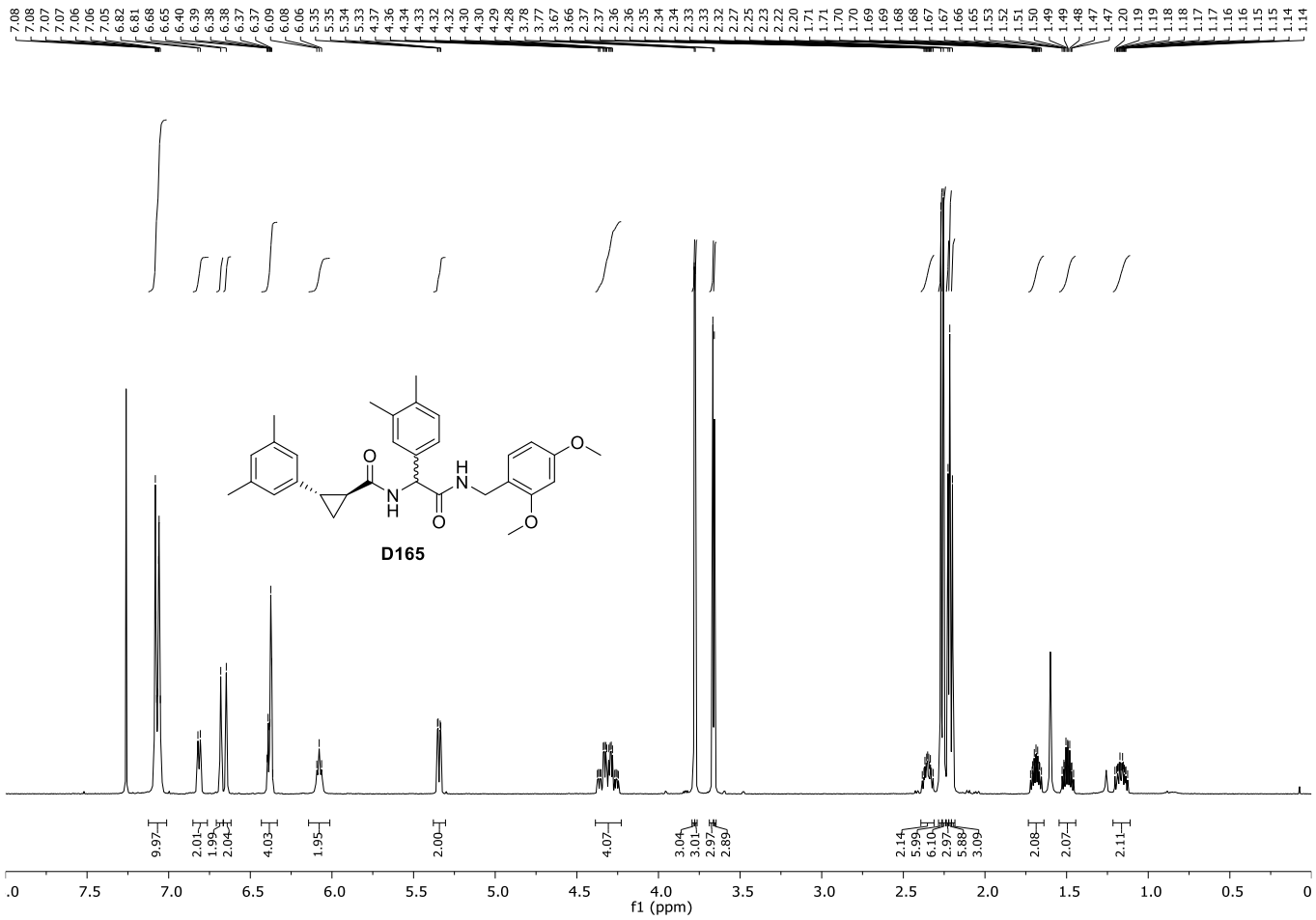

7.26
6.86
6.73
2.56
2.54
2.54
2.51
2.28
1.90
1.89
1.89
1.88
1.87
1.86
1.65
1.63
1.60
1.41
1.40
1.40
1.38
1.38
1.36
0.96
1.91
1.00
5.84
0.97
0.99
1.02
O
OH
f1 (ppm)

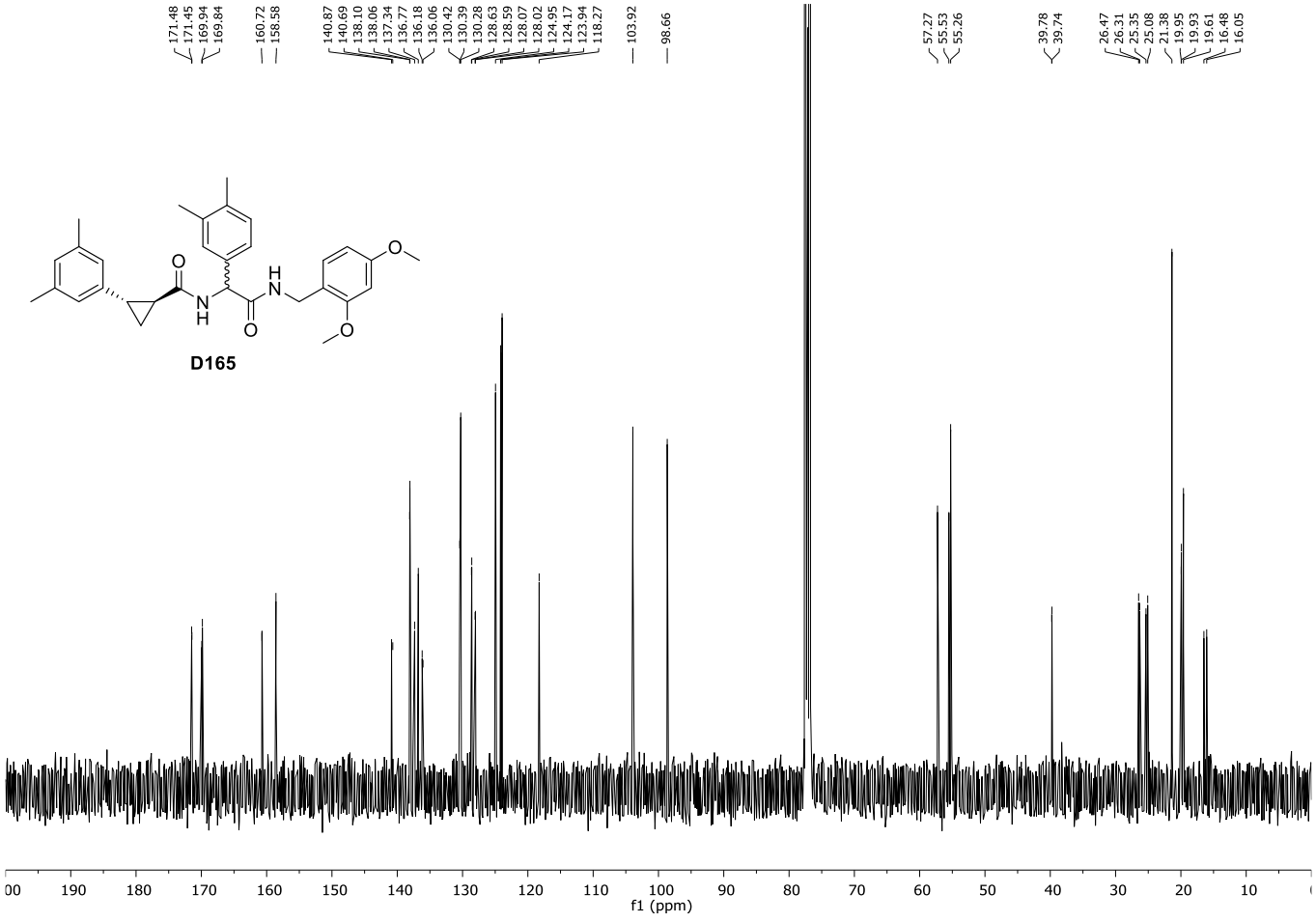
S16

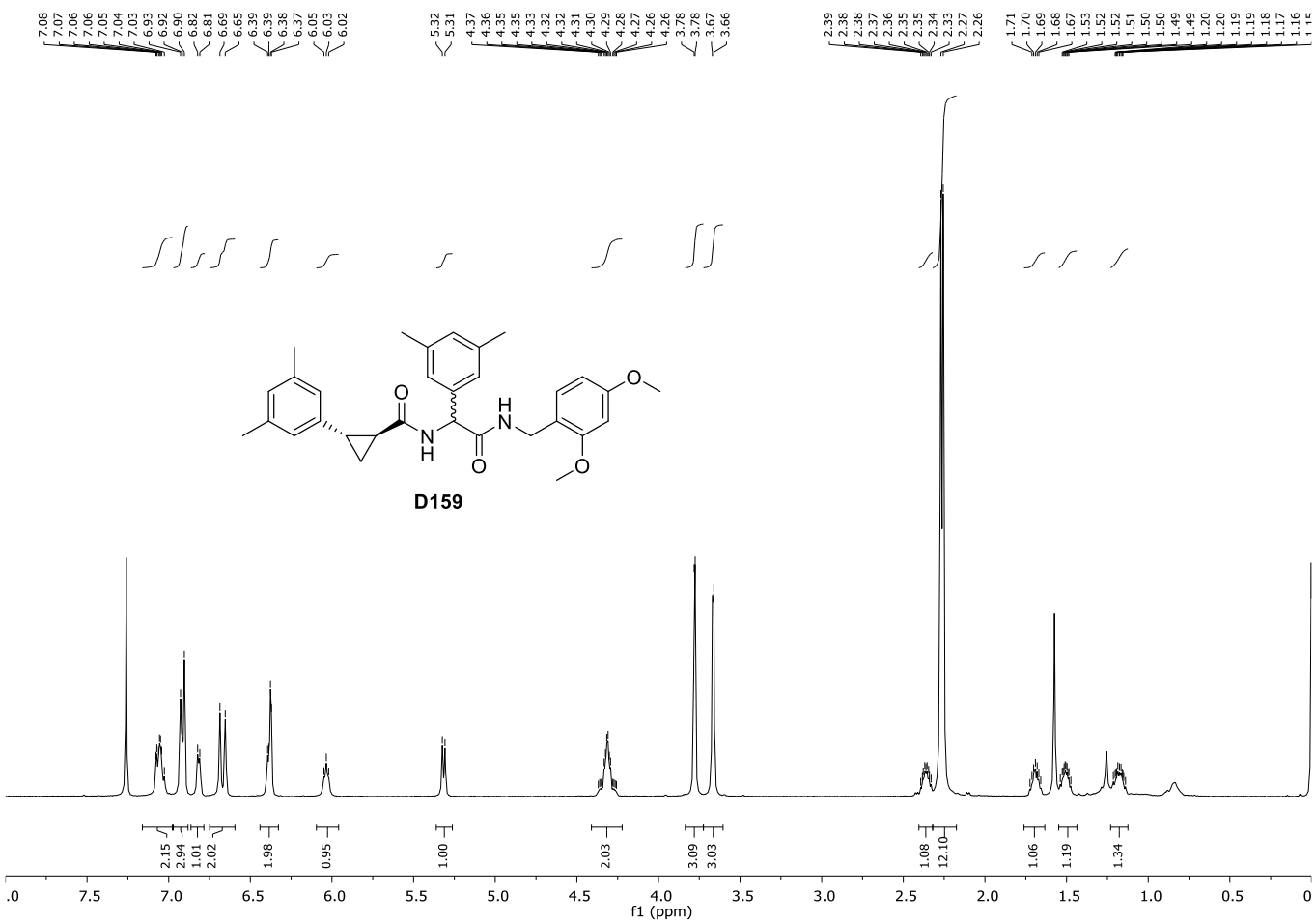

179.72
139.56
138.25
128.51
124.26
27.22
23.92
21.39
17.56
O
OH
S16
f1 (ppm)

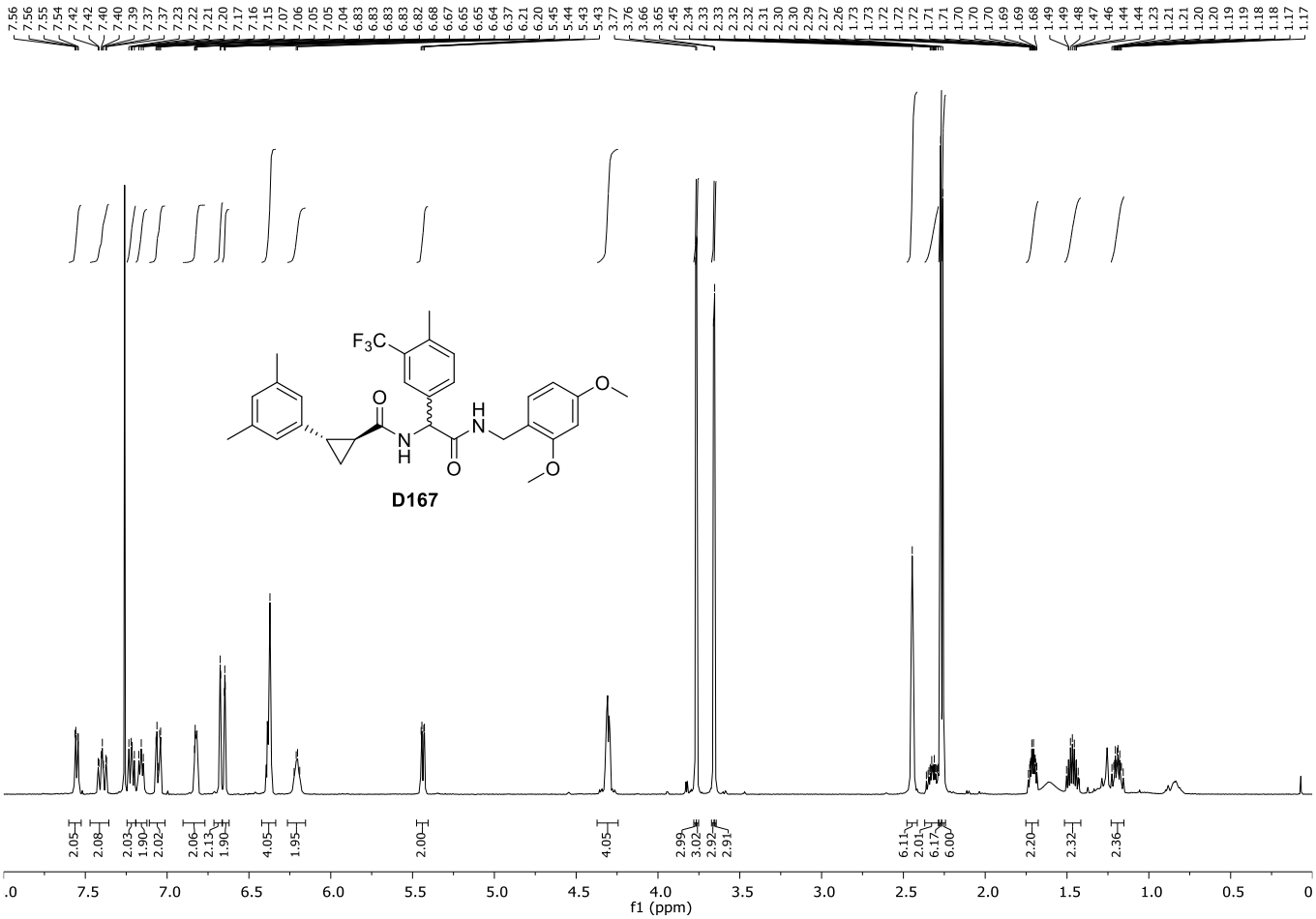

7.26
6.74
6.72
6.71
6.60
6.57
2.57
2.54
2.52
2.31
1.91
1.90
1.89
1.89
1.88
1.87
1.86
1.67
1.66
1.65
1.64
1.63
1.40
1.39
1.38
1.38
1.37
1.37
1.36
1.35
F
O
OH
S15
1.80
0.91
1.00
2.76
0.98
1.06
1.02
f1 (ppm)

