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Mild and efficient catalyst for nitrodopamine synthesis:

from milligram to multi-gram scales

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Contents

Experimental section

General: The IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR Spectrometer. The ^{1}H NMR spectra were recorded on a BrukerAvance 400 spectrometer with operating frequencies of 400 MHz in DMSO-d_6. Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of DMSO-d_6 (2.50 for ^{1}H NMR) as internal references. Organic chemicals with a purity not less than 95% were used as purchased. Solvents were routinely purified and freshly distilled prior to use, or purchased in HPLC-quality.

For LCMS analysis of samples we used Shimadzu Prominence LC-20 system with column oven and fraction collector coupled to single quadrupole mass-spectrometer Shimadzu LCMS-2020 with dual DUIS-ESI-APCI ionization source. We used analytical Phenomenex Luna 3u C18 100A column (150 x 4.6 mm). Mobile phases: A - 0.1% formic acid in water, D - acetonitrile. LCMS parameters for analyses were: gradient flow of 1 mL/min (0-0.5 min - 5% D, 0.5 -10.5 min - 5% to 100% D, 10.5-12 min - 100% D, 12-14.5 min - 100% to 5% D), column oven temperature 40 ˚C. MS parameters: drying gas 15.0 L/min, nebulizing gas 1.5 L/min, DL temperature 250 ˚C, heat block temperature 400 ˚C, interface voltage -3.5 kV, corona needle voltage -3.5 kV. Positive (mass range 160-2000 Da) and negative ions (mass range 100-2000 Da) were registered.

For HRMS analysis of samples we used quadrupole-time-of-flight mass spectrometer TripleTOF 5600+ (ABSciex, Canada), equipped with an ionization source by electrospray TurboIon Spray. 0.2 μL of the sample was injected into the 0.3 mL/min methanol stream without chromatographic separation directly into the ion source. MS parameters: curtain gas 25 psi, spray gas 30 psi, drying gas 30 psi, voltage 5.5 kV, temperature 300 ˚C. Positive (mass range 100-3000 Da) ions were registered, accumulation time 250 ms.

General procedure for the screening of catalysts:

Dopamine hydrochloride (0.010 g, 0.053 mmol, 1 eq.) and $NaNO_2$ (0.013 g, 0.18 mmol, 3.5 eq.) were dissolved in deionized water (150 μL) cooled in an ice bath to 0-5 °C. Then catalyst (Table S1) was added to the reaction mixture under vigorous stirring over 30 min. An aliquot (20 μL) was taken and analysed using LCMS.

Table S1. Amounts of catalysts used in screening assays (milligram-scale)

Catalyst	Amounts
0.1% H_2SO_4	25 μL
1% H_2SO_4	25 μL
5% H_2SO_4	25 μL
10% H_2SO_4	25 μL
20% H_2SO_4	25 μL
***p*-TsOH**	20 mg
Dowex 50WX8	10 mg
36% HCl	10 μL
TFA	8.6 μL
$NaHSO_4$	14 mg

Table S2. Results of screening assays: LCMS analysis of reaction mixtures*

Entry	Catalyst	Content of product **2** in (+) ions, %	Content of product **2** in (-) ions, %	The number of components in the mixture	The presence of dopamine in the final mixture
1	0.1% H_2SO_4	40	23	5	Trace amounts
2	1% H_2SO_4	67	76	6	Trace amounts
3	5% H_2SO_4	54	72	7	No
4	10% H_2SO_4	49	57	12	No
5	20% H_2SO_4	76	77	10	No
6	*p*-TsOH	71	4.3	9	No
7	Dowex 50WX8	65	91	6	16% (+), 3.2% (-)
8	36% HCl	57	67	9	No
9	TFA	66	15	10	No
10	$NaHSO_4$	74	33	6	No

* Table S2 is identical to Table 1 of the main text.

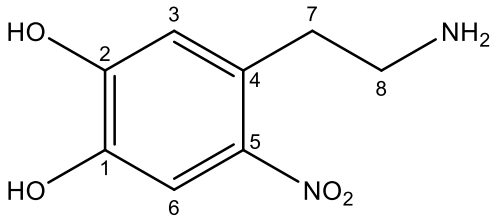


Figure S1. Nitrodopamine 2, 4-(2-aminoethyl)-5-nitrobenzene-1,2-diol

Synthesis of sample 2a:

Dopamine hydrochloride (1.00 g, 5.27 mmol, 1 equiv) and $NaNO_2$ (1.26 g, 18.26 mmol, 3.5 equiv) were dissolved in deionized water (30 mL) cooled in an ice bath to 0-5 °C. Thereafter 1% H_2SO_4 (5 mL) was slowly added dropwise to the reaction mixture under vigorous stirring over 1 min. After 3 min the resulting solution was treated with saturated aqueous $NaHCO_3$ (20 mL). The residue was washed with cold water and cold methanol and then left to air dry for 24 hours. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (s, 1H, H-6), 6.69 – 6.36 (m, 1H), 6.03 (s, 1H, H-3), 2.97 (m, 4H, H-7, H-8). HRMS (ESI-TOF, m/z) calcd. for $C_8H_{11}N_2O_4$ $(M+H)^+$, 199.0713; found 199.0714.

