Supporting Information

Protecting-Group-Free Mechanosynthesis of Amides from Hydroxycarboxylic Acids: Application to the Synthesis of Imatinib

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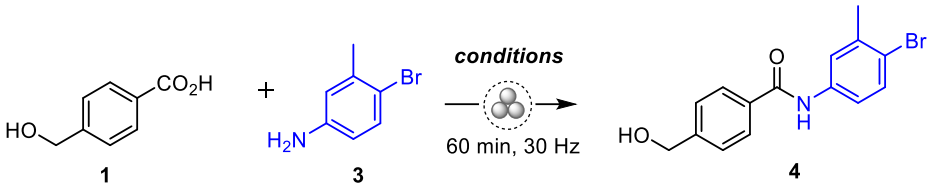
General information

All reagents were purchased from commercial suppliers (Fluorochem, BLD pharm, Sigma-Aldrich and Alfa Aesar) and used without further purification. Amine **16** is commercially available from BLDpharm (65 €/mol). Inorganic salts (e.g., K_2HPO_4, $K_4P_2O_7$) were dried prior to use by heating under reduced pressure. Mechanochemical experiments were carried out in a FTS-1000 shaker mill at 30 Hz frequency by using 14 mL ZrO_2-coated milling jars with 10 mm ZrO_2 milling balls.

Silica gel 40 – 63 μm was used for column chromatography; silica gel 60 F_{254} plates were used for TLC. Visualization of TLC plates was performed by ninhydrin stain. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on Bruker Avance III spectrometer. Chemical shifts were referenced to residual protio solvent peaks and solvent resonances (δ ^{1}H 7.26 and δ ^{13}C 77.16 measured in $CDCl_3$, δ ^{1}H 2.50 and δ ^{13}C 39.52 measured in DMSO-*d*$_6$; δ ^{1}H 3.31 and δ ^{13}C 49.00 measured in CD_3OD) as internal standards for ^{1}H NMR and ^{13}C NMR spectra, respectively. All chemical shifts are reported in ppm units. HPLC analysis was carried out on Agilent 1200 Series HPLC system equipped with a multiple wavelength detector (MWD) and a single quadrupole mass detector (MSD). HRMS data was obtained on Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS system using AJS-ESI method in positive ion detection mode. Single crystal X-ray diffraction data was collected at 123K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-*Kα* radiation (1.54178Å) from a MicroMax^{TM}-003 sealed tube microfocus X-ray source. Melting points were determined with Stuart SMP40 apparatus.

1. Screening experiments



Reaction conditions: 4-(hydroxymethyl)benzoic acid **1** (100 mg, 0.657 mmol), amine **3** (110–122 mg, 0.592–0.657 mmol, 0.9–1 equiv.) and 1,3,5-trimethoxybenzene (~11 mg) as a standard were used in the reactions performed according to the published protocols.[1–4] Ethyl ester of 4-(hydroxymethyl)benzoic acid **S1** was prepared according to the literature procedure.[5]
All the reactants (acid, amine, base and coupling reagent) and LAG additive (the latter) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ^{1}H NMR using CD_3OD as a solvent, after separation of insoluble inorganic material (Table S1).

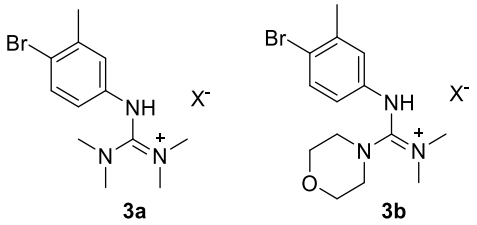
Table S1. Screening experiments

Entry	Coupling reagent	Base	LAG (η, μL·mg^{-1})	Yield of **4**, %[a]	References
1	EDC (1 equiv.)	-	CH_3NO_2 (0.25)	88 (87)[b]	Štrukil et al.[1]
2	EDC (1 equiv.)	-	Sulfolane (0.25)	92 (87)[b]	
3	EDC (1 equiv.)	-	EtOAc (0.25)	90 (89)[b]	
4	EDC (1 equiv.)	DMAP (2 equiv.)	CH_3NO_2 (0.25)	0[e]	
5	COMU (1.1 equiv.)	K_2HPO_4 (3 equiv.)	EtOAc (0.19)	83[f]	Dalidovich et al.[2]
6	TCFH (1.1 equiv.)	K_2HPO_4 (3 equiv.)	EtOAc (0.19)	26[g]	
7	TCFH (1.1 equiv.)	NMI (3 equiv.)	without	74[h]	
8	CDI (1 equiv.)[c]	-	without	10[i]	Métro et al.[3]
9	-	*t*-BuOK[d] (0.85 equiv.)	without	0[j]	Nicholson et al.[4]

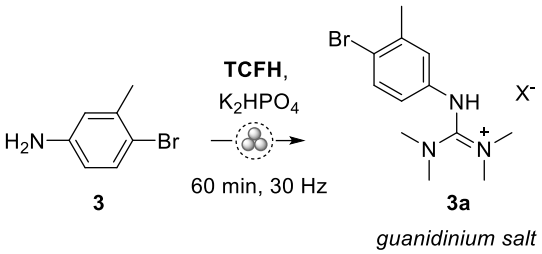
[a] Conversion of **1** into amide **4**, as determined by ^{1}H NMR (characteristic signals of aromatic CH protons from 1,3,5-trimethoxybenzene standard at δ 6.06 ppm and aromatic CH proton from amide **4** at δ 7.65 ppm were integrated). [b] In parenthesis, the yield of isolated amide **4** is given (after washing with water and further drying in air). [c] Acid **1** was pre-milled with CDI for 5 minutes, then amine was added, followed by milling for 60 minutes (according to the published conditions).[3] [d] Ethyl 4-(hydroxymethyl)benzoate **S1** (0.789 mmol, 1.2 equiv., 142 mg) was used instead of **1** according to the published protocol.[4] [e] Mixture of by-products and the starting materials was obtained. [f] Ester-type by-products derived from self-condensation of **1** (characteristic signals of benzylic CH_2

at δ 5.5–5.3 ppm in ^{1}H NMR) and guanidinium derivative **3b** (ca. 12% yield) were observed. [g] Guanidinium salt **3a** was formed as the main product (ca. 75% yield). [h] Incomplete conversion of starting amine **3** and generation of **3a** were observed. [i] Ester-type by-products derived from **1** and unreacted amine **3** were observed. [j] Unreacted starting materials.

guanidinium salts:

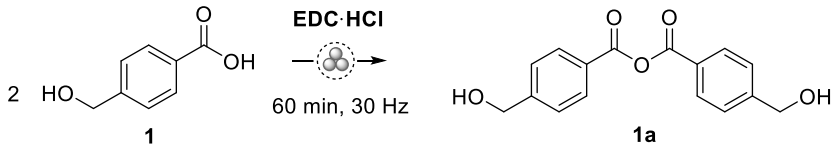


*The reaction of amine **3** with TCFH/K_2HPO_4.*



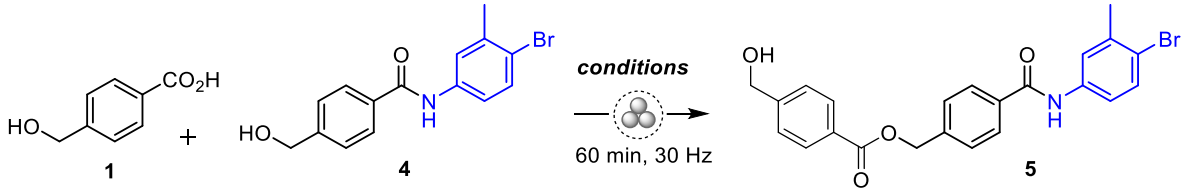
Amine **3** (122 mg, 0.657 mmol), TCFH (203 mg, 0.723 mmol, 1.1 equiv.), K_2HPO_4 (343 mg, 1.972 mmol, 3 equiv.), 1,3,5-trimethoxybenzene (~11 mg) and EtOAc (127 μL) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ^{1}H NMR using CD_3OD as a solvent, after separation of insoluble inorganic material. Characteristic signals of guanidinium salt **3a** in ^{1}H NMR (CD_3OD, 400 MHz): δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 2.7 Hz, 1H), 6.79 (ddd, *J* = 8.5, 2.7, 0.7 Hz, 1H), 2.98 (s, 12H), 2.40 (s, 3H).

*The reaction of 4-(hydroxymethyl)benzoic acid **1** with EDC.*



Acid **1** (100 mg, 0.657 mmol), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (57 μL) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ^{1}H NMR using CD_3OD as a solvent, after separation of insoluble inorganic material. Characteristic signals of anhydride **1a** in ^{1}H NMR (CD_3OD, 400 MHz): δ 8.13 (d, *J* = 7.9 Hz, 4H), 7.57 (d, *J* = 7.9 Hz, 4H), 4.73 (s, 4H). HRMS (AJS-ESI) calcd. for $C_{16}H_{14}O_5Na^+$ $[M+Na]^+$ 309.0733, found *m/z* 309.0734.

*The reaction of amide **4** with 4-(hydroxymethyl)benzoic acid **1**.*



Reaction conditions: amide **4** (0.19 mmol, 60 mg), 4-(hydroxymethyl)benzoic acid **1** (29 mg, 0.19 mmol), coupling reagent (36–88 mg, 1–1.1 equiv.), base (45–98 mg, 3 equiv.) and LAG additive (η = 0.19–0.25 µL·mg^{-1}) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ^{1}H NMR using CD_3OD as a solvent, after separation of insoluble inorganic material (Table S2).

Table S2. Screening experiments

Entry	Coupling reagent	Base	LAG (η, µL·mg^{-1})	Yield of **5**, %[a]
1	TCFH	K_2HPO_4	EtOAc (0.19)	5[b]
2	COMU	K_2HPO_4	EtOAc (0.19)	31
3	TCFH	NMI	-	40
4	EDC	-	EtOAc (0.25)	<1[c]

[a] Conversion of **4** into ester **5**, as determined by ^{1}H NMR (characteristic signals of aromatic CH protons from **4** at δ 7.90 ppm and aromatic CH protons from **5** at δ 7.61 ppm were integrated). [b] Anhydride **1a** was formed in 70% yield. [c] Starting materials are left and anhydride **1a** was formed in 30% yield.

Characteristic signals of ester **5** in ^{1}H NMR (CD_3OD, 400 MHz): δ 8.05 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 2.3 Hz, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.52–7.46 (m, 4H), 5.45 (s, 2H), 4.69 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (CD_3OD, 100.6 MHz): δ 168.39, 167.60, 148.90, 141.82, 139.37, 139.35, 135.92, 133.49, 130.73, 129.97, 129.04, 128.97, 127.70, 124.32, 121.30, 120.41, 66.95, 64.52, 23.16. MS calcd. for $C_{23}H_{21}BrNO_4^+$ $[M+H]^+$ 454.1, found m/z 454.0.

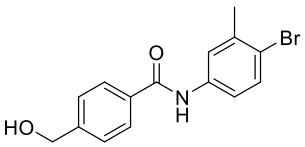
2. General procedure and characterization of products

General procedure. A hydroxy acid (1 equiv.), amine (1 equiv.), EDC·HCl (1 equiv.) and EtOAc as a LAG additive (η = 0.25 μL·mg^{-1}) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. The jar was then set to mill at 30 Hz for 60 minutes.

Work-up procedure I: water (10 mL) was added to the crude reaction mixture, followed by transferring to a glass filter and washing with water (3×10 mL). The obtained solid product was dried in air. If required, further purification by silica gel chromatography (petroleum ether/acetone) was performed.

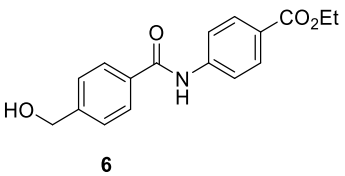
Work-up procedure II: the crude reaction mixture was mixed with water (15 mL) and extracted with ethyl acetate (3×15 mL). The combine organic layers were washed with 10% aq. $NaHSO_4$ (5 mL), sat. $NaHCO_3$ (5 mL), brine (10 mL), and dried over Na_2SO_4, then filtered, and concentrated under reduced pressure. If required, further purification by silica gel chromatography (petroleum ether/acetone) was performed.

***N*-(4-bromo-3-methylphenyl)-4-(hydroxymethyl)benzamide (4).** Prepared from **1** (100 mg, 0.657 mmol), amine **3** (122 mg, 0.657 mmol, 1 equiv.), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (87 μL). Work-up procedure I. Obtained as white solid (187 mg, 89%). Analytically pure sample was prepared by recrystallization (petroleum ether/ethyl acetate = 1:1). mp = 156–157 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 2.2 Hz, 1H), 7.54-7.42 (m, 4H), 4.69 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (CD_3OD, 100.6 MHz): δ 168.61, 147.18, 139.39, 139.30, 134.84, 133.45, 128.73, 127.74, 124.34, 121.31, 120.34, 64.56, 23.16. HRMS (AJS-ESI) calcd. for $C_{15}H_{15}BrNO_2^+$ $[M+H]^+$ 320.0281, found *m/z* 320.0276.



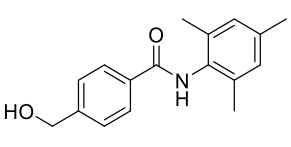
4

Ethyl 4-(4-(hydroxymethyl)benzamido)benzoate (6). Prepared from **1** (100 mg, 0.657 mmol), ethyl 4-aminobenzoate (109 mg, 0.657 mmol, 1 equiv.), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (84 μL) in 76% yield by ^{1}H NMR. Characteristic signals of amide **6** in ^{1}H NMR (CD_3OD, 400 MHz): δ 8.01 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 4.70 (s, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). HRMS (AJS-ESI) calcd. for $C_{17}H_{18}NO_4^+$ $[M+H]^+$ 300.1230, found *m/z* 300.1233.



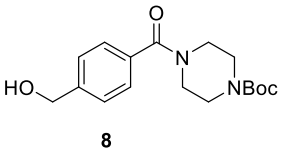
6

4-(Hydroxymethyl)-*N*-mesitylbenzamide (7). Prepared from **1** (100 mg, 0.657 mmol), 2,4,6-trimethylaniline (89 mg, 0.657 mmol, 1 equiv.), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (60 μL) in 77% yield by ^{1}H NMR. Work-up procedure II. Purified by silica gel chromatography with petroleum ether/acetone (25 to 30%) as eluent and obtained as white solid (136 mg, 77%). Analytically pure sample was prepared by recrystallization (petroleum ether/ethyl acetate = 1:2). mp = 157–158 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 6.95 (s, 2H), 4.70 (s, 2H), 3.35 (s, 1H), 2.29 (s, 3H), 2.21 (s, 6H). ^{13}C NMR (CD_3OD, 100.6 MHz): δ 169.09, 147.10, 138.17, 136.84, 134.34, 133.15, 129.75, 128.70, 127.80, 64.59, 21.05, 18.32. HRMS (AJS-ESI) calcd. for $C_{17}H_{20}NO_2^+$ $[M+H]^+$ 270.1489, found *m/z* 270.1491.



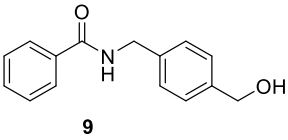
7

***tert*-Butyl 4-(4-(hydroxymethyl)benzoyl)piperazine-1-carboxylate (8).** Prepared from **1** (100 mg, 0.657 mmol), *N*-Boc piperazine (122 mg, 0.657 mmol, 1 equiv., EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (87 µL). Work-up procedure II. Obtained as white solid (191 mg, 91%). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.50–7.44 (m, 2H), 7.44–7.38 (m, 2H), 4.65 (s, 2H), 3.83–3.34 (m, 8H), 1.47 (s, 9H). ^{13}C NMR (CD_3OD, 100.6 MHz): δ 172.75, 156.24, 145.37, 135.29, 128.26, 127.97, 81.70, 64.59, 48.67 (br., HSQC, 2C), 44.72 (br., HSQC), 43.27 (br., HSQC), 28.59. HRMS (AJS-ESI) calcd. for $C_{17}H_{25}N_2O_4^+$ $[M+H]^+$ 321.1809, found *m/z* 321.1809. Spectral data are in agreement with previously reported.[6]



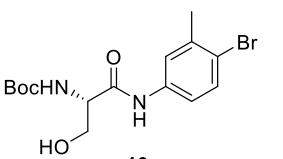
8

***N*-(4-(hydroxymethyl)benzyl)benzamide (9).** Prepared from benzoic acid (100 mg, 0.819 mmol), (4-(aminomethyl)phenyl)methanol (112 mg, 0.819 mmol, 1 equiv.), EDC·HCl (157 mg, 0.819 mmol, 1 equiv.) and EtOAc (92 µL). Work-up procedure II. Obtained as yellowish oil, which crystallizes upon standing (191 mg, 91%). Following work-up procedure I, amide **9** was obtained in 61% yield (120 mg). ^{1}H NMR (CD_3OD, 400 MHz): δ ^{1}H NMR (CD_3OD, 400 MHz): δ 7.87–7.82 (m, 2H), 7.56–7.50 (m, 1H), 7.49–7.43 (m, 2H), 7.37–7.29 (m, 4H), 4.58 (s, 2H), 4.57 (s, 2H). ^{13}C NMR (CD_3OD, 100.6 MHz): δ 170.15, 141.66, 139.27, 135.65, 132.71, 129.59, 128.56, 128.32, 128.23, 64.96, 44.27. HRMS (AJS-ESI) calcd. for $C_{15}H_{16}NO_2^+$ $[M+H]^+$ 242.1176, found *m/z* 242.1175. Spectral data are in agreement with previously reported.[7]



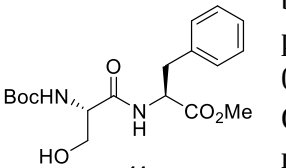
9

***tert*-Butyl (*S*)-(1-((4-bromo-3-methylphenyl) amino)-3-hydroxy-1-oxopropan-2-yl) carbamate (10).** Prepared from (*tert*-butoxycarbonyl)-L-serine (100 mg, 0.487 mmol), amine **3** (91 mg, 0.487 mmol, 1 equiv), EDC·HCl (94 mg, 0.487 mmol, 1 equiv.) and EtOAc (71 µL). Work-up procedure II. Purified by silica gel chromatography with petroleum ether/acetone (15 to 20%) as eluent and obtained as colourless oil, which crystallizes upon standing (150 mg, 82%). mp = 133–134 °C. ^{1}H NMR (CD_3OD, 400 MHz): ^{1}H NMR (CD_3OD, 400 MHz): δ 7.53 (d, *J* = 2.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.25 (t, *J* = 5.4 Hz, 1H), 3.80 (d, *J* = 5.4 Hz, 2H), 2.35 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (CD_3OD, 100.6 MHz): 171.55, 157.79, 139.29, 138.94, 133.43, 123.59, 120.56, 120.11, 80.90, 63.36, 58.58, 28.66, 23.12. HRMS (AJS-ESI) calcd. for $C_{15}H_{21}BrN_2O_4Na^+$ $[M+Na]^+$ 395.0577, found *m/z* 395.0573.

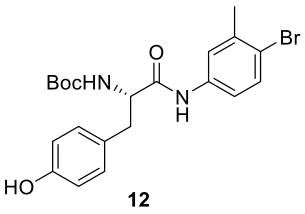


10

Methyl (*tert*-butoxycarbonyl)-L-seryl-L-phenylalaninate (11). Prepared from (*tert*-butoxycarbonyl)-L-serine (100 mg, 0.487 mmol, 1 equiv.), methyl L-phenylalaninate (87 mg, 0.487 mmol, 1 equiv.), EDC·HCl (94 mg, 0.487 mmol, 1 equiv.) and EtOAc (70 µL). Work-up procedure II. Obtained as colourless oil, which could crystallize upon standing (150 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.22 (m, 3H), 7.15–7.10 (m, 2H), 7.02 (d, *J* = 6.0 Hz, 1H), 5.48 (d, *J* = 6.5 Hz, 1H), 4.85 (q, *J* = 6.9 Hz, 1H), 4.20–4.08 (m, 1H), 3.99 (d, *J* = 9.7 Hz, 1H), 3.73 (s, 3H), 3.60 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.18 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.05 (dd, *J* = 14.0, 6.9 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.97, 171.19, 156.04, 135.83, 129.31, 128.77, 127.35, 80.60, 63.04, 55.11, 53.52, 52.64, 37.83, 28.39. HRMS (AJS-ESI) calcd. for $C_{18}H_{27}N_2O_6^+$ $[M+H]^+$ 367.1864, found *m/z* 367.1865. Spectral data are in agreement with previously reported.[8]

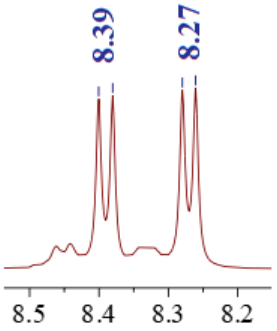


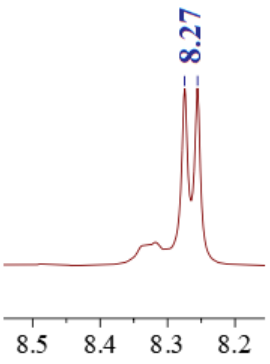
11

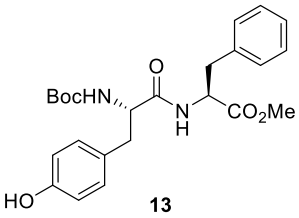
***tert*-Butyl (*S*)-(1-((4-bromo-3-methylphenyl) amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl) carbamate (12).** 

12

Prepared from (*tert*-butoxycarbonyl)-L-tyrosine (100 mg, 0.355 mmol), amine **3** (66 mg, 0.355 mmol, 1 equiv.), EDC·HCl (68 mg, 0.355 mmol, 1 equiv.) and EtOAc (59 µL). Work-up procedure I. Purified by silica gel chromatography with petroleum ether/acetone (20 to 25%) as eluent and obtained as white solid (144 mg, 90%). mp = 169–170 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.47–7.36 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 4.33 (t, *J* = 7.4 Hz, 1H), 2.99 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.84 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.33 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (CD_3OD, 100.6 MHz): δ 172.94, 157.63, 157.31, 139.25, 138.79, 133.39, 131.40, 128.87, 123.66, 120.63, 120.15, 116.20, 80.68, 58.34, 38.86, 28.67, 23.11. HRMS (AJS-ESI) calcd. for $C_{21}H_{26}BrN_2O_4^+$ $[M+H]^+$ 449.1070, found *m/z* 449.1068.

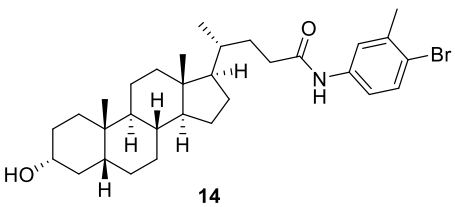
Methyl (*tert*-butoxycarbonyl)-L-tyrosyl-L-phenylalaninate (13). 





13

Prepared from (*tert*-butoxycarbonyl)-L-tyrosine (100 mg, 0.355 mmol), methyl L-phenylalaninate (64 mg, 0.355 mmol, 1 equiv.), EDC·HCl (68 mg, 0.355 mmol, 1 equiv.) and EtOAc (58 µL). Work-up procedure I. Obtained as white solid (130 mg, 83%). mp = 139–140 °C; lit. mp = 140–141 °C.[9] Mixture of (*S*,*S*)- and (*S*,*R*)-**13** diastereomers was obtained analogously from methyl D,L-phenylalaninate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.20 (m, 3H), 7.05–6.95 (m, 4H), 6.74–6.69 (m, 2H), 6.25 (d, *J* = 4.87 Hz, 1H), 4.98 (s, 1H), 4.77 (d, *J* = 7.2 Hz, 1H), 4.26 (s, 1H), 3.66 (s, 3H), 3.11–2.99 (m, 2H), 2.94 (d, *J* = 6.8 Hz, 1H), 1.41 (s, 9H).^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.54, 171.22, 155.57, 155.30, 135.70, 130.56, 129.37, 128.71, 128.03, 127.29, 115.73, 80.56, 56.07, 53.45, 52.47, 38.10, 37.67, 28.39. HRMS (AJS-ESI) calcd. for $C_{24}H_{31}N_2O_6^+$ $[M+H]^+$ 443.2177, found *m/z* 443.2175. The diastereomeric purity (99:1 dr) was confirmed by characteristic resonances in ^{1}H NMR: (*S*,*S*)-diastereormer, 8.27 ppm; (*S*,*R*)-diastereomer, 8.39 ppm (see a fragment of ^{1}H NMR spectra in DMSO-d_6). Spectral data are in agreement with previously reported.[10]

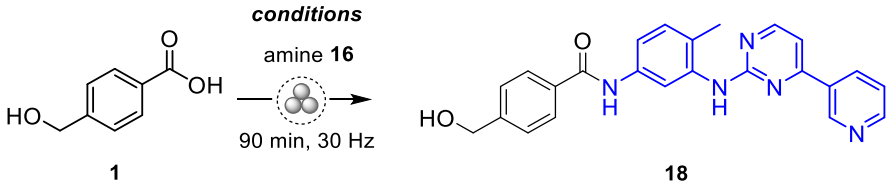
(4*R*)-*N*-(3-bromo-4-methylphenyl)-4-((3*R*, 5*R*, 10*S*, 13*R*, 17*R*)-3-hydroxy-10, 13-dimethylhexadecahydro-1*H*–cyclopenta [*α*] phenanthren-17-yl) pentanamide (14). 

