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Novel artesunate – pyrimidine-based hybrids with anticancer potential against multidrug-resistant cancer cells

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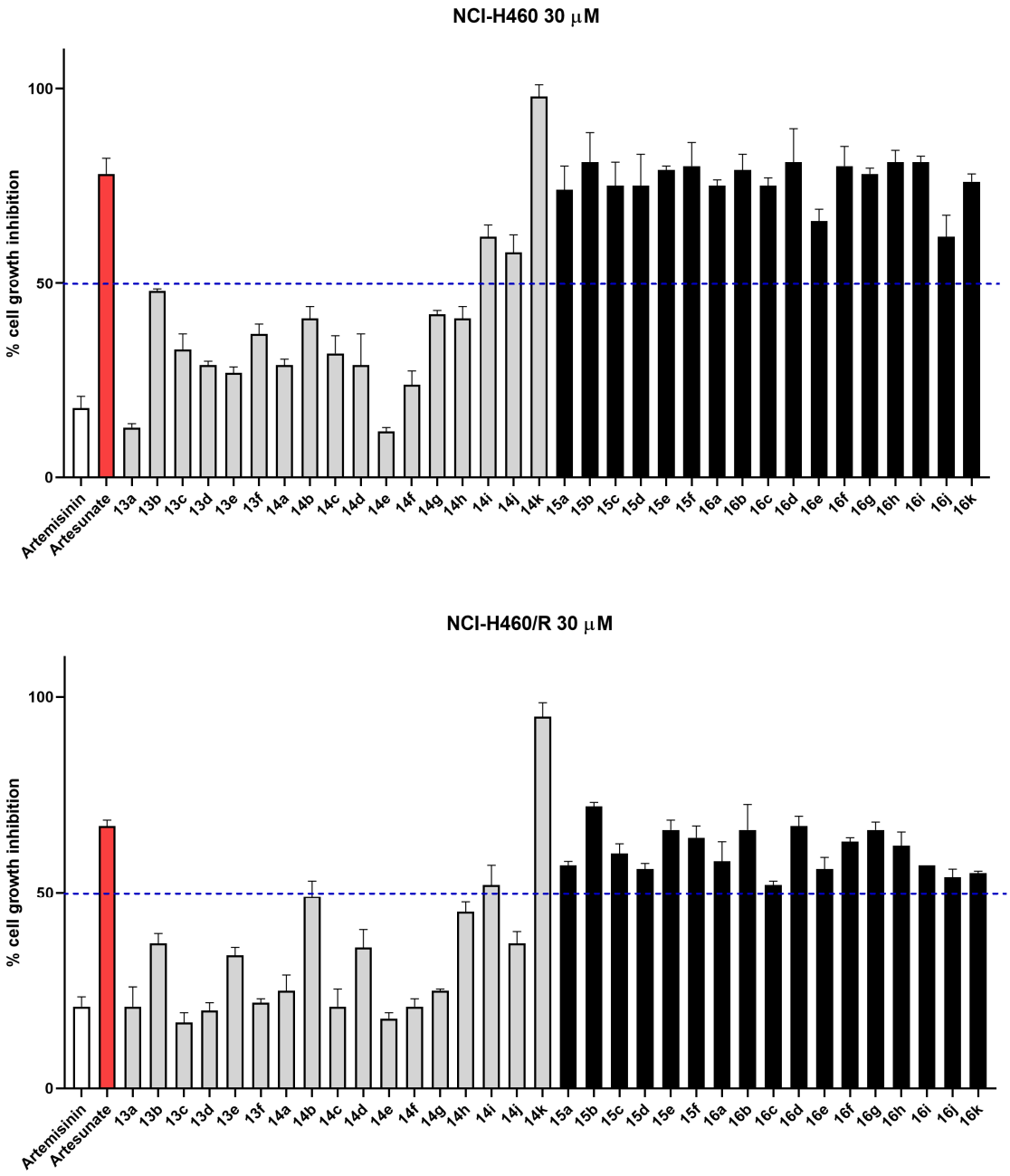
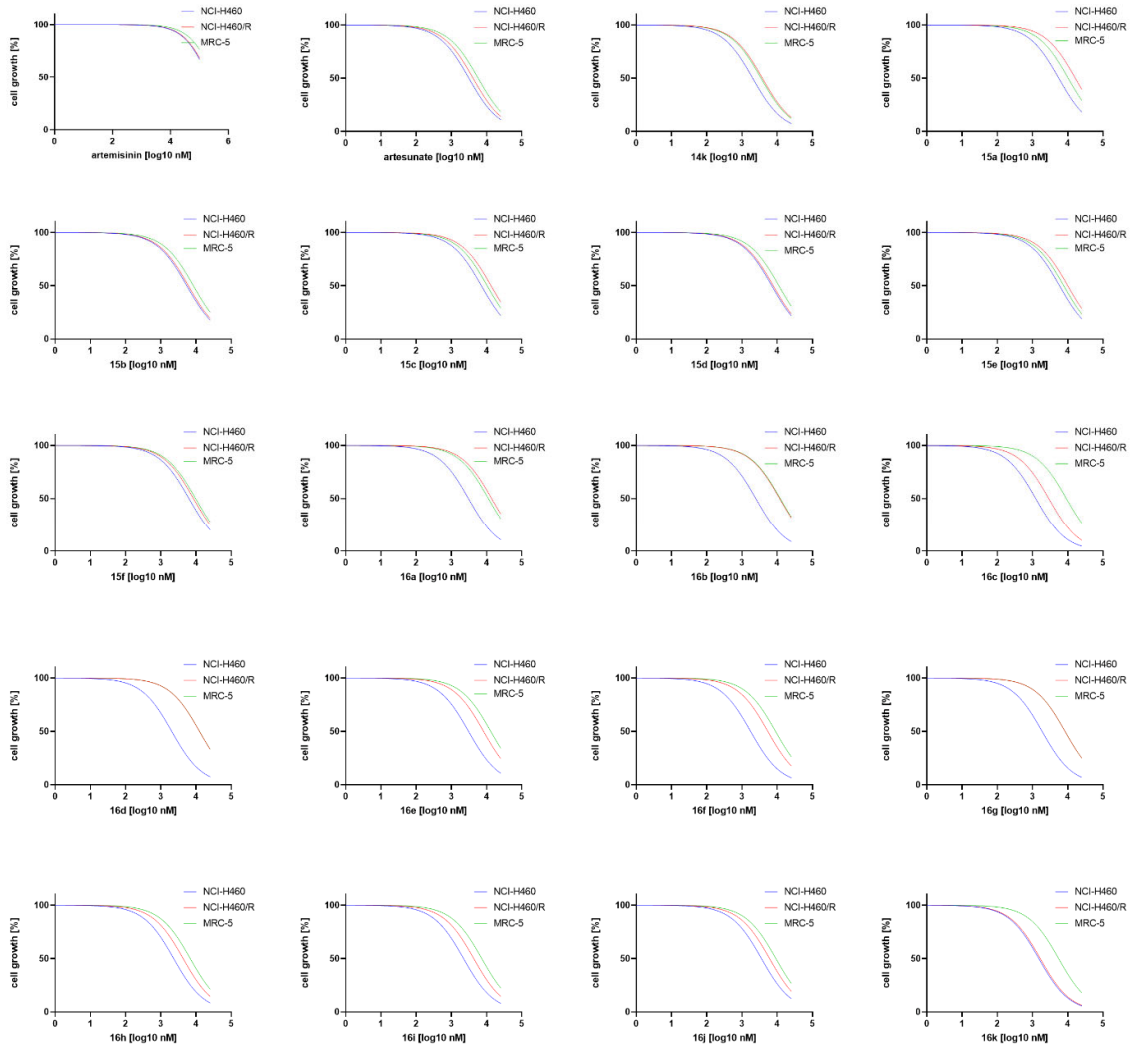
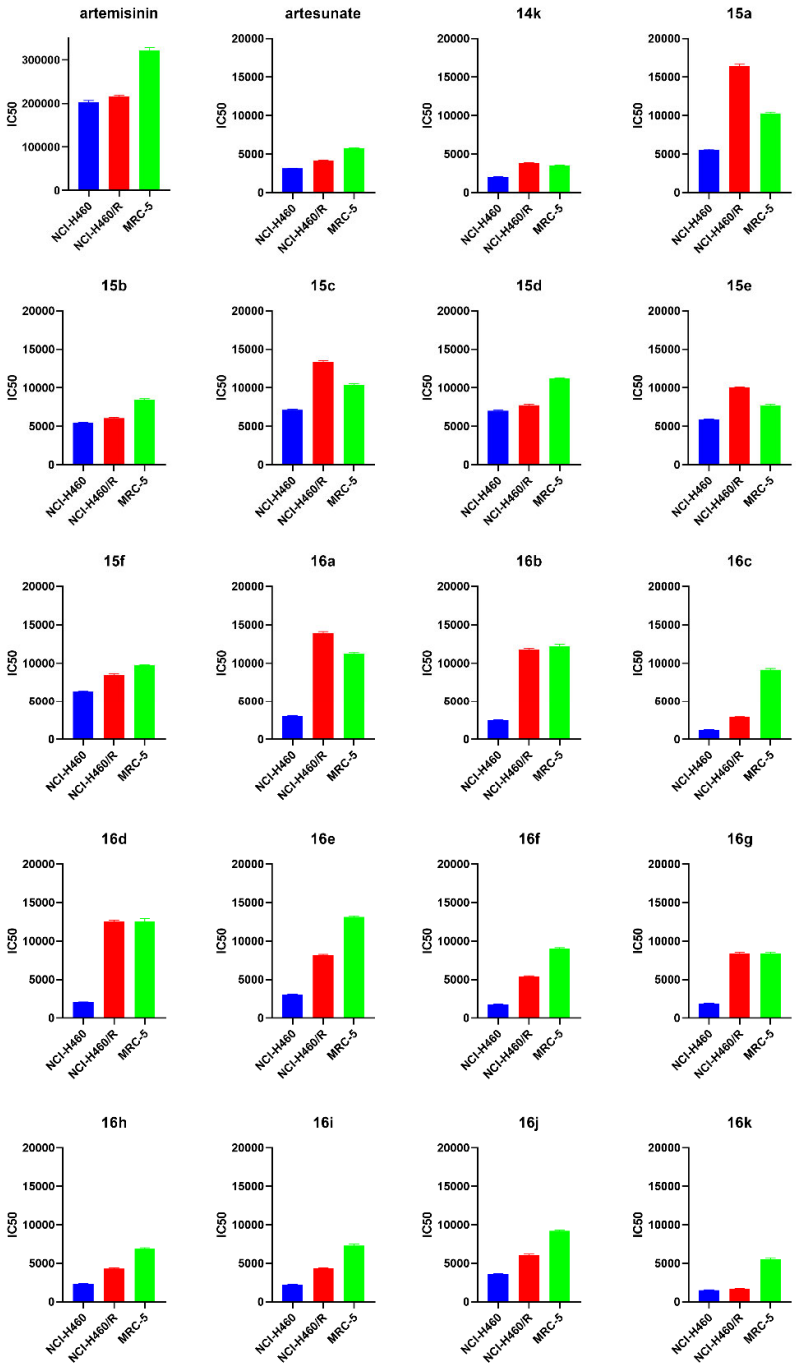


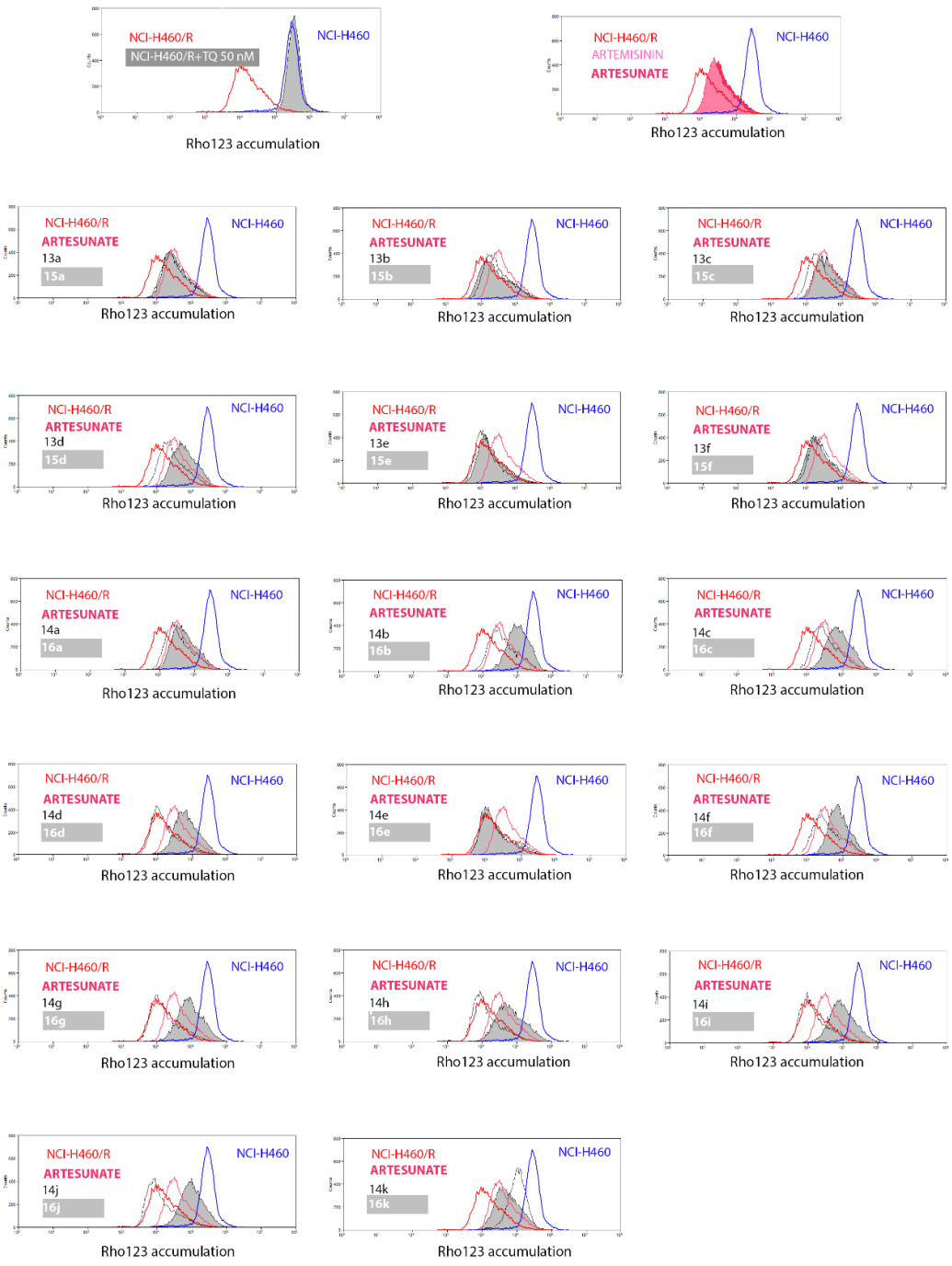
Supplementary Figure 1. Preliminary screening of novel pyrimidine derivatives and hybrid compounds. Artemisinin (white bar), artesunate (red bar), **13a-f** and **14a-k** (grey bars), and **15a-f** and **16a-k** (black bars) were applied to NCI-H460 and NCI-H460/R cells at a concentration of 30 μM. The average percentage of cell growth inhibition and standard deviation were calculated according to MTT results assayed after 72 h treatment ($n \geq 3$). The blue dashed line indicates 50% of cell growth inhibition.



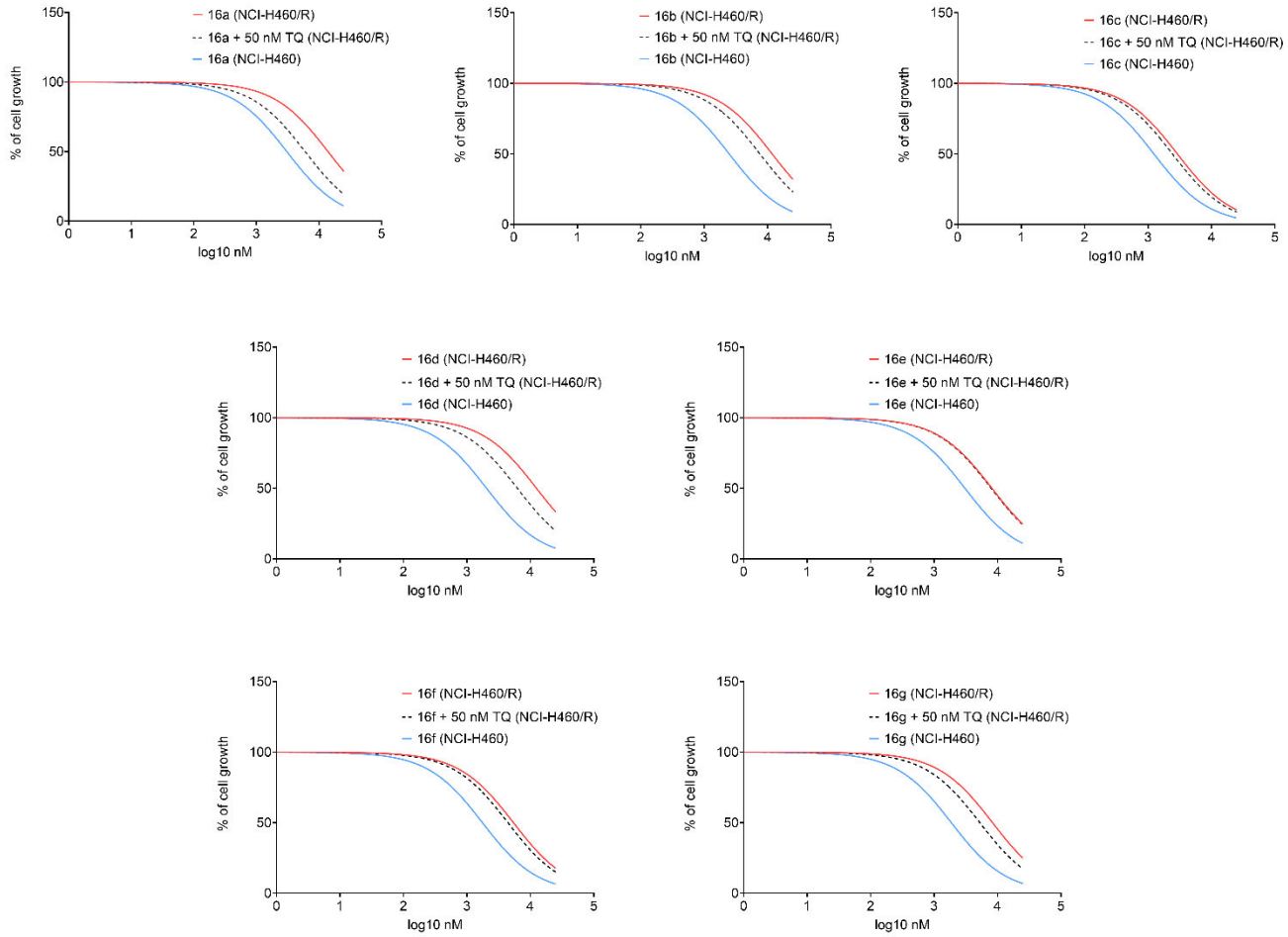
Supplementary Figure 2. Cell growth inhibition profiles obtained by non-linear regression. Artemisinin in the concentration range 5 µM - 100 µM, artesunate, pyrimidine derivatives **14k**, and hybrid compounds **15a-f**, and **16a-k** in the concentration range 1 µM - 25 µM were assayed by MTT after 72 h treatment ($n \geq 3$) and analyzed by non-linear regression in GraphPad Prism 8. The blue line represents the effects obtained in NCI-H460, the red line in NCI-H460/R, and the green line in MRC-5 cells. X-axes: log10 of nM concentration; Y-axes: % cell growth inhibition.



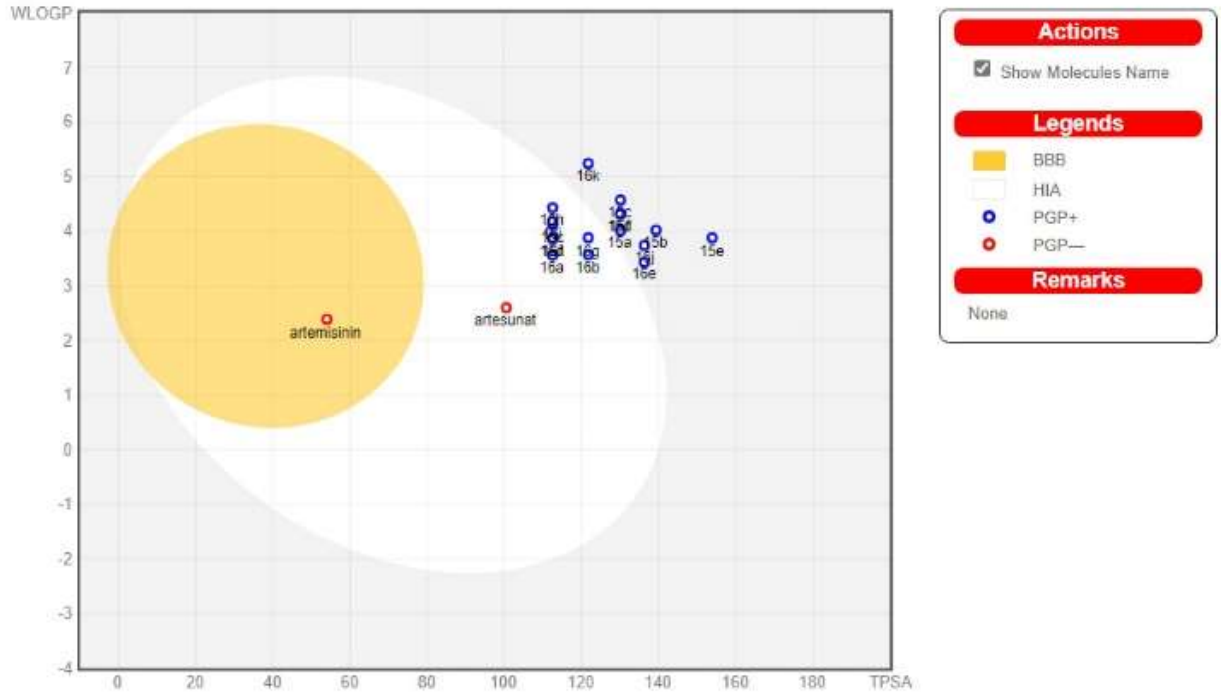
Supplementary Figure 3. Summary graph with IC50 values obtained by non-linear regression. Artemisinin in the concentration range 5 µM - 100 µM, artesunate, pyrimidine derivatives **14k**, and hybrid compounds **15a-f**, and **16a-k** in the concentration range 1 µM - 25 µM were assayed by MTT after 72 h treatment ($n \geq 3$) and analyzed by non-linear regression in GraphPad Prism 8. The blue bar represents the IC50 value obtained in NCI-H460, the red bar in NCI-H460/R, and the green bar in MRC-5 cells.



Supplementary Figure 4. Interaction with P-gp activity compared between pyrimidine derivatives and corresponding hybrid compounds. Flow cytometry profiles of rhodamine 123 (2 µM) accumulation were assessed 30 min after its simultaneous incubation with tested compounds (5 µM). The red line indicates the profile of rhodamine 123 accumulation in untreated resistant NCI-H460/R cells, the blue line in untreated NCI-H460 cells, while NCI-H460/R cells treated with pyrimidine derivatives are presented with the pink line, and NCI-H460/R cells treated with corresponding hybrid compounds are presented with the grey profile Rhodamine 123 accumulation was assessed by flow cytometry on the green channel (emission at 525 nm) and at least 10,000 events (cells) were assayed per sample.



Supplementary Figure 5. Reversal of hybrid compounds **16a-g** resistance by **TQ**. The effect of **16a-g** in NCI-H460 cells (blue line), in NCI-H460/R cells (red line), and in concurrent treatment with **TQ** in NCI-H460/R cells (black dashed line). Hybrid compounds **16a-g** were tested in the concentration range 1–25 μM, assayed by MTT after 72 h treatment ($n \geq 3$), and analyzed by non-linear regression in GraphPad Prism 8. X-axes: log10 of nM concentration; Y-axes: % cell growth inhibition.



Supplementary Figure S6. The boiled-egg plot – Brain Or IntestinaL EstimateD permeation predictive model (plot of WLOGP against TPSA) of the synthesized hybrids, artemisinin and artesunate from SwissADME. Yellow: Points located in BOILED-Egg's yolk are molecules predicted to passively permeate through the blood-brain barrier. White: Points located in the BOILED-Egg's white are molecules predicted to be passively absorbed by the gastrointestinal tract. PGP+: Blue dots are for molecules predicted to be effluated from the central nervous system by the P-glycoprotein. PGP-: Red dots are for molecules predicted not to be effluated from the central nervous system by the P-glycoprotein.

Table S1. Interaction with P-gp activity assessed by rhodamine 123 accumulation assay (30 min simultaneous treatment with tested compounds)

Cell Lines/Compounds	MFI [a]	FAR±S.E.[b]
NCI-H460[c]	340061	11.57±0.46
NCI-H460/R	29394	/
artemisinin	52361	1.78±0.15
artesunate[INH]	63674	2.17±0.16
TQ[d]	390460	13.28±0.58
13a	57434	1.95±0.20
13b	47518	1.62±0.17
13c	46024	1.57±0.14
13d	46716	1.59±0.13
13e	25161	0.86±0.09
13f	47105	1.60±0.15
14a	58586	1.99±0.16
14b	64105	2.18±0.18
14c	56502	1.92±0.16
14d	33433	1.14±0.17
14e	40590	1.38±0.13
14f	66614	2.27±0.18
14g	33466	1.14±0.12
14h	28165	0.96±0.14
14i	29903	1.02±0.10
14j	27968	0.95±0.11
14k[INH]	128209	4.36±0.21
15a	54489	1.85±0.16
15b	46478	1.58±0.19
15c[INH]	67715	2.30±0.21
15d[INH]	91112	3.10±0.20
15e	33825	1.15±0.13
15f	39075	1.33±0.12
16a[SUB]	76266	2.59±0.19
16b[SUB]	143802	4.89±0.28
16c[SUB]	114129	3.88±0.24
16d[SUB]	99563	3.39±0.20
16e	33757	1.15±0.12
16f[SUB]	111450	3.79±0.22
16g[SUB]	132961	4.52±0.30
16h[INH]	109620	3.73±0.28
16i[INH]	147315	5.01±0.36
16j[INH]	147583	5.02±0.31
16k[INH]	83011	2.82±0.19

[a]The measured mean fluorescence intensity (MFI) was used to calculate the fluorescence activity ratio (FAR).
[b]*via* the following equation: FAR = MFI of MDR treated/MFI of MDR control.
[c]Sensitive cancer cell line and its MDR counterpart used in the study: non-small cell lung carcinoma-NSCLC (NCI-H460 and NCI-H460/R).
[d]TQ (tariquidar) as a third generation P-gp inhibitor was applied as a positive control for P-gp inhibition.
[INH]Compounds that evade the MDR phenotype and inhibit P-gp activity (according to MTT assay and rhodamine 123 assay results).
[SUB]Compounds whose IC_{50} value is significantly higher in MDR than in sensitive cells (showing resistant profile according to MTT assay) but at the same time capable to increase rhodamine 123 accumulation.

Table S2. Drug-likeness properties of the investigated compounds

Molecule	MW	#H-bond acceptors	#H-bond donors	TPSA (Å^2)[a]	WLOGP[b]	MLOGP[c]
artemisinin	282.33	5	0	53.99	2.39	2.21
artesunat	384.42	8	1	100.52	2.6	2.29
15a	580.67	9	2	130.13	4.01	2.62
15b	610.70	10	2	139.36	4.02	2.33
15c	598.66	10	2	130.13	4.57	2.99
15d	594.70	9	2	130.13	4.32	2.81
15e	605.68	10	2	153.92	3.88	1.98
15f	594.70	9	2	130.13	4.32	2.81
16a	606.71	9	0	112.55	3.56	3
16b	636.74	10	0	121.78	3.57	2.69
16c	624.70	10	0	112.55	4.12	3.36
16d	620.74	9	0	112.55	3.87	3.18
16e	631.72	10	0	136.34	3.43	2.35
16f	620.74	9	0	112.55	3.87	3.18
16g	650.76	10	0	121.78	3.88	2.88
16h	638.73	10	0	112.55	4.43	3.54
16i	634.76	9	0	112.55	4.18	3.36
16j	645.75	10	0	136.34	3.74	2.53
16k	712.83	10	0	121.78	5.24	3.53

[a]Topological polar surface area. [b]logP method developed by Wildman and Crippen. [c]logP method developed by Moriguchi.

Experimental Section

Instrumentation

Unless stated otherwise, all solvents and reagents were obtained from commercial sources and used without further purification. Dry-flash chromatography was performed on SiO_2 (0.018–0.032 mm). Melting points were determined on a Boetius PMHK apparatus and are not corrected. IR spectra were recorded on a Thermo-Scientific Nicolet 6700 FT-IR Diamond Crystal instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield Avance III spectrometer (at 500 and 125 MHz, respectively) and Varian 400/54 Premium Shielded spectrometer (at 400 MHz and 100 MHz, respectively). Chemical shifts were expressed in parts per million (ppm) on the (δ) scale. Chemical shifts were calibrated relative to those of the solvent. Optical rotations were measured on a Rudolph Research Analytical Autopol IV automatic polarimeter with dichloromethane as solvent, and the compound concentration used was 1.00 mg/mL. HRESIMS and MS/MS spectra were acquired in positive mode on Q Exactive Plus (ThermoFisher Scientific, Inc., Bremen, Germany) mass spectrometer, equipped with a heated HESI-II source. Operating conditions for the HESI source used in a positive ionization mode were: +3.5 kV spray voltage, 320 °C capillary and probe heater temperature, sheath gas flow rate 36 a.u., auxiliary gas flow 11 a.u. (a.u. refer to arbitrary values set by the Exactive Tune software) and S-Lens RF level 50.00. The synthesized compounds were also analyzed by high resolution tandem mass spectrometry using LTQ Orbitrap XL (Thermo Fisher Scientific Inc., USA) mass spectrometer. The sample was dissolved in MeCN and it was injected directly. Ionization was done in positive mode on heated electrospray ionization (HESI) probe. HESI parameters were: spray voltage 4.7 kV, vaporizer temperature 60 °C, sheath and auxiliary gas flow 24 and 10 (arbitrary units), respectively, capillary voltage 49 V, capillary temperature 275 °C, tube lens voltage 80 V, resolution (at *m/z* 400): 30000. Compounds were analyzed for purity using Agilent 1200 HPLC system equipped with a Quat Pump (G1311B), an injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and a detector 1260 DAD VL+ (G1315C). All tested compounds are fully characterized and the purities were > 95% as determined by HPLC (Supplementary Material). HPLC purity analyses were performed in two diverse systems for each compound.

General procedure A for the Suzuki coupling reaction

The desired compounds **11a-i** were prepared according to the literature procedure.[1]

To a dry glass flask purged with argon $Pd(OAc)_2$ (0.05 eq), PPh_3 (0.10 eq) and appropriate solvent were added. The solution was stirred at room temperature for 5 min and appropriate 2,4-dichloropyrimidine **9** (1 eq) and Na_2CO_3 (3.1 eq) in H_2O (1.5 mL per 1.01 mmol of **9**) were added. After 5 min arylboronic acid **10** (1 eq) was added and the reaction mixture was heated in an oil bath at 95 °C under inert atmosphere for 6 h. The solution was cooled to room temperature, washed with CH_2Cl_2 and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the remaining solid was purified by dry-flash column chromatography.

2-Chloro-4-phenylpyrimidine (11a).[2] Following general procedure **A**, reaction was performed using 2,4-dichloropyrimidine **9a** (150 mg, 1.01 mmol) and phenylboronic acid **10a** (123 mg, 1.01 mmol) in DME (7.5 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford **11a** as a colorless solid (141 mg, 73%). m.p. = 85 – 87 °C. IR (ATR): 3141, 3110, 3065, 3043, 3018, 2985, 2918, 1610, 1601, 1571, 1532, 1496, 1450, 1421, 1347, 1288, 1182, 1119, 1070, 999, 985, 860, 841, 816, 784, 750, 706, 687, 623, 466, 423 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 5.2 Hz, 1H), 8.09 (d, J = 6.7 Hz, 2H), 7.64 (d, J = 5.3 Hz, 1H), 7.57 − 7.48 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 162.0, 160.0, 135.2, 132.0, 129.3, 127.6, 115.3 ppm.

2-Chloro-4-(4-methoxyphenyl)pyrimidine (11b).[2] Following general procedure **A**, reaction was performed using 2,4-dichloropyrimidine **9a** (150 mg, 1.01 mmol) and (4-methoxyphenyl)boronic acid **10b** (153 mg, 1.01 mmol) in DME (7.5 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 6/4) to afford **11b** as a colorless solid (174 mg, 78%). m.p. = 136 – 139 °C. IR (ATR): 3063, 3023, 2981, 2937, 2840, 2555, 2031, 1901, 1608, 1572, 1530, 1510, 1463, 1452, 1434, 1408, 1347, 1321, 1300, 1258, 1178, 1124, 1106, 1071, 1023, 985, 827, 804, 781, 769, 728, 688, 645, 580, 514, 425 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 5.1 Hz, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 5.1 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 163.0, 161.9, 159.6, 129.3, 127.5, 114.6, 114.3, 55.6 ppm.

2-Chloro-4-(4-fluorophenyl)pyrimidine (11c).[2] Following general procedure **A**, reaction was performed using 2,4-dichloropyrimidine **9a** (150 mg, 1.01 mmol) and (4-fluorophenyl)boronic acid **10c** (141 mg, 1.01 mmol) in DME (7.5 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 8/2) to afford **11c** as a colorless solid (159 mg, 76%). m.p. = 127 – 130 °C. IR (ATR): 3109, 3066, 2918, 1599, 1572, 1535, 1507, 1433, 1403, 1346, 1316, 1305, 1287, 1237,

1191, 1164, 1121, 1100, 1068, 1015, 986, 836, 791, 770, 689, 642, 569, 503, 494, 431, 402 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 5.3 Hz, 1H), 8.11 (dd, J = 9.0 Hz, J = 5.3 Hz, 2H), 7.60 (d, J = 5.3 Hz, 1H), 7.20 (t, J = 8.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 165.3 (d, $J_{C\text{-}F}$ = 253 Hz), 162.0, 160.0, 131.4 (d, $J_{C\text{-}F}$ = 3 Hz), 129.8 (d, $J_{C\text{-}F}$ = 9 Hz), 116.4 (d, $J_{C\text{-}F}$ = 22 Hz), 114.9 ppm.

2-Chloro-4-(*p*-tolyl)pyrimidine (11d).[3] Following general procedure **A**, reaction was performed using 2,4-dichloropyrimidine **9a** (150 mg, 1.01 mmol) and *p*-tolylboronic acid **10d** (137 mg, 1.01 mmol) in DME (7.5 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford **11d** as a colorless solid (159 mg, 77%). m.p. = 98 – 100 °C. IR (ATR): 3108, 3062, 2987, 2919, 1613, 1573, 1532, 1509, 1429, 1404, 1377, 1343, 1314, 1286, 1189, 1128, 1108, 1068, 985, 949, 863, 832, 818, 779, 767, 716, 688, 568, 542, 482, 425 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, J = 5.3 Hz, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 5.3 Hz, 1H), 7.30 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 161.9, 159.7, 142.7, 132.4, 130.0, 127.5, 114.9, 21.6 ppm.

2-Chloro-4-methyl-6-phenylpyrimidine (11e).[2] Following general procedure **A**, reaction was performed using 2,4-dichloro-6-methylpyrimidine **9b** (70 mg, 0.43 mmol) and phenylboronic acid **10a** (52 mg, 0.43 mmol) in 1,4-dioxane (2.4 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford **11e** as a colorless oil (67 mg, 76%). IR (ATR): 3064, 2985, 2923, 1578, 1521, 1495, 1436, 1379, 1354, 1302, 1280, 1250, 1205, 1083, 1073, 1030, 1002, 916, 859, 840, 828, 785, 752, 690, 645, 570, 548, 452 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 – 8.03 (m, 2H), 7.54 – 7.46 (m, 4H), 2.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 166.9, 161.5, 135.4, 131.7, 129.1, 127.5, 114.8, 24.3 ppm.

2-Chloro-4-(4-methoxyphenyl)-6-methylpyrimidine (11f).[4] Following general procedure **A**, reaction was performed using 2,4-dichloro-6-methylpyrimidine **9b** (50 mg, 0.31 mmol) and (4-methoxyphenyl)boronic acid **10b** (47 mg, 0.31 mmol) in 1,4-dioxane (1.7 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford **11f** as a colorless solid (54 mg, 75%). m.p. = 59 – 61 °C. IR (ATR): 3017, 2982, 2935, 2841, 1610, 1588, 1577, 1516, 1453, 1362, 1304, 1270, 1252, 1204, 1176, 1111, 1084, 1024, 982, 918, 866, 841, 827, 768, 647, 590, 548, 505, 443 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.6 Hz, 2H), 7.40 (s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 2.54 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 166.4, 162,7, 161.4, 129.2, 127.8, 114.5, 113.8, 55.6, 24.3 ppm.

2-Chloro-4-(4-fluorophenyl)-6-methylpyrimidine (11g).[5] Following general procedure **A**, reaction was performed using 2,4-dichloro-6-methylpyrimidine **9b** (70 mg, 0.43 mmol) and (4-fluorophenyl)boronic acid **10c** (60 mg, 0.43 mmol) in 1,4-dioxane (2.4 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford **11g** as a colorless solid (67 mg, 70%). m.p. = 100 – 102 °C. IR (ATR): 3065, 2927, 1602, 1582, 1525, 1510, 1447, 1420, 1402, 1386, 1357, 1295, 1255, 1228, 1205, 1164, 1105, 1084, 1031, 1013, 983, 919, 868, 853, 838, 790, 767, 645, 581, 546, 531, 495, 446 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, J = 8.0 Hz, J = 5.4 Hz, 2H), 7.44 (s, 1H), 7.16 (t, J = 8.2 Hz, 2H), 2.57 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 165.7, 165.1 (d, $J_{C\text{-}F}$ = 251 Hz), 161.5, 131.6 (d, $J_{C\text{-}F}$ = 3 Hz), 129.7 (d, $J_{C\text{-}F}$ = 9 Hz), 116.3 (d, $J_{C\text{-}F}$ = 22 Hz), 114.4, 24.3 ppm.

2-Chloro-4-methyl-6-(*p*-tolyl)pyrimidine (11h).[5] Following general procedure **A**, reaction was performed using 2,4-dichloro-6-methylpyrimidine **9b** (70 mg, 0.43 mmol) and *p*-tolylboronic acid **10d** (58 mg, 0.43 mmol) in 1,4-dioxane (2.4 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford **11h** as a colorless solid (65 mg, 69%). m.p. = 52 – 53 °C. IR (ATR): 3040, 2921, 2851, 1612, 1586, 1521, 1507, 1442, 1402, 1385, 1357, 1291, 1254, 1218, 1201, 1184, 1111, 1087, 1041, 1010, 984, 916, 873, 842, 824, 776, 766, 719, 649, 580, 545, 476, 444 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H), 7.29 (d, J = 7.9 Hz, 2H), 2.57 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 166.9, 161.5, 142.4, 132.6, 129.9, 127.4, 114.4, 24.3, 21.6 ppm.

2-Chloro-4-(4-methoxyphenyl)-6-phenylpyrimidine (11i).[6] Following general procedure **A**, reaction was performed using 2,4-dichloro-6-phenylpyrimidine **9c** (50 mg, 0.22 mmol) and (4-methoxyphenyl)boronic acid **10b** (33 mg, 0.22 mmol) in DME (1.7 mL), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford **11i** as a colorless solid (35 mg, 53%). m.p. = 125 – 128 °C. IR (ATR): 3042, 2977, 2935, 2839, 2599, 1603, 1583, 1571, 1518, 1503, 1452, 1423, 1403, 1376, 1305, 1265, 1231, 1186, 1173, 1114, 1070, 1025, 981, 924, 873, 847, 830, 778, 759, 729, 693, 656, 641, 580, 508, 463, 442 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.10 (m, 4H), 7.93 (s, 1H), 7.55 – 7.49 (m, 3H), 7.04 – 7.00 (m, 2H), 3.89 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 167.2, 162.8, 162.1, 136.0, 131.6, 129.3, 129.2, 128.1, 127.5, 114.6, 110.1, 55.6 ppm.

General procedure B for nucleophilic aromatic substitution

The mono Boc-protected amines **12a-b** were synthesized according to the previously reported procedures.[7]

A mixture of **11** (1 eq), appropriate monoprotected amine **12** (3 eq) and K_2CO_3 (1.2 eq) in dry 1,4-dioxane (2.8 mL per 0.37 mmol of **11**) was refluxed in an oil bath for 16 h under argon. The solution was cooled to room temperature, the residue was filtered and the solvent was removed under reduced pressure. The crude product was purified by dry-flash column chromatography and used in the next phase.

General procedure C for the deprotection of amino group

The deprotection of Boc-protected amine derivatives (1 eq) was performed using trifluoroacetic acid (16 eq) in CH_2Cl_2 (6.2 mL per 0.29 mmol of appropriate Boc-protected amine). The reaction mixture was stirred at room temperature for 15 h. After that, reaction mixture was neutralized with $NaHCO_3$ to pH 9 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure to give the desired product which was directly used in the next step without further purification.

***N*^{1}-(4-Phenylpyrimidin-2-yl)ethane-1,2-diamine (13a)**. Following general procedure **B**, reaction was performed using **11a** (69 mg, 0.36 mmol) and *tert*-butyl (2-aminoethyl)carbamate **12a** (171 mg, 1.07 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 6/4) to afford Boc-protected amine derivative as a colorless solid (108 mg, 96%). m.p. = 112 – 114 °C. IR (ATR): 3377, 3277, 3091, 3056, 3017, 2877, 2941, 2919, 1683, 1589, 1565, 1517, 1458, 1439, 1413, 1367, 1354, 1321, 1273, 1253, 1214, 1179, 1080, 1039, 1027, 1000, 980, 919, 860, 812, 783, 761, 730, 626, 589, 552, 513, 476, 432 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 5.2 Hz, 1H), 8.03 – 7.97 (m, 2H), 7.48 – 7.43 (m, 3H), 6.97 (d, J = 5.1 Hz, 1H), 5.73 (brs, 1H), 5.27 (brs, 1H), 3.61 (q, J = 5.9 Hz, 2H), 3.40 (q, J = 5.8 Hz, 2H), 1.41 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 162.9, 158.6, 156.4, 137.4, 130.7, 128.8, 127.1, 106.9, 79.3, 41.7, 41.1, 28.5 ppm.

Following general procedure **C** for the deprotection of amino group, compound **13a** was obtained as a yellow oil (62 mg, 86%) from appropriate Boc-protected amine (105 mg, 0.334 mmol). IR (ATR): 3272, 3061, 2926, 2868, 1715, 1590, 1569, 1531, 1496, 1462, 1415, 1343, 1324, 1278, 1205, 1185, 1157, 1070, 1027, 984, 925, 820, 768, 735, 696, 629 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 5.2 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.49 – 7.43 (m, 3H), 6.96 (d, J = 5.1 Hz,

1H), 5.67 (brs, 1H), 3.57 (q, *J* = 5.9 Hz, 2H), 2.97 (brs, 2H), 1.75 (brs, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 163.0, 158.6, 137.6, 130.6, 128.8, 127.1, 106.7, 44.4, 41.7 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}N_4^+$ 215.12912; found 215.12901. HPLC purity, method C: t_R = 10.22 min, area 98.83%. Method G: t_R = 5.94 min, area 99.17% (λ = 254 nm).

***N*^{1}-(4-(4-Methoxyphenyl)pyrimidin-2-yl)ethane-1,2-diamine (13b)**. Following general procedure **B**, reaction was performed using **11b** (31 mg, 0.14 mmol) and *tert*-butyl (2-aminoethyl)carbamate **12a** (70 mg, 0.44 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 6/4) to afford Boc-protected amine derivative as a colorless solid (35 mg, 75%). m.p. = 123 – 125 °C. IR (ATR): 3366, 2977, 2935, 2839, 1707, 1607, 1567, 1511, 1462, 1412, 1392, 1366, 1342, 1306, 1252, 1211, 1175, 1091, 1073, 1032, 985, 846, 807, 583 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 5.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 5.2 Hz, 1H), 5.71 (brs, 1H), 5.31 (brs, 1H), 3.84 (s, 3H), 3.60 (q, *J* = 5.8 Hz, 2H), 3.39 (q, *J* = 5.9 Hz, 2H), 1.40 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.8, 161.8, 158.3, 156.3, 129.8, 128.6, 114.1, 106.1, 79.3, 55.5, 41.6, 41.1, 28.5 ppm.

Following general procedure **C** for the deprotection of amino group, compound **13b** was obtained as a beige solid (28 mg, 86%) from appropriate Boc-protected amine (45 mg, 0.13 mmol). m.p. = 128 – 130 °C. IR (ATR): 3263, 3110, 2965, 2937, 2875, 1610, 1571, 1508, 1462, 1441, 1426, 1405, 1324, 1301, 1275, 1249, 1213, 1174, 1118, 1091, 1027, 987, 966, 848, 835, 799, 711, 657, 632, 581, 544, 531 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 5.2 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 5.2 Hz, 1H), 5.48 (brs, 1H), 3.86 (s, 3H), 3.57 (q, *J* = 5.9 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H), 1.67 (brs, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 162.9, 161.8, 158.4, 130.0 128.6, 114.2, 106.0, 55.5, 44.6, 41.9 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}ON_4^+$ 245.13969; found 245.13968. HPLC purity, method C: t_R = 8.70 min, area 97.99%. Method D: t_R = 8.53 min, area 95.56% (λ = 254 nm).

***N*^{1}-(4-(4-Fluorophenyl)pyrimidin-2-yl)ethane-1,2-diamine (13c)**. Following general procedure **B**, reaction was performed using **11c** (70 mg, 0.34 mmol) and *tert*-butyl (2-aminoethyl)carbamate **12a** (162 mg, 1.01 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 1/1) to afford Boc-protected amine derivative as a colorless solid (102 mg, 91%). m.p. = 139 – 141 °C. IR (ATR): 3379, 3265, 3019, 2984, 2929, 1682, 1603, 1574, 1538, 1519, 1506, 1456, 1416, 1369, 1356, 1319, 1273, 1226, 1171, 1104, 1085, 1041, 1013, 1000, 923, 851, 826, 813, 801, 784, 597, 571, 512, 455 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 5.2 Hz, 1H), 8.00 (dd, *J* = 8.7

Hz, J = 5.5 Hz, 2H), 7.13 (t, J = 8.6 Hz, 2H), 6.91 (d, J = 5.2 Hz, 1H), 5.68 (brs, 1H), 5.20 (brs, 1H), 3.61 (q, J = 5.8 Hz, 2H), 3.39 (q, J = 5.9 Hz, 2H), 1.41 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (d, $J_{C\text{-}F}$ = 251 Hz), 163.9, 162.9, 158.7, 156.4, 133.6 (d, $J_{C\text{-}F}$ = 3 Hz), 129.1 (d, $J_{C\text{-}F}$ = 9 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22 Hz), 106.5, 79.4, 41.7, 41.0, 28.5 ppm.

Following general procedure **C** for the deprotection of amino group, compound **13c** was obtained as a colorless solid (50 mg, 77%) from appropriate Boc-protected amine (93 mg, 0.28 mmol). m.p. = 104 – 107 °C. IR (ATR): 3257, 3153, 3050, 2989, 2936, 2877, 1722, 1649, 1602, 1572, 1535, 1504, 1464, 1426, 1399, 1342, 1317, 1285, 1267, 1231, 1157, 1087, 1013, 988, 965, 853, 818, 799, 750, 716, 658, 572, 539, 518 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 5.2 Hz, 1H), 8.02 (dd, J = 8.6 Hz, J = 5.5 Hz, 2H), 7.14 (t, J = 8.4 Hz, 2H), 6.92 (d, J = 5.2 Hz, 1H), 5.53 (brs, 1H), 3.57 (q, J = 6.0 Hz, 2H), 2.97 (t, J = 6.0 Hz, 2H), 1.52 (brs, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (d, $J_{C\text{-}F}$ = 251 Hz), 163.8, 163.0, 158.8, 133.7 (d, $J_{C\text{-}F}$ = 3 Hz), 129.1 (d, $J_{C\text{-}F}$ = 9 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22 Hz), 106.3, 44.6, 41.8 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{14}N_4F^+$ 233.11970; found 233.11964. HPLC purity, method C: t_R = 8.81 min, area 97.53%. Method D: t_R = 8.69 min, area 97.41% (λ = 254 nm).

***N*^{1}-(4-(*p*-Tolyl)pyrimidin-2-yl)ethane-1,2-diamine (13d)**. Following general procedure **B**, reaction was performed using **11d** (37 mg, 0.18 mmol) and *tert*-butyl (2-aminoethyl)carbamate **12a** (86 mg, 0.54 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 7/3) to afford Boc-protected amine derivative as a beige solid (45 mg, 77%). m.p. = 133 – 135 °C. IR (ATR): 3382, 3263, 3015, 2982, 2940, 2921, 1683, 1586, 1559, 1517, 1456, 1415, 1390, 1368, 1356, 1320, 1273, 1254, 1210, 1170, 1113, 1088, 1038, 1020, 1000, 924, 859, 835, 797, 784, 764, 703, 592, 573, 550, 500, 444 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 5.2 Hz, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.29 – 7.24 (m, 2H), 6.95 (d, J = 5.2 Hz, 1H), 5.61 (brs, 1H), 5.23 (brs, 1H), 3.62 (q, J = 5.7 Hz, 2H), 3.40 (q, J = 5.8 Hz, 2H), 2.41 (s, 3H), 1.42 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 162.9, 158.5, 156.4, 141.0, 134.6, 129.6, 127.0, 106.7, 79.3, 41.7, 41.1, 28.5, 21.5 ppm.