Synthesis of sample 2b:

Dopamine hydrochloride (1.00 g, 5.27 mmol, 1 equiv) and $NaNO_2$ (1.26 g, 18.26 mmol, 3.5 equiv) were dissolved in deionized water (30 mL) cooled in an ice bath to 0-5 °C. Thereafter 5% H_2SO_4 (5 mL) was slowly added dropwise to the reaction mixture under vigorous stirring over 1 min. After 3 min the resulting solution was treated with saturated aqueous $NaHCO_3$ (20 mL). The residue was washed with cold water and cold methanol and then left to air dry for 24 hours. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (s, 1H, H-6), 6.10 (s, 1H, H-3), 3.05 – 2.92 (m, 4H, H-7, H-8). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.09, 146.44, 130.41, 118.13, 108.36, 79.21, 33.35, 30.75. HRMS (ESI-TOF, m/z) calcd. for $C_8H_{11}N_2O_4$ $(M+H)^+$, 199.0713; found 199.0713.

Synthesis of sample 2c[S1]***:***

Dopamine hydrochloride (1.00 g, 5.27 mmol, 1 equiv) and $NaNO_2$ (1.26 g, 18.26 mmol, 3.5 equiv) were dissolved in deionized water (30 mL) cooled in an ice bath to 0-5 °C. Thereafter 20% H_2SO_4 (5 mL) was slowly added dropwise to the reaction mixture under vigorous stirring over 1 min. After 3 min the residue was filtered out and washed with cold water and cold methanol and then left to air dry for 24 hours. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (s, 1H, H-6), 6.90 (s, 1H, H-3), 3.05 (br. s, 4H, H-7, H-8). HRMS (ESI-TOF, m/z) calcd. for $C_8H_{11}N_2O_4$ $(M+H)^+$, 199.0713; found 199.0716.

Synthesis of sample 2d:

Dopamine hydrochloride (1.00 g, 5.27 mmol, 1 equiv) and $NaNO_2$ (1.26 g, 18.26 mmol, 3.5 equiv) were dissolved in deionized water cooled in an ice bath to 0-5 °C. Thereafter *p*-TsOH (2.00 g, 11.63 mmol, 2.2 equiv) in 5 mL deionized water (30 mL) was slowly added dropwise to the reaction mixture under vigorous stirring over 1 min. After 3 min the resulting solution was treated with saturated aqueous $NaHCO_3$ (20 mL). The residue was washed with cold water and cold methanol and then left to air dry for 24 hours. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.34 (s, 1H, H-6), 6.12 (s, 1H, H-3), 3.00 (td, J = 6.9, 2.7 Hz, 4H, H-7, H-8). HRMS (ESI-TOF, m/z) calcd. for $C_8H_{11}N_2O_4$ $(M+H)^+$, 199.0713; found 199.0719.

Synthesis of sample 2e:

Dopamine hydrochloride (1.00 g, 5.27 mmol, 1 equiv) and $NaNO_2$ (1.26 g, 18.26 mmol, 3.5 equiv) were dissolved in deionized water (30 mL) cooled in an ice bath to 0-5 °C. Thereafter Dowex 50WX8 (1.00 g) was added to the reaction mixture under vigorous stirring. After 3 min the resulting solution was treated with saturated aqueous $NaHCO_3$ (20 mL). The residue was washed with cold water and cold methanol and then left to air dry for 24 hours. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (s, 1H, H-6), 6.02 (s, 1H, H-3), 3.03 – 2.92 (m, 4H, H-7, H-8). HRMS (ESI-TOF, m/z) calcd. for $C_8H_{11}N_2O_4$ $(M+H)^+$, 199.0713; found 199.0713.

Synthesis of sample 2f:

Dopamine hydrochloride (1.00 g, 5.27 mmol, 1 equiv) and $NaNO_2$ (1.26 g, 18.26 mmol, 3.5 equiv) were dissolved in deionized water (30 mL) cooled in an ice bath to 0-5 °C. Thereafter solution of $NaHSO_4$ (1.39 g, 11.6 mmol, 2.2 equiv) in 5 mL deionized water was slowly added dropwise to the reaction mixture under vigorous stirring over 1 min. After 3 min the residue was filtered out and washed with cold water and cold methanol and then left to air dry for 24 hours. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (s, 1H, H-6), 6.81 (s, 1H, H-3), 3.09 – 2.99 (m, 4H, H-7, H-8). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.91, 144.92, 138.17, 126.63, 118.50, 112.12, 39.22, 31.13. HRMS (ESI-TOF, m/z) calcd. for $C_8H_{11}N_2O_4$ $(M+H)^+$, 199.0713; found 199.0719.

Synthesis of sample 2f using precipitation with $NaHCO_3$:

Dopamine hydrochloride (1.00 g, 5.27 mmol, 1 equiv) and $NaNO_2$ (1.26 g, 18.26 mmol, 3.5 equiv) were dissolved in deionized water (30 mL) cooled in an ice bath to 0-5 °C. Thereafter solution of $NaHSO_4$ (1.39 g, 11.6 mmol, 2.2 equiv) in 5 mL deionized water was slowly added dropwise to the reaction mixture under vigorous stirring over 1 min. After 3 min the resulting solution was treated with saturated aqueous $NaHCO_3$ (30 mL). The residue was washed with cold water and cold methanol and then left to air dry for 24 hours. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (s, 1H, H-6), 6.10 (s, 1H, H-3), 3.04 – 2.86 (m, 4H, H-7, H-8).

Table S3. Comparison of catalytic systems in gram-scale dopamine nitration with $NaNO_2$.

Sample	Catalyst	Yield of **2**, %*	Purity of compound **2**
2a	1% H_2SO_4	14	Pure
2b	5% H_2SO_4	52	Pure
2c	20% H_2SO_4	59	3 components, 100% (+) and 97% (–)
2d	*p*-TsOH	74	5 components, 100% (+) and 93% (–)
2e	Dowex 50WX8	24	Pure
2f	$NaHSO_4$	53	Pure

* The yields are indicated for dried crude precipitates.