14

Prepared from lithocholic acid (100 mg, 0.266 mmol), amine **3** (49 mg, 0.266 mmol, 1 equiv.), EDC·HCl (51 mg, 0.266 mmol, 1 equiv) and EtOAc (50 µL). Work-up procedure I. Obtained as white solid (134 mg, 93%). Analytically pure sample was prepared by recrystallization (dichloromethane/methanol = 3:1). mp = 240–241 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.90 (s, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.44 (d, *J* = 4.5 Hz, 1H), 3.43–3.33 (m, 1H), 2.37–2.26 (m, 1H), 2.29 (s, 3H), 2.24–2.15 (m, 1H), 1.93 (d, *J* = 8.8 Hz, 1H), 1.86–1.46 (m, 7H), 1.41–0.99

(m, 17H), 0.91 (d, J = 6.5 Hz, 3H), 0.94–0.88 (m, 1H), 0.87 (s, 3H), 0.61 (s. 3H). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 171.77, 138.89, 137.27, 132.12, 121.29, 118.47, 116.94, 69.85, 56.09, 55.55, 42.27, 41.51, 39.97, 39.70, 36.30, 35.37, 35.14, 34.95, 34.20, 33.35, 31.23, 30.38, 27.73, 26.88, 26.16, 23.85, 23.27, 22.66, 20.40, 18.31, 11.88. HRMS (AJS-ESI) calcd. for $C_{31}H_{47}BrNO_2^+$ $[M+H]^+$ 544.2785, found *m/z* 544.2785.

3. Preparation of intermediate 18: optimization studies



Reaction condition for the optimization studies: Acid **1** (54.9 mg, 0.36 mmol,), amine **16** (100.0 mg, 0.36 mmol, 1 equiv.), coupling reagent (0.36–0.40 mmol, 1–1.3 equiv.), base (1.08 mmol, 3 equiv.), triphenylmethane (in entries 5 and 6, Table S2) and LAG additive (0.19–0.25 µL·mg^{-1}) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. The jar was then set to mill at 30 Hz for 90 minutes.

A. The resulting crude reaction mixture was transferred to a beaker, diluted with distilled water (10–15 mL), stirred for 2 hours, then filtered through a glass filter and dried under vacuum (Table S2, Entries 1–4).
B. The resulting crude reaction mixture was analysed by ^{1}H NMR in DMSO-d_6, after separation of insoluble inorganic material (Table S3, Entries 5 and 6).

Table S3. Optimization studies.

Entry	Coupling reagent	Base	LAG (η, µL·mg^{-1})	Yield of **18**, %
1	EDC (1 equiv.)	-	CH_3NO_2 (0.25)	86
2	EDC (1 equiv.)	-	Sulfolane (0.25)	83
3	EDC (1 equiv.)	-	EtOAc (0.25)	93
4	COMU (1.1 equiv.)	K_2HPO_4 (3 equiv.)	EtOAc (0.19)	81
5	TCFH (1.1 equiv.)	K_2HPO_4 (3 equiv.)	EtOAc (0.19)	36[a]
6	TCFH (1.3 equiv.)	NMI (3 equiv.)	without	63[a]

[a] Conversion of **1** into **18**, as determined by ^{1}H NMR in DMSO-d_6 using an internal standard (characteristic signals of triphenylmethane CH proton at δ 5.61 ppm and CH_2-OH protons from amide **18** at δ 4.59 ppm were integrated).

HPLC-UV-MS analysis of amide 18.

The chromatographic separation was performed on Phenomenex Kinetex XB-C18 column (150 mm × 4.6 mm, 2.6 µm). Eluents A (water / 0.1% formic acid) and B (methanol) were used in A:B 60:40 (v/v) isocratic mode for 3 minutes, followed by a 10-minute gradient from A:B 60:40 (v/v) to A:B 30:70 (v/v) and a 17-minute isocratic stage with the flow rate of 0.5 mL/min. The column temperature was set at 30 °C, injection volume at 1 µL and detection wavelength at 270 nm. The peaks were characterized by ESI-MS with the following spray chamber parameters: drying gas flow 5 L/min, drying gas temperature 300 °C, nebulizer pressure 60 psig, vaporizer temperature 150 °C, capillary voltage 2000 V and charging electrode voltage 2000 V. Mass spectra were acquired in positive mode within *m/z* 100 – 2000 range and fragmentor voltage 100 V.

Sample preparation: ~0.5 mg/ml in acetonitrile: methanol 1:1 (v/v).

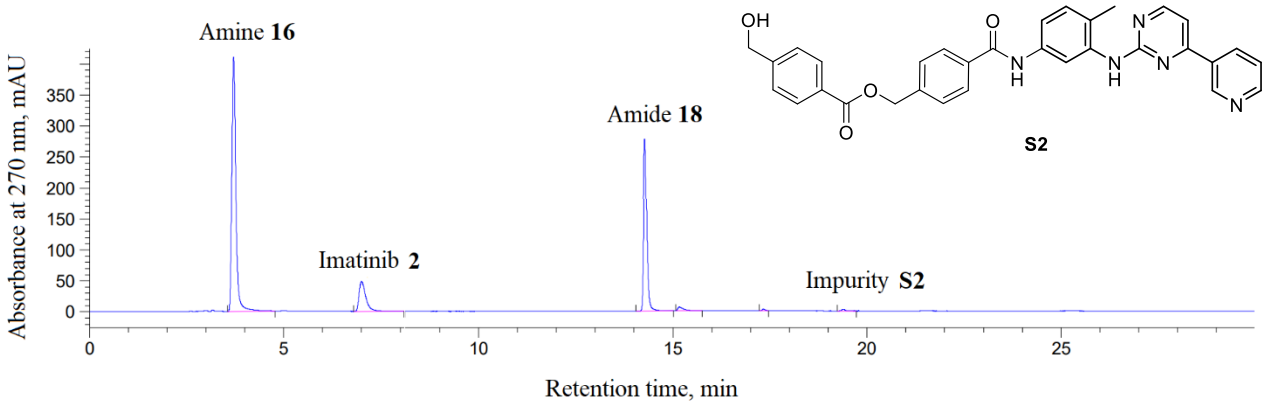


Figure S1. HPLC-UV chromatogram of the mixture of amine **16**, imatinib **2**, amide **18** and impurity **S2** at 270 nm.

MS data:

Amine **16**, calcd. for $C_{16}H_{16}N_5^+$ $[M+H]^+$ 278.1, found *m/z* 278.1.

Imatinib **2**, calcd. for $C_{29}H_{32}N_7O^+$ $[M+H]^+$ 494.3, found *m/z* 494.2.

Amide **18**, calcd. for $C_{24}H_{22}N_5O_2^+$ $[M+H]^+$ 412.2, found *m/z* 412.1.

Impurity **S2**, calcd. for $C_{32}H_{28}N_5O_4^+$ $[M+H]^+$ 546.2, found *m/z* 546.2.

Table S4. HPLC purity of amide **18** prepared under different conditions.

Entry	Coupling reagent / Base	LAG (η, $\mu L \cdot mg^{-1}$)	HPLC area percentage, %		
			18	**16**	**S2**
1	EDC (1 equiv.)	CH_3NO_2 (0.25)	98.3	1.5	0.2
2	EDC (1 equiv.)	Sulfolane (0.25)	97.3	1.3	1.3
3	EDC (1 equiv.)	EtOAc (0.25)	98.0	0.9	1.1
4	COMU (1.1 equiv.) / K_2HPO_4 (3 equiv.)	EtOAc (0.19)	94.3	0.2	4.8

The final protocol: Two identical reactions were performed simultaneously in two jars.

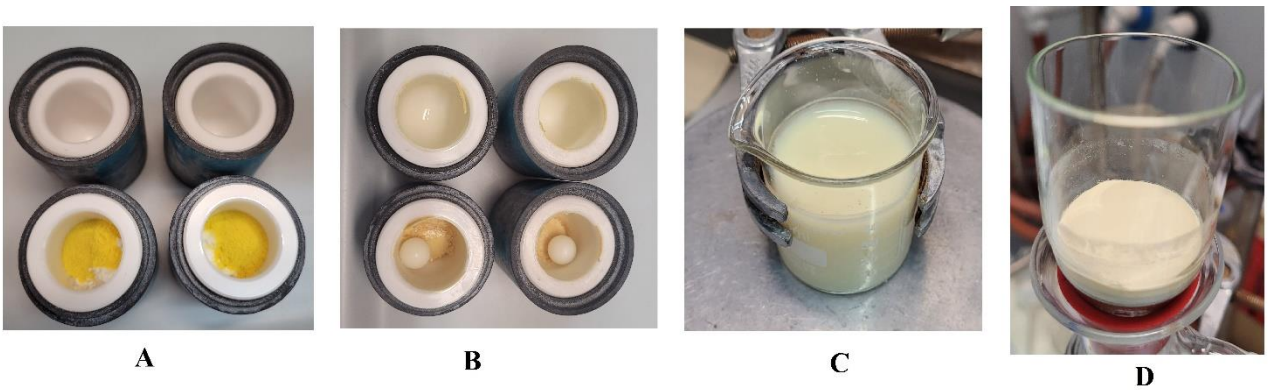


Figure S2. Synthesis of amide **18**.

Amine **16** (300 mg, 1.08 mmol), acid **1** (173 mg, 1.14 mmol, 1.05 equiv.), EDC HCl (228 mg, 1.19 mmol, 1.1 equiv.) and EtOAc (350 µL) were placed into a 14 mL ZrO_2-coated jar charged with one 10 mm ZrO_2 ball (Figure S2, A). The second jar was loaded with the same amount of chemicals and the two jars were set to mill at 30 Hz for 90 min. The resulting crude reaction mixtures (yellowish solid, Figure S2, B) were combined and transferred to a beaker, diluted with water (ca. 40 mL), stirred for 2 hours (Figure S2, C), then filtered through a glass filter (Figure S2, D) and dried first in air ant then under vacuum. Product **18** was obtained as a yellowish solid (835 mg, 94% yield, 98% HPLC purity, Figure S3). mp = 197–198 °C (CH_3OH). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ 10.16 (s, 1H, NH), 9.28 (d, *J* = 2.3 Hz, 1H), 8.98 (s, 1H, NH), 8.68 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.51 (d, *J* = 5.1 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 2.3 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.56-7.39 (m, 3H), 7.21 (d, *J* = 8.3 Hz, 1H), 5.35 (t, *J* = 5.7 Hz, 1H, OH), 4.59 (d, *J* = 5.7 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100.6 MHz): δ 165.23, 161.62, 161.20, 159.49, 151.40, 148.22, 146.27, 137.80, 137.23, 134.43, 133.35, 132.23, 130.04, 127.57, 127.52, 126.05, 123.79, 117.23, 116.76, 107.52, 62.48, 17.67. HRMS (AJS-ESI) calcd. for $C_{24}H_{22}N_5O_2^+$ $[M+H]^+$ 412.1768, found *m/z* 412.1766.

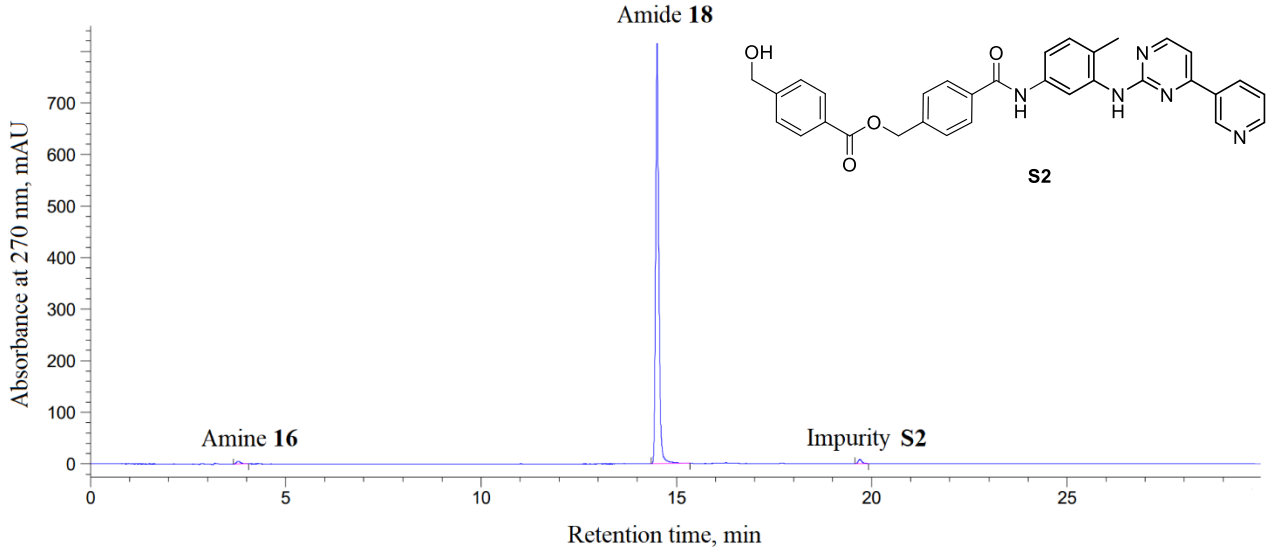


Figure S3. HPLC-UV chromatogram of amide **18** (98.0%), containing amine **16** (0.9%) and impurity **S2** (1.1%).

*The confirmation of the structure of impurity **S2** by synthesis and alkaline hydrolysis*

Amide **18** (50.0 mg, 0.12 mmol), acid **1** (19 mg, 0.12 mmol, 1 equiv.), TCFH (38 mg, 0.13 mmol, 1.1 equiv.), NMI (30 mg, 0.36 mmol, 3 equiv.) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was transferred to a beaker, diluted with distilled water (5 mL), stirred for 2 hours, then filtered through a glass filter, dried under vacuum and analysed by HPLC (Figure S4) that shows generation of **S2** and unreacted **18**. Characteristic signals of benzylic $CH_2OC(O)$ of **S2** in ^{1}H and ^{13}C NMR (DMSO-*d*$_6$): δ_H = 5.44 ppm, δ_C = 65.4 ppm. The treatment of amide **18**, containing 1.1% of **S2**, with 1M aq. NaOH at 40°C for 2 hours (in methanol) resulted in the hydrolysis of ester **S2** and its disappearance from the HPLC chromatogram (Figure S5).

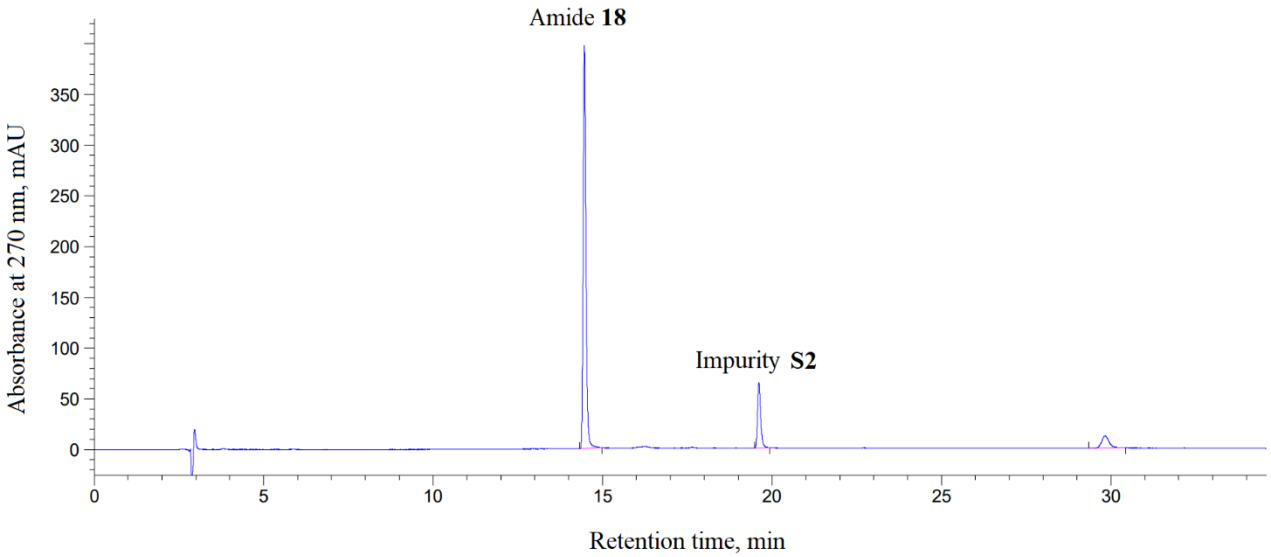


Figure S4. HPLC-UV chromatogram of amide **18**, containing impurity **S2**.

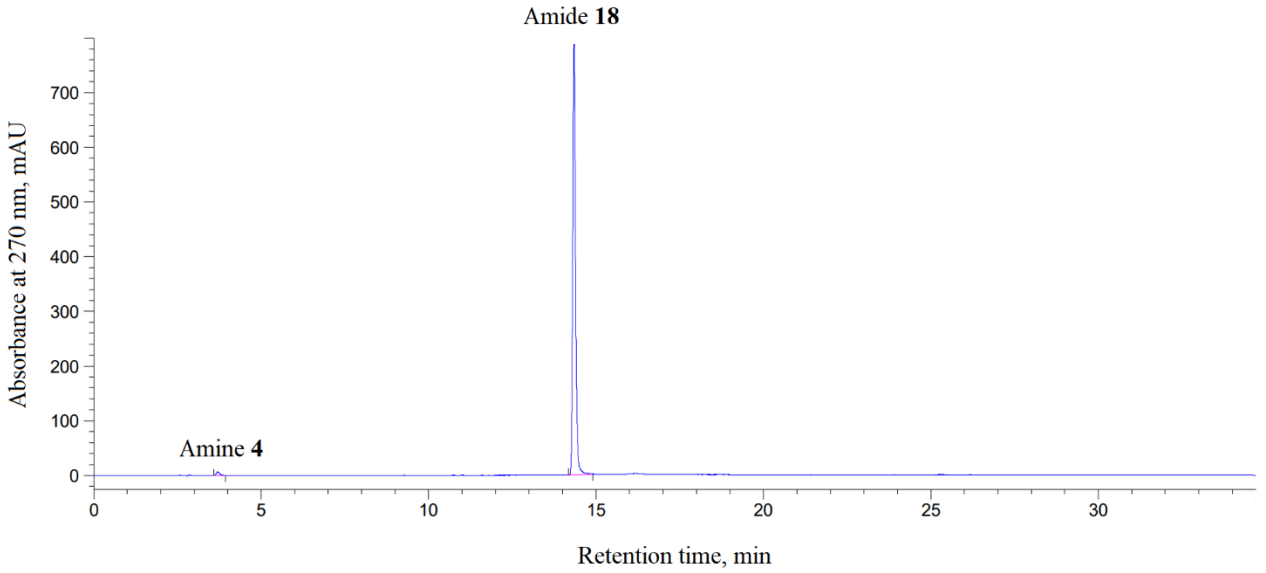
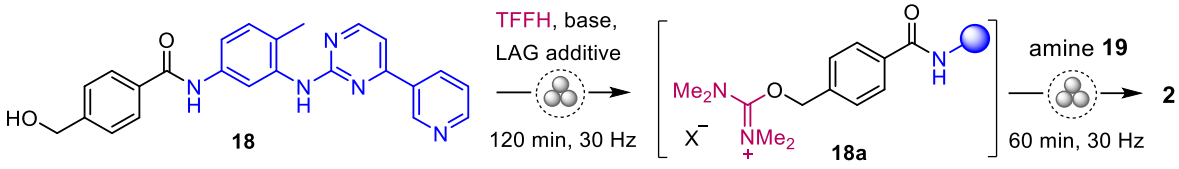


Figure S5. HPLC-UV chromatogram of amide **18** after hydrolysis with 1M NaOH solution.

4. Preparation of Imatinib 2 from amide 18: optimization studies.

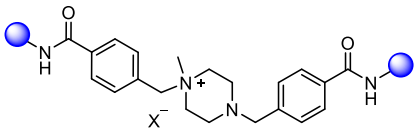


Reaction condition for the optimization studies: Amide **18** (100 mg, 0.24 mmol), TFFH (0.49 mmol, 2 equiv.) and a base (0.49–0.61 mmol, 2–2.5 equiv.) were placed into a 14 mL ZrO_2-coated jar charged with a single 10 mm ZrO_2 milling ball. Then LAG additive was added to the jar (η = 0.2–0.75 µL·mg^{-1}), which was then set to mill at 30 Hz for 120 min. 1-Methylpiperazine **7** (0.36–2.43 mmol, 1.5–10 equiv.) was added to the resulting mixture, and the jar was set to mill at 30 Hz for additional 60 min. The resulting crude reaction mixture was transferred to a beaker, diluted with cold distilled water (20–30 mL), stirred overnight, then filtered through a glass filter, dried in air and analysed by HPLC-UV-MS (Table S5).

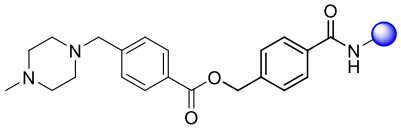
Table S5. Optimization studies.

Entry	Base (equiv.)	LAG (η, µL·mg^{-1})	Amine **7**	HPLC area percentage, %			
				2	**18**	**20**	**21**
1[6]	K_2HPO_4 (2.0 equiv.)	EtOAc (0.2)	1.5 equiv.	66[a]	-	-	-
2	K_2HPO_4 (2.5 equiv.)	Sulfolane (0.5)	2.5 equiv.	74.6	8.1	13.5	-
3	K_2HPO_4 (2.5 equiv.)	EtOAc (0.5)	5.0 equiv.	89.1	6.5	2.9	0.5
4	K_2HPO_4 (2.5 equiv.)	Sulfolane (0.5)	5.0 equiv.	91.8	1.9	5.5	0.8
5	$K_4P_2O_7$ (2.0 equiv.)	DMI (0.6)	5.0 equiv.	94.2	0.9	3.8	1.1
6	$K_4P_2O_7$ (2.0 equiv.)	EtOAc (0.5)	5.0 equiv.	84.9	13.7	0.7	0.7
7	K_2HPO_4 (2.5 equiv.)	DMI (0.65)	5.0 equiv.	93.2	0.6	5.2	1.0
8	$K_4P_2O_7$ (2.0 equiv.)	DMI (0.6)	10.0 equiv.	94.9	0.4	3.2	1.5
9	K_2HPO_4 (2.5 equiv.)	DMI (0.65)	10.0 equiv.	**95.6**	0.6	2.4	1.5
10[b]	K_2HPO_4 (2.5 equiv.)	DMI (0.65)	10.0 equiv.	**95.3**	1.3	2.0	1.4

[a] With 1.5 equiv. of TFFH, conversion of amide **18** into product **2**, as determined by ^{1}H NMR in DMSO-d_6 (characteristic signals of NH proton from amide **18** at δ 10.15 ppm and from product **2** at δ 10.16 ppm were integrated). [b] The reaction was performed starting from 300 mg of **18** in a 14 mL ZrO_2-coated jar charged with two 10 mm ZrO_2 milling balls.