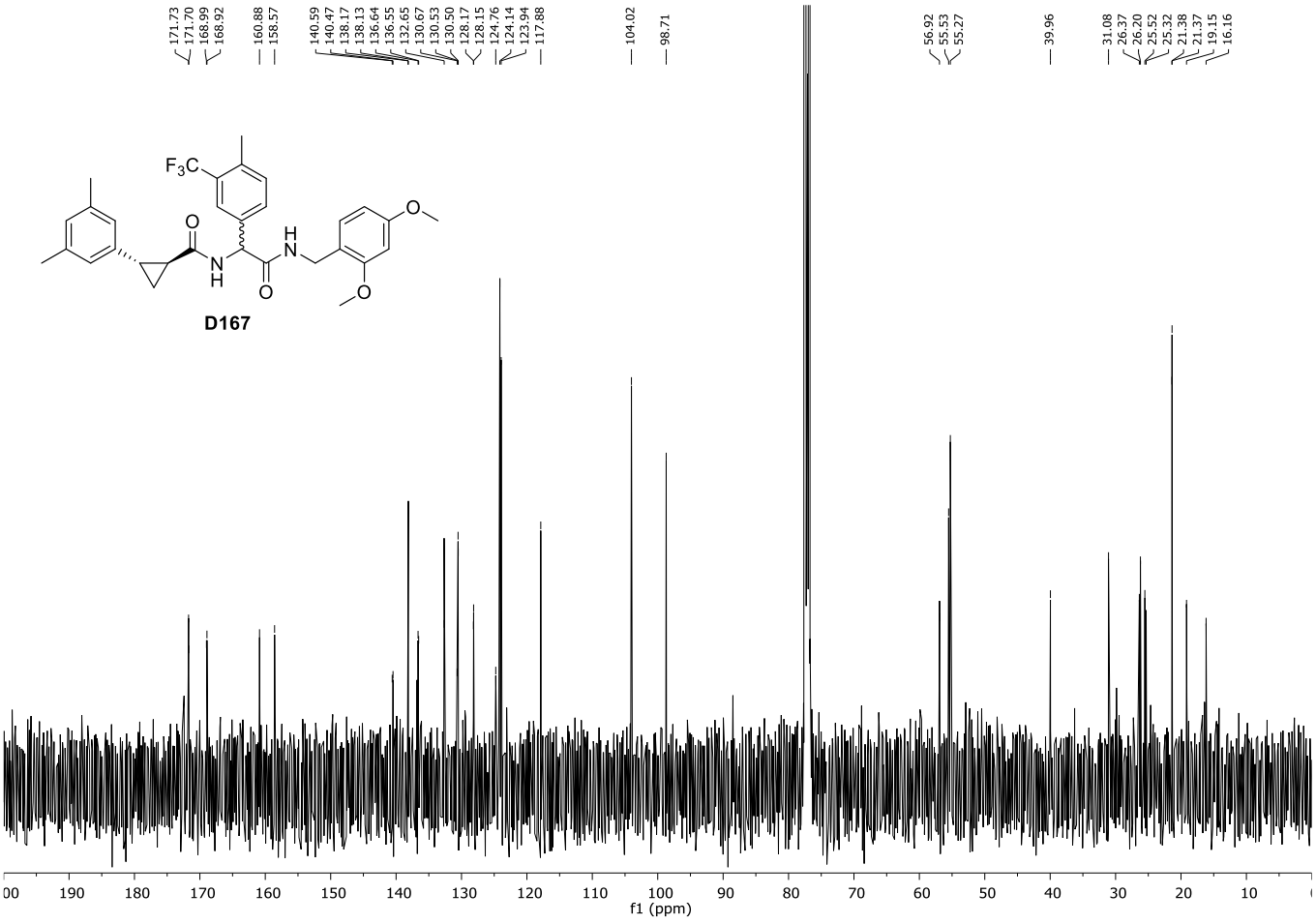

178.73
164.32
161.88
141.92
141.84
140.68
140.60
123.06
123.03
114.53
114.32
110.35
110.13
26.81
26.79
23.97
21.46
21.45
17.61
F
O
OH
S15
f1 (ppm)

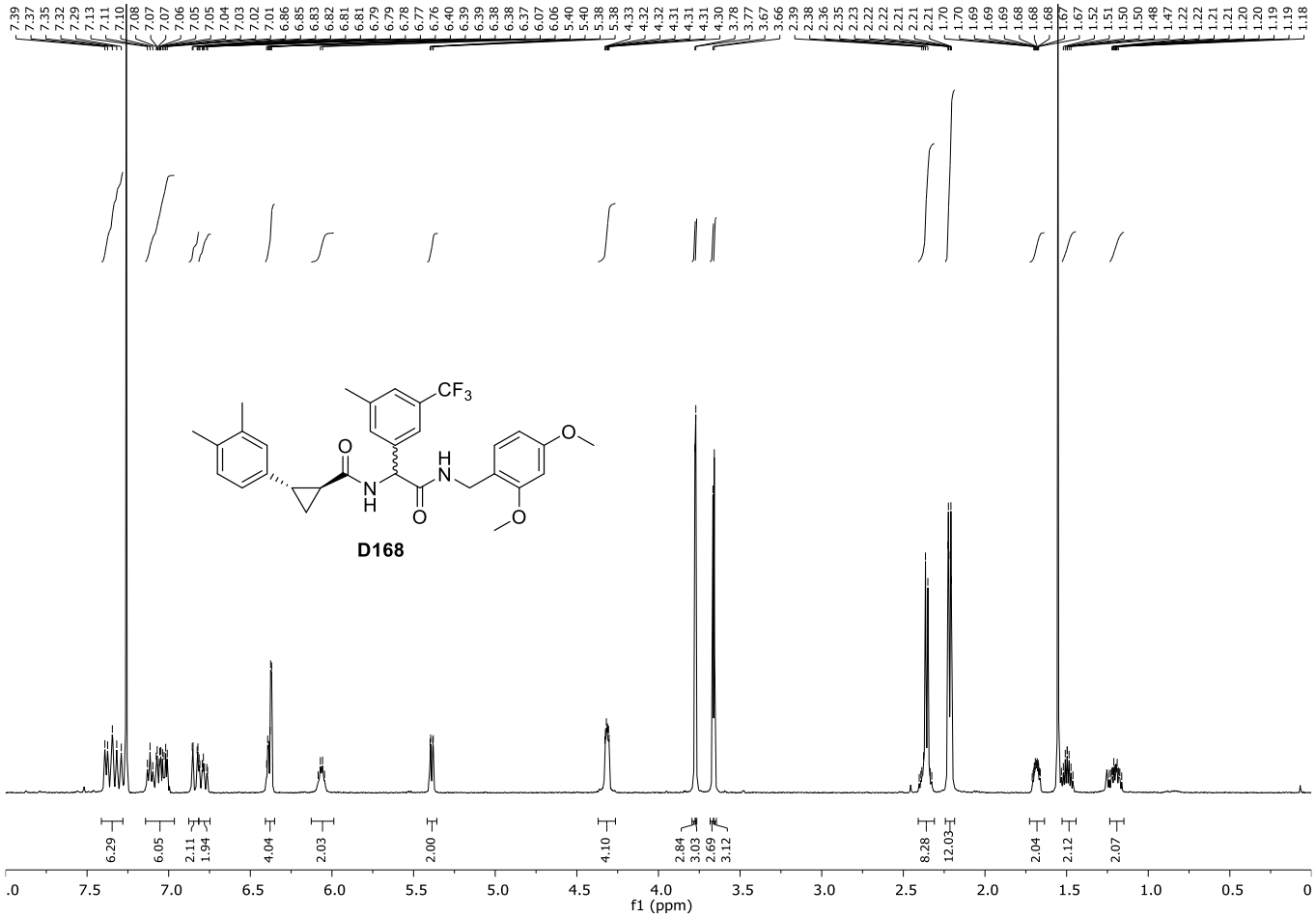

O
H
N
N
H
O
O
O
D165
9.97
2.01
1.99
2.04
4.03
1.95
2.00
4.07
3.04
3.01
2.97
2.89
2.14
5.99
6.10
2.97
5.88
3.09
2.08
2.07
2.11
f1 (ppm)

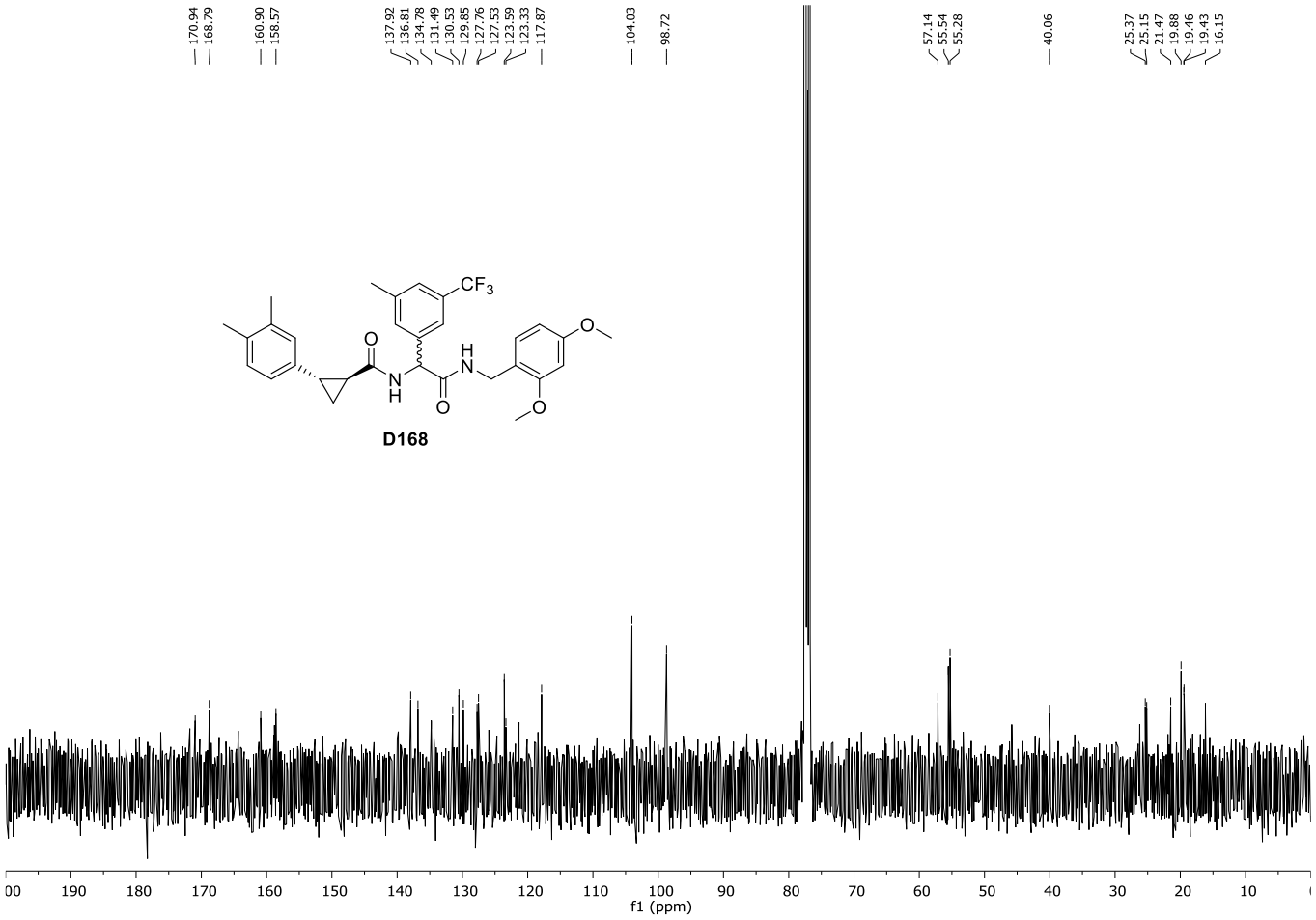

171.48
171.45
169.94
169.84
160.72
158.58
140.87
140.69
138.10
138.06
137.34
136.77
136.18
136.06
130.42
130.39
130.28
128.63
128.59
128.07
128.02
124.95
124.17
123.94
118.27
103.92
98.66
57.27
55.53
55.26
39.78
39.74
26.47
26.31
25.35
25.08
21.38
19.95
19.93
19.61
16.48
16.05
O
N
H
O
H
N
O
O
D165
f1 (ppm)

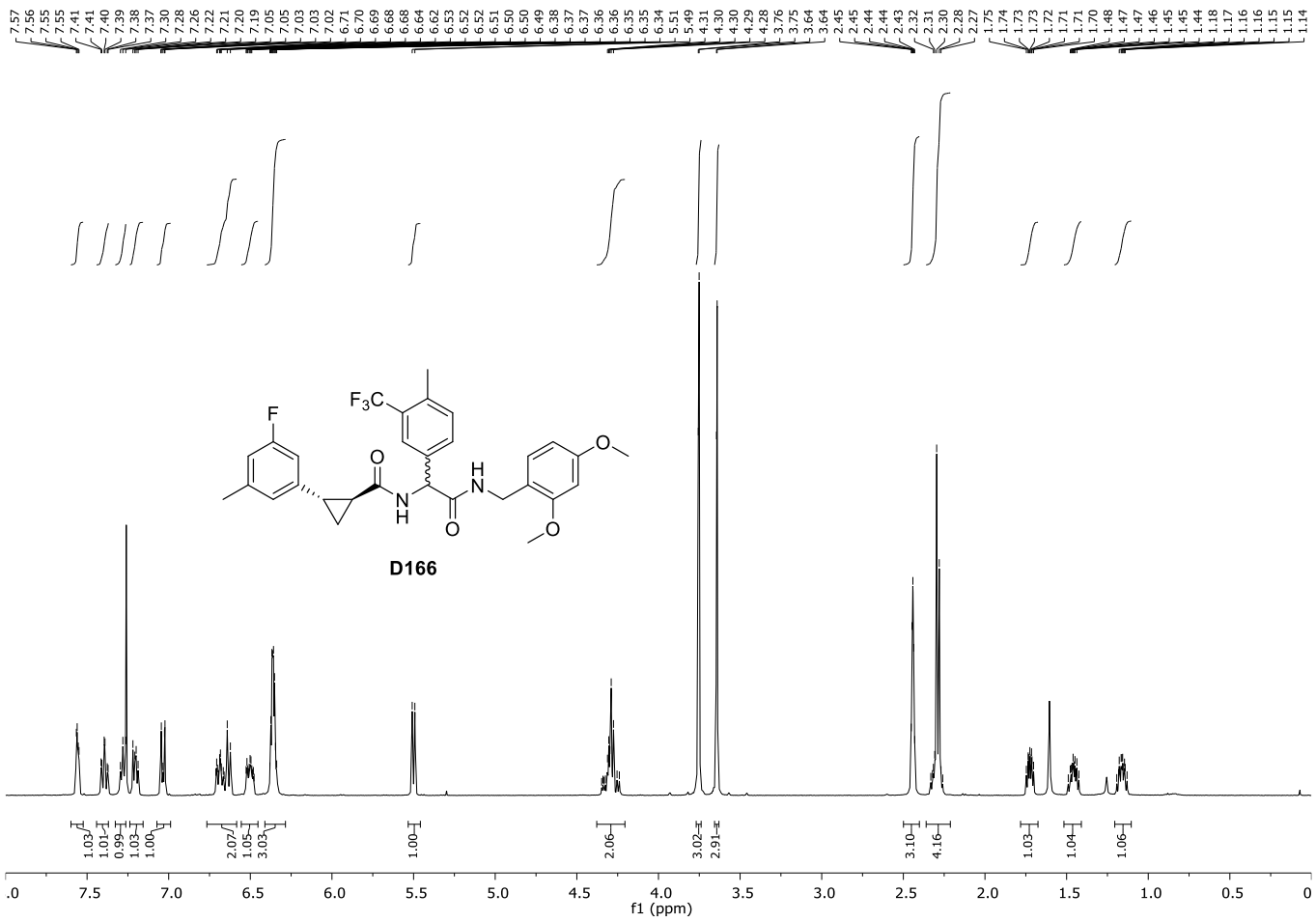

7.08
7.07
7.06
7.06
7.05
7.04
7.03
6.93
6.92
6.90
6.82
6.81
6.69
6.65
6.39
6.39
6.38
6.37
6.05
6.03
6.02
5.32
5.31
4.37
4.36
4.35
4.35
4.33
4.32
4.32
4.31
4.30
4.29
4.28
4.27
4.26
4.26
3.78
3.78
3.67
3.66
2.39
2.38
2.38
2.37
2.36
2.35
2.35
2.34
2.33
2.27
2.26
1.71
1.70
1.69
1.68
1.67
1.53
1.52
1.52
1.51
1.50
1.50
1.49
1.49
1.20
1.20
1.19
1.19
1.18
1.17
1.16
O
N
H
O
H
N
O
O
D159
2.15
2.94
1.01
2.02
1.98
0.95
1.00
2.03
3.09
3.03
1.08
12.10
1.06
1.19
1.34
f1 (ppm)