Table S4. Physicochemical characteristics of samples 2a–f

Sample	Catalyst	m.p., °C	λ *, nm	Log_{10} ε **, $L \cdot mol^{-1} \cdot cm^{-1}$	ν_{as} (NO_2), cm^{-1}	ν (N-H), cm^{-1}
2a	1% H_2SO_4	218.0	286, 452	3.59, 4.20	1511, 1520	–
2b	5% H_2SO_4	218.2	286, 450–451	3.58, 4.20	1510, 1518	–
2c	20% H_2SO_4	200	288, 360, 451–452	3.36, 3.36, 3.76	1512	3182
2d	*p*-TsOH	217.4	286, 450	3.64, 4.25	1508, 1518	3181
2e	Dowex 50WX8	221.2	286, 452	3.60, 4.22	1511, 1519	–
2f	$NaHSO_4$	199	287–288, 360–365, 451–452	3.37, 3.28, 3.88	1512	3178

* λ – local maximum wavelength;

** Log_{10} ε – decimal logarithm of the molar extinction coefficient.

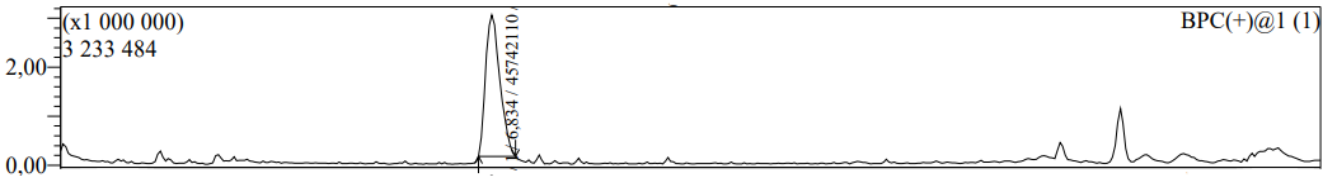
The resulting scaled precipitates were analyzed using IR spectroscopy. The assignments of some of the detected signals are shown in Table S3. The band of antisymmetric NO_2 vibrations is between 1540 and 1510 cm^{-1} and deviations from these values can occur with multiple substitutions in the ring or as a result of steric effects. However, no deviation of values is observed for all precipitates. The symmetric vibration of NO_2 is complex in shape and, in the case of a number of aromatic compounds, is associated with certain ring vibrations. Therefore, substituents that cause changes in the cycle vibrations should also lead to a change in the considered NO_2 frequency. As a result, in the 1355-1338 cm^{-1} region, the frequencies change rather randomly. In systems with hydrogen bonds, $\nu_s(NO_2)$ decreases to 1260 cm^{-1}.

Table S2 also shows that the melting points of samples **2a**, **2b**, **2d**, and **2e** corresponded to the literature data for nitrodopamine **2** and were in the range of 218–225 °C.[S3] Melting points of 199–200 °C of samples **2c** and **2f** differed from the others and did not correspond to the literature data. To explain this result, we investigated the compounds obtained by IR spectroscopy and found similar patterns. As previously, the obtained IR spectra could be divided into two groups: Group 1 – samples **2a**, **2b**, **2d** and **2e**; Group 2 – samples **2c** and **2f**. These two groups differed in the number of NO_2 and NH group peaks (Table S4). Thus, according to the melting points and the results of IR spectroscopy, the samples of nitrodopamine **2** from Group 1 corresponded to free amines, while in Group 2 they were present in the form of protonated salt.

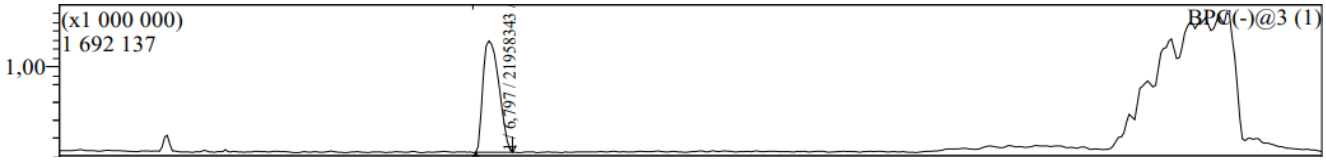
Further, samples **2a–2f** were characterised by UV spectroscopy. The data obtained were compared with the existing literature data; the characteristic constants of the UV spectra are shown in Table S4. The observed results confirmed that the samples obtained with 20% H_2SO_4 and $NaHSO_4$ corresponded to dopamine hydrosulfate.[2]

To further confirm the structure of the isolated products of reactions **2a–2f**, we carried out ^1H NMR spectroscopy. The spectrum of sample **2c** was in complete agreement with the published data.[2] The same correspondence was found for the product of reaction **2f** with the participation of $NaHSO_4$. The proton NMR spectra of the remaining samples of compound **2** showed a broad singlet at 4.2–4.6 ppm and shifting of the aromatic singlets of H-3 and H-6 to the high-field region (7.3 and 6.0 ppm instead of 7.5 and 6.8 ppm described in the literature, respectively). Hence, such a result may be due to the different electron-donating or electron-withdrawing effects of NH_2 and NH_3^+ groups.