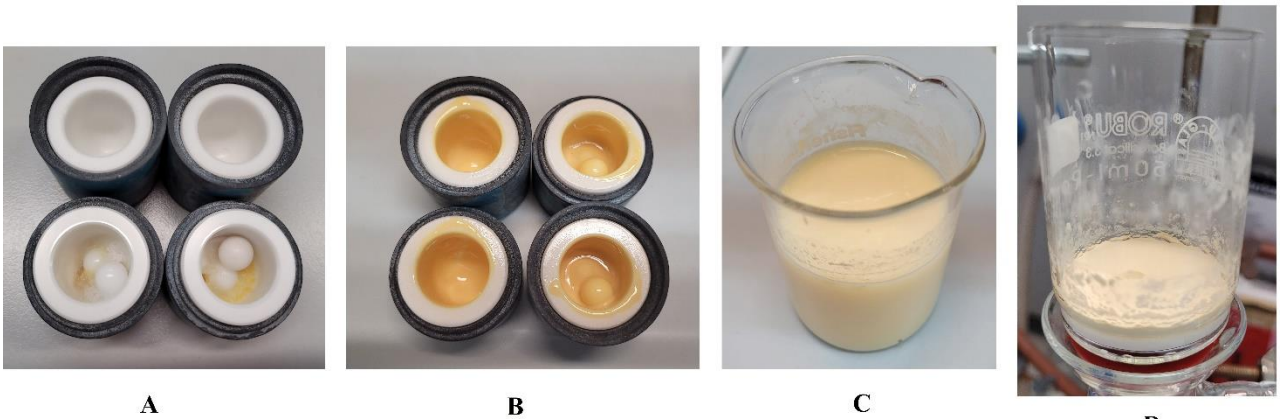
20, possible structure



21

20, MS calcd. for $C_{53}H_{51}N_{12}O_2^+$ $[M]^+$ 887.4, found ***m/z*** 887.4.
21, MS calcd. for $C_{37}H_{38}N_7O_3^+$ $[M+H]^+$ 628.3, found ***m/z*** 628.3.

The final protocol: Two identical reactions were performed simultaneously in two jars.



A **B** **C** **D**

Figure S6. Preparation of Imatinib **2** from intermediate **18**.

Amide **18** (300 mg, 0.73 mmol, 98% purity, crude material obtained in the previous step and used without any additional purification), TFFH (385 mg, 1.46 mmol, 2 equiv.) and K_2HPO_4 (318 mg, 1.82 mmol, 2.5 equiv.) were placed into a 14 mL ZrO_2-coated jar charged with two 10 mm ZrO_2 milling balls. Dimethyl isosorbide was added (655 µL) as a LAG additive. The second jar was loaded with the same amount of chemicals (Figure S6, A) and the two jars were set to mill at 30 Hz for 120 minutes. Then 1-methylpiperazine **7** (810 µL, 7.30 mmol, 10 equiv.) was added to each jar to the formed reaction mixture. The two jars were set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixtures (yellowish viscous paste, Figure S6, B) were combined and transferred to a beaker, diluted with distilled water (100 mL), stirred overnight (Figure S6, C), then filtered through a glass filter (Figure S6, D), dried first in air and then under vacuum. Imatinib **2** was obtained as off-white solid (690 mg, 96% yield, 95% HPLC purity, Figure S7). Analytically pure sample was obtained by crystallization from methanol/ethyl acetate (1:1) to give Imatinib **2** with 99% HPLC purity (Figure S8). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.16 (s, 1H), 9.28 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.98 (s, 1H), 8.68 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.51 (d, *J* = 5.1 Hz, 1H), 8.48 (dt, *J* = 8.0, 1.9 Hz, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.55-7.46 (m, 2H), 7.45-7.39 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 1H), 3.52 (s, 2H), 2.47-2.20 (m, 8H), 2.22 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.25, 161.60, 161.19, 159.47, 151.39, 148.21, 142.11, 137.80, 137.21, 134.42, 133.77, 132.22, 130.03, 128.62, 127.58, 123.78, 117.20, 116.72, 107.51, 61.62, 54.71, 52.58, 45.74, 17.67. HRMS (AJS-ESI) calcd. for $C_{29}H_{32}N_7O^+$ $[M+H]^+$ 494.2663, found *m/z* 494.2665. Spectral data are in agreement with previously reported.[11]

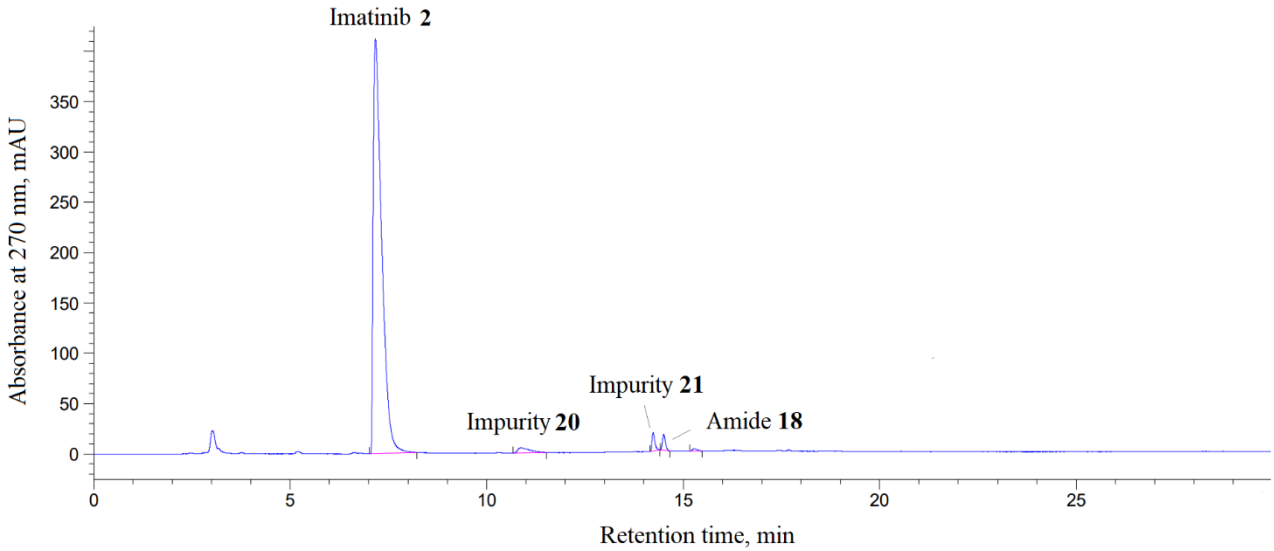


Figure S7. HPLC-UV chromatogram of Imatinib **2** (95.3%), containing impurities **20** (1.4%), **21** (2.0%) and amide **18** (1.3%).

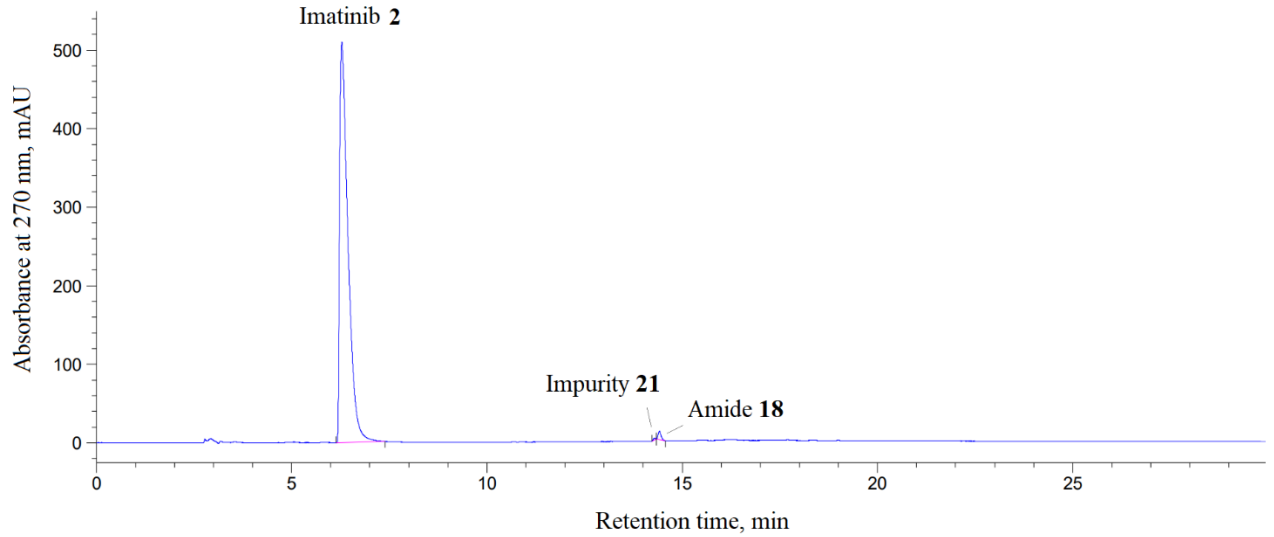


Figure S8. HPLC-UV chromatogram of Imatinib **2** (99.2%), containing impurity **21** (0.1%) and amide **18** (0.7%).

5. SC-XRD characterization of 18.

Single crystal X-ray diffraction data was collected at 123K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-*Kα* radiation (1.54178Å) from a MicroMax^{TM}-003 sealed tube microfocus X-ray source. The data was solved by intrinsic phasing (SHELXT)[12] and refined by full-matrix least squares on F^2 using Olex2[13] utilising the SHELXL module.[12] Anisotropic displacement parameters were assigned to non-H atoms and isotropic displacement parameters for all H atoms were constrained to multiples of the equivalent displacement parameters of their parent atoms with U_{iso}(H) = 1.2 U_{eq} (methylene, methine) or U_{iso}(H) = 1.5 Ueq(methyl, hydroxy) of their respective parent atoms. Appropriate restraints were applied to the geometry and thermal displacement parameters of the atoms involved in the disordered parts of the structures. Restrain DFIX was used to fix the distance between carbon and oxygen atoms (C1A O1A bond distance was fixed to be 1.43) to be equal within the standard uncertainty s value 0.02. Terminal OH-group was modelled as a 60:40% disorder model.

The crystallographic data is deposited with the Cambridge Crystallographic Data Centre (CCDC 2287665) and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Single-crystal XRD analysis unambiguously revealed that we obtained a crystal structure of amide **18** with methanol coordinated to it (Figure S9).

Crystallographic details for amide 18

$[C_{24}H_{21}N_5O_2]\cdot[C_1H_4O_1]$: Single crystals of the compound were obtained from a methanol solution of amide **18** by slow evaporation of the solvent.

$C_{25}H_{25}N_5O_3$, M = 426.71 g/mol 1, colorless blocks, 0.06 × 0.20 × 0.20, monoclinic, $P2_1/c$, a = 14.3819(4) Å, b = 15.9349(5) Å, c = 9.4755(3) Å, α =90°, β = 99.199(3)°, γ = 90°, V = 2143.61(11) Å^3 , Z = 4, Cu-Kα radiation (λ = 1.54184 Å), at T = 123.0(1) K, μ(Cu-*Kα*) = 0.701 mm^{-1} , 13786 reflections measured (6.208° ≤ 2Θ ≤ 129.382°), R_{int} = 0.028, 314 parameters, 1 restraints, $R_1[F^2>2\sigma(F^2)]$ = 0.061, wR_2(all data) = 0.188, S = 1.095, 0.21 < dΔρ < - 0.30 eÅ^{-3}.

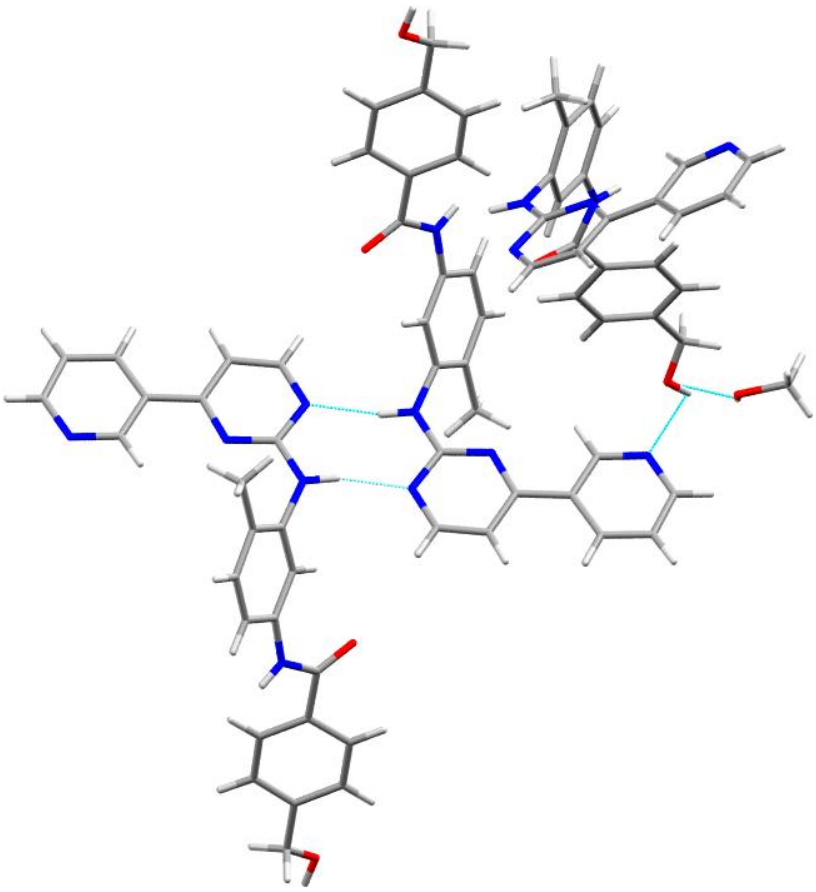
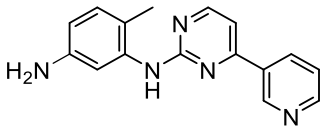


Figure S9. Crystal structure of amide **18**.

6. Determination of Amine 16 (Impurity F) according to the European Pharmacopoeia and optimization studies for its content reduction.

6.1. Quantification of Amine 16.



Amine **16** (Impurity **F**)

Determination of genotoxic impurity **F** (amine **16**) was carried out according to the method established by European Pharmacopoeia 9.2, 07/2017:2736 used in analysis of Imatinib mesylate. The allowed limit is maximum 20 ppm.

Imatinib **2** with 99% HPLC purity was analysed (the synthetic procedure is described in the section 4, p. S14).

Sample preparation:

0.5 mg/ml in acetonitrile: methanol 1:1 (v/v).

Reference solution of impurity F:

0.00001 mg/ml in acetonitrile: methanol 1:1 (v/v). The concentration of impurity **F** corresponds to 20 ppm in test solution.

General HPLC-MS conditions:

The chromatographic separation was performed on Macherey-Nagel RP18 column (150 mm × 3.0 mm, 2.7 µm). Eluents A (1.26 g/L solution of ammonium formate in water adjusted to pH 3.5 with formic acid) and B (0.05% formic acid in acetonitrile) were used in a gradient mode starting with A:B 80:20 (v/v) isocratic stage for 6 minutes, followed by a 4-minute gradient from A:B 80:20 (v/v) to A:B 20:80 (v/v) and holding the latter as 5-minute isocratic stage, with the flow rate of 0.5 mL/min. The column temperature was set at 40 °C and injection volume at 10 µL. Impurity **F** was followed by mass detector operated in single ion monitoring (SIM) mode with the following parameters: ESI, positive polarity, detection *m/z* 278.2, gas temperature 350 °C, drying gas flow 12 L/min, nebulizer pressure 60 psig, capillary voltage 3000 V. MS acquisition was started at 3.5 min and stopped at 6 min.

The content of impurity **F** (*X*, ppm) was calculated via formula (1):

$$X = \frac{S_i \cdot m_0 \cdot A_0 \cdot V_i \cdot 10^6}{S_0 \cdot m_i \cdot V_0 \cdot 100} \quad (1)$$

where S_i – peak area of impurity **F** on the chromatogram of test solution, ion counts; S_0 – peak area of impurity **F** on the chromatogram of reference solution, ion counts; m_i – weight of the sample, mg; m_0 – weight of the reference standard, mg; A_0 – reference standard purity or assay, %; V_0 – total volume of reference solution; V_i – total volume of test solution.

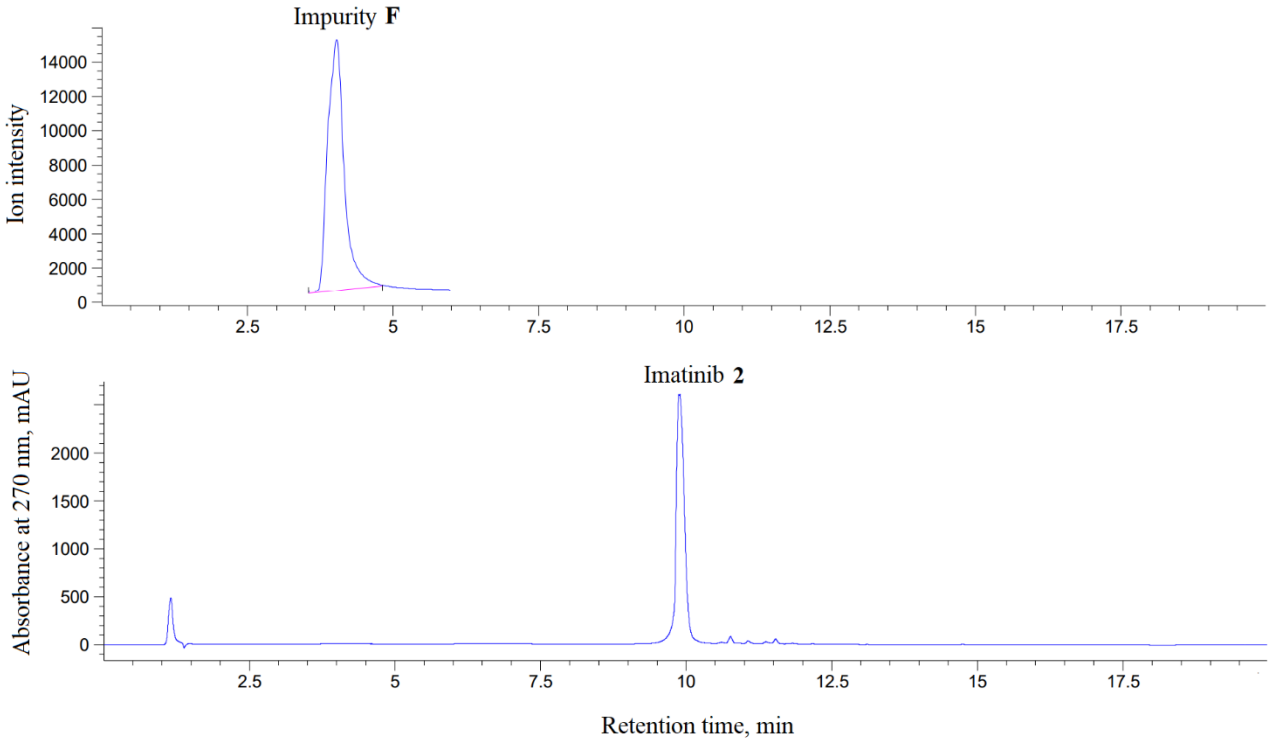


Figure S10. Upper: HPLC monitored ion count chromatogram of impurity **F**, lower: HPLC-UV chromatogram of Imatinib **2** at 270 nm.

X = 556±25 ppm

6.2. Optimization studies for reducing the content of amine 16.

In order to decrease the content of impurity F, slight modifications in the previously described protocol for the synthesis of amide **18** (see section 3, p. S11) were performed (modifications are underlined):

Amine **16** (300 mg, 1.08 mmol), acid **1** (214 mg, 1.41 mmol, 1.3 equiv.), EDC HCl (228 mg, 1.19 mmol, 1.1 equiv.) and EtOAc (375 µL) were placed into a 14 mL ZrO_2-coated jar charged with one 10 mm ZrO_2 ball. The second jar was loaded with the same amount of chemicals and the two jars were set to mill at 30 Hz for 90 min. The resulting crude reaction mixtures were combined and transferred to a beaker, diluted with 5% KOH solution (ca. 20 mL), stirred for 2 hours, then filtered through a glass filter, washed with water (2×10 mL) and dried first in air ant then under vacuum. Product **18** was obtained as a yellowish solid (840 mg, 94% yield, 99% HPLC purity, Figure S11). Next, dichloromethane (ca. 25 mL) was added to the obtained solid amide **18**, and the resulting suspension was stirred for 1 hour, then filtered through a glass filter, washed with dichloromethane (2×10 mL) and dried first in air ant then under vacuum. Product **18** was obtained as a yellowish solid (805 mg, 90% yield, 99.6% HPLC purity, Figure S12).

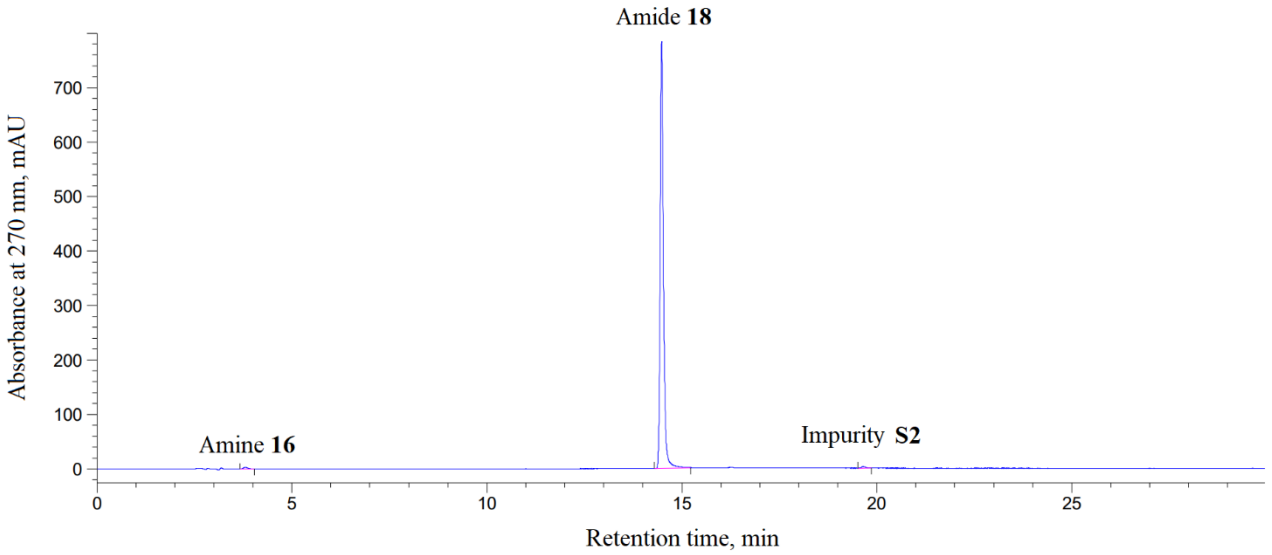


Figure S11. HPLC-UV chromatogram of amide **18** (99.0%), containing impurity **S2** (0.46) and amine **16** (0.51).

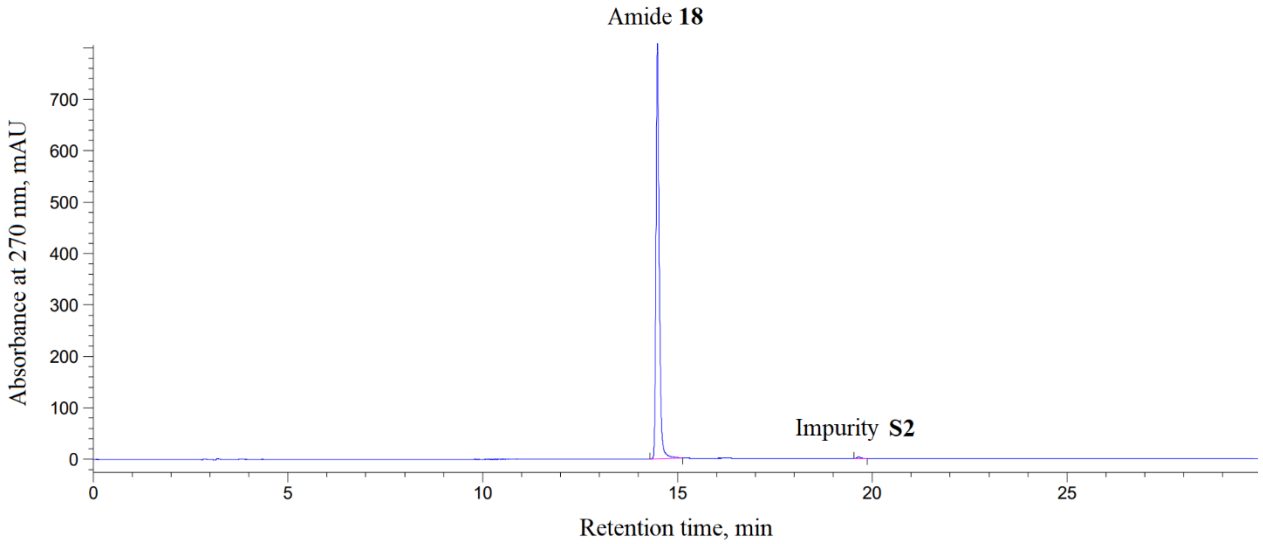


Figure S12. HPLC-UV chromatogram of amide **18** (99.6%), containing impurity **S2** (0.44).