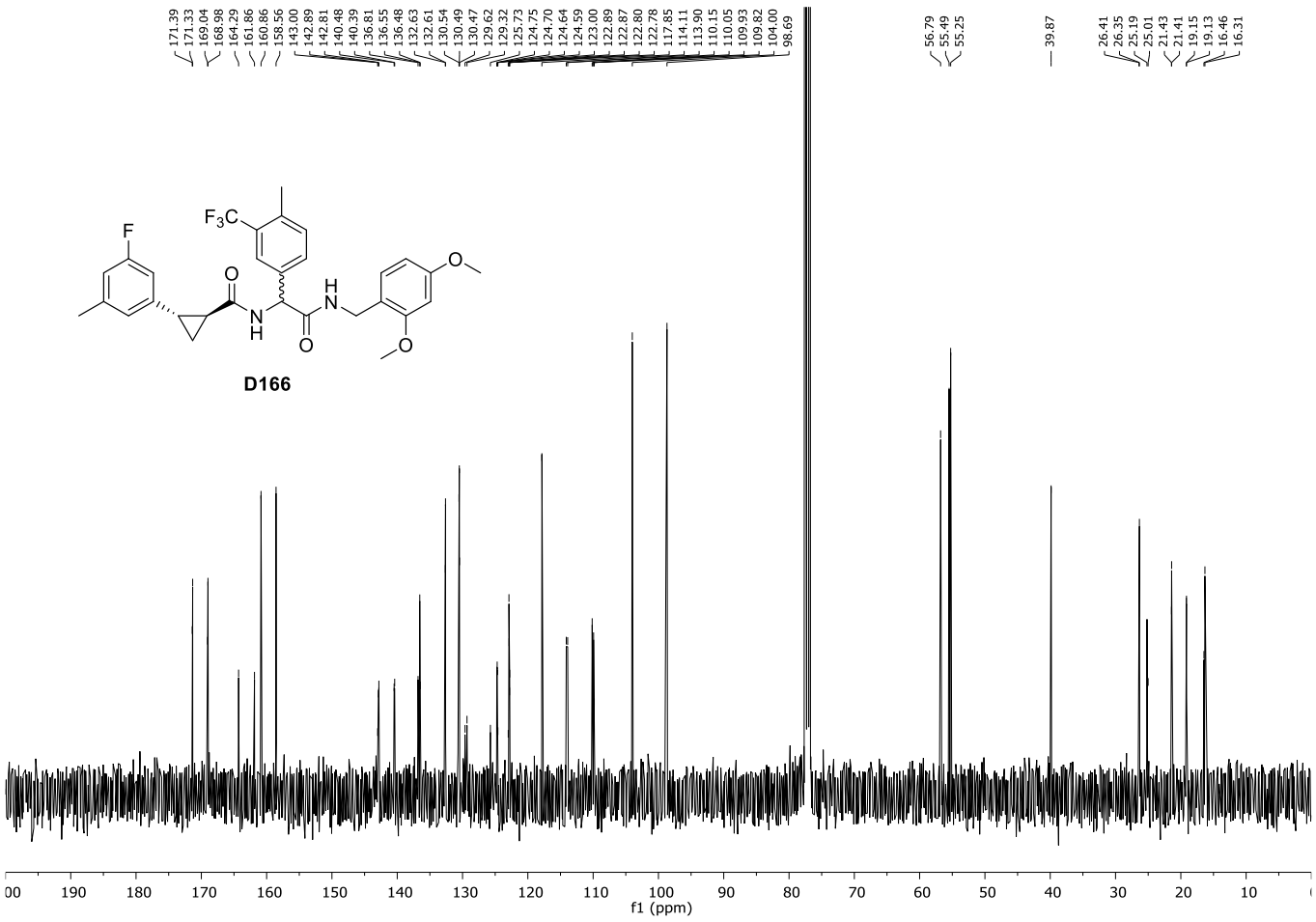

F3C
O
N
H
H
N
O
O
O
D167
f1 (ppm)

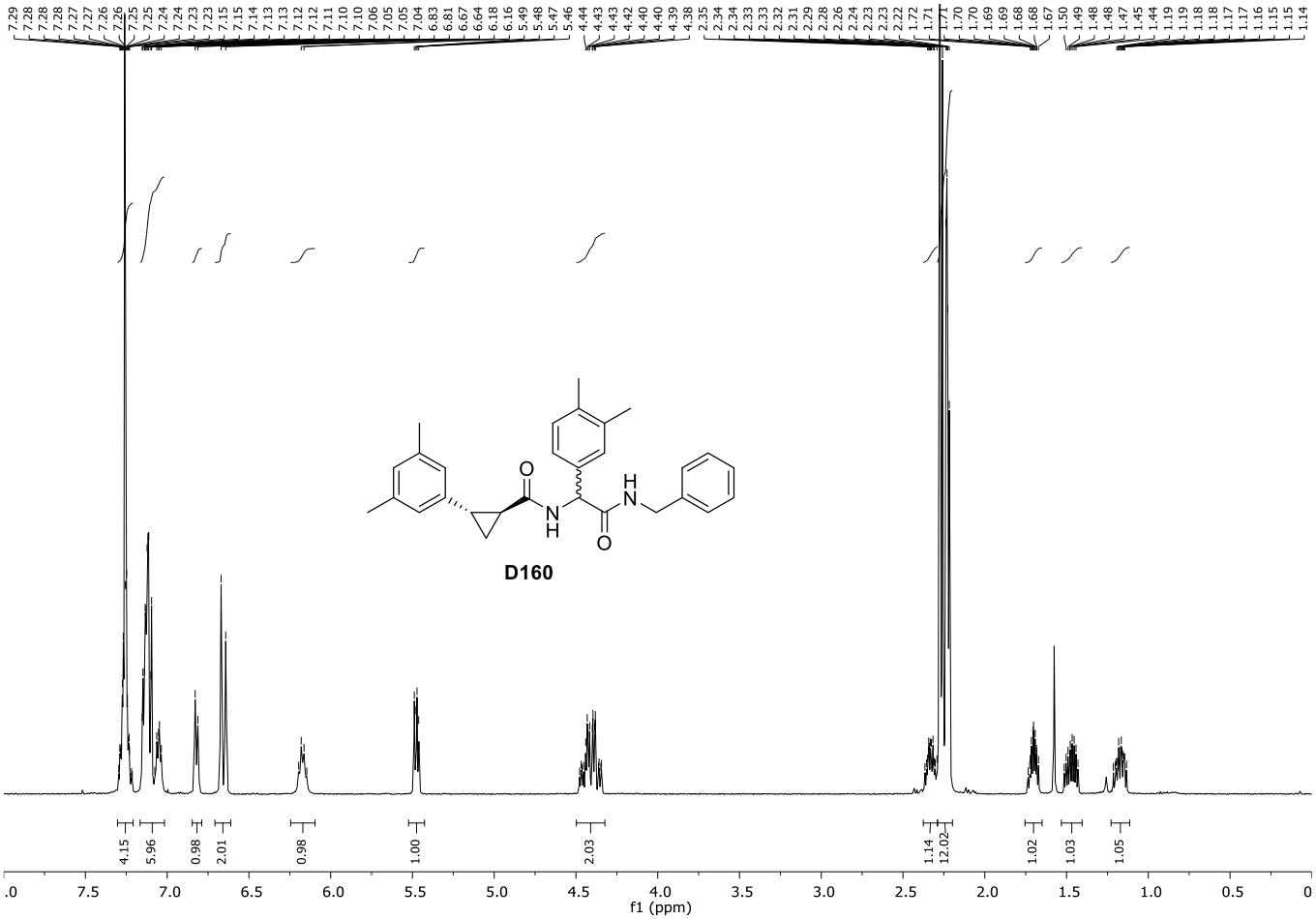

F3C
O
N
H
H
N
O
O
O
D167
f1 (ppm)

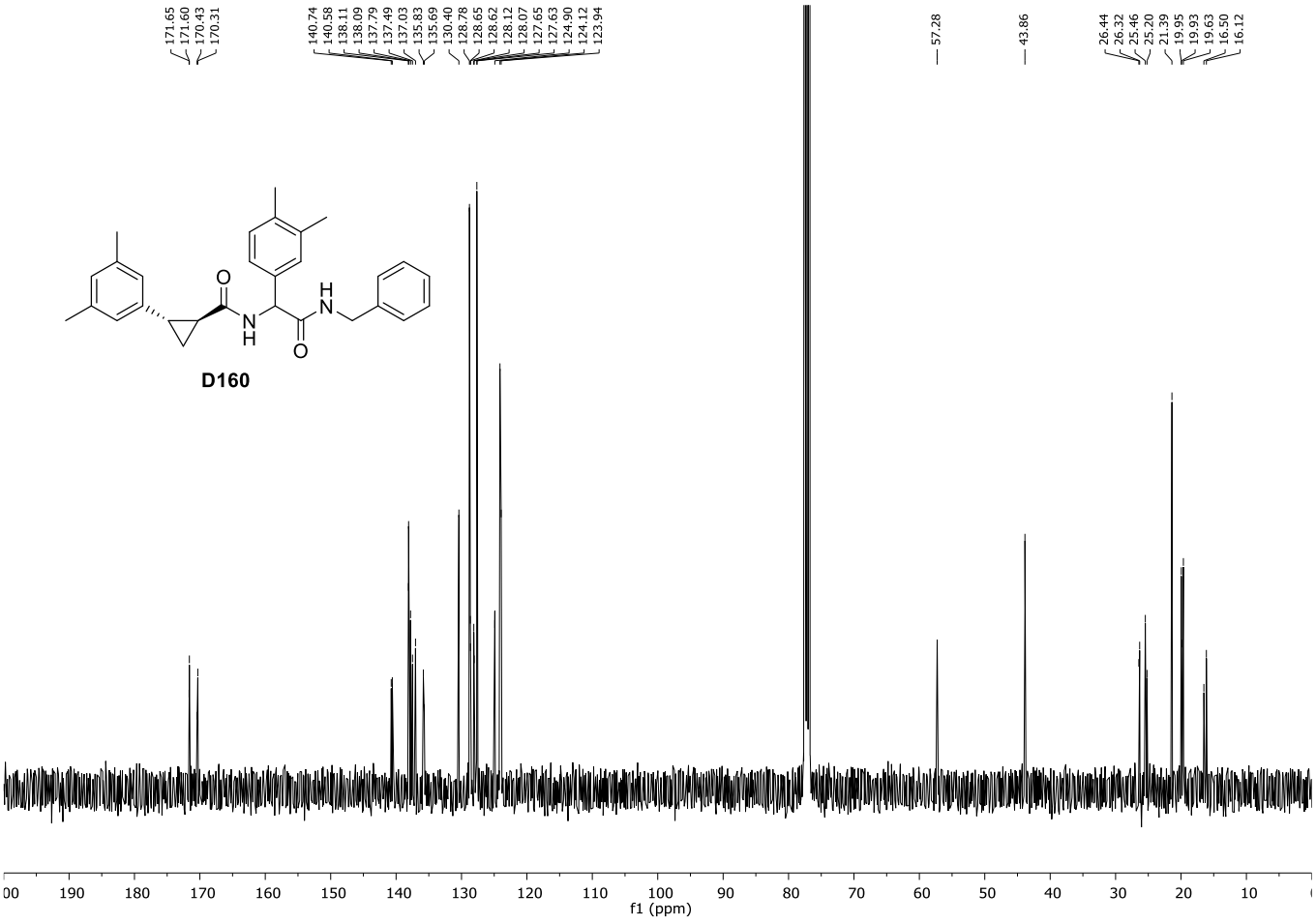

CF3
O
N
H
H
N
O
O
O
D168
6.29
6.05
2.11
1.94
4.04
2.03
2.00
4.10
2.84
3.03
2.69
3.12
8.28
12.03
2.04
2.12
2.07
f1 (ppm)

