Supporting Information

Assessing a Sustainable Manufacturing Route to Lapatinib

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Contents

1. General information

CAUTION! Lapatinib is a highly potent EGFR (IC_{50} 10.8 nM) and ErbB2 (IC_{50} 9.2 nM) inhibitor, extra precautions must be in place for handling such an extremely potent compound. All waste material that are contaminated with Lapatinib and the late-stage precursors must be regarded as extremely toxic and must be treated, contained and disposed of according to safe practices, see: https://www.hse.gov.uk/pubns/indg136.pdf.

Reactions were conducted in standard laboratory glassware that were pre-dried in an oven. Unless otherwise specified, precursors and solvents were procured from commercial suppliers and used without purification. Formamidine acetate was recrystallised from refluxing ethanol before use.

Anhydrous solvents, when used, were dried by molecular sieves in a solvent purification tower. NMR spectra were recorded on AV400 Bruker spectrometers (^{1}H, 400 MHz; ^{13}C, 101 MHz). Chemical shifts (δ) are reported in ppm with referenced to residual ^{1}H or ^{13}C in the deuterated solvents used in the preparation of the samples ($CHCl_3$, δ_H 7.26 ppm; δ_C 77 ppm; DMSO-d_5, δ_H 2.50 ppm, δ_C 39.5 ppm). The multiplicity of the NMR signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), broad singlet (bs), or multiplet (m); app. t = apparent triplet, where J values converge. J values are reported in Hz.

High-resolution (APCI or ESI) mass spectrometry was performed by Dr. Lisa Haigh, using a Micromass Autospec Premier system in the Mass Spectrometry Facility at the Department of Chemistry, Imperial College London. Melting points (uncorrected) were determined using a Gallenkamp melting point apparatus. Infrared spectra of isolated solid samples were recorded on an Agilent Cary 630 FT-IR spectrometer equipped with a diamond ATR module.

Unless otherwise stated, batch reactions were performed using standard laboratory glassware. Reactions monitored by IR spectroscopy were performed in either a Mettler-Toledo EasyMax 102 reactor, or a Mettler-Toledo OptiMax 1001 reactor (for larger volumes >100 mL), fitted with a Mettler-Toledo ReactIR-15 with a liquid N_2 cooled MCT. The IR probe was a Mettler-Toledo DST Series 6.3 mm AgX Fiber Conduit probe (6mm x 1.5m). The *in situ* IR spectra were recorded with a sampling window of 3000 to 650 cm^{-1}, resolution set to normal (8 wavenumbers), and the gain was set to 1x. In most instances the IR sampling interval was set to 1 min.

Continuous flow reactions were performed on a ThalesNano H-Cube Pro reactor. 30 mm CatCart cartridges (4 mm inner diameter x 24 mm internal length) were filled with catalyst as defined in the individual experiments and used on the H-Cube Pro without further preparation.

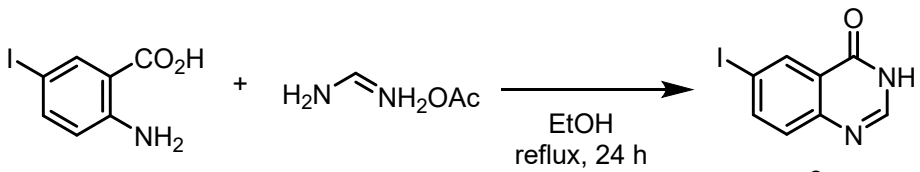
HPLC analysis was performed on an Agilent 1260 Infinity II SFC/UHPLC Hybrid System operating in UHPLC mode. A Phenomenex Gemini NX-C18 column (3 µm, 50 x 2 mm, 110 Å pore size, model: 00B-453-B0, S/N: H16-237206, B/N: 5560-0053) was utilised for the HPLC separation. The UHPLC method used a 3.0 µL injection volume, a mobile phase flow rate of 0.7 mL/min, and a column temperature of 35.0 ºC. The mobile phase was a gradient of 0.1% (v/v) formic acid in water with MeCN, with the gradient held constant at 5% MeCN until 0.50 min, then increasing at a constant rate to 50% at 3.00 min, then held constant at 50% until

the run ended at 5.50 min. A post run time of 1.00 min allowed the mobile phase to re-equilibrate between runs. Detection was by Diode Array Detector (DAD, Agilent 1260 DAD WR G7115A) and Electrospray Mass Spectrometry (ESI-MS, Agilent LC/MSD G6125B). The DAD acquired signals at 210, 220 and 230 nm, with a bandwidth of 4 nm, and a reference (600 nm, 100 nm bandwidth). The ESI-MS was operated with spray chamber settings of 350 ºC gas temperature, 12.0 L/min drying gas flow rate, 35 psig nebuliser pressure, 100 ºC quadrupole temperature, and capillary voltage of 3000 V. The ESI-MS was scanned in positive mode between 100.00 and 750.00 Da, at a fragmentor voltage of 70 V, and electron multiplier voltage (EMV) gain of 1.0. With this UHPLC method the analytes had the following retention times: lapatinib (**1**) at 3.4 min, 1,3,5-trimethoxybenzene at 4.3 min, compound **11** at 4.7 min. Compound **13** underwent hydrolysis to form **11** during UHPLC analysis (confirmed by DAD integration and ESI-MS spectrum).

The UHPLC method was calibrated against standard solutions of **11**, **13**, and lapatinib (**1**). Stock solutions (100 mM) were prepared by dissolution of known masses of standard compounds in DMSO (500 µL). Standard solutions (100 mM to 1000 mM) were subsequently prepared by dilution of aliquats of the stock solutions with 800 µL of a solution of 1,3,5-trimethoxybenzene in methanol (internal standard, 6.25 mM), and addition of methanol to make the combined volume 1.00 mL.

Samples were prepared for UHPLC analysis by dilution of aliquots (100 µL), with 900 µL of a stock solution of 1,3,5-trimethoxybenzene (internal standard, 5.55 mM) in methanol.

2. Formation of the quinazolinone ring



Representative procedure (optimization): A 2-neck 50 mL round bottom flask fitted with a reflex condenser was charged with 5-iodoanthranilic acid **2** (1.45 g, 5.50 mmol), formamidine acetate (676 mg, 6.50 mmol, 1.2 equiv.), and suspended in absolute ethanol (20 mL). The reaction mixture was heated at reflux for 24 hours, during which time a white precipitate was observed to form in the brown solution. The reaction mixture was cooled to ambient temperature, then further cooled to 0 °C (ice bath) for 1 h to complete the precipitation process. The solid was subsequently collected by suction filtration, washed with cold ethanol, diethyl ether and dried *in vacuo* to yield **3** as an off-white solid.

Table S1. Optimization of the condensation reaction.

Entry	[**2**]/mmol	(Molar) equivalents of formamidine acetate	Yield/%[a]
1	5.50	1.0	68

2	5.50	1.2	78
3	5.50	1.4	88
4	17.0	1.3	85
5	50.0	1.3	84
6	95.0	1.3	84

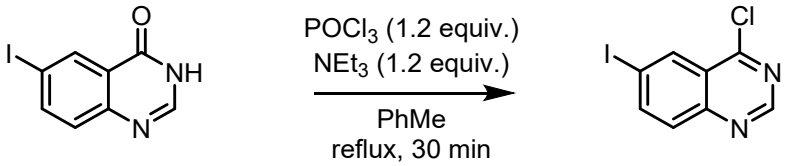
[a] Isolated yield.

Preparative procedure: The reaction was replicated in a 1 L round bottom flask, where a mixture of 5-iodoanthranilic acid (25.0 g, 95.0 mmol), formamidine acetate (12.7 g, 124 mmol, 1.3 equiv.) was heated in absolute ethanol (380 mL, [0.25 M]) for 24 hours. The same workup procedure was applied to furnish the final product **3** (21.4 g, 78.8 mmol, 84% yield), which was dried *in vacuo*.

The ^{1}H NMR spectral data is more closely matched to that reported in the patent literature.[1] ^{13}C NMR data for this compound was not previously reported.

Mpt: 276–278 °C (lit.[2] 263–266 °C). δ_H (400 MHz, DMSO-d_6): 12.36 (s, 1H), 8.38 (d, J = 2.1, 1H), 8.13 (s, 1H), 8.10 (dd, J = 8.6, 2.1, 1H), 7.46 (d, J = 8.2, 1H). δ_C (101 MHz, DMSO-d_6) 159.9, 148.5, 146.6, 143.1, 134.6, 129.9, 124.9, 92.3. IR (FTIR-ATR) ν_{max} (cm^{-1}): 1666, 1610, 1454, 1320, 1241, 906, 831. HRMS (APCI): $[C_8H_5N_2O^{127}I+H]^+$ calc. 272.9519 found. 272.9519.

3. Formation of 4-chloroquinazoline using $POCl_3$



3 **4**

Table S2. Chlorination of 6-iodoquinazolin-4-ol **3** using $POCl_3$.[a]

Entry	Reaction atmosphere	T/°C	t/h	Yield[b]/%
1	N_2	75	2	72
2	N_2	110	2.5	84
3	air	110	2.5	84
4	air	110	0.25	81

[a]**3** (1.0 equiv.), $POCl_3$ (1.2 equiv.), toluene (0.8 L/mol). [b] Isolated yield of dried product obtained after filtration.

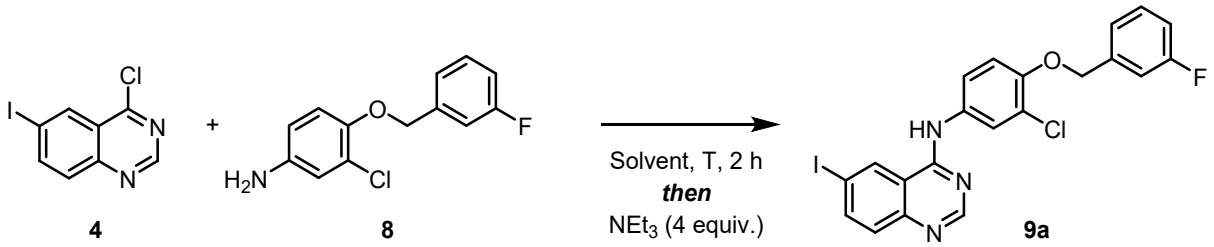
Preparative procedure: In a 25 mL round bottom flask fitted with a condenser under an atmosphere of dry N_2, $POCl_3$ (1.12 mL, 12.0 mmol, 1.20 equiv.) was added slowly to a mixture of 6-iodoquinazolin-4-ol **3** (2.72 g, 10.0 mmol) and triethylamine (1.68 mL, 12.0 mmol, 1.2 equiv.) in anhydrous toluene (8.5 mL). The resultant suspension was heated at reflux, whereupon the reaction mixture turned clear over 15 minutes, as the starting material is converted into the product, which precipitated as the mixture was cooled to room temperature.

The reaction mixture was transferred to a larger vessel from the flask, which was rinsed by a small amount of toluene (~2 mL). An aqueous NaOH (1 M, 200 mL) was added to the transferred suspension and the resultant biphasic solution was stirred vigorously at room temperature for 30 min. The solid was then collected under suction filtration and dried under a vacuum to deliver **4** (2.54 g, 8.72 mmol, 87%) as pale brown needles.

^{1}H and ^{13}C NMR data of compound **4** matched the reported literature.[3]

δ_H (400 MHz, $CDCl_3$): 9.06 (s, 1H), 8.66 (d, *J* = 1.9, 1H), 8.20 (dd, *J* = 8.8, 1.9, 1H), 7.80 (d, *J* = 8.8, 1H). δ_C (101 MHz, $CDCl_3$): 160.9, 154.0, 150.0, 143.8, 134.5, 130.2, 125.3, 94.6. IR (FTIR-ATR) ν_{max} (cm^{-1}): 1550, 1535, 1468, 1353, 1312, 988, 842. HRMS (APCI): $[C_8H_4N_2{}^{35}Cl^{127}I+H]^+$ calc. 290.9180 found 290.9182.

4. Synthesis of 9a by an S_NAr reaction



Representative procedure (optimization): A 2-neck 50 mL round bottom flask fitted with an air condenser was charged with 4-chloro-6-iodoquinazoline **4** (581 mg, 2.00 mmol) and 3-chloro-4-(3-fluorobenzyloxy)aniline **8** (554 mg, 2.20 mmol, 1.1 equiv.), before the addition of isopropanol (20 mL) to form a suspension. The reaction mixture was heated at reflux for 2 h, before cooling to room temperature. Triethylamine (1.11 mL, 8 mmol, 4 equiv.) was added and the mixture was stirred at room temperature for 30 min, before the precipitated solids were collected by vacuum filtration and dried, to furnish **9a** as an off-white solid.