Imatinib **2** was synthesised according to the previously described protocol (see section 4, p. S14). Further assay of impurity F was determined in the crude product **2** prior to the recrystallization.

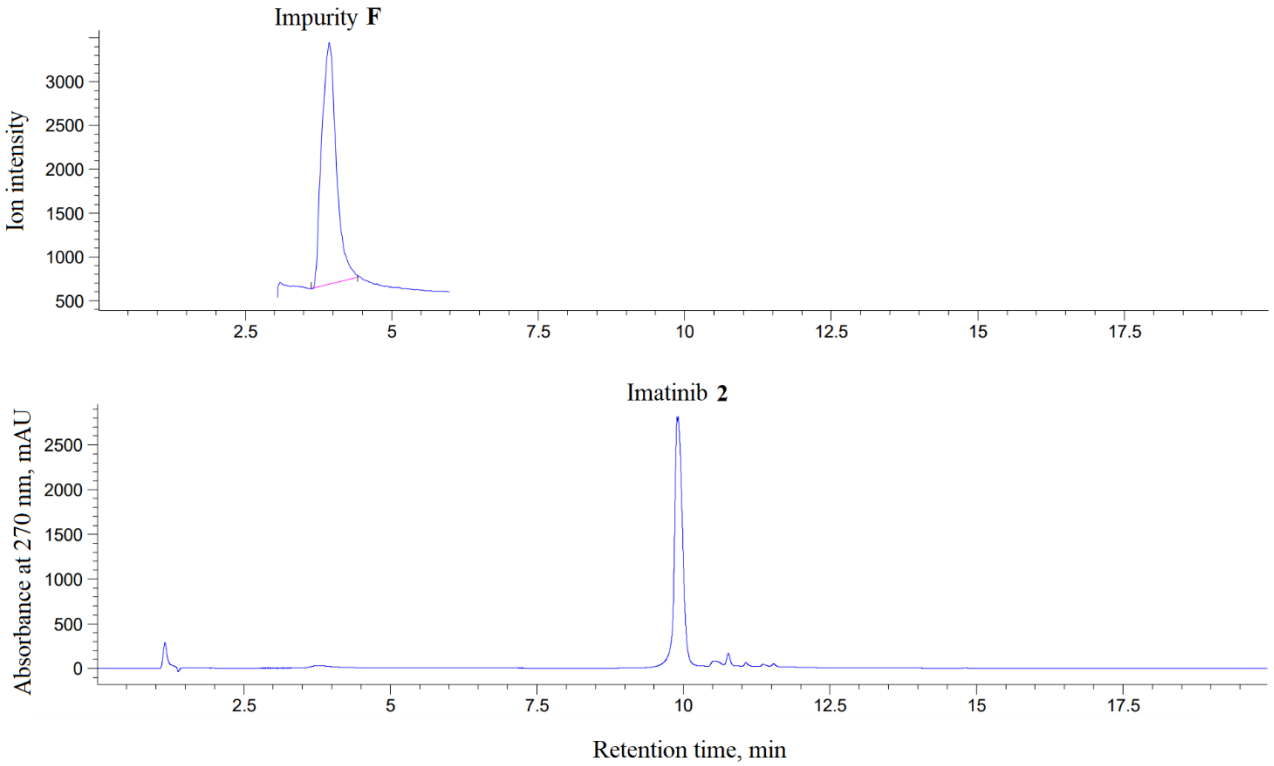


Figure S13. Upper: HPLC monitored ion count chromatogram of impurity **F**, lower: HPLC-UV chromatogram of Imatinib **2** at 270 nm.

X = 86±3 ppm

7. Green Chemistry metrics

Green chemistry metrics analysis have been performed for the developed mechanochemical procedure and six previously published protocols,[14–19] including three patents and three research articles (Table S6). The described protocols start from 4-(chloromethyl)benzoic acid **S3** (Table S6, entry 1), or 4-(chloromethyl)benzoyl chloride **15** (Table S6, entries 2, 5 and 6), or 4-(hydroxylmethyl)benzoic acid **1** (Table S6, entries 3, 4 and 7). The metrics were evaluated for the total process (2 or 3 steps).

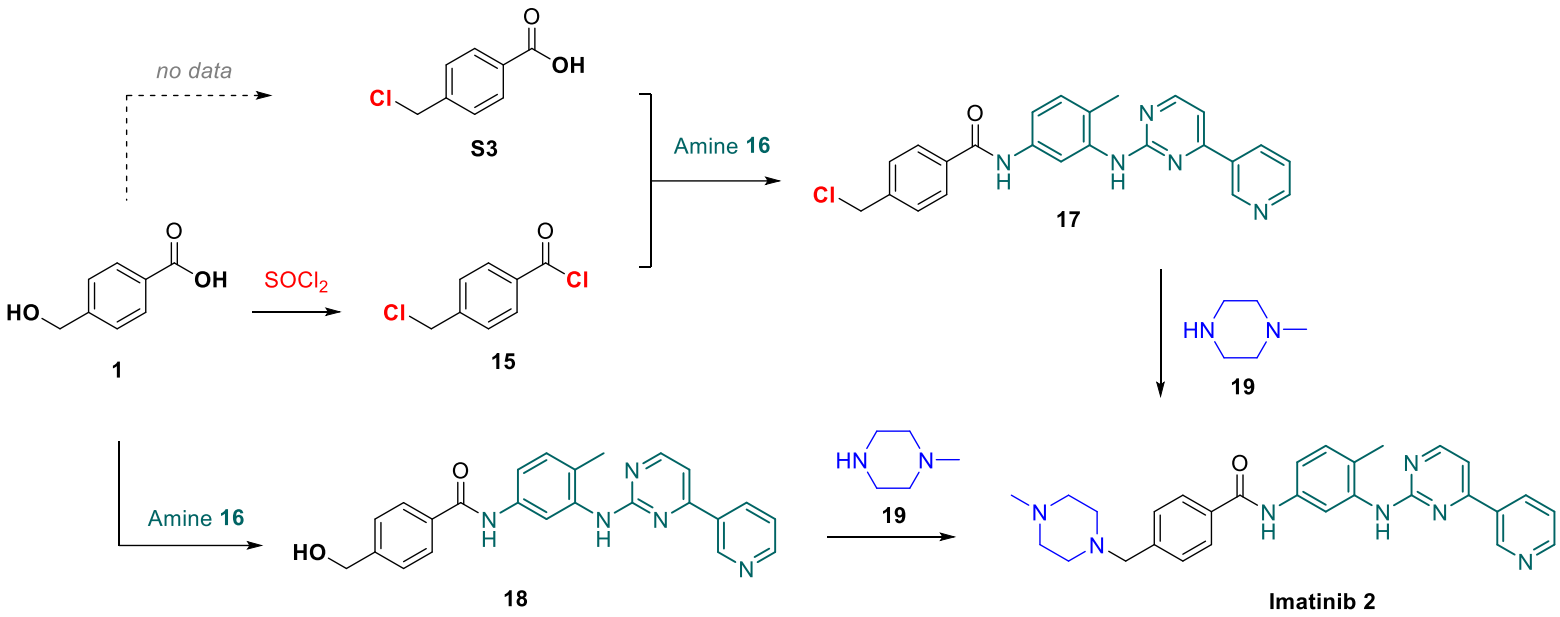


Table S6. Comparison of green metrics for mechanochemical and solution-based key-step synthesis of Imatinib **2**.

Entry	Manufacturer or Publication	St. material	№ of constructive/total steps	Mass of product	Total yield	AE	RME	Total PMI	PMI r-n	PMI r-n solvents	PMI work-up solvents	Solvents	Hazards			
													Thermal	Reagent	Products	Genotoxic intermediates
1	**ACTAVIS GROUP PTC EHF**[14]	**S3**	2/2	240g	78	58.3	9.5	131.9	20.1	9.6	110.5	1,4-dioxane, DMF, THF, Acetone, EtOAc, H_2O	65-70°C	1,4-dioxane (H350), DMF (H360D)	SO_2, HCl	**16, 17**
2	**Y. Heo et al.**[15]	**15**	2/2	0.51 g	84	68.8	38.4	>36.8	36.8	34.1		DMF, THF, H_2O	90°C	DMF (H360D)		**16, 17**
3	**Liu et al. 2008**[16]	**1**	2/3	0.45 g	85	50.9	3.8	563.5	43.5	17	520	CH_2Cl_2, THF, H_2O	140°C		SO_2, HCl	**16, 17**
4	**NATCO Pharma LTD**[17]	**1**	2/3	9.8 kg	43	50.9	13.2	192.2	46.6	39.0	144.6	DMF, $CHCl_3$, Toluene, EtOAc, H_2O	60°C	DMF (H360D), $CHCl_3$ H372)	SO_2, HCl	**16, 17**
5	**Z. Szakács et al.**[18]	**15**	2/2	1.25 g	41	74.1	17.0	>364.8	158.4	152.5	206.4	DMF, ACN, EtOH, H_2O	80°C	DMF (H360D)		**16, 17**
6	**W. Szczepek et al.** [19]	**15**	2/2	60.6 g	95	74.1	44.0	42.6	12.1	9.2	30.4	THF, H_2O	140°C			**16, 17**
7	**This work**	**1**	2/2	0.66 g	86[a]	39.1	17.0	221.0	8.9	3.0	212.1	EtOAc, DMI, H_2O	r.t.	EDC (H410)	TMU (H360)	**16, -**

[a]Yield is adjusted considering HPLC purity (95%) of obtained product.

Among the described protocols,[14–19] the shortest routes for which the complete data were available for calculations, was an early-stage development described by Liu et al.[16] and an example of kilo-scale preparation patented by NATCO Pharma LTD.[17] Activation of hydroxy acid **1** by its conversion into the corresponding chloride by the reaction with $SOCl_2$ was used in both approaches as an additional non-constructive step.

The mass-based metrics have been calculated considering all steps of the respective preparation route combined. In terms of total yield (86%), the mechanochemical approach delivered comparable or superior results as the benchmark solution-state approaches. Atom economy (AE), which reflects the theoretical efficiency of reactant utilization, is lower in the mechanochemical route (AE = 39.1) due to the higher molecular weight of the reagents involved. However, reaction mass efficiency (RME), which represents the actual maximum efficiency of reactant utilization,[20] is noticeably better (RME = 17.0) compared to the solution-based protocols, in which larger excesses of chemicals was used. Finally, total process mass intensity (total PMI), which reflects the amount of waste generated per unit of product, is about 2.5 times lower than in a similar early-stage development solution route (PMI = 563.5 vs 221.0) and is comparable with PMI of a kilo-scale preparation (PMI = 192.2). It is important to note that the main contributor to PMI in the case of mechanochemical synthesis was work-up solvent (water, PMI = 212.1) rather than chemicals (PMI = 8.9) and reactions solvents (PMI = 3.0). In terms of two former, the mechanochemical route greatly surpasses the benchmarking solution approaches, in which excess of reactants and use of bulk solvents increase the PMI significantly. Furthermore, the mechanochemical protocol relies on the use of green and sustainable solvents for work-up (water) and as LAG additives (ethyl acetate, dimethyl isosorbide). This contrasts a larger portfolio of solvents which was involved in the solution-based preparations and includes several toxic compounds (DMF, CH_2Cl_2, chloroform). It worth also noting a room temperature operation as an additional benefit of mechanochemistry, in contrast to the solution methods which rely on thermal activation and involve heating up to 140 °C. The streamlined isolation protocol of **18** and **2** by filtration and washing with water brings an additional advantage. Although the solvent-related and thermal hazards have been greatly attenuated in our approach, it still relies on a use of stoichiometric amide coupling reagents (EDC and TFFH) which themselves, or their reaction products (e.g., tetramethyl urea, TMU), could pose environmental or health hazards,[21] thus representing a disadvantage. On the other hand, TFFH is an air-stable and non-hygroscopic solid that offer a better safety profile[21,22] than other amide couplers.

Exclusion of the genotoxic intermediate **17** was another important advantage which is especially relevant to pharma synthesis. Since intermediate **18** with unknown properties was involved instead, additional *in silico* assessment was performed for the designed route to evaluate the safety profile of all known chemical entities involved. Knowledge-based and statistical systems were used to predict potential mutagenicity following the recommendations of the ICH M7 (R1) (2018) guideline. The knowledge-based system Derek Nexus and the statistical system Sarah Nexus were used to predict mutagenicity. Derek Nexus (Lhasa Ltd. Leeds, UK), is a rule-based expert system, which has been designed on the basis of open accessible and proprietary data. It generates predictions based on the knowledge about the relationship of substructures and biological activity in a given molecule. Sarah Nexus (Lhasa Ltd. Leeds, UK) is a statistical-based system. Structures submitted for processing were fragmented and these fragments are reviewed for activity vs inactivity. The model then arranges those 'interesting' fragments into a network of hypotheses (or nodes) and relevant hypotheses are used to inform an overall prediction of toxicity. Sarah Nexus predicts activity or inactivity in the Ames test and provides information on coverage of a query compound. As a result, intermediate **18** displayed no structural concern for mutagenicity.

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
1	Amine	173.30	277.00	0.63					1,4 - dioxane	590.00	1.03	607.70	K_2CO_3	173.00	Water	19561.00	1.00	19561.00
1	4-chloromethyl benzoic acid	118.00	170.59	0.69					DMF	251.00	0.94	236.94	AcOH	129.00	Acetone	2673.00	0.78	2095.63
1	Thionyl chloride	280.80	118.97	2.36					THF	1651.00	0.89	1467.74			EtOAc	3875.00	0.90	3495.25
2	N-methylpiperazine	1580.00	100.17	15.77								0.00			aq. NH_3	1500.00	0.91	1365.00
1	Pyridine	370.60	79.00	4.69								0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	2522.70	845.89			0.00		0.00				2312.38		302.00				26516.88

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

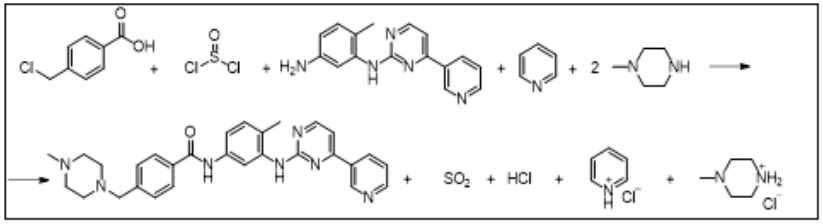
$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

		Flag	
Yield	77.8	77.8	
Conversion	100.0	100.0	
Selectivity	77.8	77.8	
AE	58.3		
RME	9.5	OE	16.3
PMI total	131.9		
PMI Reaction	20.1		
reactants, reagents,	10.5		
PMI reaction solvents	9.6		
PMI Workup	111.7		
PMI Workup chemical	1.3		
PMI workup solvents	110.5		

	Mass	MW	Mol
Product	240.00	493.00	0.49
	mass		
Unreacted limiting reactant	0.00		

Stoichiometric equation



Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	+
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	+
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	+
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

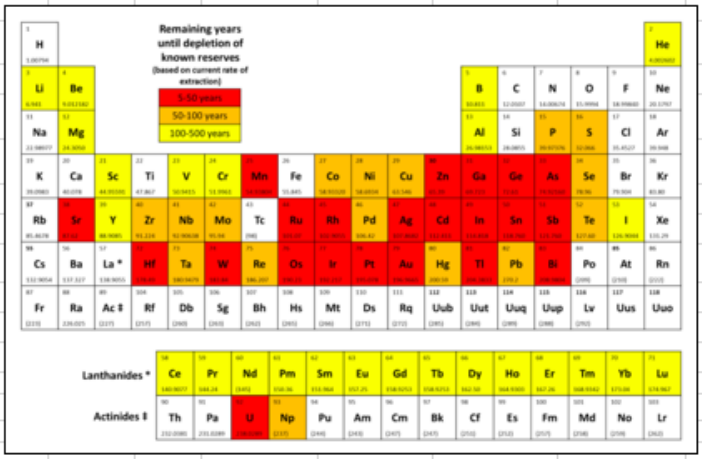
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	+

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	+
+500 years	Green Flag	



Energy (First Pass)		Tick
Reaction run between 0 to 70°C	Green Flag	+
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	+
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	+

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	+
solvent exchange, quenching into aqueous solvent	Amber Flag	+
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			$SOCl_2$	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		DMF, 1,2 - dioxane	THF	
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		st substances of very high conce
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	DMF, 1,2 - dioxane

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
1	Amine	0.34	277.00	0.00123					THF	14.00	0.89	12.45			water			0.00
1	Chloromethyl-benzoyl chloride	0.28	188.00	0.00149					DMF	5.00	0.99	4.97						0.00
1	N-methylpiperazine	0.23	100.17	0.00230								0.00						0.00
1	Triethylamine	0.25	101.19	0.00244								0.00						0.00
0.5	$CaCO_3$	0.23	100.09	0.00230								0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	1.33	716.41			0.00		0.00				17.42		0.00				0.00

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

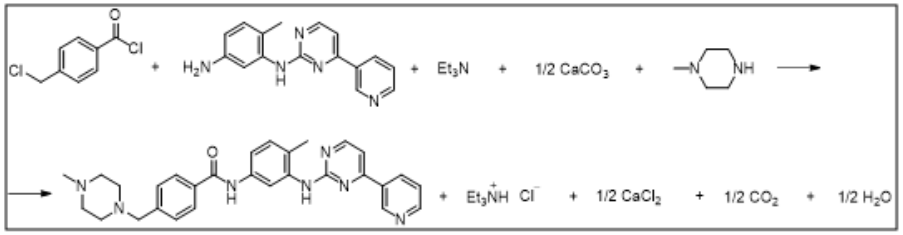
$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

		Flag
Yield	83.8	83.8
Conversion	100.0	100.0
Selectivity	83.8	83.8
AE	68.8	
RME	38.4	OE 55.8
PMI total	36.8	
PMI Reaction	36.8	
reagents, catlyst	2.6	
PMI reaction solvents	34.1	
PMI Workup	0.0	
PMI Workup chemical	0.0	
PMI workup solvents	0.0	

	Mass	MW	Mol
Product	0.51	493.00	0.00
	mass		
Unreacted limiting reactant	0.00		

Stoichiometric equation



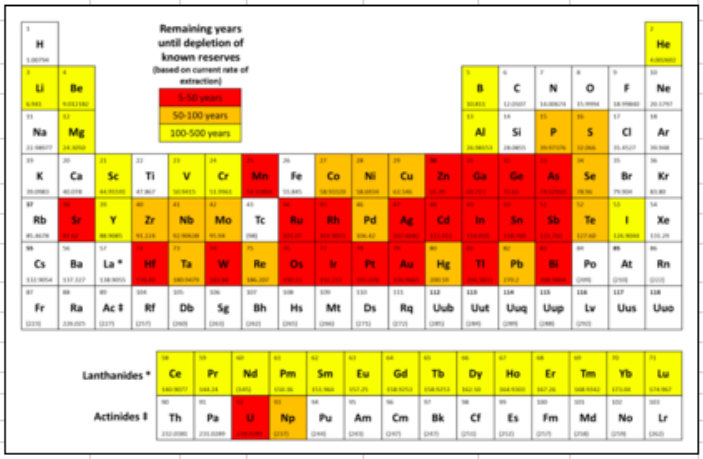
Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	+
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	+
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, **or** reaction takes place without	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	+

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	+



Energy (First Pass)		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	+
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	+
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	+

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	+
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		DMF	THF	
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		t substances of very high conce
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	DMF

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
1	Amine	0.30	277.00	0.00108					CH_2Cl_2	0.71	1.33	0.94			Water	234.00	1.00	234.00
1	4-hydroxymethyl benzoic acid	0.22	152.00	0.00141					THF	7.55	0.89	6.71						0.00
2	Thionyl chloride	1.16	118.97	0.00975								0.00						0.00
2	N-methylpiperazine	10.00	100.17	0.09984								0.00						0.00
1	Triethylamine	0.23	101.19	0.00223								0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	11.90	968.46			0.00		0.00				7.66		0.00				234.00

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

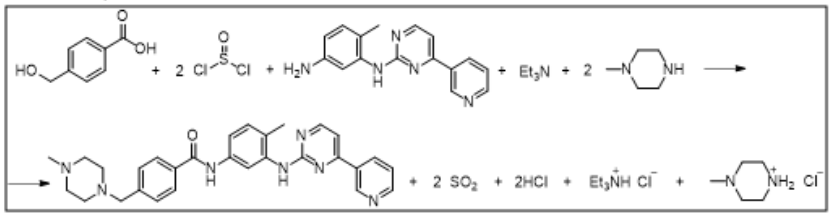
$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

		Flag
Yield	84.8	84.8
Conversion	100.0	100.0
Selectivity	84.8	84.8
AE	50.9	
RME	3.8	OE 7.4
PMI total	563.5	
PMI Reaction	43.5	
reagents, catlyst	26.4	
PMI reaction solvents	17.0	
PMI Workup	520.0	
PMI Workup chemical	0.0	
PMI workup solvents	520.0	

	Mass	MW	Mol
Product	0.45	493.00	0.00
	mass		
Unreacted limiting reactant	0.00		

Stoichiometric equation



Solvents (First Pass)

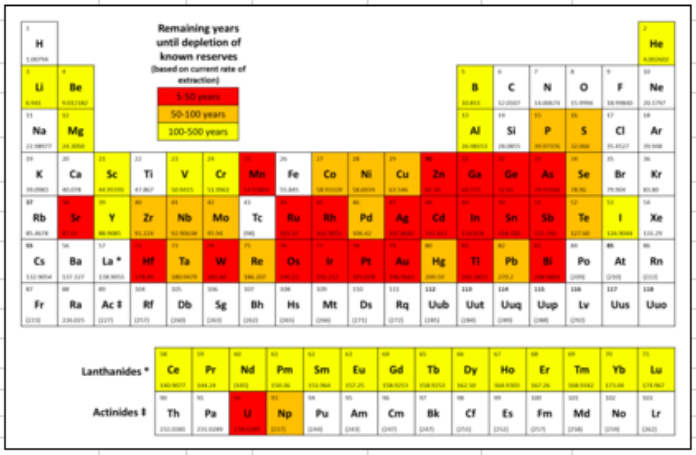
		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	+
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	+
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, **or** reaction takes place without	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	+

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	+
+500 years	Green Flag	



Energy (First Pass)		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	+
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	+
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	+

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	+
solvent exchange, quenching into aqueous solvent	Amber Flag	+
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			$SOCl_2$	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		DMF	THF	
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		st substances of very high conce
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	DMF

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
1	Amine	12800.00	277.00	46.21					$CHCl_3$	230850.00	1.49	343966.50	NaOH	10000.00	Toluene	40430.00	0.87	35052.81
1	4-hydroxymethyl benzoic acid	8410.00	152.00	55.33					DMF	40810.00	0.94	38524.64			Water	795000.00	1.00	795000.00
2	Thionyl chloride	24300.00	118.97	204.25								0.00			EtOAc	155000.00	0.90	139810.00
2	N-methylpiperazine	19700.00	100.17	196.68								0.00			$CHCl_3$	300000.00	1.49	447000.00
1	Triethylamine	9300.00	101.19	91.91								0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	74510.00	968.46			0.00		0.00				382491.14		10000.00				1416862.81

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

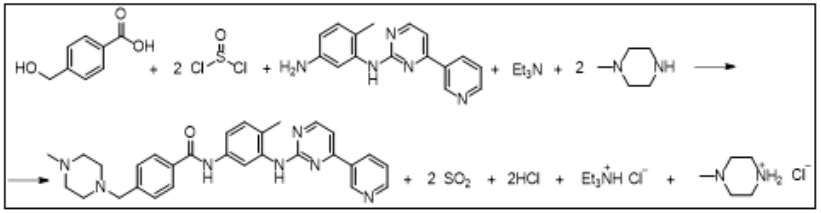
$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