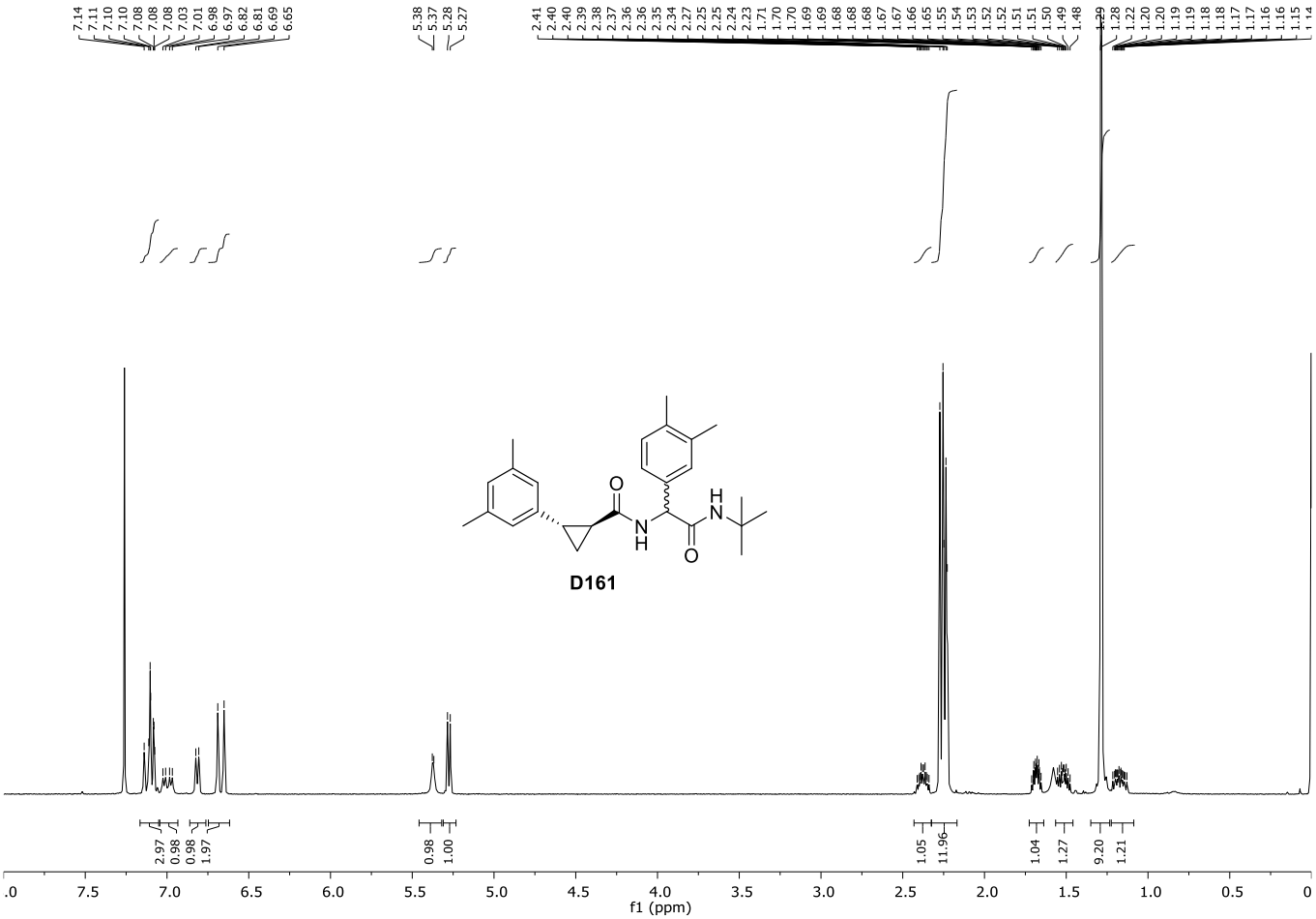

170.94
168.79
160.90
158.57
137.92
136.81
134.78
131.49
130.53
129.85
127.76
127.53
123.59
123.33
117.87
104.03
98.72
57.14
55.54
55.28
40.06
25.37
25.15
21.47
19.88
19.46
19.43
16.15
CF3
O
N
H
H
N
O
O
O
D168
f1 (ppm)

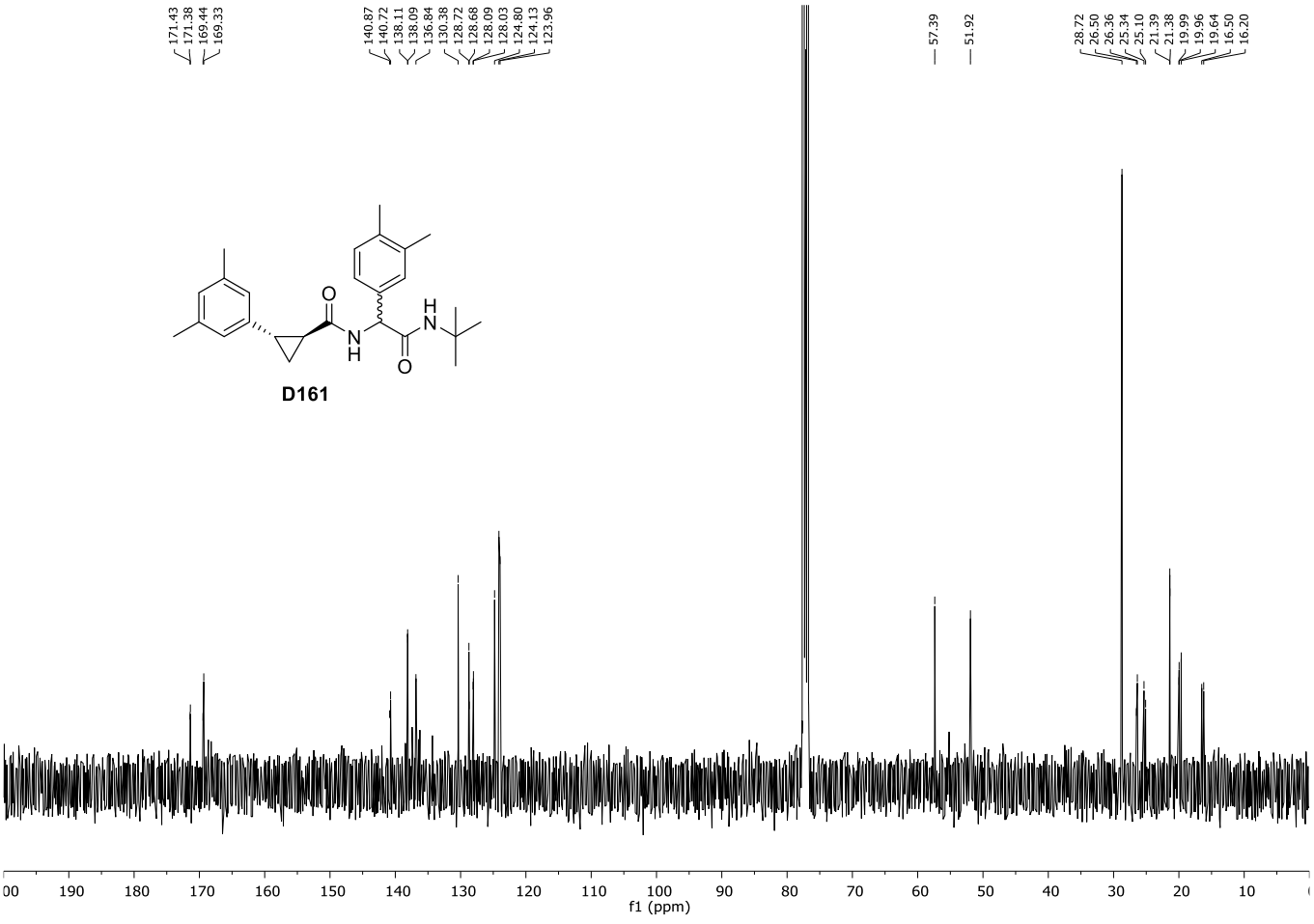

F3C
F
O
N
H
O
H
N
O
O
D166
f1 (ppm)

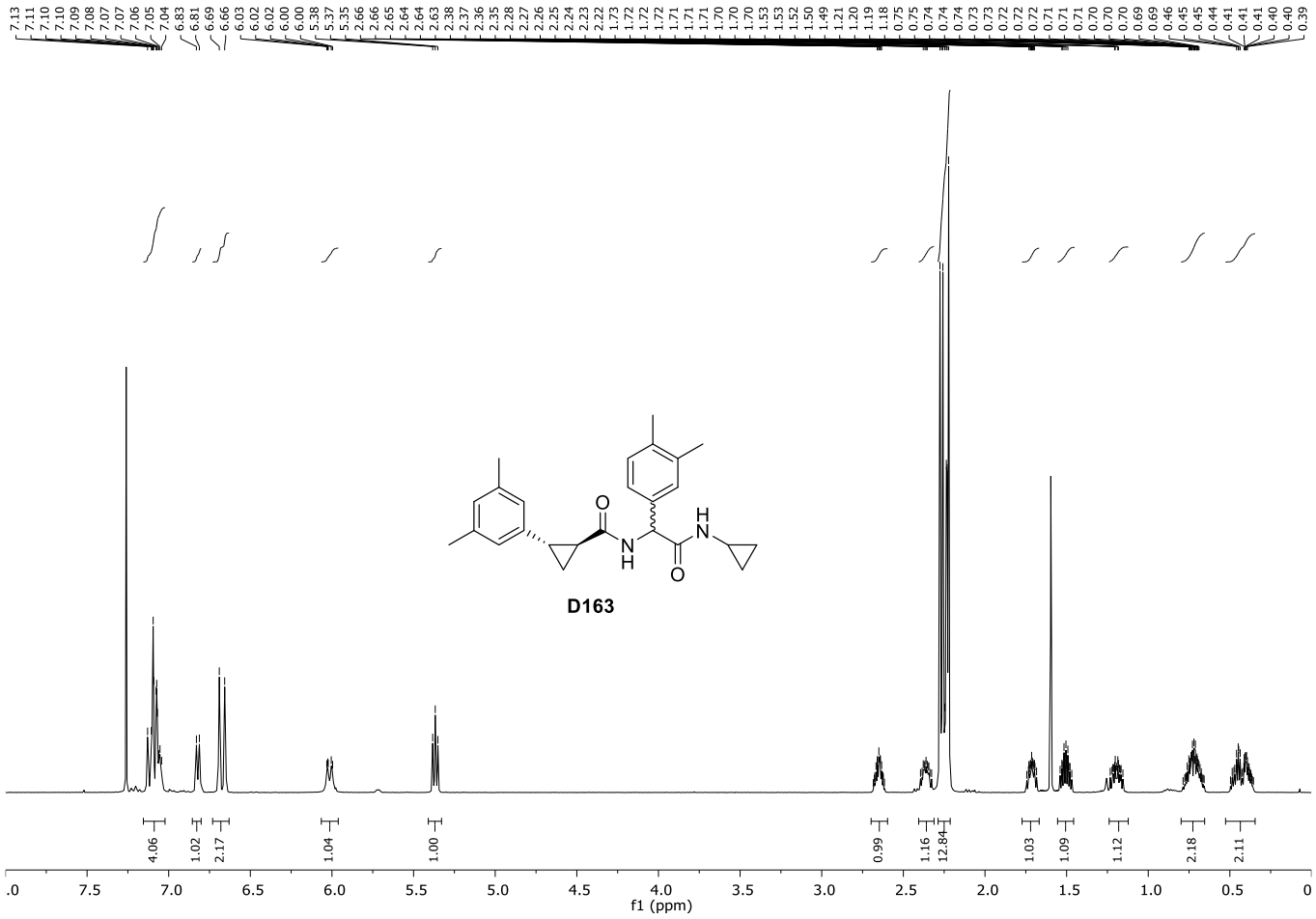

F3C
F
O
N
H
O
H
N
O
O
D166
f1 (ppm)

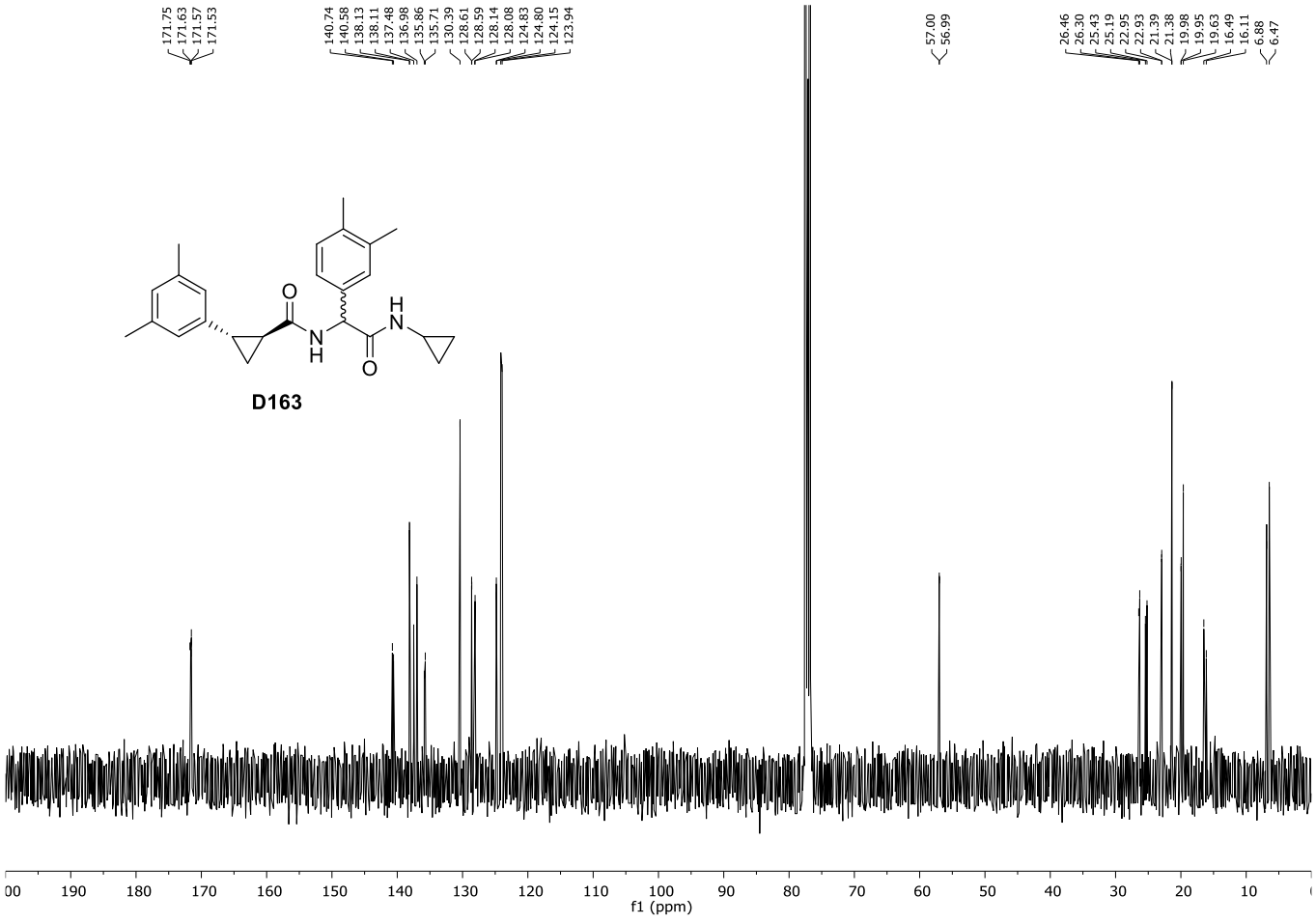

D160
f1 (ppm)