Following general procedure **C** for the deprotection of amino group, compound **13d** was obtained as a colorless solid (24 mg, 86%) from appropriate Boc-protected amine (39 mg, 0.12 mmol). m.p. = 135 – 136 °C. IR (ATR): 3326, 3253, 3167, 3108, 3068, 3026, 2993, 2949, 2930, 2862, 1600, 1583, 1566, 1536, 1507, 1464, 1416, 1353, 1344, 1323, 1281, 1264, 1213, 1184, 1138, 1114, 1088, 1039, 1020, 990, 966, 865, 835, 798, 749, 703, 625, 574, 505, 476 cm^{-1}. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 8.29 (d, J = 5.2 Hz, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.27 – 7.23 (m, 2H), 6.93 (d, J = 5.2 Hz, 1H), 5.50 (brs, 1H), 3.56 (q, J = 6.0 Hz, 2H), 2.96 (t, J = 6.0 Hz, 2H), 2.39 (s, 3H), 1.59 (brs, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 163.0, 158.5, 141.0, 134.7, 129.6, 127.0, 106.5, 44.6, 41.8, 21.6 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}N_4^+$ 229.14477; found 229.14469. HPLC purity, method C: t_R = 8.95 min, area 98.48%. Method D: t_R = 9.08 min, area 98.77% (λ = 254 nm).

4-(2-((2-Aminoethyl)amino)pyrimidin-4-yl)benzonitrile (13e). To a dry glass flask purged with argon $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), PPh_3 (26.4 mg, 0.10 mmol) and DME (7.5 mL) were added. The solution was stirred at room temperature for 5 min and 2,4-dichloro-pyrimidine **9a** (150 mg, 1.01 mmol) and Na_2CO_3 (331 mg, 3.12 mmol) in H_2O (1.5 mL) were added. After 5 min 4-cyanophenylboronic acid **10e** (148 mg, 1.01 mmol) was added and reaction mixture was heated in an oil bath at 95 °C under inert atmosphere for 5 h. The solution was cooled to room temperature, washed with CH_2Cl_2 and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the remaining solid was used directly in the next step.

Following general procedure **B**, reaction was performed using compound from the first step (54 mg, 0.25 mmol) and *tert*-butyl (2-aminoethyl)carbamate **12a** (120 mg, 0.751 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 6/4) to afford Boc-protected amine derivative as a colorless solid (62 mg, 74%). m.p. = 166 °C. IR (ATR): 3394, 3253, 3117, 3051, 2981, 2916, 2226, 1714, 1686, 1600, 1580, 1561, 1524, 1454, 1422, 1392, 1366, 1325, 1280, 1249, 1193, 1160, 1093, 1074, 1042, 1020, 985, 952, 855, 803, 728, 697, 675, 636, 550, 530, 461, 436 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 5.1 Hz, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 5.1 Hz, 1H), 5.80 (brs, 1H), 5.13 (brs, 1H), 3.61 (q, J = 5.9 Hz, 2H), 3.39 (q, J = 5.9 Hz, 2H), 1.40 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 162.7, 159.3, 156.4, 141.7, 132.6, 127.7, 118.6, 114.0, 107.0, 79.5, 41.8, 40.8, 28.5 ppm.

Following general procedure **C** for the deprotection of amino group, compound **13e** was obtained as a yellow oil (25 mg, 62%) from appropriate Boc-protected amine (56 mg, 0.16 mmol). IR (ATR): 3369, 3255, 3081, 2919, 2851, 2225, 1678, 1582, 1559, 1502, 1463, 1419, 1350, 1327, 1277, 1249, 1205, 1150, 1101, 1058, 1017, 991, 954, 912, 857, 827, 800, 750, 721, 693, 645, 618, 547, 482 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 8.43 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 5.2 Hz, 1H), 3.66 (t, J = 6.2 Hz, 2H), 3.03 (t, J = 6.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 164.2, 164.2, 160.3, 142.9, 133.6, 128.8, 119.4, 115.0,

107.7, 43.7, 41.7 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}N_5^+$ 240.12437; found 240.12435. HPLC purity, method C: t_R = 10.26 min, area 99.52%. Method G: t_R = 6.34 min, area 99.72% (λ = 254 nm).

***N*^{1}-(4-Methyl-6-phenylpyrimidin-2-yl)ethane-1,2-diamine (13f)**. Following general procedure **B**, reaction was performed using **11e** (62 mg, 0.30 mmol) and *tert*-butyl (2-aminoethyl)carbamate **12a** (146 mg, 0.91 mmol) followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 6/4) to afford Boc-protected amine derivative as a colorless solid (80 mg, 80%). m.p. = 97 – 99 °C. IR (ATR): 3376, 3263, 3070, 2986, 2935, 1686, 1593, 1580, 1559, 1514, 1466, 1435, 1422, 1391, 1358, 1345, 1274, 1249, 1215, 1167, 1084, 1032, 1001, 983, 956, 923, 885, 867, 853, 827, 787, 769, 693, 644, 591, 549, 465 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.03 – 7.97 (m, 2H), 7.48 – 7.43 (m, 3H), 6.88 (s, 1H), 5.51 – 5.49 (m, 2H), 3.63 (q, *J* = 5.8 Hz, 2H), 3.40 (q, *J* = 5.6 Hz, 2H), 2.39 (s, 3H), 1.41 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.5, 164.8, 162.9, 156.3, 137.7, 130.5, 128.8, 127.1, 106.7, 79.2, 41.6, 28.5, 24.4 ppm.

Following the general procedure C for the amine synthesis, compound **13f** was obtained as a beige solid (43 mg, 90%) from appropriate Boc-protected amine (70 mg, 0.21 mmol). m.p. = 79 – 80 °C. IR (ATR): 3355, 3266, 3067, 2943, 2922, 2864, 1676, 1591, 1556, 1495, 1463, 1436, 1419, 1375, 1337, 1213, 1181, 1135, 1090, 1070, 1027, 960, 924, 881, 854, 826, 767, 692, 642, 592, 549 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.03 – 7.99 (m, 2H), 7.48 – 7.42 (m, 3H), 6.87 (s, 1H), 5.39 (brs, 1H), 3.59 (q, *J* = 6.0 Hz, 2H), 2.97 (t, *J* = 5.9 Hz, 2H), 2.39 (s, 3H), 1.64 (brs, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.5, 164.7, 163.1, 137.9, 130.4, 128.8, 127.1, 106.4, 44.6, 42.0, 24.5 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}N_4^+$ 229.14477; found 229.14475. HPLC purity, method A: t_R = 4.82 min, area 98.12%. Method C: t_R = 9.40 min, area 98.99% (λ = 254 nm).

4-Phenyl-2-(piperazin-1-yl)pyrimidine (14a). Following general procedure **B**, reaction was performed using **11a** (70 mg, 0.37 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (205 mg, 1.10 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford Boc-protected amine derivative as a colorless solid (123 mg, 99%). m.p. = 120 – 123 °C. IR (ATR): 2994, 2968, 2919, 2853, 1700, 1587, 1566, 1553, 1504, 1450, 1419, 1366, 1344, 1280, 1243, 1164, 1133, 1112, 1077, 1026, 1001, 983, 957, 926, 862, 844, 820, 768, 692, 629, 533 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.37 (d, *J* = 5.1 Hz, 1H), 8.07 – 8.01 (m, 2H), 7.49 – 7.44 (m, 3H), 6.96 (d, *J* = 5.2 Hz, 1H), 3.91 (t, *J* = 5.3 Hz, 4H), 3.54 (t, *J* = 5.3 Hz, 4H), 1.50 (s, 9H) ppm. ^{13}C NMR (100

MHz, $CDCl_3$): δ 164.5, 162.0, 158.5, 155.0, 137.7, 130.7, 128.8, 127.1, 106.2, 80.0, 43.8, 28.6 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14a** was obtained as a yellow oil (71 mg, 100%) from appropriate Boc-protected amine (100 mg, 0.294 mmol). IR (ATR): 3296, 2942, 2914, 2848, 2740, 1588, 1567, 1551, 1495, 1448, 1345, 1317, 1258, 1217, 1141, 1057, 1026, 984, 965, 819, 768, 695, 629 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 5.1 Hz, 1H), 8.06 – 8.01 (m, 2H), 7.47 – 7.43 (m, 3H), 6.92 (d, J = 5.1 Hz, 1H), 3.90 (t, J = 5.1 Hz, 4H), 2.96 (t, J = 5.1 Hz, 4H), 1.98 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.1, 158.4, 137.8, 130.5, 128.7, 127.1, 105.7, 46.2, 45.0 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}N_4^+$ 241.14477; found 241.14472. HPLC purity, method C: t_R = 9.03 min, area 96.36%. Method D: t_R = 9.06 min, area 95.64% (λ = 254 nm).

4-(4-Methoxyphenyl)-2-(piperazin-1-yl)pyrimidine (14b). Following general procedure **B**, reaction was performed using **11b** (70 mg, 0.32 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (177 mg, 0.95 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 8/2) to afford Boc-protected amine derivative as a colorless solid (110 mg, 93%). m.p. = 103 – 106 °C. IR (ATR): 2979, 2897, 2862, 1685, 1607, 1585, 1567, 1552, 1510, 1441, 1411, 1365, 1345, 1313, 1278, 1244, 1170, 1133, 1113, 1092, 1080, 1027, 999, 982, 957, 864, 846, 822, 800, 770, 736, 699, 581, 558, 531 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 5.2 Hz, 1H) 3.90 (t, J = 5.3 Hz, 4H), 3.87 (s, 3H), 3.53 (t, J = 5.3 Hz, 4H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 161.9, 158.2, 155.4, 155.0, 130.1, 128.6, 114.2, 105.4, 80.0, 55.5, 43.8, 28.6 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14b** was obtained as a beige solid (66 mg, 100%) from appropriate Boc-protected amine (91 mg, 0.24 mmol). m.p. = 115 – 117 °C. IR (ATR): 3309, 2985, 2950, 2837, 1721, 1606, 1583, 1550, 1509, 1480, 1437, 1371, 1341, 1311, 1253, 1172, 1149, 1119, 1106, 1056, 1033, 983, 963, 840, 808, 774, 729, 700, 681, 644, 633, 582, 539, 515 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 5.3 Hz, 1H), 3.89 (t, J = 5.0 Hz, 4H), 3.86 (s, 3H), 2.97 (t, J = 5.0 Hz, 4H), 1.98 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 162.1, 161.8, 158.1, 130.3, 128.6, 114.1, 105.1, 55.5, 46.2, 45.0 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}ON_4^+$ 271.15534; found 271.15524. HPLC purity, method A: t_R = 5.36 min, area 97.53%. Method C: t_R = 9.15 min, area 97.01% (λ = 254 nm).

4-(4-Fluorophenyl)-2-(piperazin-1-yl)pyrimidine (14c). Following general procedure **B**, reaction was performed using **11c** (70 mg, 0.34 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (188 mg, 1.01 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford Boc-protected amine derivative as a colorless solid (117 mg, 97%). m.p. = 111 – 115 °C. IR (ATR): 2975, 2930, 2862, 1686, 1603, 1571, 1556, 1510, 1484, 1459, 1444, 1425, 1387, 1364, 1341, 1328, 1281, 1243, 1221, 1159, 1131, 1111, 1091, 1073, 1054, 1017, 1002, 984, 968, 953, 863, 851, 807, 764, 731, 702, 683, 652, 625, 572, 550, 503, 458, 424 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 5.2 Hz, 1H), 8.04 (dd, J = 8.7 Hz, J = 5.5 Hz, 2H), 7.14 (t, J = 8.5 Hz, 2H), 6.91 (d, J = 5.1 Hz, 1H), 3.90 (t, J = 5.3 Hz, 4H), 3.53 (t, J = 5.3 Hz , 4H), 1.50 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (d, $J_{C\text{-}F}$ = 251 Hz), 163.4, 162.0, 158.6, 155.0, 133.8 (d, $J_{C\text{-}F}$ = 3 Hz), 129.1 (d, $J_{C\text{-}F}$ = 9 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22 Hz), 105.8, 80.1, 43.8, 28.6 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14c** was obtained as a brown oil (72 mg, 100%) from appropriate Boc-protected amine (100 mg, 0.279 mmol). IR (ATR): 3304, 2918, 2850, 1724, 1678, 1602, 1570, 1507, 1442, 1407, 1344, 1317, 1291, 1257, 1231, 1157, 1101, 1055, 1015, 984, 964, 850, 806, 731, 573 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 5.2 Hz, 1H), 8.02 (dd, J = 8.6 Hz, J = 5.6 Hz, 2H), 7.12 (t, J = 8.7 Hz, 2H), 6.86 (d, J = 5.3 Hz, 1H), 3.88 (t, J = 5.0 Hz, 4H), 2.95 (t, J = 5.1 Hz, 4H), 2.20 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (d, $J_{C\text{-}F}$ = 251 Hz), 163.2, 162.0, 158.5, 133.9 (d, $J_{C\text{-}F}$ = 3 Hz), 129.1 (d, $J_{C\text{-}F}$ = 9 Hz), 115.7 (d, $J_{C\text{-}F}$ = 22 Hz), 105.3, 46.1, 45.0 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{16}N_4F^+$ 259.13535; found 259.13530. HPLC purity, method C: t_R = 9.12 min, area 96.70%. Method D: t_R = 9.16 min, area 97.09% (λ = 254 nm).

2-(Piperazin-1-yl)-4-(*p*-tolyl)pyrimidine (14d). Following general procedure **B**, reaction was performed using **11d** (80 mg, 0.39 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (218 mg, 1.17 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 8/2) to afford Boc-protected amine derivative as a colorless solid (132 mg, 95%). m.p. = 120 – 122 °C. IR (ATR): 3018, 3001, 2969, 2889, 2859, 1680, 1611, 1583, 1564, 1551, 1496, 1437, 1405, 1375, 1364, 1343, 1306, 1287, 1276, 1246, 1226, 1169, 1127, 1112, 1092, 1047, 1018, 1000, 982, 960, 928, 865, 848, 801, 774, 760, 724, 700, 664, 640, 620, 573, 551, 526, 495, 451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 5.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 6.94 (d, J = 5.2 Hz, 1H), 3.90 (t, J = 5.2 Hz, 4H), 3.53 (t, J = 5.2 Hz, 4H), 2.41 (s, 3H), 1.50 (s, 3H) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$): δ 164.5, 162.0, 158.3, 155.0, 141.0, 134.8, 129.5, 127.0, 105.9, 80.0, 43.8, 28.6, 21.5 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14d** was obtained as a beige solid (85 mg, 86%) from appropriate Boc-protected amine (138 mg, 0.389 mmol). m.p. = 80 – 82 °C. IR (ATR): 3292, 2987, 2935, 2846, 1698, 1610, 1584, 1567, 1509, 1482, 1444, 1371, 1341, 1321, 1292, 1258, 1215, 1182, 1152, 1119, 1070, 1018, 985, 966, 827, 802, 700, 677, 648, 636, 575, 543, 495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 5.2 Hz, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 5.2 Hz, 1H), 3.90 (t, J = 5.0 Hz, 4H), 2.97 (t, J = 5.1 Hz, 4H), 2.41 (s, 3H), 1.95 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.1, 158.2, 140.8, 135.0, 129.5, 127.0, 105.5, 46.2, 45.1, 21.5 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}N_4^+$ 255.16023; found 255.16031. HPLC purity, method C: t_R = 10.84 min, area 98.44%. Method G: t_R = 6.18 min, area 98.54% (λ = 254 nm).

4-(2-(Piperazin-1-yl)pyrimidin-4-yl)benzonitrile (14e). To a dry glass flask purged with argon $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), PPh_3 (26.4 mg, 0.10 mmol) and DME (7.5 mL) were added. The solution was stirred at room temperature for 5 min after which 2,4-dichloro-pyrimidine **9a** (150 mg, 1.01 mmol) and Na_2CO_3 (331 mg, 3.12 mmol) in H_2O (1.5 mL) were added. After 5 min 4-cyanophenylboronic acid **10e** (148 mg, 1.01 mmol) was added and reaction mixture was heated in an oil bath at 95 °C under inert atmosphere for 5 h. The solution was cooled to room temperature, washed with CH_2Cl_2 and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the remaining solid was used directly in the next step.

Following general procedure **B**, reaction was performed using compound from the first step (70 mg, 0.32 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (181 mg, 0.974 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 7/3) as a yellow solid (87 mg, 73%). m.p. = 162 – 164 °C. IR (ATR): 2989, 2969, 2927, 2859, 2227, 1693, 1583, 1556, 1511, 1460, 1426, 1363, 1344, 1289, 1277, 1250, 1229, 1171, 1140, 1108, 1087, 1041, 1018, 998, 982, 957, 865, 841, 802, 762, 688, 615, 565, 548, 535 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, J = 5.1 Hz, 1H), 8.14 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 5.1 Hz, 1H), 3.91 (t, J = 5.2 Hz, 4H), 3.54 (t, J = 5.2 Hz, 4H), 1.50 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 162.0, 159.2, 155.0, 141.9, 132.6, 127.7, 118.7, 114.0, 106.3, 80.2, 43.8, 28.6 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14e** was obtained as a yellow solid (58 mg, 100%) from appropriate Boc-protected amine (80 mg, 0.22 mmol). m.p.

= 197 – 199 °C. IR (ATR): 3316, 2917, 2850, 2228, 1583, 1561, 1503, 1441, 1345, 1317, 1289, 1259, 1214, 1140, 1058, 1018, 984, 965, 856, 805, 689, 547 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, J = 5.1 Hz, 1H), 8.12 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 5.1 Hz, 1H), 3.89 (t, J = 5.1 Hz, 4H), 2.95 (t, J = 5.1 Hz, 4H), 1.93 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 162.1, 159.1, 142.1, 132.5, 127.6, 118.7, 113.8, 105.8, 46.1, 45.0 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N_5^+$ 266.14002; found 266.13991. HPLC purity, method A: t_R = 5.26 min, area 95.58%. Method C: t_R = 8.77 min, area 97.12% (λ = 254 nm).

4-Methyl-6-phenyl-2-(piperazin-1-yl)pyrimidine (14f). Following general procedure **B**, reaction was performed using **11e** (40 mg, 0.20 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (109 mg, 0.586 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford Boc-protected amine derivative as a colorless solid (66 mg, 95%). m.p. = 144 – 146 °C. IR (ATR): 3006, 2969, 2898, 2861, 1685, 1586, 1556, 1514, 1479, 1429, 1380, 1364, 1346, 1288, 1262, 1234, 1176, 1139, 1119, 1082, 1003, 989, 967, 929, 889, 869, 828, 794, 772, 695, 650, 632, 584, 545 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 – 8.00 (m, 2H), 7.47 – 7.43 (m, 3H), 6.86 (s, 1H), 3.92 (t, J = 5.3 Hz, 4H), 3.53 (t, J = 5.3 Hz, 4H), 2.41 (s, 3H), 1.50 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 164.3, 162.1, 155.1, 138.0, 130.4, 128.7, 127.1, 105.8, 80.0, 43.9, 28.6, 24.7 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14f** was obtained as a beige solid (32 mg, 100%) from appropriate Boc-protected amine (45 mg, 0.13 mmol). m.p. = 94 – 96 °C. IR (ATR): 2940, 2849, 2823, 1587, 1564, 1509, 1495, 1442, 1379, 1346, 1314, 1294, 1268, 1225, 1186, 1136, 1072, 1052, 1028, 1012, 989, 905, 873, 819, 795, 770, 693, 653, 617, 588, 526, 460 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 – 8.01 (m, 2H), 7.47 – 7.42 (m, 3H), 6.83 (s, 1H), 3.92 (t, J = 5.0 Hz, 4H), 2.97 (t, J = 5.1 Hz, 4H), 2.40 (s, 3H), 2.21 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 164.2, 162.3, 138.2, 130.3, 128.7, 127.1, 105.4, 46.2, 45.0, 24.7 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}N_4^+$ 255.16042; found 255.16027. HPLC purity, method A: t_R = 5.50 min, area 99.63%. Method C: t_R = 9.34 min, area 99.70% (λ = 254 nm).

4-(4-Methoxyphenyl)-6-methyl-2-(piperazin-1-yl)pyrimidine (14g). Following general procedure **B**, reaction was performed using **11f** (49 mg, 0.21 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (117 mg, 0.626 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford Boc-protected amine derivative as a colorless solid (79 mg, 98%).

m.p. = 114 – 117 °C. IR (ATR): 2969, 2932, 2840, 1701, 1606, 1584, 1549, 1511, 1459, 1420, 1381, 1364, 1347, 1305, 1277, 1251, 1234, 1209, 1170, 1143, 1118, 1082, 1056, 1024, 1002, 891, 863, 845, 829, 817, 791, 768, 731, 636, 594, 541, 511 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.80 (s, 1H), 3.90 (t, J = 5.2 Hz, 4H), 3.86 (s, 3H), 3.52 (t, J = 5.2 Hz, 4H), 2.39 (s, 3H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 163.8, 162.1, 161.6, 155.1, 130.4, 128.6, 114.1, 105.0, 80.0, 55.5, 43.8, 28.6, 24.6 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14g** was obtained as a beige solid (52 mg, 98%) from appropriate Boc-protected amine (72 mg, 0.19 mmol). m.p. = 107 – 108 °C. IR (ATR): 3255, 2953, 2938, 2886, 2849, 2828, 1722, 1609, 1585, 1569, 1549, 1512, 1469, 1447, 1413, 1378, 1366, 1344, 1321, 1307, 1263, 1226, 1209, 1181, 1142, 1109, 1070, 1033, 1016, 993, 953, 888, 853, 817, 792, 733, 679, 658, 637, 594, 544, 510 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.78 (s, 1H), 3.90 (t, J = 5.0 Hz, 4H), 3.86 (s, 3H), 2.96 (t, J = 5.0 Hz, 4H), 2.38 (s, 3H), 2.00 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 163.7, 162.2, 161.5, 130.6, 128.6, 114.0, 104.6, 55.5, 46.2, 45.1, 24.7 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{21}ON_4^+$ 285.17099; found 285.17112. HPLC purity, method A: t_R = 5.51 min, area 96.70%. Method C: t_R = 9.37 min, area 97.26% (λ = 254 nm).

4-(4-Fluorophenyl)-6-methyl-2-(piperazin-1-yl)pyrimidine (14h). Following general procedure **B**, reaction was performed using **11g** (60 mg, 0.27 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (151 mg, 0.808 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford Boc-protected amine derivative as a colorless solid (98 mg, 98%). m.p. = 90 – 92 °C. IR (ATR): 3004, 2977, 2897, 2860, 1688, 1601, 1561, 1508, 1451, 1426, 1378, 1365, 1346, 1285, 1259, 1234, 1174, 1157, 1137, 1122, 1081, 1004, 990, 968, 891, 869, 848, 834, 813, 790, 770, 731, 674, 639, 592, 544, 501, 426 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 – 8.00 (m, 2H), 7.16 – 7.10 (m, 2H), 6.81 (s, 1H), 3.90 (t, J = 5.2 Hz, 4H), 3.52 (t, J = 5.3 Hz, 4H), 2.40 (s, 3H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 164.4 (d, $J_{C\text{-}F}$ = 251 Hz), 163.2, 162.1, 155.1, 134.1 (d, $J_{C\text{-}F}$ = 3 Hz), 129.1 (d, $J_{C\text{-}F}$ = 9 Hz), 115.7 (d, $J_{C\text{-}F}$ = 22 Hz), 105.4, 80.0, 43.8, 28.6, 24.7 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14h** was obtained as a beige solid (65 mg, 99%) from appropriate Boc-protected amine (90 mg, 0.24 mmol). m.p. = 103 – 106 °C. IR (ATR): 3214, 2997, 2933, 2904, 2847, 1601, 1558, 1506, 1446, 1378, 1346,

1293, 1275, 1224, 1155, 1127, 1088, 1014, 974, 943, 887, 847, 810, 788, 613, 597, 544, 505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 – 8.00 (m, 2H), 7.15 – 7.09 (m, 2H), 6.78 (s, 1H), 3.91 (t, J = 5.1 Hz, 4H), 2.97 (t, J = 5.1 Hz, 4H), 2.39 (s, 3H), 2.12 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 164.3 (d, J_{C-F} = 251 Hz), 163.1, 162.2, 134.3 (d, J_{C-F} = 3 Hz), 129.1 (d, J_{C-F} = 9 Hz), 115.6 (d, J_{C-F} = 22 Hz), 105.0, 46.2, 45.0, 24.7 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}N_4F^+$ 273.15100; found 273.15093. HPLC purity, method A: t_R = 5.57 min, area 98.04%. Method C: t_R = 9.39 min, area 99.37% (λ = 254 nm).

4-Methyl-2-(piperazin-1-yl)-6-(*p*-tolyl)pyrimidine (14i). Following general procedure **B**, reaction was performed using **11h** (59 mg, 0.27 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (153 mg, 0.82 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford Boc-protected amine derivative as a colorless solid (99 mg, 98%). m.p. = 114 – 116 °C. IR (ATR): 1688, 1614, 1570, 1554, 1512, 1481, 1462, 1445, 1420, 1366, 1347, 1282, 1252, 1169, 1121, 1087, 1002, 893, 861, 846, 812, 789, 772, 593, 534, 480 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.2 Hz, 3H), 6.84 (s, 1H), 3.91 (t, J = 5.1 Hz, 4H), 3.52 (t, J = 5.0 Hz, 4H), 2.42 – 2.39 (m, 6H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 164.2, 162.1, 155.1, 140.6, 135.2, 129.5, 127.0, 105.5, 80.0, 43.9, 28.6, 24.6, 21.5 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14i** was obtained as a beige solid (63 mg, 96%) from appropriate Boc-protected amine (90 mg, 0.24 mmol). m.p. = 95 – 97 °C. IR (ATR): 3242, 3065, 3001, 2982, 2941, 2886, 2851, 2825, 2656, 1611, 1569, 1550, 1511, 1468, 1443, 1377, 1344, 1322, 1298, 1262, 1223, 1204, 1185, 1167, 1141, 1109, 1071, 1013, 991, 889, 852, 812, 791, 720, 680, 657, 588, 546, 478 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H), 7.27 – 7.23 (m, 2H), 6.81 (s, 1H), 3.91 (t, J = 5.0 Hz, 4H), 2.97 (t, J = 5.1 Hz, 4H), 2.40 (s, 3H), 2.39 (s, 3H), 1.91 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 164.1, 162.3, 140.5, 135.4, 129.4, 127.0, 105.1, 46.3, 45.1, 24.7, 21.5 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{21}N_4^+$ 269.17607; found 269.17611. HPLC purity, method A: t_R = 5.67 min, area 97.46%. Method C: t_R = 9.63 min, area 96.69% (λ = 254 nm).

4-(6-Methyl-2-(piperazin-1-yl)pyrimidin-4-yl)benzonitrile (14j). To a dry glass flask purged with argon $Pd(OAc)_2$ (4.8 mg, 0.02 mmol), PPh_3 (11.3 mg, 0.04 mmol) and 1,4-dioxane (2.4 mL) were added. The solution was stirred at room temperature for 5 min after which 2,4-dichloro-6-methylpyrimidine **9b** (70 mg, 0.43 mmol) and Na_2CO_3 (141 mg, 1.33 mmol) in H_2O (0.6 mL) were added. After 5 min 4-cyanophenylboronic acid **10e** (63 mg, 0.43 mmol) was added and reaction

mixture was heated in an oil bath at 95 °C under inert atmosphere for 5 h. The solution was cooled to room temperature, washed with CH_2Cl_2 and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the remaining solid was used directly in the next step.

Following general procedure **B**, reaction was performed using compound from the first step (53 mg, 0.23 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (129 mg, 0.692 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 8/2) to afford Boc-protected amine derivative as a yellow solid (75 mg, 86%). m.p. = 89 – 91 °C. IR (ATR): 2999, 2971, 2898, 2863, 2227, 1699, 1581, 1568, 1552, 1505, 1480, 1446, 1419, 1379, 1364, 1350, 1280, 1250, 1173, 1137, 1120, 1084, 1017, 993, 894, 862, 844, 808, 784, 754, 733, 665, 630, 592, 540, 492, 429 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 6.85 (s, 1H), 3.90 (t, J = 5.2 Hz, 4H), 3.52 (t, J = 5.2 Hz, 4H), 2.42 (s, 3H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 162.1, 162.1, 155.0, 142.3, 132.5, 127.7, 118.8, 113.7, 106.0, 80.1, 43.8, 28.6, 24.7 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14j** was obtained as a yellow solid (41 mg, 89%) from appropriate Boc-protected amine (62 mg, 0.16 mmol). m.p. = 65 – 67 °C. IR (ATR): 3594, 3330, 3207, 3079, 2990, 2947, 2917, 2850, 2746, 2228, 1725, 1641, 1582, 1566, 1551, 1505, 1450, 1374, 1347, 1316, 1296, 1269, 1225, 1137, 1108, 1017, 995, 888, 837, 815, 788, 590, 544 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 6.82 (s, 1H), 3.90 (t, J = 5.0 Hz, 4H), 2.96 (t, J = 5.1 Hz, 4H), 2.41 (s, 3H), 1.85 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 162.2, 162.0, 142.5, 132.5, 127.7, 118.8, 113.5, 105.6, 46.2, 45.1, 24.7 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{18}N_5^+$ 280.15567; found 280.15574. HPLC purity, method A: t_R = 5.45 min, area 98.52%. Method C: t_R = 9.07 min, area 98.93% (λ = 254 nm).

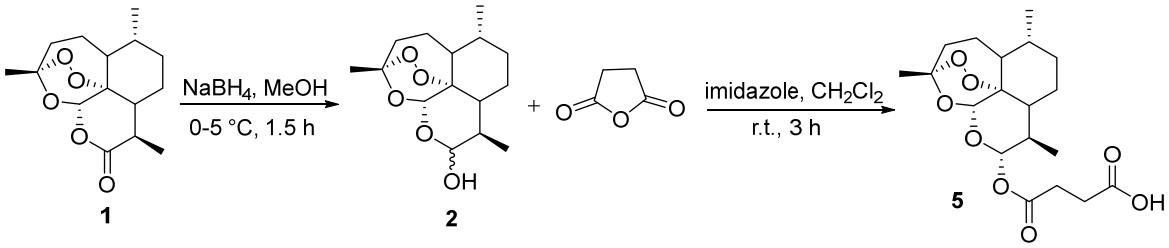
4-(4-Methoxyphenyl)-6-phenyl-2-(piperazin-1-yl)pyrimidine (14k). Following general procedure **B**, reaction was performed using **11i** (53 mg, 0.18 mmol) and *tert*-butyl piperazine-1-carboxylate **12b** (102 mg, 0.546 mmol), followed by dry-flash column chromatography (SiO_2: Hex/EtOAc = 9/1) to afford Boc-protected amine derivative as a bright yellow solid (81 mg, 100 %). m.p. = 151 – 153 °C. IR (ATR): 3003, 2979, 2932, 2852, 1678, 1607, 1585, 1565, 1543, 1512, 1494, 1450, 1429, 1364, 1306, 1284, 1252, 1237, 1172, 1127, 1084, 1030, 1004, 986, 967, 867, 846, 827, 772, 752, 693, 665, 648, 581, 541, 517 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.07 (m, 4H), 7.52 – 7.47 (m, 3H), 7.38 (s, 1H), 7.03 – 6.98 (m, 2H), 4.01 (t, J = 5.2 Hz, 4H), 3.88 (s,

3H), 3.57 (t, J = 5.3 Hz, 4H), 1.51 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 164.9, 162.3, 161.8, 155.1, 138.4, 130.6, 130.4, 128.8, 128.7, 127.2, 114.1, 101.6, 80.0, 55.6, 43.9, 28.6 ppm.

Following general procedure **C** for the deprotection of amino group, compound **14k** was obtained as a bright yellow solid (60 mg, 90%) from appropriate Boc-protected amine (86 mg, 0.19 mmol). m.p. = 139 – 142 °C. IR (ATR): 2944, 2921, 2836, 1722, 1689, 1608, 1584, 1565, 1542, 1512, 1494, 1460, 1442, 1358, 1301, 1256, 1239, 1171, 1118, 1073, 1029, 985, 969, 923, 897, 835, 820, 768, 734, 693, 654, 638, 605, 581, 536, 517, 466 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.07 (m, 4H), 7.51 – 7.45 (m, 3H), 7.35 (s, 1H), 7.03 – 6.98 (m, 2H), 4.03 (t, J = 5.0 Hz, 4H), 3.88 (s, 3H), 3.02 (t, J = 5.1 Hz, 4H), 2.27 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 164.8, 162.4, 161.7, 138.5, 130.8, 130.3, 128.7, 128.7, 127.2, 114.1, 101.3, 55.5, 46.2, 45.0 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{23}ON_4^+$ 347.18664; found 347.18672. HPLC purity, method A: t_R = 6.07 min, area 95.03%. Method B: t_R = 7.66 min, area 97.19% (λ = 254 nm).

General procedure D for the synthesis of artemisinin-pyrimidine hybrids

The dihydroartemisinin and artesunate were synthesized according to the reported procedures with slight modifications.[8] Hybrids were prepared according to the literature procedure.[9]



Artemisinin **1** (50 mg, 0.18 mmol) was dissolved in methanol (0.55 mL) and $NaBH_4$ (20 mg, 0.54 mmol) was added in portion at 0 – 5 °C over a period of 10 min. After being stirred for 90 min under the same reaction conditions, the mixture was neutralized to pH 6 - 7 using acetic acid and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with water and brine, and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure to give the desired product **2** (49 mg, 98%) as a colorless solid.

To a stirred solution of dihydroartemisinin **2** (1 eq) in CH_2Cl_2 (3.7 mL) succinic anhydride (1.6 eq) and imidazole (1.2 eq) were added. After being stirred for 3 h on room temperature, 1 M HCl

was added until pH 3 was reached. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The organic solution was washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure to give the desired product **5** which was directly used in the next step without further purification. Compound **5** was dissolved in CH_2Cl_2 (2.5 mL) and EDCI × HCl (1 eq) and HOBt × H_2O (1 eq) were added. The reaction mixture was stirred at room temperature for 1 h, after which the appropriate pyrimidine based amine **13a-f** or **14a-k** (1 eq) was added and the resulting mixture was stirred at room temperature for 13 h. The solution was diluted with H_2O and the mixture was extracted with CH_2Cl_2 (3 × 15 mL) and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the remaining solid was purified by dry-flash column chromatography.

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-oxo-4-((2-((4-phenylpyrimidin-2-yl)amino)ethyl)amino)butanoate (15a). Following general procedure **D**, compound **15a** was obtained as a beige oil (23 mg, 56%). IR (ATR): 3378, 2954, 2926, 2871, 2854, 1749, 1703, 1634, 1590, 1571, 1530, 1497, 1461, 1415, 1377, 1363, 1326, 1278, 1250, 1228, 1202, 1162, 1132, 1098, 1051, 1036, 1018, 949, 927, 910, 877, 849, 824, 770, 737, 697, 629, 551, 487 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + CD_3OD): δ 8.20 – 8.15 (m, 1H), 7.96 – 7.89 (m, 2H), 7.44 – 7.41 (m, 1H), 7.40 – 7.36 (m, 3H), 6.93 – 6.90 (m, 1H), 5.63 (d, J = 9.9 Hz, 1H), 5.32 (s, 1H), 3.56 – 3.50 (m, 2H), 3.43 – 3.32 (m, 2H), 2.66 – 2.55 (m, 2H), 2.46 – 2.30 (m, 3H), 2.25 (td, J = 14.0 Hz, J = 4.0 Hz, 1H), 1.95 – 1.89 (m, 1H), 1.82 – 1.75 (m, 1H), 1.68 – 1.54 (m, 2H), 1.49 (dt, J = 13.8 Hz, J = 4.5 Hz, 1H), 1.37 – 1.28 (m, 4H), 1.27 – 1.12 (m, 3H), 0.93 – 0.82 (m, 4H), 0.73 (d, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD): δ 172.4, 171.9, 165.3, 162.3, 158.0, 136.9, 130.8, 128.8, 127.0, 106.6, 104.5, 92.2, 91.5, 80.2, 51.4, 45.1, 40.7, 39.9, 37.2, 36.1, 33.9, 31.6, 30.5, 29.7, 25.5, 24.5, 21.8, 20.0, 11.8 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{41}O_7N_4^+$ 581.29698; found 581.29757. HPLC purity, method B: t_R = 9.50 min, area 98.36%. Method H: t_R = 12.90 min, area 98.33% (λ = 254 nm). $[\alpha]_D^{25}$ –2.5 (c 0.08, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-((2-((4-(4-methoxyphenyl)pyrimidin-2-yl)amino)ethyl)amino)-4-oxobutanoate (15b). Following general procedure **D**, compound **15b** was obtained as a colorless oil (15 mg, 36%). IR (ATR): 3374, 2926, 2871, 2854, 1748, 1660, 1607, 1573, 1529, 1510, 1461, 1413, 1377, 1362, 1326, 1306, 1281, 1251, 1207, 1132, 1098, 1035, 1018, 949, 927, 910, 877,

846, 808, 762, 736, 700, 582, 551, 523, 487 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 5.3 Hz, 1H), 8.01 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 5.3 Hz, 1H), 6.75 (t, J = 4.9 Hz, 1H), 5.76 (d, J = 9.8 Hz, 1H), 5.73 – 5.67 (m, 1H), 5.38 (s, 1H), 3.87 (s, 3H), 3.62 – 3.71 (m, 2H), 3.58 – 3.45 (m, 2H), 2.80 – 2.63 (m, 2H), 2.57 – 2.29 (4H), 1.99 (dt, J = 14.6 Hz, J = 4.1 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.75 – 1.68 (m, 1H), 1.67 – 1.54 (m, 2H), 1.46 –1.39 (m, 4H), 1.37 – 1.20 (m, 3H), 1.01 – 0.91 (m, 4H), 0.82 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 171.8, 164.5, 162.8, 162.0, 158.2, 129.6, 128.7, 114.3, 106.2, 104.5, 92.3, 91.6, 80.2, 55.6, 51.6, 45.3, 41.1, 40.9, 37.3, 36.3, 34.2, 31.8, 31.3, 30.2, 26.0, 24.7, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{43}O_8N_4^+$ 611.30754; found 611.30725. HPLC purity, method B: t_R = 9.26 min, area 99.90%. Method E: t_R = 10.02 min, area 98.10% (λ = 254 nm). $[\alpha]_D^{25}$ +7.5 (c 0.07, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-((2-((4-(4-fluorophenyl)pyrimidin-2-yl)amino)ethyl)amino)-4-oxobutanoate (15c). Following general procedure **D**, compound **15c** was obtained as a yellow oil (42 mg, 51%). IR (ATR): 3378, 2953, 2926, 2871, 2854, 1748, 1703, 1664, 1602, 1574, 1531, 1508, 1461, 1413, 1377, 1363, 1298, 1277, 1229, 1159, 1132, 1098, 1036, 1017, 949, 927, 877, 851, 809, 762, 736, 701, 571, 515 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 – 8.24 (m, 1H), 8.09 – 8.00 (m, 2H), 7.18 – 7.12 (m, 2H), 6.96 – 6.93 (m, 1H), 6.71 (brs, 1H), 5.75 (d, J = 9.8 Hz, 1H), 5.38 (s, 1H), 3.71 – 3.61 (m, 2H), 3.58 – 3.44 (m, 2H), 2.78 – 2.64 (m, 2H), 2.56 – 2.28 (m, 4H), 2.02 – 1.95 (m, 1H), 1.89 – 1.80 (m, 1H), 1.75 – 1.54 (m, 3H), 1.45 – 1.34 (m, 4H), 1.33 – 1.17 (m, 3H), 1.02 – 0.87 (m, 4H), 0.82 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 171.9, 164.7 (d, $J_{C\text{-}F}$ = 252 Hz), 164.3, 164.1, 162.3, 133.2 (d, $J_{C\text{-}F}$ = 3 Hz), 129.3 (d, $J_{C\text{-}F}$ = 9 Hz), 116.0 (d, $J_{C\text{-}F}$ = 22 Hz), 106.3, 104.6, 92.3, 91.6, 80.2, 51.6, 45.3, 41.2, 40.4, 37.3, 36.3, 34.2, 31.8, 31.2, 30.1, 26.0, 24.7, 22.1, 20.3, 12.1 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{40}O_7N_4F^+$ 599.28755; found 599.28769. HPLC purity, method B: t_R = 9.70 min, area 97.72%. Method I: t_R = 10.35 min, area 98.49% (λ = 254 nm). $[\alpha]_D^{25}$ –7.5 (c 0.08, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-oxo-4-((2-((4-(*p*-tolyl)pyrimidin-2-yl)amino)ethyl)amino)butanoate (15d). Following general procedure **D**, compound **15d** was obtained as a brown oil (36 mg, 64%). IR (ATR): 3353, 2953, 2925, 2870, 2854, 1748, 1659, 1586, 1574, 1530, 1511, 1461, 1415, 1377, 1362, 1277, 1250, 1228, 1207, 1184, 1162, 1132, 1098, 1036, 1018, 948, 927, 910, 877, 848, 825,

803, 762, 738, 704, 573, 502 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 – 8.19 (m, 1H), 7.95 – 7.90 (m, 2H), 7.29 – 7.25 (m, 2H), 6.98 – 6.95 (m, 1H), 6.79 – 6.74 (m, 1H), 5.75 (d, J = 9.8 Hz, 1H), 5.38 (s, 1H), 3.69 – 3.62 (m, 2H), 3.56 – 3.48 (m, 2H), 2.78 –2.62 (m, 2H), 2.57 – 2.28 (m, 7H), 2.02 – 1.96 (m, 1H), 1.89 – 1.81 (m, 1H), 1.76 – 1.54 (m, 3H), 1.48 – 1.37 (m, 4H), 1.35 – 1.18 (m, 3H), 1.02 – 0.88 (m, 4H), 0.81 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 171.9, 171.8, 165.5, 164.8, 141.5, 134.2, 129.7, 127.2, 106.4, 104.5, 92.2, 91.5, 80.2, 51.6, 45.3, 41.0, 40.6, 37.3, 36.3, 34.2, 31.8, 31.0, 30.0, 26.0, 24.7, 22.0, 21.6, 20.3, 12.1 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{43}O_7N_4^+$ 595.31263; found 595.31210. HPLC purity, method B: t_R = 9.61 min, area 99.70% (λ = 254 nm). Method H: t_R = 13.55 min, area 99.38%. $[\alpha]_D^{25}$ –5.0 (c 0.06, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-((2-((4-(4-cyanophenyl)pyrimidin-2-yl)amino)ethyl)amino)-4-oxobutanoate (15e). Following general procedure **D**, compound **15e** was obtained as a brown oil (20 mg, 31%). IR (ATR): 3369, 2953, 2925, 2870, 2854, 2228, 1747, 1657, 1585, 1555, 1531, 1503, 1459, 1416, 1377, 1276, 1249, 1228, 1202, 1163, 1129, 1096, 1035, 1017, 927, 910, 877, 855, 824, 810, 762, 737, 695, 550 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.13 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.00 (s, 1H), 6.64 (s, 1H), 5.74 (d, J = 9.8 Hz, 1H), 5.38 (s, 1H), 3.69 – 3.45 (m, 4H), 2.76 – 2.66 (m, 2H), 2.54 – 2.29 (m, 4H), 1.98 (dt, J = 14.7 Hz, J = 3.6 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.75 – 1.55 (m, 3H), 1.44 – 1.34 (m, 4H), 1.33 – 1.16 (m, 3H), 1.01 – 0.89 (m, 4H), 0.81 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 163.1, 158.6, 141.3, 132.6, 127.7, 118.5, 114.2, 106.9, 104.5, 92.3, 91.5, 80.2, 51.6, 45.2, 41.3, 40.0, 37.3, 36.3, 34.1, 31.8, 31.2, 30.1, 28.3, 26.0, 24.6, 22.0, 20.3, 12.1 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{40}O_7N_5^+$ 606.29223; found 606.29261. HPLC purity, method B: t_R = 9.27 min, area 97.60%. Method I: t_R = 9.98 min, area 96.15% (λ = 254 nm). $[\alpha]_D^{25}$ +45.0 (c 0.04, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-((2-((4-methyl-6-phenylpyrimidin-2-yl)amino)ethyl)amino)-4-oxobutanoate (15f). Following general procedure **D**, compound **15f** was obtained as a beige oil (36 mg, 58%). IR (ATR): 3345, 2954, 2925, 2870, 2854, 1748, 1704, 1659, 1578, 1558, 1496, 1461, 1377, 1346, 1250, 1227, 1206, 1161, 1131, 1098, 1035, 1017, 946, 926, 877, 848, 825, 771, 737, 696, 644, 592, 549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.98 (m, 2H), 7.49 – 7.43 (m, 3H), 6.96 (s, 1H), 6.90 (s, 1H), 5.75 (d, J = 9.8 Hz, 1H), 5.58 (t, J = 6.1 Hz, 1H), 5.39 (s, 1H), 3.70

– 3.62 (m, 2H), 3.56 – 3.45 (m, 2H), 2.79 – 2.47 (m, 4H), 2.42 – 2.28 (m, 5H), 2.03 – 1.97 (m, 1H), 1.90 – 1.82 (m, 1H), 1.77 – 1.54 (m, 3H), 1.48 – 1.39 (m, 4H), 1.38 – 1.21 (m, 3H), 1.02 – 0.90 (m, 4H), 0.81 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.9, 171.6, 168.6, 164.7, 163.1, 137.5, 130.6, 128.9, 127.1, 106.7, 104.5, 92.2, 91.6, 80.2, 51.7, 45.3, 41.5, 41.1, 37.3, 36.3, 34.2, 31.9, 31.1, 30.0, 26.0, 24.7, 24.5, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{43}O_7N_4^+$ 595.31263; found 595.31258. HPLC purity, method B: t_R = 9.42 min, area 99.52%. Method E: t_R = 10.48 min, area 98.59% (λ = 254 nm). $[\alpha]_D^{25}$ –1.4 (c 0.07, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-oxo-4-(4-(4-phenylpyrimidin-2-yl)piperazin-1-yl)butanoate (16a). Following general procedure **D**, compound **16a** was obtained as a colorless oil (64 mg, 73%). IR (ATR): 3059, 2926, 2872, 1750, 1650, 1588, 1567, 1554, 1495, 1440, 1376, 1344, 1277, 1255, 1218, 1163, 1132, 1100, 1036, 1017, 983, 927, 877, 845, 825, 770, 735, 698, 629 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.39 (d, *J* = 4.9 Hz, 1H), 8.07 – 8.01 (m, 2H), 7.50 – 7.45 (m, 3H), 6.99 (d, *J* = 4.6 Hz, 1H), 5.80 (d, *J* = 9.8 Hz, 1H), 5.43 (s, 1H), 4.01 – 3.90 (m, 4H), 3.77 – 3.71 (m, 2H), 3.64 – 3.58 (m, 2H), 2.91 – 2.54 (m, 5H), 2.37 (td, *J* = 14.0 Hz, *J* = 3.9 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.93 – 1.84 (m, 1H), 1.81 – 1.67 (m, 2H), 1.62 (dt, *J* = 13.8 Hz, *J* = 4.5 Hz, 1H), 1.53 – 1.41 (m, 4H), 1.40 – 1.22 (m, 3H), 1.05 – 0.93 (m, 4H), 0.88 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 172.0, 169.9, 164.6, 161.8, 158.5, 155.4, 137.5, 130.8, 128.8, 127.1, 106.4, 104.6, 92.2, 91.6, 80.3, 51.7, 45.4, 43.9, 43.8, 41.8, 37.4, 36.4, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{43}O_7N_4^+$ 607.31263; found 607.31189. HPLC purity, method A: t_R = 9.56 min, area 99.72%. Method F: t_R = 11.91 min, area 99.51% (λ = 254 nm). $[\alpha]_D^{25}$ –4.33 (c 0.3 , CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-(4-methoxyphenyl)pyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16b). Following general procedure **D**, compound **16b** was obtained as a colorless oil (58 mg, 62%). IR (ATR): 2927, 2872, 1750, 1650, 1608, 1586, 1566, 1511, 1439, 1376, 1344, 1303, 1277, 1252, 1217, 1173, 1132, 1100, 1036, 1017, 983, 927, 877, 846, 809, 735, 701, 584 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.32 (d, *J* = 5.2 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 5.3 Hz, 1H), 5.79 (d, *J* = 9.8 Hz, 1H), 5.43 (s, 1H), 3.99 – 3.98 (m, 4H), 3.86 (s, 3H), 3.72 (t, *J* = 5.2 Hz, 2H), 3.59 (t, *J* = 5.2 Hz, 2H), 2.90 – 2.54 (m, 5H), 2.36 (td, *J* =