Table S3. S_NAr reaction of quinazoline **4** and **8** to product **9a**.[a]

Entry	Equiv. of **8**[b]	Solvent(s) (v/v) [conc]	T/°C	t/h	Yield[c]/%
1	1	*i*-PrOH [10 L/mol]	70	3	94
2	1	Toluene [5 L/mol]	110	2.5	87
3	1	Toluene [5 L/mol]	110	1	62
4	1	DME:MeOH (2:1) [10 L/mol]	70	1	80
5[d]	1	DME:MeOH (2:1) [10 L/mol]	70	1	-
6	1.06	DME:MeOH (2:1) [10 L/mol]	50	1	82
7	1.1	DME:MeOH (2:1) [10 L/mol]	50	2	89
8	1.1	MeOH [10 L/mol]	reflux	2	88
9	1.05	*i*-PrOH [10 L/mol]	reflux	2	95

[a] See representative procedure (above). [b]With respect to **4**. [c]Isolated yield. [d]15 equiv of NEt_3 was added to the reaction mixture.

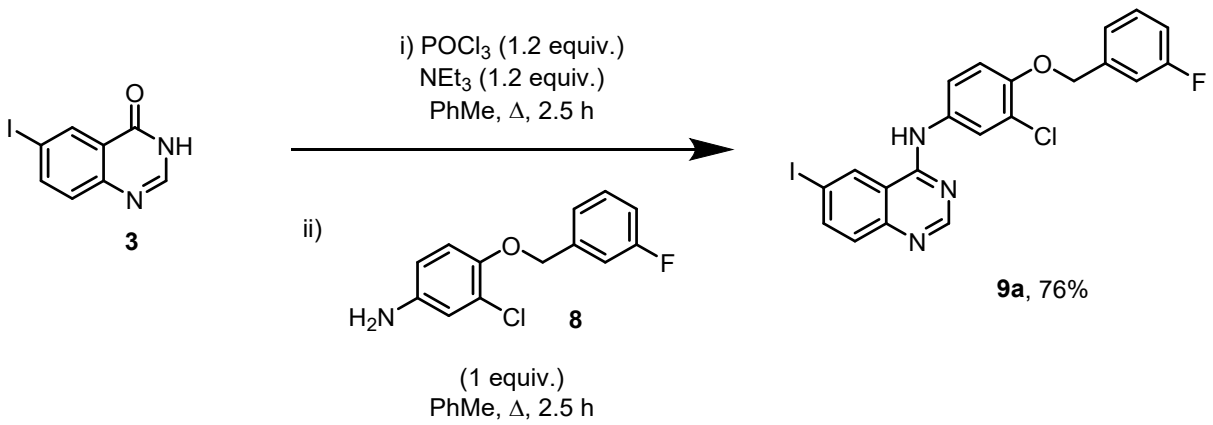
Preparative procedure. The optimal conditions were replicated on a larger scale, in a 250 mL round bottom flask, by refluxing a mixture of **4** (5.81 g, 20.0 mmol) and **8** (5.28 g, 21.0 mmol, 1.05 equiv.) and isopropanol (100 mL) for 2 hours, during which a bright yellow solid precipitated. After cooling to room temperature, NEt_3 (11.1 mL, 79.6 mmol, 4.0 equiv.) was added, and stirring was continued at room temperature for a further 30 min. The resulting precipitate was collected by filtration, washed with cold isopropanol, and dried *in vacuo* to furnish **9a** (9.51 g, 18.8 mmol, 94% yield) as a pale beige solid.

^1H and ^{13}C NMR data for **9a** broadly agree with previously reported;[4] some additional resolved *J* couplings are observed in this work (see expanded spectra).

Mpt: 230–232 °C (lit.[4] 221-224 °C). δ_H (400 MHz, DMSO-d_6): 9.84 (s, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.11 (d, *J* = 8.8, 1H), 8.02 (d, *J* = 2.4, 1H), 7.73 (dd, *J* = 8.9, 2.4, 1H), 7.55 (d, *J* = 8.7, 1H), 7.47 (dd, *J* = 14.2, 7.9, 1H), 7.32 (app. t, *J* = 8.1, 2H), 7.27 (d, *J* = 9.0, 1H), 7.18 (td, *J* = 8.9, 2.1, 1H), 5.25 (s, 2H). δ_C (101 MHz, DMSO-d_6): 162.2 (d, *J* = 243.6), 156.3, 154.8, 149.8, 148.7, 141.3, 139.6 (d, *J* = 7.5), 133.0, 131.4, 130.6 (d, *J* = 8.2), 129.8, 124.0, 123.3 (d, *J* = 2.4 Hz), 122.1, 121.0, 116.8, 114.7 (d, *J* = 20.9), 114.3, 114.0 (d, *J* = 21.9), 91.5, 69.4. δ_F (377 MHz, DMSO-d_6) –113.00 (s). IR (FTIR-ATR) ν_{max} (cm^{-1}): 1618, 1592, 1558, 1528, 1498, 1420, 1271, 1058, 1036, 779. HRMS (APCI): $[C_{21}H_{14}N_3OF^{35}Cl^{127}I+H]^+$ calc. 505.9926 found 505.9927.

Solubility of 9a. Attempts were made to dissolve 50.5 mg of **9a** in 1 mL of the following solvents to form a 0.1 M solution: DME, methanol, DME: methanol (2:1, v/v) – none of these resulted in a homogeneous solution at room temperature. Further portions of the solvents were added (0.05 M), and while **9a** dissolved in DME, it remained insoluble in methanol even after sonication, and was only partially soluble in the 2:1 solvent mixture. **9a** is also insoluble in isopropanol.

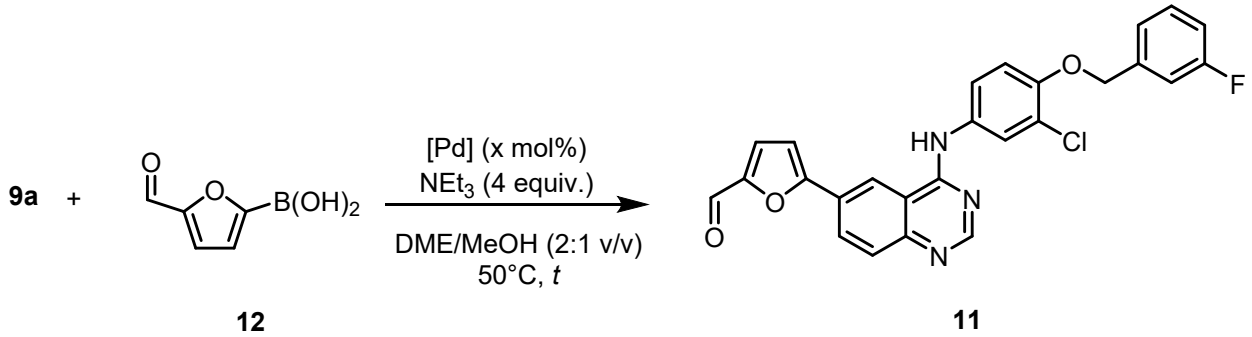
5. Telescoping the chlorination and S_NAr steps.



In a 100 mL 3-neck round bottom flask fitted with a condenser, triethylamine (1.12 g, 11.0 mmol) was added slowly to a solution of 6-iodo-quinazolinone **3** (2.50 g, 9.2 mmol) and $POCl_3$ (1.69 g, 11.0 mmol, 1.2 equiv.) in anhydrous toluene (7.5 mL) at room temperature. The reaction mixture was heated to reflux with stirring for 2.5 h. Meanwhile, 3-chloro-4-(3-fluorobenzyloxy)aniline **8** (2.3 g, 9.2 mmol) was dissolved in hot toluene (45 mL) before it was added to the reaction mixture, whereupon the formation of a bright yellow precipitate can be observed in 2 minutes. The reaction mixture was heated and stirred for a further 2.5 h, before it was

cooled to room temperature, and then immersed in an ice bath for 20 min. The bright yellow solid precipitate was collected by filtration, and then suspended in aqueous NaOH (1 M, 200 mL) and stirred overnight. The product was collected by filtration, washed with water, and dried in vacuo, to furnish **9a** (3.51 g, 6.94 mmol, 76% yield) as a pale yellow solid.

6. Synthesis of 11 (Suzuki cross-coupling)



12 **11**

Representative procedure (Optimization, Table 2, entry 8): A 50 mL round bottom flask was charged with 5-formyl-2-furanylboronic acid **12** (154 mg, 1.10 mmol, 1.1 equiv.), **9a** (505 mg, 1.00 mmol)) and $Pd(OAc)_2$ (2.30 mg, 1.0 mol%). The solids were suspended in DME/MeOH (20 mL, 2:1 v/v), NEt_3 (560 µL) was added, and the reaction mixture was heated at 50 °C for 4 hours. It was then cooled to room temperature and filtered over Celite, which was rinsed with MeOH (~10 mL). The filtrate was evaporated *in vacuo,* and the residue was suspended in MeOH (20 mL) and refluxed for a further hour. The mixture was cooled to room temperature and put in an ice bath. The solids were collected by vacuum filtration, washed with cold MeOH (~ 5 mL) and dried to deliver **11** as an orange/yellow solid.

Preparative procedure: The optimized conditions were replicated on a larger scale in a 1L reaction vessel, using **9a** (20.2 g, 40.0 mmol), **12** (5.88 g, 42.0 mmol, 1.05 equiv.), $Pd(OAc)_2$ (9.20 mg, 0.1 mol%), triethylamine (11.2 mL, 80.0 mmol, 2.0 equiv.) and DME/MeOH (600 mL, 2:1 v/v). The reaction mixture was heated at 50 °C for 24 h before it was worked up (as described above) to afford **11** (17.13 g, 36.1 mmol) in 91% yield.

^{1}H NMR data for **11** broadly agrees with previously reported;[5] ^{13}C NMR data for this compound was not previously reported.

Mp: 224–226 °C (lit.[6] 224-228 °C). δ_H (400 MHz, DMSO-d_6): 10.13 (s, 1H), 9.67 (s, 1H), 8.98 (d, *J* = 1.7, 1H), 8.60 (s, 1H), 8.31 (dd, *J* = 8.8, 1.8, 1H), 7.99 (d, *J* = 2.6, 1H), 7.87 (d, *J* = 8.8, 1H), 7.76 (d, *J* = 3.8, 1H), 7.71 (dd, *J* = 8.9, 2.6, 1H), 7.48 (td, *J* = 8.0, 6.0, 1H), 7.42 (d, *J* = 3.7, 1H), 7.29-7.36 (m, 3H), 7.19 (td, *J* = 8.6, 2.0, 1H), 5.27 (s, 2H). δ_C (101 MHz, DMSO-d_6): 177.8, 162.2 (d, *J* = 243.6), 157.8, 157.6, 155.3, 152.1, 150.1, 150.0, 139.6 (d, *J* = 7.4), 132.8, 130.6 (d, *J* = 8.3), 129.6, 128.7, 126.3, 125.7, 124.6, 123.3 (d, *J* = 2.3), 122.8, 121.0, 119.5, 115.3, 114.7 (d, *J* = 21.0), 114.3, 114.0 (d, *J* = 22.0), 109.8, 69.4. δ_F NMR (377 MHz, DMSO-d_6) –113.02 (s). IR (FTIR-ATR) ν_{max} (cm^{-1}): 1662, 1573, 1536, 1487, 1379, 1260, 1033, 775. HRMS (APCI): $[C_{26}H_{18}N_3O_3F^{35}Cl+H]^+$ calc. 474.1015 found 474.1013.

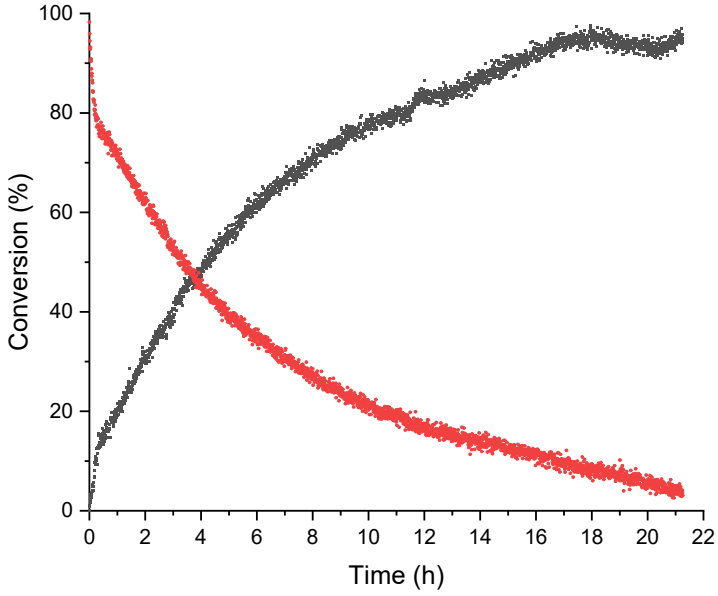


Figure S1. Reaction progress of the Suzuki-Miyaura cross coupling between **9a** and **12** in the presence of 0.01 mol% of [Pd].