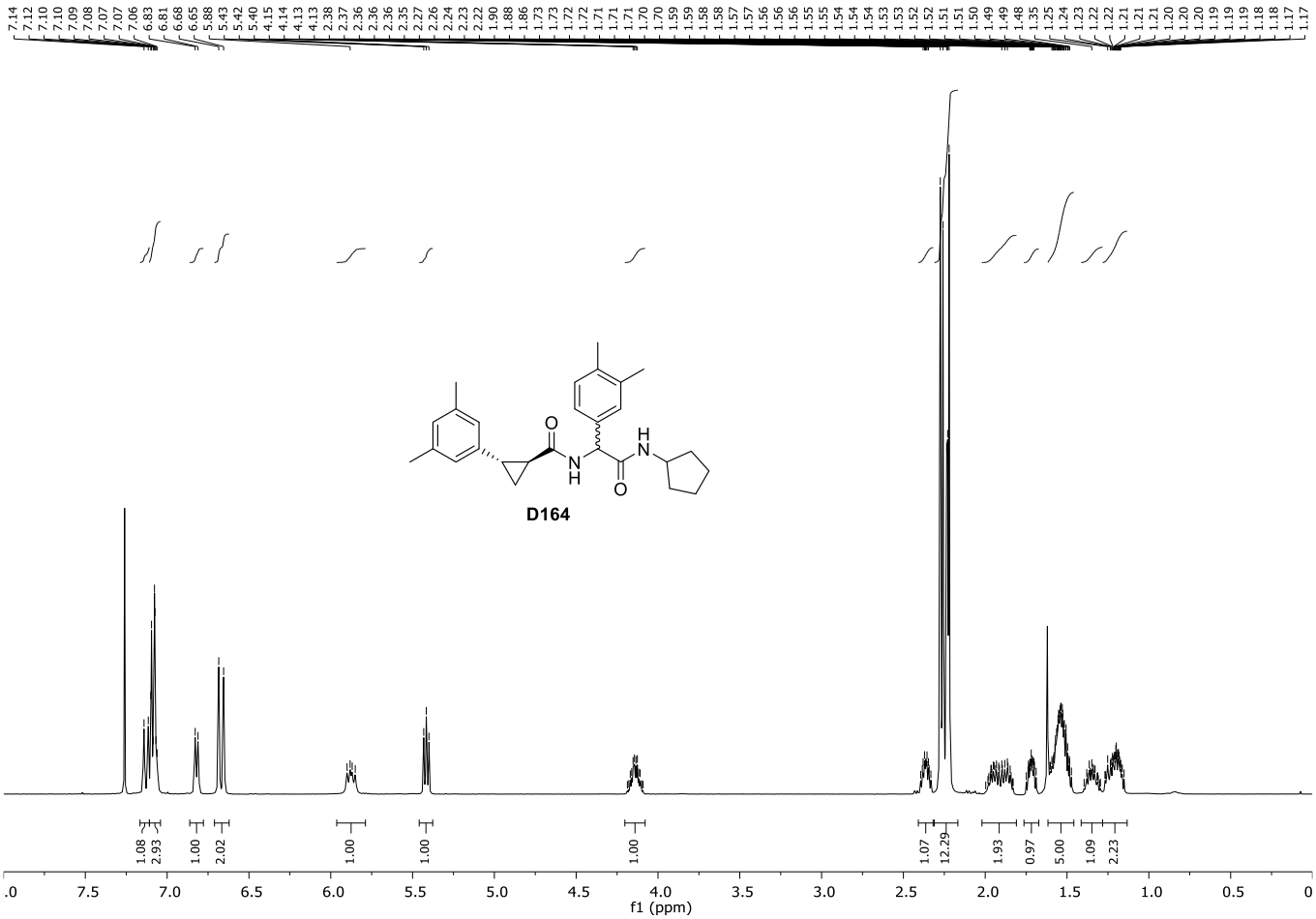

D160
f1 (ppm)

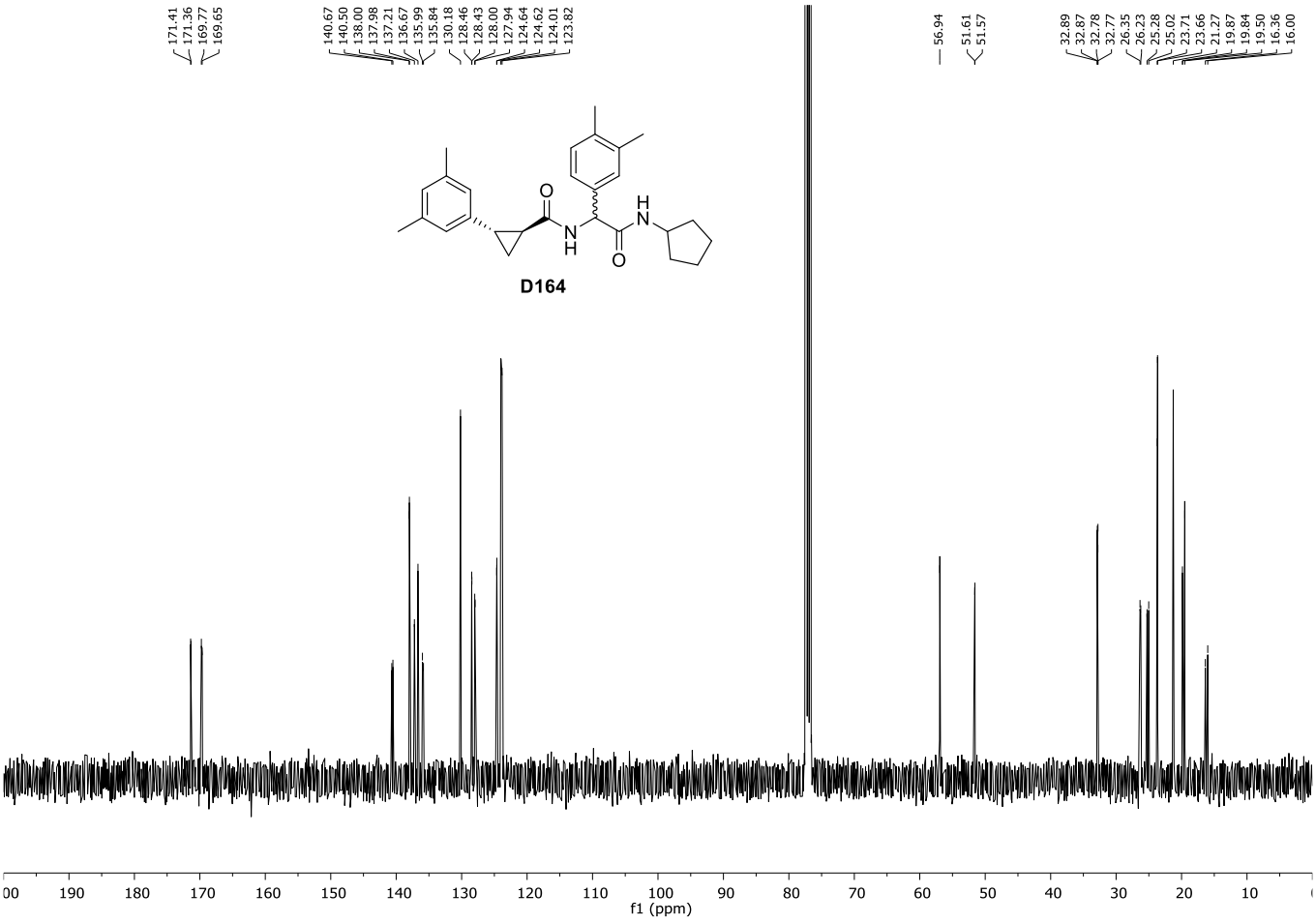

D161
f1 (ppm)

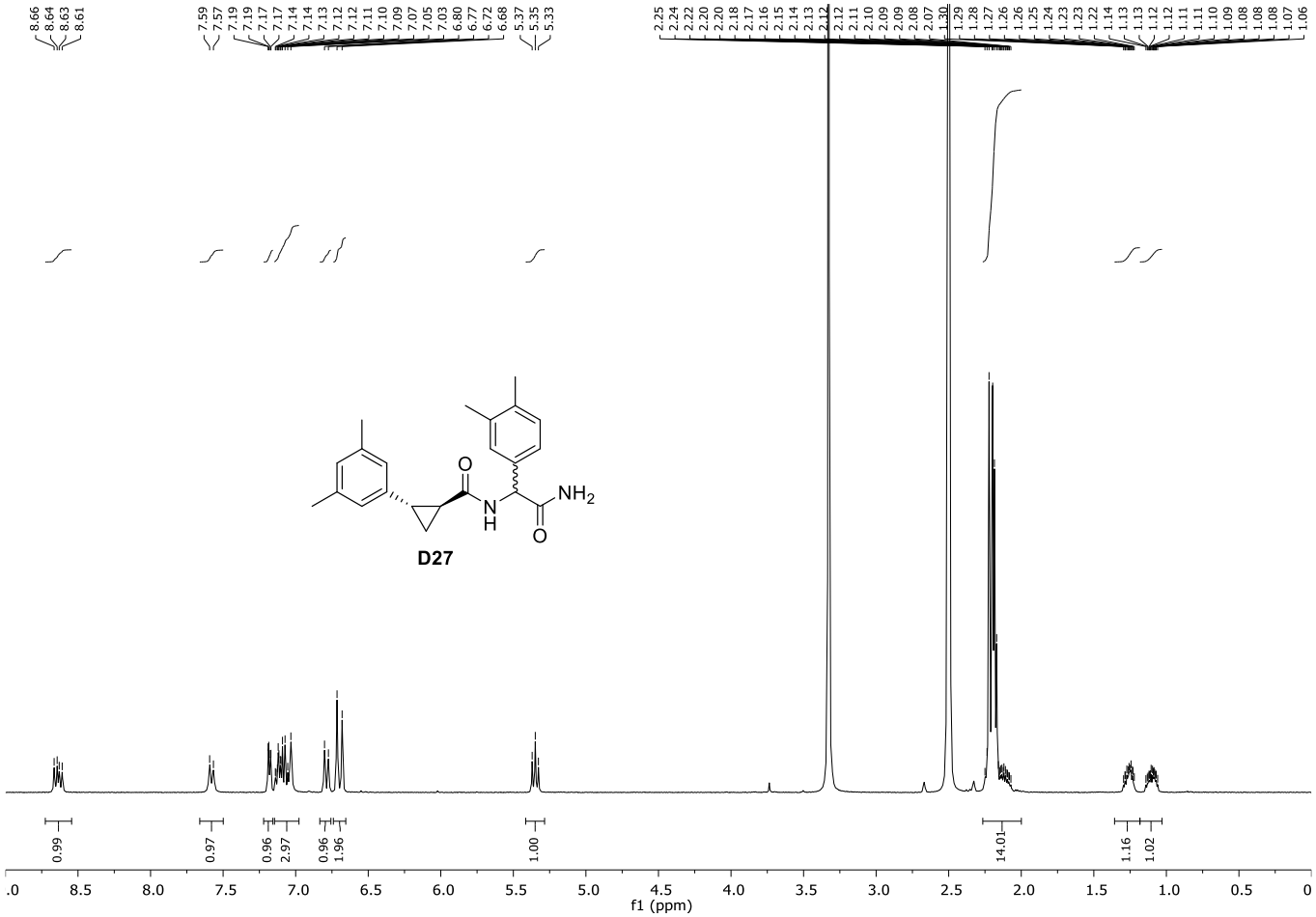

D161
f1 (ppm)

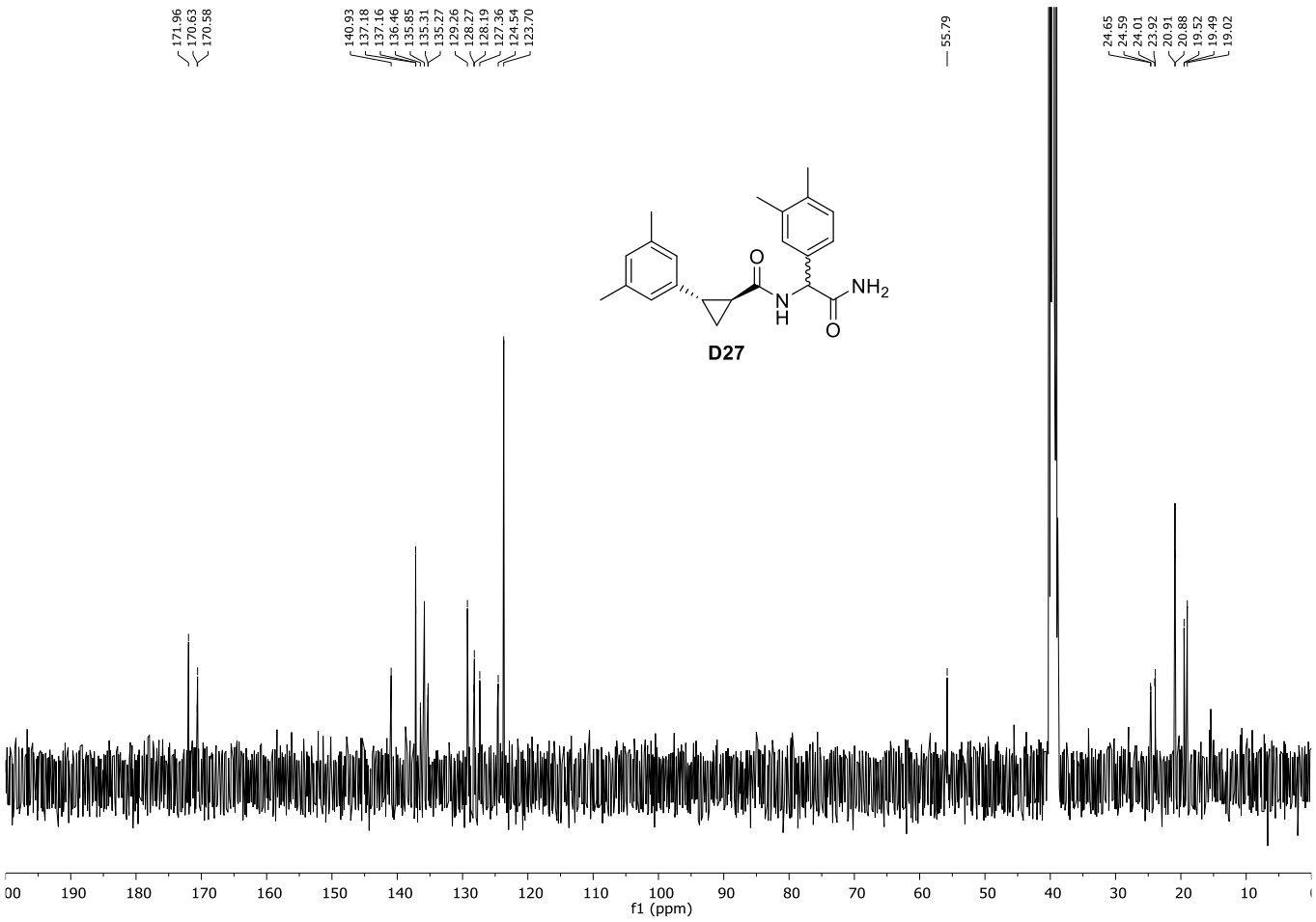

D163
f1 (ppm)

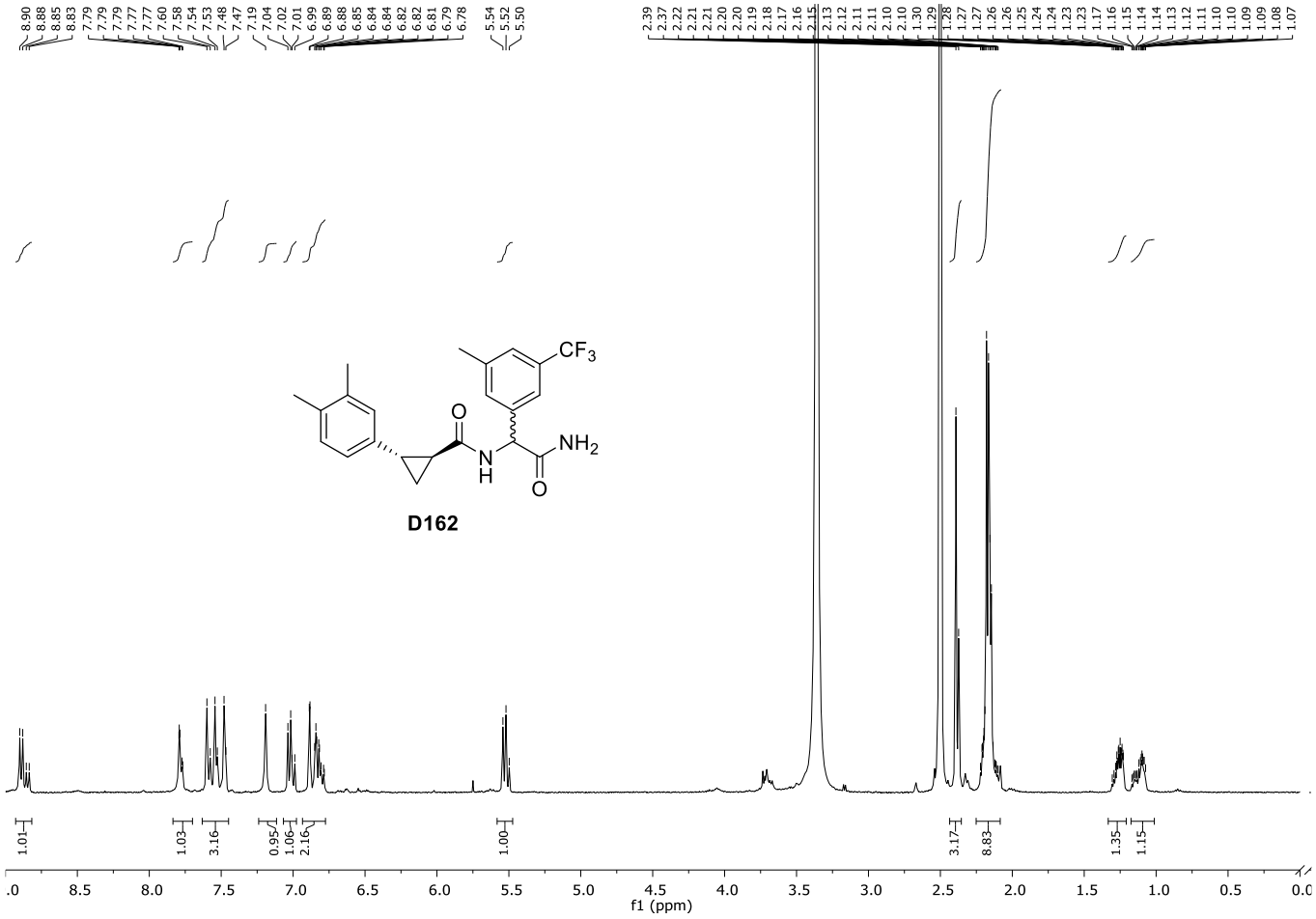

D163
f1 (ppm)