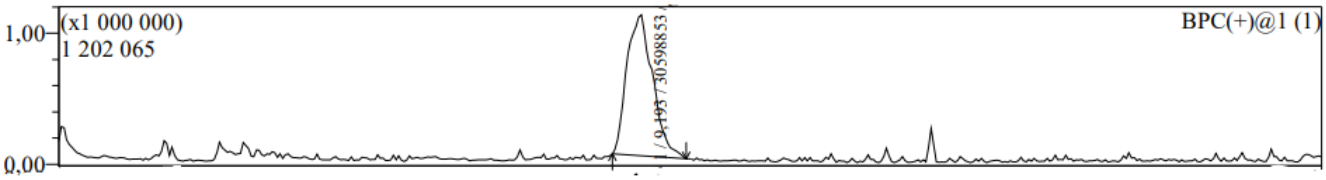
LCMS of samples from gram-scale synthesis



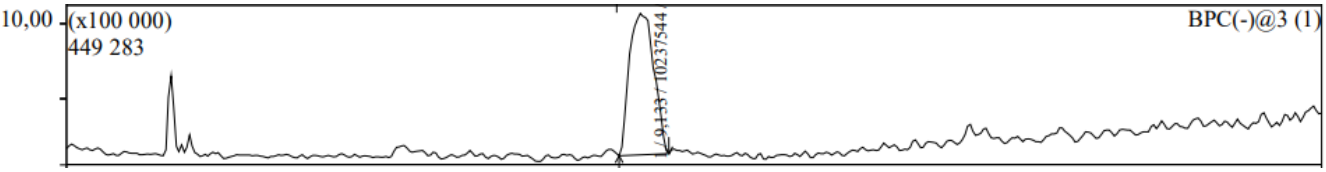
LCMS chromatogram of **2a**: MS detection of + ions



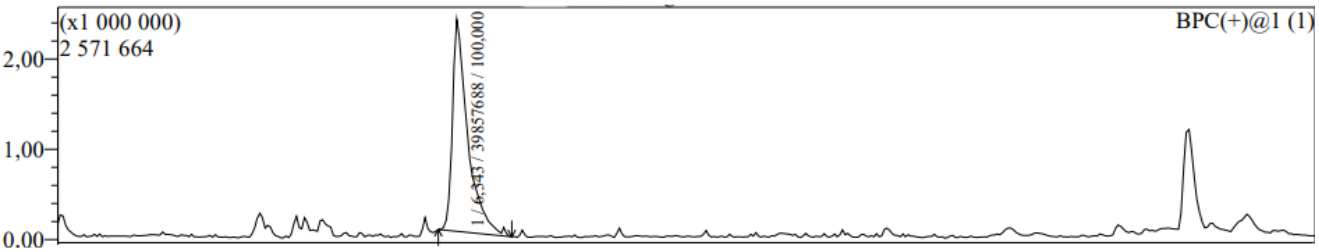
LCMS chromatogram of **2a**: MS detection of - ions



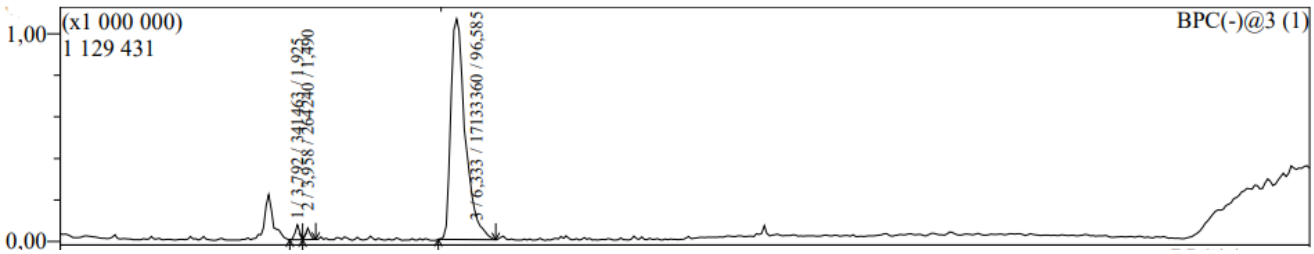
LCMS chromatogram of **2b**: MS detection of + ions