14.0, J = 3.9 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.92 – 1.83 (m, 1H), 1.80 – 1.66 (m, 2H), 1.61 (dt, J = 13.9, J = 4.4 Hz, 1H), 1.52 – 1.40 (m, 4H), 1.39 – 1.19 (m, 3H), 1.05 – 0.92 (m, 4H), 0.87 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.9, 164.1, 161.9, 161.7, 158.1, 129.9, 128.6, 114.1, 105.7, 104.5, 92.2, 91.6, 80.2, 55.5, 51.7, 45.4, 43.9, 43.7, 41.8, 37.4, 36.3, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{45}O_8N_4^+$ 637.32319; found 637.32255. HPLC purity, method A: t_R = 9.56 min, area 98.74%. Method F: t_R = 11.91 min, area 99.46% (λ = 254 nm). $[\alpha]_D^{25}$ –2.5 (c 0.16, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-(4-fluorophenyl)pyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16c). Following general procedure **D**, compound **16c** was obtained as a colorless oil (51 mg, 62%). IR (ATR): 3457, 2953, 2925, 2870, 2854, 1749, 1650, 1602, 1569, 1508, 1441, 1377, 1344, 1291, 1276, 1224, 1158, 1131, 1099, 1017, 983, 926, 910, 877, 851, 824, 809, 762, 736, 700, 573, 512 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 5.1 Hz, 1H), 8.06 – 8.01 (m, 2H), 7.18 – 7.11 (m, 2H), 6.93 (d, J = 5.1 Hz, 1H), 5.79 (d, J = 9.8 Hz, 1H), 5.43 (s, 1H), 3.99 – 3.88 (m, 4H), 3.72 (t, J = 5.3 Hz, 2H), 3.60 (t, J = 5.2 Hz, 2H), 2.91 – 2.52 (m, 5H), 2.36 (td, J = 14.0, J = 4.0 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.92 – 1.83 (m, 1H), 1.80 – 1.67 (m, 2H), 1.61 (dt, J = 13.9, J = 4.5 Hz, 1H), 1.53 – 1.40 (m, 4H), 1.39 – 1.22 (m, 3H), 1.05 – 0.92 (m, 4H), 0.87 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.9, 164.5 (d, $J_{C\text{-}F}$ = 251 Hz), 163.5, 161.8, 158.6, 133.7 (d, $J_{C\text{-}F}$ = 3 Hz), 129.1 (d, $J_{C\text{-}F}$ = 9 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22 Hz), 106.0, 104.6, 92.2, 91.6, 80.3, 51.7, 45.4, 45.3, 43.9, 43.7, 41.8, 37.4, 36.3, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{42}O_7N_4F^+$ 625.30320; found 625.30266. HPLC purity, method B: t_R = 9.89 min, area 98.83%. Method E: t_R = 11.16 min, area 98.53% (λ = 254 nm). $[\alpha]_D^{25}$ –1.36 (c 0.07, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-oxo-4-(4-(4-(*p*-tolyl)pyrimidin-2-yl)piperazin-1-yl)butanoate (16d). Following general procedure **D**, compound **16d** was obtained as a colorless oil (35 mg, 49%). IR (ATR): 3427, 2953, 2925, 2870, 2854, 1748, 1650, 1584, 1567, 1553, 1493, 1440, 1377, 1343, 1277, 1252, 1215, 1184, 1163, 1131, 1099, 1036, 1017, 983, 927, 877, 846, 824, 804, 762, 737, 699, 574, 498 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 5.2 Hz, 1H), 7.96 – 7.92 (m, 2H), 7.29 – 7.24 (m, 2H), 6.96 (d, J = 5.2 Hz, 1H), 5.80 (d, J = 9.8 Hz, 1H), 5.44 (s, 1H), 4.00 – 3.88 (m, 4H), 3.72 (t, J = 5.3 Hz, 2H), 3.60 (t, J = 5.3 Hz, 2H), 2.90 – 2.54 (m, 5H), 2.41 (s, 3H), 2.38

– 2.31 (m, 1H), 2.06 – 1.98 (m, 1H), 1.92 – 1.84 (m, 1H), 1.80 – 1.67 (m, 2H), 1.61 (dt, *J* = 14.1, *J* = 4.5 Hz, 1H), 1.53 – 1.40 (m, 4H), 1.39 – 1.22 (m, 3H), 1.06 – 0.93 (m, 4H), 0.87 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 170.0, 167.4, 164.6, 161.8, 158.2, 155.6, 141.1, 134.7, 129.6, 127.1, 106.2, 104.6, 92.2, 91.6, 80.3, 51.7, 45.4, 43.9, 43.7, 41.8, 37.4, 36.4, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 22.1, 21.6, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{45}O_7N_4^+$ 621.32828; found 621.32768. HPLC purity, method A: t_R = 9.92 min, area 99.06%. Method E: t_R = 12.97 min, area 99.25% (λ = 254 nm). $[\alpha]_D^{25}$ –7.5 (c 0.08, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-(4-cyanophenyl)pyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16e). Following general procedure **D**, compound **16e** was obtained as a yellow oil (23 mg, 44%). IR (ATR): 3428, 2954, 2925, 2870, 2854, 2228, 1748, 1649, 1582, 1561, 1501, 1439, 1377, 1344, 1278, 1251, 1219, 1163, 1131, 1099, 1017, 983, 927, 877, 856, 810, 762, 737, 691, 549 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 5.1 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 5.1 Hz, 1H), 5.79 (d, *J* = 9.8 Hz, 1H), 5.43 (s, 1H), 4.00 – 3.88 (m, 4H), 3.73 (t, *J* = 5.3 Hz, 2H), 3.61 (t, *J* = 5.2 Hz, 2H), 2.91 – 2.52 (m, 5H), 2.36 (td, *J* = 14.0 Hz, *J* = 3.9 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.92 – 1.84 (m, 1H), 1.80 – 1.66 (m, 2H), 1.61 (dt, *J* = 13.9 Hz, *J* = 4.5 Hz, 1H), 1.52 – 1.40 (m, 4H), 1.39 – 1.22 (m, 3H), 1.06 – 0.93 (m, 4H), 0.87 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 170.0, 162.5, 161.8, 159.2, 141.8, 132.6, 127.7, 118.6, 114.0, 106.6, 104.6, 92.2, 91.6, 80.3, 51.7, 45.4, 45.3, 43.9, 43.7, 41.7, 37.4, 36.3, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+Na]^+$ calcd for $C_{34}H_{41}O_7N_5Na^+$ 654.28982; found 654.28938. HPLC purity, method B: t_R = 9.69 min, area 97.49%. Method E: t_R = 9.14 min, area 99.21% (λ = 254 nm). $[\alpha]_D^{25}$ –3.0 (c 0.07, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-methyl-6-phenylpyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16f). Following general procedure **D**, compound **16f** was obtained as a colorless oil (24 mg, 56%). IR (ATR): 3352, 2954, 2924, 2870, 2853, 1747, 1649, 1570, 1553, 1493, 1444, 1377, 1348, 1277, 1249, 1221, 1162, 1132, 1099, 1017, 949, 926, 910, 878, 849, 825, 770, 738, 696, 591 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 8.01 (m, 2H), 7.48 – 7.44 (m, 3H), 6.88 (s, 1H), 5.80 (d, *J* = 9.8 Hz, 1H), 5.44 (s, 1H), 4.03 – 3.87 (m, 4H), 3.72 (t, *J* = 5.4 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 2.90 – 2.53 (m, 5H), 2.44 – 2.32 (m, 4H), 2.05 – 1.98 (m, 1H), 1.92 – 1.85 (m, 1H), 1.81 – 1.68 (m, 2H), 1.62 (dt, *J* = 13.8 Hz, *J* = 4.5 Hz, 1H), 1.54 – 1.41 (m, 4H), 1.40 – 1.23 (m, 3H), 1.11 –

0.94 (m, 4H), 0.88 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.9, 168.4, 164.3, 162.0, 137.9, 130.5, 128.8, 127.1, 106.0, 104.6, 92.2, 91.6, 80.3, 51.7, 45.4, 45.4, 44.0, 43.8, 41.9, 37.4, 36.4, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 24.6, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{45}O_7N_4^+$ 621.32828; found 621.32789. HPLC purity, method B: t_R = 10.21 min, area 99.32%. Method E: t_R = 12.90 min, area 97.38% (λ = 254 nm). $[\alpha]_D^{25}$ –24.0 (c 0.07, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-(4-methoxyphenyl)-6-methylpyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16g). Following general procedure **D**, compound **16g** was obtained as a colorless oil (57 mg, 62%). IR (ATR): 3478, 2953, 2925, 2870, 2854, 1749, 1649, 1608, 1585, 1571, 1550, 1513, 1493, 1443, 1377, 1350, 1305, 1277, 1254, 1222, 1172, 1132, 1099, 1035, 1017, 947, 926, 910, 877, 846, 824, 790, 762, 736, 701, 646, 593, 547, 514, 486 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 6.82 (s, 1H), 5.80 (d, J = 9.8 Hz, 1H), 5.43 (s, 1H), 4.03 – 3.88 (m, 4H), 3.86 (s, 3H), 3.71 (t, J = 5.3 Hz, 2H), 3.59 (t, J = 5.3 Hz, 2H), 2.91 – 2.54 (m, 5H), 2.42 – 2.32 (m, 4H), 2.05 – 1.99 (m, 1H), 1.92 – 1.84 (m, 1H), 1.81 – 1.67 (m, 2H), 1.61 (dt, J = 13.7 Hz, J = 4.5 Hz, 1H), 1.53 – 1.41 (m, 4H), 1.40 – 1.19 (m, 3H), 1.08 – 0.93 (m, 4H), 0.87 (d, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.9, 168.1, 163.8, 161.9, 161.7, 130.3, 128.6, 114.1, 105.2, 104.6, 92.2, 91.6, 80.3, 55.5, 51.7, 45.5, 45.4, 44.0, 43.8, 41.9, 37.4, 36.4, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 24.6, 22.1, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{47}O_8N_4^+$ 651.33884; found 651.33893. HPLC purity, method A: t_R = 9.80 min, area 99.65%. Method E: t_R = 12.66 min, area 99.08% (λ = 254 nm). $[\alpha]_D^{25}$ +20.0 (c 0.08, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-(4-fluorophenyl)-6-methylpyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16h). Following general procedure **D**, compound **16h** was obtained as a beige oil (54 mg, 54%). IR (ATR): 3475, 2953, 2925, 2870, 2854, 1749, 1650, 1602, 1572, 1556, 1510, 1494, 1446, 1377, 1348, 1295, 1276, 1224, 1159, 1132, 1099, 1036, 1017, 948, 926, 878, 850, 825, 790, 762, 737, 701, 591, 546, 503 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.98 (m, 2H), 7.15 – 7.08 (m, 2H), 6.81 (s, 1H), 5.78 (d, J = 9.8 Hz, 1H), 5.41 (s, 1H), 3.99 – 3.84 (m, 4H), 3.70 (t, J = 5.2 Hz, 2H), 3.57 (t, J = 5.2 Hz, 2H), 2.88 – 2.49 (m, 5H), 2.41 – 2.28 (m, 4H), 2.03 – 1.96 (m, 1H), 1.90 – 1.82 (m, 1H), 1.78 – 1.65 (m, 2H), 1.59 (dt, J = 13.9 Hz, J = 4.4 Hz, 1H), 1.51 –

1.38 (m, 4H), 1.37 – 1.20 (m, 3H), 1.04 – 0.90 (m, 4H), 0.86 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.8, 168.5, 164.3 (d, $J_{C\text{-}F}$ = 251 Hz), 163.1, 161.8, 133.9 (d, $J_{C\text{-}F}$ = 3 Hz), 129.0 (d, $J_{C\text{-}F}$ = 9 Hz), 115.6 (d, $J_{C\text{-}F}$ = 22 Hz), 105.5, 104.5, 92.1, 91.6, 80.2, 51.6, 45.3, 45.3, 43.9, 43.7, 41.8, 37.3, 36.3, 34.1, 31.9, 29.5, 27.8, 26.0, 24.6, 24.6, 22.0, 20.3, 12.1 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{44}O_7N_4F^+$ 639.31885; found 639.31876. HPLC purity, method B: t_R = 10.22 min, area 97.58%. Method E: t_R = 11.04 min, area 99.18% (λ = 254 nm). $[\alpha]_D^{25}$ –4.1 (c 0.4 , CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-methyl-6-(*p*-tolyl)pyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16i). Following general procedure **D**, compound **16i** was obtained as a colorless oil (45 mg, 51%). IR (ATR): 3430, 2954, 2925, 2869, 2854, 1749, 1650, 1570, 1551, 1512, 1493, 1445, 1377, 1348, 1276, 1248, 1222, 1163, 1131, 1099, 1017, 948, 926, 910, 878, 849, 813, 789, 762, 737, 696, 592, 485 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.91 (m, 2H), 7.28 – 7.24 (m, 2H), 6.86 (s, 1H), 5.80 (d, J = 9.8 Hz, 1H), 5.44 (s, 1H), 4.01 – 3.88 (m, 4H), 3.72 (t, J = 5.3 Hz, 2H), 3.59 (t, J = 5.3 Hz, 2H), 2.91 – 2.53 (m, 5H), 2.43 – 2.33 (m, 7H), 2.05 – 1.98 (m, 1H), 1.92 – 1.85 (m, 1H), 1.80 – 1.68 (m, 3H), 1.62 (dt, J = 13.8 Hz, J = 4.5 Hz, 1H), 1.53 – 1.41 (m, 4H), 1.40 – 1.23 (m, 3H), 1.06 – 0.93 (m, 4H), 0.88 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.9, 168.2, 164.3, 164.2, 161.9, 140.7, 135.0, 129.5, 127.0, 105.7, 104.6, 92.2, 91.6, 80.3, 51.7, 45.4, 45.4, 44.0, 43.8, 41.9, 37.4, 36.3, 34.2, 32.0, 29.6, 27.9, 26.1, 24.7, 24.6, 22.1, 21.5, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{47}O_7N_4^+$ 635.34393; found 635.34378. HPLC purity, method B: t_R = 10.56 min, area 95.92%. Method E: t_R = 12.24 min, area 97.27% (λ = 254 nm). $[\alpha]_D^{25}$ +3.0 (c 0.07, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-(4-cyanophenyl)-6-methylpyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16j). Following general procedure **D**, compound **16j** was obtained as a yellow oil (60 mg, 66%). IR (ATR): 3428, 2954, 2925, 2870, 2854, 2228, 1748, 1649, 1581, 1566, 1549, 1495, 1446, 1377, 1347, 1278, 1248, 1222, 1162, 1132, 1099, 1035, 1017, 949, 926, 910, 877, 854, 824, 788, 761, 737, 700, 592, 543 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 7.8 Hz, 2H), 6.87 (s, 1H), 5.78 (d, J = 9.8 Hz, 1H), 5.42 (s, 1H), 4.00 – 3.88 (m, 4H), 3.74 – 3.68 (m, 2H), 3.62 – 3.56 (m, 2H), 2.87 – 2.51 (m, 5H), 2.46 – 2.30 (m, 4H), 2.04 – 1.97 (m, 1H), 1.91 – 1.84 (m, 1H), 1.79 – 1.66 (m, 2H), 1.60 (dt, J = 14.1 Hz, J = 4.5 Hz, 1H),

1.52 – 1.39 (m, 4H), 1.38 – 1.21 (m, 3H), 1.05 – 0.92 (m, 4H), 0.86 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 170.0, 169.2, 162.2, 161.8, 142.1, 132.5, 127.7, 118.7, 113.7, 106.3, 104.6, 92.2, 91.6, 80.2, 51.6, 45.4, 45.3, 43.9, 43.7, 41.8, 37.4, 36.3, 34.2, 31.9, 29.6, 27.9, 26.0, 24.7, 24.6, 22.1, 20.3, 12.1 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{43}O_7N_5Na^+$ 668.30547; found 668.30517. HPLC purity, method B: t_R = 9.93 min, area 98.60%. Method E: t_R = 10.12 min, area 99.55% (λ = 254 nm). $[\alpha]_D^{25}$ +6.67 (c 0.06, CH_2Cl_2).

(3*R*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10-yl 4-(4-(4-(4-methoxyphenyl)-6-phenylpyrimidin-2-yl)piperazin-1-yl)-4-oxobutanoate (16k). Following general procedure **D**, compound **16k** was obtained as a beige oil (34 mg, 34%).IR (ATR): 3430, 2954, 2925, 2870, 2853, 1748, 1649, 1607, 1585, 1564, 1542, 1513, 1495, 1445, 1376, 1361, 1305, 1254, 1173, 1132, 1099, 1017, 984, 926, 910, 877, 846, 827, 772, 736, 696, 646, 613, 580, 517 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.06 (m, 4H), 7.52 – 7.47 (m, 3H), 7.39 (s, 1H), 7.04 – 6.99 (m, 2H), 5.81 (d, *J* = 9.7 Hz, 1H), 5.44 (s, 1H), 4.17 – 3.98 (m, 4H), 3.89 (s, 3H), 3.80 – 3.74 (m, 2H), 3.68 – 3.61 (m, 2H), 2.91– 2.54 (m, 5H), 2.42 – 2.32 (m, 1H), 2.06 – 1.99 (m, 1H), 1.93 – 1.84 (m, 1H), 1.80 – 1.68 (m, 2H), 1.66 – 1.58 (m, 1H), 1.54 – 1.41 (m, 4H), 1.40 – 1.19 (m, 3H), 1.10 – 0.93 (m, 4H), 0.89 (d, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.9, 167.1, 165.2, 164.9, 162.1, 161.8, 138.3, 130.5, 130.5, 128.8, 128.7, 127.2, 114.2, 104.6, 101.9, 92.2, 91.7, 80.3, 55.6, 51.7, 45.6, 45.4, 44.1, 43.9, 42.0, 37.4, 36.4, 34.2, 32.0, 29.7, 28.0, 26.1, 24.7, 22.2, 20.3, 12.2 ppm. HRMS (HESI/Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{49}O_8N_4^+$ 713.35449; found 713.35460. HPLC purity, method B: t_R = 11.36 min, area 95.13%. Method E: t_R = 12.66 min, area 95.11% (λ = 254 nm). $[\alpha]_D^{25}$ –2.8 (c 0.04, CH_2Cl_2).

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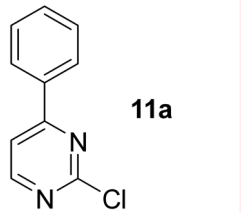
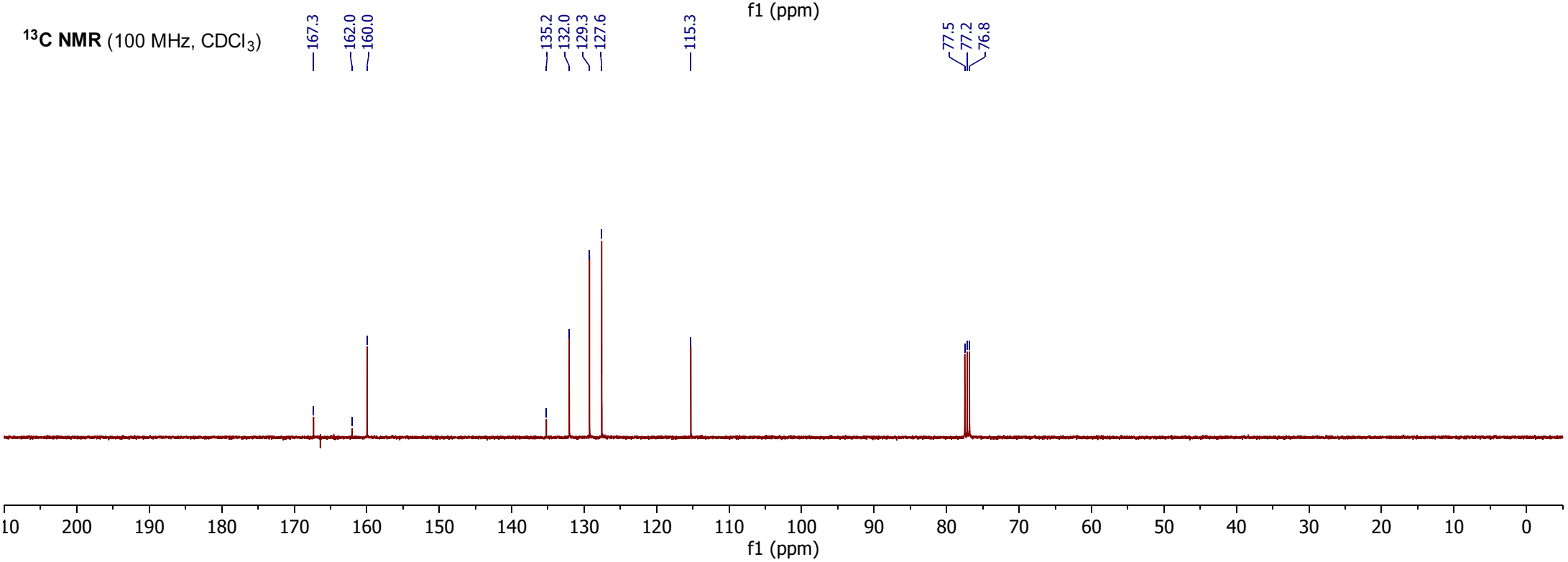
^{1}H NMR (400 MHz, $CDCl_3$)

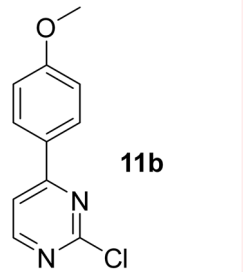


11a

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



11b

8.55 8.54 8.07 8.05 7.56 7.54 7.26 7.01 6.98 3.88

1.00 2.06 1.04 2.12 3.13

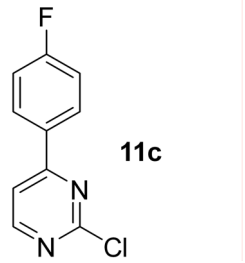
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

166.8 163.0 161.9 159.6 129.3 127.5 114.6 114.3 77.5 77.2 76.8 55.6

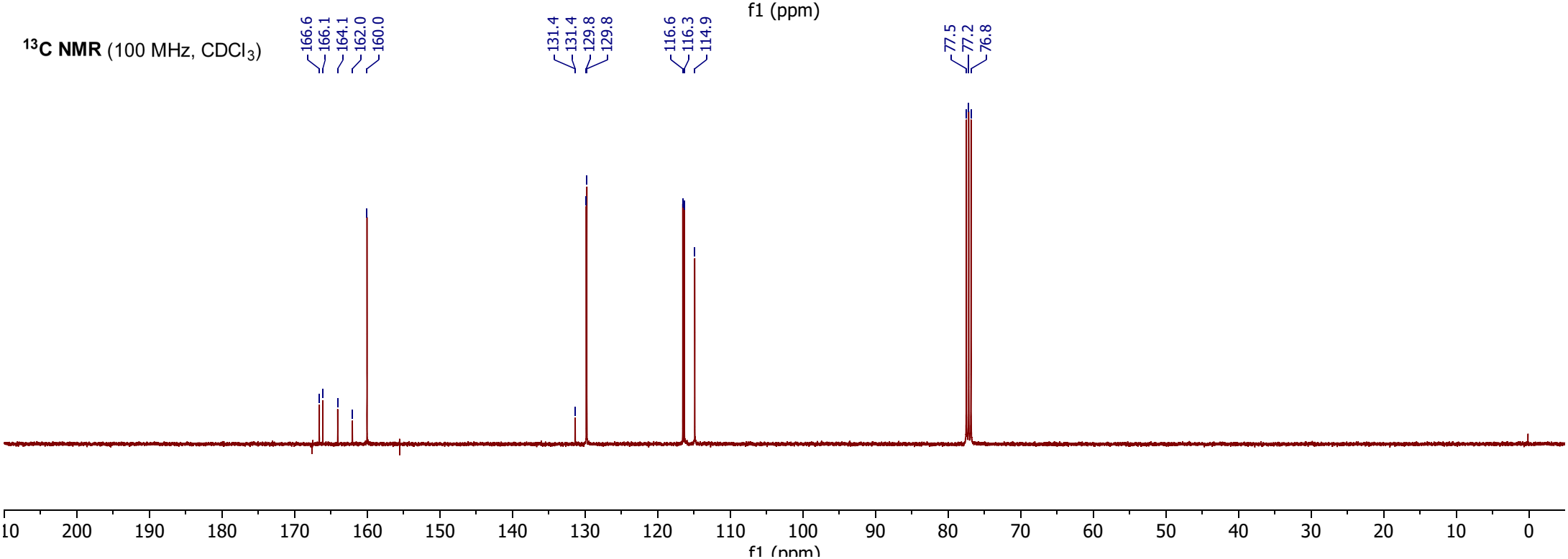
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

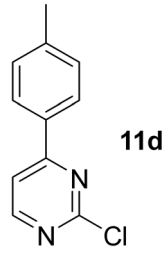


11c

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



11d

8.59
8.58
7.99
7.97
7.61
7.59
7.31
7.29
7.26
2.42

0.93
2.00
1.00
2.00
3.05

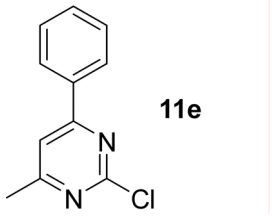
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

167.2
161.9
159.7
142.7
132.4
130.0
127.5
114.9
77.5
77.2
76.8
21.6

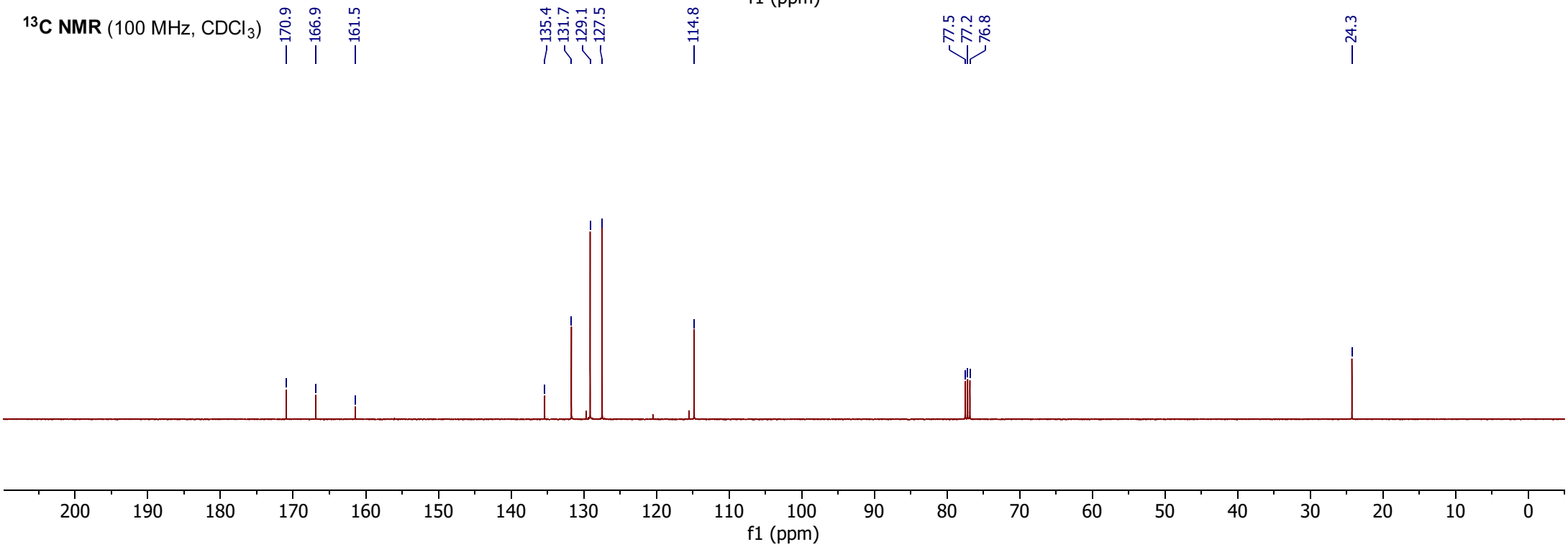
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

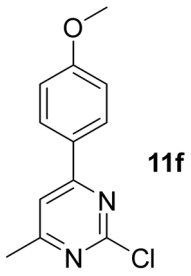


11e

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



11f

8.04 8.02 7.40 7.26 6.99 6.97 3.87 2.54

2.00 1.00 2.00 3.00 3.00

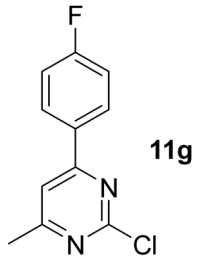
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

170.5 166.4 162.7 161.4 129.2 127.8 114.5 113.8 77.5 77.2 76.8 55.6 24.3

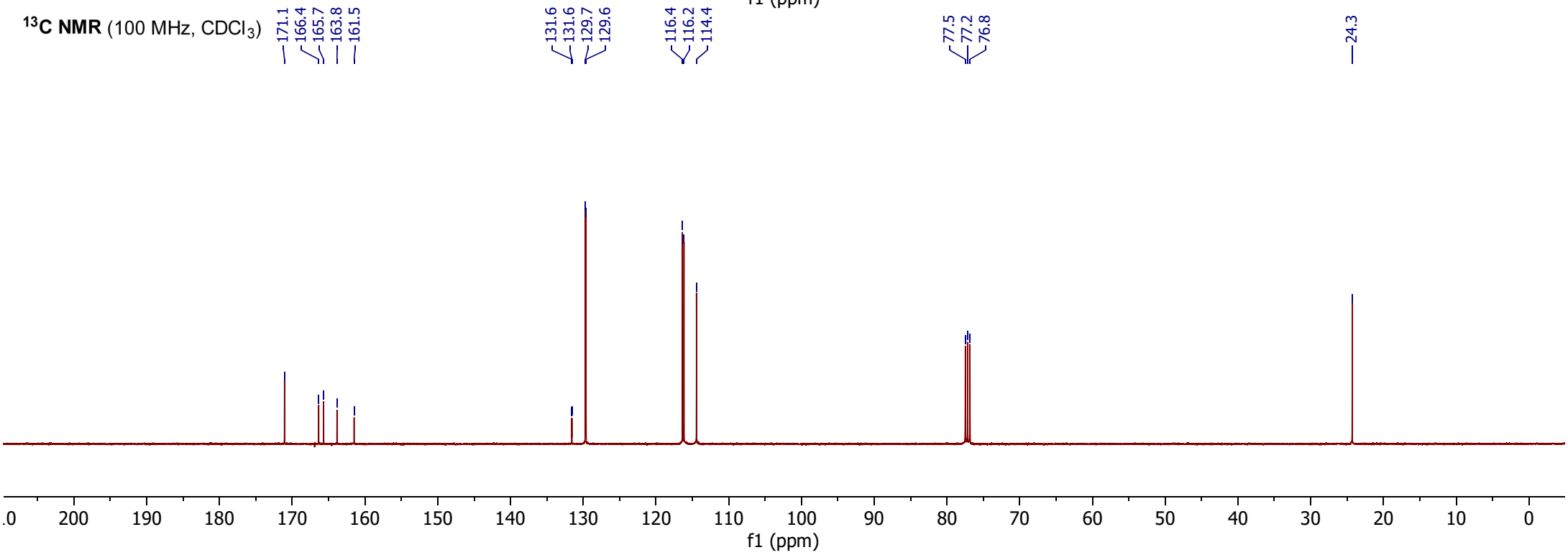
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

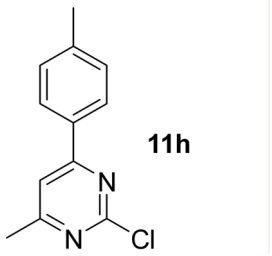


11g

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



11h

7.98
7.96
7.46
7.30
7.28
7.26
2.57
2.42

2.00
1.00
2.00
3.00
3.00

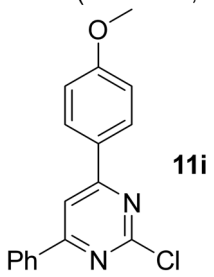
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

170.7
166.9
161.5
142.4
132.6
129.9
127.4
114.4
77.5
77.2
76.8
24.3
21.6

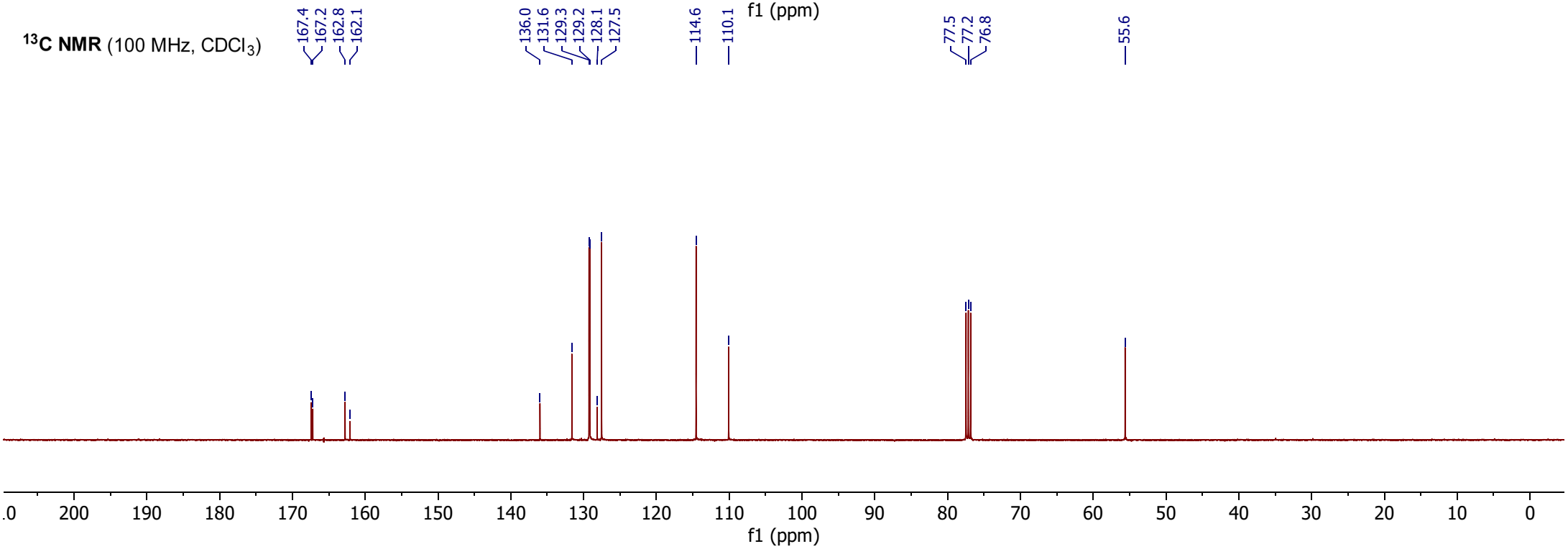
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

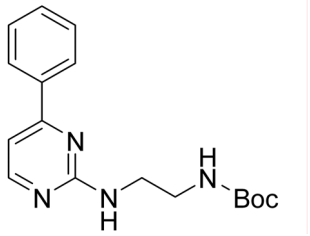


11i

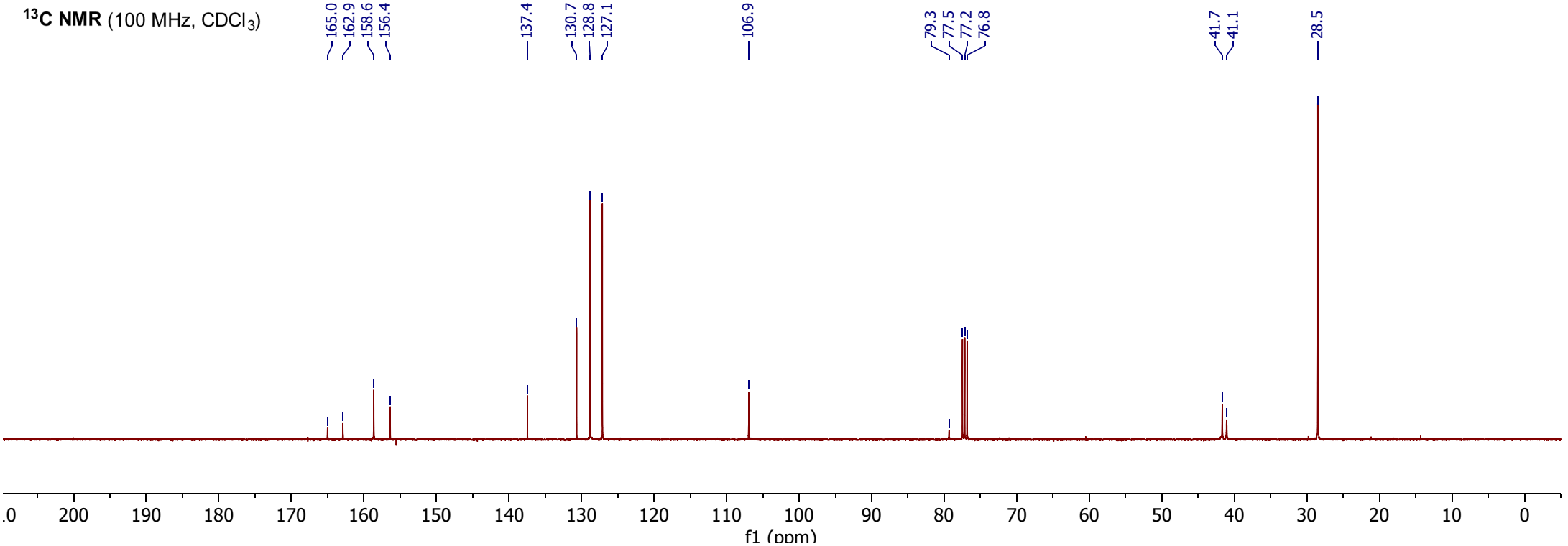
^{13}C NMR (100 MHz, $CDCl_3$)



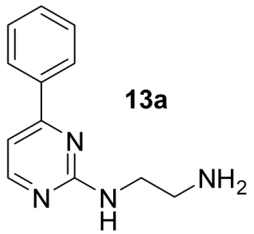
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.32 8.31 8.02 8.02 8.01 8.00 7.46 7.45 7.45 7.26 6.96 6.95 5.67 3.59 3.58 3.56 3.55 2.97 1.75

1.00 2.00 3.04 0.97 0.93 2.01 1.70 1.77

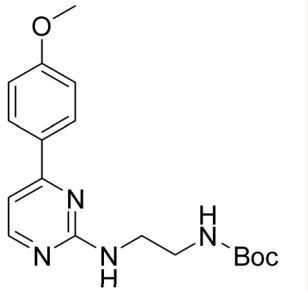
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

164.9 163.0 158.6 137.6 130.6 128.8 127.1 106.7 77.5 77.2 76.8 44.4 41.7

f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



8.25 8.24 7.98 7.96 7.26 6.96 6.94 6.90 6.89 5.71 5.31 3.84 3.61 3.59 3.39 3.38 1.40

0.94 2.00 2.00 1.00 0.90 0.88 2.98 1.96 1.93 9.19

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

f1 (ppm)

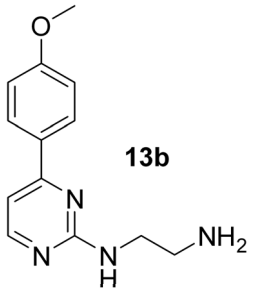
^{13}C NMR (100 MHz, $CDCl_3$)

164.4 162.8 161.8 158.3 156.3 129.8 128.6 114.1 106.1 79.3 77.5 77.2 76.8 55.5 41.6 41.1 28.5

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

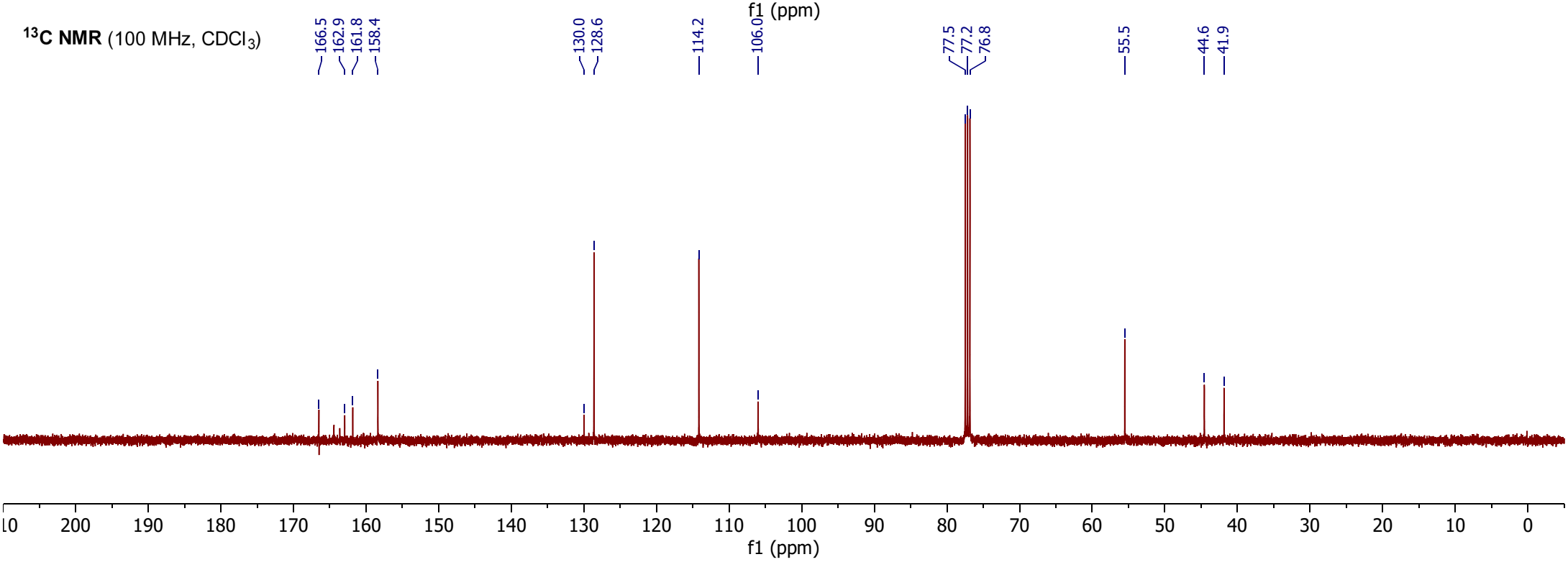
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

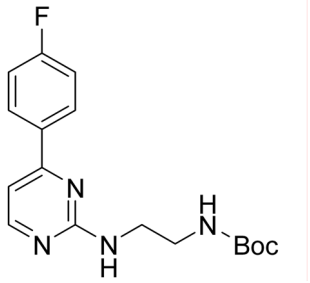


13b

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.30 8.29 8.02 8.01 8.00 7.99 7.26 7.15 7.15 7.13 7.11 7.10 6.92 6.91 5.68 5.20 3.63 3.62 3.60 3.59 3.41 3.40 3.39 3.37 1.41

0.97 2.00 2.00 1.00 0.95 0.96 2.03 2.01 9.00

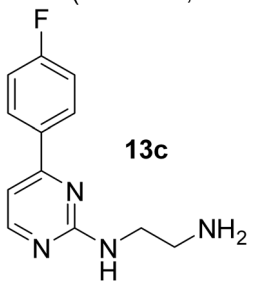
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

165.8 163.9 163.3 162.9 158.7 156.4 133.6 133.6 129.2 129.1 115.9 115.7 106.5 79.4 77.5 77.2 76.8 41.7 41.0 28.5

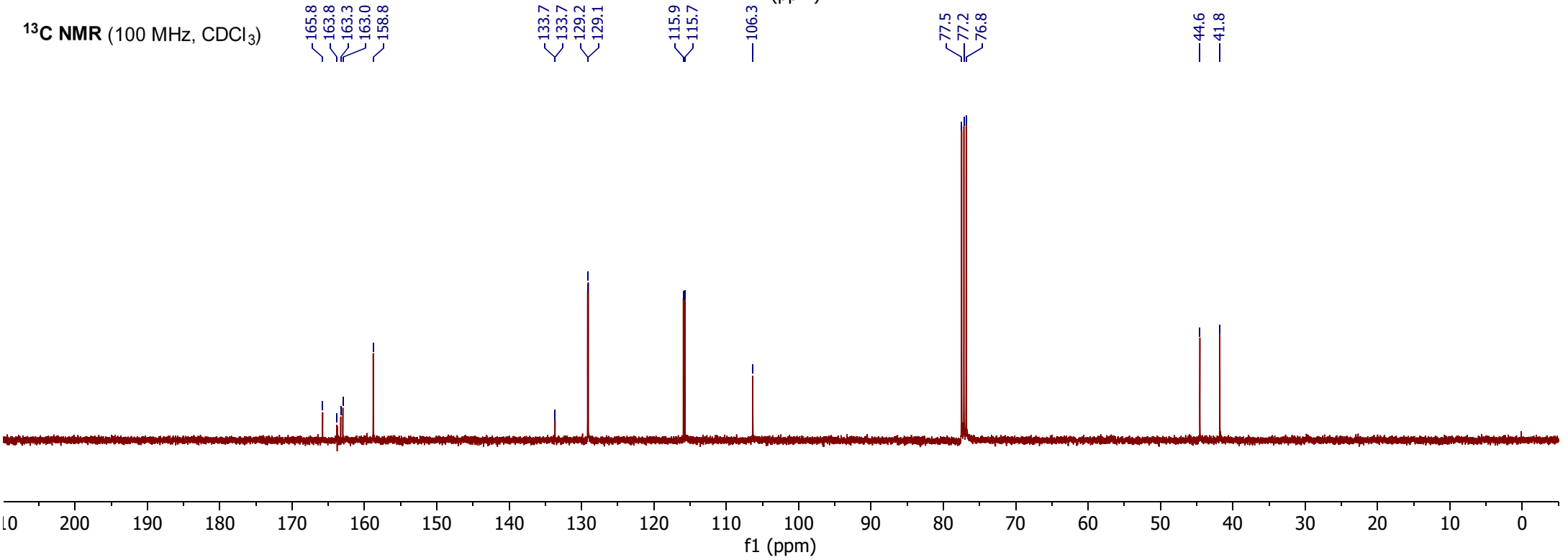
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

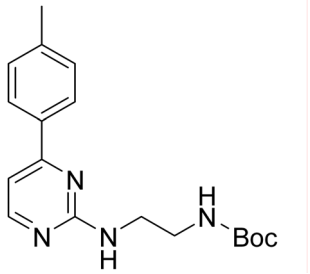


13c

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.30 8.29 7.92 7.90 7.27 7.26 7.25 6.96 6.95 5.61 5.23 3.63 3.62 3.41 3.40 2.41 1.42

1.00 2.02 2.25 1.00 1.02 1.01 2.00 2.00 3.00 9.21

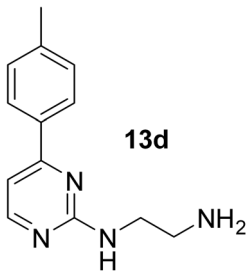
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

165.0 162.9 158.5 156.4 141.0 134.6 129.6 127.0 106.7 79.3 77.5 77.2 76.8 41.7 41.1 28.5 21.5

f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



8.29 8.28 7.92 7.90 7.26 7.25 7.24 6.94 6.93 5.50 3.58 3.57 3.55 3.54 2.97 2.96 2.94 2.39 1.59

1.00 2.00 2.39 1.00 0.95 2.10 2.00 3.05 2.64

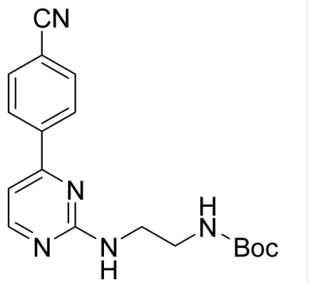
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

166.9 163.0 158.5 141.0 134.7 129.6 127.0 106.5 77.5 77.2 76.8 44.6 41.8 21.6

f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



8.37 8.36 8.11 8.09 7.74 7.72 7.26 6.97 6.96 5.80 5.13 3.63 3.62 3.60 3.59 3.41 3.40 3.39 3.37 1.40

1.00 2.00 2.03 1.03 1.01 0.97 2.07 2.05 9.55

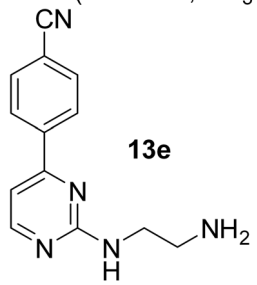
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

162.9 162.7 159.3 156.4 141.7 132.6 127.7 118.6 114.0 107.0 79.5 77.5 77.2 76.8 41.8 40.8 28.5

f1 (ppm)

^{1}H NMR (400 MHz, CD_3OD)



13e

8.44 8.42 8.31 8.29 7.89 7.87 7.23 7.21 4.87 3.69 3.68 3.66 3.64 3.38 3.38 3.37 3.37 3.37 3.05 3.03 3.02

0.90 2.01 2.03 1.00 2.07 1.78

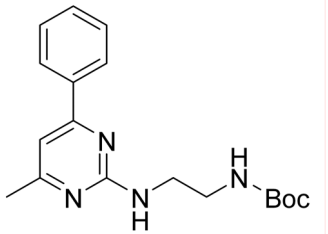
f1 (ppm)

^{13}C NMR (100 MHz, CD_3OD)

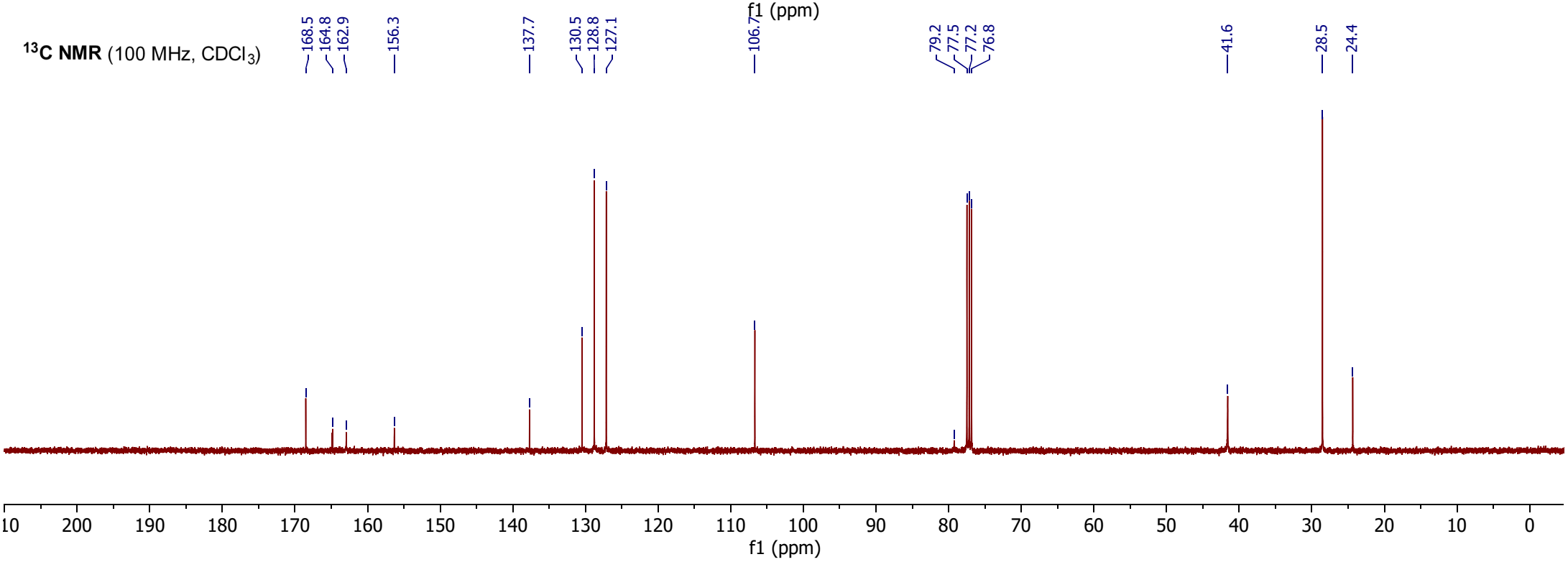
164.2 164.2 160.3 142.9 133.6 128.8 119.4 115.0 107.7 49.6 49.4 49.2 49.0 48.8 48.6 48.4 43.7 41.7

f1 (ppm)