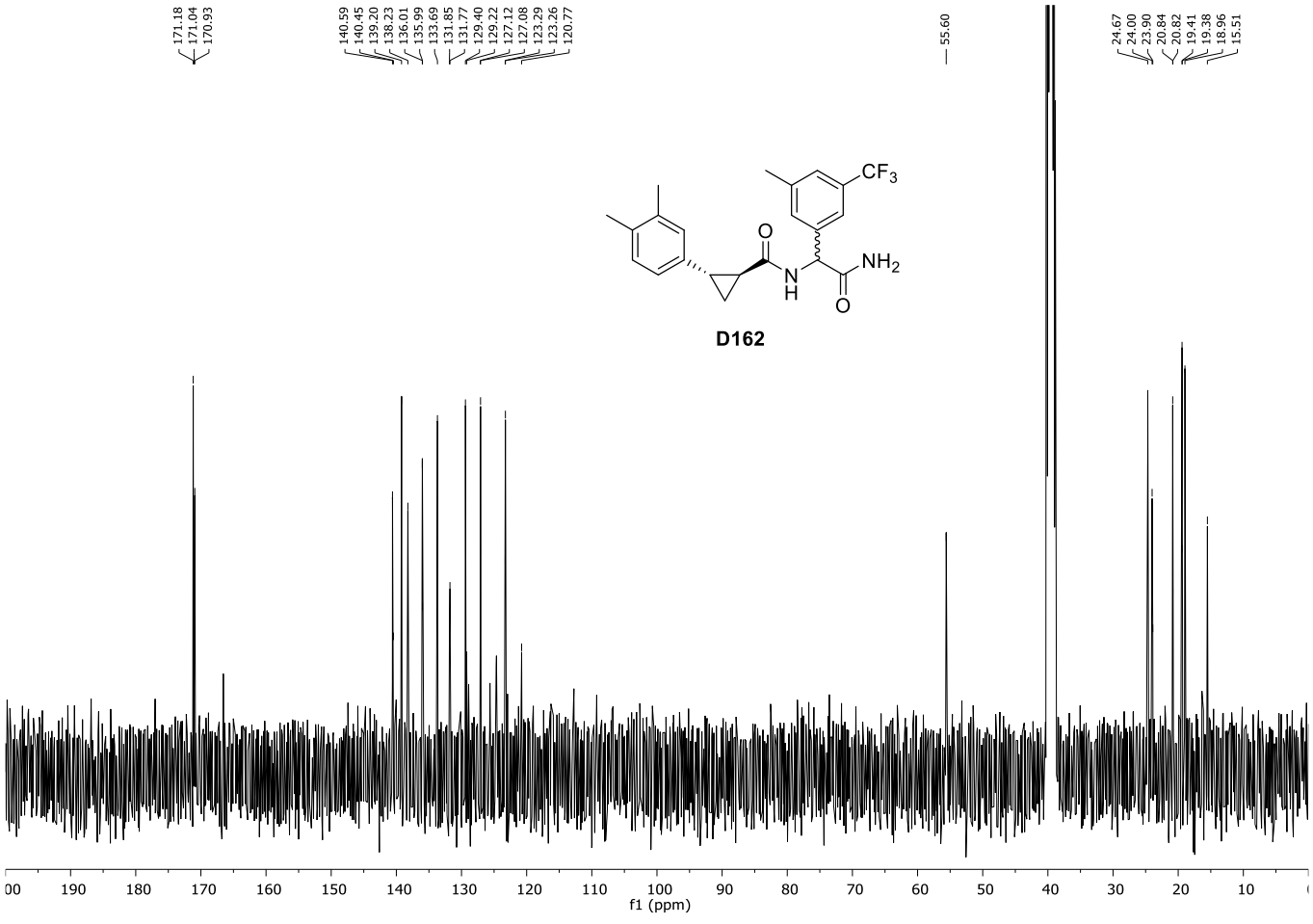

D164
1.08
2.93
1.00
2.02
1.00
1.00
1.00
1.07
12.29
1.93
0.97
5.00
1.09
2.23
f1 (ppm)

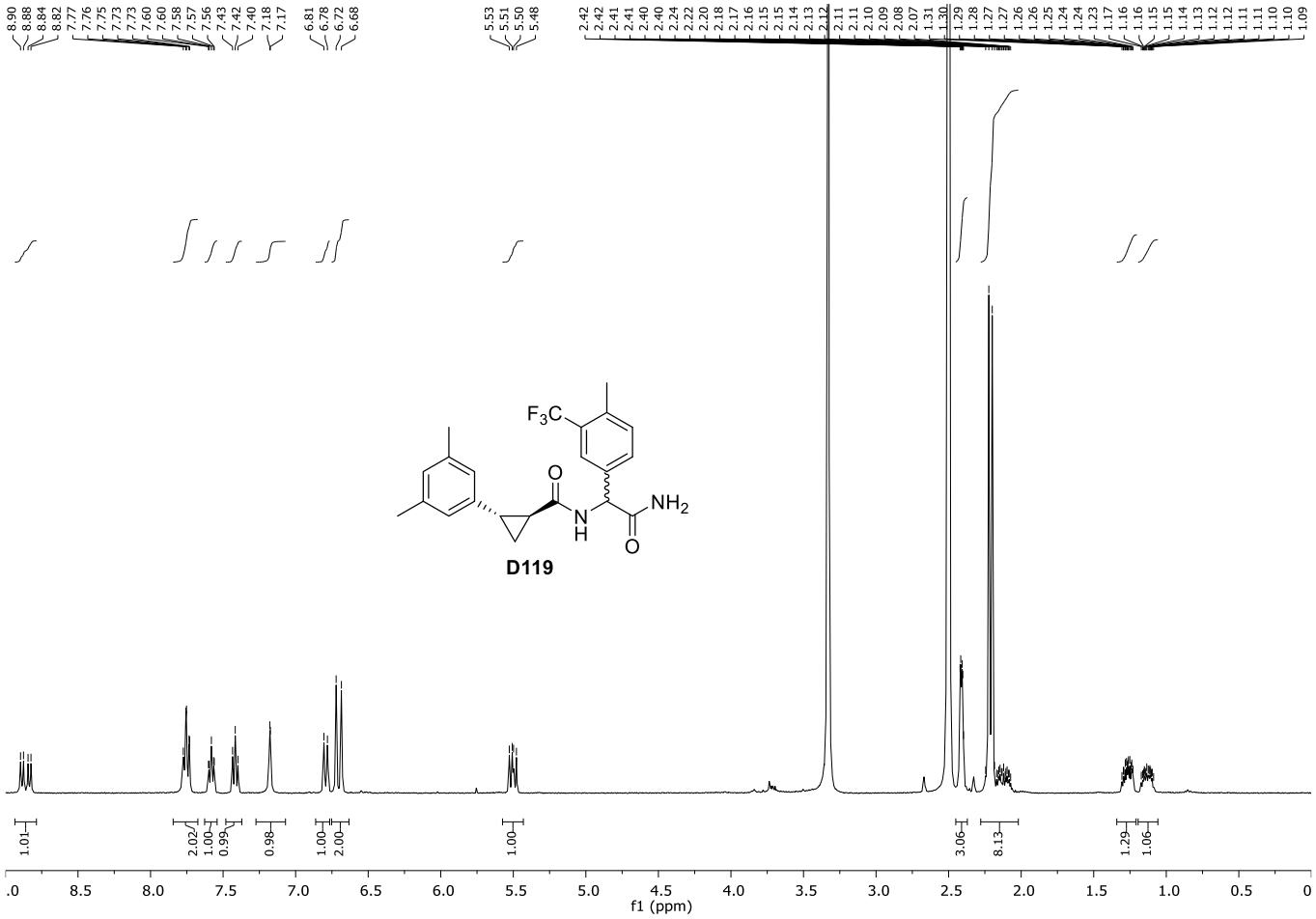

D164
f1 (ppm)

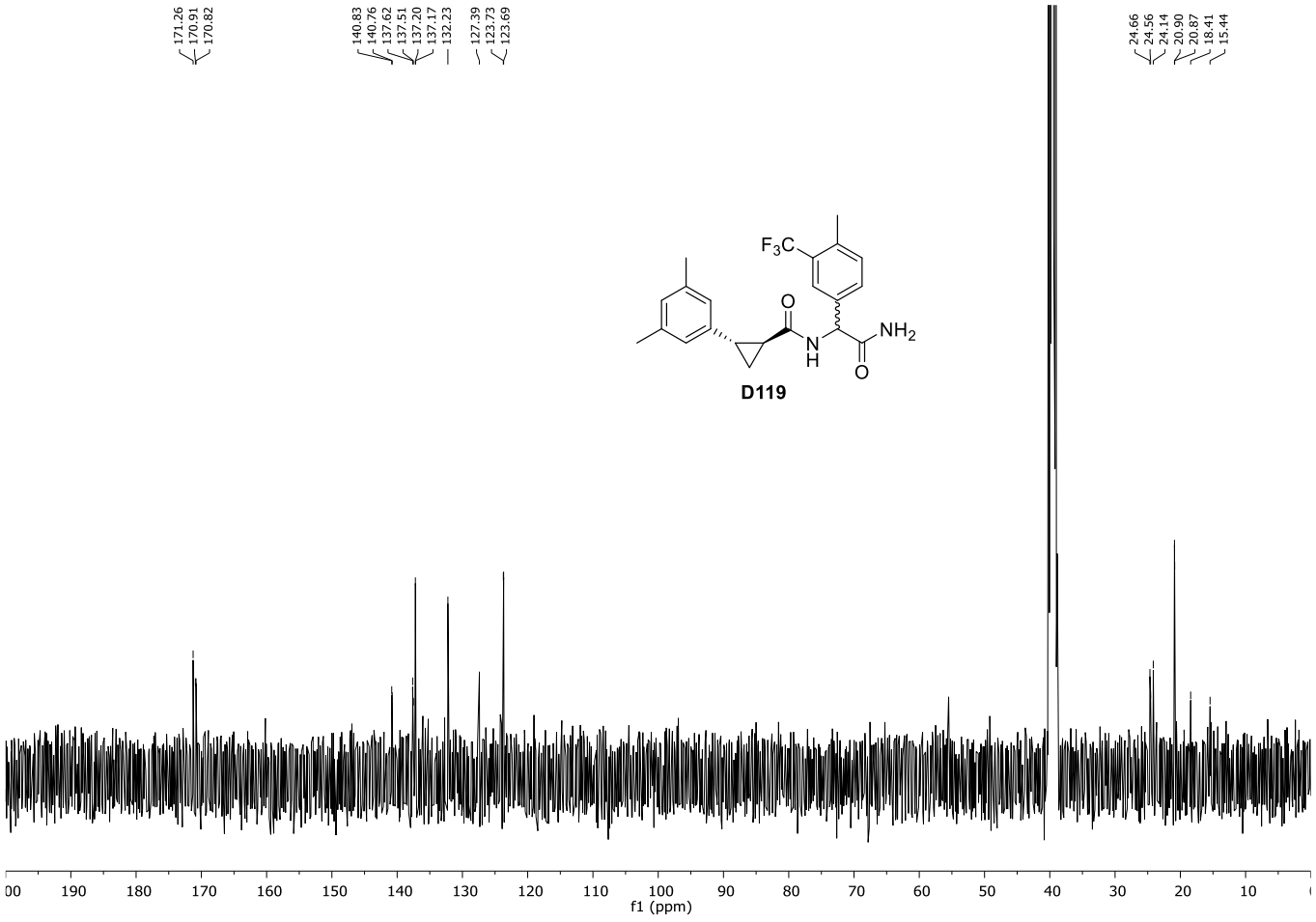

8.66 8.64 8.63 8.61
7.59 7.57 7.19 7.19 7.17 7.17 7.14 7.14 7.13 7.12 7.12 7.11 7.10 7.09 7.07 7.05 7.03 6.80 6.77 6.72 6.68
5.37 5.35 5.33
2.25 2.24 2.22 2.20 2.20 2.18 2.17 2.16 2.15 2.14 2.13 2.12 2.12 2.11 2.10 2.09 2.09 2.08 2.07 1.30 1.29 1.28 1.27 1.26 1.26 1.25 1.24 1.23 1.23 1.22 1.14 1.13 1.13 1.12 1.12 1.11 1.11 1.10 1.09 1.08 1.08 1.08 1.07 1.06
O
N
H
NH2
O
D27
0.99
0.97
0.96
2.97
0.96
1.96
1.00
14.01
1.16
1.02
f1 (ppm)