7. Preparation and isolation of imine 13.

Furan-2-carbaldehyde **11** (2.37 g, 4.99 mmol.) and 2-aminoethylmethyl sulfone hydrochloride (878 mg, 5.5 mmol, 1.1 equiv.) were suspended in anhydrous MeOH (80 mL [0.05 M]) with stirring. Triethylamine (840 µL, 607 mg, 6 mmol, 1.2 equiv.) was added and the solution was heated to reflux and stirred overnight for 24 h. After cooling to room temperature, the solid precipitate was collected by filtration, washed with a small amount of MeOH to yield imine **13** (2.51 g, 4.34 mmol., 87%) as an off-white/light yellow solid.

The ^{1}H and ^{13}C NMR data broadly agree with that previous reported (in patent literature);[6] although additional fine couplings were observed in this work (see expanded spectrum below)

δ_H (400 MHz, DMSO-d_6) 10.04 (s, 1H), 8.86 (d, J = 1.6, 1H), 8.58 (s, 1H), 8.34 (s, 1H), 8.23 (dd, J = 8.7, 1.8, 1H), 8.00 (d, J = 2.6, 1H), 7.85 (d, J = 8.8, 1H), 7.72 (dd, J = 9.0, 2.6, 1H), 7.48 (td, J = 8.0, 6.0, 1H), 7.37 – 7.26 (m, 4H), 7.23 – 7.16 (m, 2H), 5.27 (s, 2H), 3.97 (app t, J = 6.4, 2H), 3.51 (app t, J = 6.7, 2H), 3.06 (s, 3H). δ_C (101 MHz, DMSO-d_6) δ 162.2 (d, J = 243.8), 157.7, 154.8, 154.6, 151.8, 151.2, 149.9, 149.6, 139.7 (d, J = 7.4), 132.9, 130.6 (d, J = 8.4), 129.1, 128.7, 127.3, 124.4, 123.4 (d, J = 2.2), 122.6, 121.1, 118.1, 117.6, 115.4, 114.7 (d, J = 20.9), 114.3, 114.1 (d, J = 22.0), 109.3, 69.4, 54.3, 53.9, 41.8. δ_F (377 MHz, DMSO-d_6) –113.03 (s). IR (FTIR-ATR) ν_{max} (cm^{-1}): 1636, 1603, 1506, 1424, 1305, 1260, 1118, 1033, 969, 794. HRMS (APCI): $[C_{29}H_{24}N_4O_4F^{35}ClS+H]^+$ calc. 579.1264 found 579.1257.

8. IR monitoring of the *in situ* formation of imine 13 from 11.

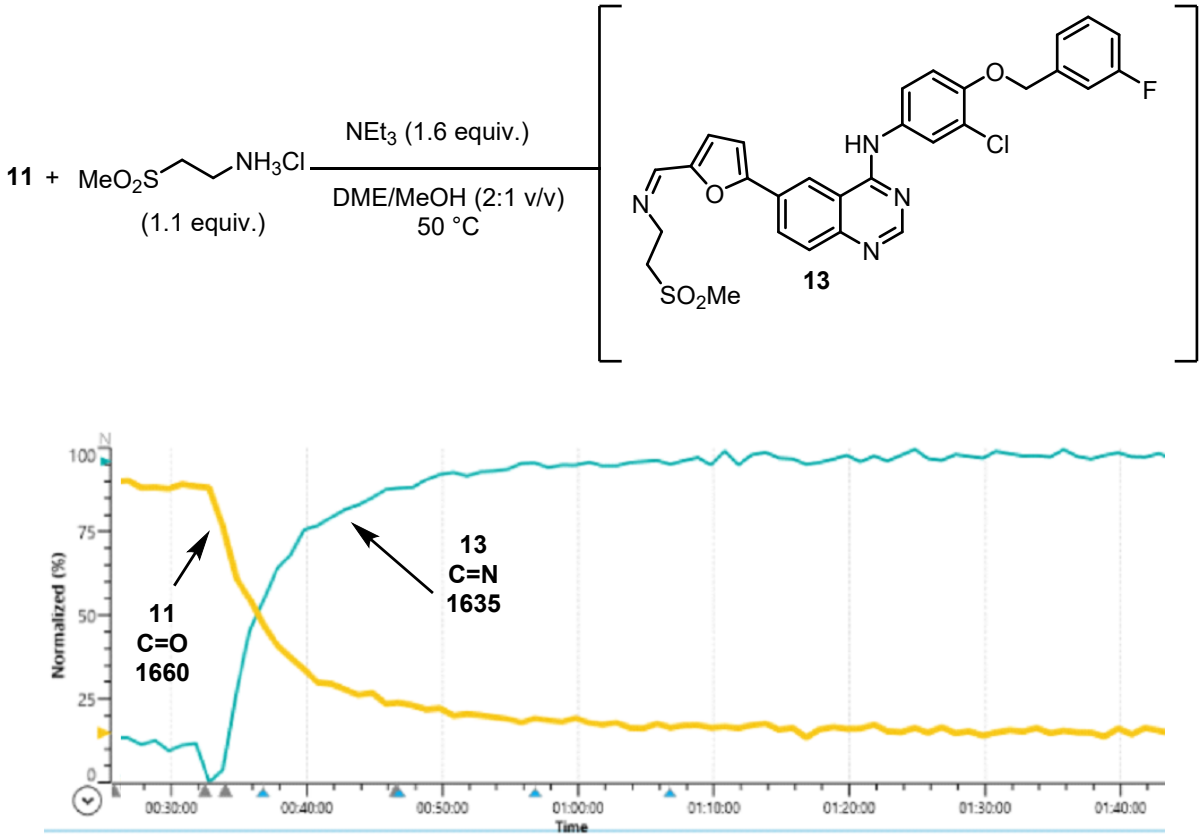


Figure S2. Progress of the imine formation tracked by *in situ* IR spectroscopy.

A 50 mL EasyMax 102 jacketed reactor vessel, fitted with an IR probe and thermocouple, was charged with a magnetic cross stirrer bar and DME/MeOH (2:1 v/v, 10 mL), and a reference spectrum was recorded. Furan-2-carbaldehyde **11** was added (474 mg, 1.00 mmol.) via funnel, and the spectrum of the solution was recorded, before the reactor temperature was set to 50 °C. A stock solution of 2-aminoethylmethylsulfone hydrochloride (1 equiv.) and triethylamine (2 equiv. was required to ensure dissolution of the amine salt) in DME/MeOH (5 mL) was then added, and the condensation reaction was monitored, by the disappearance of the carbaldehyde carbonyl peak [$\tilde{\nu}$(C=O) = 1680 cm^{-1}] and the emergence of an imine peak [$\tilde{\nu}$(C=N) = 1640 cm^{-1}]. The reaction reached completion/steady state after 90 min (Figure S1).

9. Reductive amination procedures

(i) Using a hydride reagent: *N*,*N*-Diisopropylethylamine (348 µL, 6 mmol, 4 equiv.) and AcOH (114 µL, 6 mmol, 4 equiv.) were added sequentially to a stirred suspension of furan-2-carbaldehyde **11** (237 mg, 0.499 mmol) and 2-aminoethylmethylsulfone hydrochloride (127 mg, 0.796 mmol, 1.6 equiv.) in THF (2.5 mL, [0.2]), and the reaction mixture was heated at 40 °C for 1 h, before it was cooled to room temperature, whereupon $NaBH(OAc)_3$ (212 mg, 1.00 mmol, 2 equiv.) was added. The mixture was stirred at ambient temperature for 3 h, then quenched by the addition of aq. NaOH (2 mL, 2 M). Stirring was continued for a further 30 min, before the solution was extracted using EtOAc (3 x 5 mL). The combined organic extracts

were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to deliver lapatinib **1** (271 mg, 0.467 mmol, 93% yield) as an orange solid.

The ^{1}H NMR data agree with that previously reported;[5] ^{13}C NMR data was not previously reported.

δ_H (400 MHz, DMSO-d_6): 9.92 (s, 1H), 8.73 (d, *J* = 1.5, 1H), 8.55 (s, 1H), 8.16 (dd, *J* = 8.7, 1.8, 1H), 8.02 (d, *J* = 2.6, 1H), 7.80 (d, *J* = 8.7, 1H), 7.75 (dd, J = 9.0, 2.6, 1H), 7.51-7.48 (m, 1H), 7.36–7.27 (m, 3H), 7.21-7.16 (m, 1H), 7.07 (d, J = 3.3, 1H), 6.49 (d, *J* = 3.3, 1H), 5.27 (s, 2H), 3.87 (s, 2H), 3.28 (app t, *J* = 6.7, 2H), 3.03 (s, 3H), 2.99 (app t, *J* = 6.7, 2H). δ_C (101 MHz, DMSO-d_6): 162.2 (d, *J* = 243.6), 157.5, 154.5, 154.2, 151.6, 149.75, 148.8, 139.6 (d, *J* = 7.1), 133.0, 130.6 (d, *J* = 8.2), 128.6, 128.4, 128.3, 124.3, 123.3 (d, *J* = 2.8), 122.5, 121.0, 116.4, 115.3, 114.6, 114.2, 114.0 (d, *J* = 21.8), 109.7, 107.8, 69.4, 53.4, 45.1, 42.0, 41.4. δ_F (377 MHz, DMSO-d_6) δ –113.0 (s). IR (FTIR-ATR) ν_{max} (cm^{-1}): 1737, 1589, 1523, 1491, 1420, 1275, 1118, 790. HRMS (ESI): $[C_{29}H_{26}N_4O_4F^{35}ClS+H]^+$ calc. 581.1426 found 581.1421.

(ii) Transfer hydrogenation protocol (optimization studies, Table 4): The screening and optimization experiments were performed in parallel in a Radley's reaction carousel. Each of the 20 mL reaction tube was charged with imine **13** (116 mg, 0.200 mmol) and 5% Pd/C (21 mg, 5.0 mol%), before being suspended in DME/MeOH (2:1 v/v, 4 mL) and heated to 50 °C. The requisite hydrogen surrogate (5 equiv.) was added to the reaction mixture. The reaction was monitored by extracting reaction aliquots (100 µL), which were diluted by the addition of 900 µL of a stock solution containing trimethoxybenzene as internal standard, before subjecting to HPLC analysis (Figure S3).

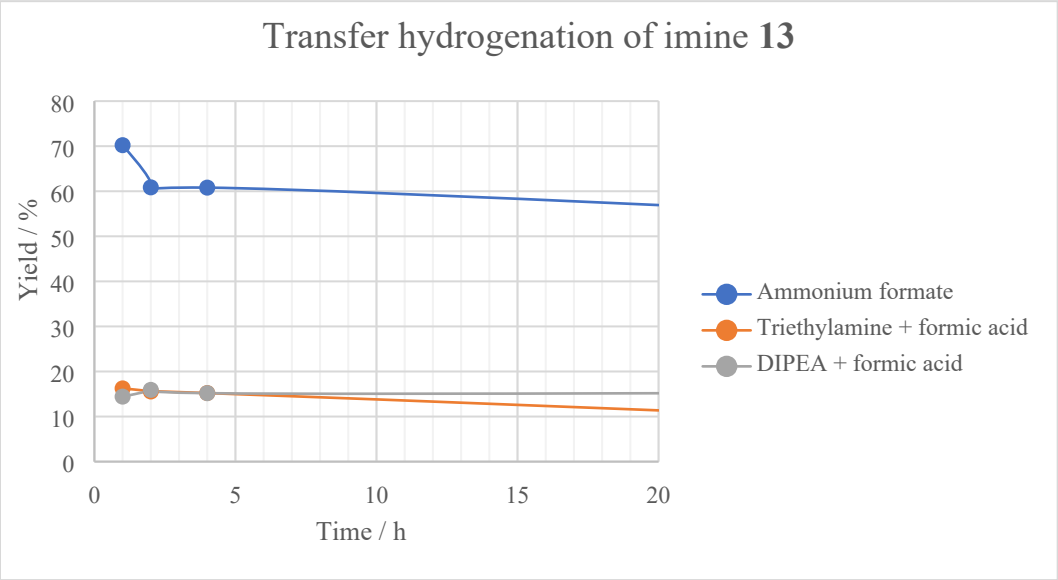


Figure S3. Yield of lapatinib formed under transfer hydrogenation conditions using Pd/C.