		Flag
Yield	43.0	43.0
Conversion	100.0	100.0
Selectivity	43.0	43.0
AE	50.9	
RME	13.2	OE 25.8
PMI total	192.2	
PMI Reaction	46.6	
reactants, reagents,	7.6	
PMI reaction solvents	39.0	
PMI Workup	145.6	
PMI Workup chemical	1.0	
PMI workup solvents	144.6	

	Mass	MW	Mol
Product	9800.00	493.00	19.88
	mass		
Unreacted limiting reactant	0.00		

Stoichiometric equation



Solvents (First Pass)

		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	+
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	+

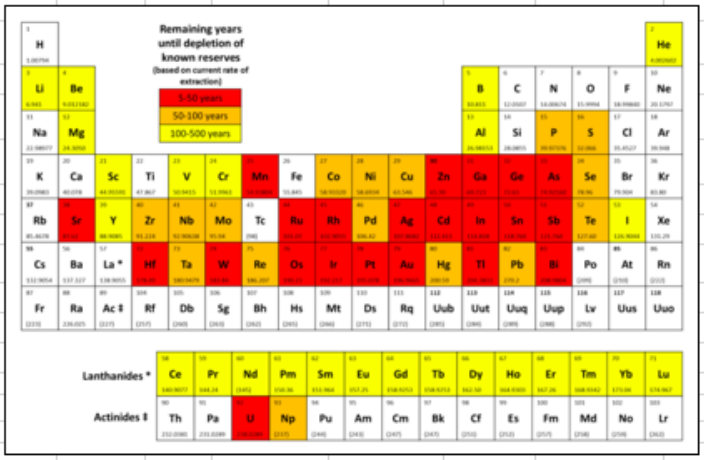
Catalyst/enzyme (First Pass)

		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	+

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	+
+500 years	Green Flag	



Energy (First Pass)		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	+
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	+
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	+

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	+
solvent exchange, quenching into aqueous solvent	Amber Flag	+
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			$SOCl_2$, $CHCl_3$	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		DMF, $CHCl_3$	$CHCl_3$, toluene	
Environmental implications	H400, H410, H411, H420	H401, H412			Toluene	

Use of chemicals of environmental concern		st substances of very high conce
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	DMF, $CHCl_3$

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
1	Amine	1.70	277.00	0.00615					DMF	77.40	0.94	72.76	$NaHCO_3$		water	258.00	1.00	258.00
1	Chloromethyl-benzoyl chloride	1.75	188.00	0.00931					Acetonitrile	150.00	0.79	117.90			EtOH			0.00
2	N-methylpiperazine	3.88	100.17	0.03876								0.00			Acetonitrile			0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	7.34	665.34			0.00		0.00				190.66		0.00				258.00

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

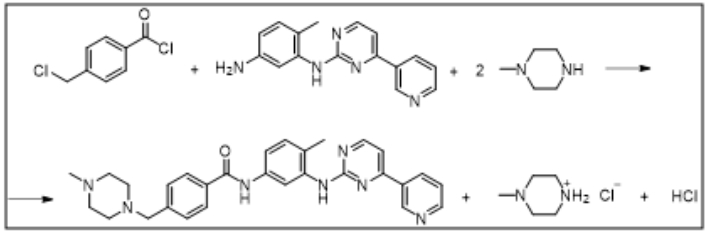
$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

		Flag	
Yield	41.2		41.2
Conversion	100.0		100.0
Selectivity	41.2		41.2
AE	74.1		
RME	17.0	OE	23.0
PMI total	364.8		
PMI Reaction	158.4		
reagents, catlyst	5.9		
PMI reaction solvents	152.5		
PMI Workup	206.4		
PMI Workup chemical	0.0		
PMI workup solvents	206.4		

	Mass	MW	Mol
Product	1.25	493.00	0.00
	mass		
Unreacted limiting reactant	0.00		

Stoichiometric equation



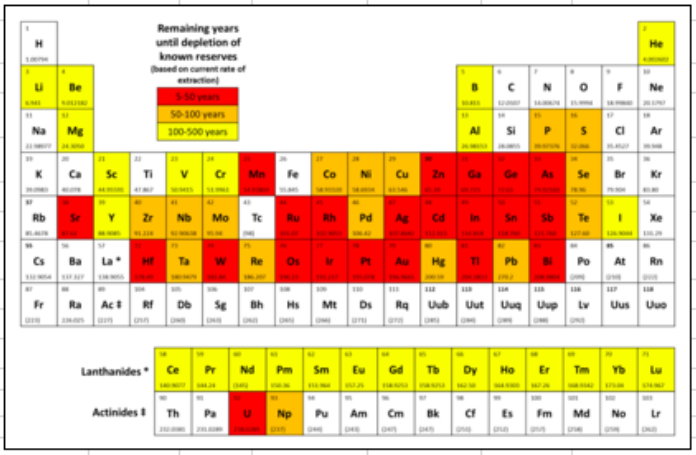
Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	+
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	+
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, **or** reaction takes place	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	+

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	+



Energy (First Pass)		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	+
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	+
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	+

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	+
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		DMF		
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		st substances of very high conce
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	DMF

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
1	Amine	35.84	277.00	0.12939			K_2CO_3	38.52	THF	628.10	0.89	558.38	NaOH	5.12	Water	1844.00	1.00	1844.00
1	Chloromethyl-benzoyl chloride	26.88	188.00	0.14296								0.00						0.00
2	N-methylpiperazine	74.95	100.17	0.74822								0.00						0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	137.67	665.34			0.00		38.52				558.38		5.12				1844.00

		Flag	
Yield	95.0	95.0	
Conversion	100.0	100.0	
Selectivity	95.0	95.0	
AE	74.1		
RME	44.0	OE	59.4
PMI total	42.6		
PMI Reaction	12.1		
reagents, catlyst	2.9		
PMI reaction solvents	9.2		
PMI Workup	30.5		
PMI Workup chemical	0.1		
PMI workup solvents	30.4		

	Mass	MW	Mol
Product	60.60	493.00	0.12
	mass		
Unreacted limiting reactant	0.00		

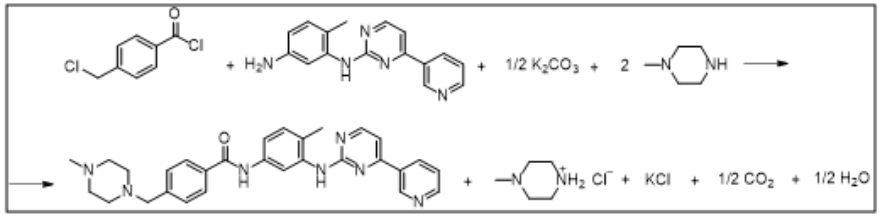
$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

Stoichiometric equation



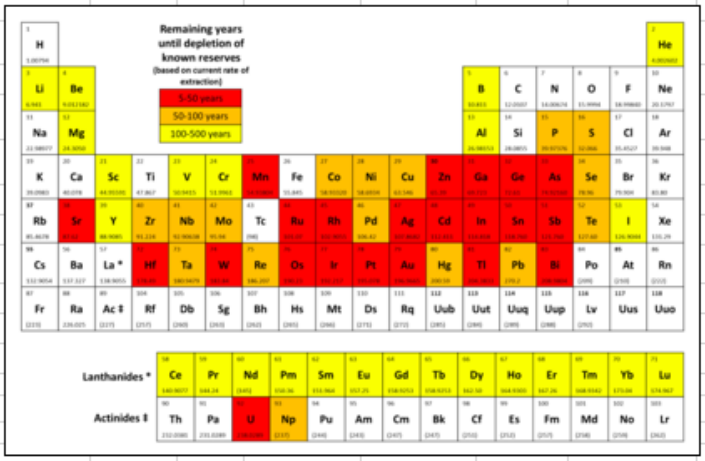
Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	+
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, **or** reaction takes place	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	+

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	+



Energy (First Pass)		Tick
Reaction run between 0 to 70°C	Green Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	+
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	+
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	+

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	+
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			THF	
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		st substances of very high conce
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

This work

Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
1	Amine	0.43	277.00	0.00156					EtOAc	0.51	0.90	0.46			Water	140.00	1.00	140.00
1	4-hydroxymethyl benzoic acid	0.25	152.00	0.00163					DMI	1.30	1.15	1.50						0.00
1	EDC HCl	0.33	191.70	0.00174								0.00						0.00
2	N-methylpiperazine	1.46	100.17	0.01460								0.00						0.00
1	TFFH	0.77	264.12	0.00292								0.00						0.00
1	K_2HPO_4	0.64	174.20	0.00365								0.00						0.00
												0.00						0.00
	Total	3.88	1259.35			0.00		0.00				1.96		0.00				140.00

		Flag	
Yield	86.0		86.0
Conversion	100.0		100.0
Selectivity	86.0		86.0
AE	39.1		
RME	17.0	OE	43.4
PMI total	221.0		
PMI Reaction	8.9		
reagents, catlyst	5.9		
PMI reaction solvents	3.0		
PMI Workup	212.1		
PMI Workup chemical	0.0		
PMI workup solvents	212.1		

	Mass	MW	Mol
Product	0.66	493.00	0.00
	mass		
Unreacted limiting reactant	0.00		

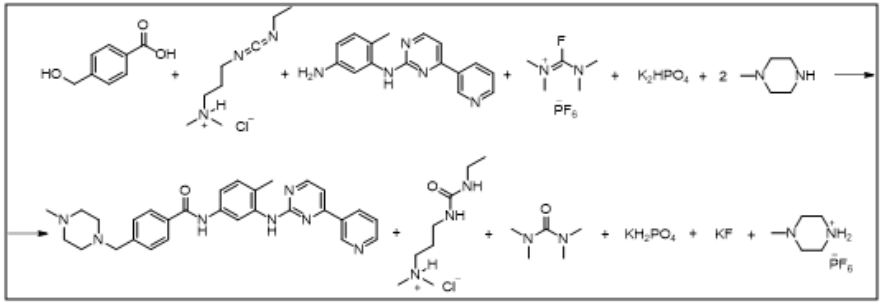
$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

Stoichiometric equation



Solvents (First Pass)

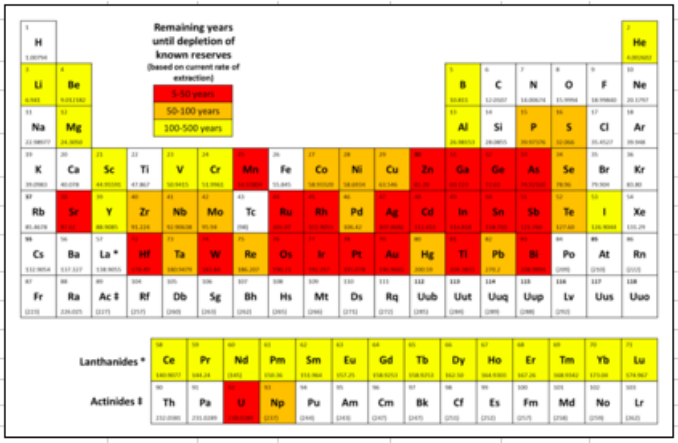
		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	+
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, **or** reaction takes place	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	+

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	+
+500 years	Green Flag	



Energy (First Pass)		Tick
Reaction run between 0 to 70°C	Green Flag	+
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	
Reaction run below -20 or above 140°C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5°C or more below the solvent boiling point	Green Flag	+

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	+

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (<	Green Flag	+
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		TMU		
Environmental implications	H400, H410, H411, H420	H401, H412		EDC HCl		

Use of chemicals of environmental concern		ist substances of very high concer
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	TMU, EDC HCl

8. References

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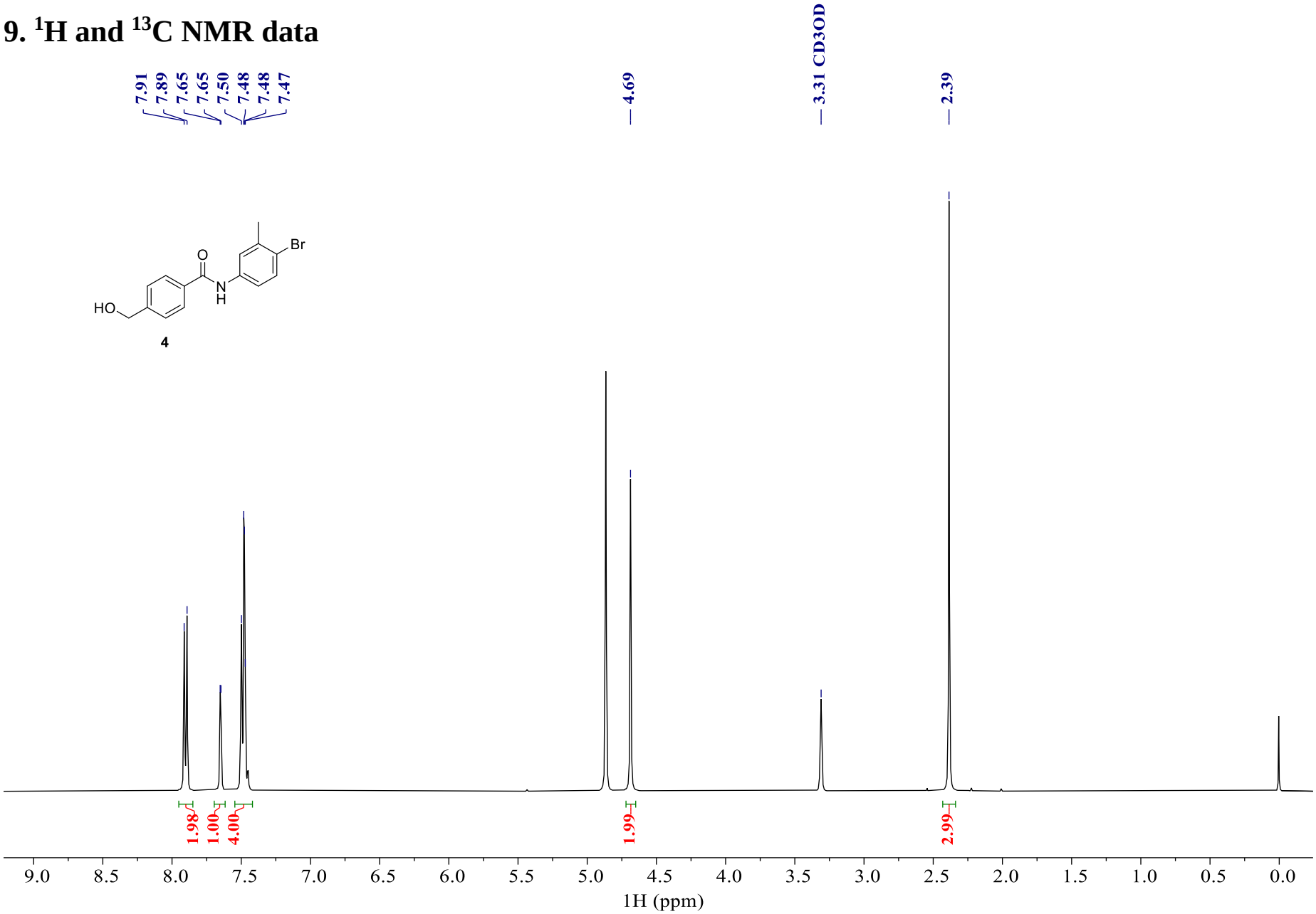
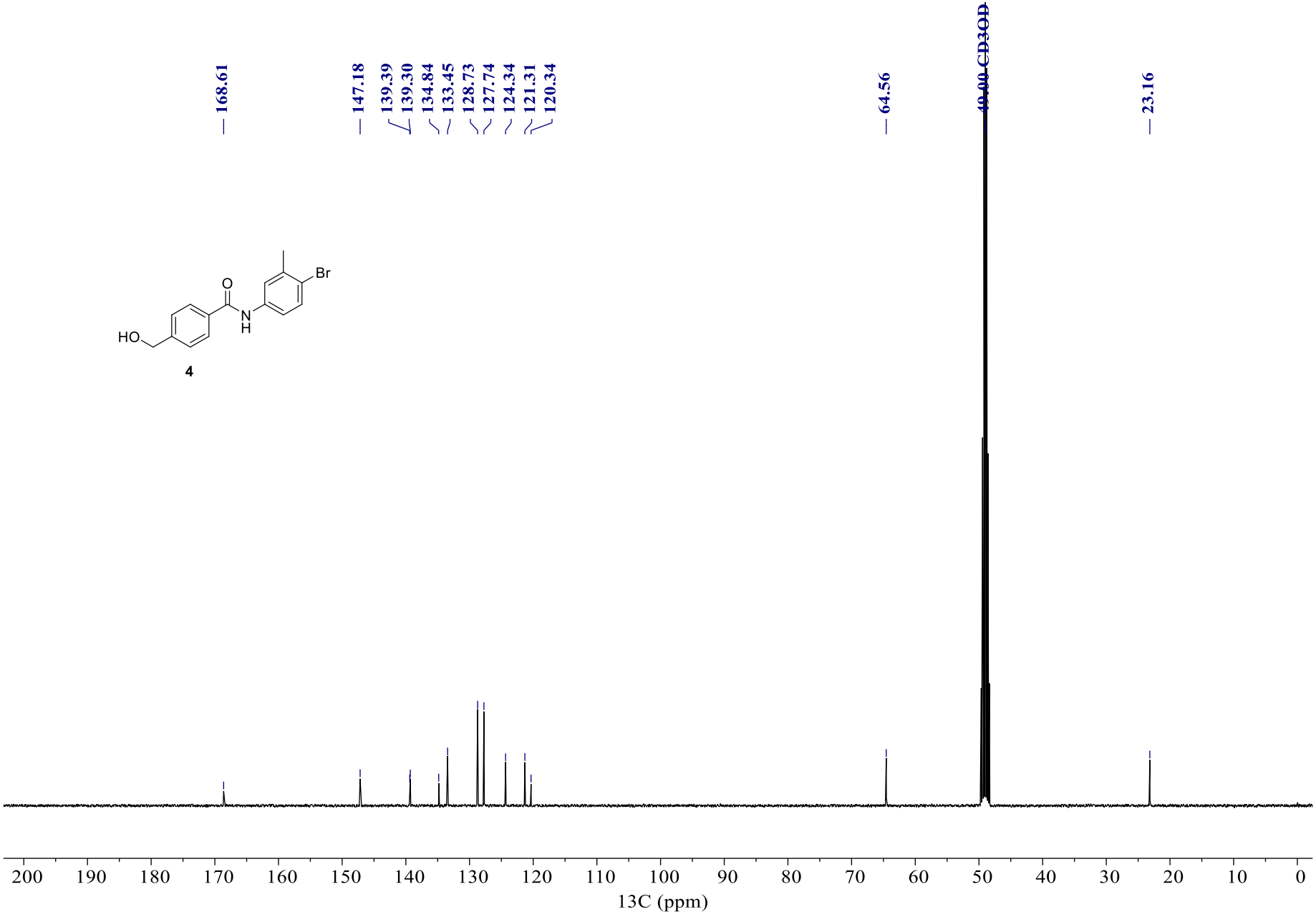
9. ^{1}H and ^{13}C NMR data