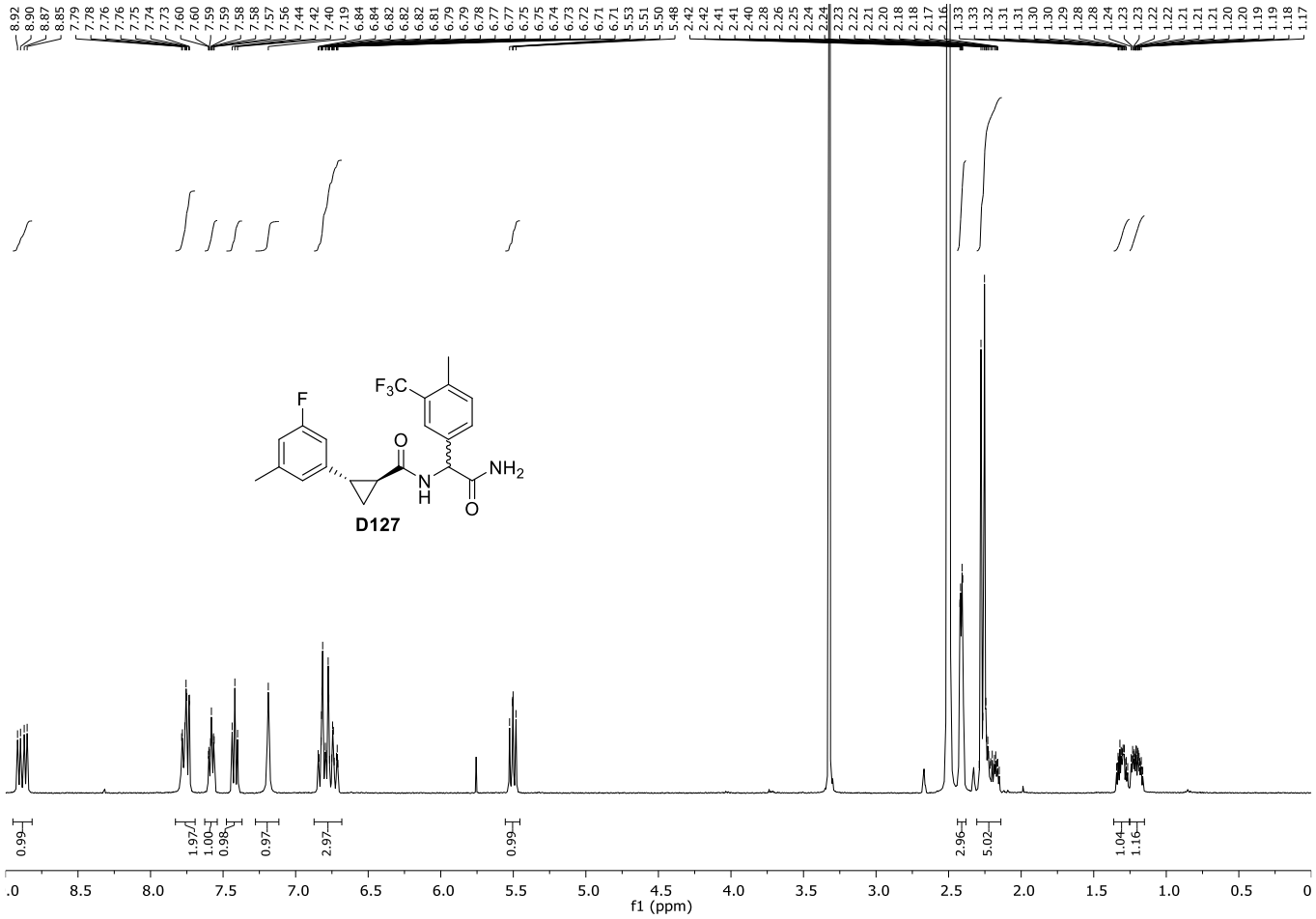

171.96 170.63 170.58
140.93 137.18 137.16 136.46 135.85 135.31 135.27 129.26 128.27 128.19 127.36 124.54 123.70
55.79
24.65 24.59 24.01 23.92 20.91 20.88 19.52 19.49 19.02
O
N
H
NH2
O
D27
f1 (ppm)

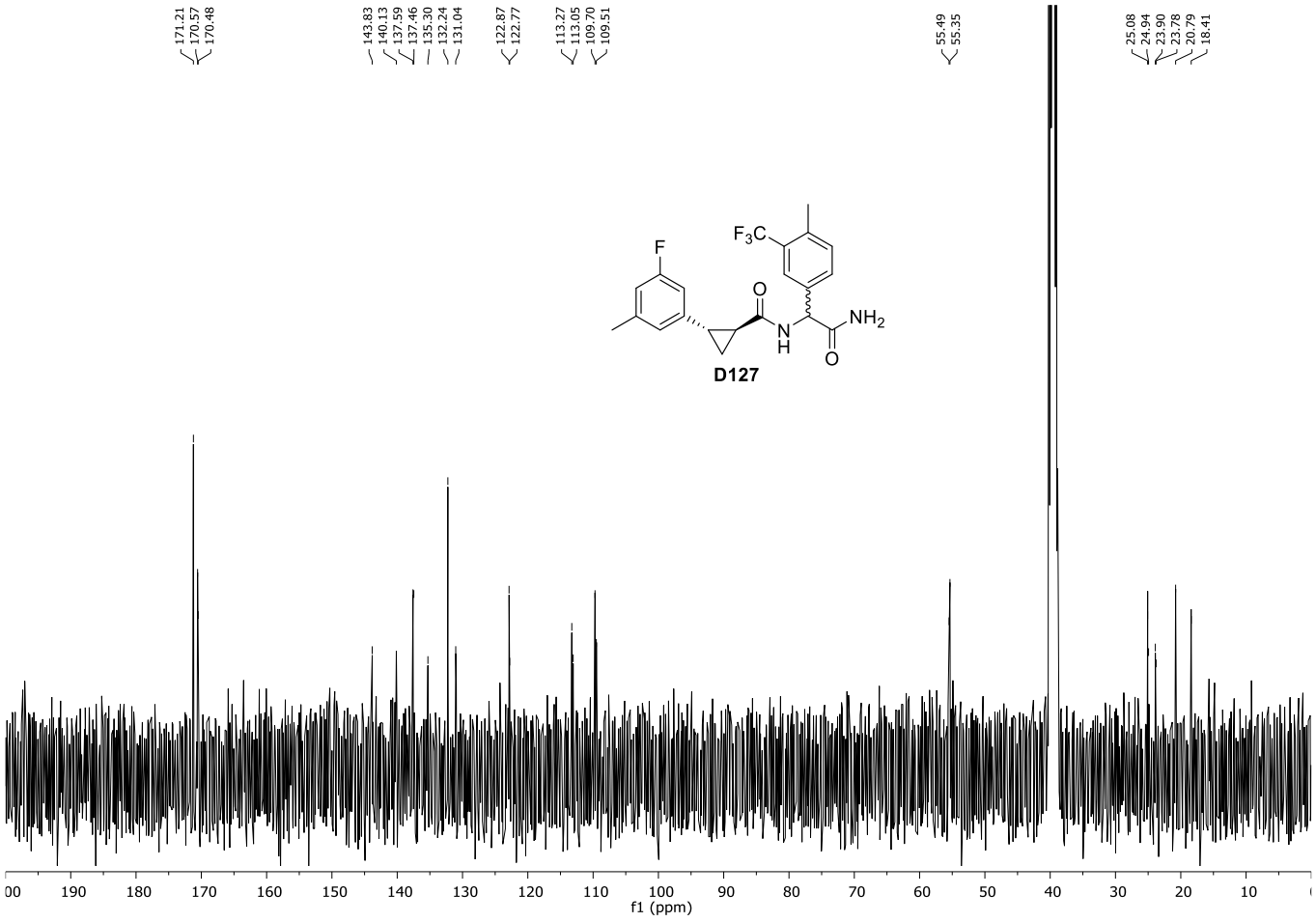

D162
f1 (ppm)

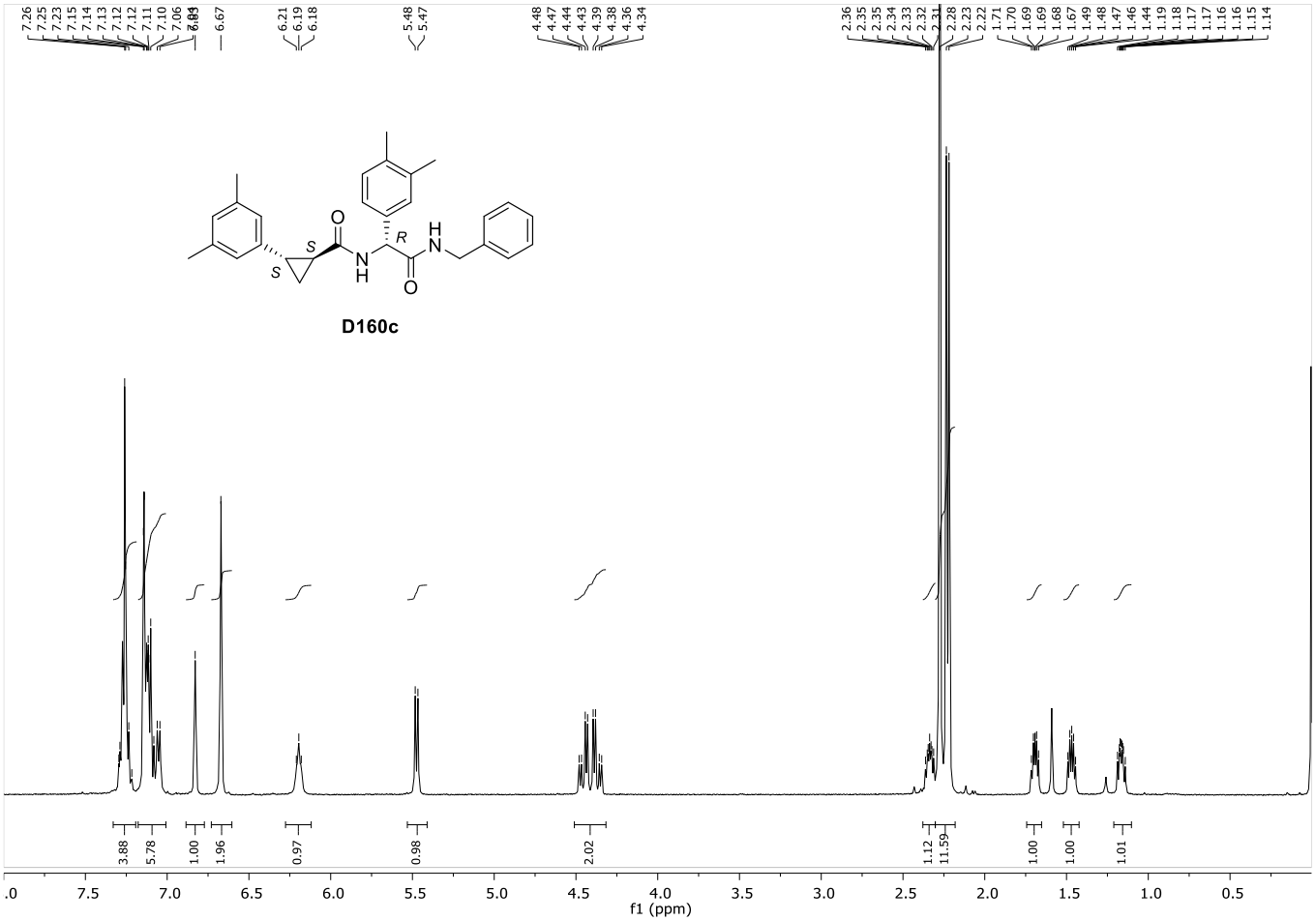

D162
f1 (ppm)


F3C
O
N
H
NH2
O
D119
f1 (ppm)

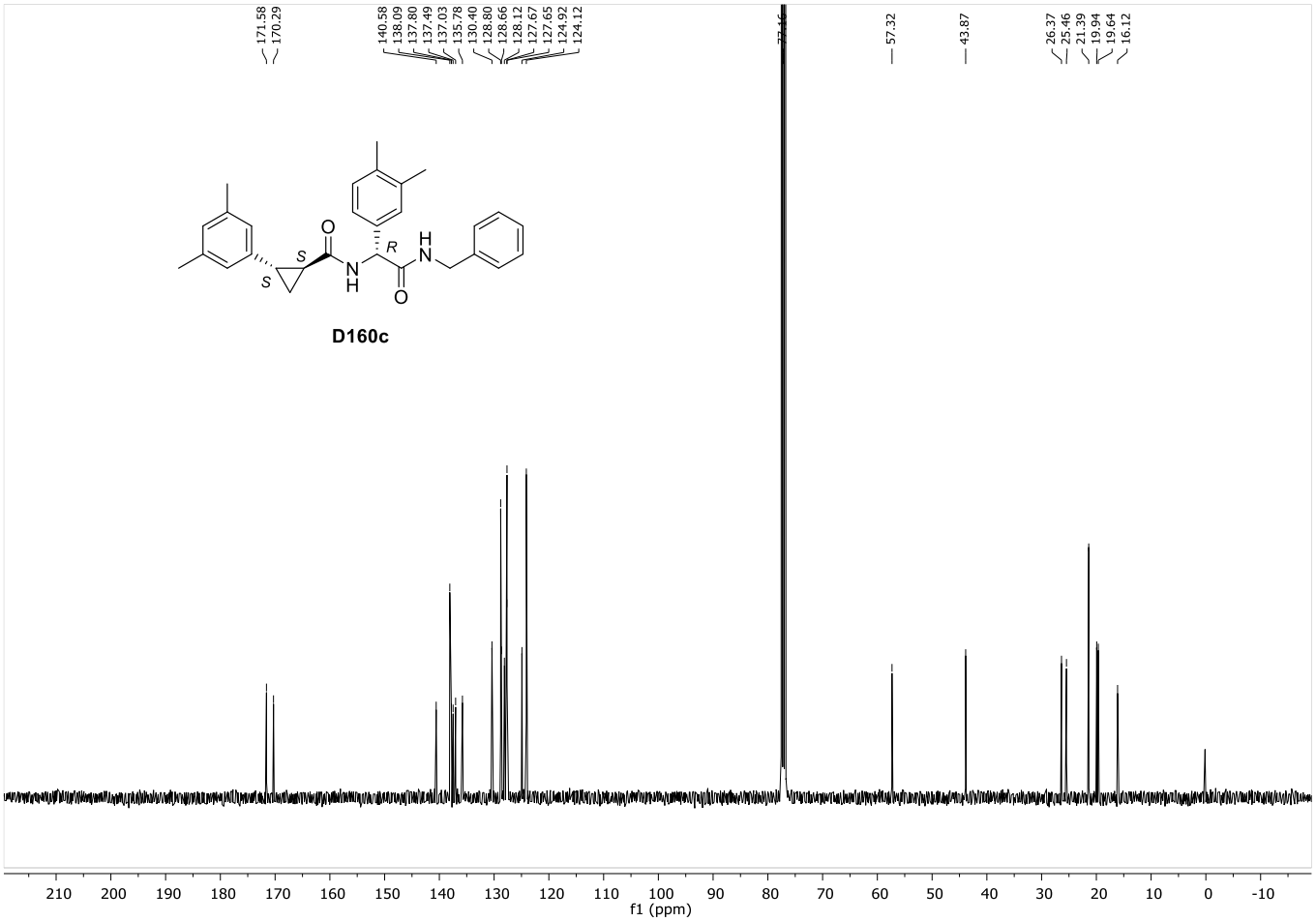

F3C
O
N
H
NH2
O
D119
f1 (ppm)


F
F3C
O
N
H
NH2
O
D127
f1 (ppm)