(iii) Catalytic reductive amination in flow (optimization). To a 100 mL EasyMax 102 reaction vessel fitted with a cross stirrer bar, ReactIR probe and thermocouple, was added DME/MeOH (2:1 v/v, 30 mL) and the background spectrum was recorded. Carbaldehyde **11** (1.42 g, 3.00 mmol) was added via a funnel, which was rinsed with 10 mL of solvent mixture, and reactor set to 50 °C. A solution of triethylamine and 2-

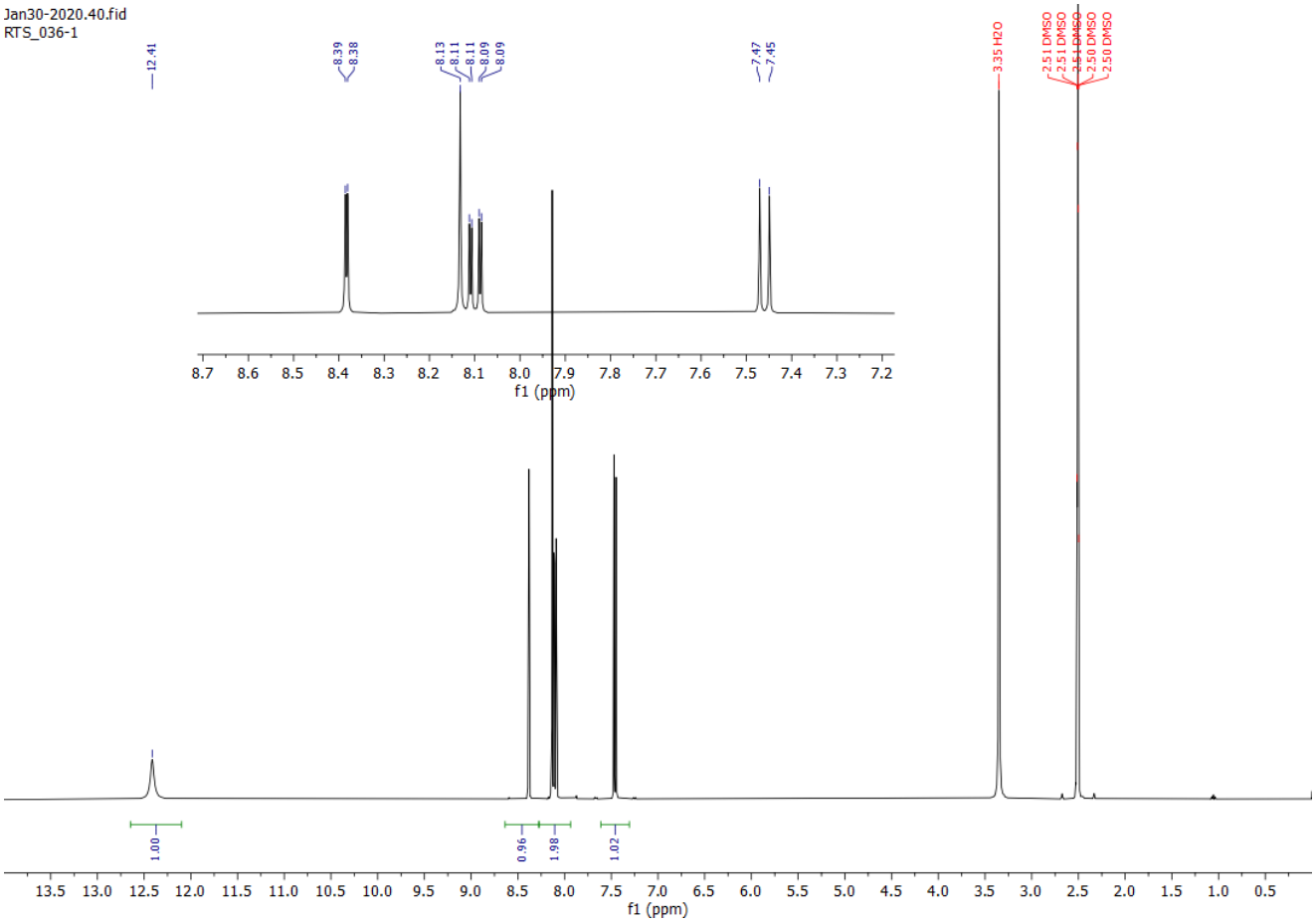
aminoetthylmethylsulfone hydrochloride dissolved in DME/MeOH (20 mL, 1.6 equiv. and 1.1 equiv. respectively) was added to the preheated vessel ($[0.05\ M]_{final}$). The imine formation was monitored via IR, by the disappearance of $\tilde{\nu}$(C=O) = 1680 cm^{-1} and emergence of $\tilde{\nu}$(C=N) = 1640 cm^{-1} (see fig S1). No further changes were observed after 30 min, and the reaction mixture was stirred for a further 30 minutes to ensure completion. The solution was then decanted into a flask and subjected directly to the hydrogenation reaction using a H-Cube Pro flow reactor, fitted with a catalyst cartridge containing 5% Pd/C (50 mg dispersed in sand, void volume approximately 0.1 mL). The results shown in Table 4 were obtained from the HPLC analysis of aliquots collected after equilibration and 3 reactor volumes.

(Preparative) Synthesis of lapatinib. A solution of imine **13** in DME/MeOH (2:1 v/v, 200 mL) was generated in the OptiMax 1001 reactor, monitored by ReactIR, as described above. The solution was then passed through the H-Cube Pro with a catalyst cartridge containing Pd/C (50 mg dispersed in sand, 5% weight, void volume approximately 0.1 mL) at a flow rate of 0.5 mL min^{-1} at 50°C under 2 bar of H_2 pressure. Following the first three reactor volumes, reaction aliquots were collected over a 4.5 h period (total volume = 135 mL). The combined mixture was washed with water, and the aqueous layer was back-extracted with ethyl acetate (50 mL). The combined organic extracts were washed with aq. Sodium bisulfite (1M, 2 x 30 mL), brine (50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was triturated with diethyl ether to afford lapatinib **1** as an orange solid, which was collected and dried in an oven at 50 °C (2.82, 4.84 mmol, 71%).

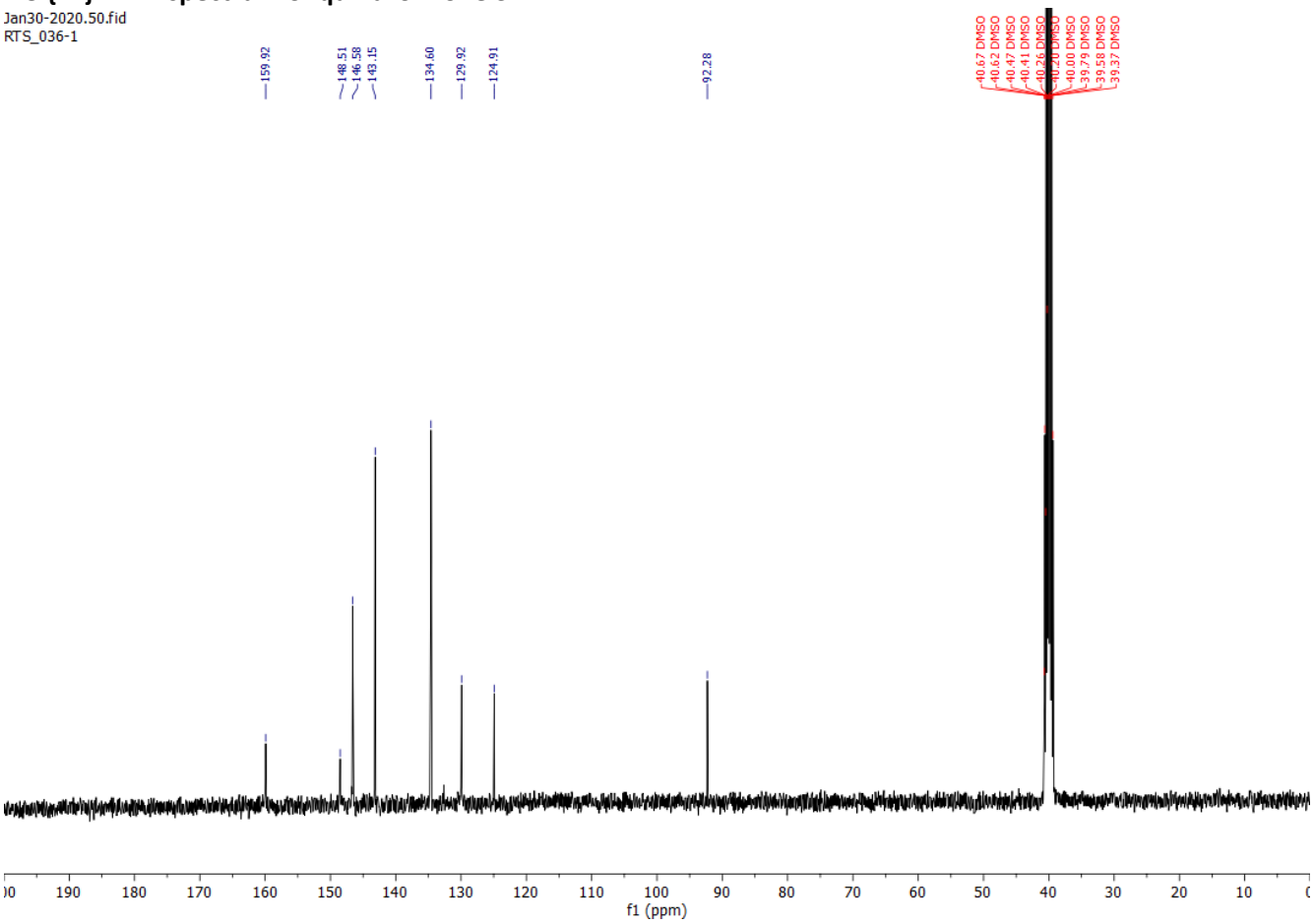
10. Telescoping Suzuki-Miyaura and catalytic hydrogenation (laboratory scale only).

To a mixture of 5-formyl-2-furanylboronic acid **12** (194 mg, 1.40 mmol), **9a** (0.50 g, 0.99 mmol), 2-aminoethylmethylsulfone hydrochloride (240 mg, 1.5 mmol), and $Pd(OAc)_2$ (11.9 mg, 5.4 mol%) was added dimethoxyethane (13.3 mL) and methanol (6.7 mL) at ambient temperature. The reaction mixture was degassed by three cycles of vacuum (10 seconds/N_2 purge), before the addition of triethylamine (2.1 mL, 14.9 mmol). The reaction mixture was then stirred at room temperature, during which the complete consumption of **9a** was observed after 18 hours (TLC). The reaction mixture was then purged with H_2 and then stirred at room temperature 1 atm. of H_2 (provided by a balloon). After 72 hours, 1,3,5-trimethoxybenzene was added to the reaction mixture (as an internal standard) An aliquot of the reaction mixture was extracted, filtered, and evaporated removed under reduced pressure. NMR analysis of the residue showed the conversion to lapatinib in 95% yield.

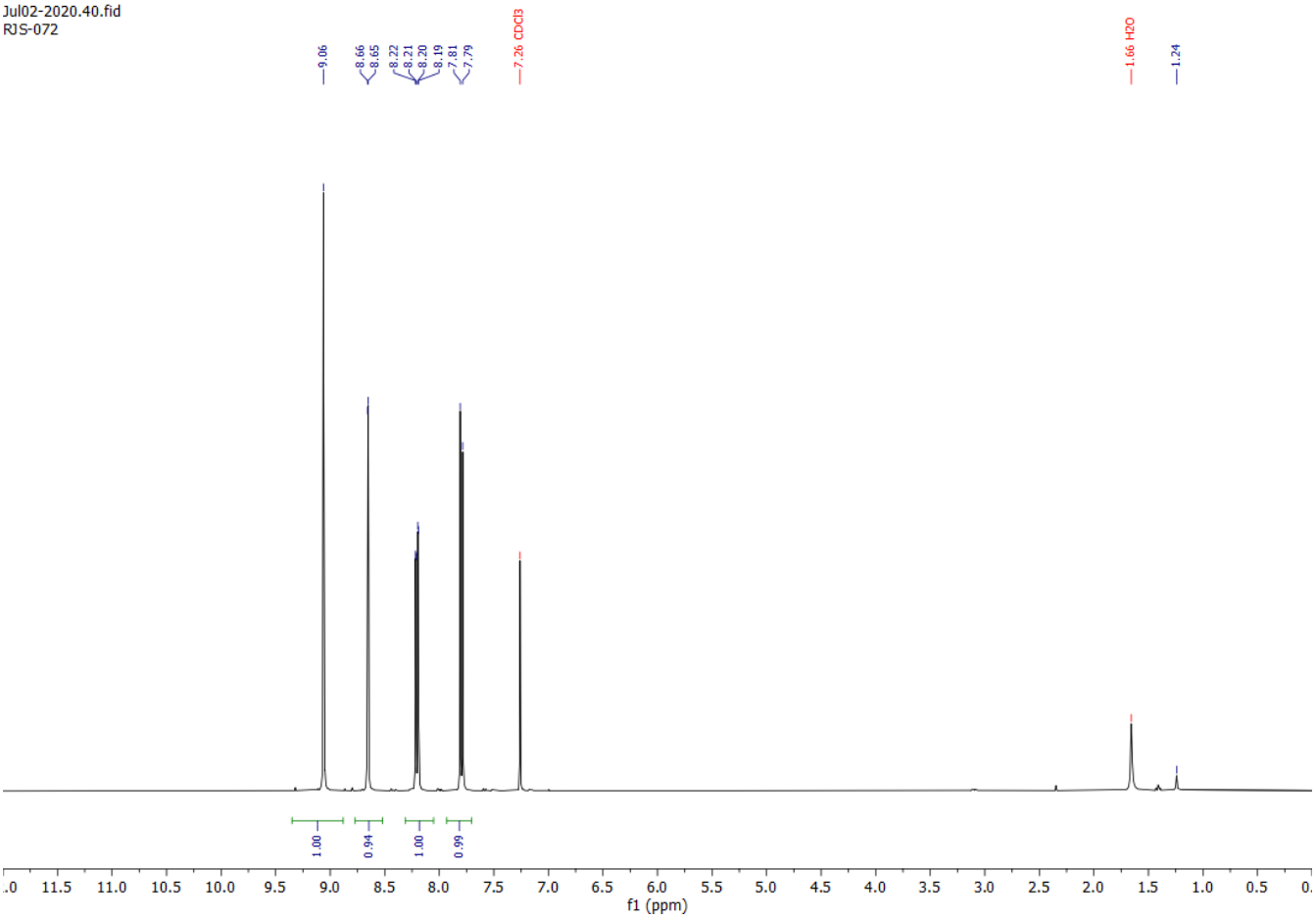
^{1}H NMR spectrum of quinazolinone 3:



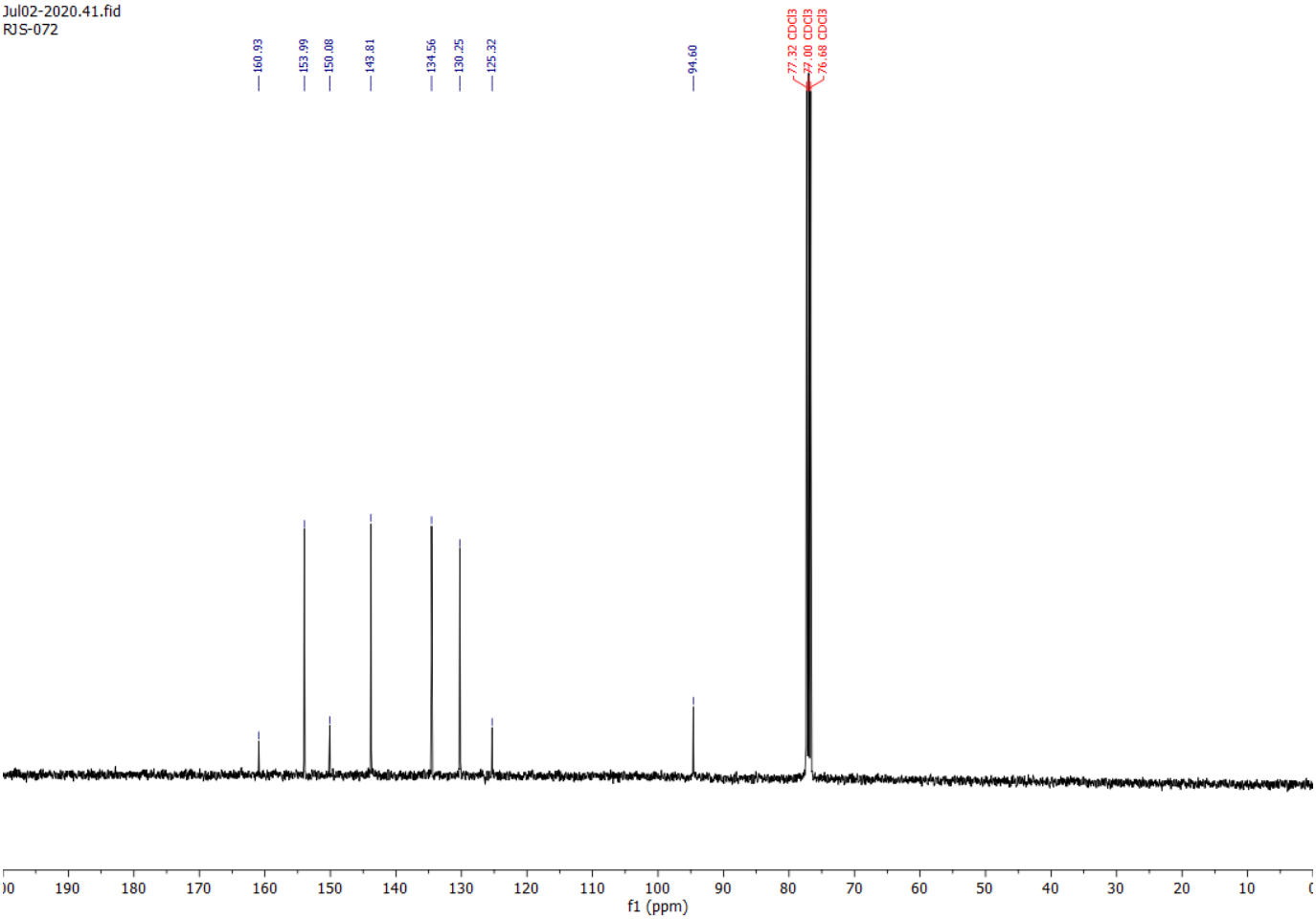
^{13}C-{^{1}H} NMR spectrum of quinazolinone 3:



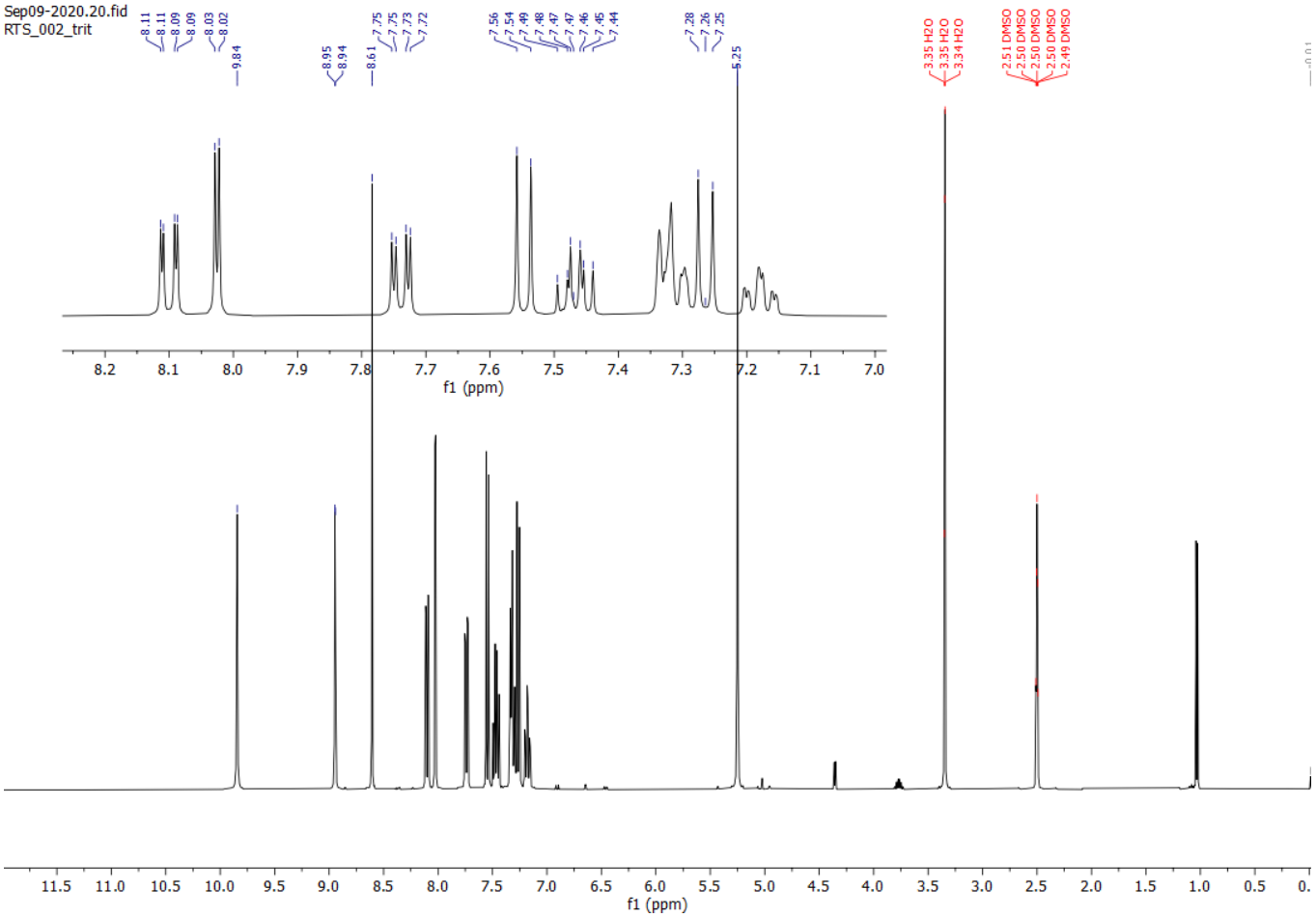
^{1}H NMR spectrum of 4-chloroquinazoline, 4:



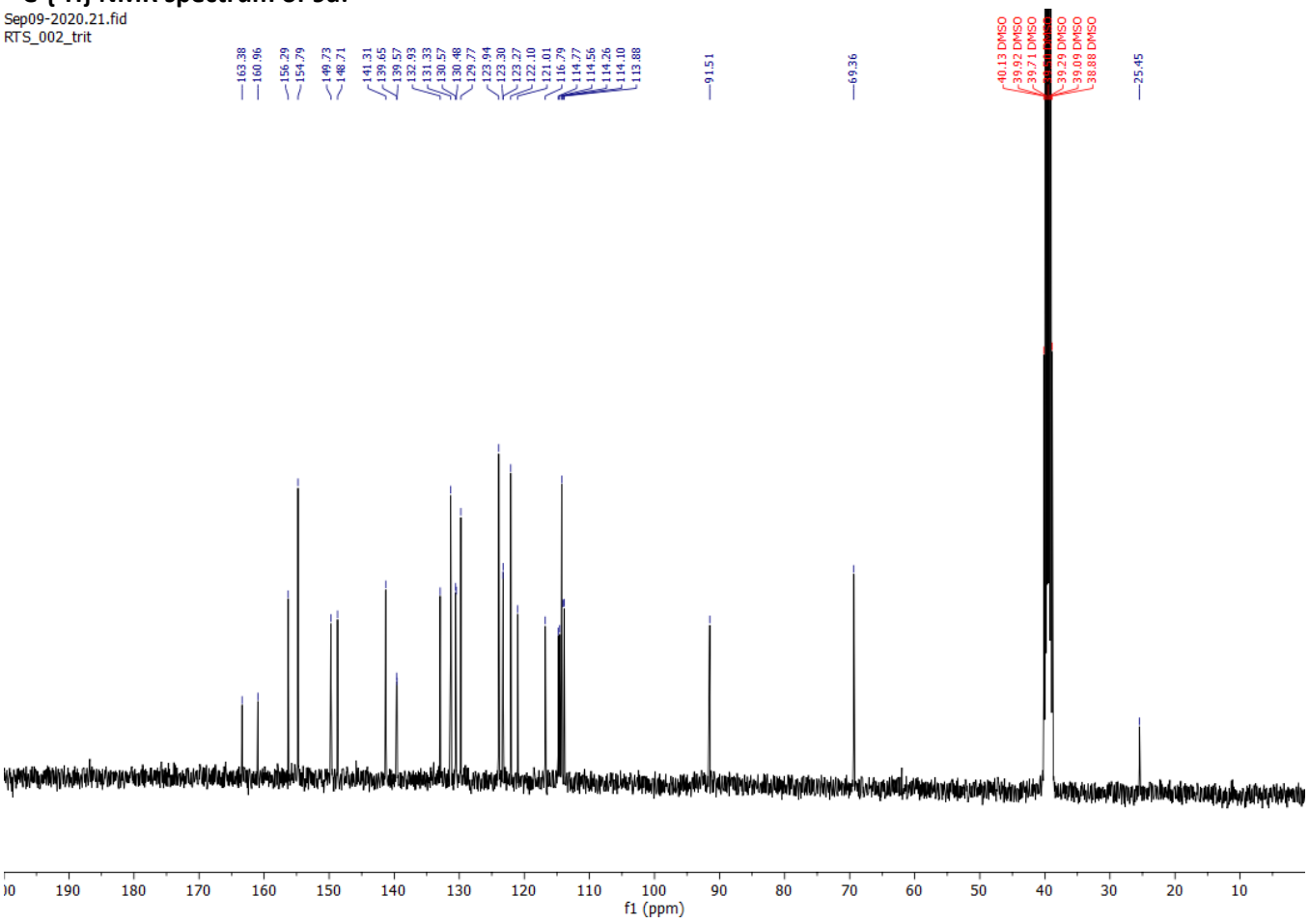
^{13}C-{^{1}H} NMR spectrum of 4-chloroquinazoline, 4:



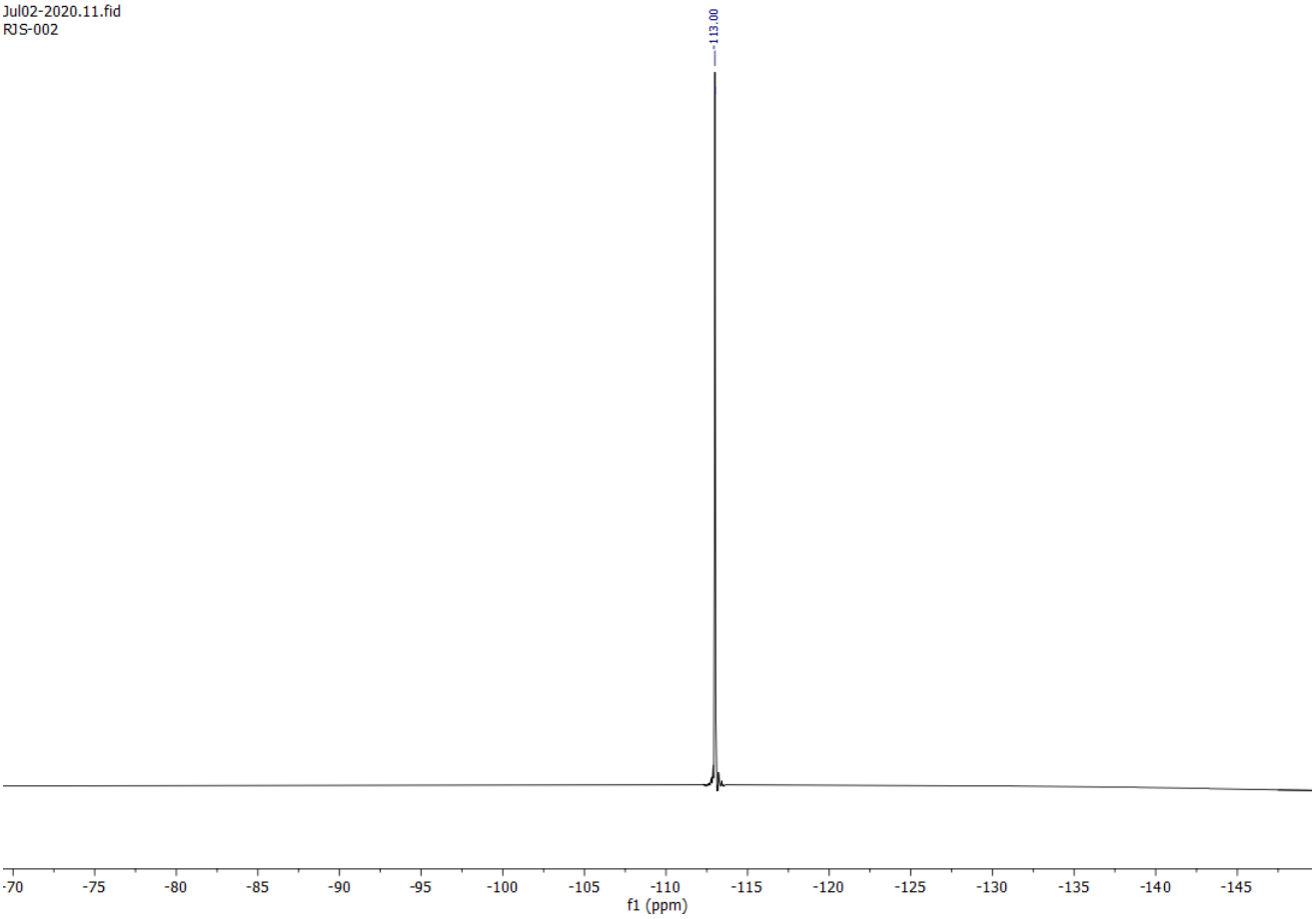
^{1}H NMR spectrum of 9a:



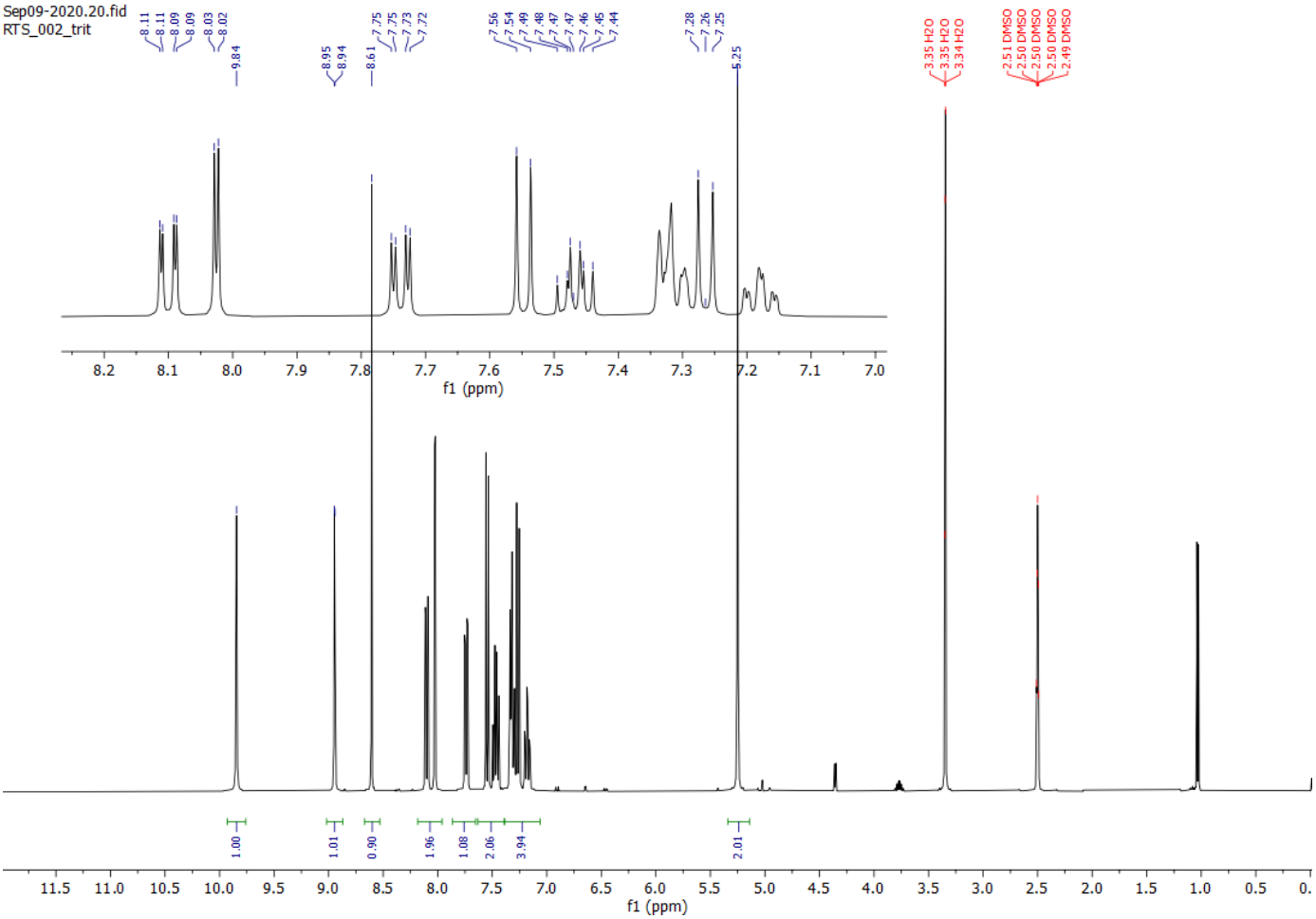
^{13}C-{^{1}H} NMR spectrum of 9a:



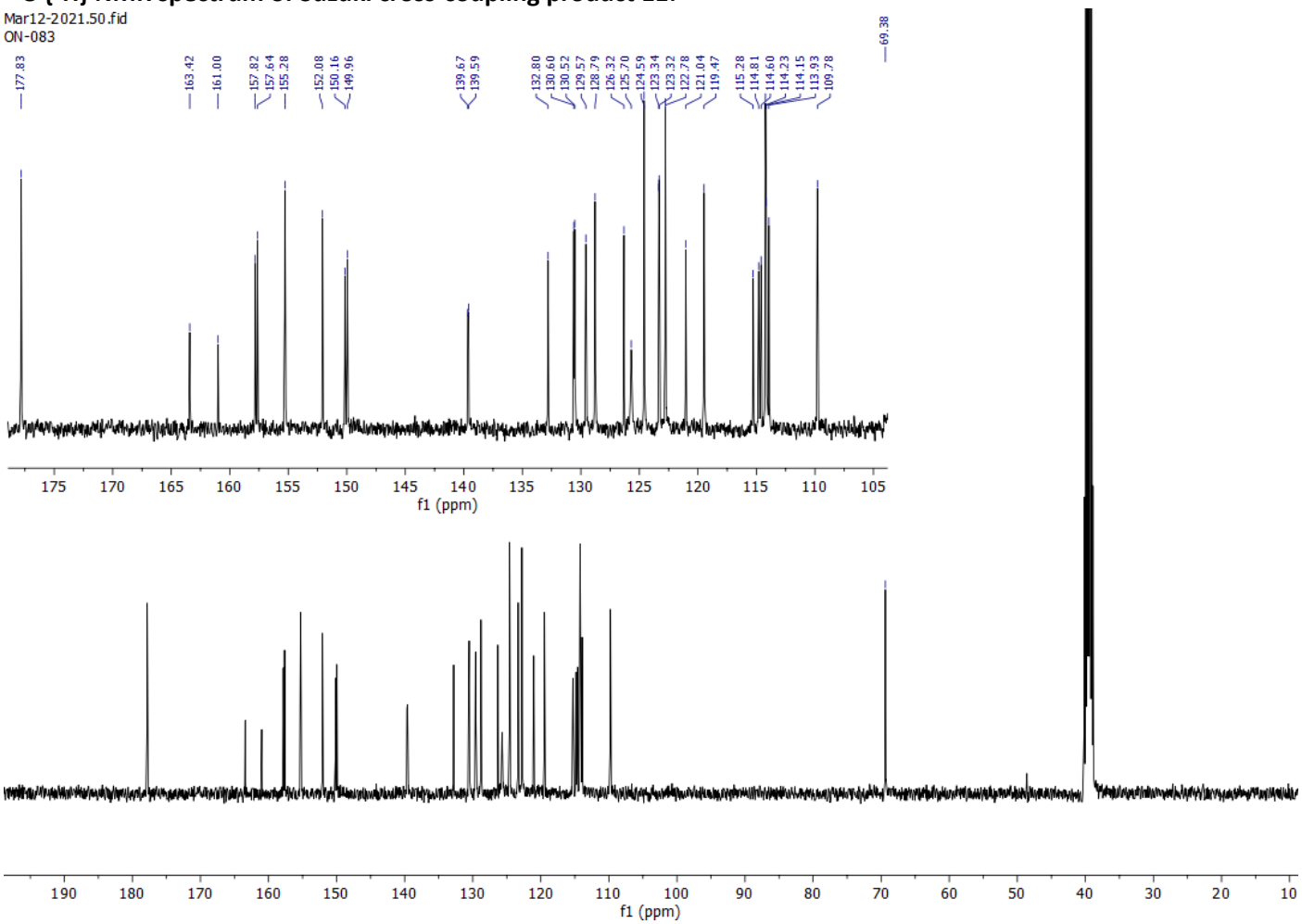
^{19}F-{^{1}H} NMR spectrum of 9a:



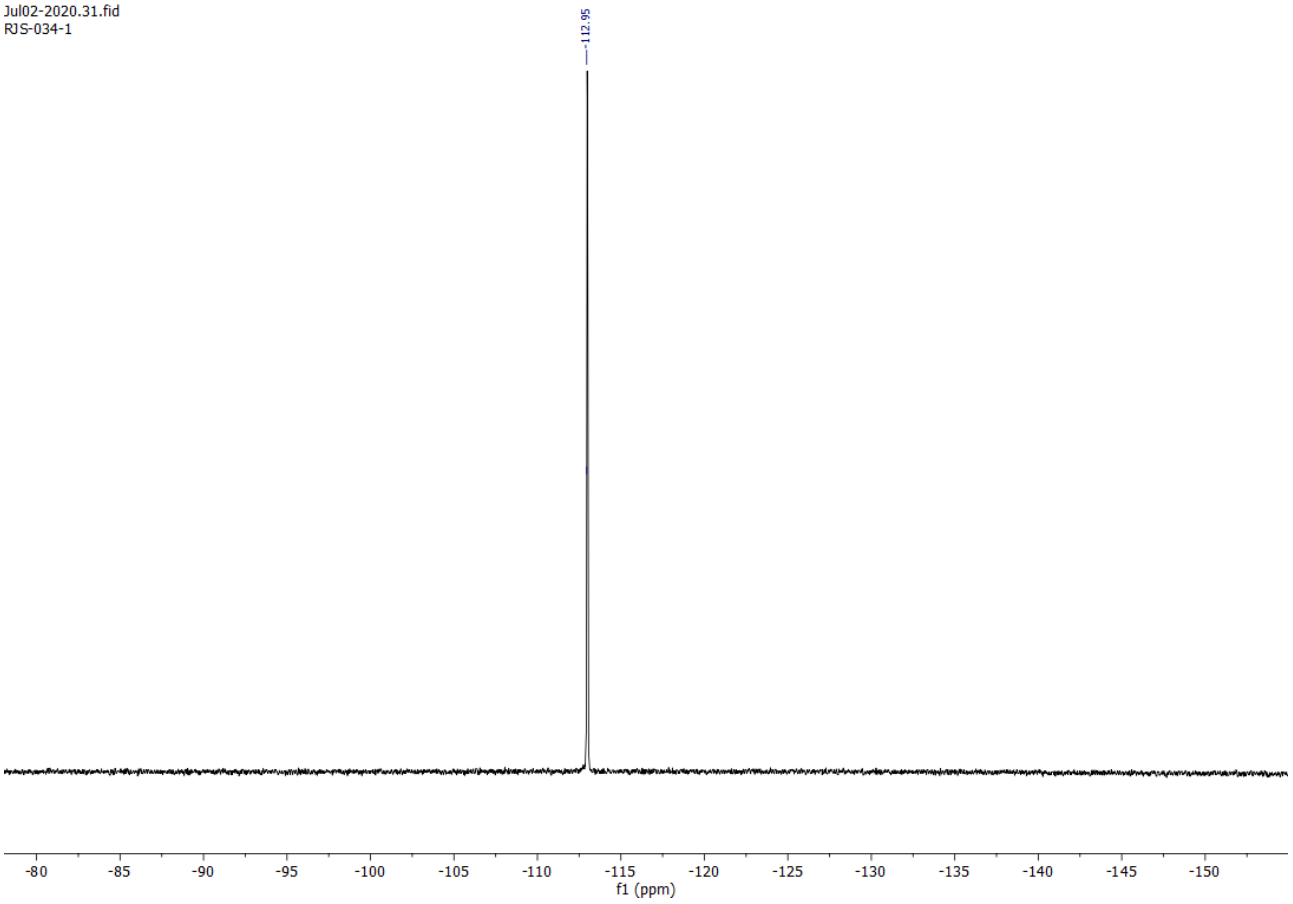
^{1}H NMR spectrum of Suzuki cross-coupling product 11:



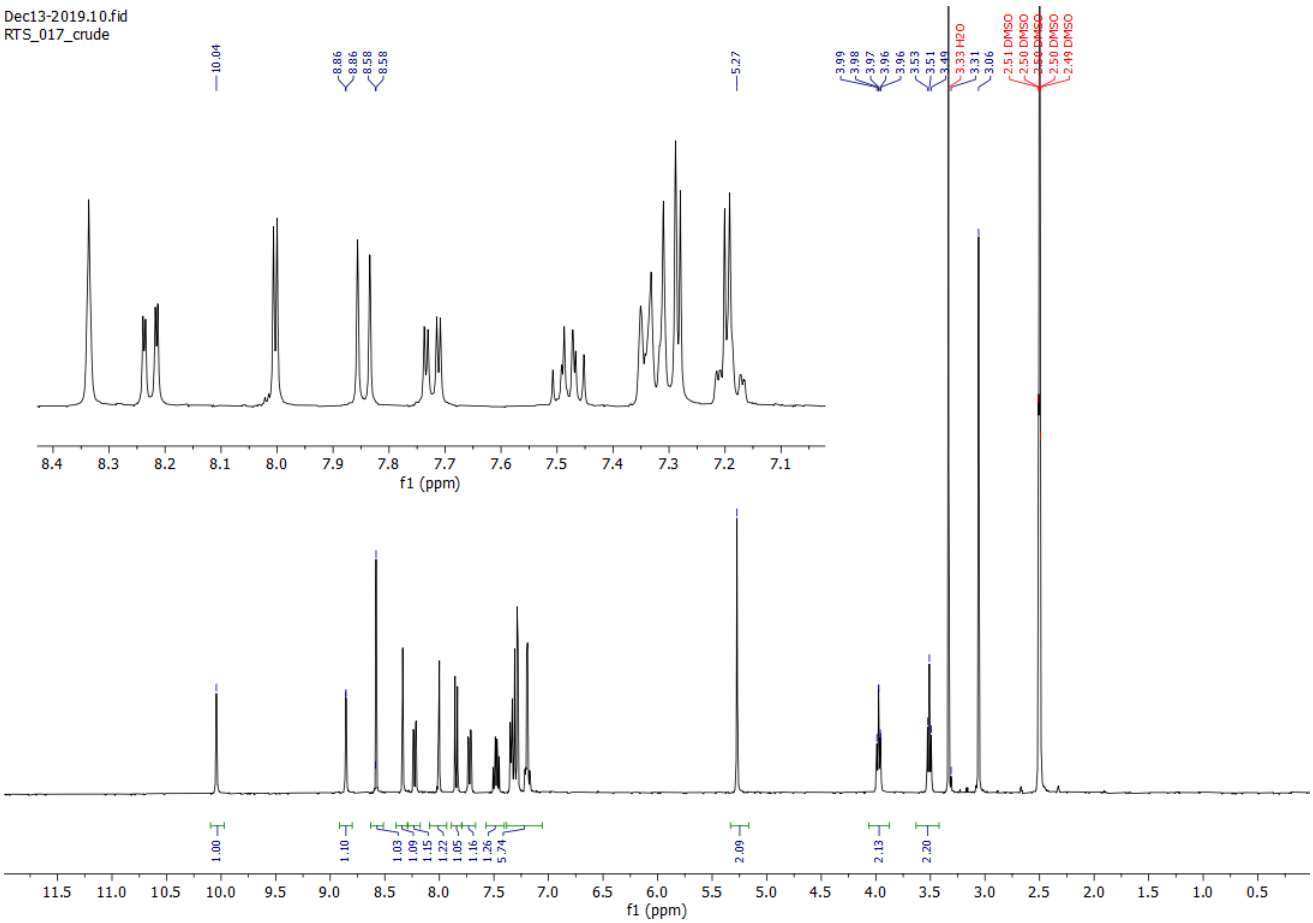
^{13}C-{^{1}H} NMR spectrum of Suzuki cross-coupling product 11:



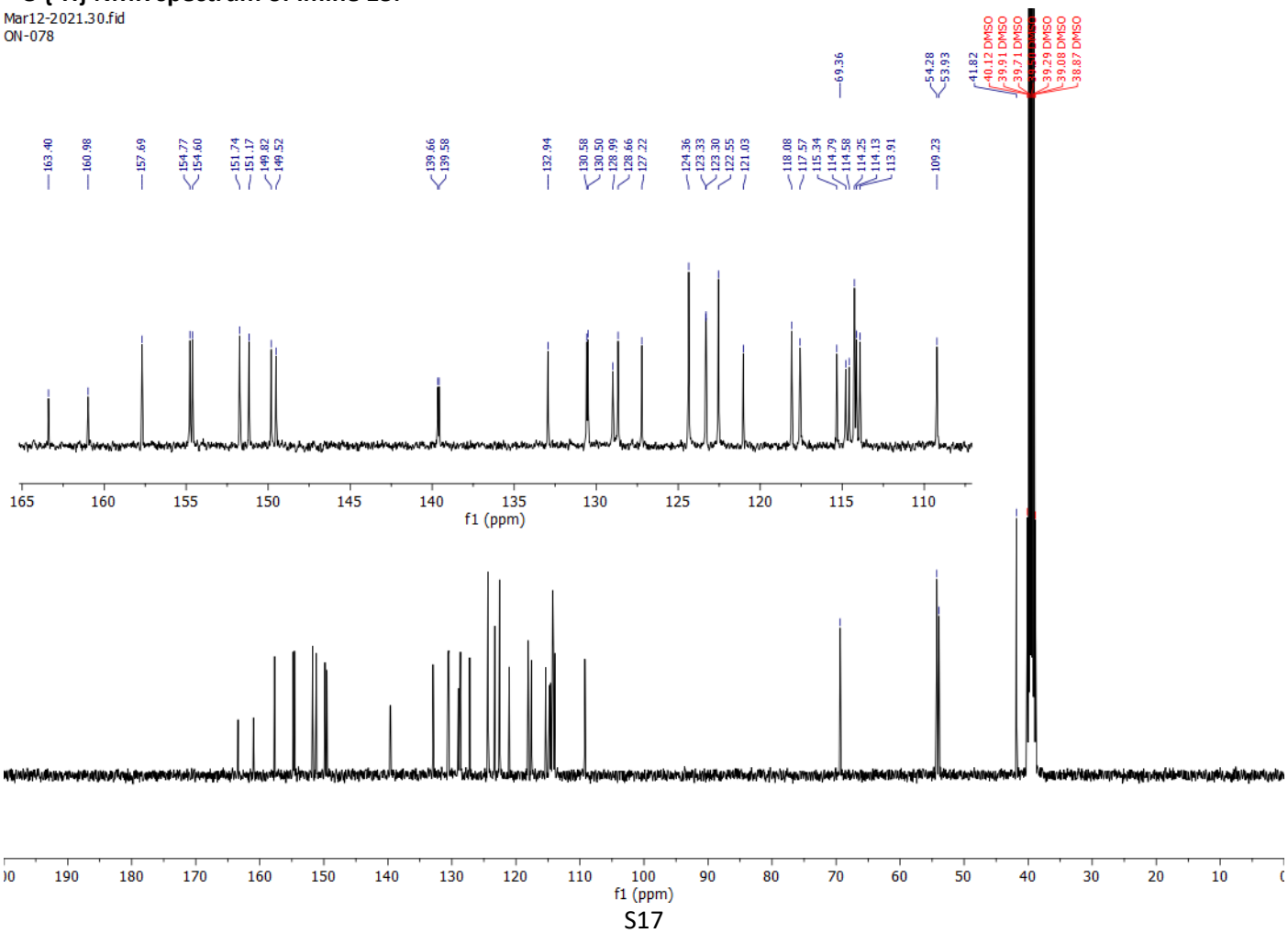
^{19}F-{^{1}H} NMR spectrum of Suzuki cross-coupling product 11:



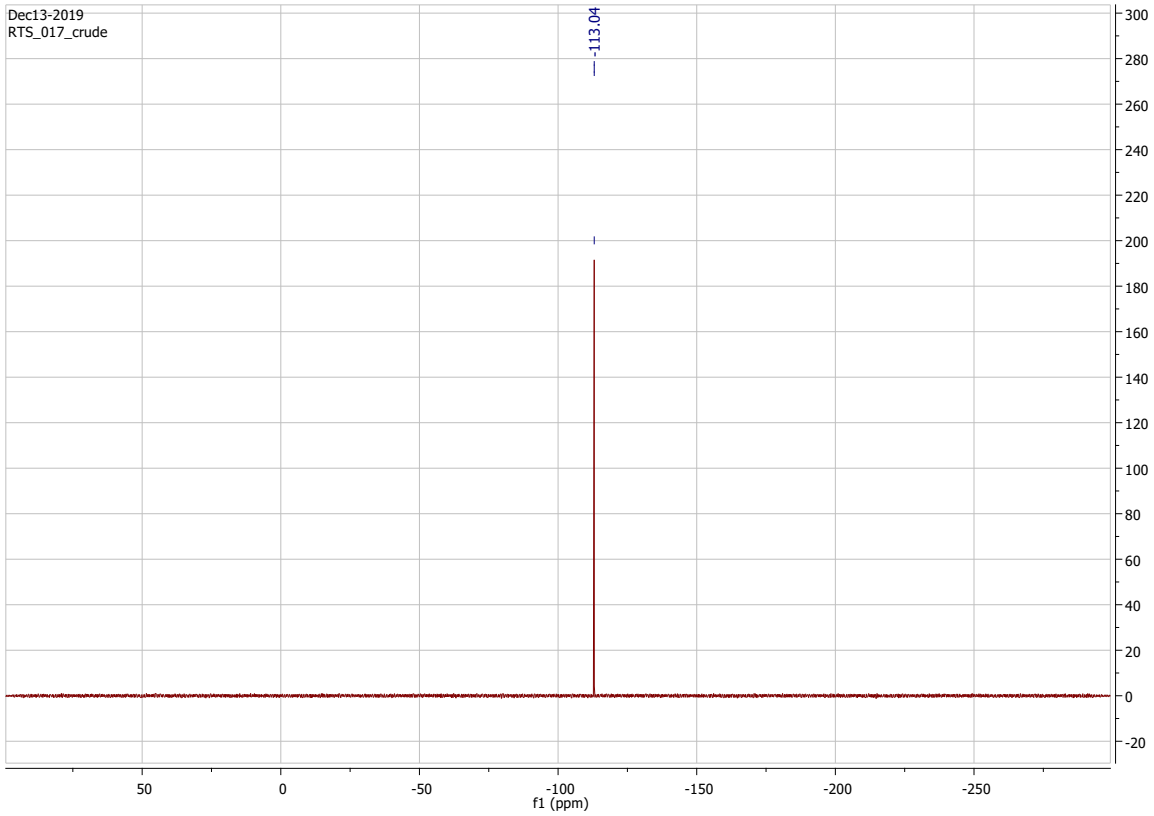
^{1}H NMR spectrum of imine 13:



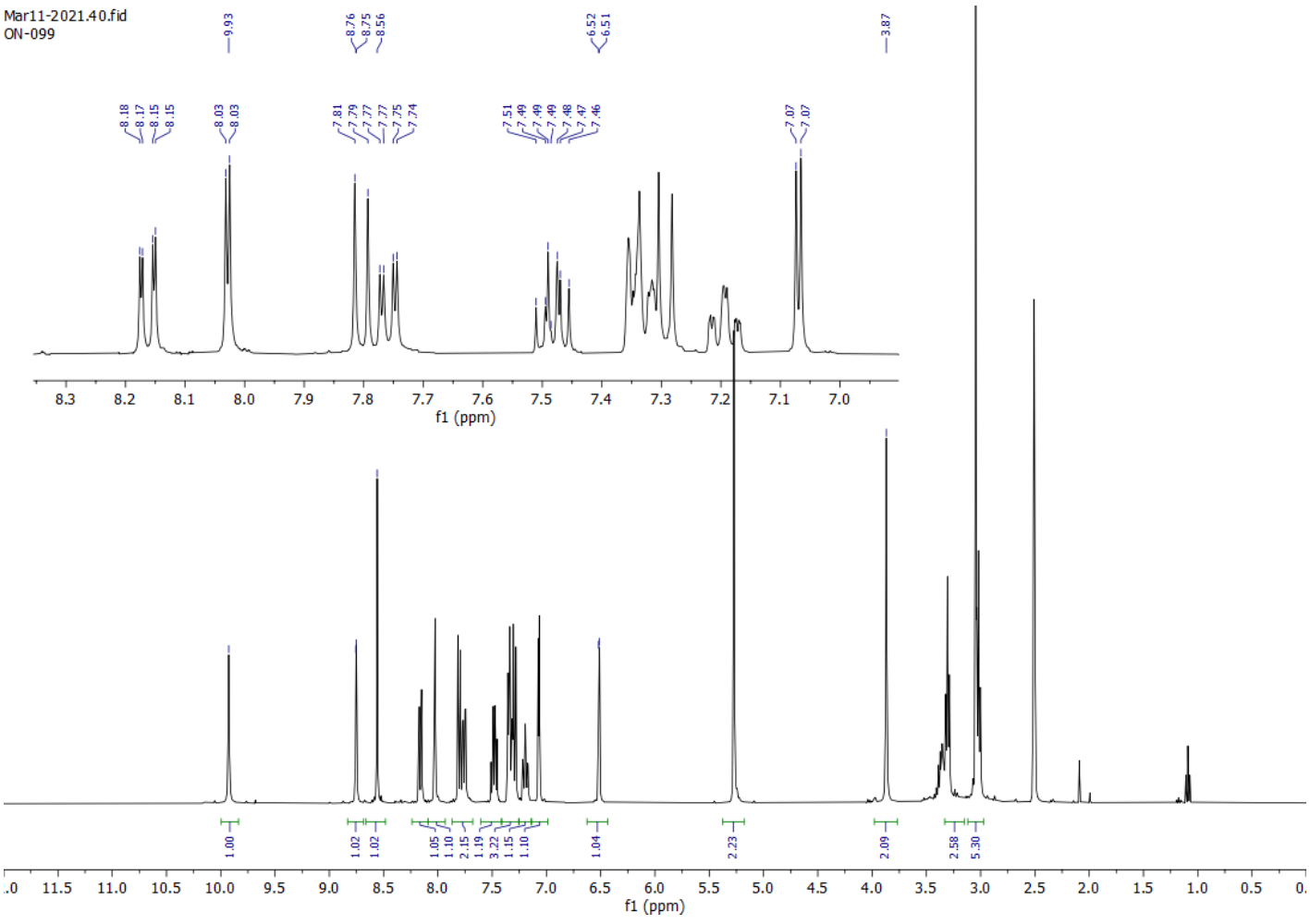
^{13}C-{^{1}H} NMR spectrum of imine 13:



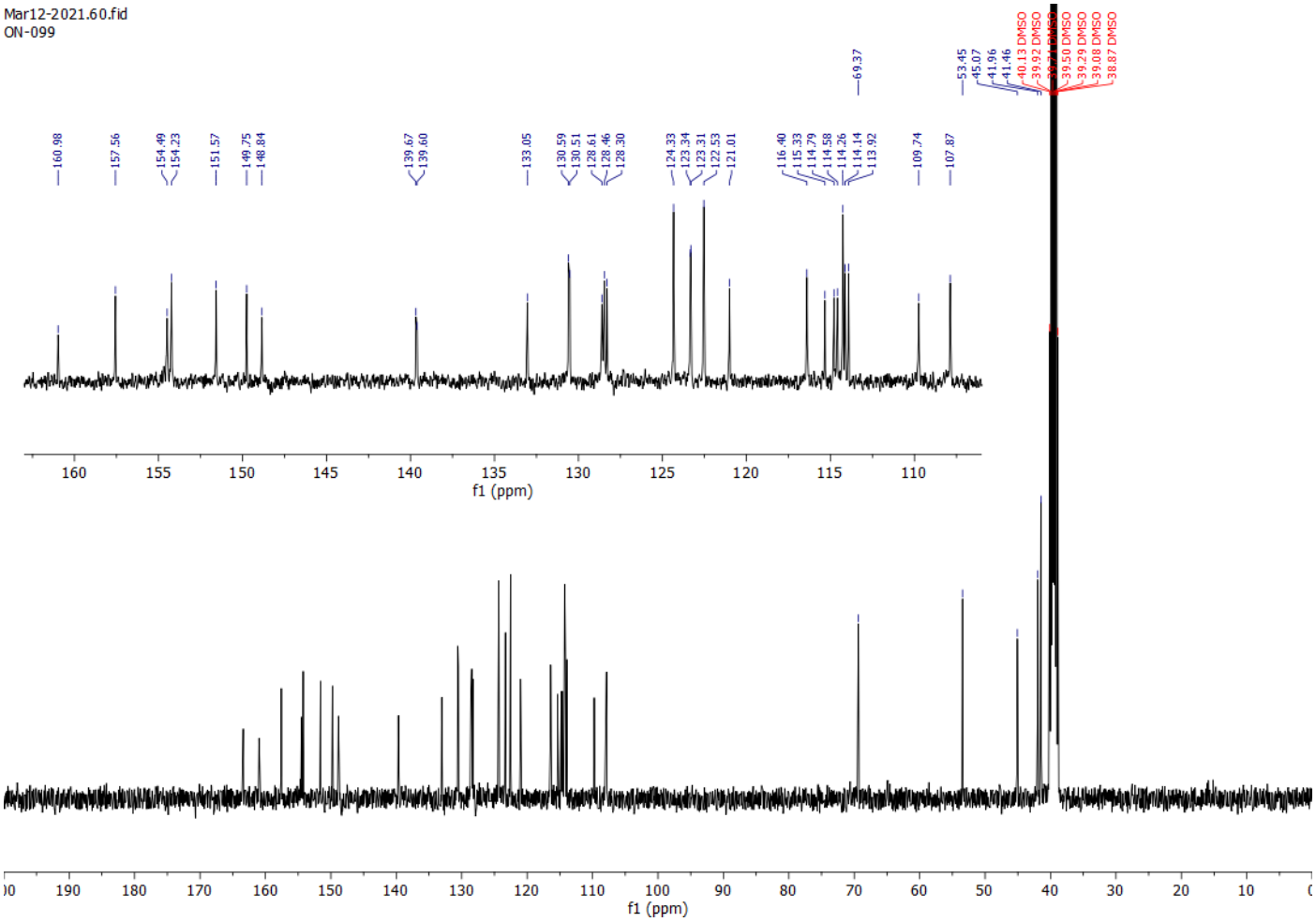
^{19}F-{^{1}H} NMR spectrum of imine 13:



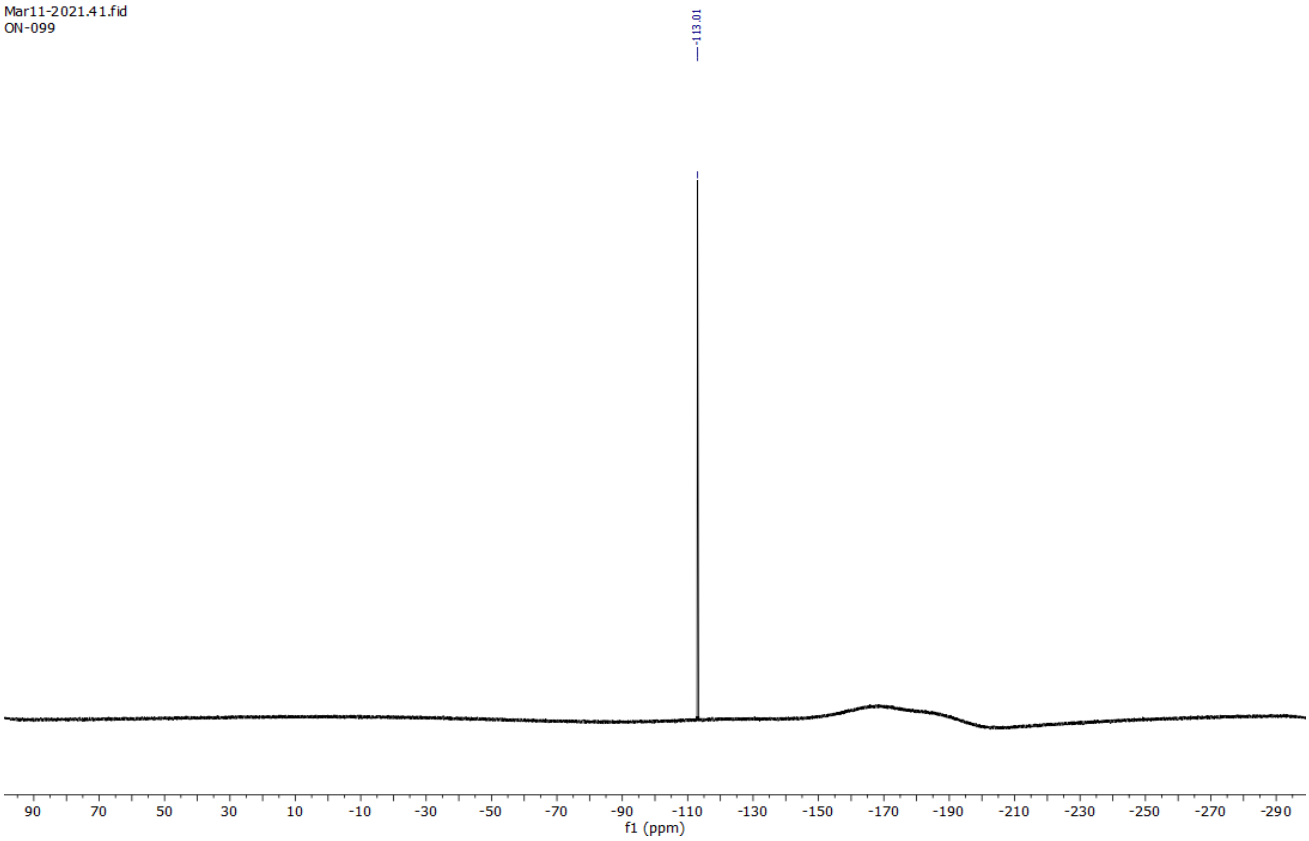
^{1}H NMR spectrum of lapatinib, 1:



^{13}C-{^{1}H} NMR spectrum of lapatinib, 1:



^{19}F-{^{1}H} NMR spectrum of lapatinib, 1:



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