LCMS chromatogram of **2b**: MS detection of - ions

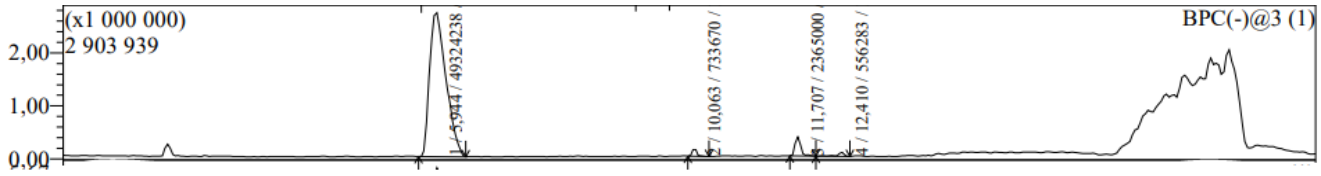


LCMS chromatogram of **2c**: MS detection of + ions

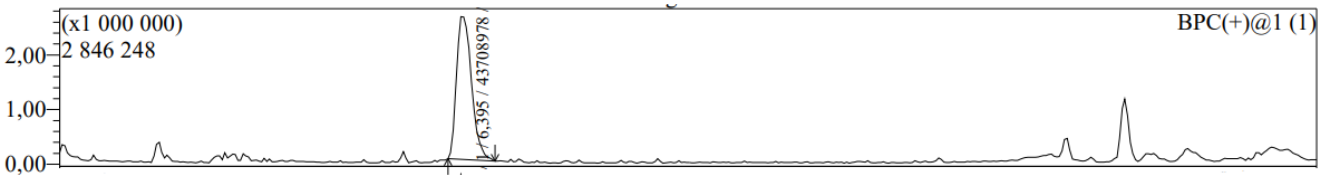


LCMS chromatogram of **2c**: MS detection of - ions

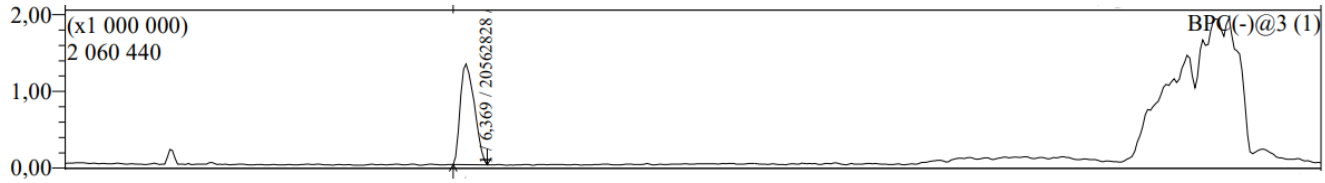
LCMS chromatogram of **2d**: MS detection of + ions



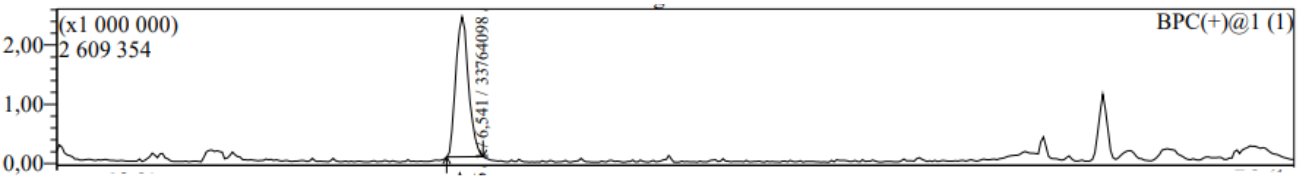
LCMS chromatogram of **2d**: MS detection of - ions



LCMS chromatogram of **2e**: MS detection of + ions



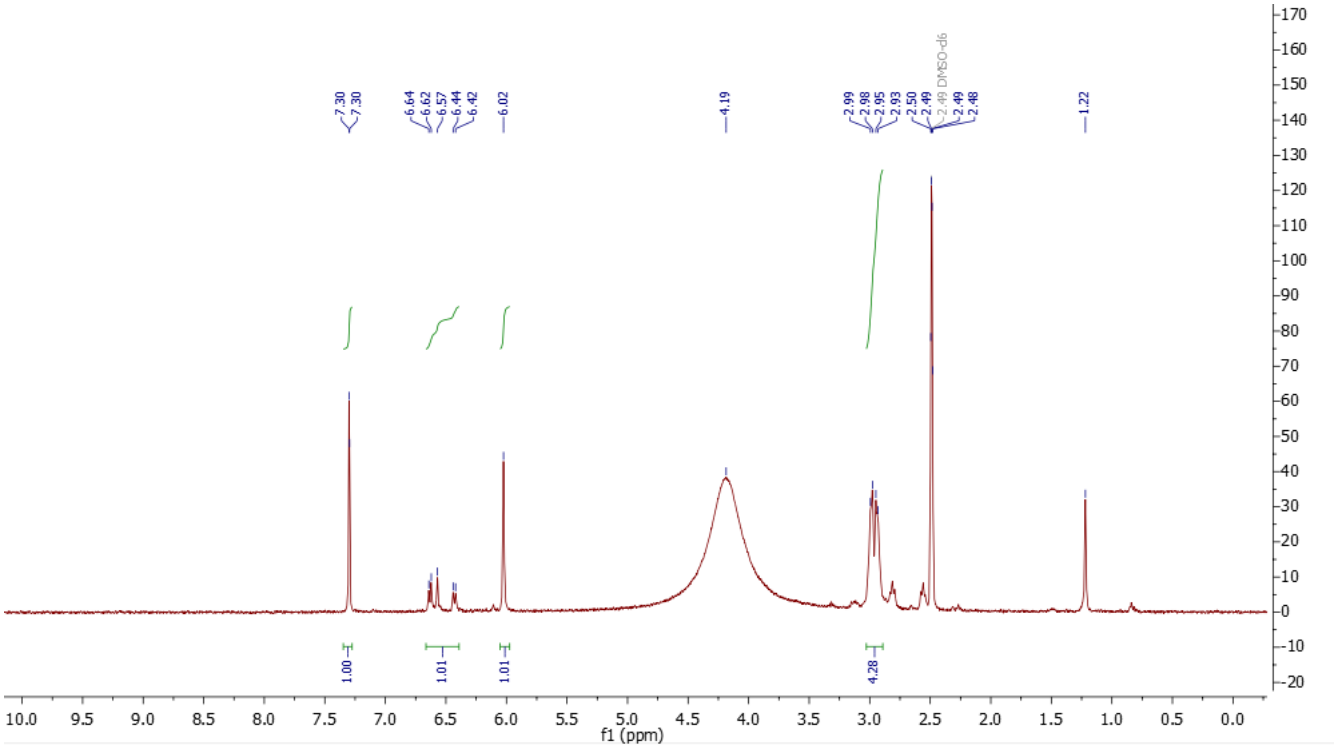
LCMS chromatogram of **2e**: MS detection of – ions