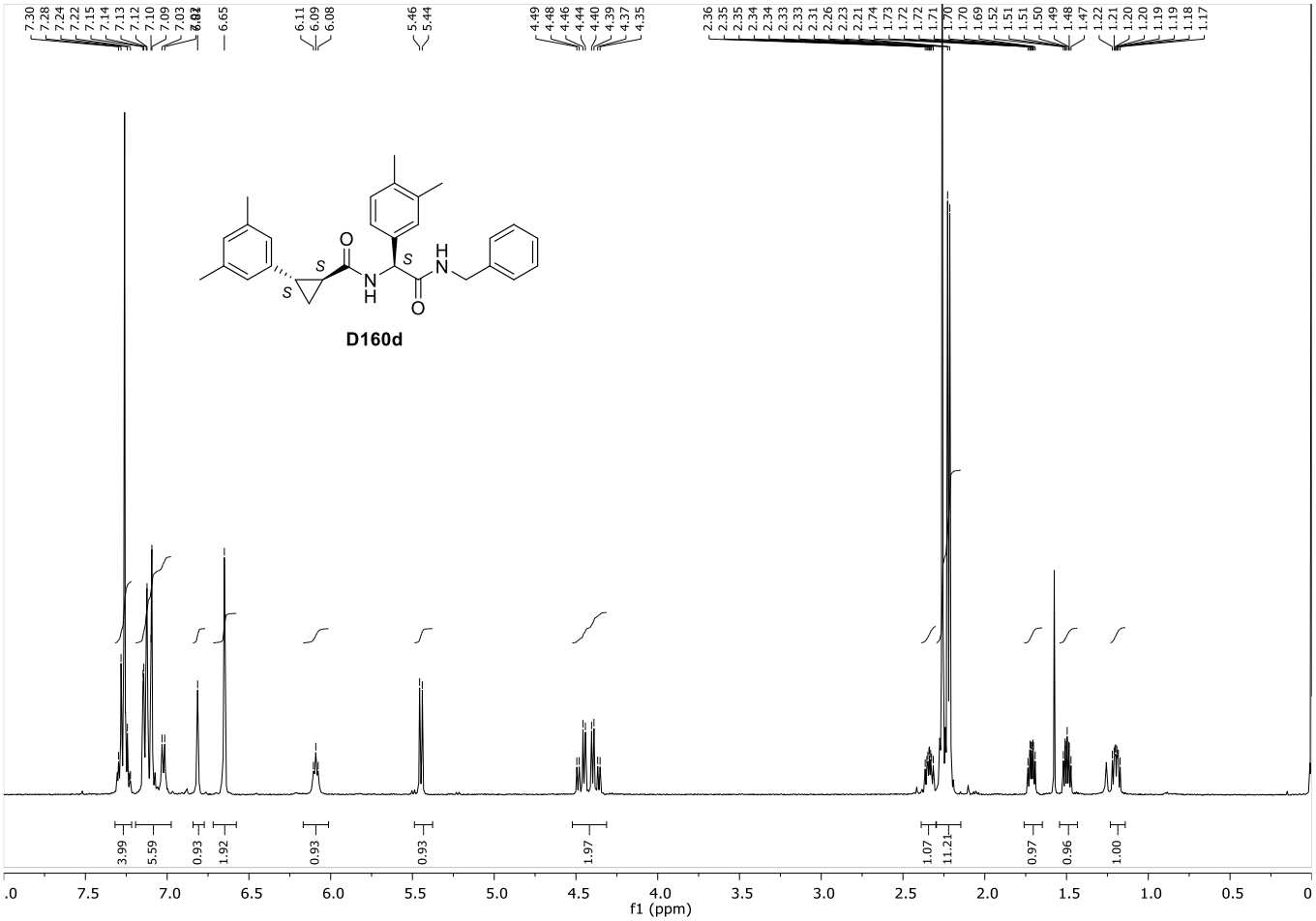

F
F3C
O
N
H
NH2
O
D127
f1 (ppm)

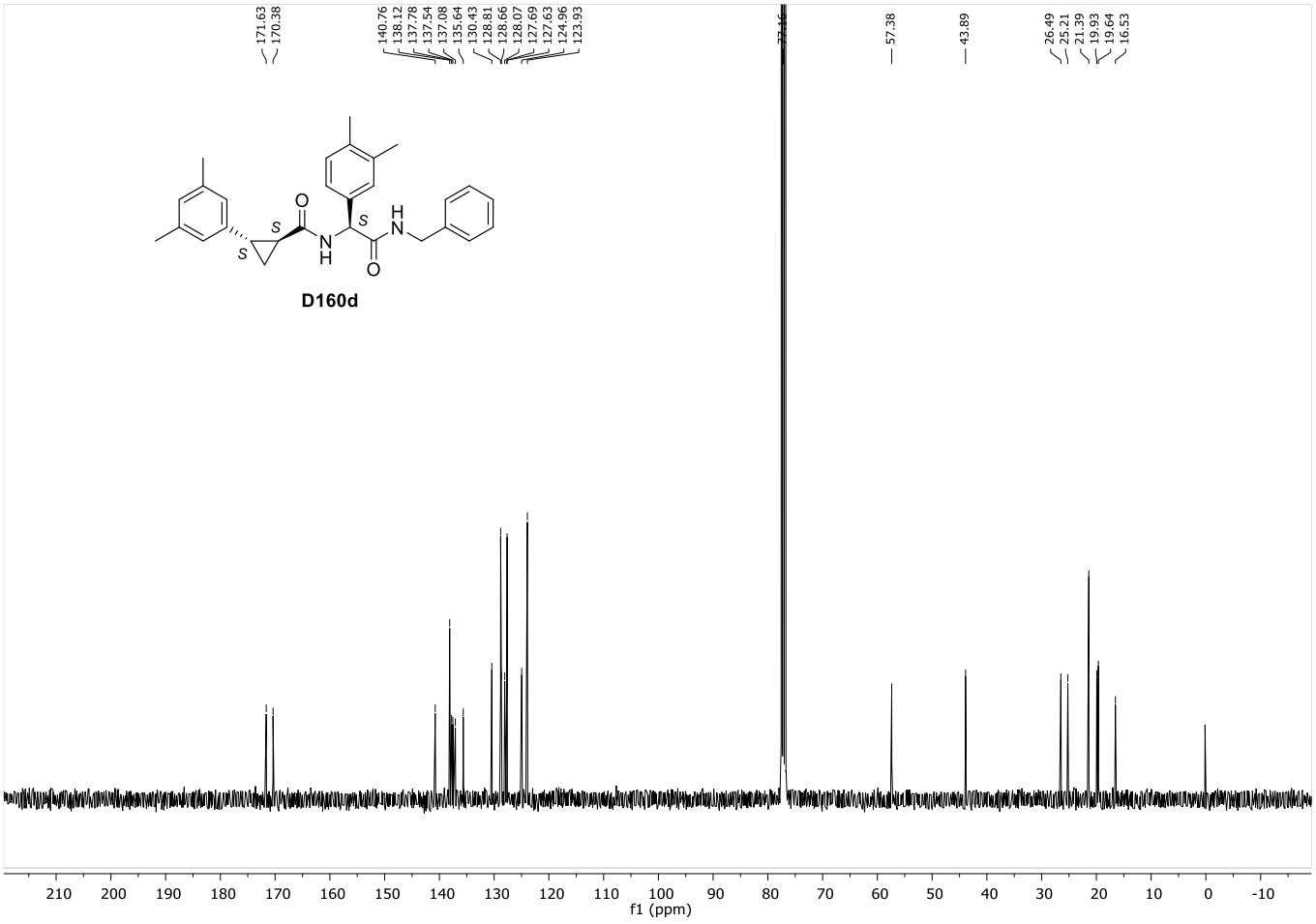

7.26 7.25 7.23 7.15 7.14 7.13 7.12 7.12 7.11 7.10 7.06 6.67 6.21 6.19 6.18 5.48 5.47 4.48 4.47 4.44 4.43 4.39 4.38 4.36 4.34 2.36 2.35 2.35 2.34 2.33 2.32 2.31 2.28 2.23 2.22 1.71 1.70 1.69 1.69 1.68 1.67 1.49 1.48 1.47 1.46 1.44 1.19 1.18 1.17 1.17 1.16 1.16 1.15 1.14
3.88 5.78 1.00 1.96 0.97 0.98 2.02 1.12 11.59 1.00 1.00 1.01
f1 (ppm)

D160c


171.58 170.29 140.58 138.09 137.80 137.49 137.03 135.78 130.40 128.80 128.66 128.12 127.67 127.65 124.92 124.12 77.16 57.32 43.87 26.37 25.46 21.39 19.94 19.64 16.12
f1 (ppm)

D160c


D160d
f1 (ppm)


D160d
f1 (ppm)

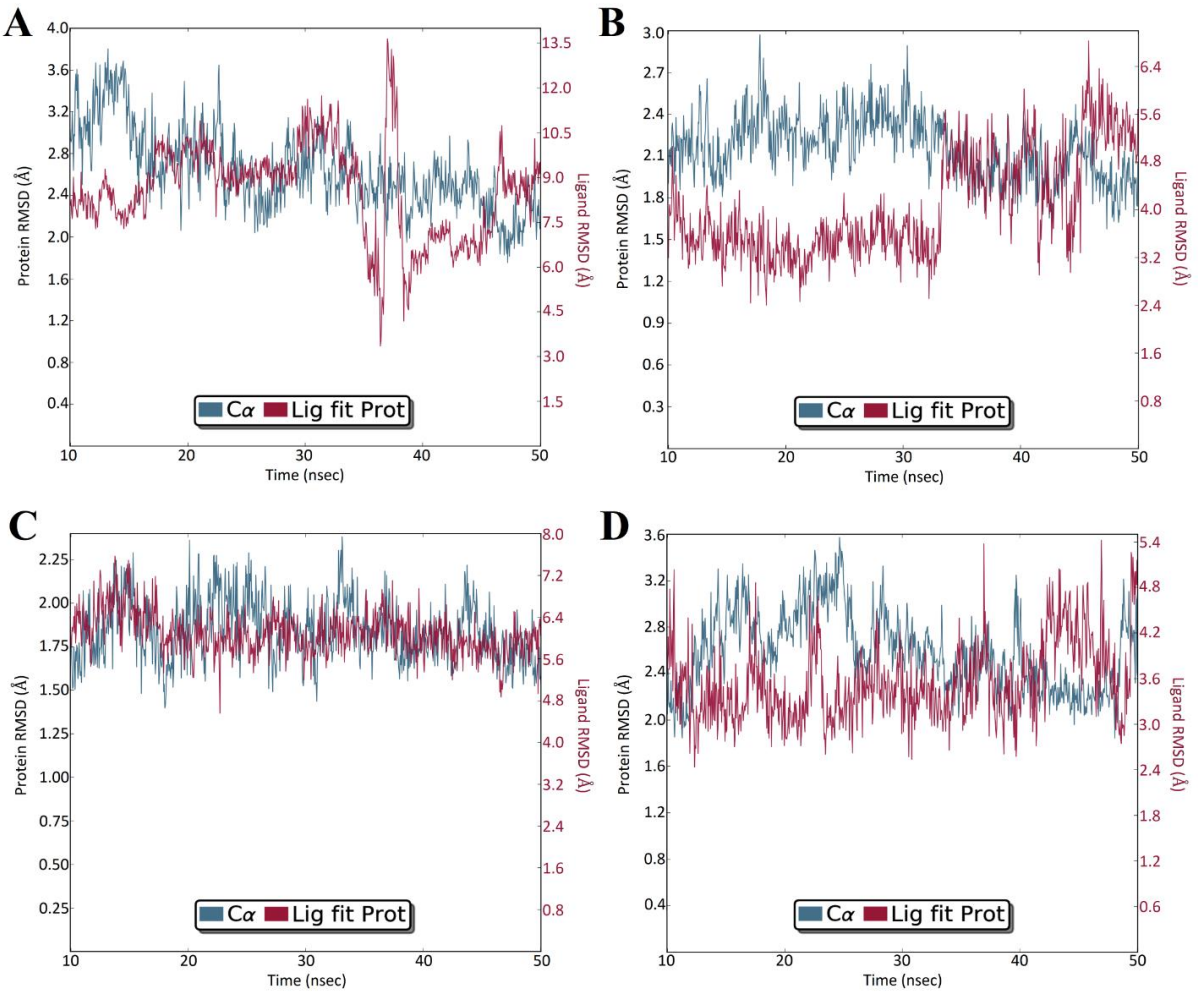


Figure S1. RMSD of the atomic positions for the stereoisomers **D160a** and **D160d** (in red, Lig fit Prot) and CHIKV nsP2 (Cα positions in blue) of the 50 ns MD simulations using the Desmond package: (A) – **D160a** at potential binding site **1**; (B) – **D160d** at potential binding site **1**; (C) – **D160a** at potential binding site **2**; (D) – **D160d** at potential binding site **2**. PDB ID of CHIKV nsP2: 3TRK.

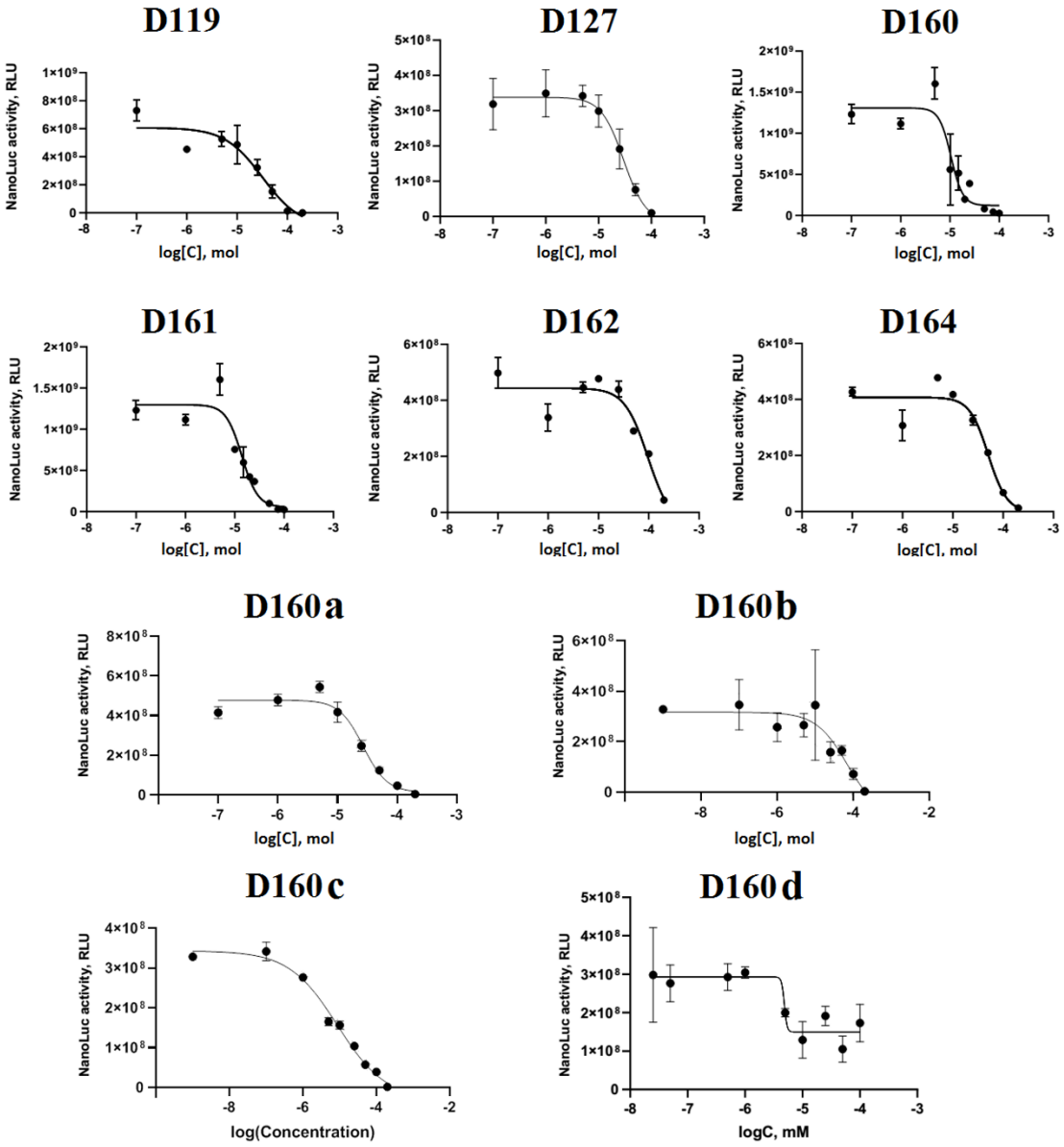


Figure S2. Determination of EC_{50} of the selected compounds in BHK-21 cells.

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