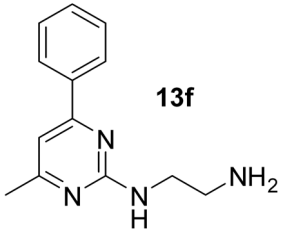
^{1}H NMR (400 MHz, $CDCl_3$)



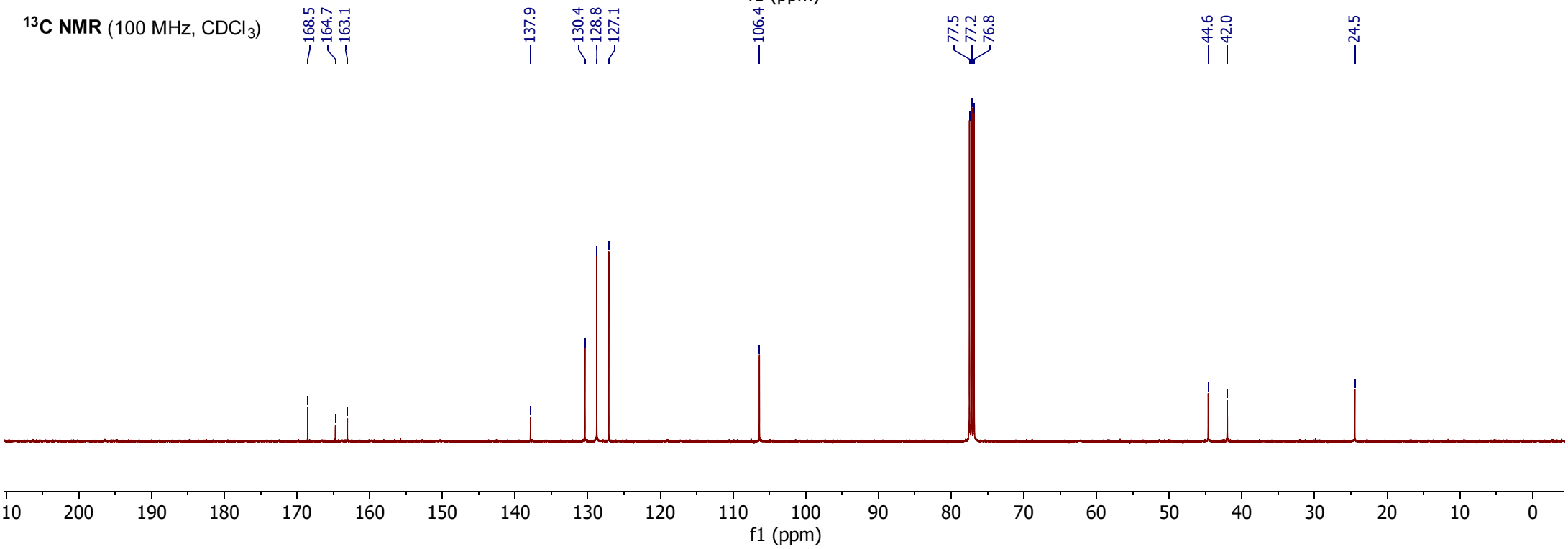
^{13}C NMR (100 MHz, $CDCl_3$)

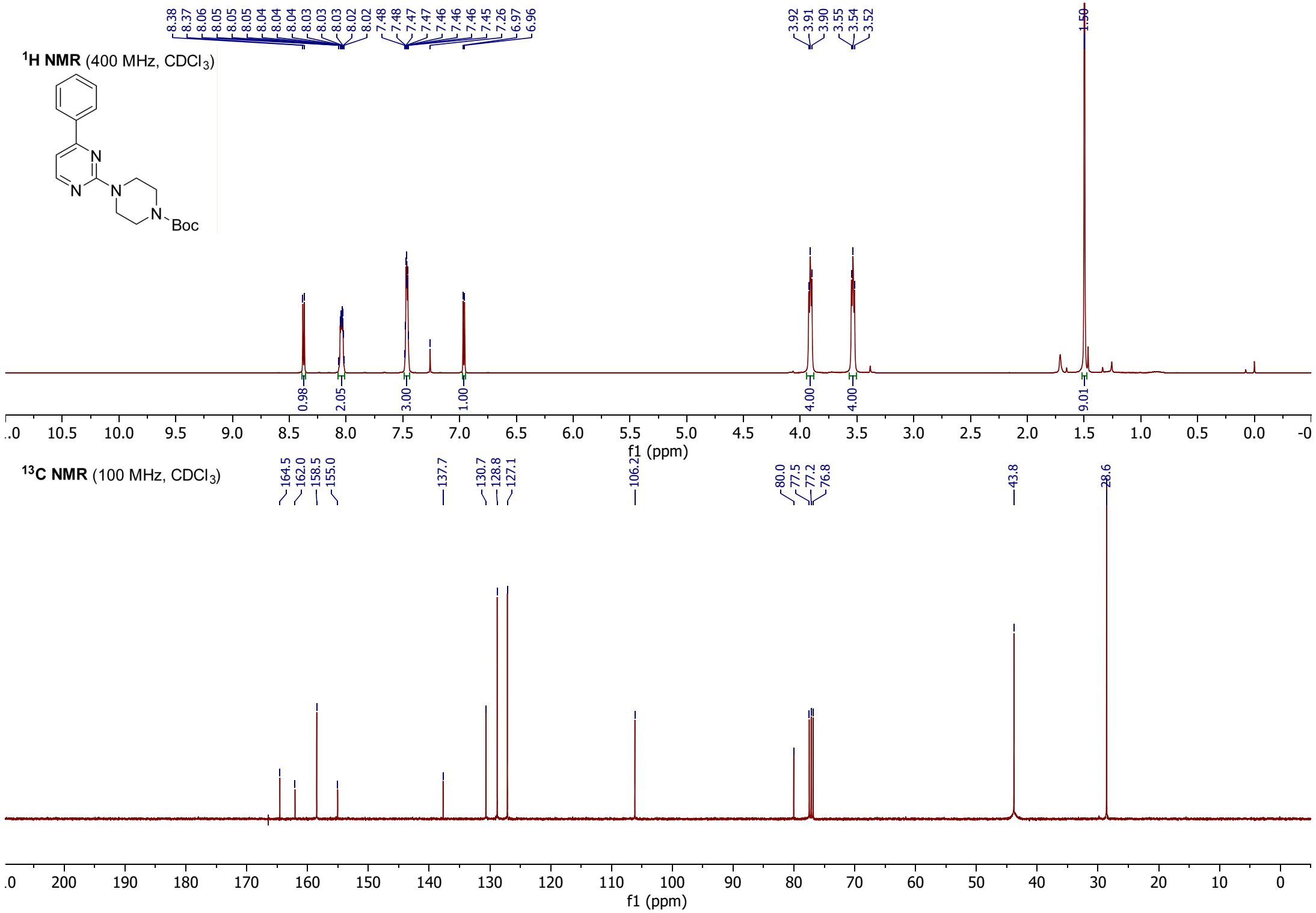


^{1}H NMR (400 MHz, $CDCl_3$)

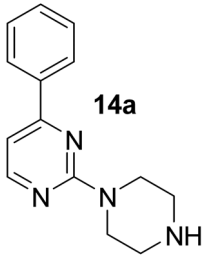


^{13}C NMR (100 MHz, $CDCl_3$)

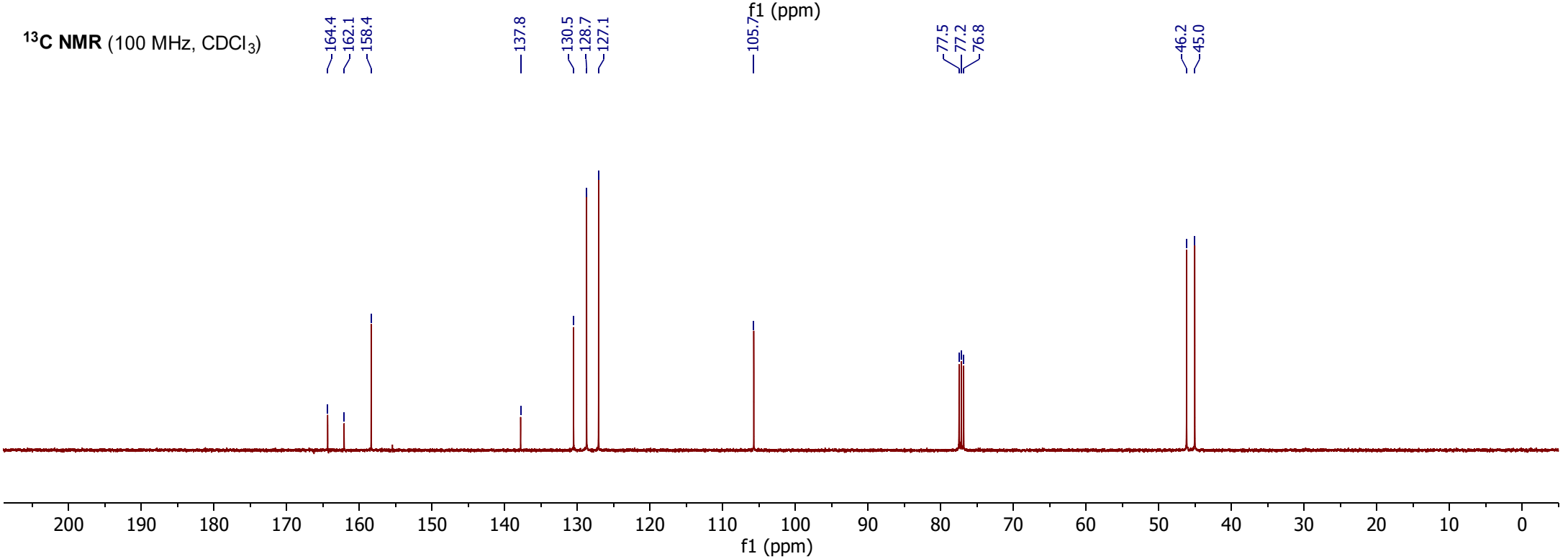



8.38 8.37 8.06 8.05 8.05 8.05 8.04 8.04 8.04 8.03 8.03 8.03 8.02 8.02 7.48 7.48 7.47 7.47 7.46 7.46 7.46 7.45 7.26 6.97 6.96
3.92 3.91 3.90 3.55 3.54 3.52
1.50
^{1}H NMR (400 MHz, $CDCl_3$)
N
N
N
N
Boc
0.98 2.05 3.00 1.00 4.00 4.00 9.01
f1 (ppm)
^{13}C NMR (100 MHz, $CDCl_3$)
164.5 162.0 158.5 155.0 137.7 130.7 128.8 127.1 106.2 80.0 77.5 77.2 76.8 43.8 28.6
f1 (ppm)

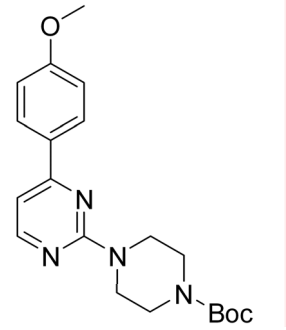
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.33 8.32 8.03 8.01 7.26 6.99 6.96 6.91 6.90 3.91 3.90 3.88 3.87 3.54 3.53 3.52 1.49

0.96 2.03 2.04 1.00 4.00 3.03 4.02 8.98

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

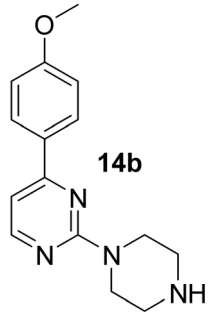
^{13}C NMR (100 MHz, $CDCl_3$)

164.0 161.9 158.2 155.4 155.0 130.1 128.6 114.2 105.4 80.0 77.5 77.2 76.8 55.5 43.8 28.6

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



14b

8.33 8.31 8.03 8.01 7.26 6.98 6.96 6.89 6.87 3.91 3.89 3.88 3.86 2.98 2.97 2.96 1.98

0.96 2.00 2.00 1.00 3.89 2.96 3.82 1.48

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

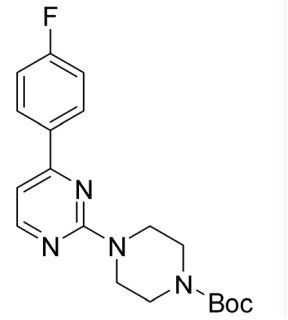
^{13}C NMR (100 MHz, $CDCl_3$)

163.9 162.1 161.8 158.1 130.3 128.6 114.1 105.1 77.5 77.2 76.8 55.5 46.2 45.0

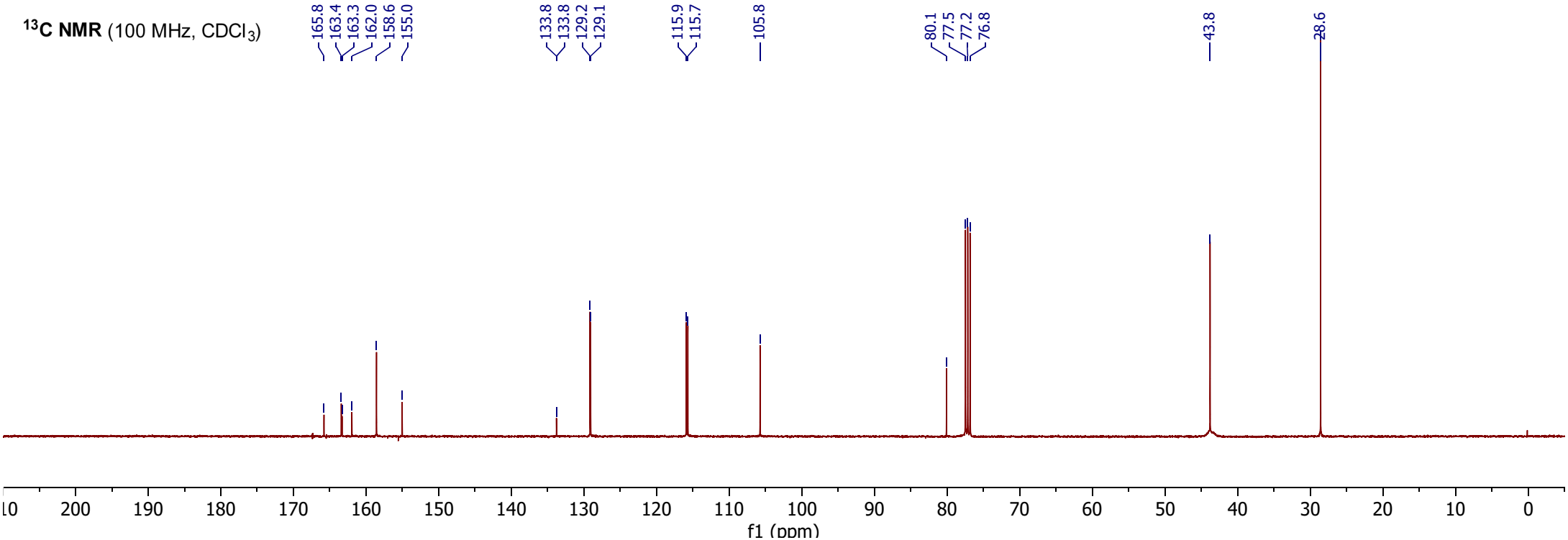
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

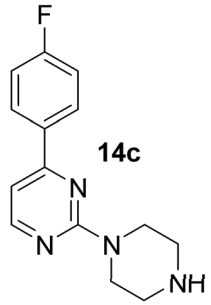
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

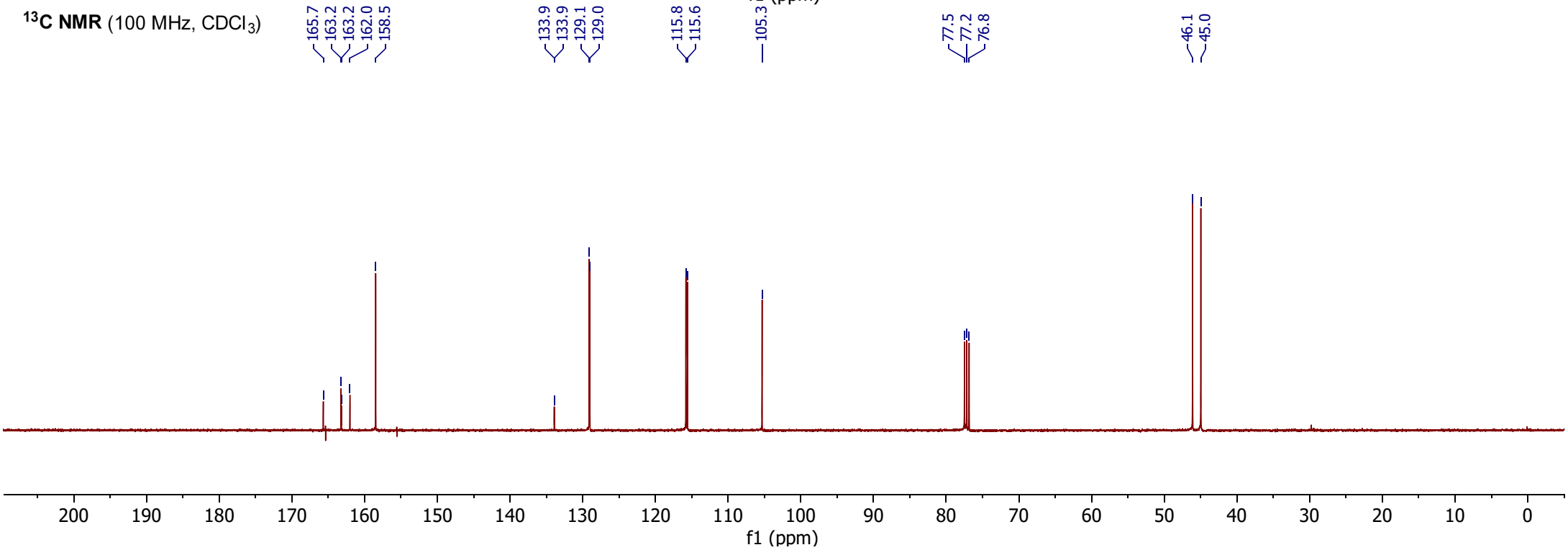


^{1}H NMR (400 MHz, $CDCl_3$)

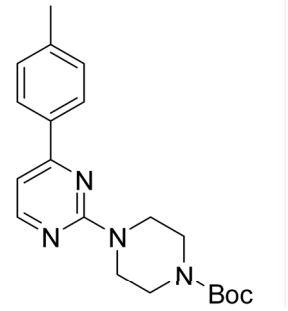


14c

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.35 8.34 7.95 7.93 7.27 7.25 6.94 6.93 3.92 3.90 3.89 3.55 3.53 3.52 2.41 1.50

0.94 2.00 2.11 1.00 3.86 3.95 3.00 8.92

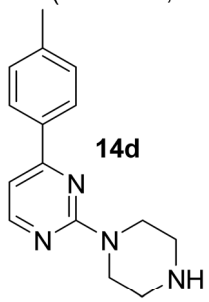
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

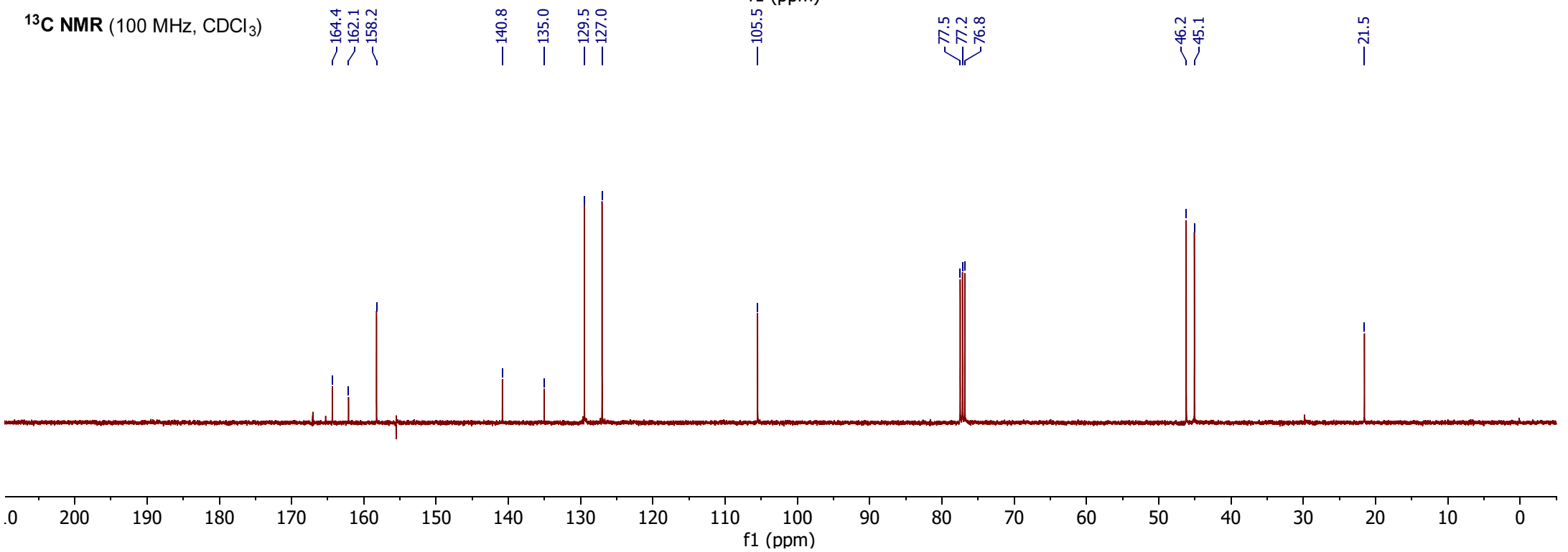
164.5 162.0 158.3 155.0 141.0 134.8 129.5 127.0 105.9 80.0 77.5 77.2 76.8 43.8 28.6 21.5

f1 (ppm)

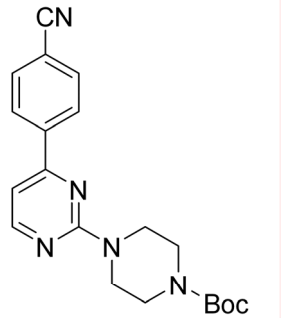
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.45 8.44 8.15 8.13 7.77 7.75 7.26 6.97 6.96 3.92 3.91 3.89 3.55 3.54 3.52 1.50

1.00 2.00 2.00 1.00 4.00 4.00 8.96

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

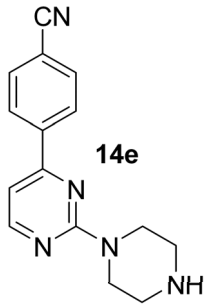
^{13}C NMR (100 MHz, $CDCl_3$)

162.4 162.0 159.2 155.0 141.9 132.6 127.7 118.7 114.0 106.3 80.2 77.5 77.2 76.8 43.8 28.6

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

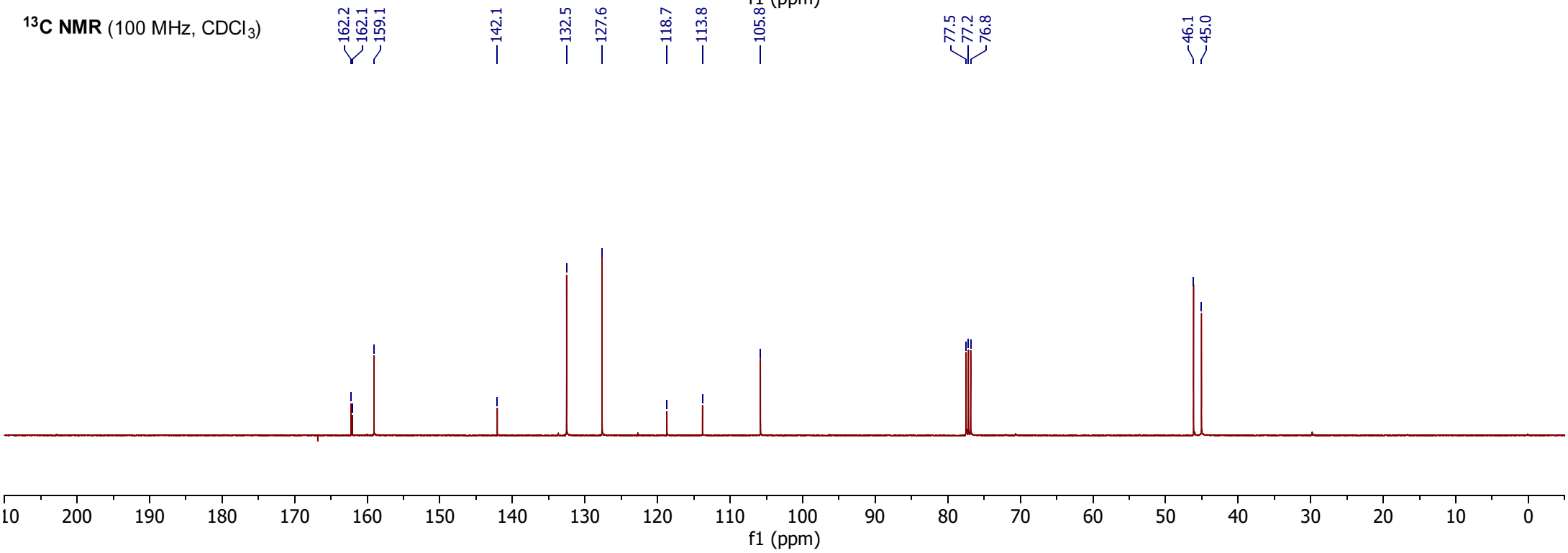
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

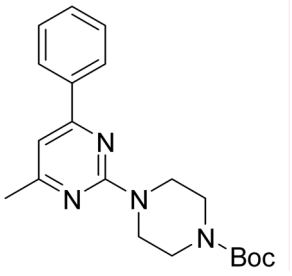


14e

^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.04 8.04 8.03 8.02 7.46 7.45 7.45 7.26 6.86 3.93 3.92 3.90 3.54 3.53 3.52 2.41 1.50

2.19 3.14 1.00 4.09 4.11 3.01 9.36

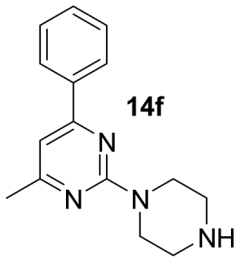
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

168.4 164.3 162.1 155.1 138.0 130.4 128.7 127.1 105.8 80.0 77.5 77.2 76.8 43.9 28.6 24.7

f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



8.05 8.04 8.03 8.02 7.45 7.44 7.44 7.26 6.83 3.93 3.92 3.91 2.98 2.97 2.96 2.40 2.21

2.13 3.11 1.00 4.08 4.05 3.02 1.03

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

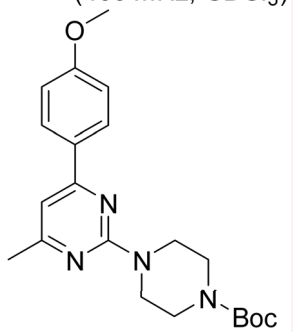
^{13}C NMR (100 MHz, $CDCl_3$)

168.2 164.2 162.3 138.2 130.3 128.7 127.1 105.4 77.5 77.2 76.8 46.2 45.0 24.7

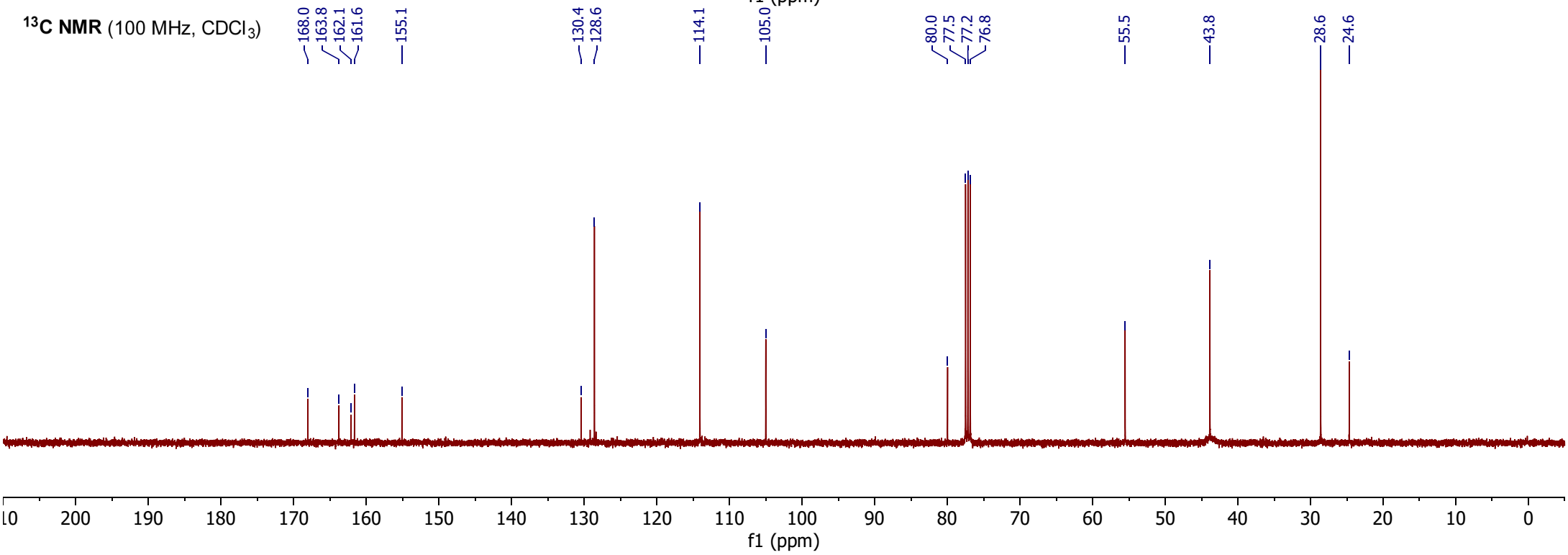
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

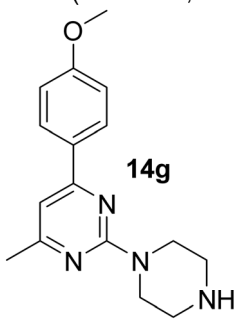
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



8.02 8.00 7.26 6.97 6.95 6.78 3.91 3.90 3.89 3.86 2.97 2.96 2.95 2.38 2.00

2.00 2.00 0.96 4.00 2.98 3.88 2.88 1.59

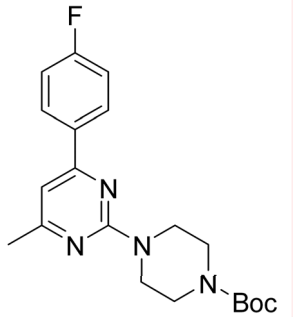
f1 (ppm)

^{13}C NMR (100 MHz, $CDCl_3$)

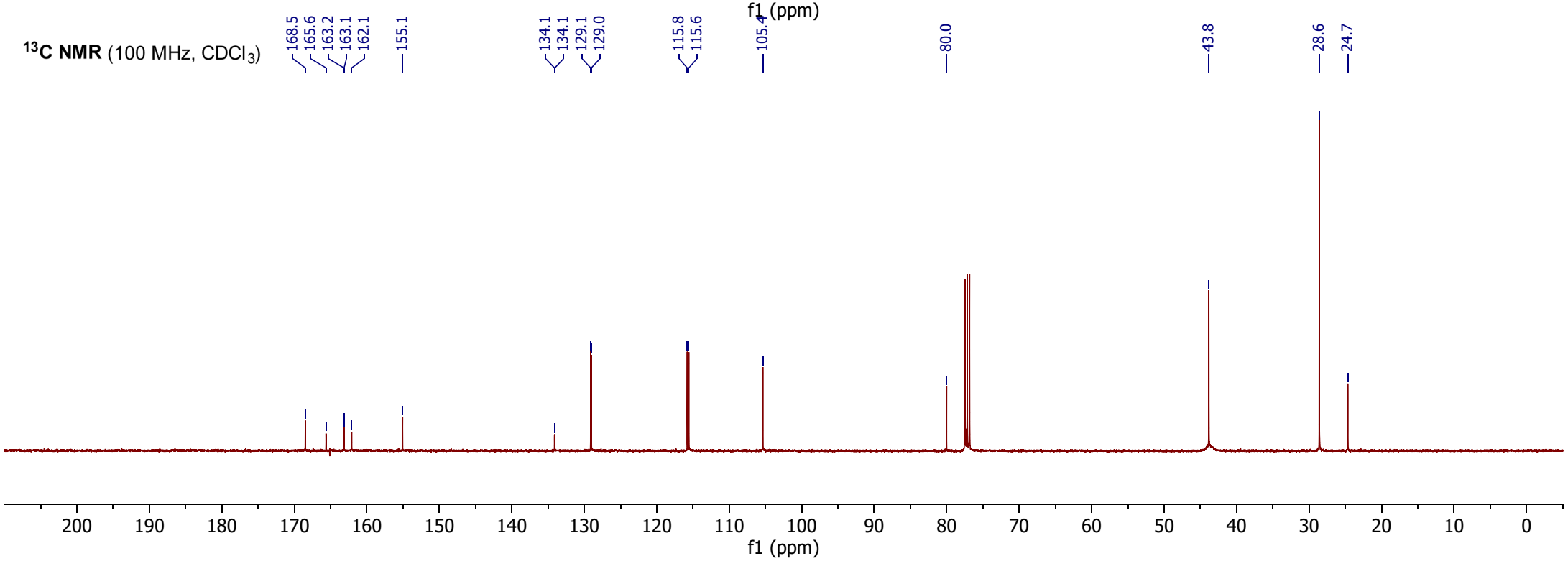
167.9 163.7 162.2 161.5 130.6 128.6 114.0 104.6 77.5 77.2 76.8 55.5 46.2 45.1 24.7

f1 (ppm)

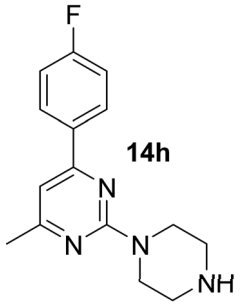
^{1}H NMR (400 MHz, $CDCl_3$)



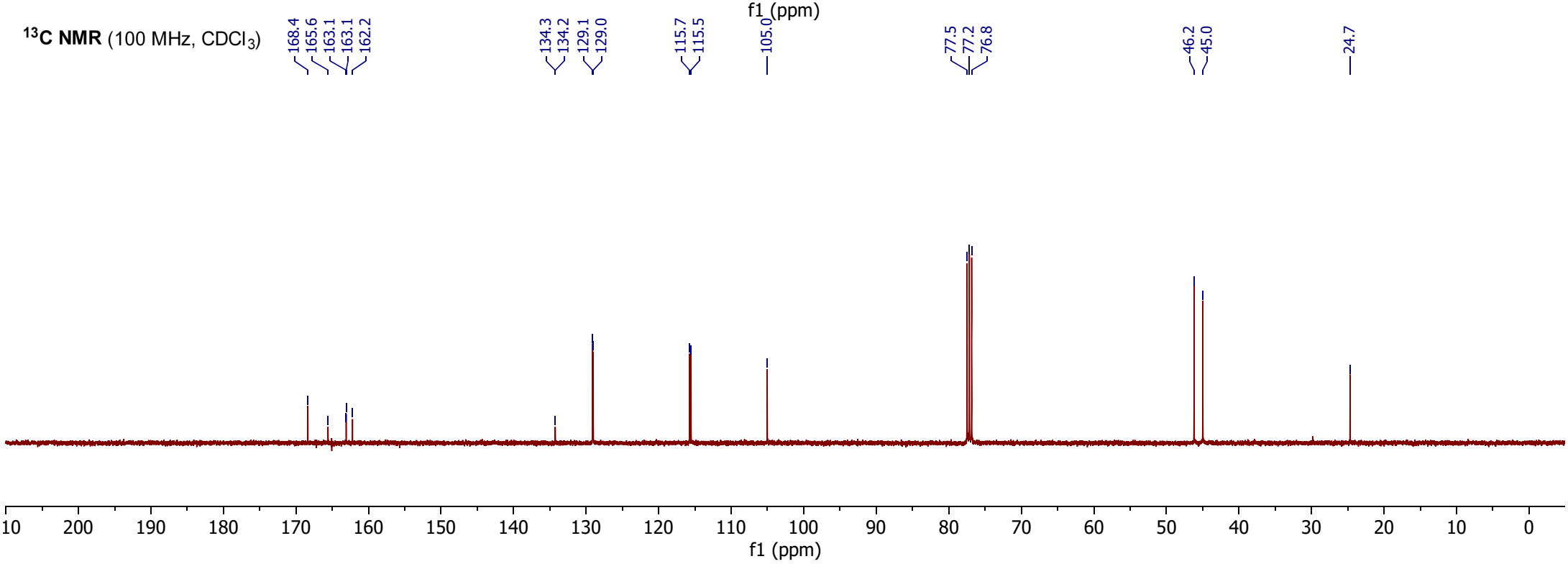
^{13}C NMR (100 MHz, $CDCl_3$)



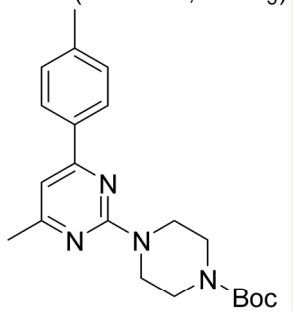
^{1}H NMR (400 MHz, $CDCl_3$)



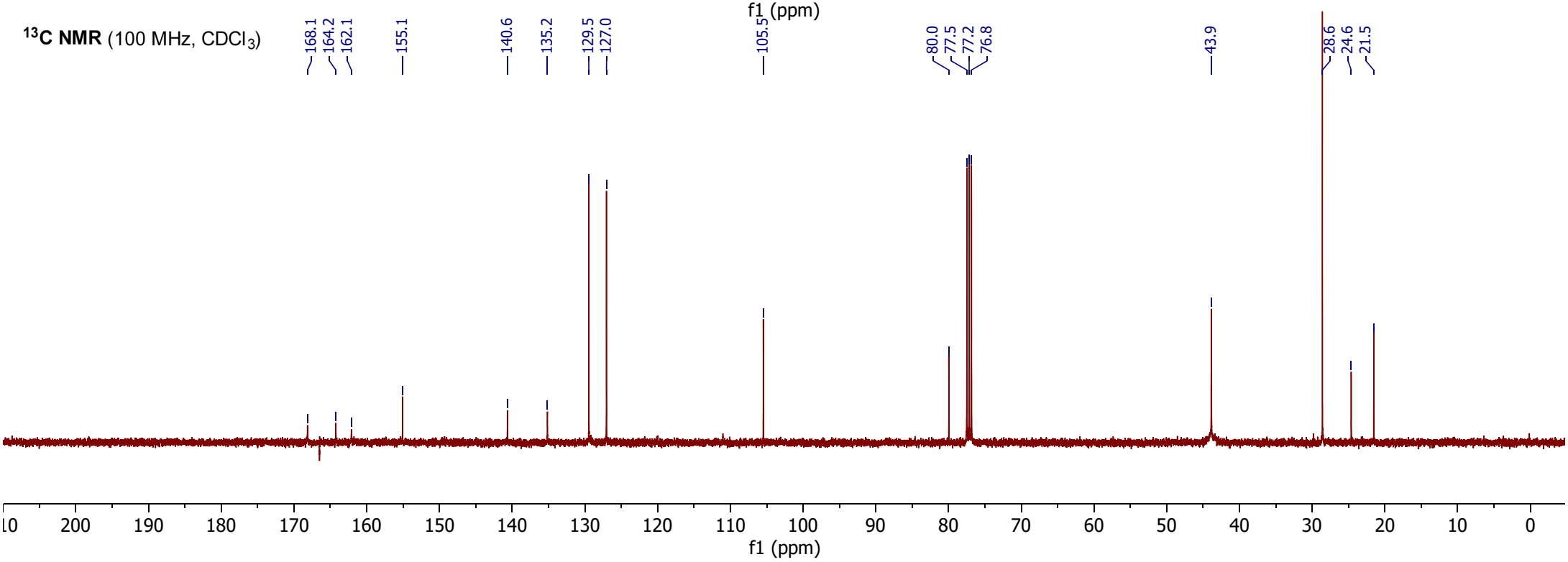
^{13}C NMR (100 MHz, $CDCl_3$)



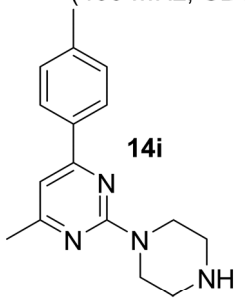
^{1}H NMR (400 MHz, $CDCl_3$)



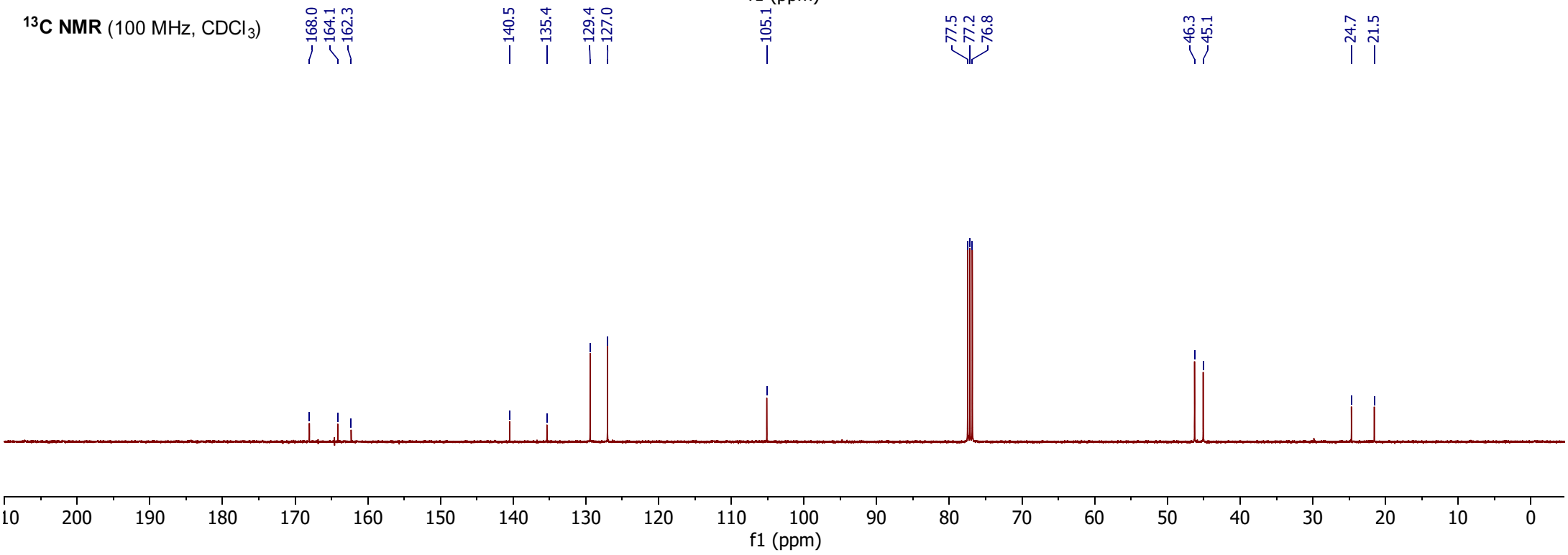
^{13}C NMR (100 MHz, $CDCl_3$)



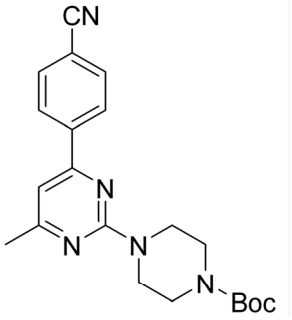
^{1}H NMR (400 MHz, $CDCl_3$)



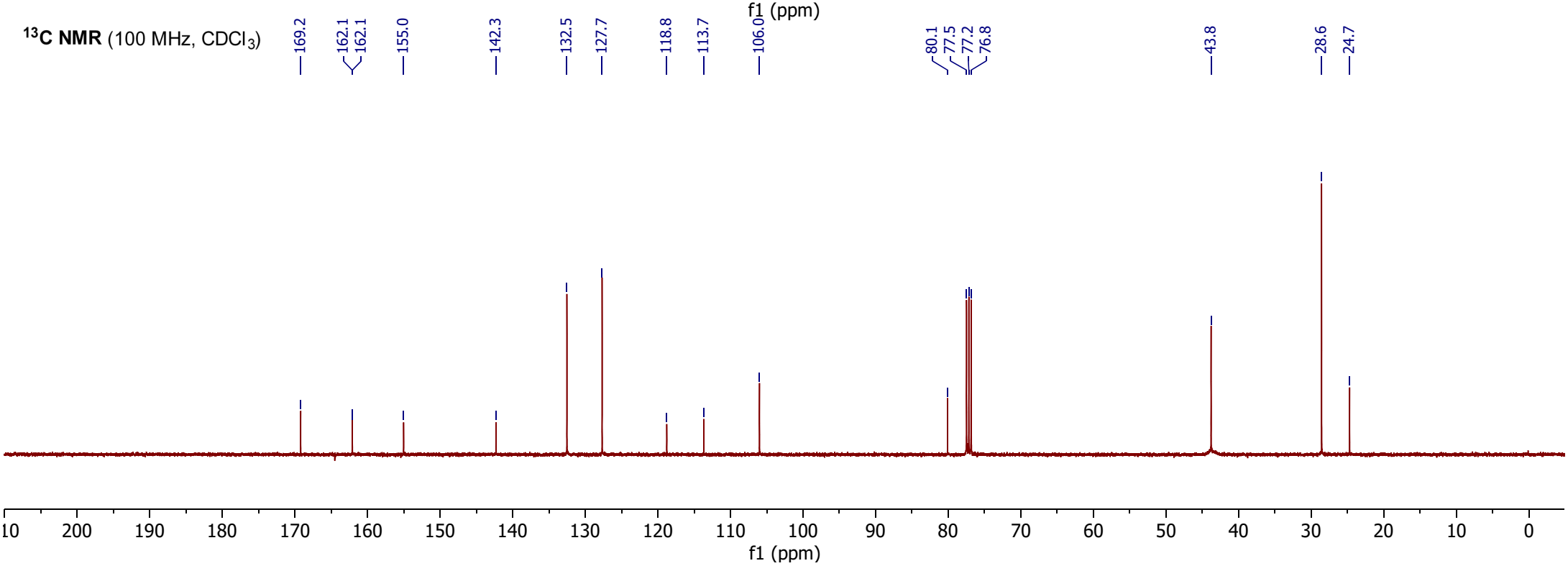
^{13}C NMR (100 MHz, $CDCl_3$)



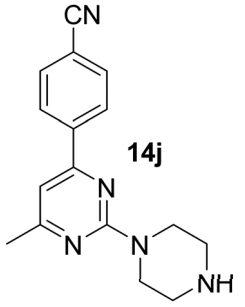
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

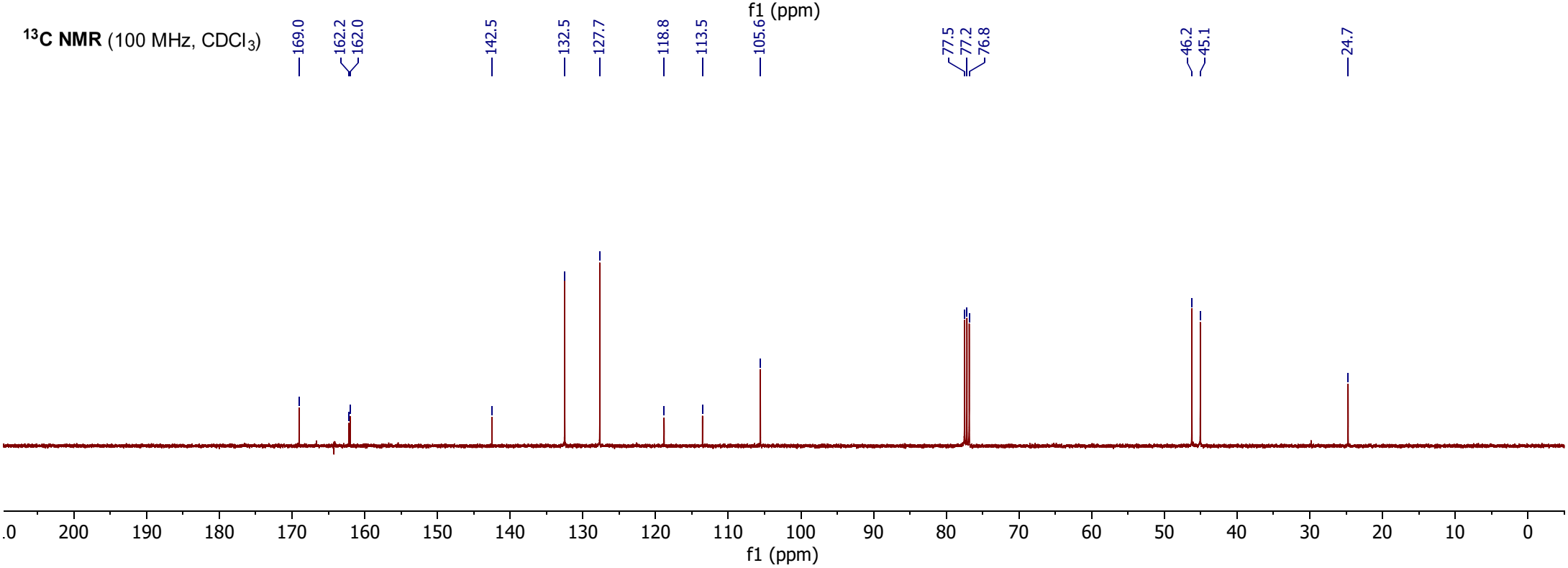


^{1}H NMR (400 MHz, $CDCl_3$)



14j

^{13}C NMR (100 MHz, $CDCl_3$)



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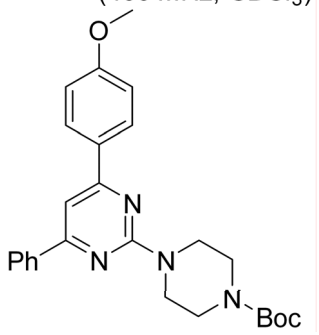