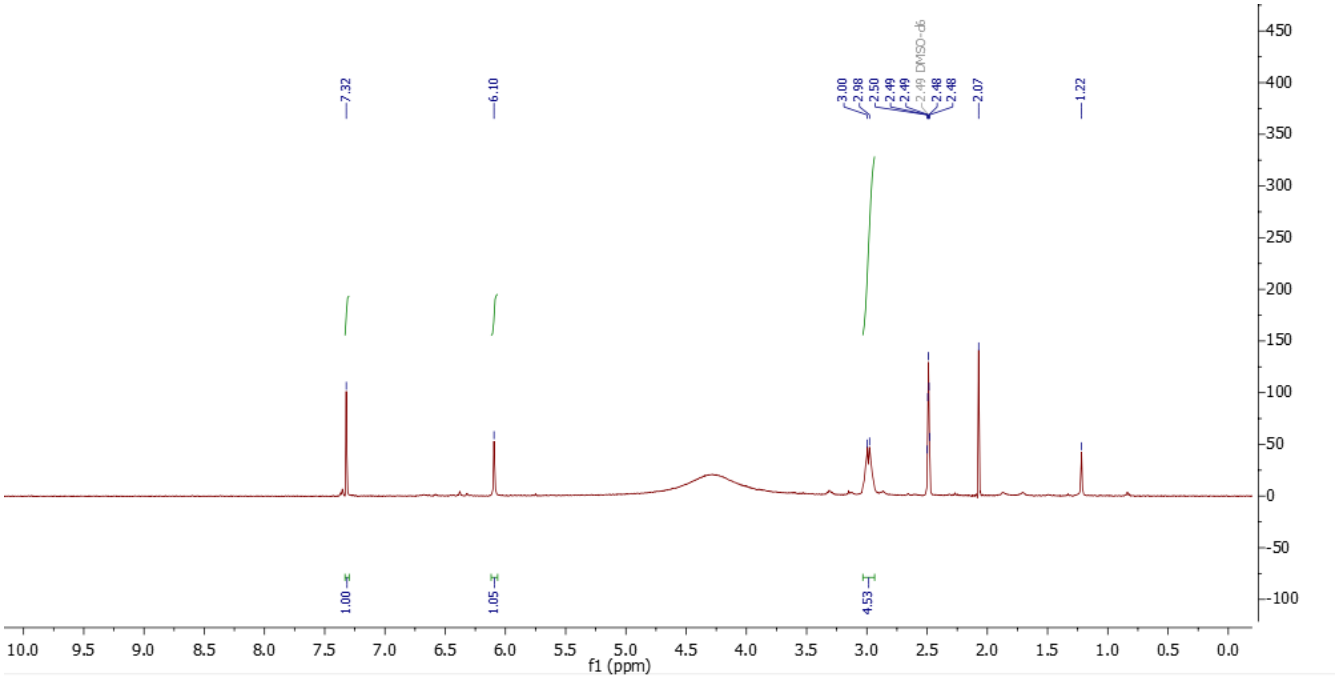
LCMS chromatogram of **2f**: MS detection of + ions

LCMS chromatogram of **2f**: MS detection of – ions

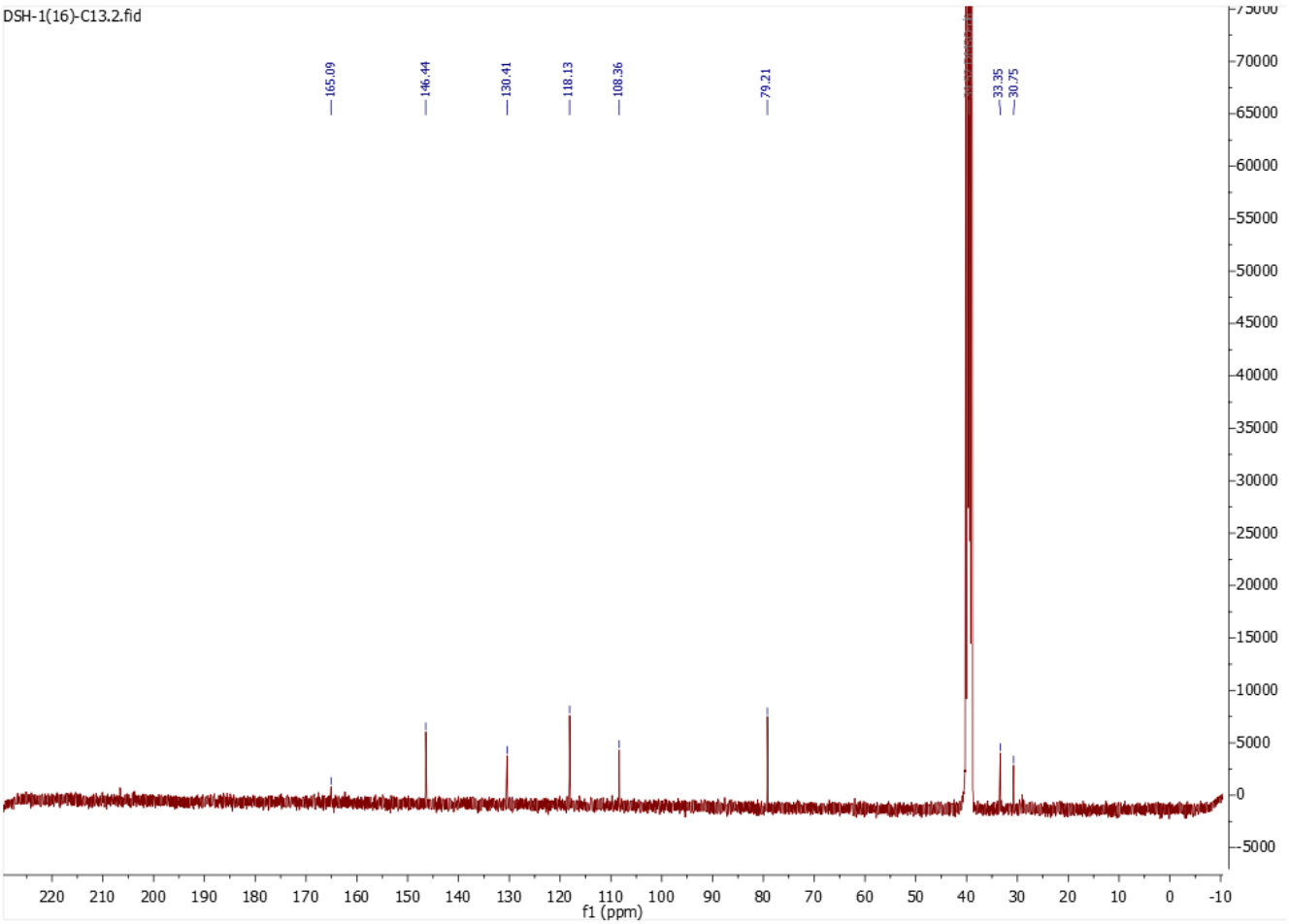
NMR-spectroscopy of samples from gram-scale synthesis