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121.31
120.34
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23.16
HO
O
N
H
Br
4
200
190
180
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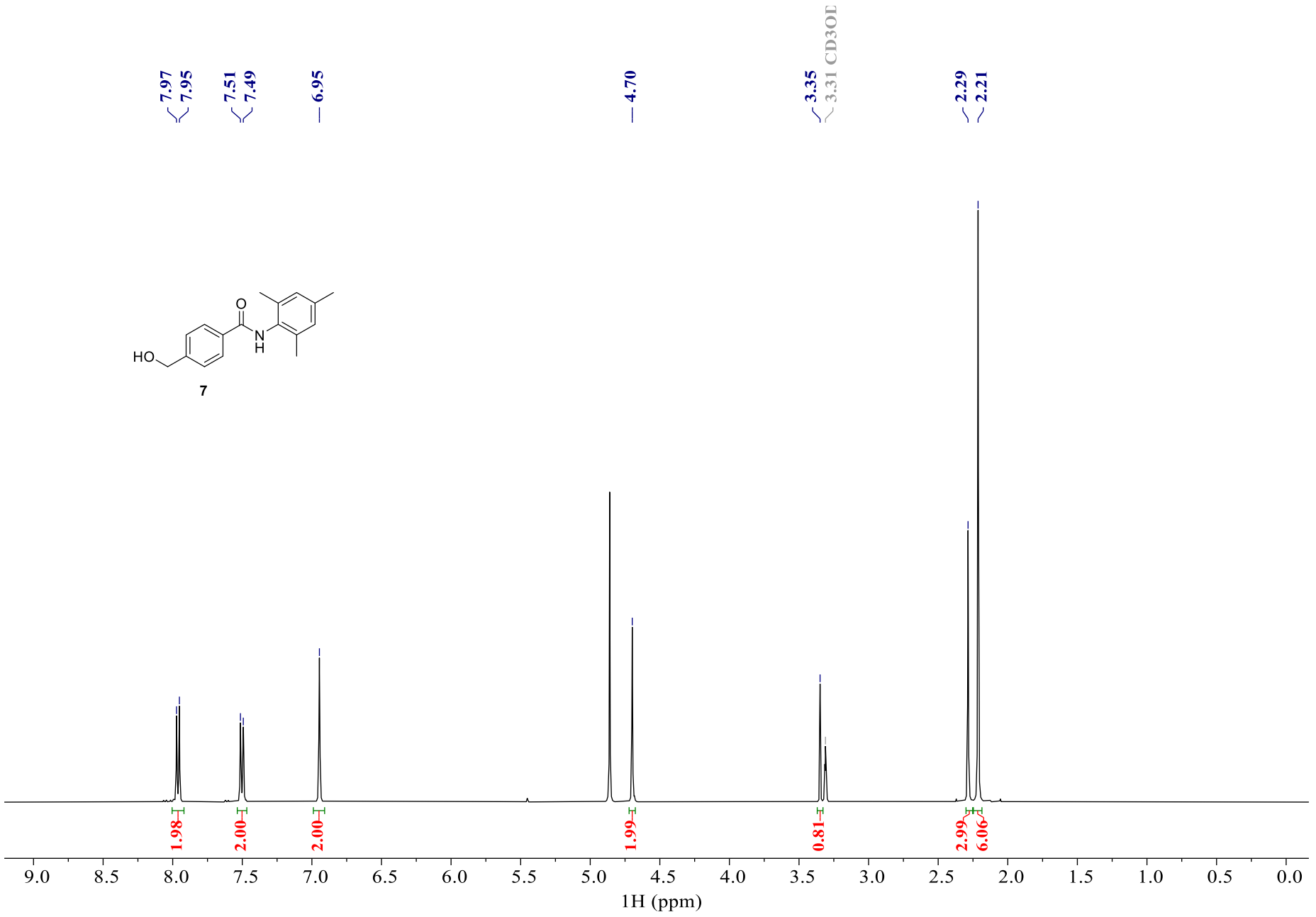
13C (ppm)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H
7
1.98
2.00
2.00
1.99
0.81
2.99
6.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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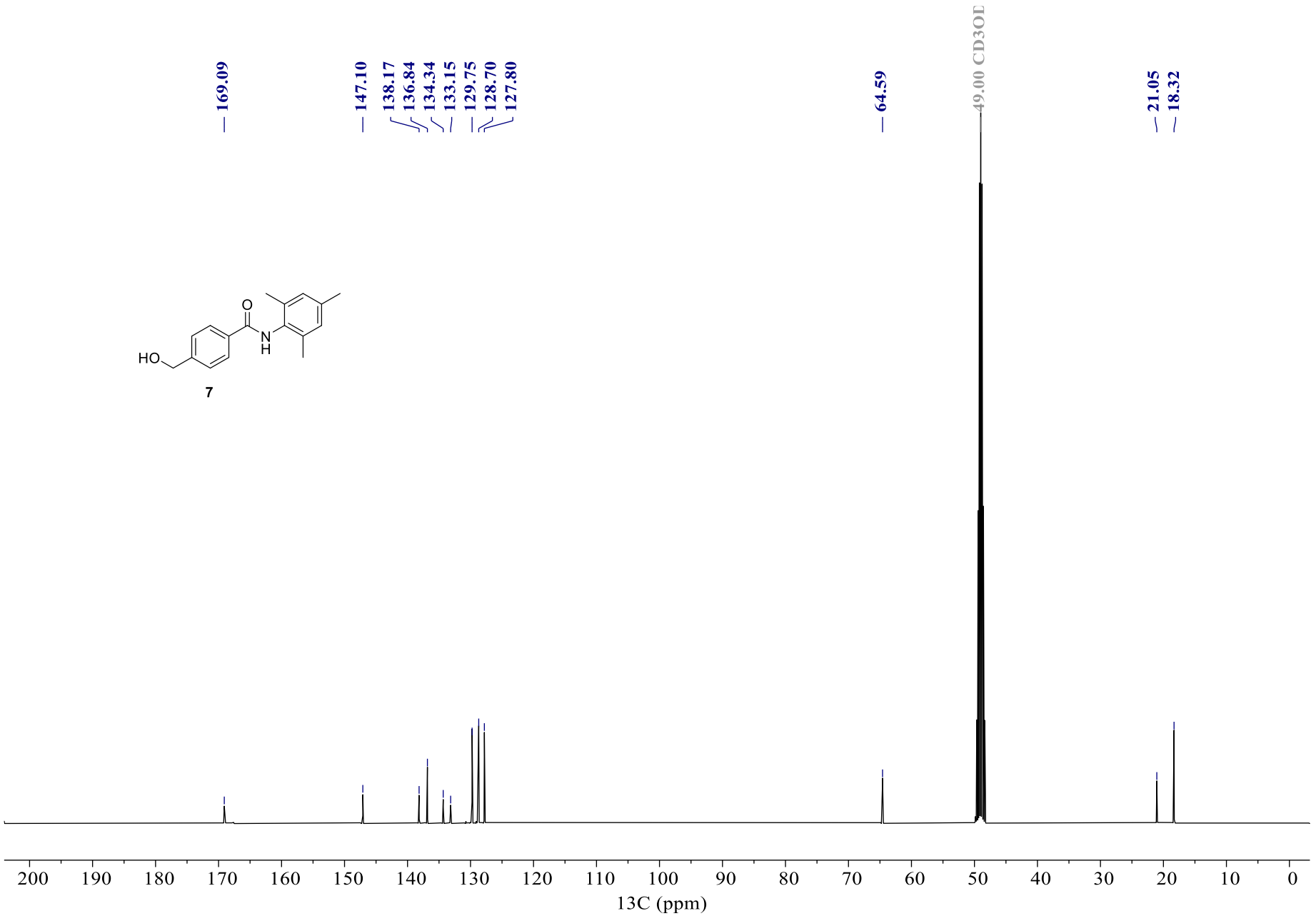
1H (ppm)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18.32
HO
O
N
H
7
200
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180
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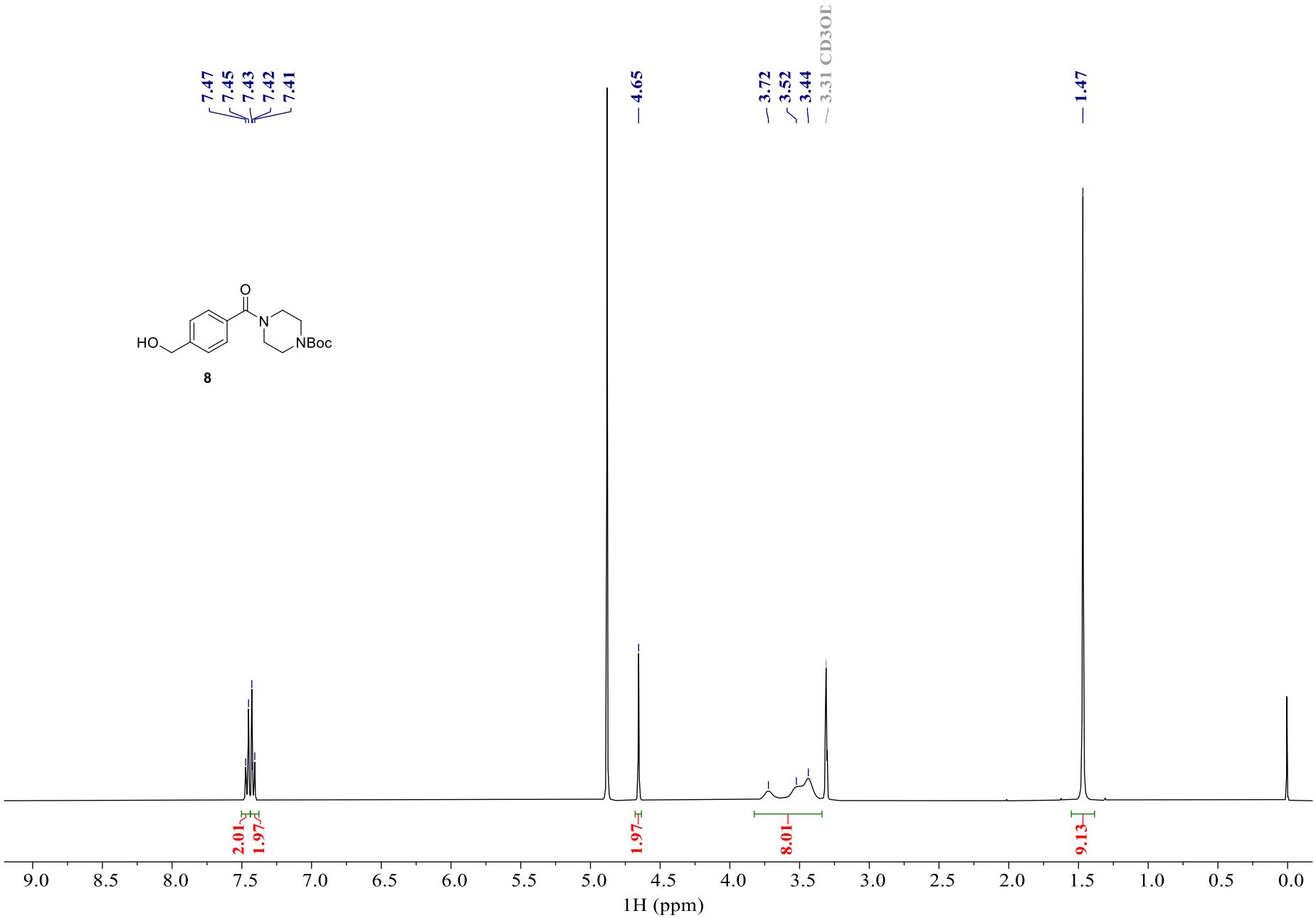
13C (ppm)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O
N
NBoc
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8.01
9.13
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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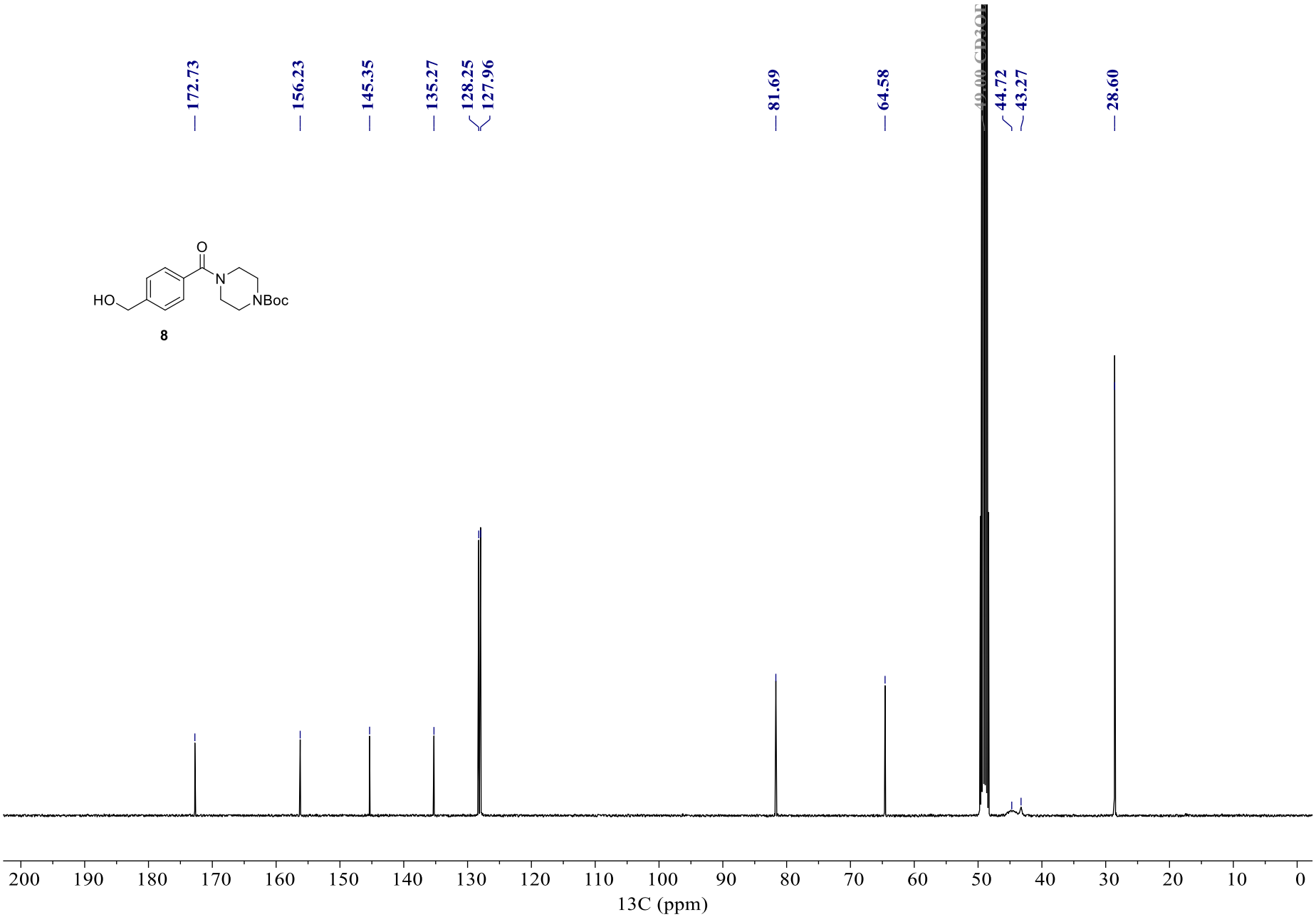
1H (ppm)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O
N
NBoc
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180
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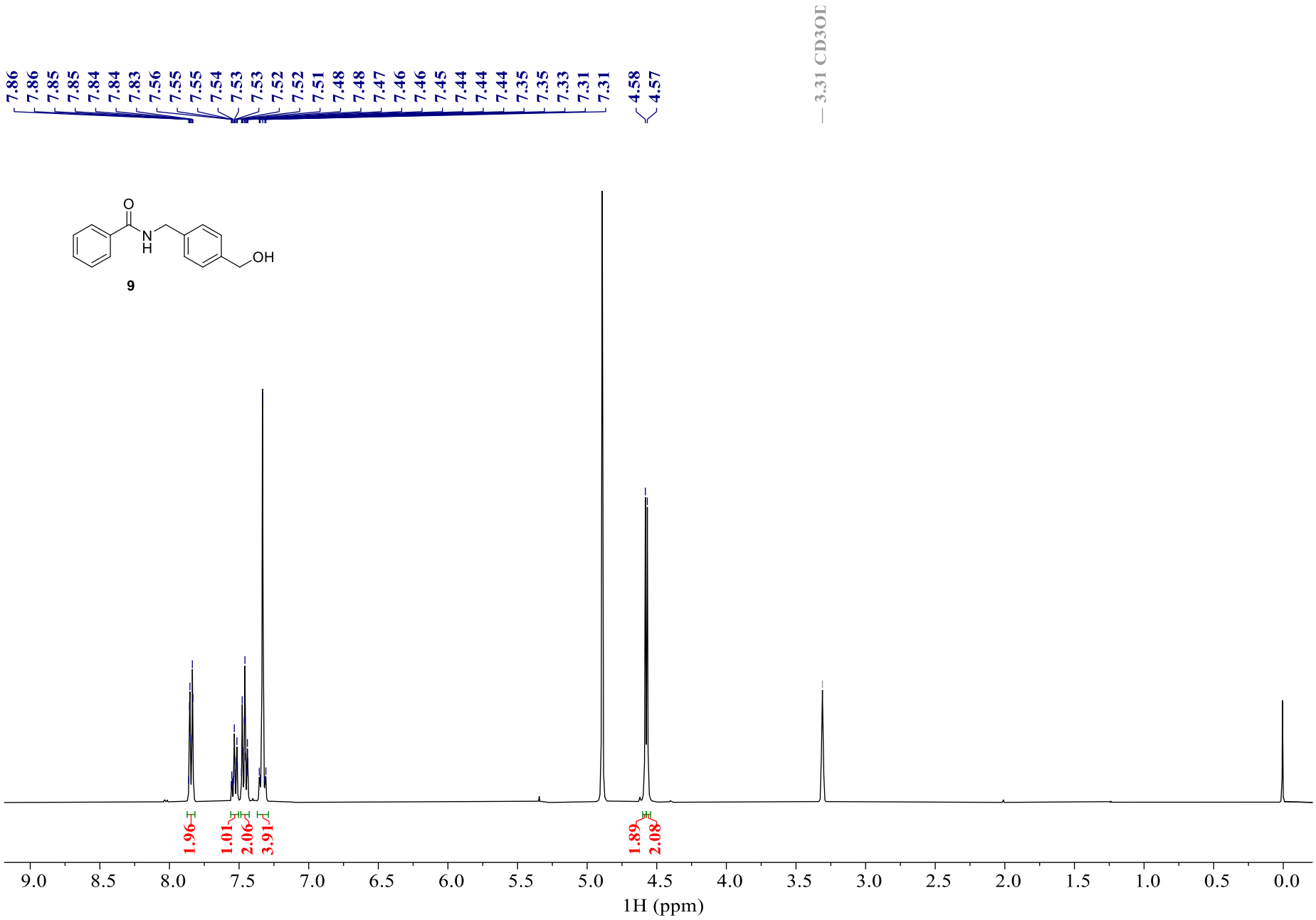
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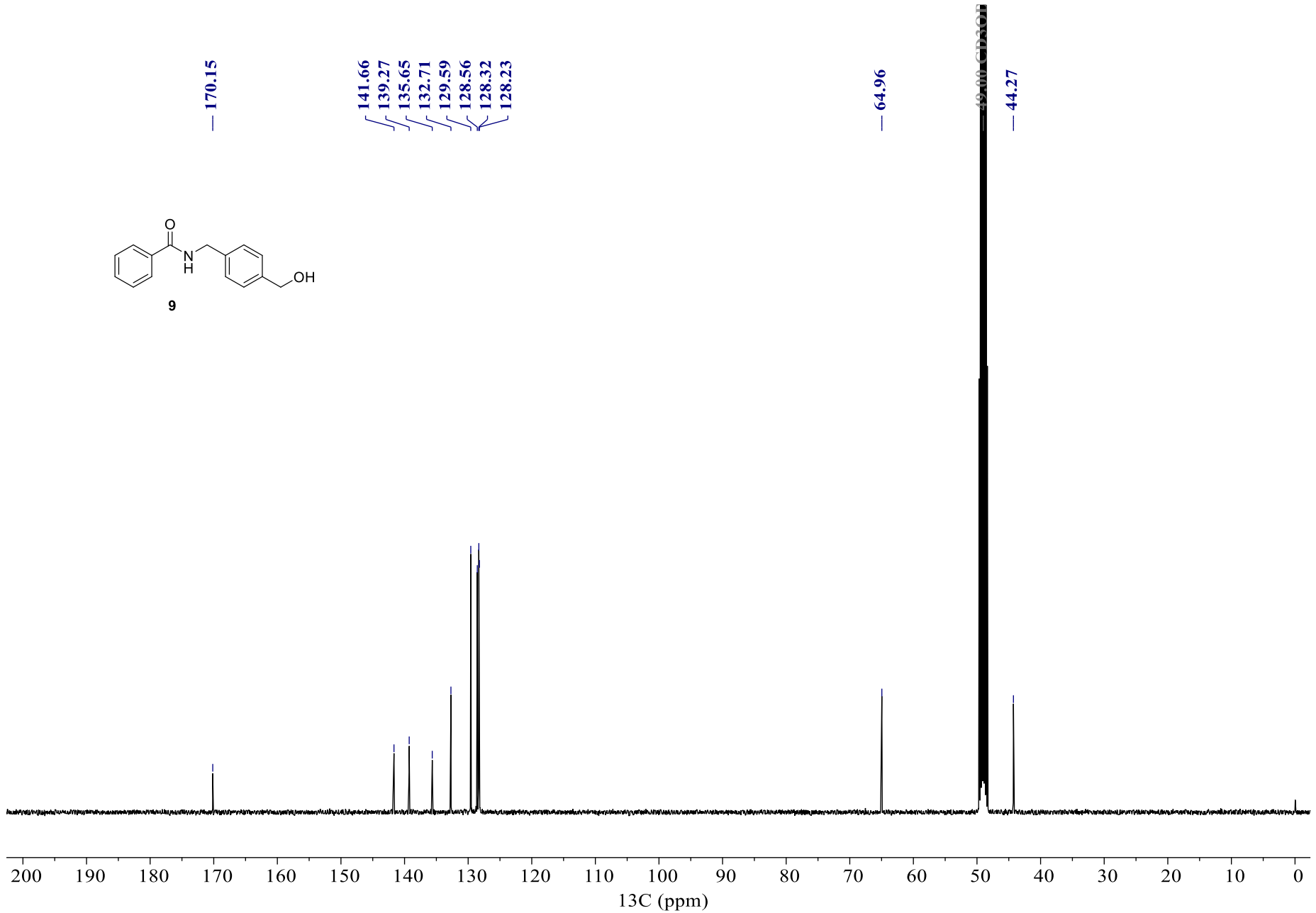
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H
OH
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10
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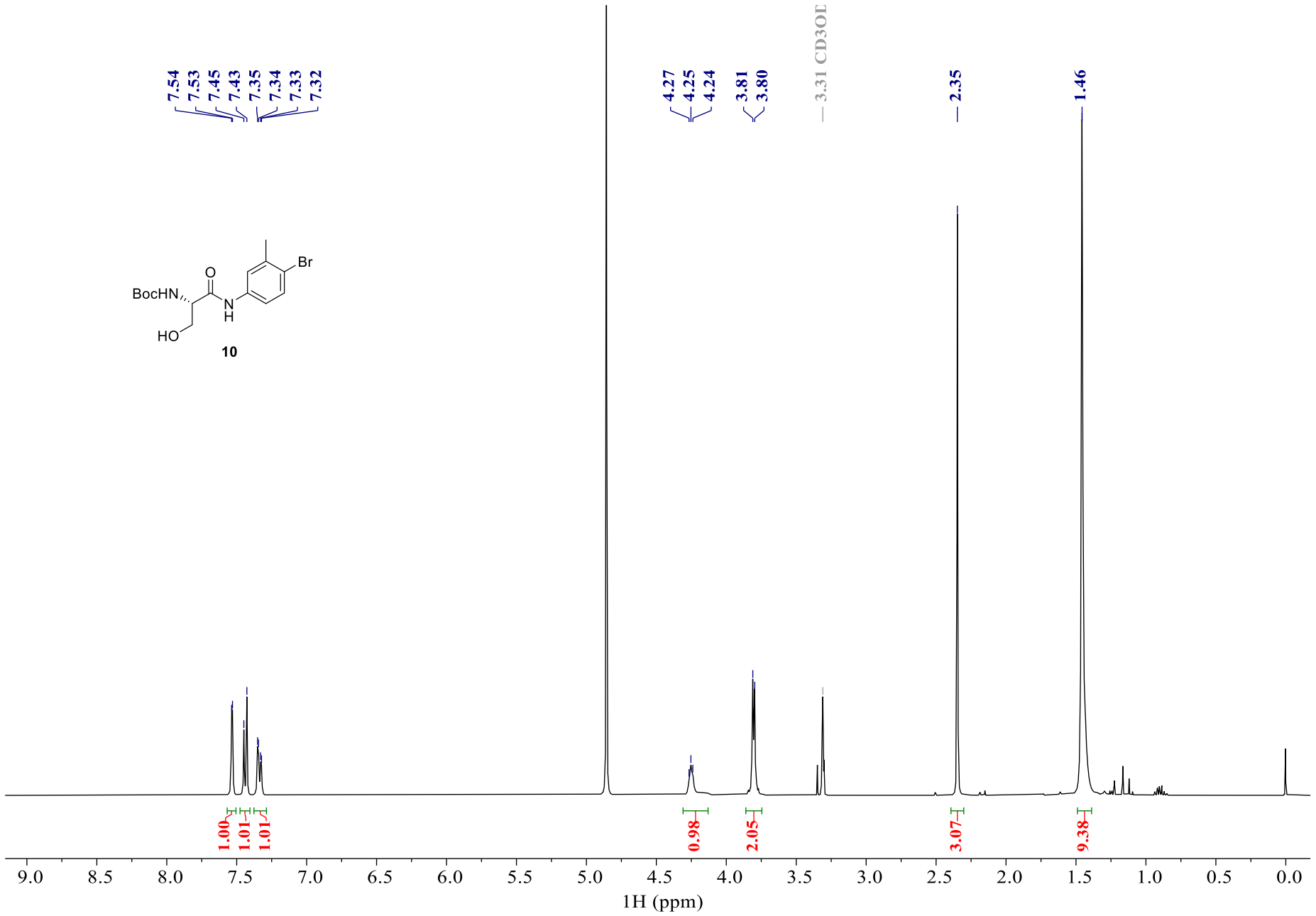