8.12 8.12 8.11 8.10 8.09 8.09 8.09 8.08 8.08 7.52 7.51 7.50 7.50 7.49 7.48 7.48 7.48 7.47 7.38 7.26 7.02 7.00

4.02 4.01 4.00 3.88 3.59 3.57 3.56

1.51

3.97 3.00 0.92 2.00 3.75 2.91 3.89 8.60

..0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

f1 (ppm)

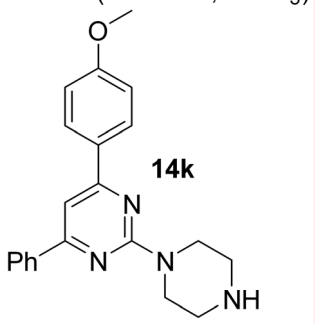
^{13}C NMR (100 MHz, $CDCl_3$)

165.2 164.9 162.3 161.8 155.1 138.4 130.6 130.4 128.8 128.7 127.2 114.1 101.6 80.0 55.6 43.9 28.6

10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



8.12 8.11 8.10 8.10 8.09 8.09 8.08 7.51 7.50 7.49 7.49 7.48 7.47 7.47 7.46 7.35 7.26 7.01 6.99 4.04 4.03 4.01 3.88 3.03 3.02 3.01 2.27

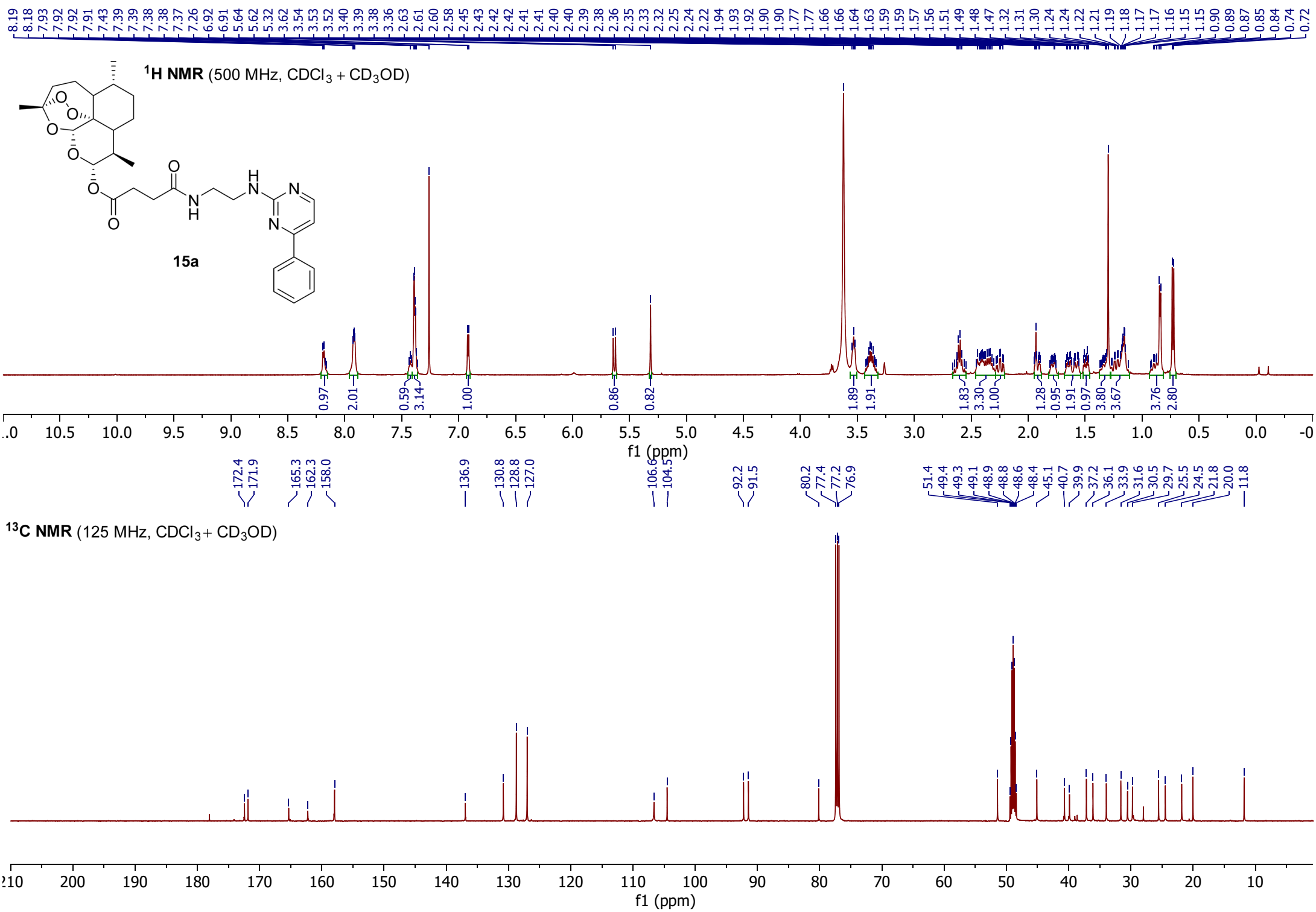
4.00 3.00 0.89 2.00 3.70 2.87 3.65 1.14

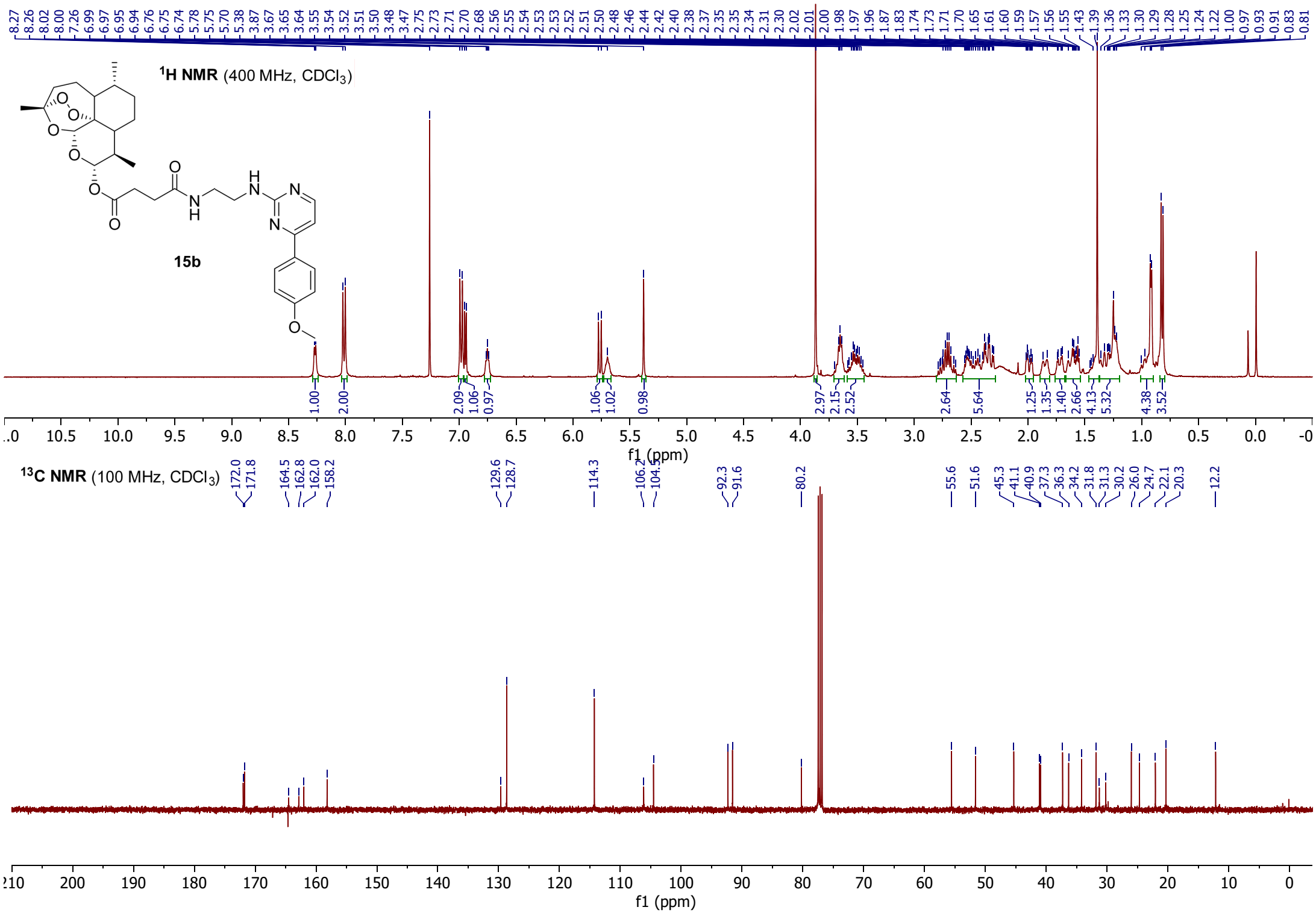
f1 (ppm)

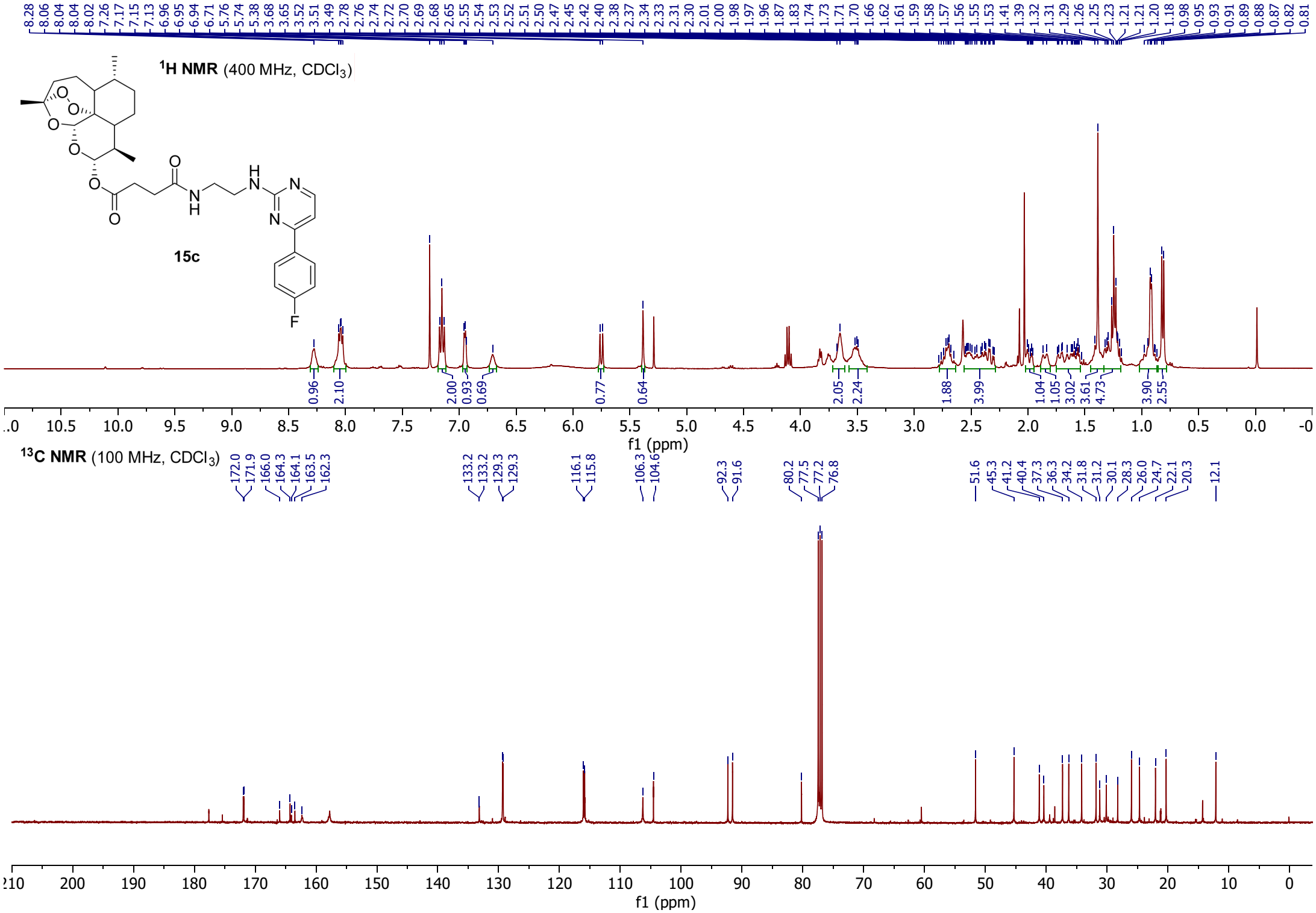
^{13}C NMR (100 MHz, $CDCl_3$)

165.1 164.8 162.4 161.7 138.5 130.8 130.3 128.7 128.7 127.2 114.1 101.3 77.5 77.2 76.8 55.5 46.2 45.0

f1 (ppm)


8.19 8.18 7.93 7.92 7.92 7.91 7.43 7.39 7.39 7.38 7.38 7.37 7.26 6.92 6.91 5.64 5.62 5.32 3.62 3.54 3.53 3.52 3.40 3.39 3.38 3.36 2.63 2.61 2.60 2.58 2.45 2.43 2.42 2.42 2.41 2.41 2.40 2.40 2.39 2.38 2.36 2.35 2.33 2.32 2.25 2.24 2.22 1.94 1.93 1.92 1.90 1.90 1.77 1.77 1.66 1.66 1.64 1.63 1.59 1.59 1.57 1.56 1.51 1.49 1.48 1.47 1.32 1.31 1.30 1.24 1.24 1.22 1.21 1.19 1.18 1.17 1.17 1.16 1.15 1.15 0.90 0.89 0.87 0.85 0.84 0.74 0.72
1H NMR (500 MHz, CDCl3 + CD3OD)
15a
0.97 2.01 0.59 3.14 1.00 0.86 0.82 1.89 1.91 1.83 3.30 1.00 1.28 0.95 1.91 0.97 3.80 3.67 3.76 2.80
f1 (ppm)
172.4 171.9 165.3 162.3 158.0 136.9 130.8 128.8 127.0 106.6 104.5 92.2 91.5 80.2 77.4 77.2 76.9 51.4 49.4 49.3 49.1 48.9 48.8 48.6 48.4 45.1 40.7 39.9 37.2 36.1 33.9 31.6 30.5 29.7 25.5 24.5 21.8 20.0 11.8
13C NMR (125 MHz, CDCl3+ CD3OD)
f1 (ppm)


^{1}H NMR (400 MHz, $CDCl_3$)
15b
f1 (ppm)
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)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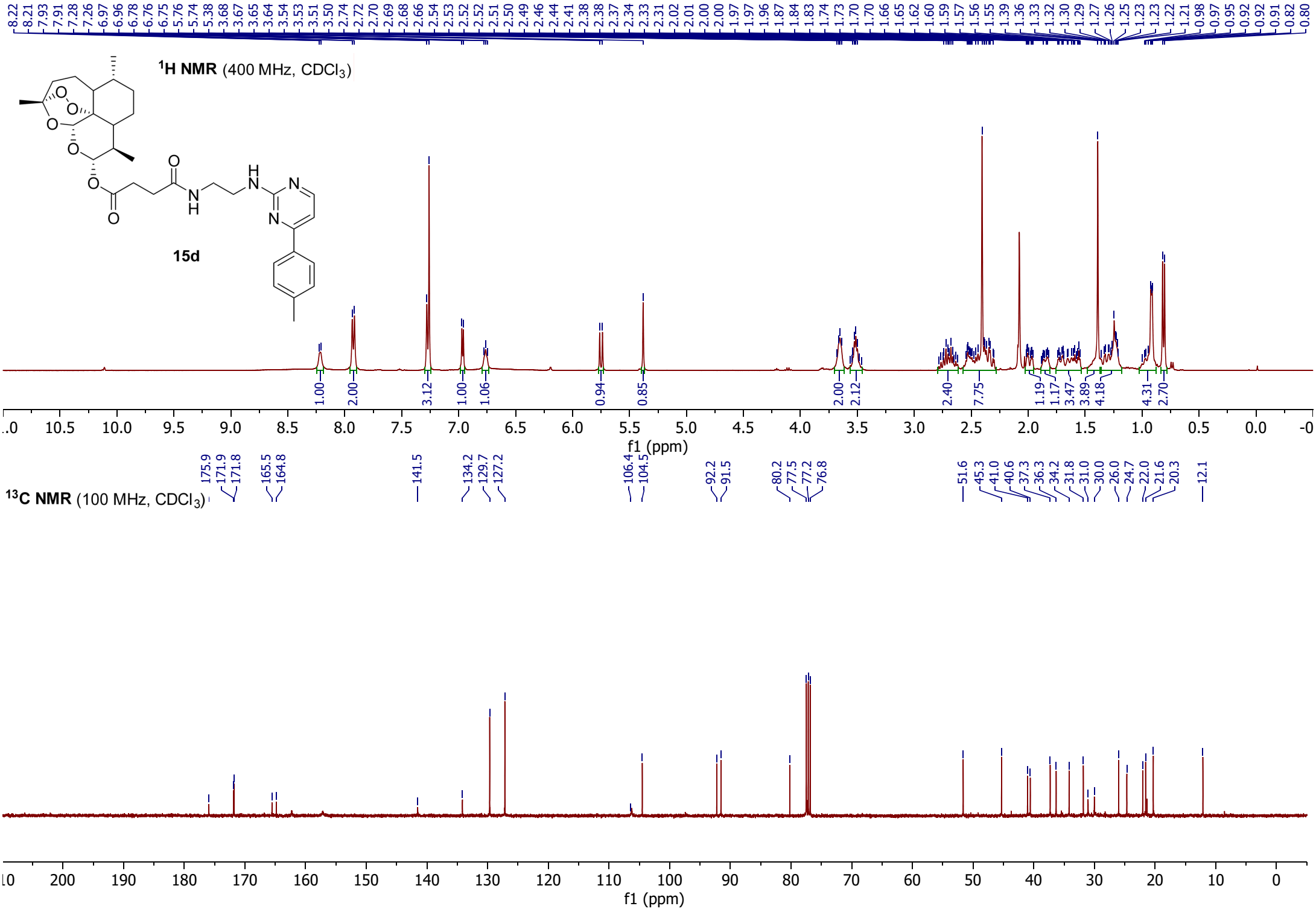
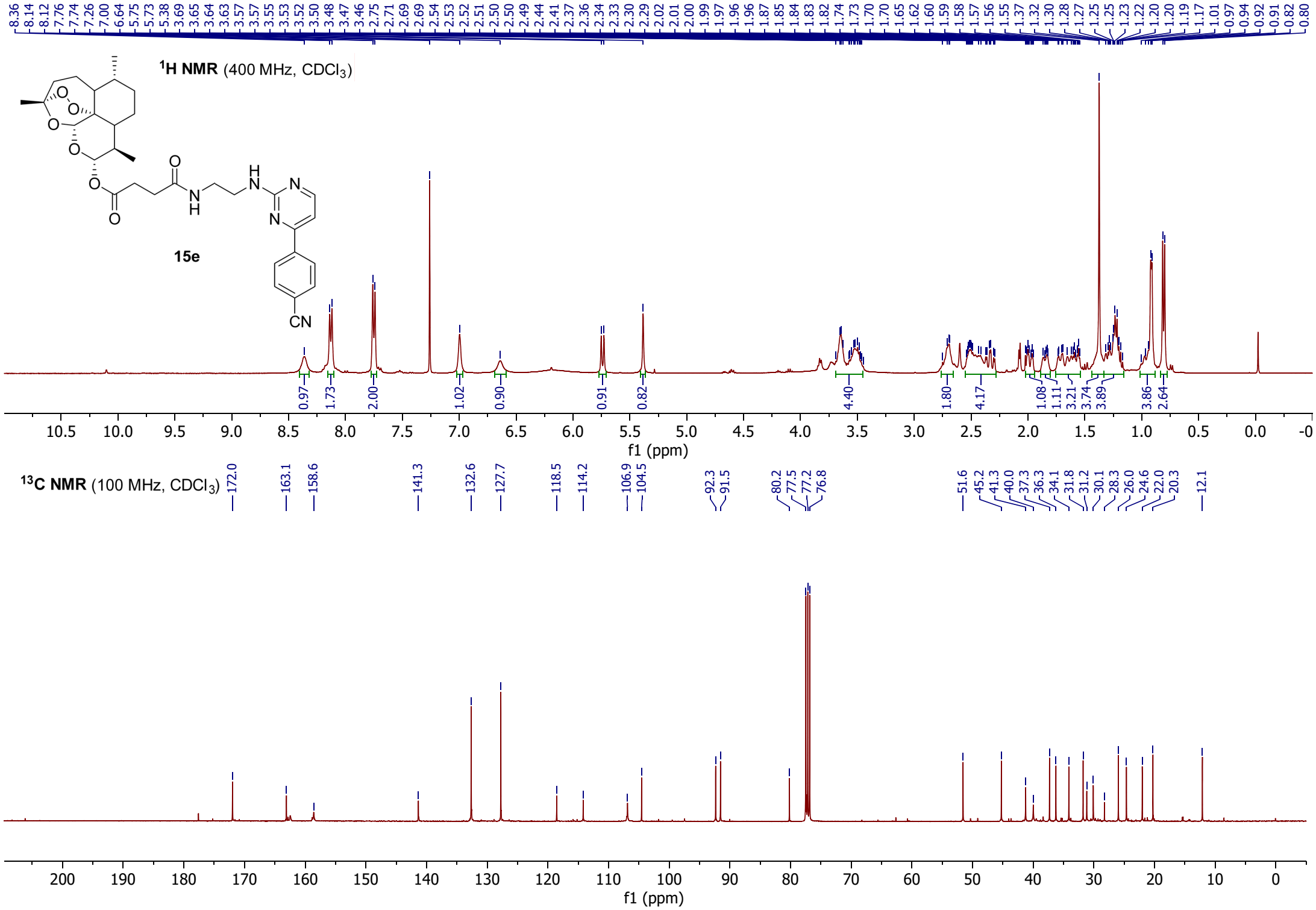
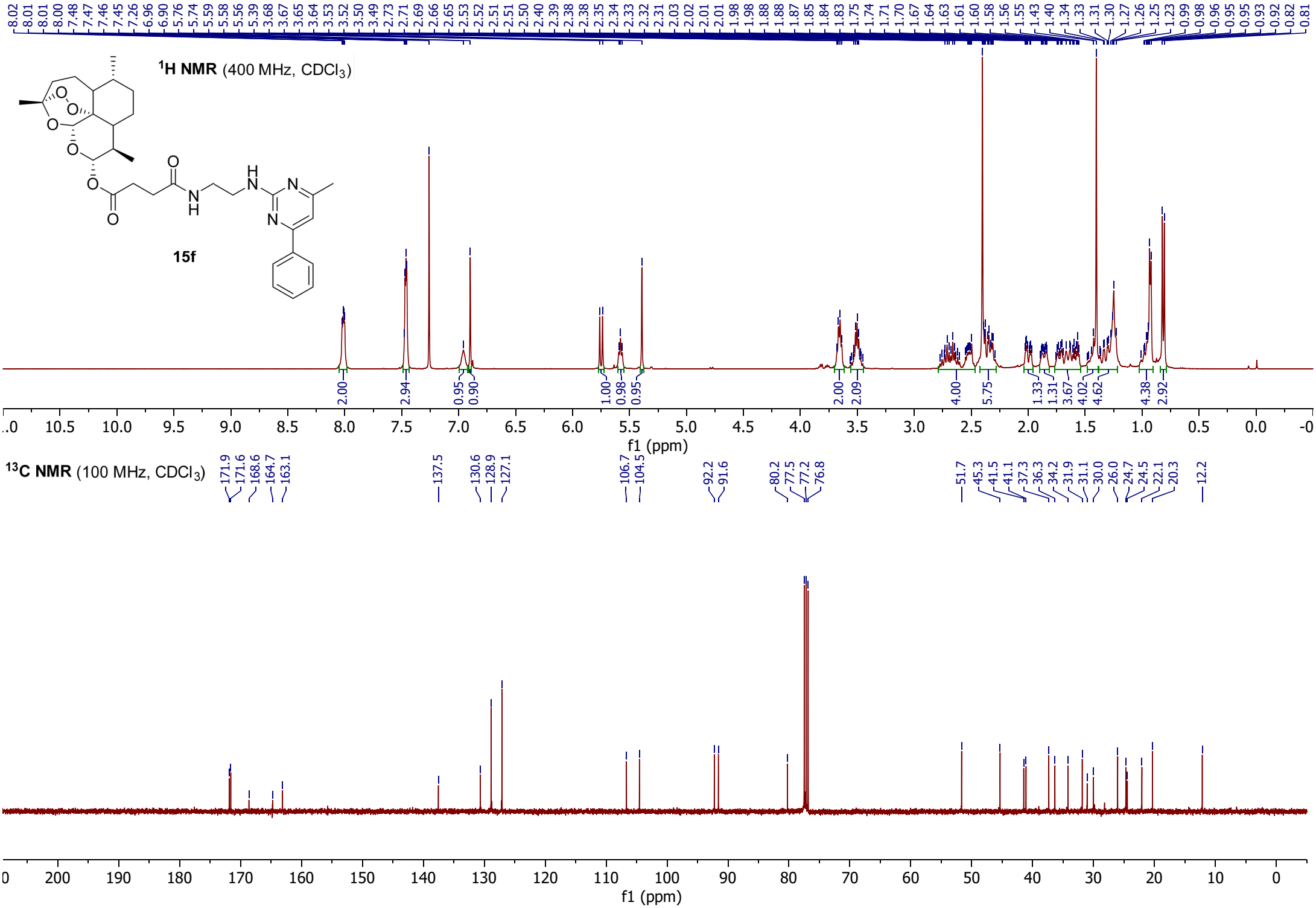
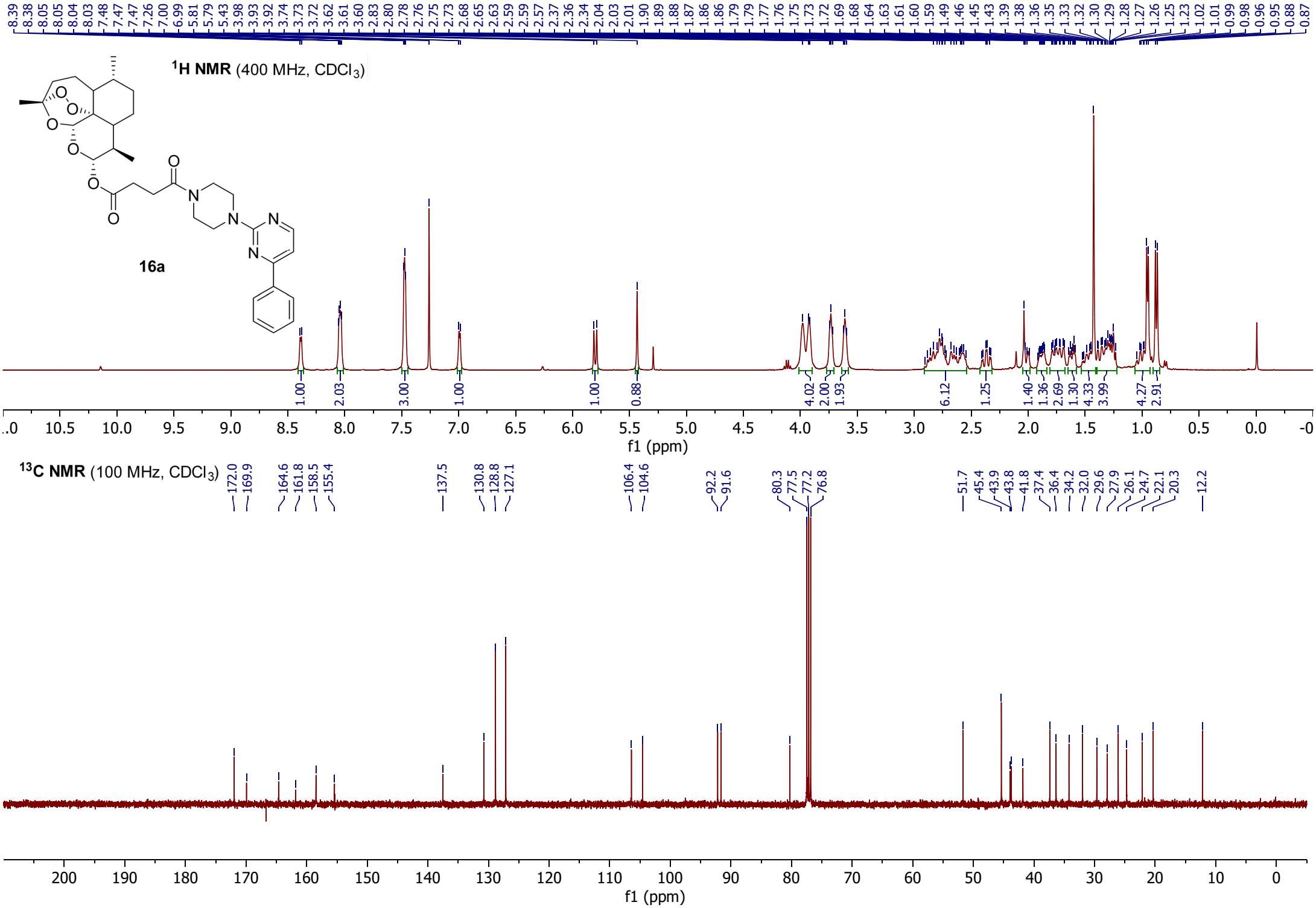
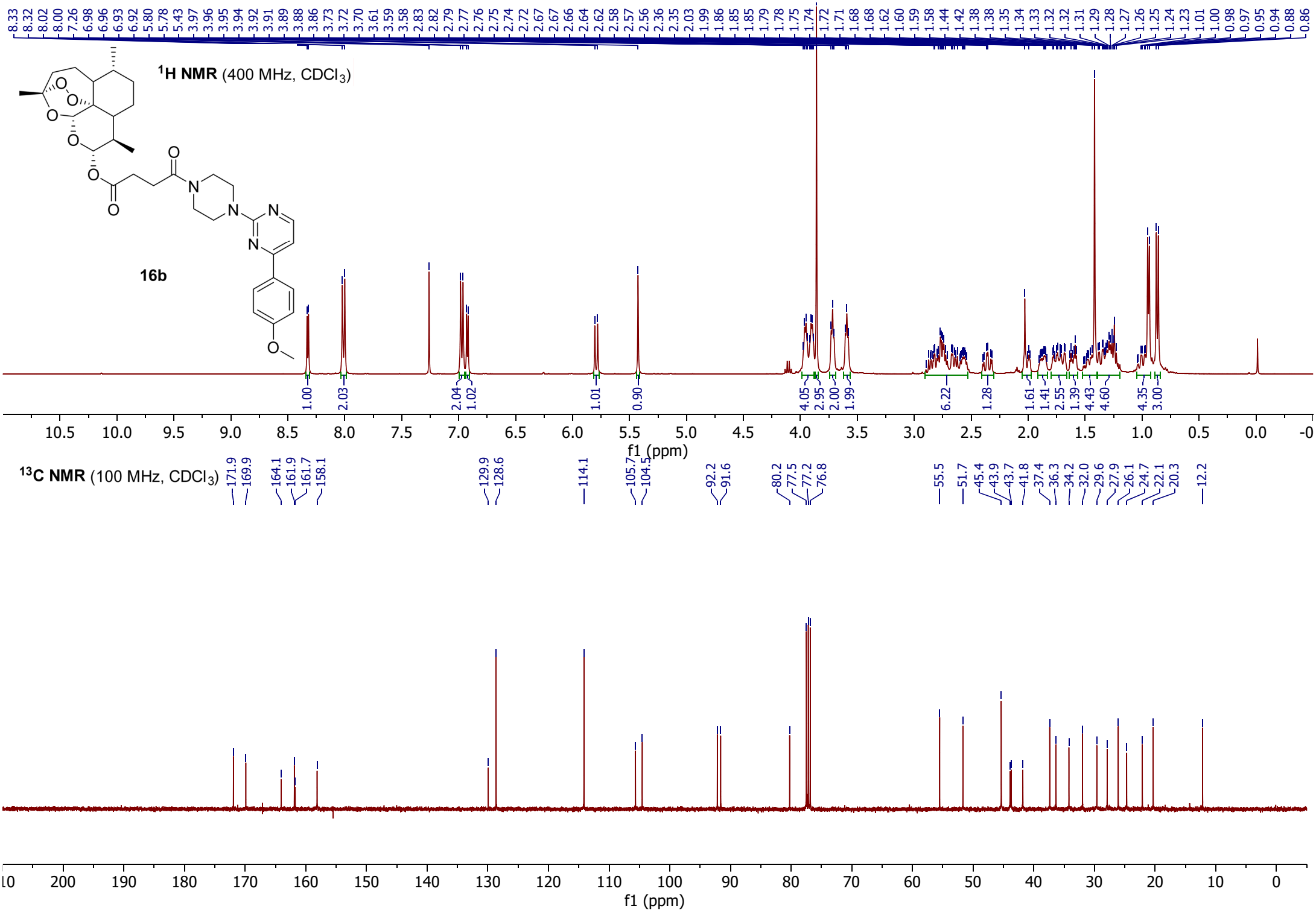
15c
f1 (ppm)
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

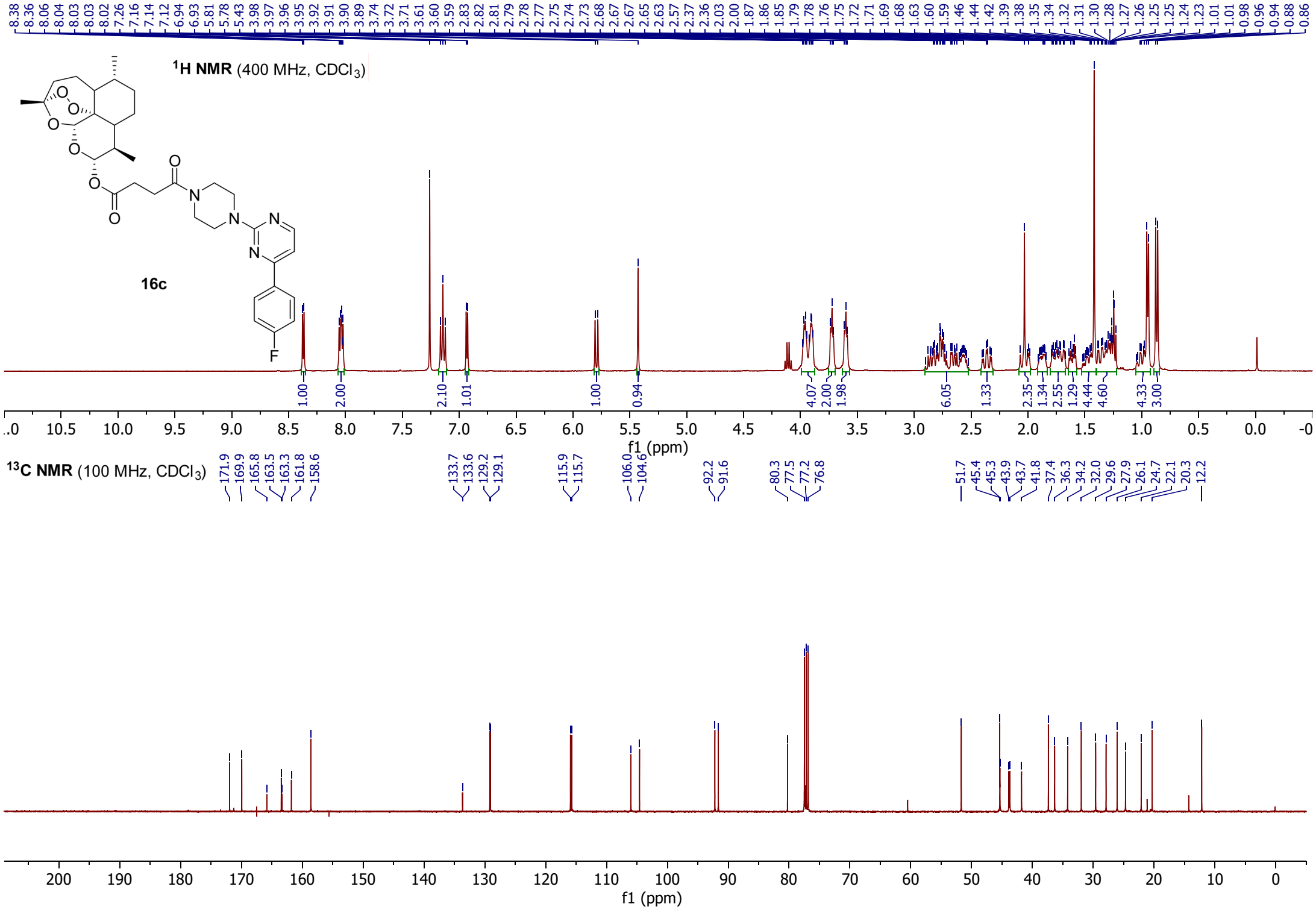

8.22 8.21 7.93 7.91 7.28 7.26 6.97 6.96 6.78 6.76 6.75 5.76 5.74 5.38 3.68 3.67 3.65 3.64 3.54 3.53 3.51 3.50 2.74 2.72 2.70 2.69 2.68 2.66 2.54 2.53 2.52 2.52 2.51 2.50 2.49 2.46 2.44 2.41 2.38 2.38 2.37 2.34 2.33 2.31 2.02 2.01 2.00 2.00 1.97 1.97 1.96 1.87 1.84 1.83 1.74 1.73 1.70 1.70 1.66 1.65 1.62 1.60 1.59 1.57 1.56 1.55 1.39 1.36 1.33 1.32 1.30 1.29 1.27 1.26 1.25 1.23 1.23 1.22 1.21 0.98 0.97 0.95 0.92 0.92 0.91 0.82 0.80
1H NMR (400 MHz, CDCl3)
15d
1.00 2.00 3.12 1.00 1.06 0.94 0.85 2.00 2.12 2.40 7.75 1.19 1.17 3.47 3.89 4.18 4.31 2.70
f1 (ppm)
13C NMR (100 MHz, CDCl3)
175.9 171.9 171.8 165.5 164.8 141.5 134.2 129.7 127.2 106.4 104.5 92.2 91.5 80.2 77.5 77.2 76.8 51.6 45.3 41.0 40.6 37.3 36.3 34.2 31.8 31.0 30.0 26.0 24.7 22.0 21.6 20.3 12.1
f1 (ppm)

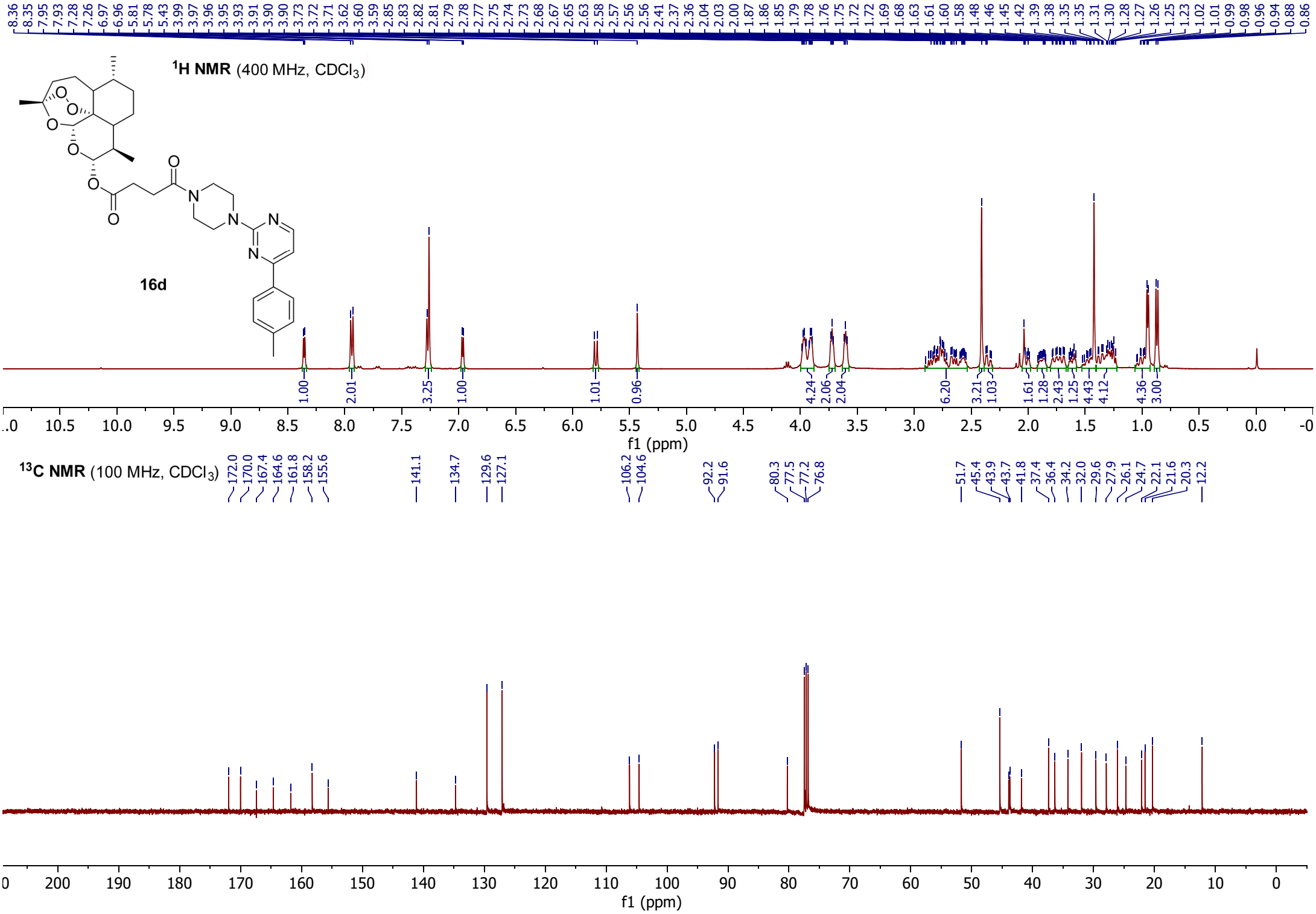

8.36 8.14 8.12 7.76 7.74 7.26 7.00 6.64 5.75 5.73 5.38 3.69 3.65 3.64 3.63 3.57 3.55 3.53 3.52 3.50 3.48 3.47 3.46 2.75 2.71 2.69 2.69 2.54 2.53 2.52 2.51 2.50 2.50 2.49 2.44 2.41 2.37 2.36 2.34 2.33 2.30 2.29 2.02 2.01 2.00 1.99 1.97 1.96 1.96 1.87 1.85 1.84 1.83 1.82 1.74 1.73 1.70 1.70 1.65 1.62 1.60 1.59 1.58 1.57 1.56 1.55 1.37 1.32 1.30 1.28 1.27 1.25 1.25 1.23 1.22 1.20 1.20 1.19 1.17 1.01 0.97 0.94 0.92 0.91 0.82 0.80
1H NMR (400 MHz, CDCl3)
15e
0.97 1.73 2.00 1.02 0.90 0.91 0.82 4.40 1.80 4.17 1.08 1.11 3.21 3.74 3.89 3.86 2.64
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)
13C NMR (100 MHz, CDCl3)
172.0 163.1 158.6 141.3 132.6 127.7 118.5 114.2 106.9 104.5 92.3 91.5 80.2 77.5 77.2 76.8 51.6 45.2 41.3 40.0 37.3 36.3 34.1 31.8 31.2 30.1 28.3 26.0 24.6 22.0 20.3 12.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

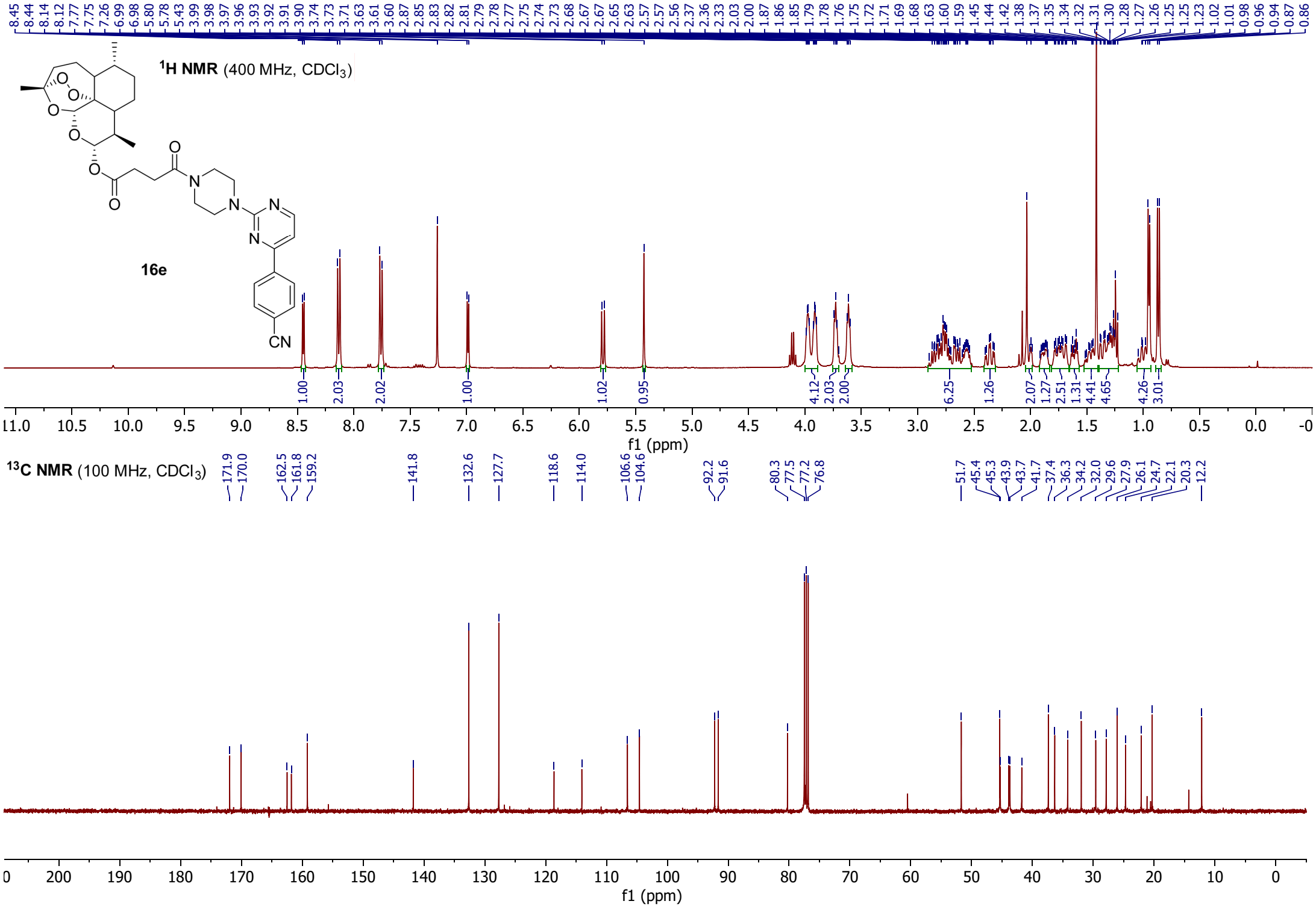

^{1}H NMR (400 MHz, $CDCl_3$)
15f
f1 (ppm)
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

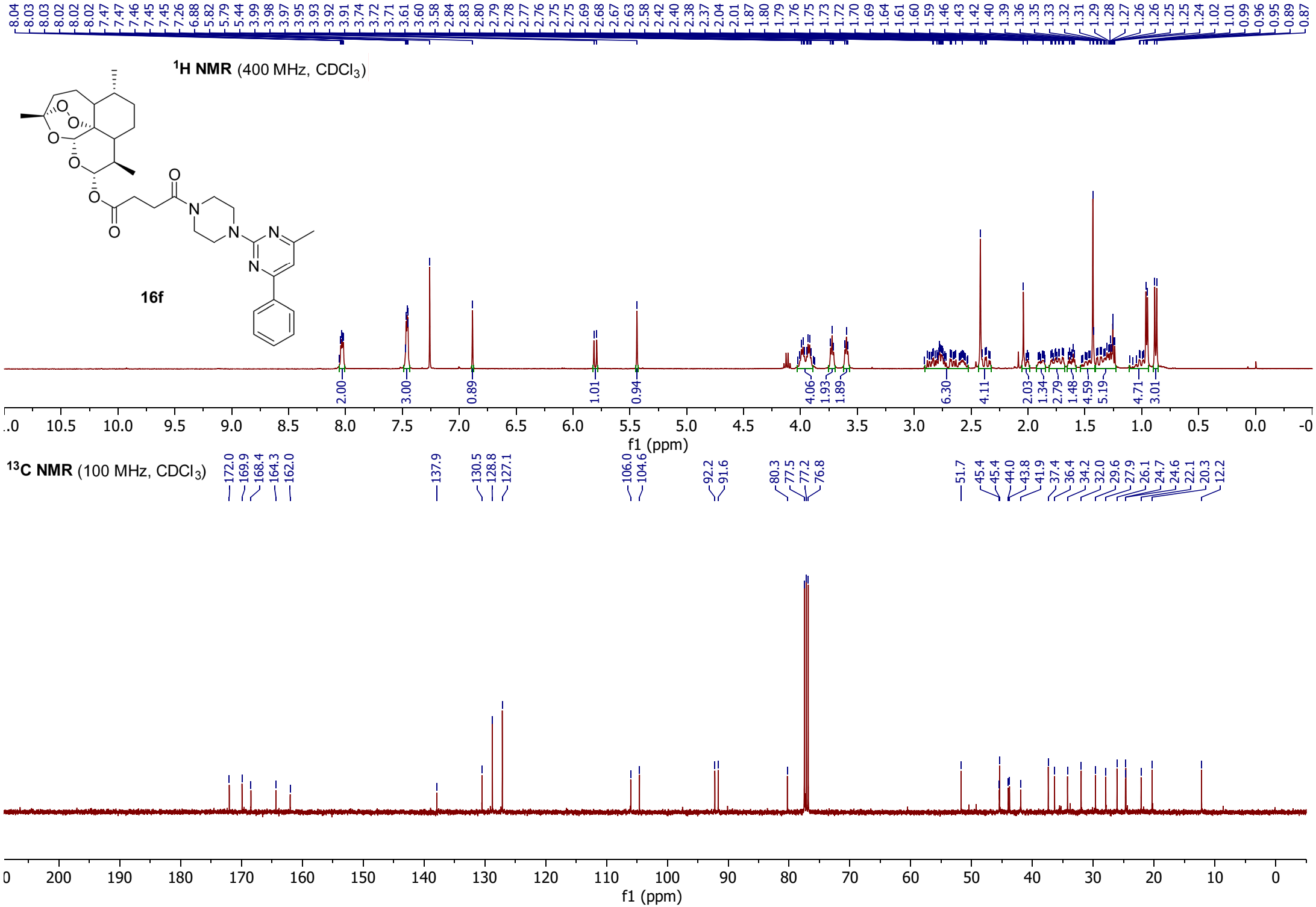

8.39 8.38 8.05 8.05 8.04 8.03 7.48 7.47 7.47 7.26 7.00 6.99 5.81 5.79 5.43 3.98 3.93 3.92 3.74 3.73 3.72 3.62 3.61 3.60 2.83 2.80 2.78 2.76 2.75 2.73 2.68 2.65 2.63 2.59 2.59 2.57 2.37 2.36 2.34 2.04 2.03 2.01 1.90 1.89 1.88 1.87 1.86 1.86 1.79 1.79 1.77 1.76 1.75 1.73 1.72 1.69 1.68 1.64 1.63 1.61 1.60 1.59 1.49 1.46 1.45 1.43 1.39 1.38 1.36 1.35 1.33 1.32 1.30 1.29 1.28 1.27 1.26 1.25 1.23 1.02 1.01 0.99 0.98 0.96 0.95 0.88 0.87
1H NMR (400 MHz, CDCl3)
16a
1.00 2.03 3.00 1.00 1.00 0.88 4.02 2.00 1.93 6.12 1.25 1.40 1.36 2.69 1.30 4.33 3.99 4.27 2.91
f1 (ppm)
13C NMR (100 MHz, CDCl3)
172.0 169.9 164.6 161.8 158.5 155.4 137.5 130.8 128.8 127.1 106.4 104.6 92.2 91.6 80.3 77.5 77.2 76.8 51.7 45.4 43.9 43.8 41.8 37.4 36.4 34.2 32.0 29.6 27.9 26.1 24.7 22.1 20.3 12.2
f1 (ppm)