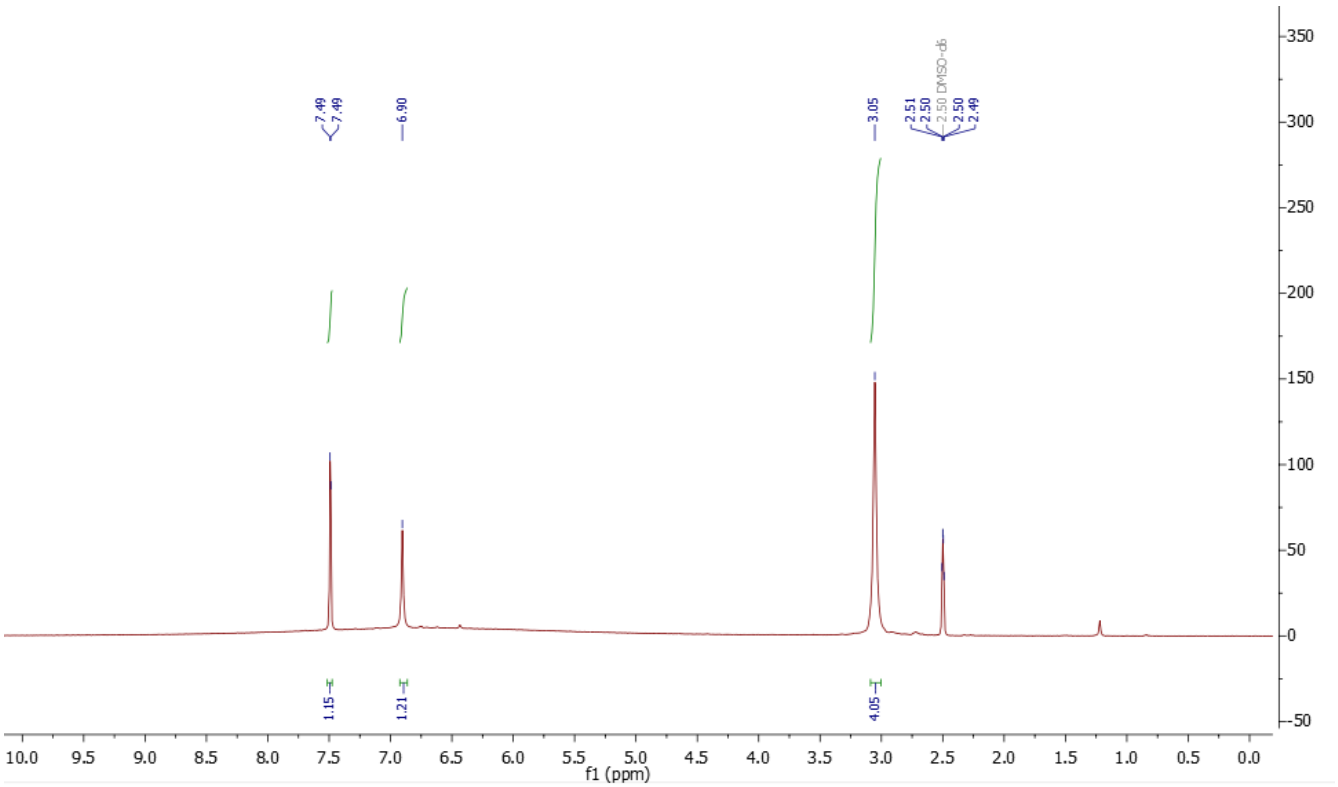
^{1}H NMR of **2a**



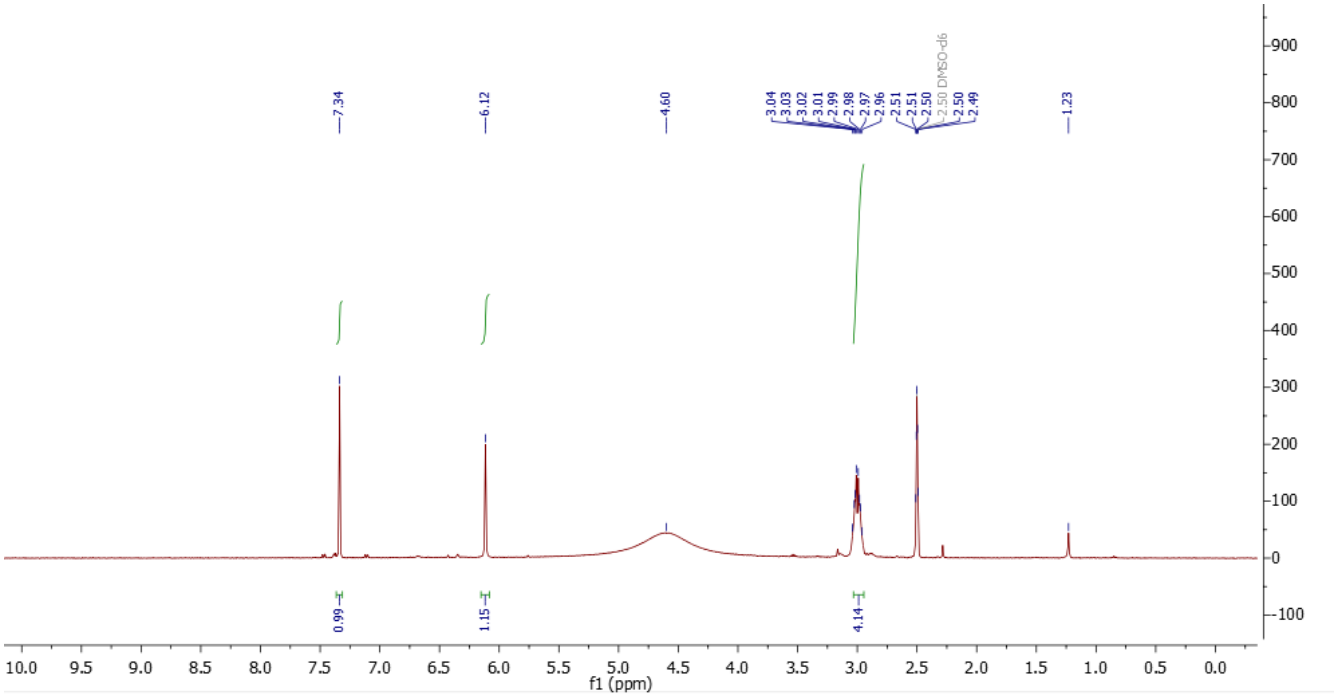