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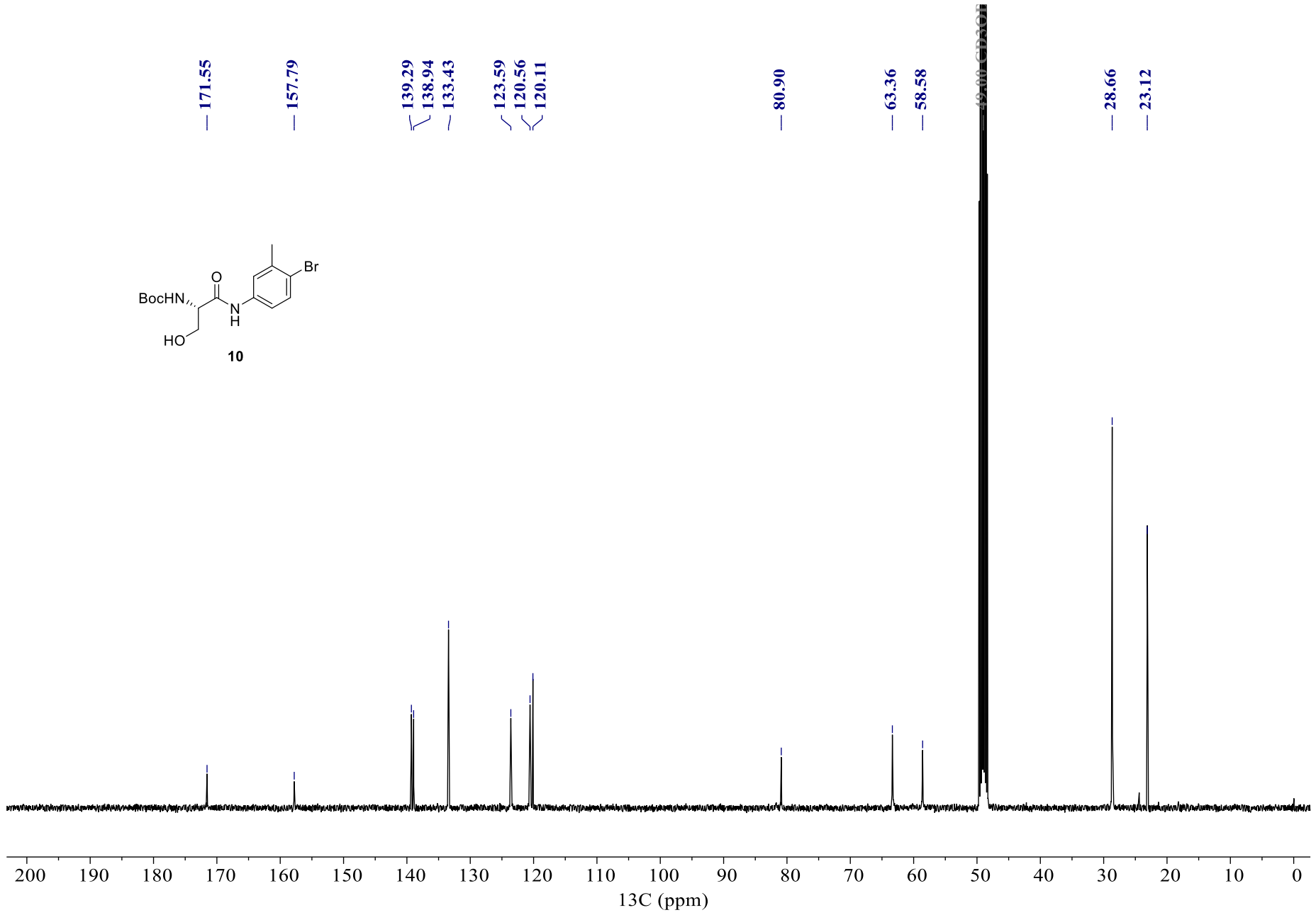
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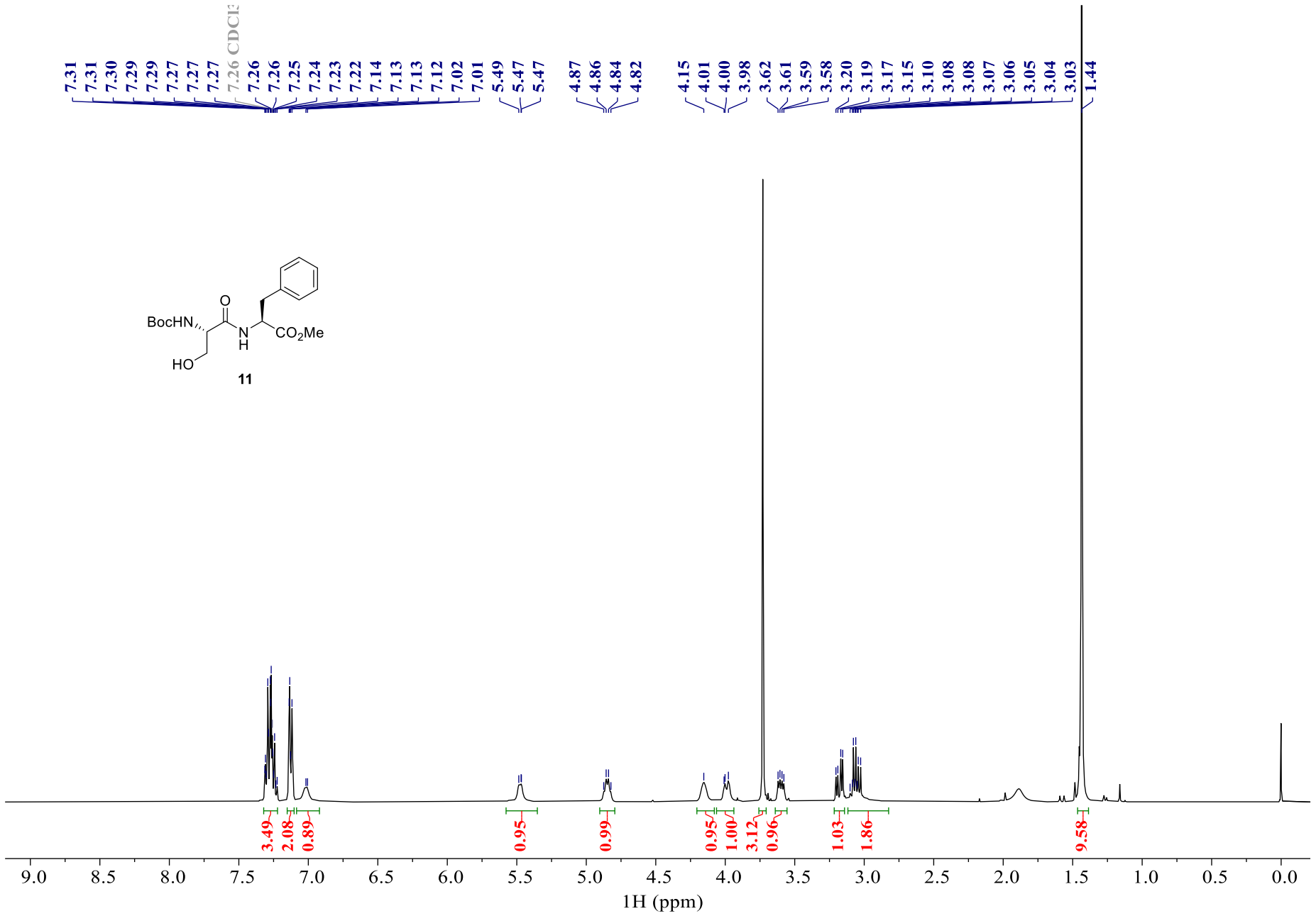
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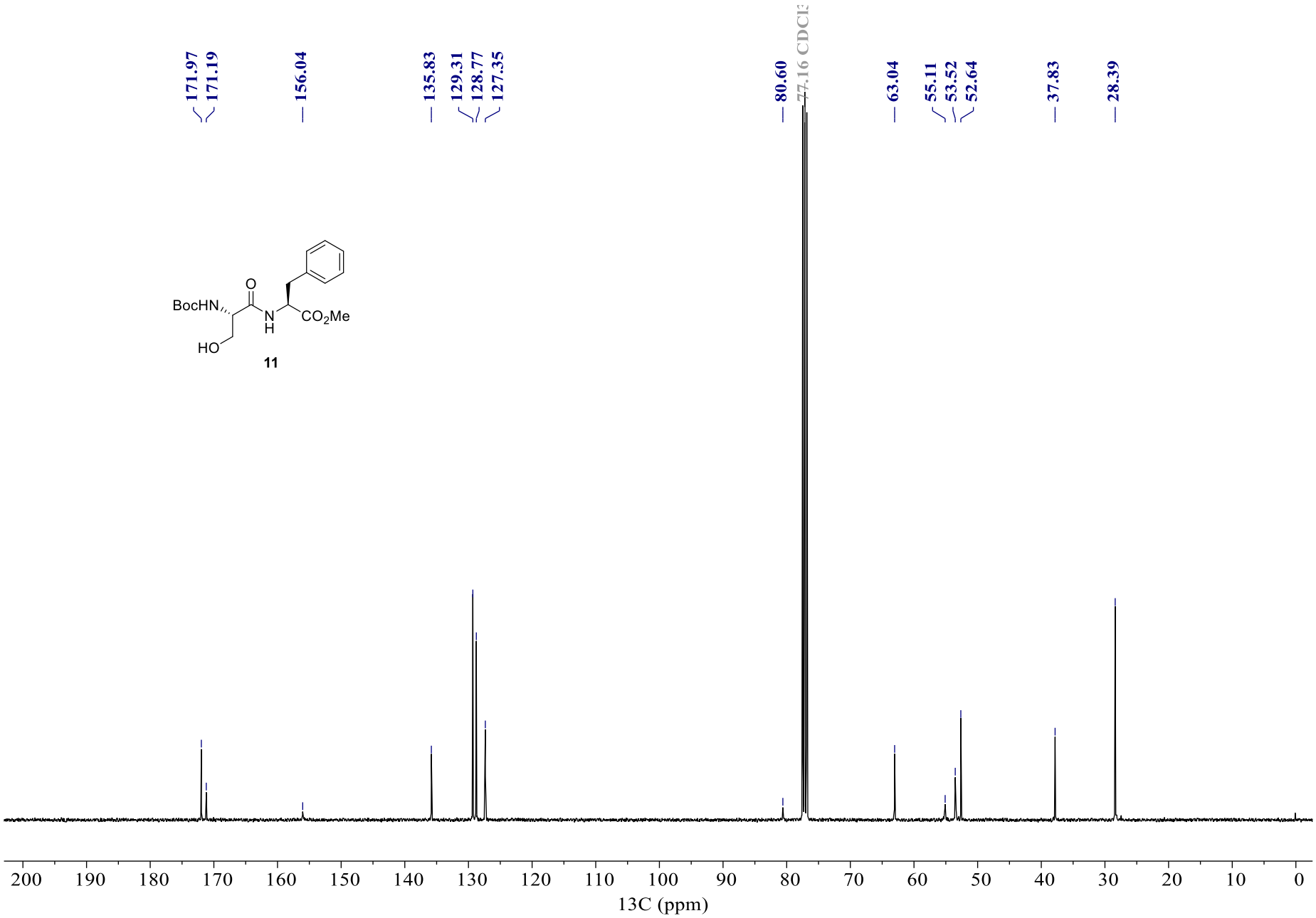
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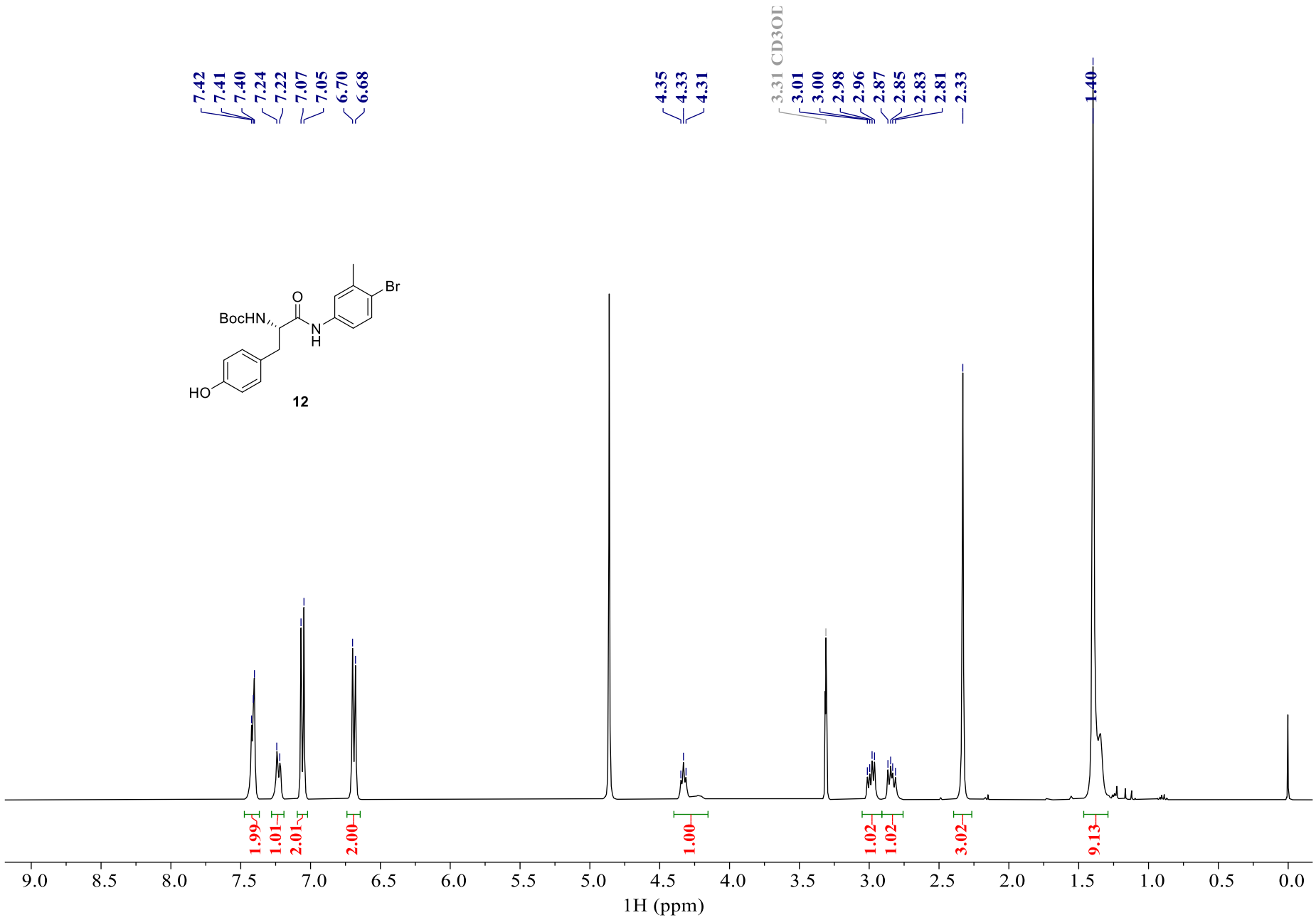
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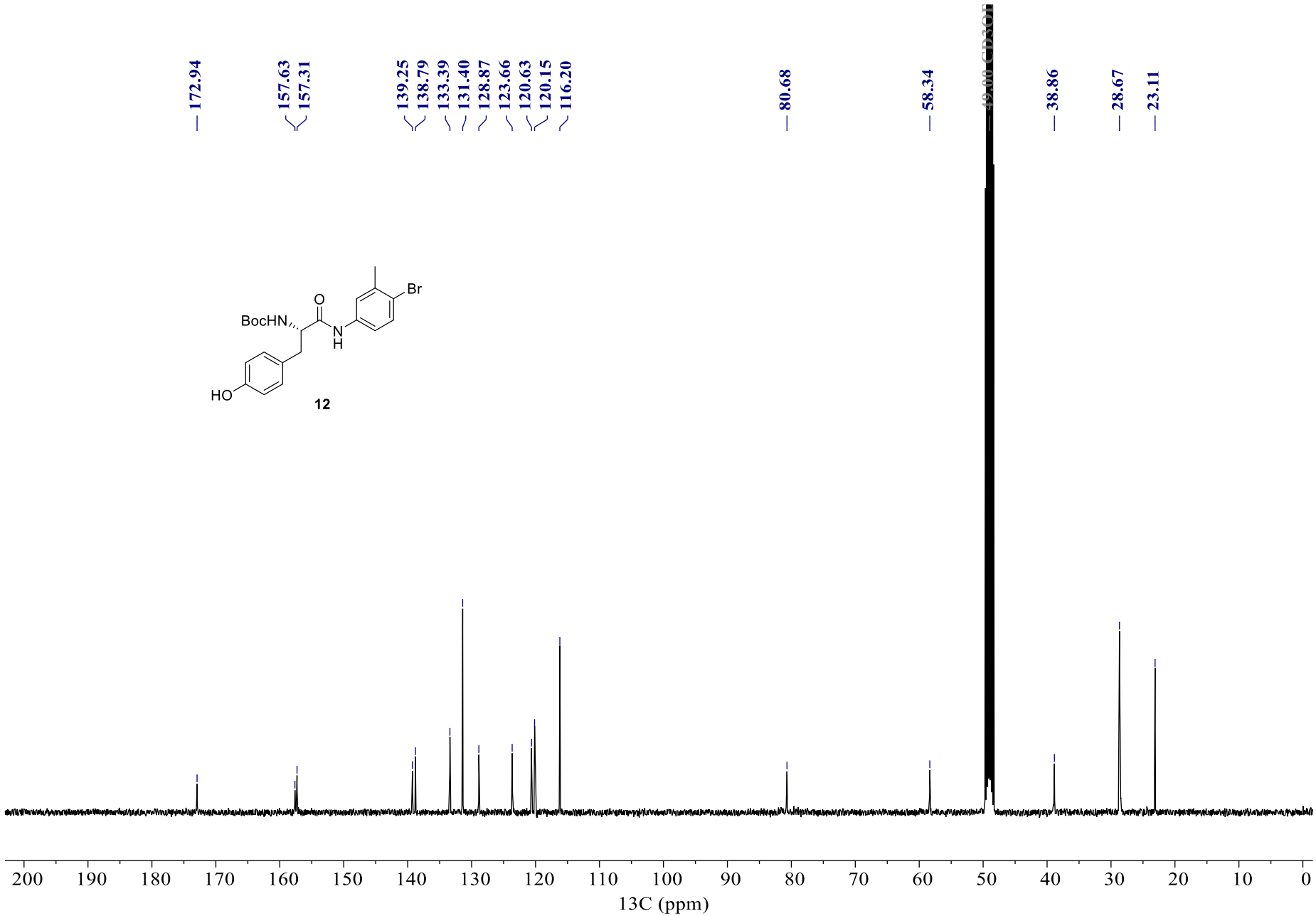
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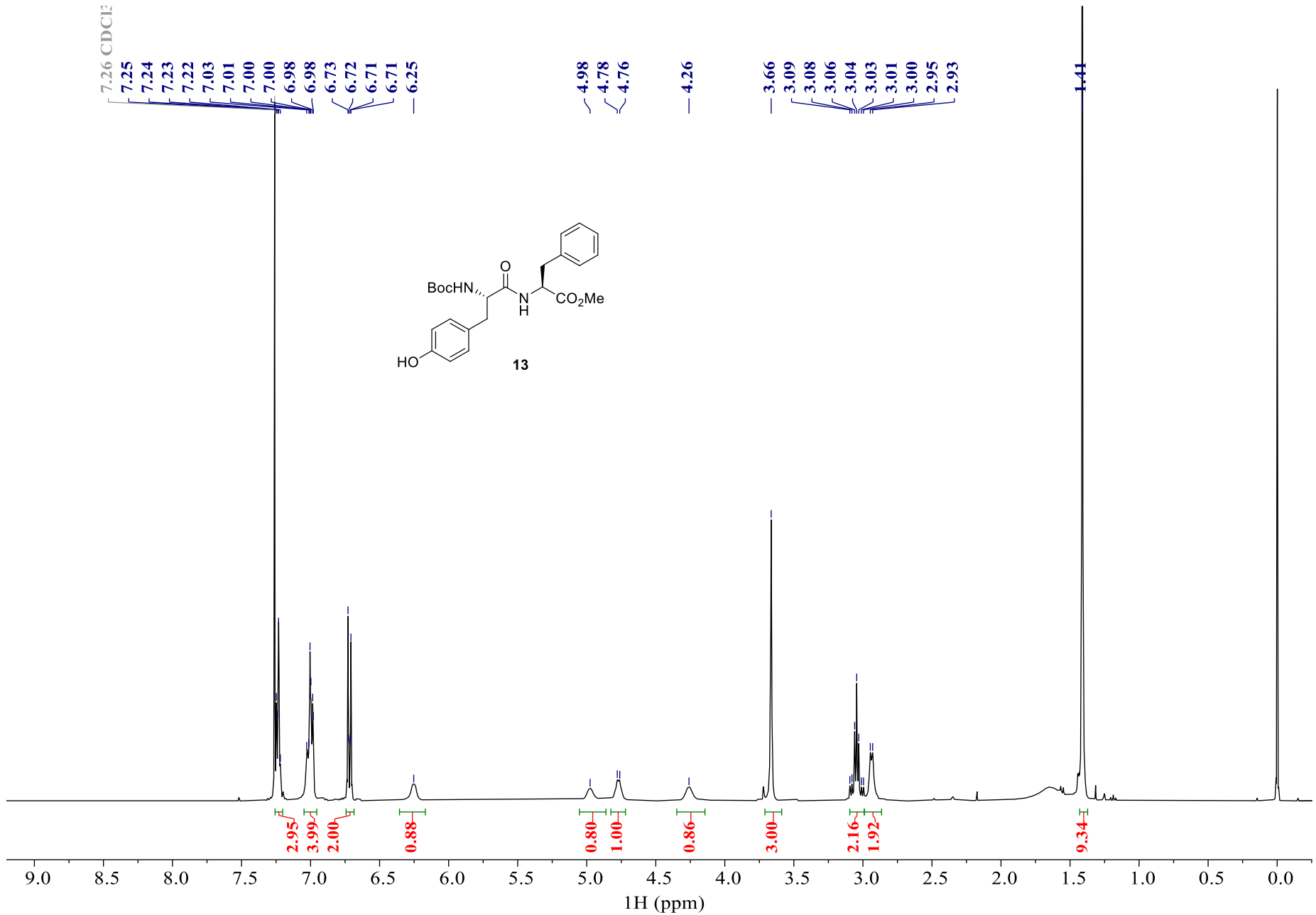
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CO2Me
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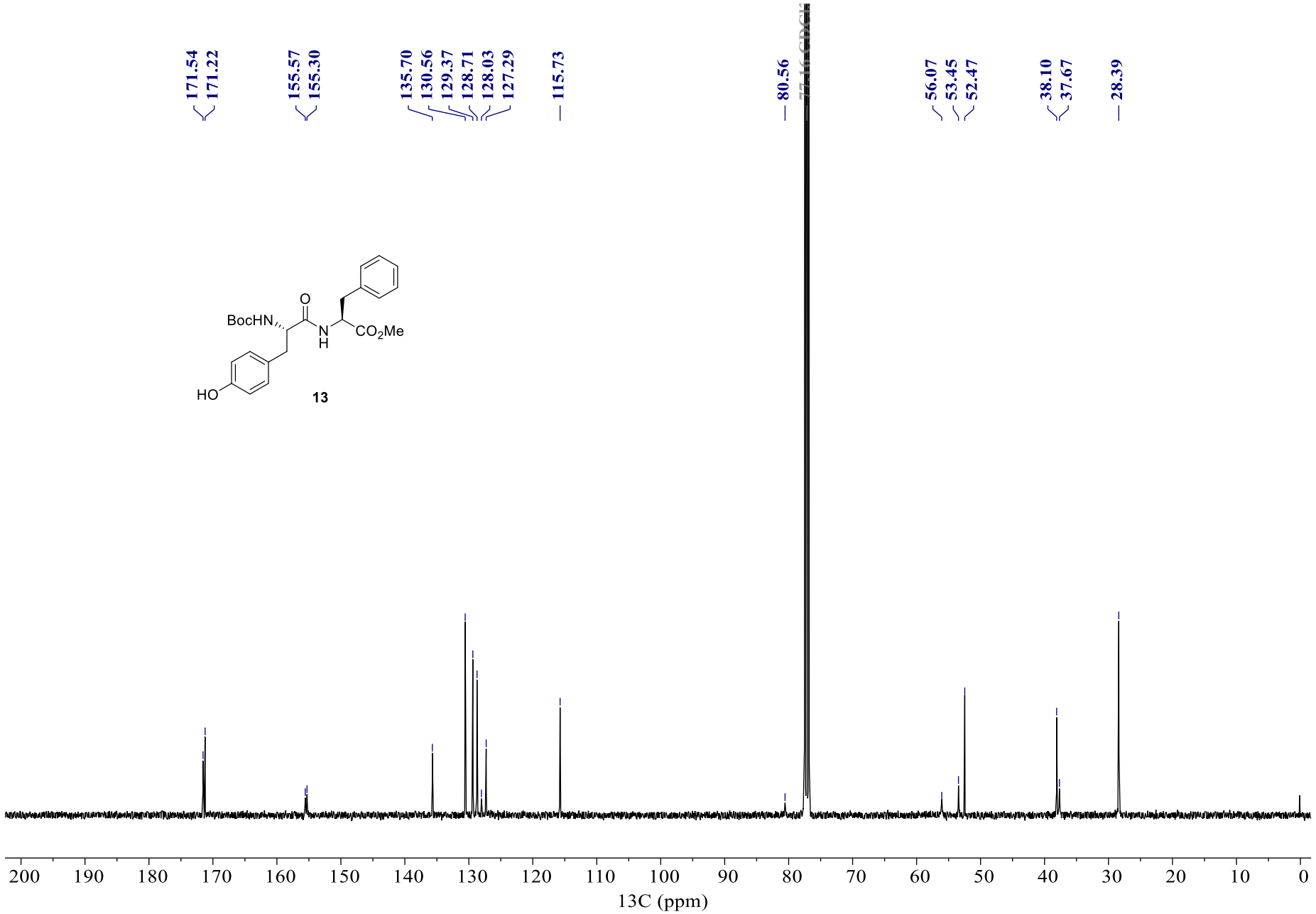
1H (ppm)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H
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200
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180
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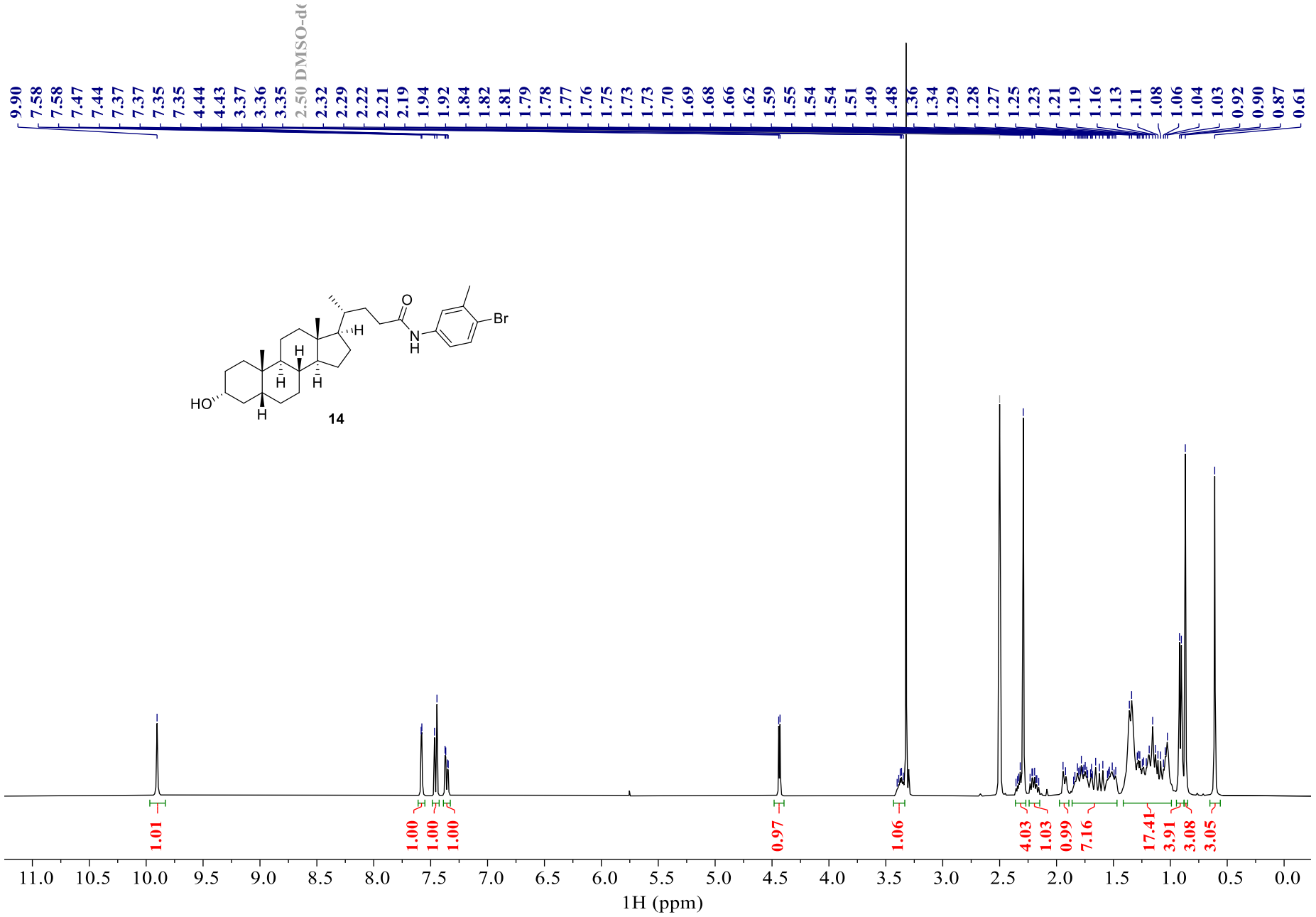
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HO
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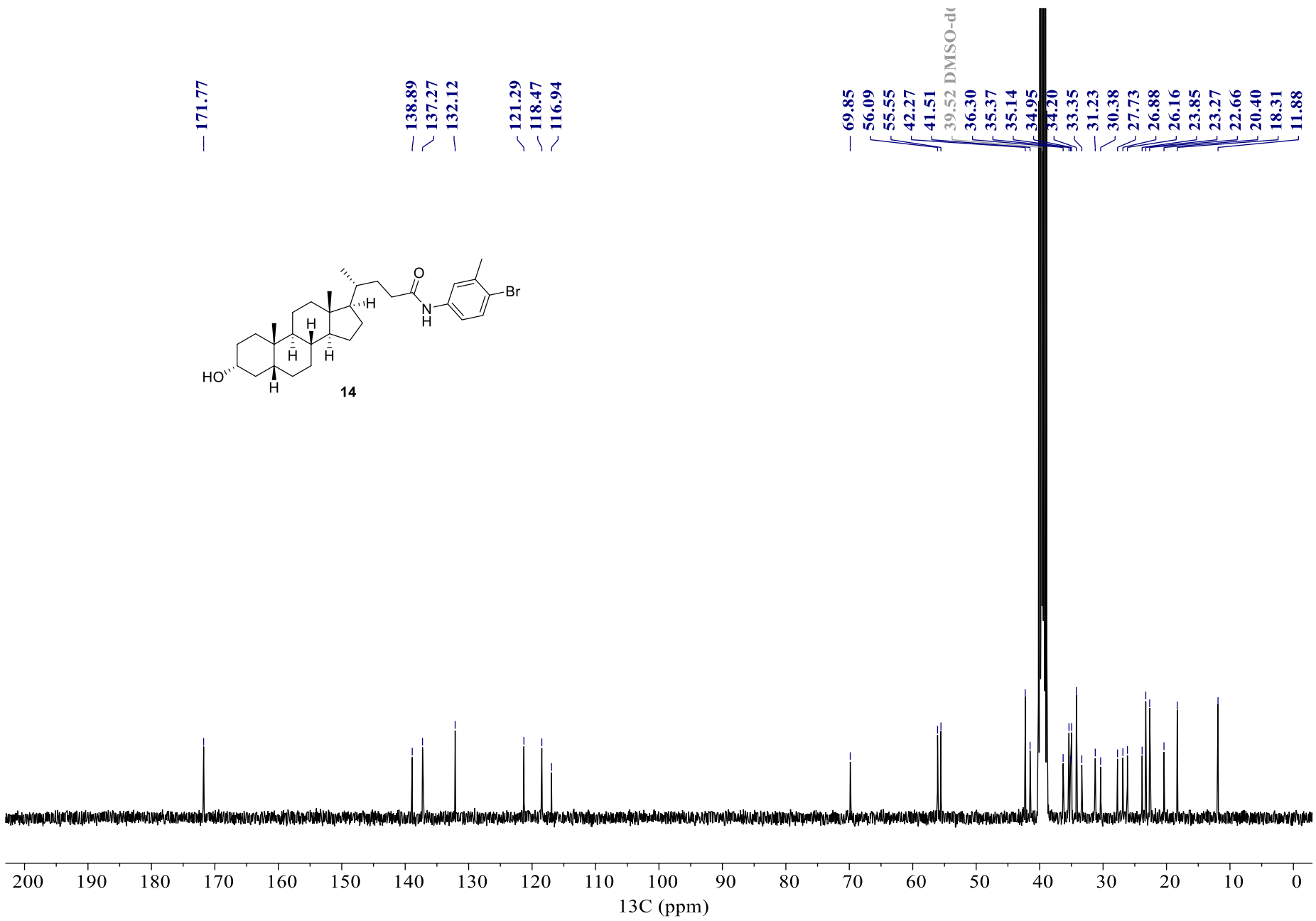
3.91
3.08
3.05
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1H (ppm)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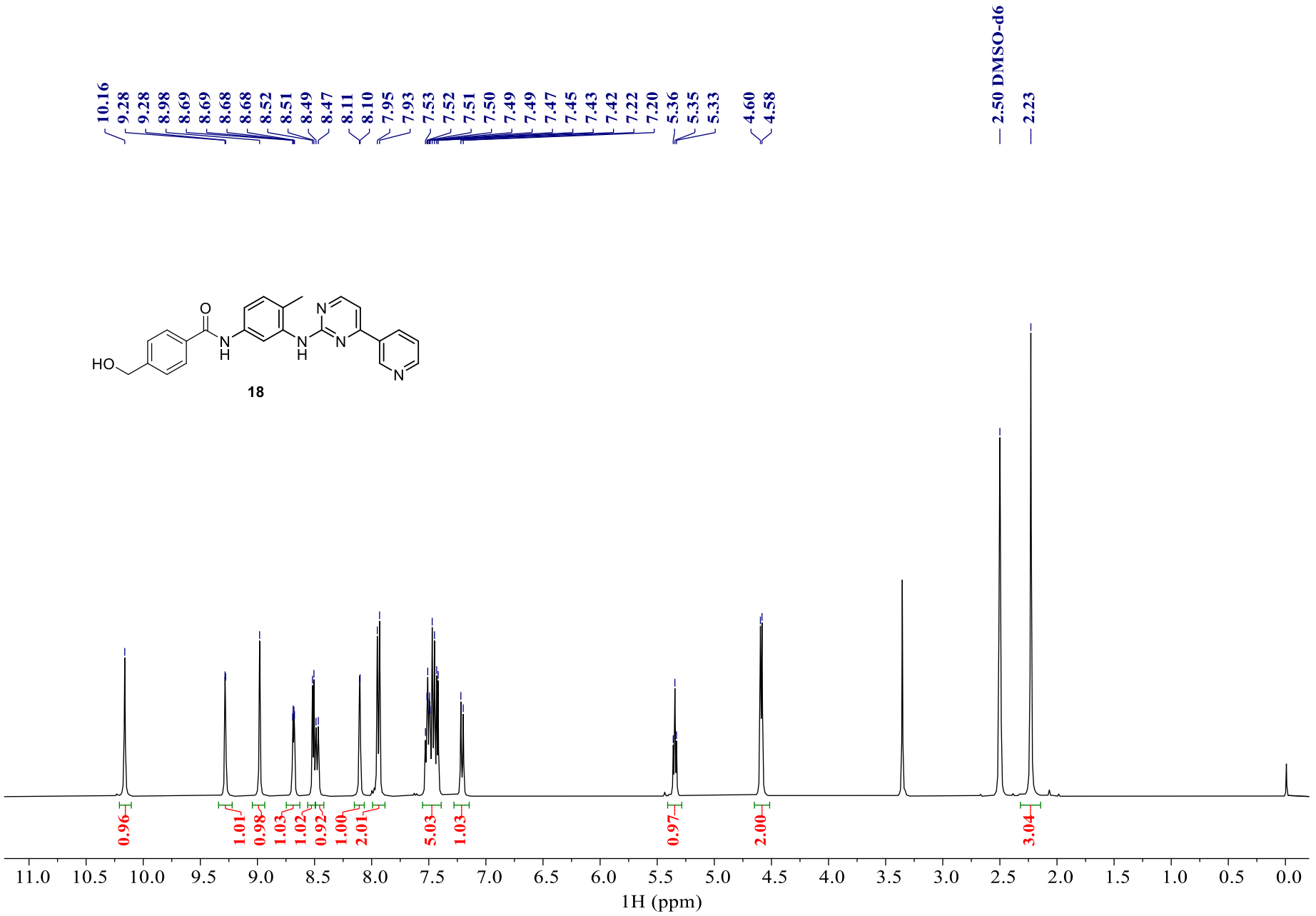
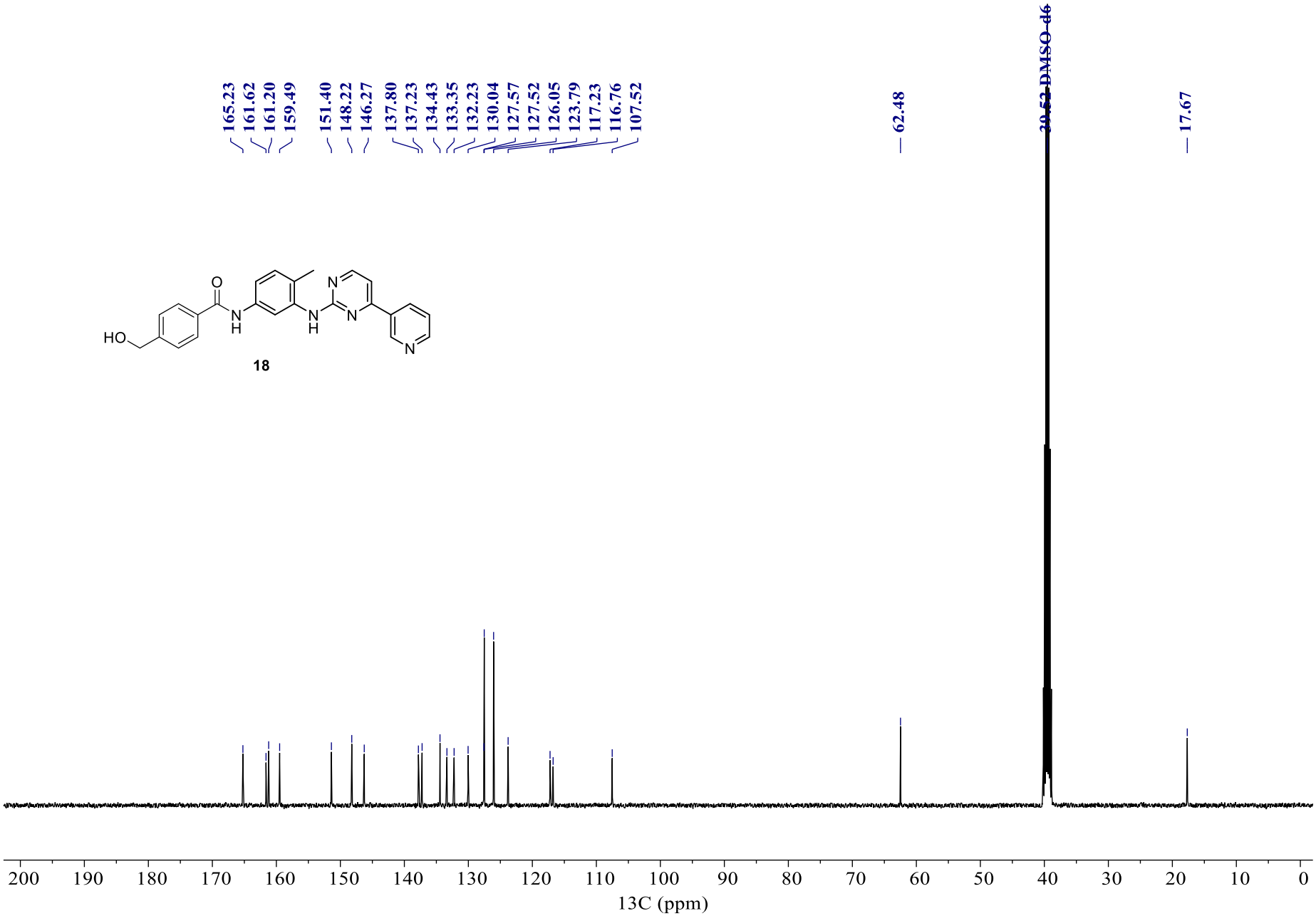
137.27
132.12
121.29
118.47
116.94
69.85
56.09
55.55
42.27
41.51
39.52 DMSO-d6
36.30
35.37
35.14
34.95
34.20
33.35
31.23
30.38
27.73
26.88
26.16
23.85
23.27
22.66
20.40
18.31
11.88
HO
H
O
N
H
Br
14
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)