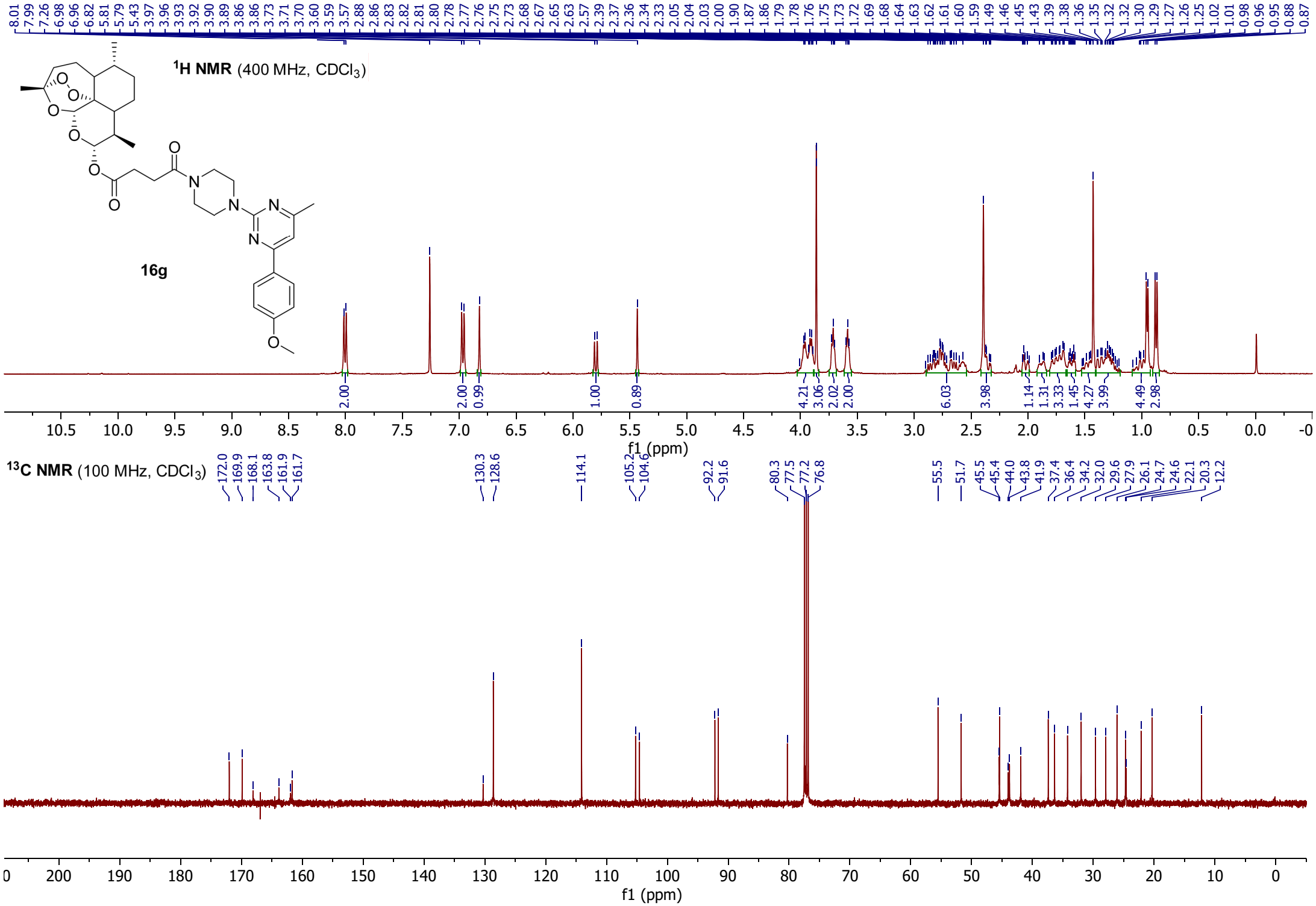

^{1}H NMR (400 MHz, CDCl$_3$)
16b
f1 (ppm)
^{13}C NMR (100 MHz, CDCl$_3$)
f1 (ppm)

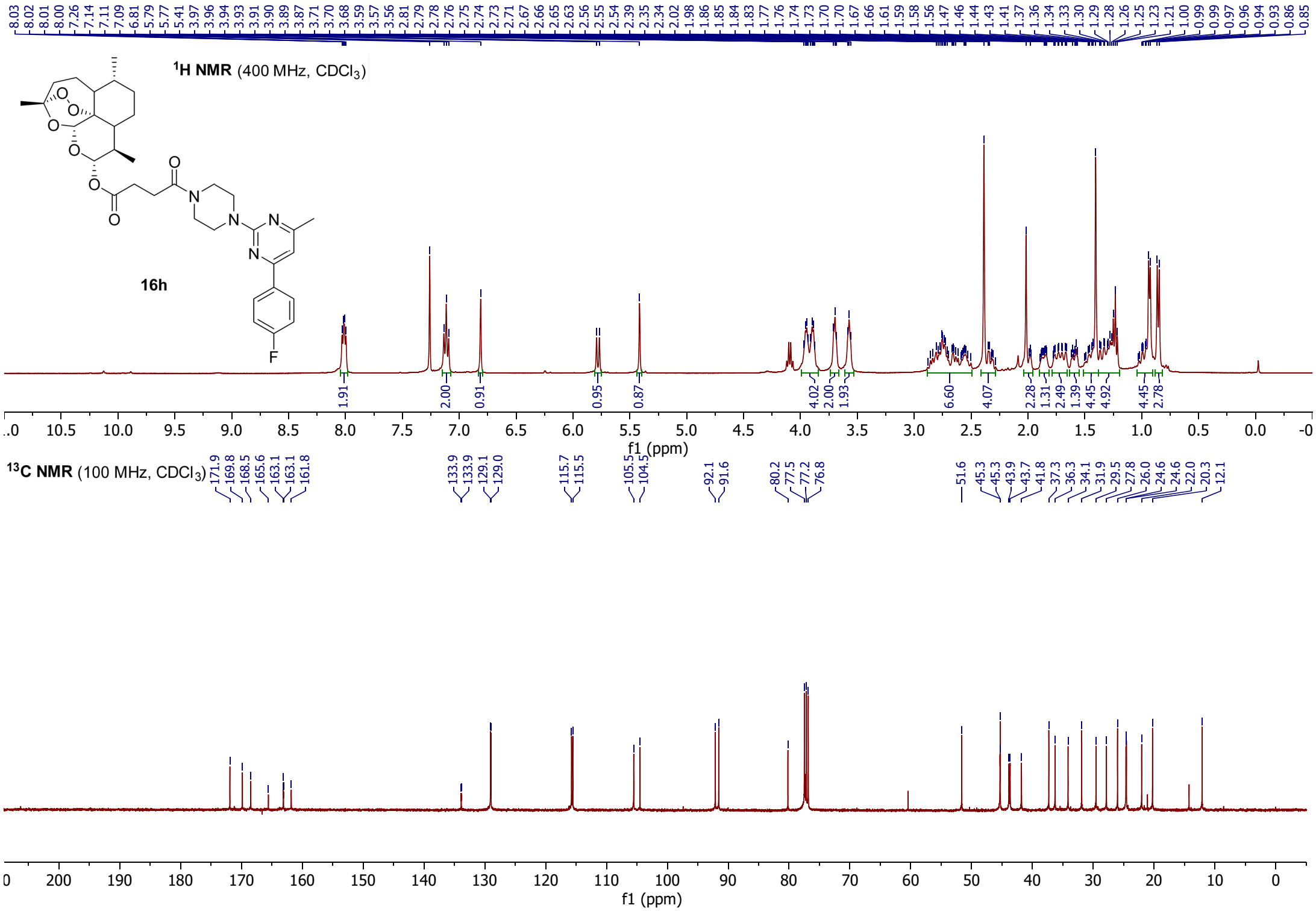

8.38 8.36 8.06 8.04 8.03 8.03 8.02 7.26 7.16 7.14 7.12 6.94 6.93 5.81 5.78 5.43 3.98 3.97 3.96 3.95 3.92 3.91 3.90 3.89 3.74 3.72 3.71 3.61 3.60 3.59 2.83 2.82 2.81 2.79 2.78 2.77 2.75 2.74 2.73 2.68 2.67 2.67 2.65 2.63 2.57 2.37 2.36 2.03 2.00 1.87 1.86 1.85 1.79 1.78 1.76 1.75 1.72 1.71 1.69 1.68 1.63 1.60 1.59 1.46 1.44 1.42 1.39 1.38 1.35 1.34 1.32 1.31 1.30 1.28 1.27 1.26 1.25 1.25 1.24 1.23 1.01 1.01 0.98 0.96 0.94 0.88 0.86
1H NMR (400 MHz, CDCl3)
16c
1.00 2.00 2.10 1.01 1.00 0.94 4.07 2.00 1.98 6.05 1.33 2.35 1.34 2.55 1.29 4.44 4.60 4.33 3.00
f1 (ppm)
13C NMR (100 MHz, CDCl3)
171.9 169.9 165.8 163.5 163.3 161.8 158.6 133.7 133.6 129.2 129.1 115.9 115.7 106.0 104.6 92.2 91.6 80.3 77.5 77.2 76.8 51.7 45.4 45.3 43.9 43.7 41.8 37.4 36.3 34.2 32.0 29.6 27.9 26.1 24.7 22.1 20.3 12.2
f1 (ppm)

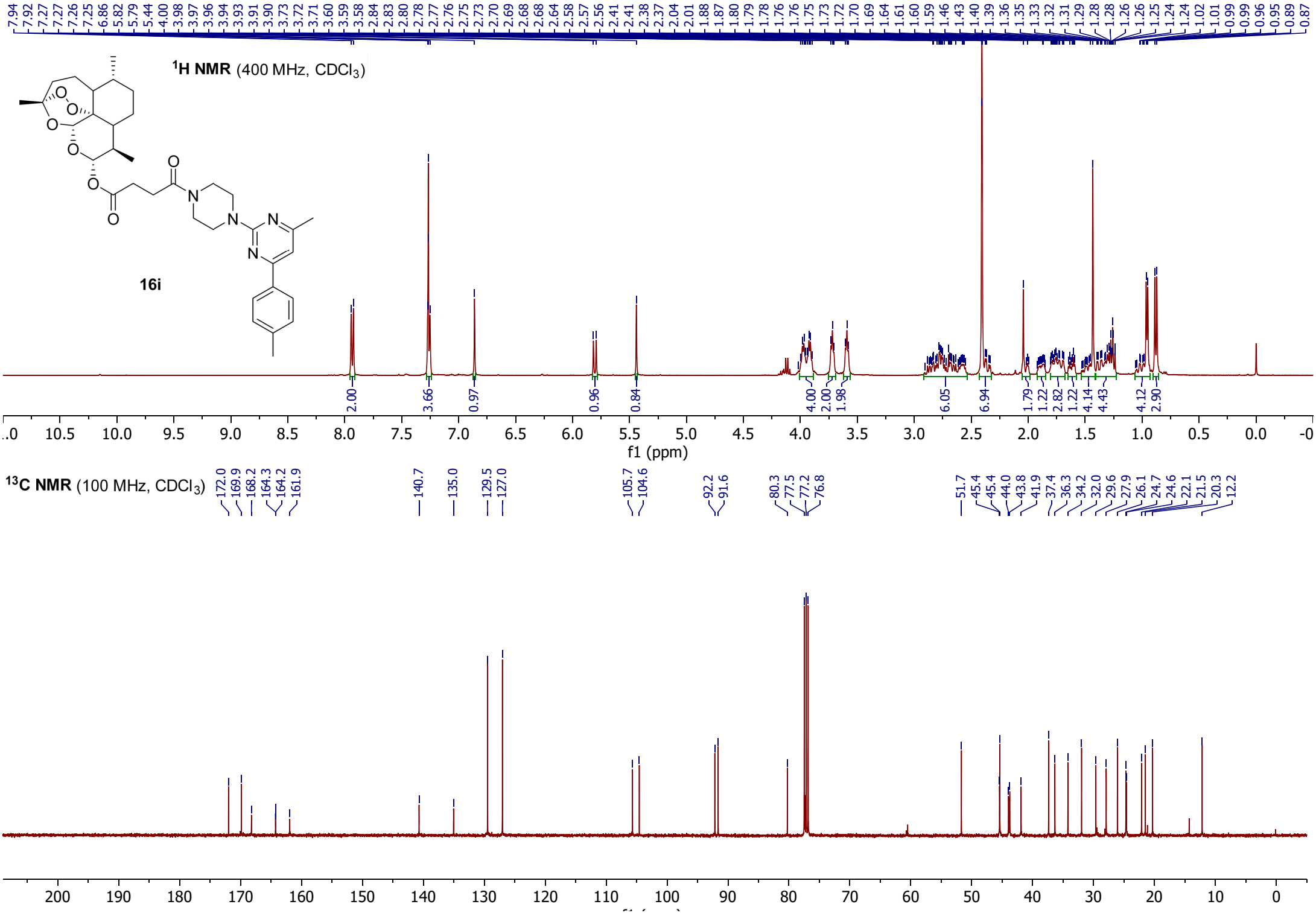

8.36 8.35 7.95 7.93 7.28 7.26 6.97 6.96 5.81 5.78 5.43 3.99 3.97 3.96 3.95 3.93 3.91 3.90 3.90 3.73 3.72 3.71 3.62 3.60 3.59 2.85 2.83 2.82 2.81 2.79 2.78 2.77 2.75 2.74 2.73 2.68 2.67 2.65 2.63 2.58 2.57 2.56 2.56 2.41 2.37 2.36 2.04 2.03 2.00 1.87 1.86 1.85 1.79 1.78 1.76 1.75 1.72 1.72 1.69 1.68 1.63 1.61 1.60 1.58 1.48 1.46 1.45 1.42 1.39 1.38 1.35 1.35 1.31 1.30 1.28 1.27 1.26 1.25 1.23 1.02 1.01 0.99 0.98 0.96 0.94 0.88 0.86
1H NMR (400 MHz, CDCl3)
16d
1.00 2.01 3.25 1.00 1.01 0.96 4.24 2.06 2.04 6.20 3.21 1.03 1.61 1.28 2.43 1.25 4.43 4.12 4.36 3.00
f1 (ppm)
13C NMR (100 MHz, CDCl3)
172.0 170.0 167.4 164.6 161.8 158.2 155.6 141.1 134.7 129.6 127.1 106.2 104.6 92.2 91.6 80.3 77.5 77.2 76.8 51.7 45.4 43.9 43.7 41.8 37.4 36.4 34.2 32.0 29.6 27.9 26.1 24.7 22.1 21.6 20.3 12.2
f1 (ppm)

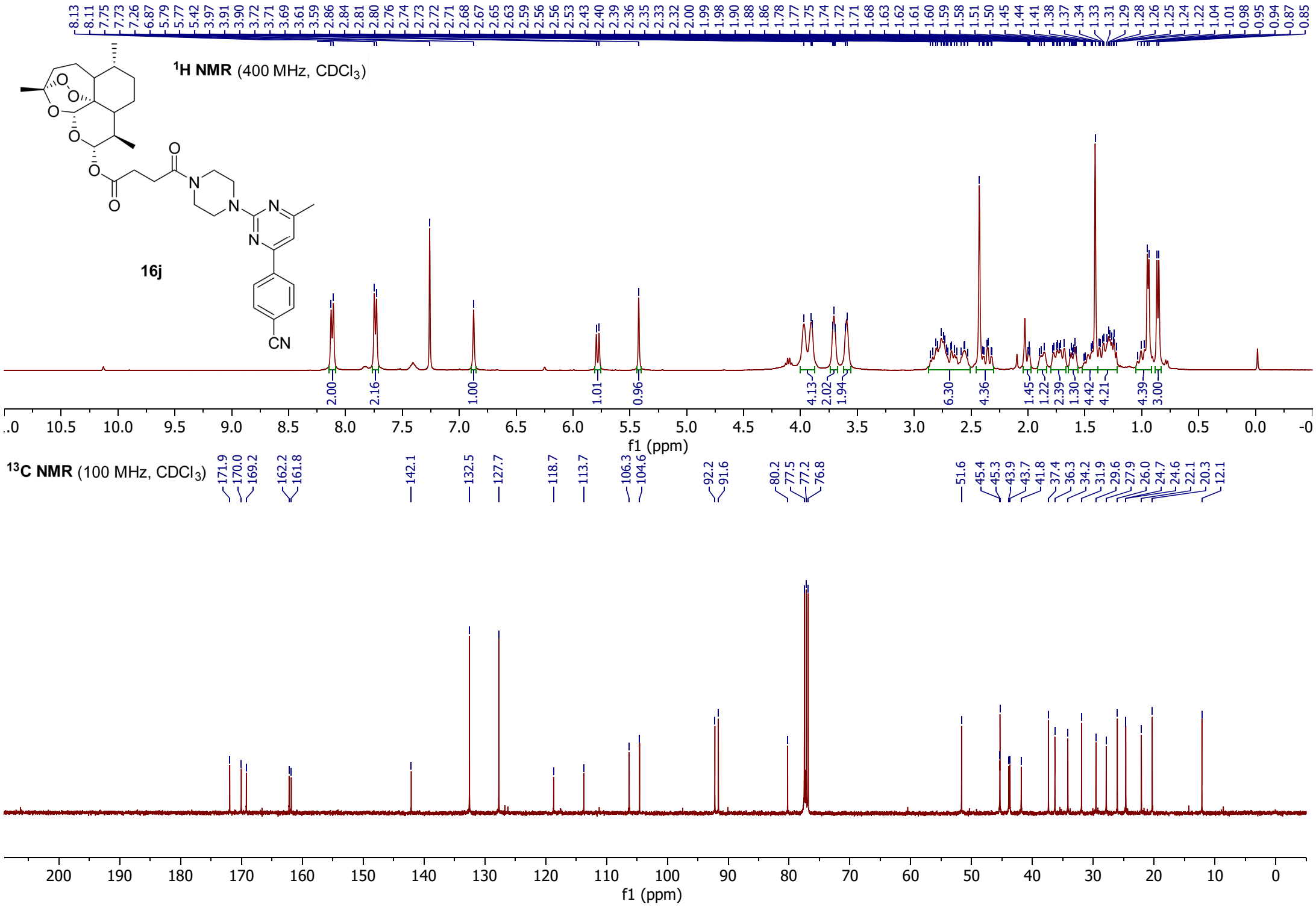

8.45 8.44 8.14 8.12 7.77 7.75 7.26 6.99 6.98 5.80 5.78 5.43 3.99 3.98 3.97 3.96 3.93 3.92 3.91 3.90 3.74 3.73 3.71 3.63 3.61 3.60 2.87 2.85 2.83 2.82 2.81 2.79 2.78 2.77 2.75 2.74 2.73 2.68 2.67 2.67 2.65 2.63 2.57 2.56 2.37 2.36 2.33 2.03 2.00 1.87 1.86 1.85 1.79 1.78 1.76 1.75 1.72 1.71 1.69 1.68 1.63 1.60 1.59 1.45 1.44 1.42 1.38 1.37 1.35 1.34 1.32 1.31 1.30 1.28 1.27 1.26 1.25 1.25 1.23 1.02 1.01 0.98 0.96 0.94 0.87 0.86
1H NMR (400 MHz, CDCl3)
16e
CN
1.00 2.03 2.02 1.00 1.02 0.95 4.12 2.03 2.00 6.25 1.26 2.07 1.27 2.51 1.31 4.41 4.65 4.26 3.01
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)
13C NMR (100 MHz, CDCl3)
171.9 170.0 162.5 161.8 159.2 141.8 132.6 127.7 118.6 114.0 106.6 104.6 92.2 91.6 80.3 77.5 77.2 76.8 51.7 45.4 45.3 43.9 43.7 41.7 37.4 36.3 34.2 32.0 29.6 27.9 26.1 24.7 22.1 20.3 12.2
0 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

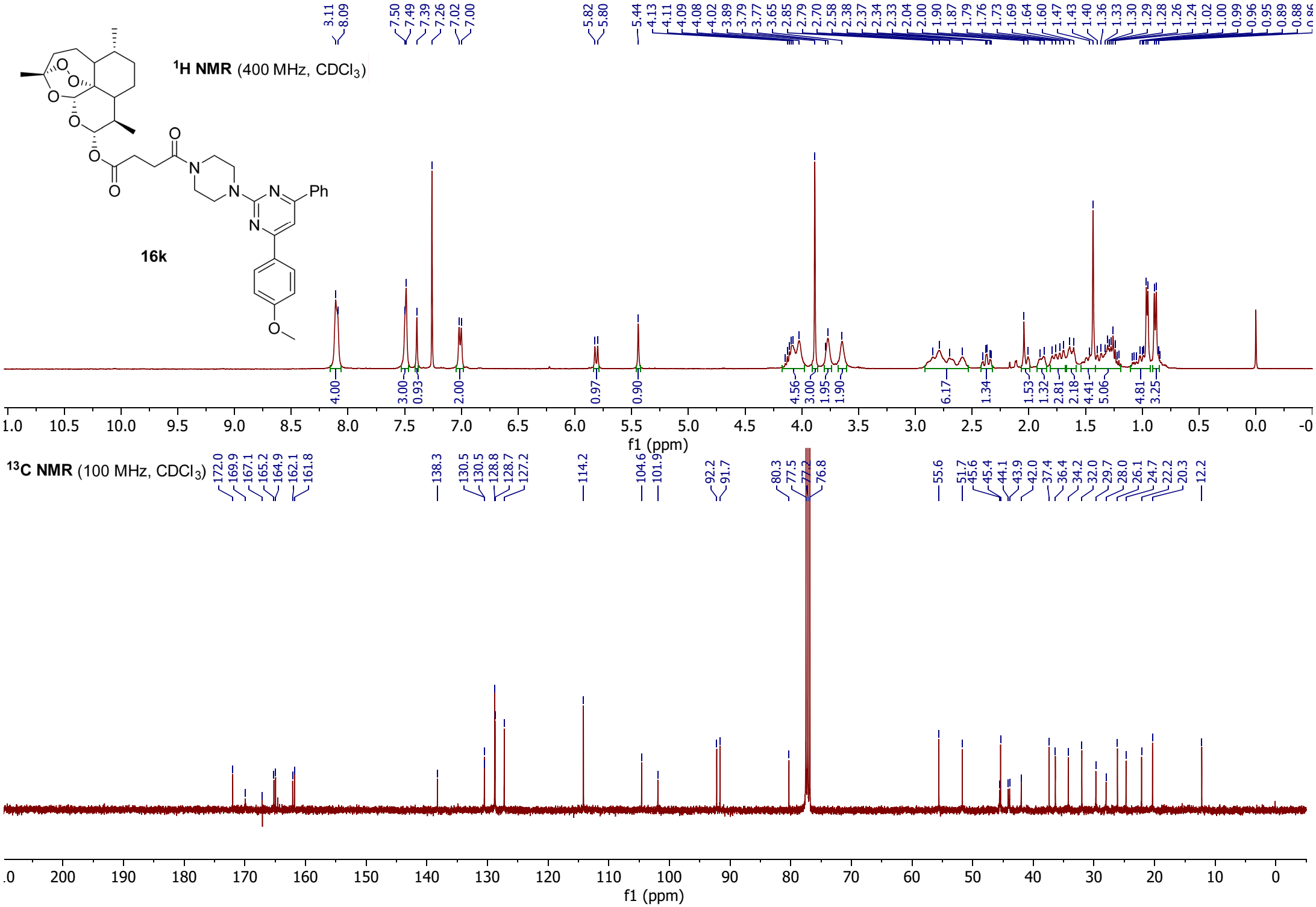

8.04 8.03 8.03 8.02 8.02 8.02 7.47 7.47 7.46 7.45 7.45 7.26 6.88 5.82 5.79 5.44 3.99 3.98 3.97 3.95 3.93 3.92 3.91 3.74 3.72 3.71 3.61 3.60 3.58 2.84 2.83 2.80 2.79 2.78 2.77 2.76 2.75 2.75 2.69 2.68 2.67 2.63 2.58 2.42 2.40 2.38 2.37 2.04 2.01 1.87 1.80 1.79 1.76 1.75 1.73 1.72 1.70 1.69 1.64 1.61 1.60 1.59 1.46 1.43 1.42 1.40 1.39 1.36 1.35 1.33 1.32 1.31 1.29 1.28 1.27 1.26 1.26 1.25 1.25 1.24 1.02 1.01 0.99 0.96 0.95 0.89 0.87
1H NMR (400 MHz, CDCl3)
16f
2.00 3.00 0.89 1.01 0.94 4.06 1.93 1.89 6.30 4.11 2.03 1.34 2.79 1.48 4.59 5.19 4.71 3.01
f1 (ppm)
13C NMR (100 MHz, CDCl3)
172.0 169.9 168.4 164.3 162.0 137.9 130.5 128.8 127.1 106.0 104.6 92.2 91.6 80.3 77.5 77.2 76.8 51.7 45.4 45.4 44.0 43.8 41.9 37.4 36.4 34.2 32.0 29.6 27.9 26.1 24.7 24.6 22.1 20.3 12.2
f1 (ppm)


8.01 7.99 7.26 6.98 6.96 6.82 5.81 5.79 5.43 3.97 3.96 3.93 3.92 3.90 3.89 3.86 3.86 3.73 3.71 3.70 3.60 3.59 3.57 2.88 2.86 2.83 2.82 2.81 2.80 2.78 2.77 2.76 2.75 2.73 2.68 2.67 2.65 2.63 2.57 2.39 2.37 2.36 2.34 2.33 2.05 2.04 2.03 2.00 1.90 1.87 1.86 1.79 1.78 1.76 1.75 1.73 1.72 1.69 1.68 1.64 1.63 1.62 1.61 1.60 1.59 1.49 1.46 1.45 1.43 1.39 1.38 1.36 1.35 1.32 1.32 1.30 1.29 1.27 1.26 1.25 1.02 1.01 0.98 0.96 0.95 0.88 0.87
1H NMR (400 MHz, CDCl3)
16g
2.00 2.00 0.99 1.00 0.89 4.21 3.06 2.02 2.00 6.03 3.98 1.14 1.31 3.33 1.45 4.27 3.99 4.49 2.98
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)
13C NMR (100 MHz, CDCl3)
172.0 169.9 168.1 163.8 161.9 161.7 130.3 128.6 114.1 105.2 104.6 92.2 91.6 80.3 77.5 77.2 76.8 55.5 51.7 45.5 45.4 44.0 43.8 41.9 37.4 36.4 34.2 32.0 29.6 27.9 26.1 24.7 24.6 22.1 20.3 12.2
0 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.03 8.02 8.01 8.00 7.26 7.14 7.11 7.09 6.81 5.79 5.77 5.41 3.97 3.96 3.94 3.93 3.91 3.90 3.89 3.87 3.71 3.70 3.68 3.59 3.57 3.56 2.81 2.79 2.78 2.76 2.75 2.74 2.73 2.71 2.67 2.66 2.65 2.63 2.56 2.55 2.54 2.39 2.35 2.34 2.02 1.98 1.86 1.85 1.84 1.83 1.77 1.76 1.74 1.73 1.70 1.70 1.67 1.66 1.61 1.59 1.58 1.56 1.47 1.46 1.44 1.43 1.41 1.37 1.36 1.34 1.33 1.30 1.29 1.28 1.26 1.25 1.23 1.21 1.00 0.99 0.99 0.97 0.96 0.94 0.93 0.86 0.85
1H NMR (400 MHz, CDCl3)
16h
1.91 2.00 0.91 0.95 0.87 4.02 2.00 1.93 6.60 4.07 2.28 1.31 2.49 1.39 4.45 4.92 4.45 2.78
f1 (ppm)
13C NMR (100 MHz, CDCl3)
171.9 169.8 168.5 165.6 163.1 163.1 161.8 133.9 133.9 129.1 129.0 115.7 115.5 105.5 104.5 92.1 91.6 80.2 77.5 77.2 76.8 51.6 45.3 45.3 43.9 43.7 41.8 37.3 36.3 34.1 31.9 29.5 27.8 26.0 24.6 24.6 22.0 20.3 12.1
f1 (ppm)


7.94 7.92 7.27 7.27 7.26 7.25 6.86 5.82 5.79 5.44 4.00 3.98 3.97 3.96 3.94 3.93 3.91 3.90 3.73 3.72 3.71 3.60 3.59 3.58 2.84 2.83 2.80 2.78 2.77 2.76 2.75 2.73 2.70 2.69 2.68 2.68 2.64 2.58 2.57 2.56 2.41 2.41 2.38 2.37 2.04 2.01 1.88 1.87 1.80 1.79 1.78 1.76 1.76 1.75 1.73 1.72 1.70 1.69 1.64 1.61 1.60 1.59 1.46 1.43 1.40 1.39 1.36 1.35 1.33 1.32 1.31 1.29 1.28 1.28 1.26 1.26 1.25 1.24 1.24 1.02 1.01 0.99 0.99 0.96 0.95 0.89 0.87
1H NMR (400 MHz, CDCl3)
16i
2.00 3.66 0.97 0.96 0.84 4.00 2.00 1.98 6.05 6.94 1.79 1.22 2.82 1.22 4.14 4.43 4.12 2.90
f1 (ppm)
13C NMR (100 MHz, CDCl3)
172.0 169.9 168.2 164.3 164.2 161.9 140.7 135.0 129.5 127.0 105.7 104.6 92.2 91.6 80.3 77.5 77.2 76.8 51.7 45.4 45.4 44.0 43.8 41.9 37.4 36.3 34.2 32.0 29.6 27.9 26.1 24.7 24.6 22.1 21.5 20.3 12.2


8.13 8.11 7.75 7.73 7.26 6.87 5.79 5.77 5.42 3.97 3.91 3.90 3.72 3.71 3.69 3.61 3.59 2.86 2.84 2.81 2.80 2.76 2.74 2.73 2.72 2.71 2.68 2.67 2.65 2.63 2.59 2.56 2.56 2.53 2.43 2.40 2.39 2.36 2.35 2.33 2.32 2.00 1.99 1.98 1.90 1.88 1.86 1.78 1.77 1.75 1.74 1.72 1.71 1.68 1.63 1.62 1.61 1.60 1.59 1.58 1.51 1.50 1.45 1.44 1.41 1.38 1.37 1.34 1.33 1.31 1.29 1.28 1.26 1.25 1.24 1.22 1.04 1.01 0.98 0.95 0.94 0.87 0.85
1H NMR (400 MHz, CDCl3)
16j
CN
2.00 2.16 1.00 1.01 0.96 4.13 2.02 1.94 6.30 4.36 1.45 1.22 2.39 1.30 4.42 4.21 4.39 3.00
f1 (ppm)
13C NMR (100 MHz, CDCl3)
171.9 170.0 169.2 162.2 161.8 142.1 132.5 127.7 118.7 113.7 106.3 104.6 92.2 91.6 80.2 77.5 77.2 76.8 51.6 45.4 45.3 43.9 43.7 41.8 37.4 36.3 34.2 31.9 29.6 27.9 26.0 24.7 24.6 22.1 20.3 12.1
f1 (ppm)


16k
^{1}H NMR (400 MHz, CDCl$_3$)
^{13}C NMR (100 MHz, CDCl$_3$)
f1 (ppm)
f1 (ppm)

High resolution mass spectrometry data

HRESIMS and MS/MS spectra were acquired in positive mode on Q Exactive Plus (ThermoFisher Scientific, Inc., Bremen, Germany) mass spectrometer, equipped with a heated HESI-II source. Operating conditions for the HESI source used in a positive ionization mode were: +3.5 kV spray voltage, 320 °C capillary and probe heater temperature, sheath gas flow rate 36 a.u., auxiliary gas flow 11 a.u. (a.u. refer to arbitrary values set by the Exactive Tune software) and S-Lens RF level 50.00. Nitrogen was used for sample nebulization and collision gas in the HCD cell. The aliquots of 2 μL of the solutions of the samples (30 μg mL^{-1}) were introduced into mass spectrometer through LC system Thermo Scientific Dionex Ultimate 3000 RSLC (Germering, Germany) consisting of 6-channel degasser SRD-3600, high-pressure gradient pump HPG-3400RS, autosampler WPS-3000TRS, and column compartment TCC-3000RS equipped with narrow bore Hypersil GOLD™ C18 (2.1 × 50 mm, 1.9 μm) column. Each chromatographic run was carried out with a binary mobile phase consisting of water containing 0.1% (v/v) formic acid (A) and acetonitrile also with 0.1% (v/v) formic acid (B). A gradient program was used as follows: 0–1 min, 5% B; 1–12.5 min, 5–95% B; 12.5–14.5 min, 95% B. The system was equilibrated with initial conditions for 3.5 min. The solvent flow rate was 300 μL min^{-1}. Top5 was used for MS experiments, where in full MS mode the resolution, automatic gain control (AGC) target, maximum injection time (IT), and mass range were 70,000 (at *m/z* 200), 3e6, 80 ms, and *m/z* 100–1500, respectively, while $ddMS^2$ conditions were set to resolution 17,500 (at *m/z* 200), AGC target 1e5, max. IT 50 ms, isolation window 2.0 *m/z*, and stepped normalized collision energy (NCE) of 10, 20, and 40. Xcalibur (Thermo Fisher Scientific) ver. 4.0 and FreeStyle (Thermo Fisher Scientific) ver. 1.8 SP1 were used for data acquisition and processing, respectively.

The synthesized compounds were also analyzed by high resolution tandem mass spectrometry using LTQ Orbitrap XL (Thermo Fisher Scientific Inc., USA) mass spectrometer. The sample was dissolved in MeCN and it was injected directly. Ionization was done in positive mode on heated electrospray ionization (HESI) probe. HESI parameters were: spray voltage 4.7 kV, vaporizer temperature 60 °C, sheath and auxiliary gas flow 24 and 10 (arbitrary units), respectively, capillary voltage 49 V, capillary temperature 275 °C, tube lens voltage 80 V, resolution (at m/z 400): 30000.

HPLC analyses for purity

Compounds were analyzed for purity using a Agilent 1200 HPLC system equipped with Quat Pump (G1311B), Injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and Detector 1260 DAD VL+ (G1315C). The analysis was performed at 254 nm to maximize selectivity. Compounds were dissolved in methanol, final concentrations were ~1mg/mL. Following methods were used:

METHOD A

InfinityLab Poroshell 120 CS-C18, 4.6 × 100 nm, 2.7 µm, S.N. USKBM01053 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and acetonitrile (B). Flow rate was 0.6 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A → 5% A, 6 – 12 min 5% A, 12 – 14 min 5% A → 95% A, 14 – 15 min 95% A.

METHOD B

InfinityLab Poroshell 120 CS-C18, 4.6 × 100 nm, 2.7 µm, S.N. USKBM01053 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and methanol (B). Flow rate was 0.6 mL/min**.** Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A → 5% A, 6 – 12 min 5% A, 12 – 14 min 5% A → 95% A, 14 – 15 min 95% A.

METHOD C

ZORBAX Eclipse Plus C18, 4.6 × 150 nm, 1.8 µm, S.N. USWKY01594 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and methanol (B). Flow rate was 0.5 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A → 5% A, 6 – 12 min 5% A, 12 – 14 min 5% A → 95% A, 14 – 15 min 95% A.

METHOD D

ZORBAX SB-C18, 4.6 × 150 nm, 5 µm, S.N. USCM074615 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and methanol (B). Flow rate was 0.5 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A → 5% A, 6 – 12 min 5% A, 12 – 14 min 5% A → 95% A, 14 – 15 min 95% A.

METHOD E

ZORBAX SB-C18, 4.6 × 150 nm, 5 µm, S.N. USCM074615 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and acetonitrile (B). Flow rate was 0.6 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A → 5% A, 6 – 11 min 5% A, 11 – 14 min 5% A → 95% A, 14 – 17 min 95% A.

METHOD F

ZORBAX SB-C18, 4.6 × 150 nm, 5 µm, S.N. USCM074615 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and methanol (B). Flow rate was 0.6 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 5 min 95% A → 5% A, 5 – 12 min 5% A, 12 – 15 min 5% A → 95% A, 15 – 17 min 95% A.

METHOD G

InfinityLab Poroshell 120, CS-C18 4.6 × 100 nm, 2.7 µm, S.N. USKBM01053 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and acetonitrile (B). Flow rate was 0.5 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A → 5% A, 6 – 12 min 5% A, 12 – 14 min 5% A → 95% A, 14 – 15 min 95% A.

METHOD H

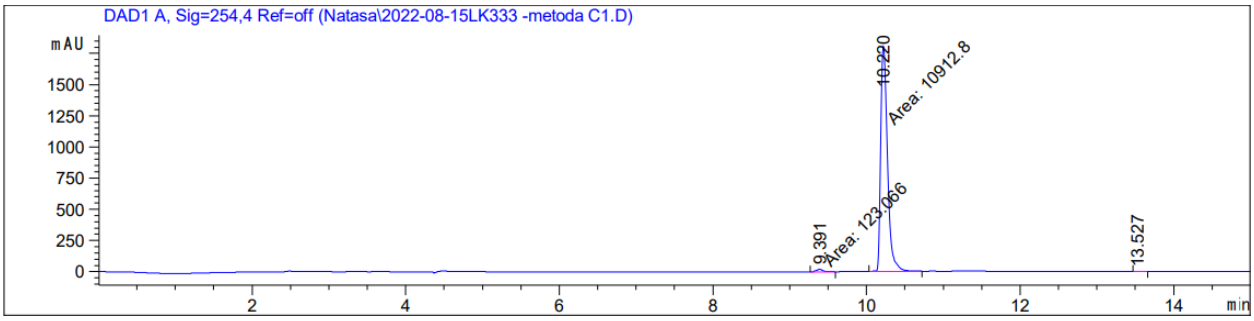
ZORBAX SB-C18, 4.6 × 150 nm, 5 µm, S.N. USCM074615 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and methanol (B). Flow rate was 0.5 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 8 min 95% A → 5% A, 8 – 12 min 5% A, 12 – 14 min 5% A → 95% A, 14 – 17 min 95% A.

METHOD I

ZORBAX SB-C18, 4.6 × 150 nm, 5 µm, S.N. USCM074615 column was used. Eluent was made from the following solvents: 0.1% formic acid in water (A) and acetonitrile (B). Flow rate was 0.6 mL/min. Compounds were eluted using gradient protocol: 0 – 1 min 95% A, 1 – 6 min 95% A → 5% A, 6 – 12 min 5% A, 12 – 14 min 5% A → 95% A, 14 – 15 min 95% A.

Compound **13a**

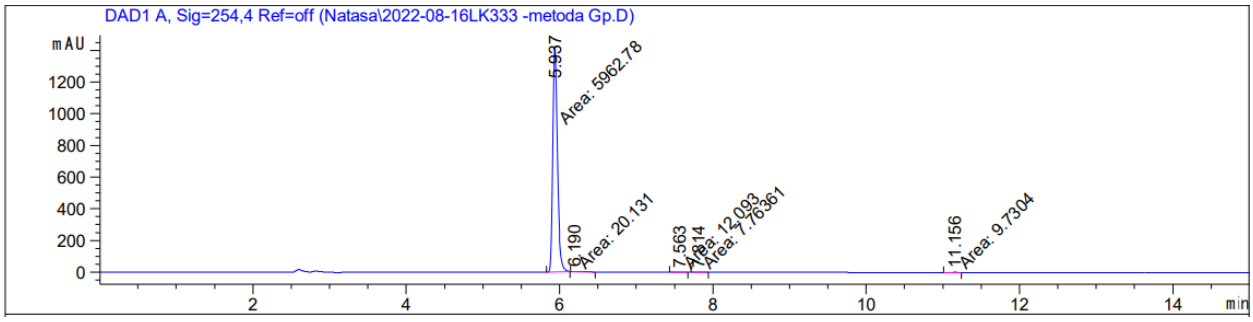
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.391	MM	0.1053	123.06567	19.47984	1.1145
2	10.220	MM	0.1003	1.09128e4	1814.05835	98.8302
3	13.527	VV	0.0809	6.10635	1.13323	0.0553

Method **G**

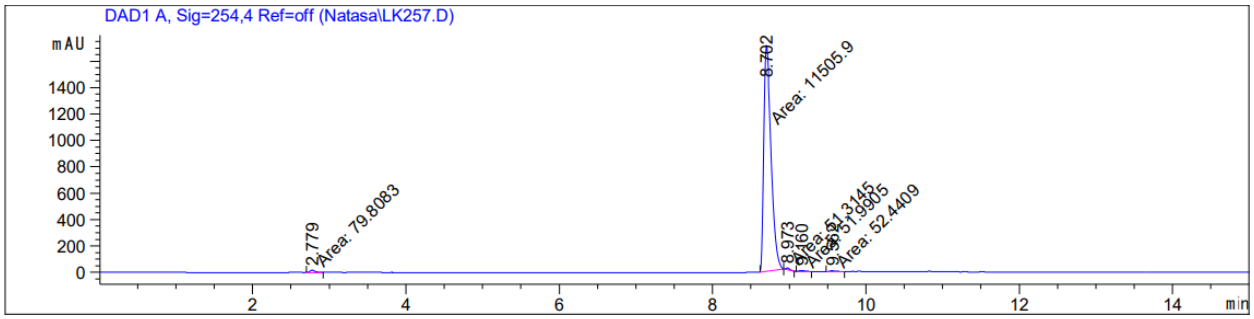


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.937	MM	0.0696	5962.78174	1427.91650	99.1731
2	6.190	MM	0.1922	20.13104	1.74564	0.3348
3	7.563	MM	0.1665	12.09300	1.21049	0.2011
4	7.814	MM	0.1301	7.76361	9.94790e-1	0.1291
5	11.156	MM	0.0995	9.73040	1.63054	0.1618

Compound **13b**

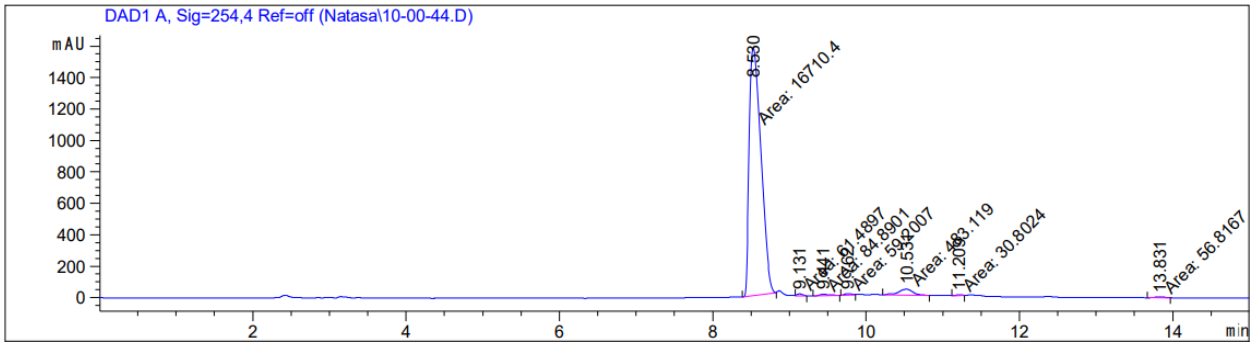
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.779	MM	0.0765	79.80828	17.38011	0.6797
2	8.702	MM	0.1122	1.15059e4	1709.76050	97.9938
3	8.973	MM	0.0647	51.31450	13.21901	0.4370
4	9.160	MM	0.1033	51.99053	8.38733	0.4428
5	9.562	MM	0.1273	52.44090	6.86799	0.4466

Method **D**

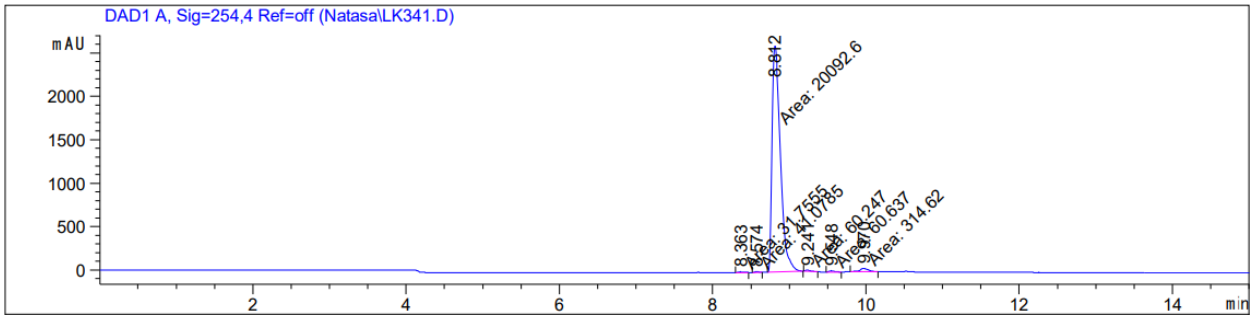


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.530	MM	0.1764	1.67104e4	1579.06055	95.5605
2	9.131	MM	0.0872	61.48974	11.74831	0.3516
3	9.441	MM	0.1432	84.89014	9.87881	0.4855
4	9.762	MM	0.1055	59.20075	9.34941	0.3385
5	10.531	MM	0.2179	483.11890	36.95458	2.7628
6	11.209	MM	0.1166	30.80239	4.40372	0.1761
7	13.831	MM	0.1440	56.81673	6.57682	0.3249

Compound **13c**

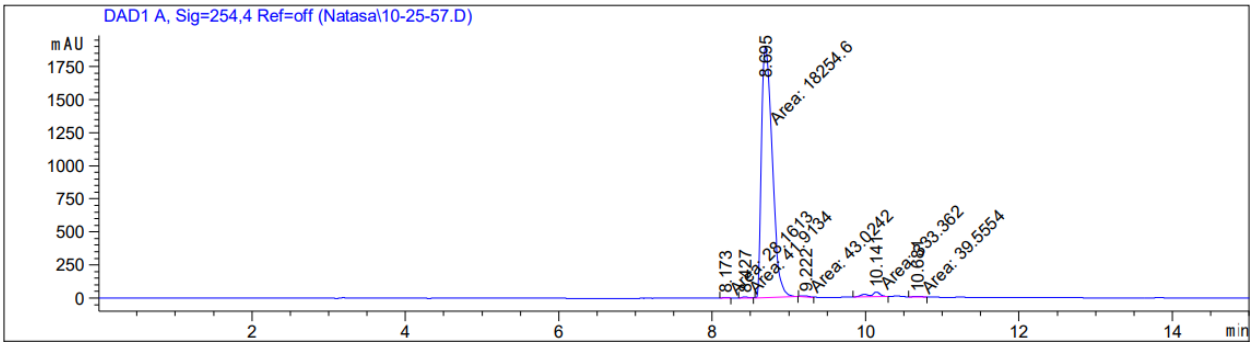
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.363	MM	0.0749	31.75554	7.06880	0.1541
2	8.574	MM	0.0641	41.07849	10.67639	0.1994
3	8.812	MM	0.1285	2.00926e4	2605.85522	97.5325
4	9.241	MM	0.0799	60.24701	12.56148	0.2924
5	9.548	MM	0.0777	60.63699	13.00276	0.2943
6	9.970	MM	0.1371	314.61972	38.24098	1.5272

Method **D**

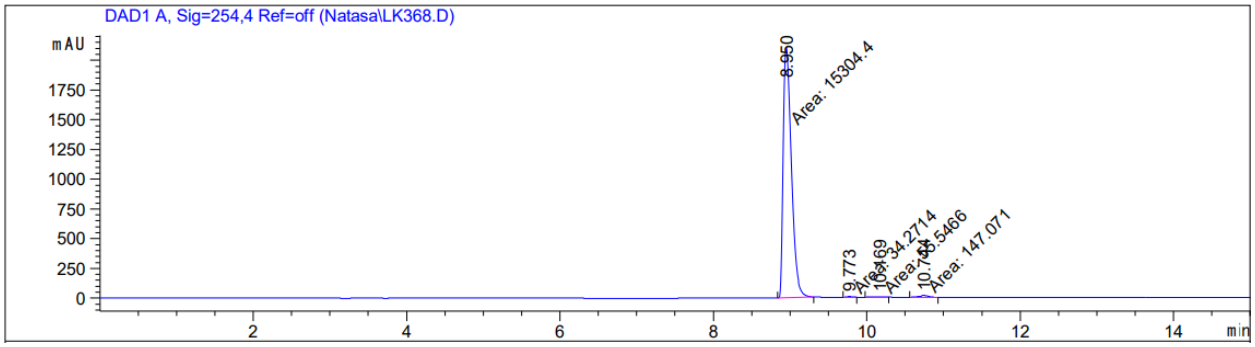


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.173	MM	0.0856	28.16128	5.48078	0.1503
2	8.427	MM	0.0909	41.91338	7.68725	0.2236
3	8.695	MM	0.1610	1.82546e4	1889.60059	97.4066
4	9.222	MM	0.1156	43.02417	6.20234	0.2296
5	10.141	MM	0.1612	333.36160	34.47386	1.7788
6	10.681	MM	0.1178	39.55540	5.59541	0.2111

Compound **13d**

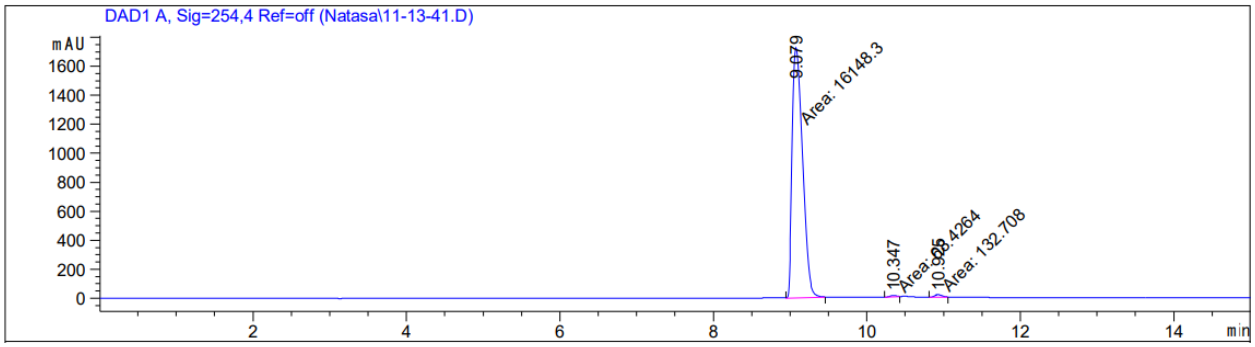
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.950	MM	0.1210	1.53044e4	2108.38208	98.4757
2	9.773	MM	0.0871	34.27142	6.55477	0.2205
3	10.169	MM	0.1923	55.54659	4.81365	0.3574
4	10.744	MM	0.1432	147.07149	17.12169	0.9463

Method **D**

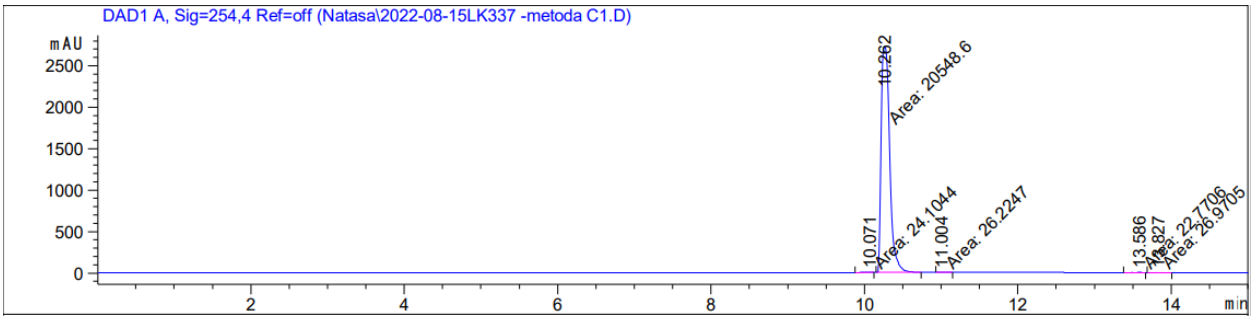


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.079	MM	0.1561	1.61483e4	1724.68188	98.7698
2	10.347	MM	0.1072	68.42635	10.63860	0.4185
3	10.925	MM	0.1182	132.70847	18.70688	0.8117

Compound **13e**

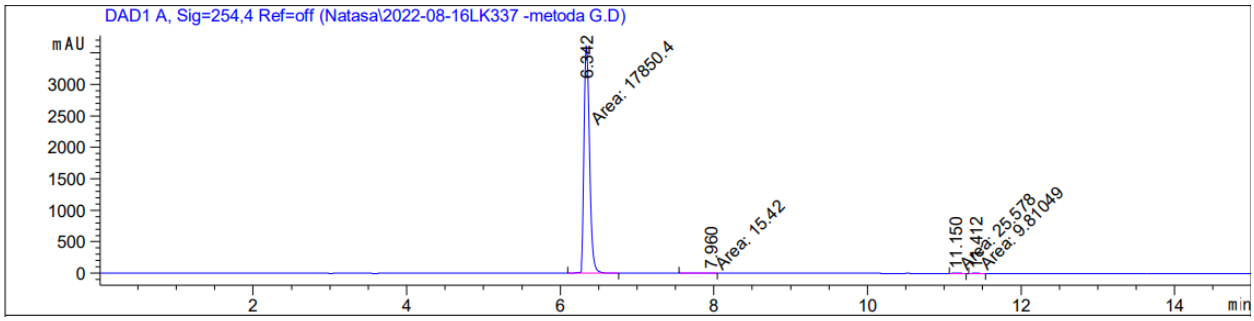
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.071	MM	0.1353	24.10436	2.97019	0.1167
2	10.262	MM	0.1256	2.05486e4	2727.51929	99.5154
3	11.004	MM	0.1198	26.22468	3.64713	0.1270
4	13.586	MM	0.2092	22.77062	1.81440	0.1103
5	13.827	MM	0.1785	26.97053	2.51771	0.1306

Method **G**

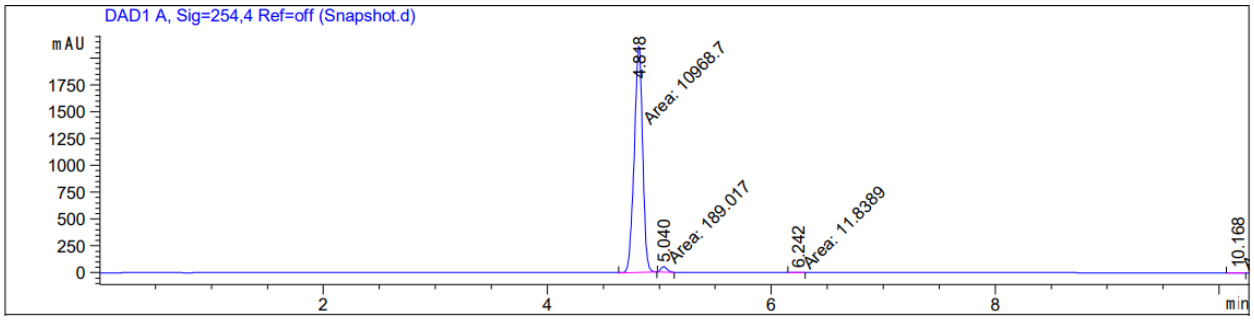


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.342	MM	0.0822	1.78504e4	3619.06982	99.7162
2	7.960	MM	0.2863	15.41996	8.97785e-1	0.0861
3	11.150	MM	0.0828	25.57802	5.14753	0.1429
4	11.412	MM	0.1189	9.81049	1.37555	0.0548

Compound **13f**

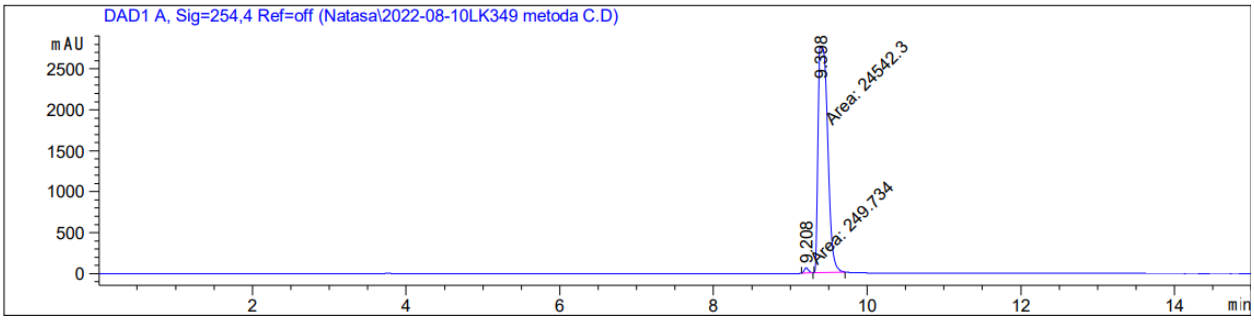
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.818	MM	0.0864	1.09687e4	2114.72314	98.1219
2	5.040	MM	0.0600	189.01691	52.46375	1.6909
3	6.242	MM	0.0739	11.83894	2.66862	0.1059
4	10.168	MM	0.0818	9.08700	1.85177	0.0813

Method **C**

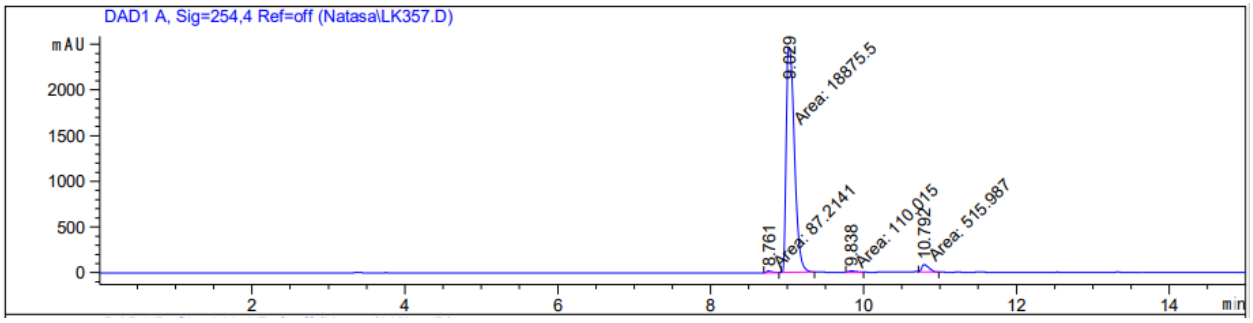


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.208	MM	0.0634	249.73416	65.61532	1.0073
2	9.398	MM	0.1481	2.45423e4	2762.42822	98.9927

Compound **14a**

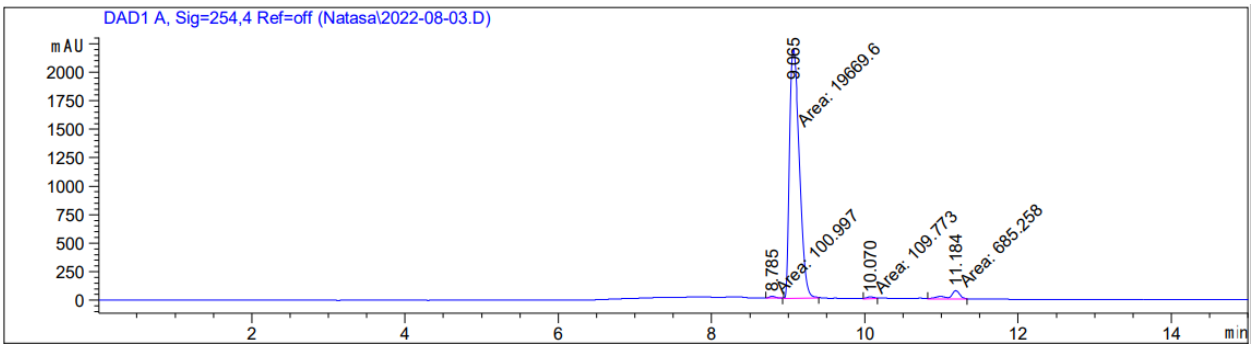
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.761	MM	0.0800	87.21409	18.17994	0.4452
2	9.029	MM	0.1276	1.88755e4	2465.06396	96.3590
3	9.838	MM	0.1186	110.01527	15.46392	0.5616
4	10.792	MM	0.1067	515.98669	80.61823	2.6341

Method **D**

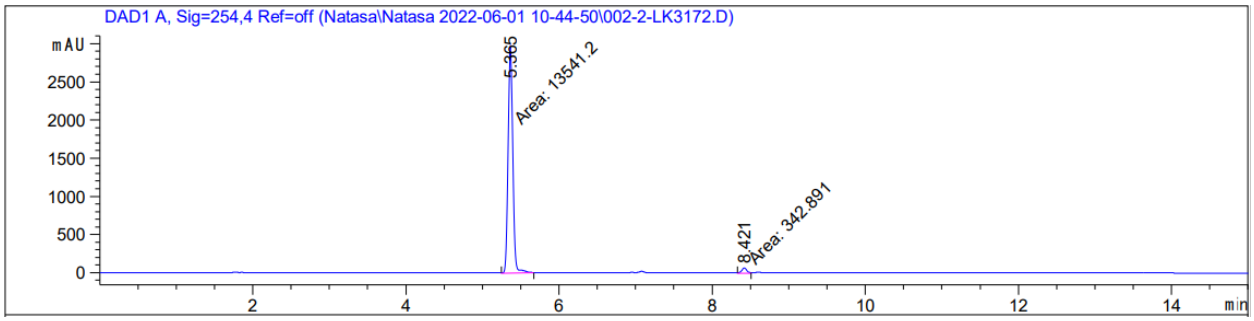


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.785	MM	0.1011	100.99702	16.65637	0.4911
2	9.065	MM	0.1501	1.96696e4	2184.38721	95.6431
3	10.070	MM	0.1126	109.77345	16.24261	0.5338
4	11.184	MM	0.1607	685.25824	71.08672	3.3320

Compound **14b**

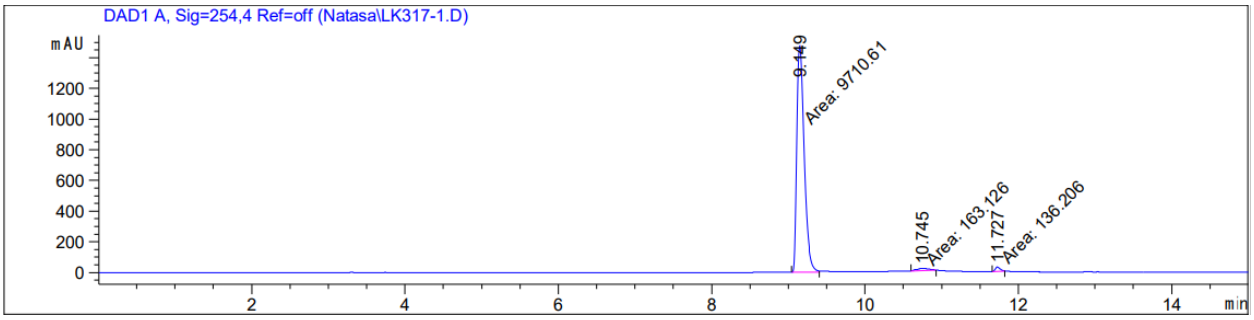
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.365	MM	0.0759	1.35412e4	2974.21875	97.5303
2	8.421	MM	0.0799	342.89090	71.50201	2.4697

Method **C**

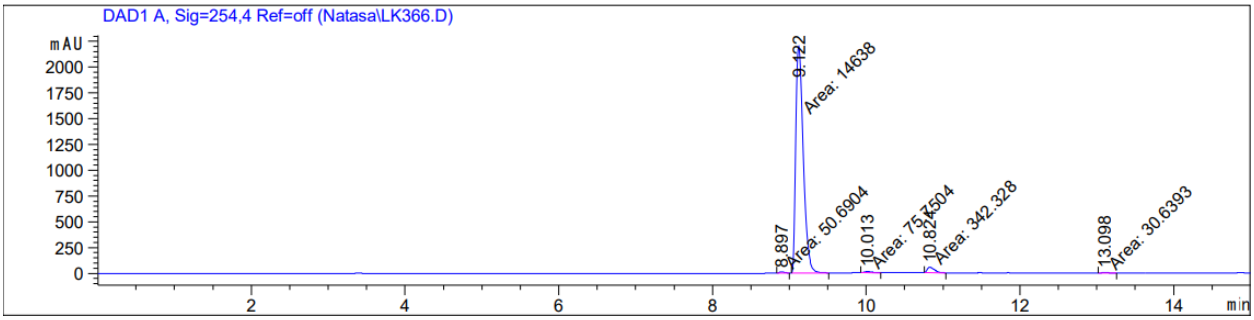


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.149	MM	0.1099	9710.61230	1473.24084	97.0097
2	10.745	MM	0.1743	163.12605	15.60141	1.6296
3	11.727	MM	0.0765	136.20561	29.68567	1.3607

Compound **14c**

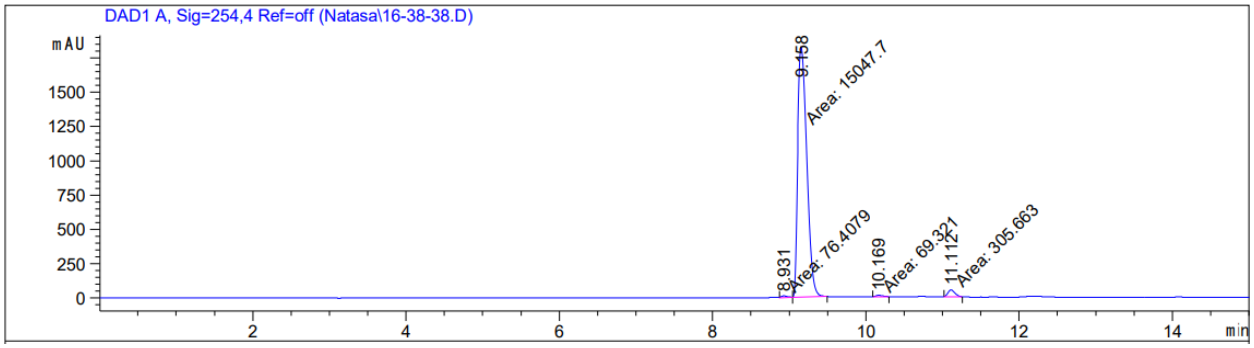
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.897	MM	0.0719	50.69042	11.75121	0.3349
2	9.122	MM	0.1109	1.46380e4	2199.07788	96.7008
3	10.013	MM	0.1109	75.75038	11.38018	0.5004
4	10.824	MM	0.1064	342.32767	53.62927	2.2615
5	13.098	MM	0.1004	30.63935	5.08369	0.2024

Method **D**

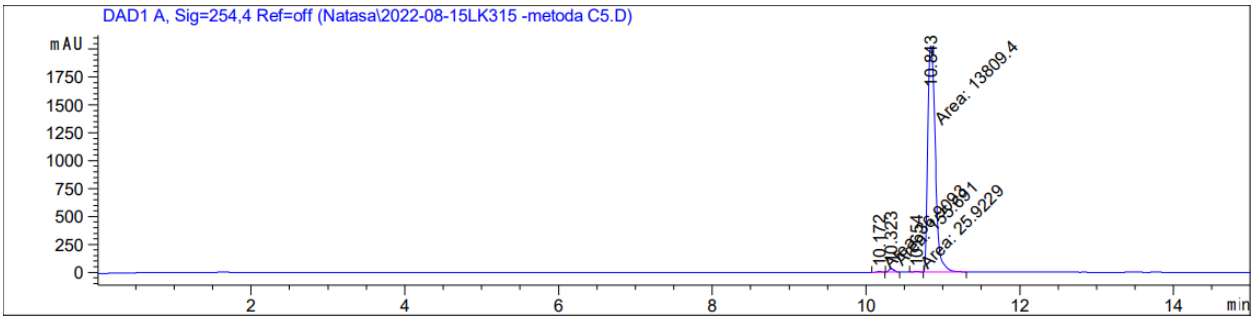


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.931	MM	0.0962	76.40792	13.23646	0.4930
2	9.158	MM	0.1376	1.50477e4	1822.89270	97.0876
3	10.169	MM	0.1120	69.32098	10.31111	0.4473
4	11.112	MM	0.1029	305.66327	49.49546	1.9721

Compound **14d**

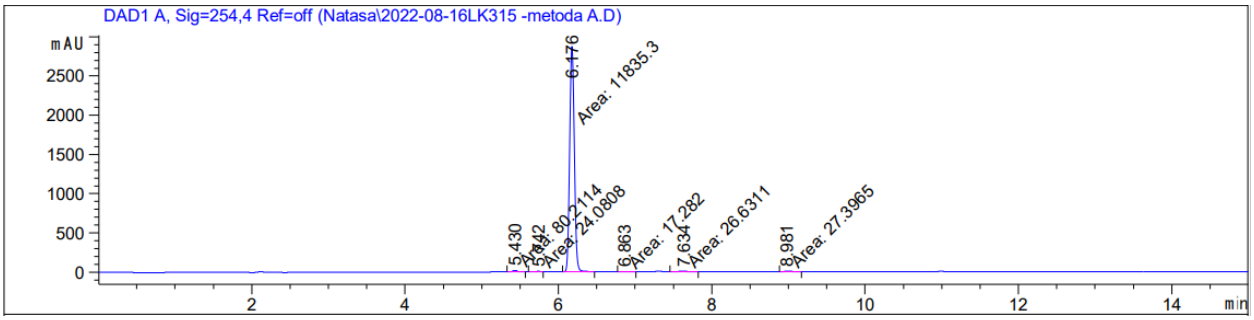
Method **C**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.172	MM	0.0819	36.90928	7.50681	0.2631
2	10.323	MM	0.0778	155.69051	33.36429	1.1099
3	10.654	MM	0.0914	25.92290	4.72847	0.1848
4	10.843	MM	0.1137	1.38094e4	2025.09644	98.4422

Method **G**

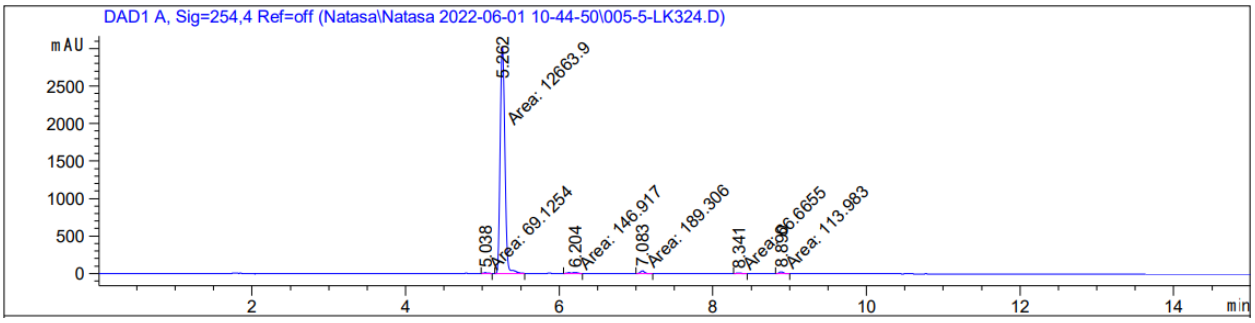


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.430	MM	0.0712	80.21138	18.77726	0.6678
2	5.742	MM	0.0908	24.08082	4.41996	0.2005
3	6.176	MM	0.0685	1.18353e4	2878.85083	98.5380
4	6.863	MM	0.1429	17.28198	2.01539	0.1439
5	7.634	MM	0.1431	26.63113	3.10202	0.2217
6	8.981	MM	0.1476	27.39648	3.09295	0.2281

Compound **14e**

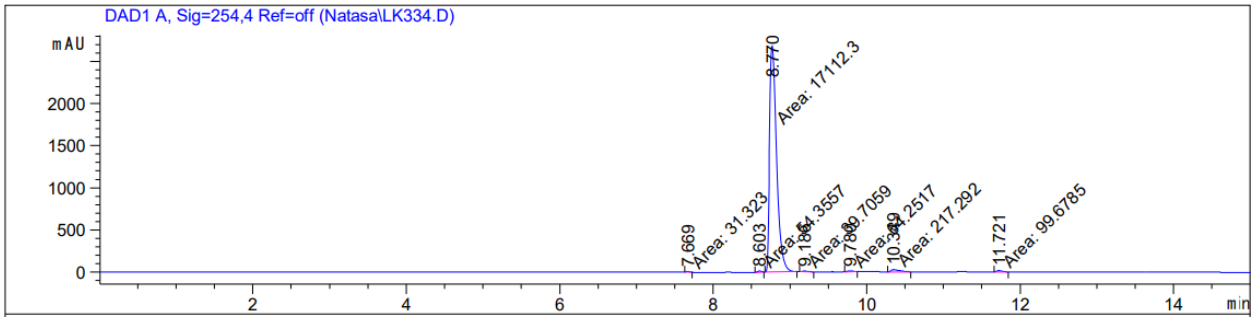
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.038	MM	0.0834	69.12542	13.80974	0.5217
2	5.262	MM	0.0693	1.26639e4	3047.84351	95.5773
3	6.204	MM	0.1314	146.91727	18.64195	1.1088
4	7.083	MM	0.0804	189.30585	39.24721	1.4287
5	8.341	MM	0.0859	66.66551	12.93463	0.5031
6	8.890	MM	0.0696	113.98289	27.30070	0.8603

Method **C**

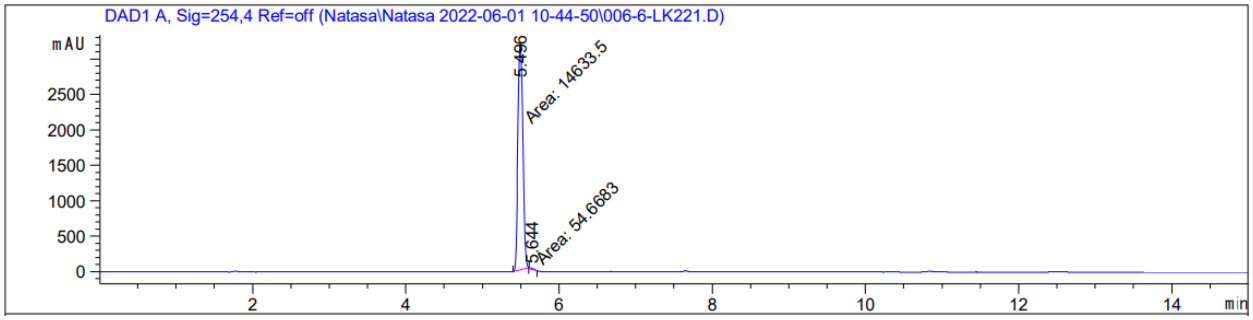


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.669	MM	0.0549	31.32297	9.51665	0.1778
2	8.603	MM	0.0635	54.35567	14.25598	0.3085
3	8.770	MM	0.1062	1.71123e4	2686.05566	97.1246
4	9.186	MM	0.1022	39.70594	6.47439	0.2254
5	9.780	MM	0.0875	64.25175	12.23954	0.3647
6	10.349	MM	0.1353	217.29234	26.77524	1.2333
7	11.721	MM	0.0903	99.67846	18.39374	0.5657

Compound **14f**

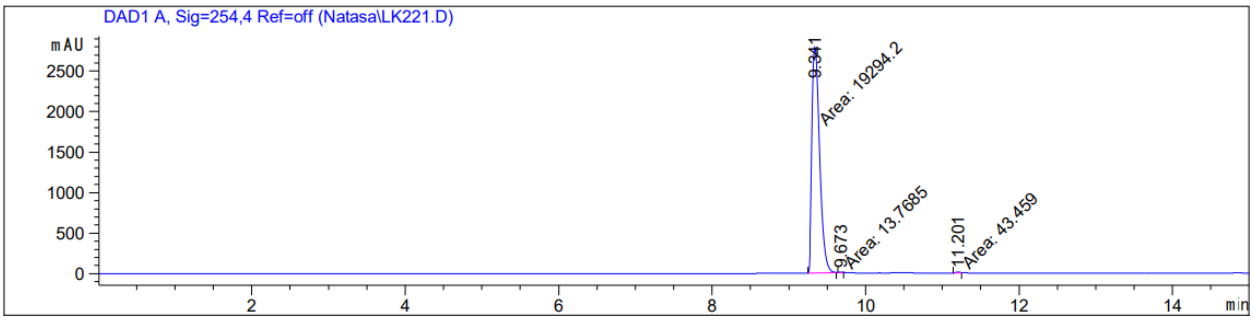
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.496	MM	0.0770	1.46335e4	3165.42236	99.6278
2	5.644	MM	0.0573	54.66831	15.91438	0.3722

Method **C**

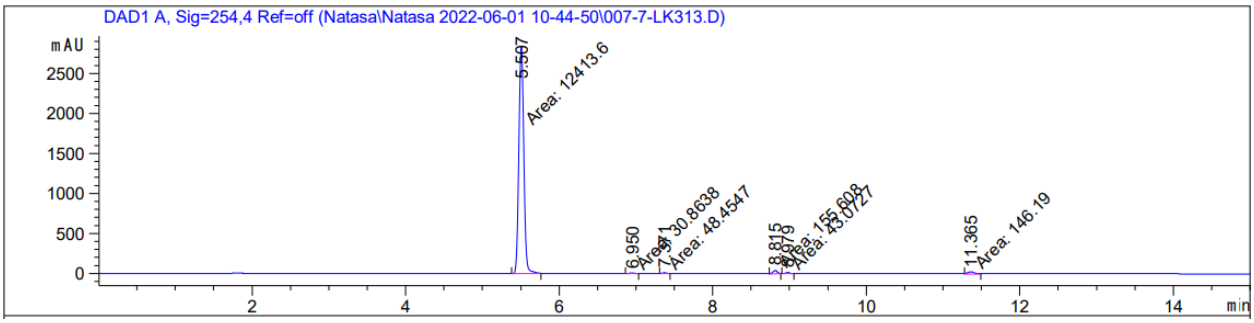


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.341	MM	0.1154	1.92942e4	2787.49487	99.7043
2	9.673	MM	0.0493	13.76849	4.65140	0.0711
3	11.201	MM	0.0726	43.45898	9.98199	0.2246

Compound **14g**

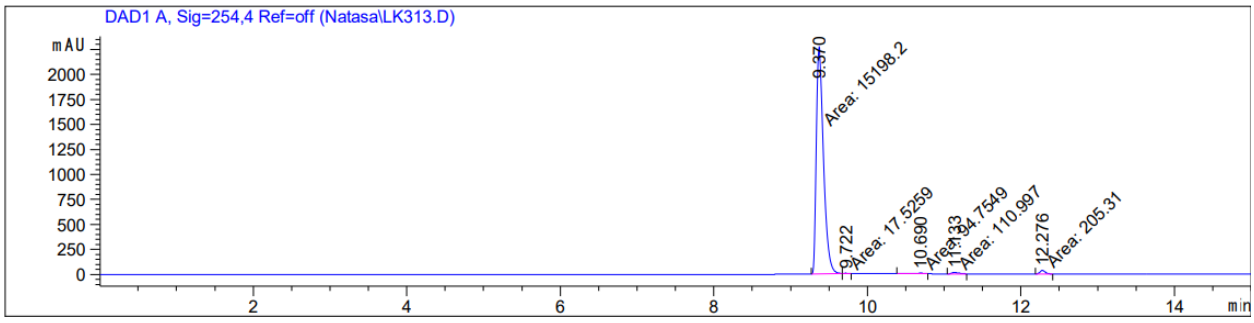
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.507	MM	0.0726	1.24136e4	2849.21777	96.6958
2	6.950	MM	0.0728	30.86380	7.06163	0.2404
3	7.371	MM	0.0701	48.45473	11.51545	0.3774
4	8.815	MM	0.0664	155.60794	39.05905	1.2121
5	8.979	MM	0.0553	43.07273	12.97477	0.3355
6	11.365	MM	0.0956	146.18964	25.48085	1.1387

Method **C**

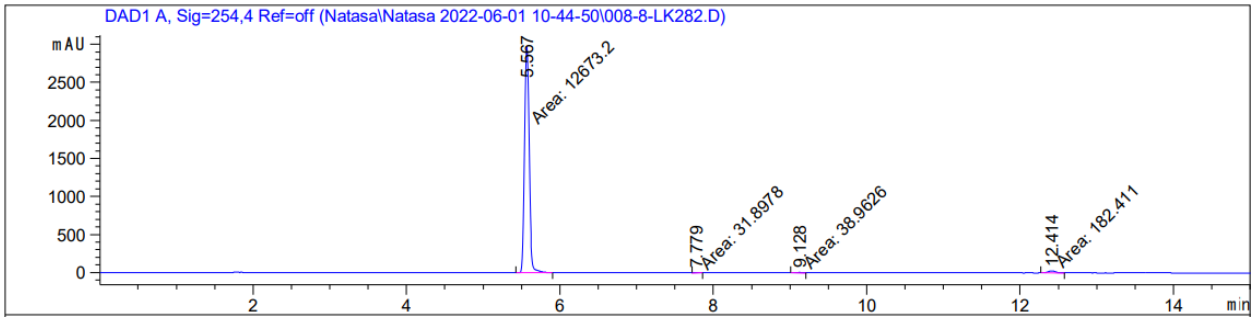


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.370	MM	0.1117	1.51982e4	2267.10547	97.2573
2	9.722	MM	0.0740	17.52592	3.94801	0.1122
3	10.690	MM	0.2839	94.75485	5.56184	0.6064
4	11.133	MM	0.1259	110.99697	14.69890	0.7103
5	12.276	MM	0.0883	205.30988	38.77125	1.3138

Compound **14h**

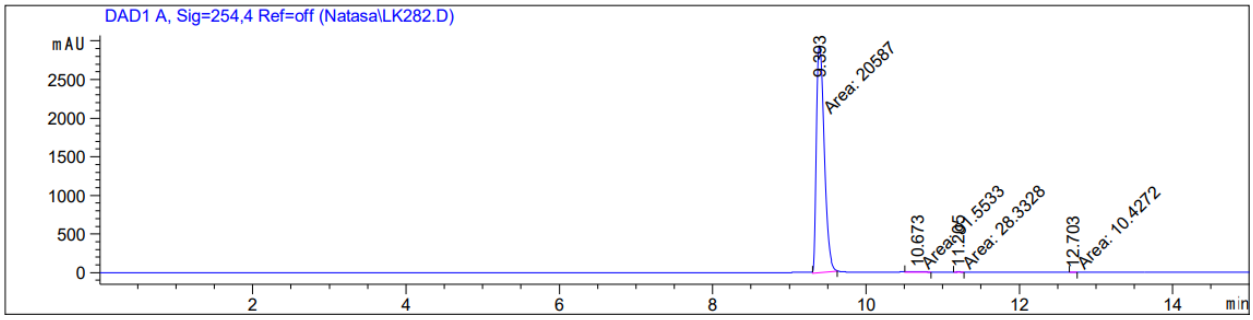
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.567	MM	0.0708	1.26732e4	2985.13135	98.0407
2	7.779	MM	0.0865	31.89779	6.14630	0.2468
3	9.128	MM	0.0855	38.96255	7.59754	0.3014
4	12.414	MM	0.1110	182.41150	27.39791	1.4111

Method **C**

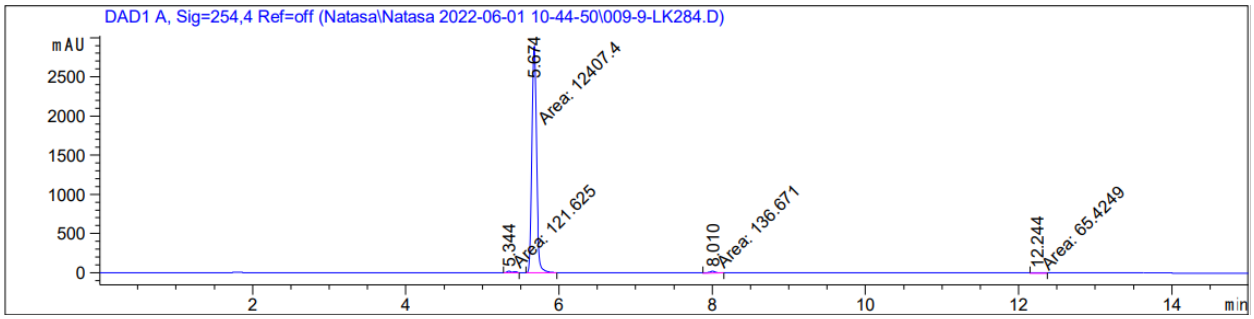


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.393	MM	0.1172	2.05870e4	2928.81470	99.3710
2	10.673	MM	0.2581	91.55329	5.91087	0.4419
3	11.205	MM	0.0897	28.33283	5.26480	0.1368
4	12.703	MM	0.0653	10.42719	2.66018	0.0503

Compound **14i**

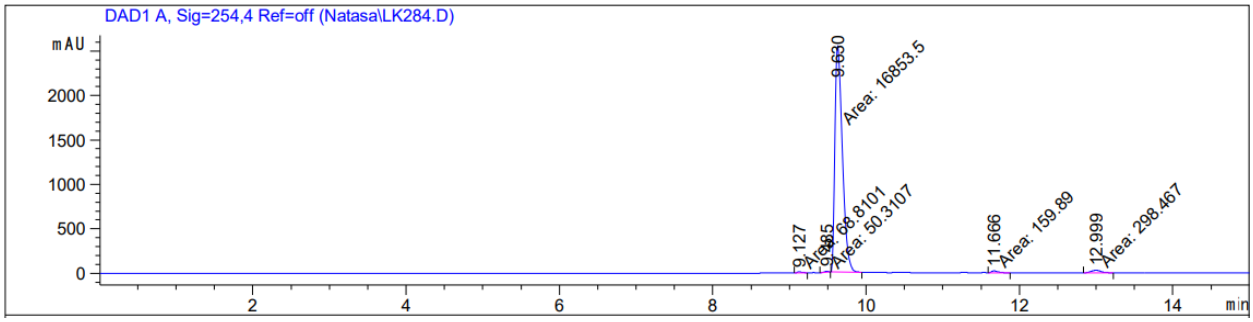
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.344	MM	0.0981	121.62514	20.65821	0.9553
2	5.674	MM	0.0713	1.24074e4	2902.04224	97.4573
3	8.010	MM	0.1005	136.67096	22.65976	1.0735
4	12.244	MM	0.1434	65.42495	7.60492	0.5139

Method **C**

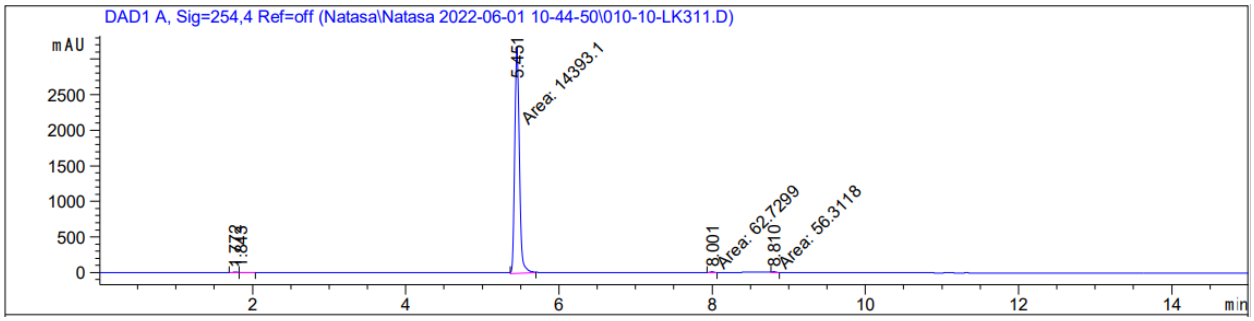


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.127	MM	0.0870	68.81007	13.18810	0.3948
2	9.485	MM	0.0677	50.31073	12.38600	0.2886
3	9.630	MM	0.1105	1.68535e4	2542.79614	96.6871
4	11.666	MM	0.1157	159.88983	23.03969	0.9173
5	12.999	MM	0.1593	298.46671	31.22750	1.7123

Compound **14j**

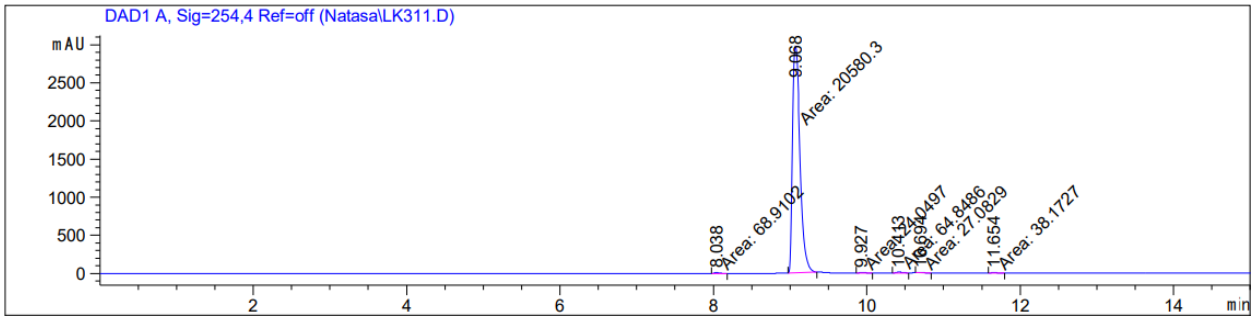
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.772	BV	0.0842	42.40785	7.95890	0.2903
2	1.843	VB	0.1088	54.29598	6.41205	0.3717
3	5.451	MM	0.0752	1.43931e4	3190.22656	98.5232
4	8.001	MM	0.0692	62.72993	15.11348	0.4294
5	8.810	MM	0.0686	56.31180	13.69048	0.3855

Method C

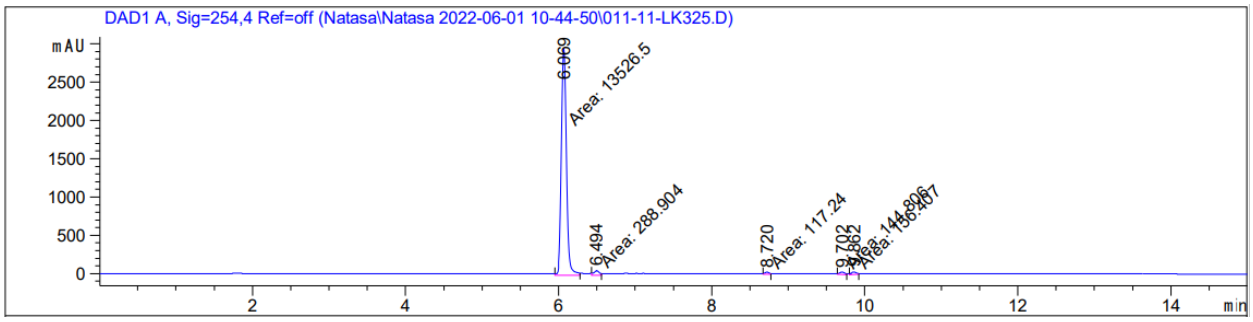


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.038	MM	0.0708	68.91022	16.22084	0.3312
2	9.068	MM	0.1154	2.05803e4	2971.59546	98.9278
3	9.927	MM	0.1039	24.04970	3.85677	0.1156
4	10.413	MM	0.1021	64.84860	10.58871	0.3117
5	10.694	MM	0.1020	27.08290	4.42385	0.1302
6	11.654	MM	0.0849	38.17265	7.49285	0.1835

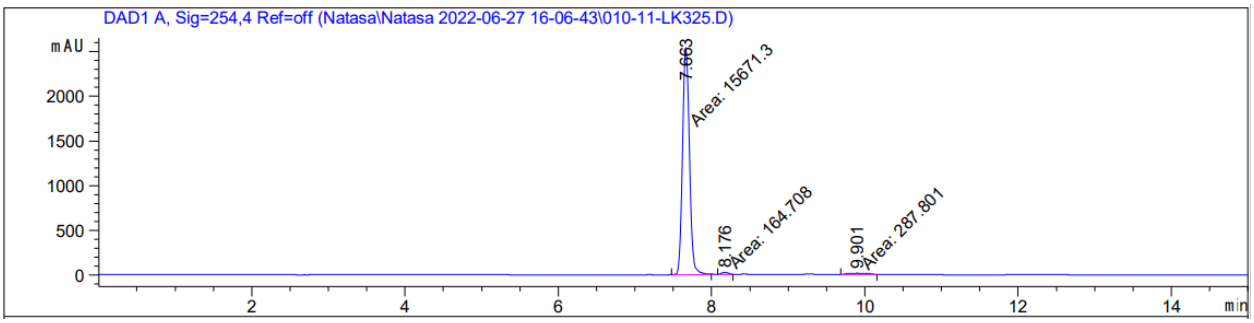
Compound **14k**

Method **A**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.069	MM	0.0758	1.35265e4	2972.80859	95.0305
2	6.494	MM	0.0854	288.90390	56.40264	2.0297
3	8.720	MM	0.0686	117.23960	28.46454	0.8237
4	9.702	MM	0.0770	144.80577	31.33510	1.0173
5	9.862	MM	0.0767	156.40691	33.99267	1.0988

Method **B**

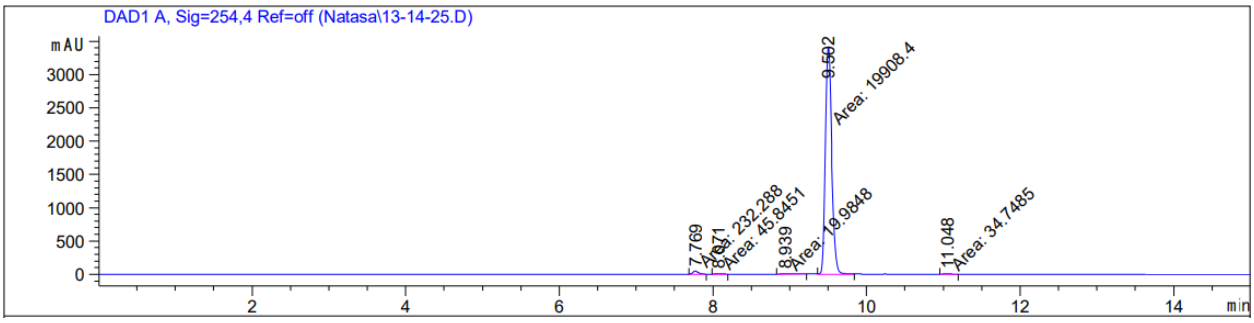


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.663	MM	0.1032	1.56713e4	2530.73242	97.1935
2	8.176	MM	0.1107	164.70808	24.80031	1.0215
3	9.901	MM	0.3042	287.80090	15.76761	1.7849

Compound **15a**

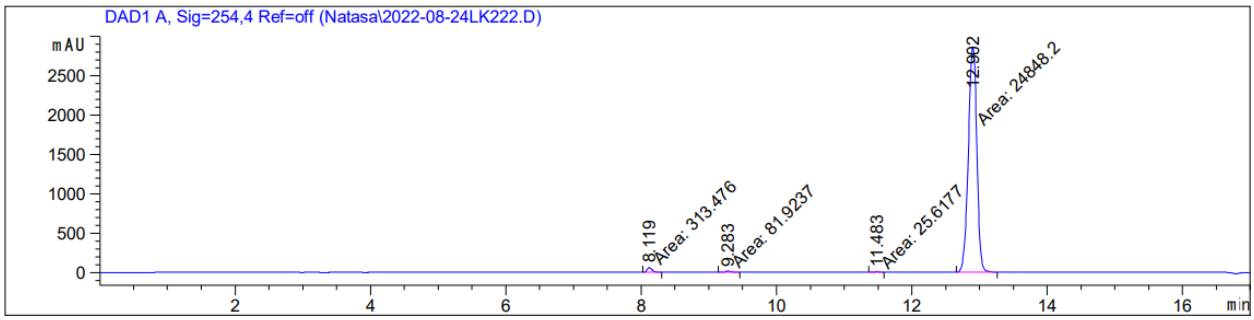
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.769	MM	0.0807	232.28828	48.00134	1.1476
2	8.071	MM	0.0841	45.84514	9.08761	0.2265
3	8.939	MM	0.1469	19.98484	2.26715	0.0987
4	9.502	MM	0.0972	1.99084e4	3414.09912	98.3555
5	11.048	MM	0.1004	34.74845	5.76656	0.1717

Method **H**

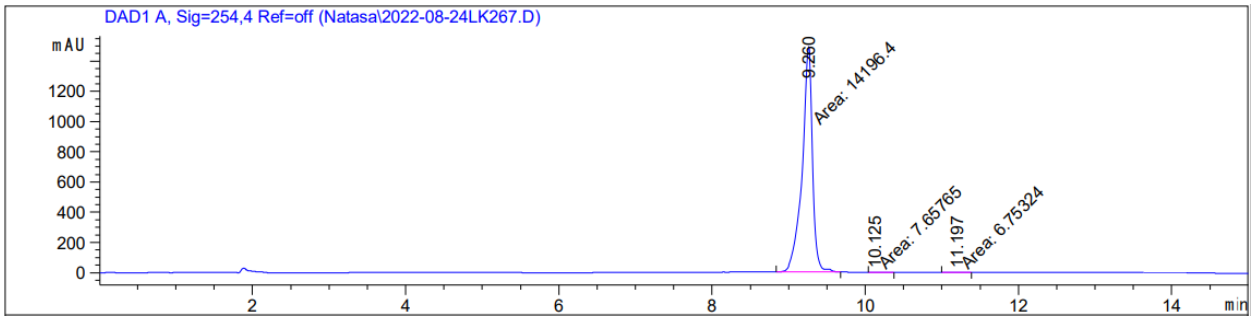


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.119	MM	0.0870	313.47559	60.04585	1.2405
2	9.283	MM	0.1076	81.92374	12.69166	0.3242
3	11.483	MM	0.1211	25.61773	3.52507	0.1014
4	12.902	MM	0.1449	2.48482e4	2858.23535	98.3339