10.16
9.28
9.28
8.98
8.69
8.69
8.68
8.68
8.52
8.51
8.49
8.47
8.11
8.10
7.95
7.93
7.53
7.52
7.51
7.50
7.49
7.49
7.47
7.45
7.43
7.42
7.22
7.20
5.36
5.35
5.33
4.60
4.58
2.50 DMSO-d6
2.23
HO
O
N
H
N
H
N
N
N
18
0.96
1.01
0.98
1.03
1.02
0.92
1.00
2.01
5.03
1.03
0.97
2.00
3.04
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
1H (ppm)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161.62
161.20
159.49
151.40
148.22
146.27
137.80
137.23
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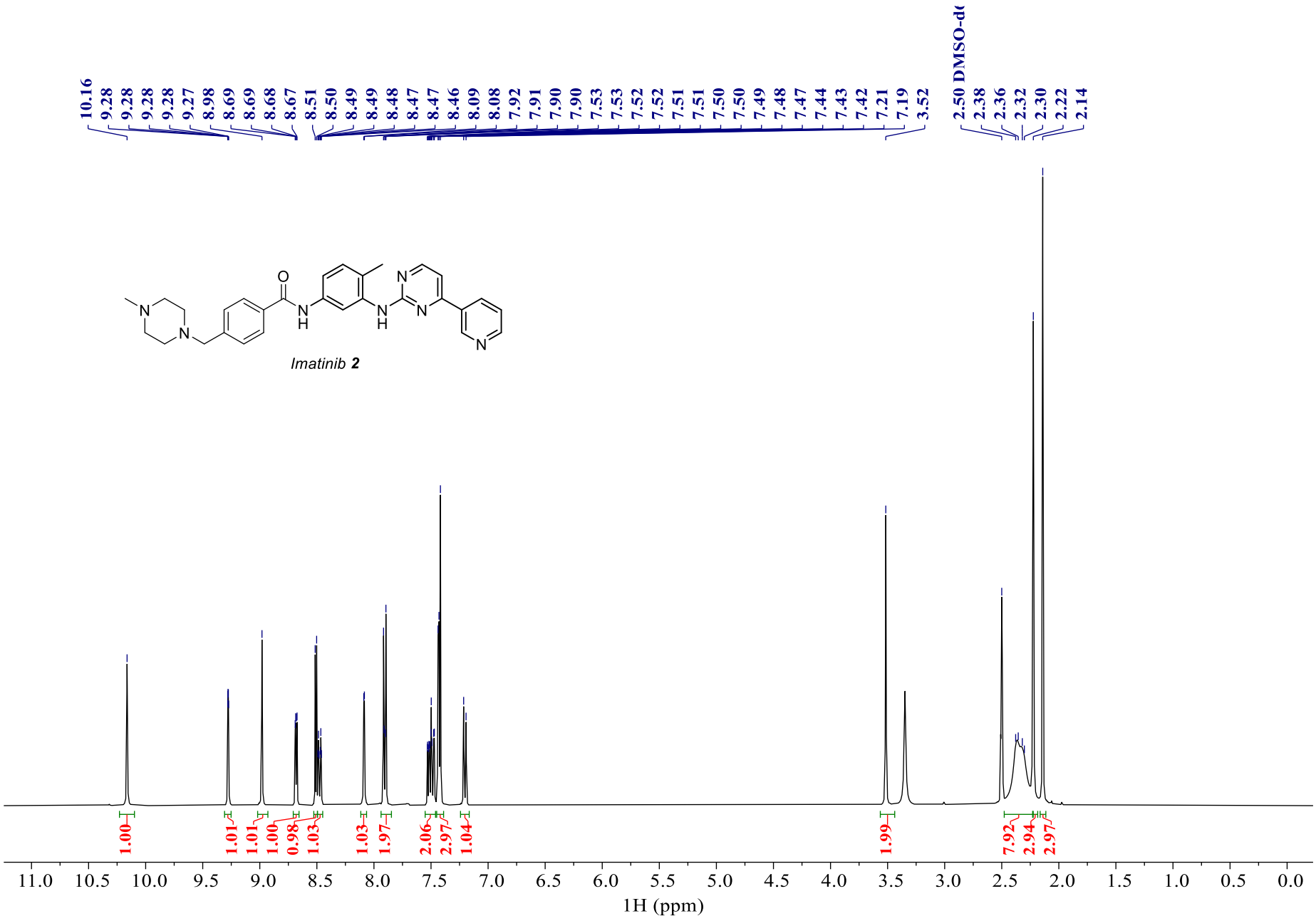
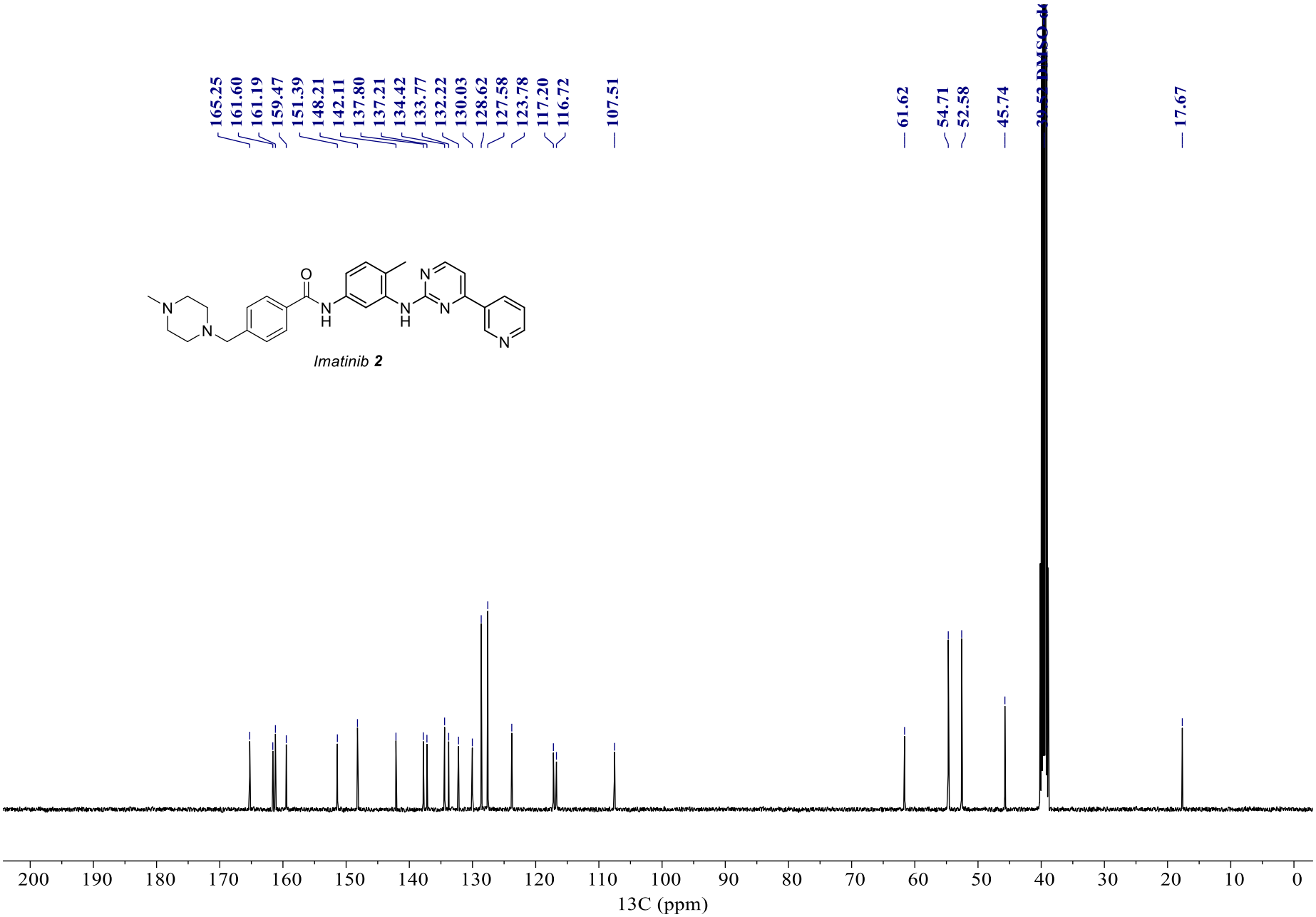
133.35
132.23
130.04
127.57
127.52
126.05
123.79
117.23
116.76
107.52
62.48
39.52 DMSO-d6
17.67
HO
O
N
H
N
H
N
N
N
18
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)


10.16
9.28
9.28
9.28
9.28
9.27
8.98
8.69
8.69
8.68
8.67
8.51
8.50
8.49
8.49
8.48
8.47
8.47
8.46
8.09
8.08
7.92
7.91
7.90
7.90
7.53
7.53
7.52
7.52
7.51
7.51
7.50
7.50
7.49
7.48
7.47
7.44
7.43
7.42
7.21
7.19
3.52
2.50 DMSO-d
2.38
2.36
2.32
2.30
2.22
2.14
Imatinib 2
1.00
1.01
1.01
1.00
0.98
1.03
1.03
1.97
2.06
2.97
1.04
1.99
7.92
2.94
2.97
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
1H (ppm)


165.25
161.60
161.19
159.47
151.39
148.21
142.11
137.80
137.21
134.42
133.77
132.22
130.03
128.62
127.58
123.78
117.20
116.72
107.51
61.62
54.71
52.58
45.74
39.52 DMSO-d6
17.67
Imatinib 2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)