Compound **15b**

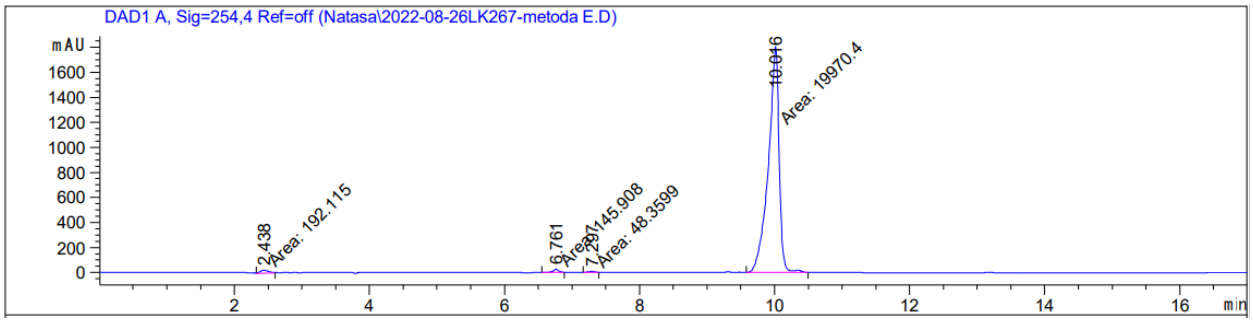
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.260	MM	0.1588	1.41964e4	1489.61060	99.8986
2	10.125	MM	0.1087	7.65765	1.17377	0.0539
3	11.197	MM	0.1302	6.75324	8.64343e-1	0.0475

Method **E**

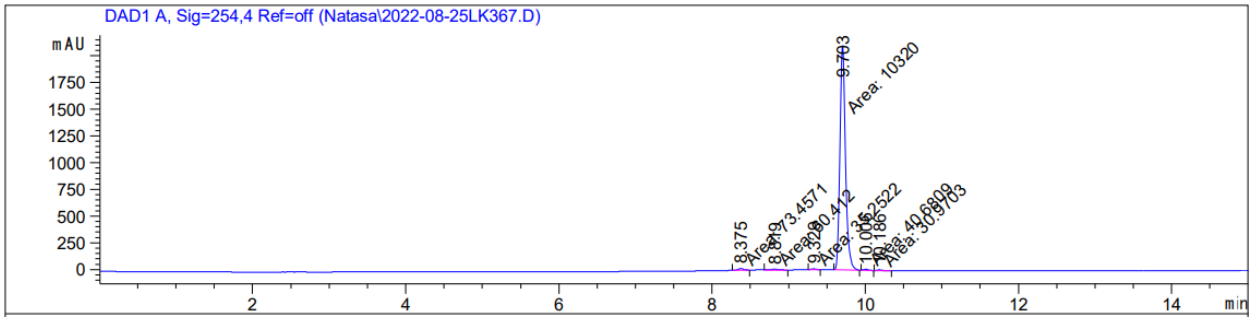


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.438	MM	0.1446	192.11534	22.14987	0.9437
2	6.761	MM	0.0959	145.90825	25.36299	0.7168
3	7.297	MM	0.1145	48.35987	7.03969	0.2376
4	10.016	MM	0.1847	1.99704e4	1801.83594	98.1019

Compound **15c**

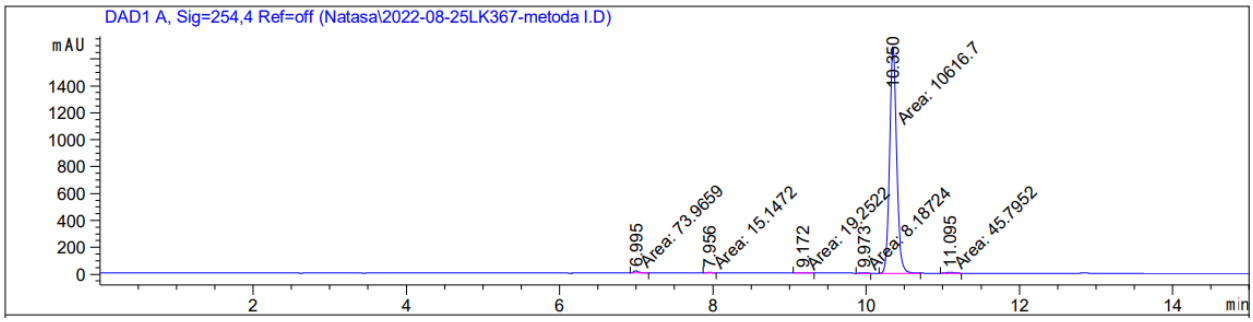
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.375	MM	0.0797	73.45706	15.36834	0.6956
2	8.819	MM	0.1566	60.41203	6.43138	0.5720
3	9.329	MM	0.0750	35.25222	7.83305	0.3338
4	9.703	MM	0.0817	1.03200e4	2104.47778	97.7201
5	10.006	MM	0.0771	40.68087	8.78870	0.3852
6	10.186	MM	0.0725	30.97030	7.11651	0.2933

Method **I**

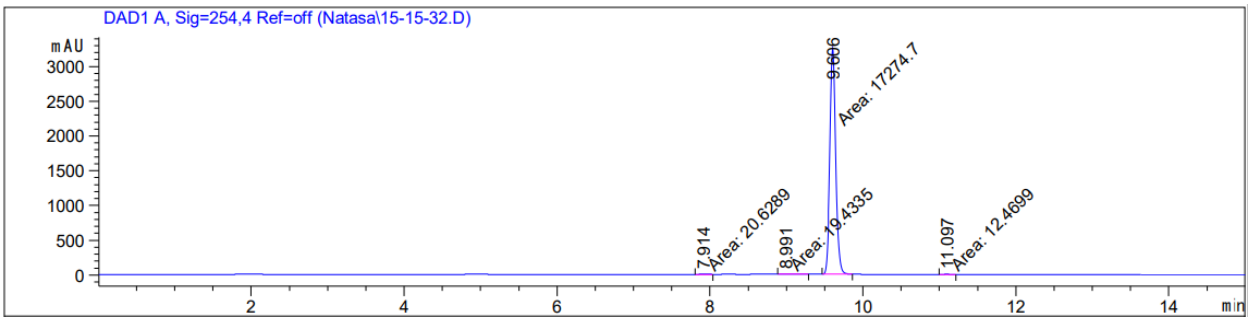


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.995	MM	0.0789	73.96587	15.63085	0.6862
2	7.956	MM	0.0804	15.14724	3.14000	0.1405
3	9.172	MM	0.1328	19.25223	2.41616	0.1786
4	9.973	MM	0.1060	8.18724	1.28697	0.0760
5	10.350	MM	0.1049	1.06167e4	1686.86902	98.4939
6	11.095	MM	0.1084	45.79525	7.04122	0.4249

Compound **15d**

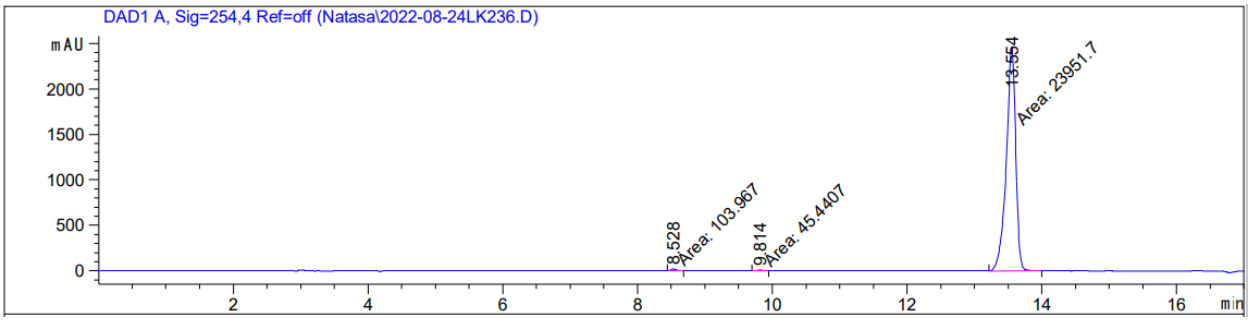
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.914	MM	0.0864	20.62892	3.97967	0.1191
2	8.991	MM	0.1797	19.43347	1.80205	0.1122
3	9.606	MM	0.0884	1.72747e4	3258.48438	99.6968
4	11.097	MM	0.0989	12.46987	2.10037	0.0720

Method **H**

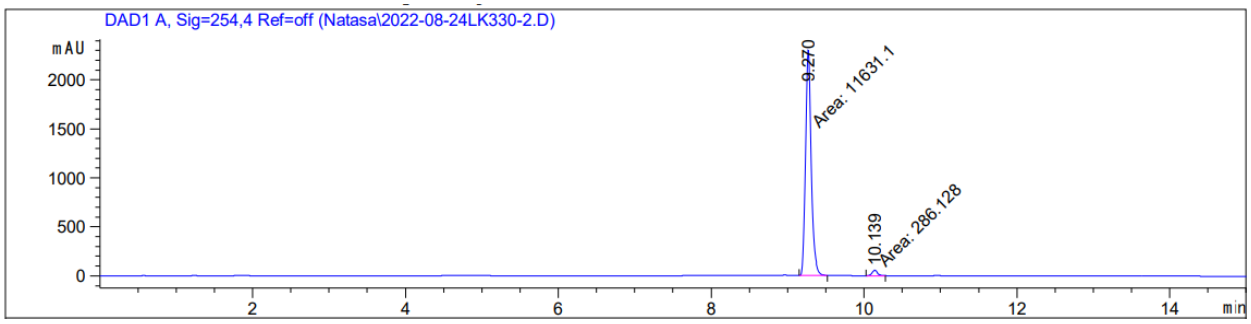


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.528	MM	0.0886	103.96688	19.54945	0.4314
2	9.814	MM	0.1150	45.44066	6.58720	0.1885
3	13.554	MM	0.1622	2.39517e4	2461.12305	99.3801

Compound **15e**

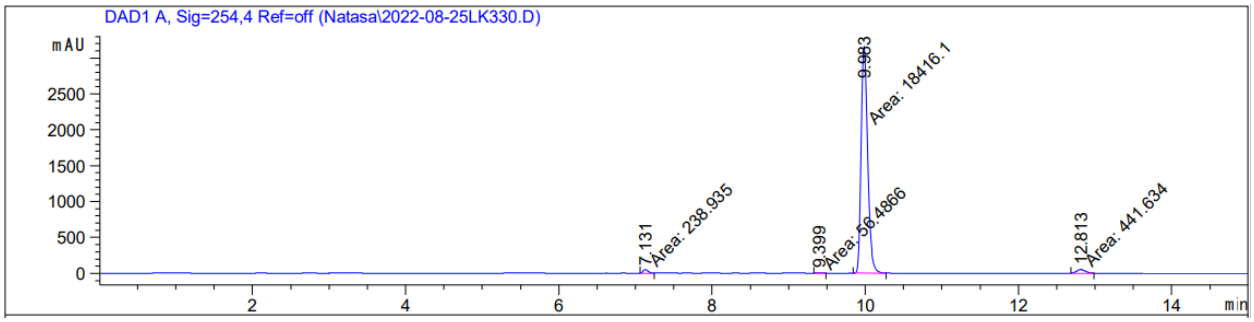
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.270	MM	0.0838	1.16311e4	2313.91675	97.5990
2	10.139	MM	0.0852	286.12823	55.95965	2.4010

Method **I**

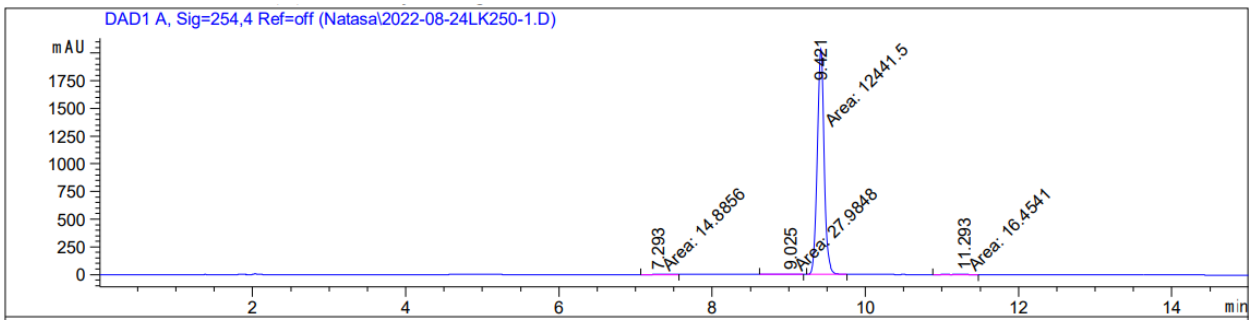


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.131	MM	0.0773	238.93513	51.54005	1.2475
2	9.399	MM	0.1027	56.48661	9.16662	0.2949
3	9.983	MM	0.0974	1.84161e4	3152.80908	96.1518
4	12.813	MM	0.1362	441.63403	54.06108	2.3058

Compound **15f**

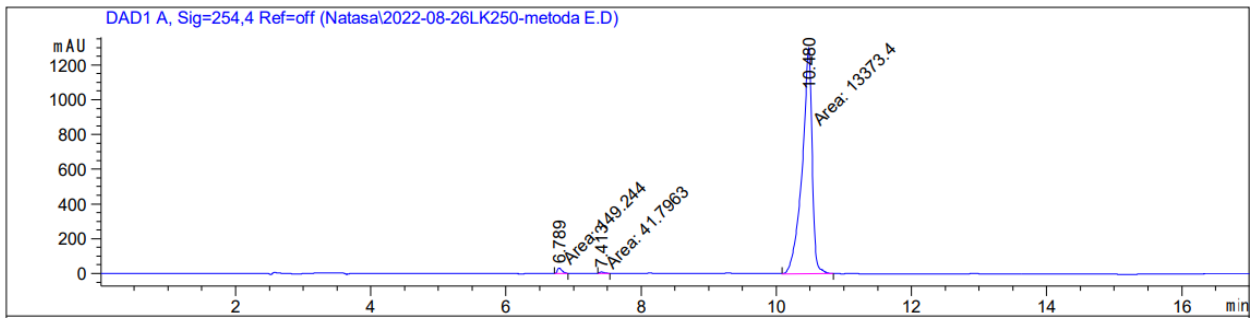
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.293	MM	0.0998	14.88563	2.48520	0.1191
2	9.025	MM	0.2581	27.98475	1.80697	0.2239
3	9.421	MM	0.1017	1.24415e4	2038.65955	99.5254
4	11.293	MM	0.2943	16.45410	9.31911e-1	0.1316

Method **E**

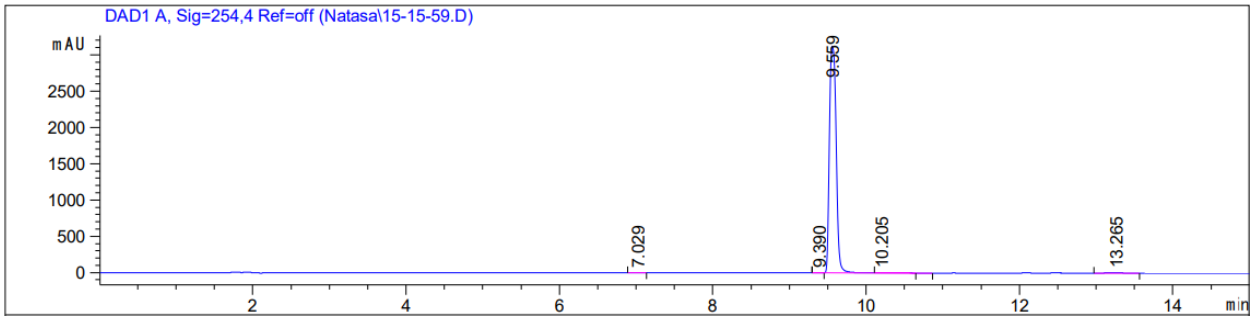


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.789	MM	0.0777	149.24388	32.01181	1.1003
2	7.413	MM	0.0826	41.79629	8.43414	0.3081
3	10.480	MM	0.1716	1.33734e4	1298.87952	98.5916

Compound **16a**

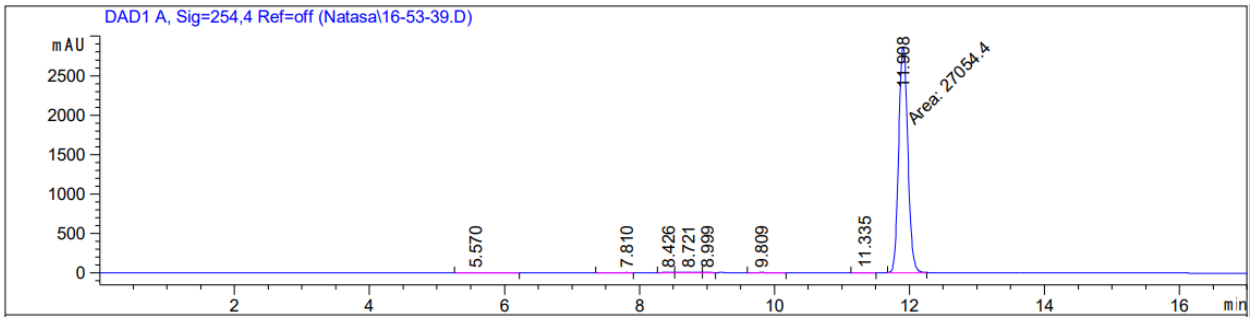
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.029	BB	0.1026	9.05418	1.19194	0.0454
2	9.390	BV E	0.0657	16.91146	4.13523	0.0848
3	9.559	VV R	0.1044	1.98988e4	3121.31641	99.7216
4	10.205	VB E	0.1076	8.72536	1.11145	0.0437
5	13.265	BB	0.1692	20.86964	1.72389	0.1046

Method **F**

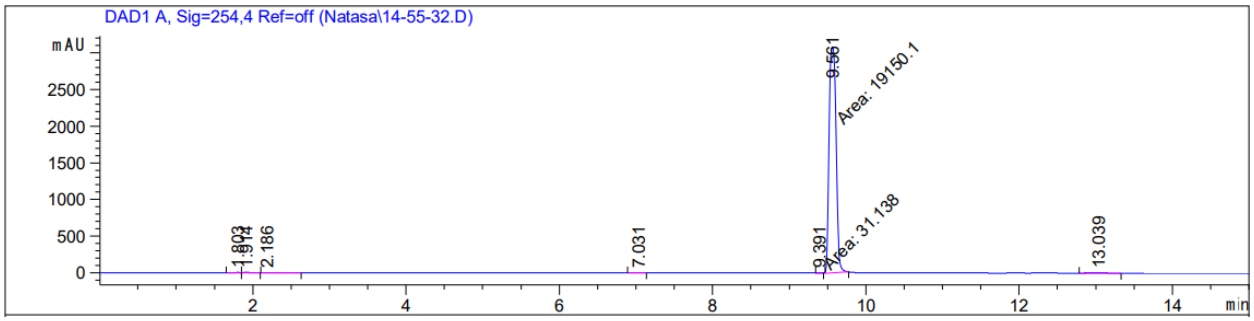


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.570	BB	0.2603	24.24450	1.13919	0.0892
2	7.810	BB	0.1574	14.44872	1.32326	0.0531
3	8.426	BV	0.1240	12.31778	1.52809	0.0453
4	8.721	VV	0.1996	41.50621	2.88897	0.1527
5	8.999	VB	0.0988	8.23294	1.25126	0.0303
6	9.809	BB	0.1718	20.89222	1.71939	0.0768
7	11.335	BV	0.1272	12.74694	1.52959	0.0469
8	11.908	MM	0.1575	2.70544e4	2862.63599	99.5057

Compound **16b**

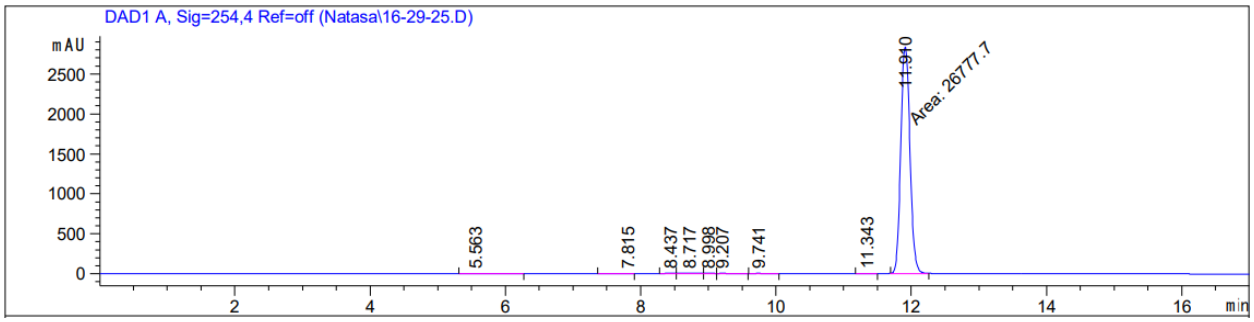
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.803	BV	0.1009	54.69610	7.17773	0.2820
2	1.914	VB	0.1181	66.58273	8.25688	0.3433
3	2.186	BB	0.1941	61.31032	4.10737	0.3161
4	7.031	BB	0.0999	8.96511	1.21798	0.0462
5	9.391	MM	0.0737	31.13797	7.03885	0.1606
6	9.561	MM	0.1036	1.91501e4	3081.63574	98.7437
7	13.039	BB	0.1916	20.95003	1.67891	0.1080

Method **F**

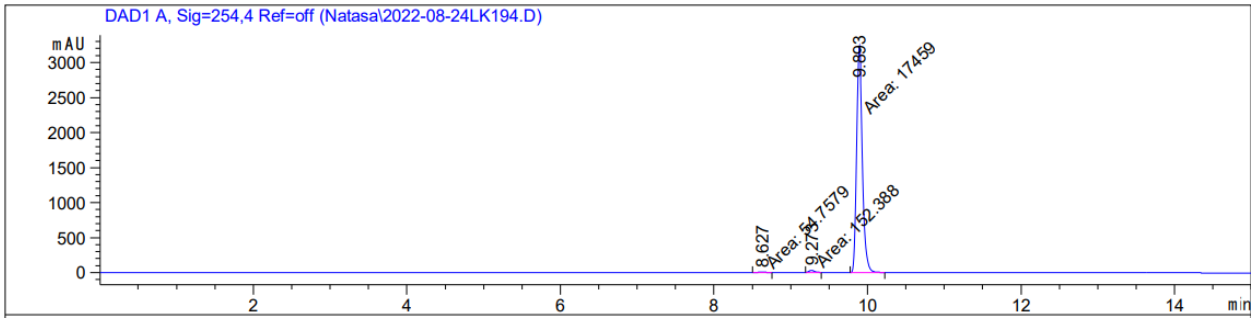


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.563	BB	0.2457	22.03274	1.07235	0.0818
2	7.815	BB	0.1551	11.27630	1.01871	0.0419
3	8.437	BV	0.1260	11.26215	1.34073	0.0418
4	8.717	VV	0.2083	43.95977	2.87663	0.1633
5	8.998	VV	0.1187	14.77815	1.78259	0.0549
6	9.207	VB	0.1681	14.48287	1.09676	0.0538
7	9.741	BB	0.1866	16.04023	1.36978	0.0596
8	11.343	BB	0.1222	11.37897	1.43964	0.0423
9	11.910	MM	0.1574	2.67777e4	2834.76025	99.4606

Compound **16c**

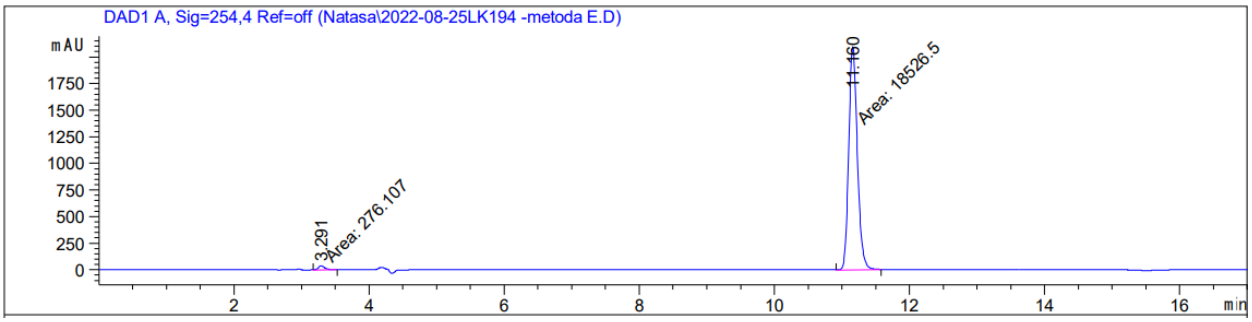
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.627	MM	0.0999	54.75792	9.13115	0.3100
2	9.273	MM	0.0819	152.38789	31.01922	0.8626
3	9.893	MM	0.0899	1.74590e4	3238.50244	98.8274

Method **E**

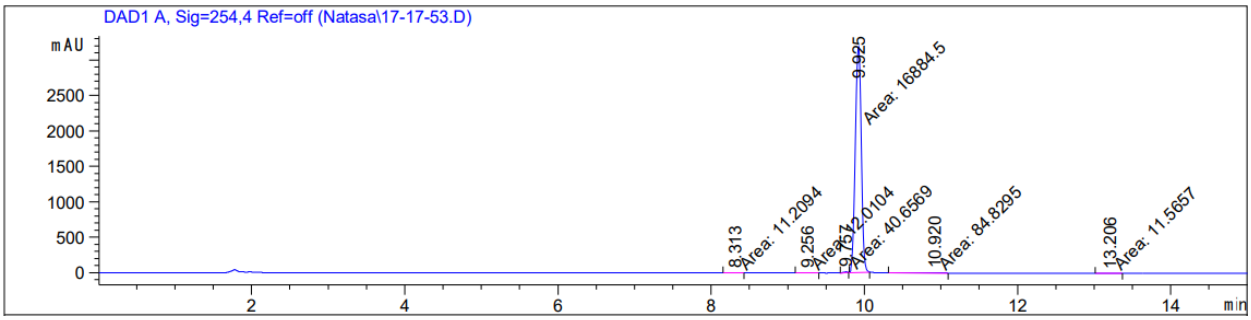


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.291	MM	0.1154	276.10693	39.89371	1.4684
2	11.160	MM	0.1475	1.85265e4	2093.79321	98.5316

Compound **16d**

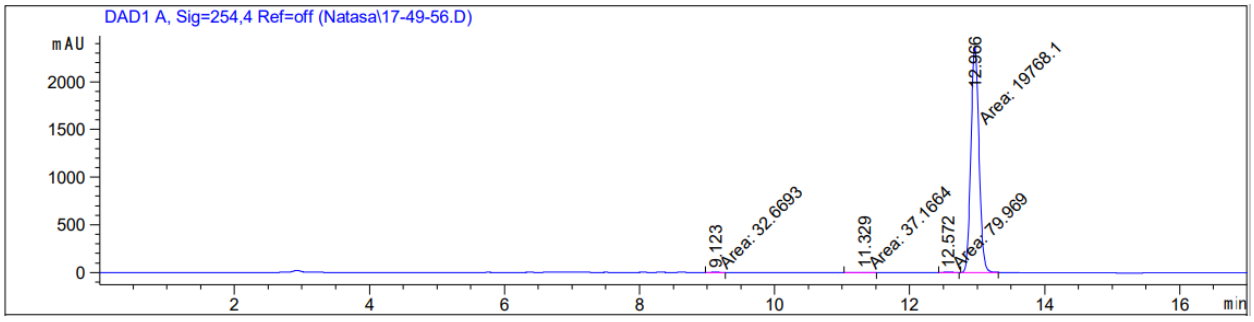
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.313	MM	0.1188	11.20935	1.57246	0.0658
2	9.256	MM	0.0810	12.01036	2.47253	0.0705
3	9.757	MM	0.0608	40.65691	11.14277	0.2385
4	9.925	MM	0.0884	1.68845e4	3184.48315	99.0597
5	10.920	MM	0.3723	84.82954	3.79706	0.4977
6	13.206	MM	0.2133	11.56566	9.03802e-1	0.0679

Method **E**

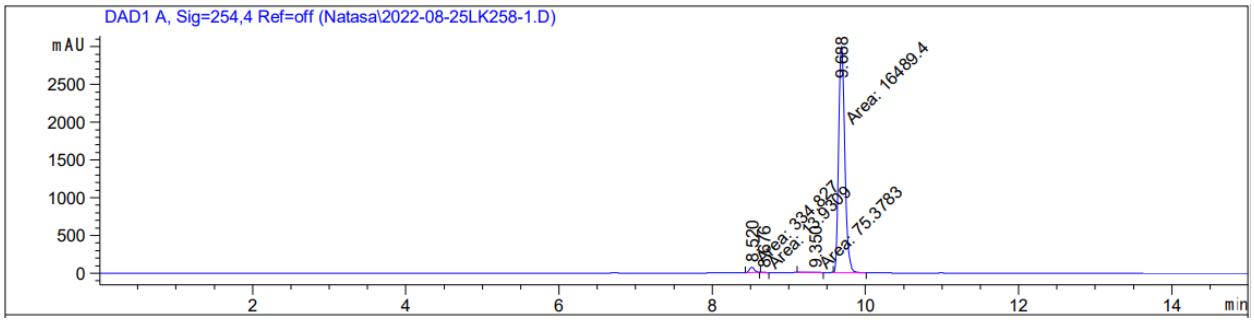


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.123	MM	0.1166	32.66927	4.67116	0.1640
2	11.329	MM	0.2716	37.16638	2.28066	0.1866
3	12.572	MM	0.1375	79.96903	9.69643	0.4015
4	12.966	MM	0.1388	1.97681e4	2373.46216	99.2479

Compound **16e**

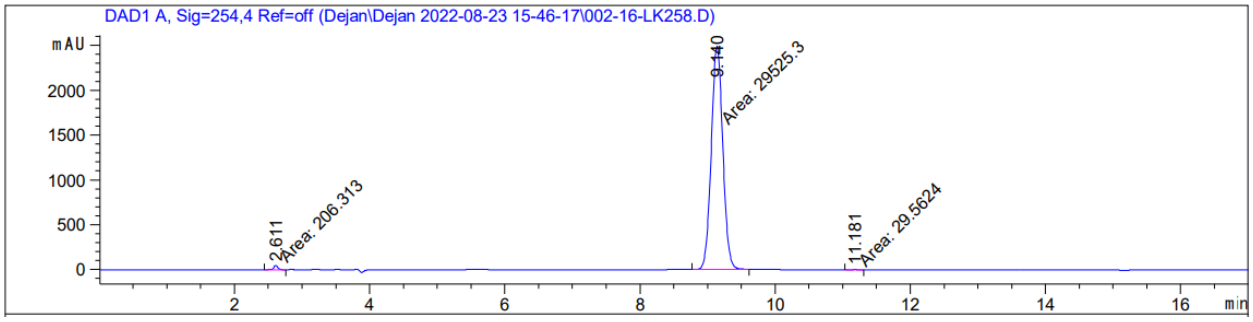
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.520	MM	0.0760	334.82709	73.38389	1.9796
2	8.676	MM	0.0580	13.93094	4.00391	0.0824
3	9.350	MM	0.2174	75.37827	5.77997	0.4457
4	9.688	MM	0.0918	1.64894e4	2993.94629	97.4923

Method **E**

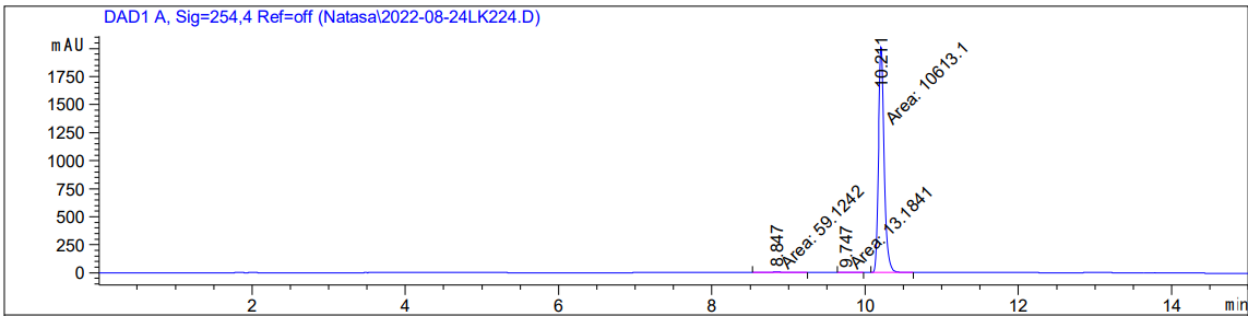


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.611	MM	0.0732	206.31331	46.96367	0.6932
2	9.140	MM	0.1978	2.95253e4	2488.19971	99.2074
3	11.181	MM	0.1543	29.56238	3.19246	0.0993

Compound **16f**

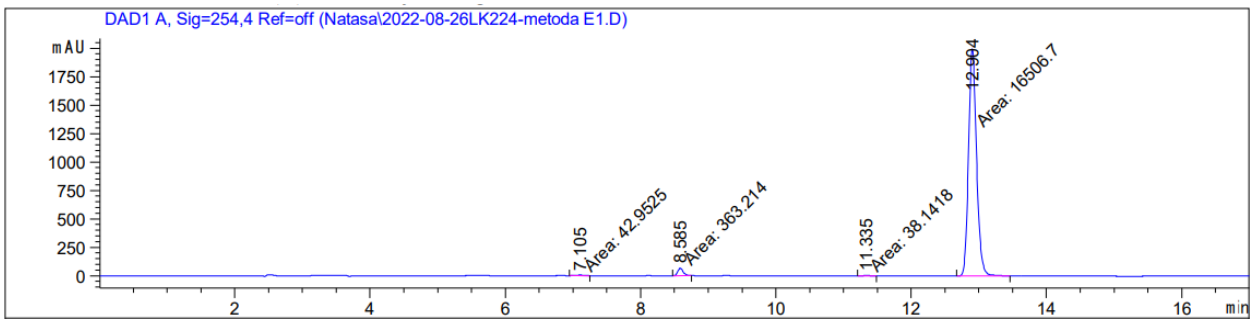
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.847	MM	0.2010	59.12420	4.90133	0.5533
2	9.747	MM	0.1381	13.18406	1.59123	0.1234
3	10.211	MM	0.0875	1.06131e4	2020.96582	99.3233

Method **E**

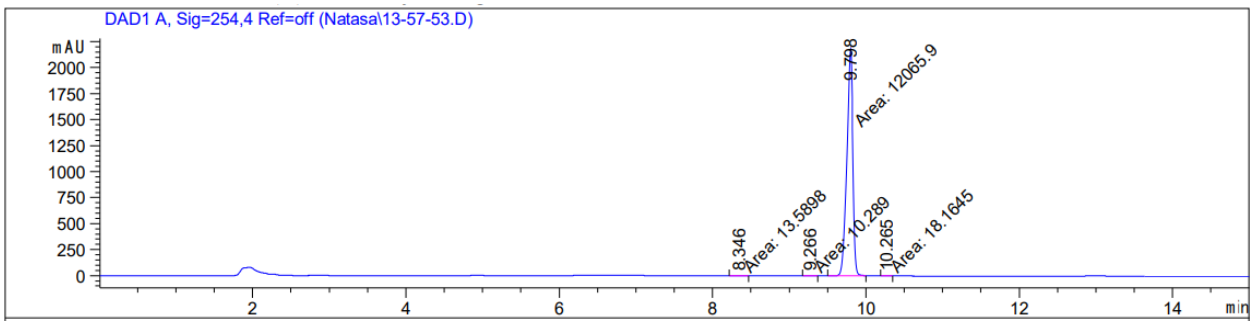


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.105	MM	0.1256	42.95246	5.70005	0.2534
2	8.585	MM	0.0926	363.21399	65.37572	2.1427
3	11.335	MM	0.1254	38.14180	5.06741	0.2250
4	12.904	MM	0.1381	1.65067e4	1992.06848	97.3789

Compound **16g**

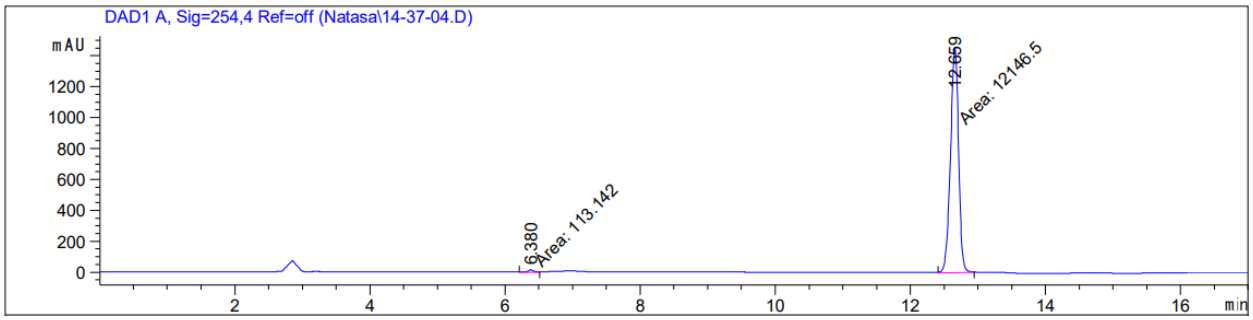
Method **A**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.346	MM	0.1480	13.58979	1.53035	0.1122
2	9.266	MM	0.1037	10.28904	1.65296	0.0850
3	9.798	MM	0.0921	1.20659e4	2182.47827	99.6528
4	10.265	MM	0.0783	18.16450	3.86732	0.1500

Method **E**

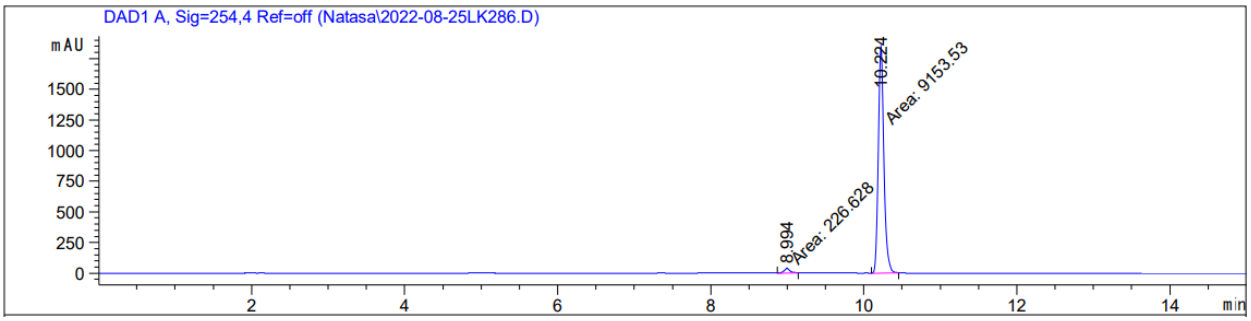


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.380	MM	0.1196	113.14217	15.77062	0.9229
2	12.659	MM	0.1387	1.21465e4	1459.92224	99.0771

Compound **16h**

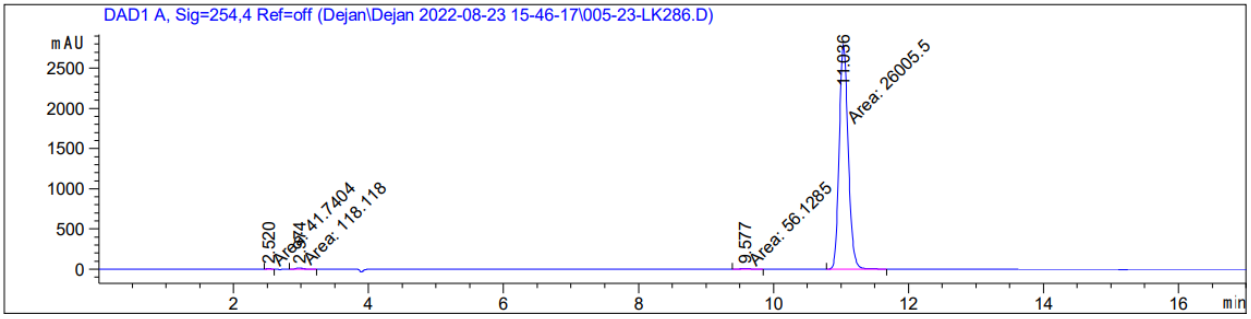
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.994	MM	0.0949	226.62837	39.79708	2.4160
2	10.224	MM	0.0825	9153.53418	1848.14844	97.5840

Method **E**

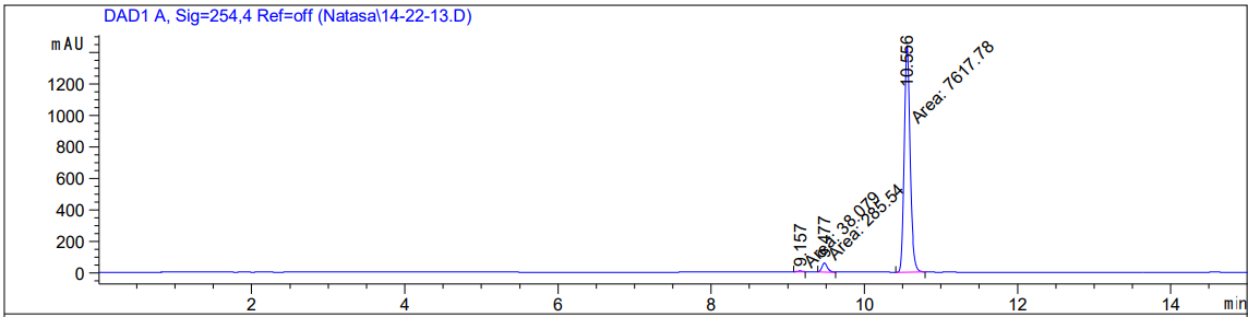


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.520	MM	0.0698	41.74036	9.97280	0.1592
2	2.974	MM	0.1244	118.11772	15.82619	0.4505
3	9.577	MM	0.2370	56.12852	3.94771	0.2141
4	11.036	MM	0.1557	2.60055e4	2784.41699	99.1763

Compound **16i**

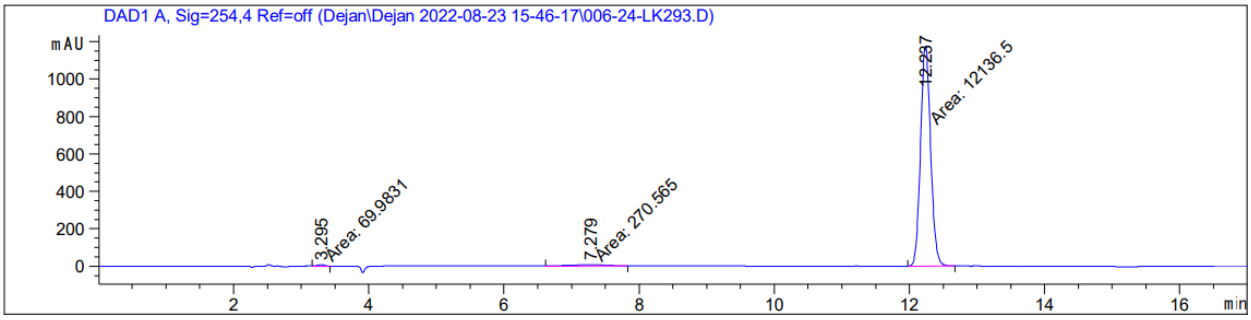
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.157	MM	0.0934	38.07897	6.79221	0.4795
2	9.477	MM	0.0826	285.53955	57.58363	3.5956
3	10.556	MM	0.0880	7617.78223	1442.44360	95.9249

Method **E**

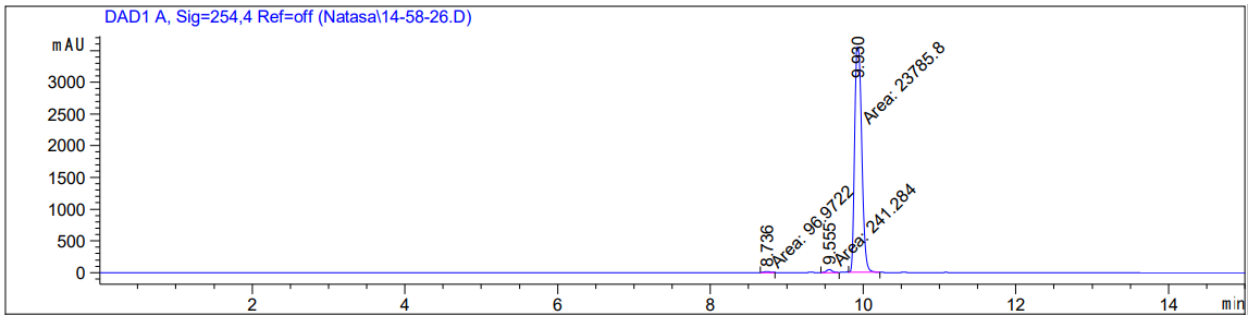


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.295	MM	0.1288	69.98306	9.05656	0.5609
2	7.279	MM	0.6780	270.56519	6.65124	2.1685
3	12.237	MM	0.1721	1.21365e4	1175.45325	97.2706

Compound **16j**

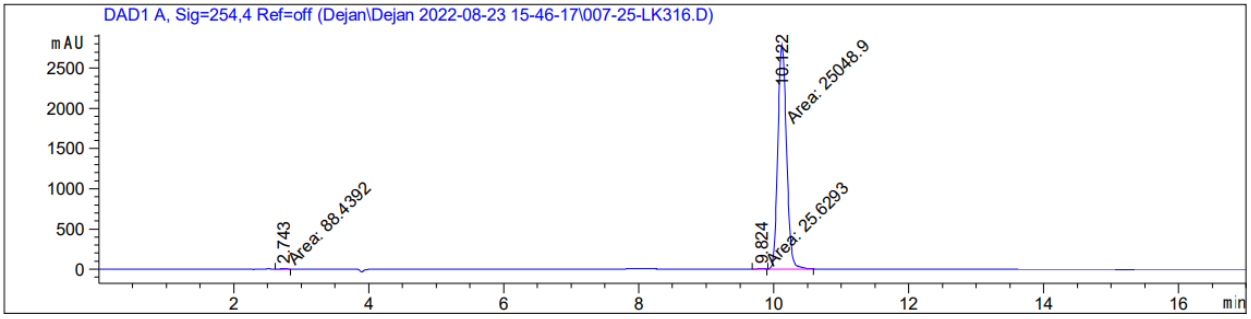
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.736	MM	0.0910	96.97218	17.75268	0.4020
2	9.555	MM	0.0798	241.28427	50.37180	1.0002
3	9.930	MM	0.1118	2.37858e4	3547.19458	98.5978

Method **E**

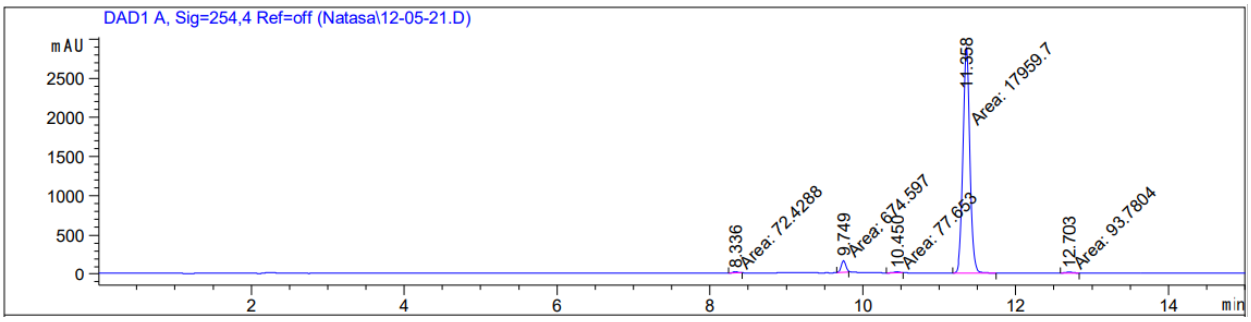


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.743	MM	0.1146	88.43916	12.86010	0.3515
2	9.824	MM	0.1197	25.62933	3.56796	0.1019
3	10.122	MM	0.1500	2.50489e4	2782.35303	99.5467

Compound **16k**

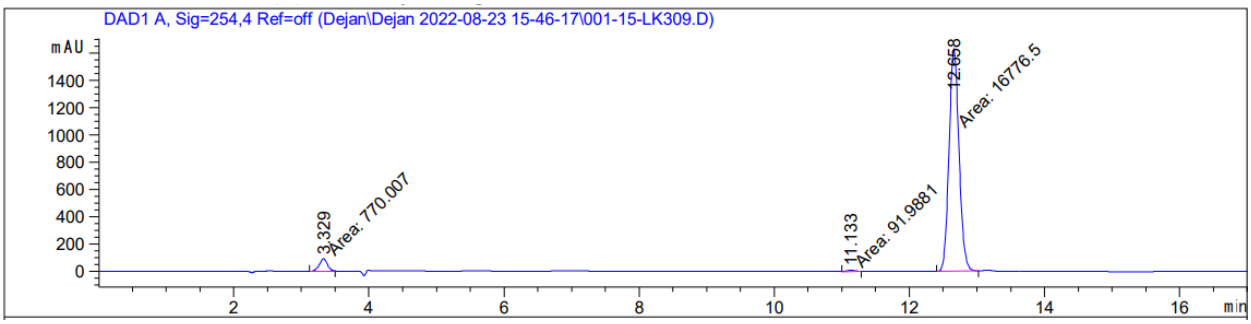
Method **B**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.336	MM	0.0725	72.42885	16.65102	0.3837
2	9.749	MM	0.0720	674.59705	156.24164	3.5734
3	10.450	MM	0.0821	77.65300	15.77344	0.4113
4	11.358	MM	0.1039	1.79597e4	2881.99805	95.1348
5	12.703	MM	0.1200	93.78045	13.02350	0.4968

Method **E**



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.329	MM	0.1398	770.00745	91.82471	4.3655
2	11.133	MM	0.1653	91.98811	9.27355	0.5215
3	12.658	MM	0.1715	1.67765e4	1629.96619	95.1130