^{1}H NMR of **2b**



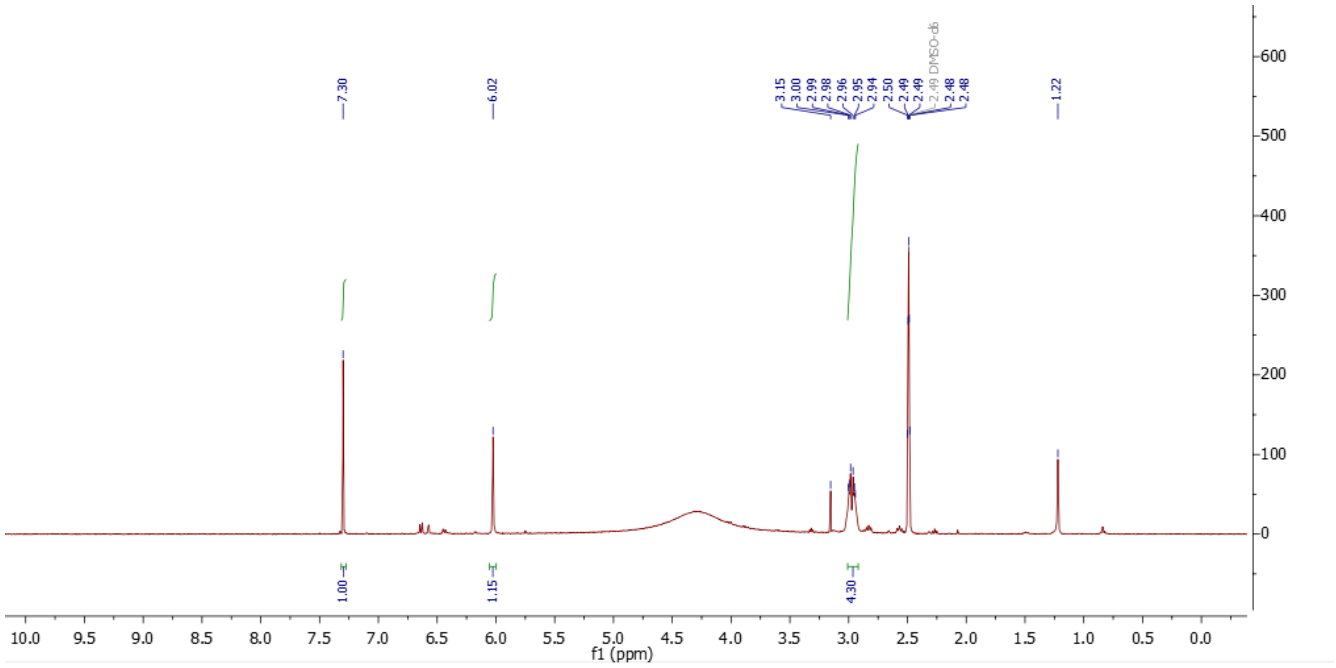
^{13}C NMR of **2b**



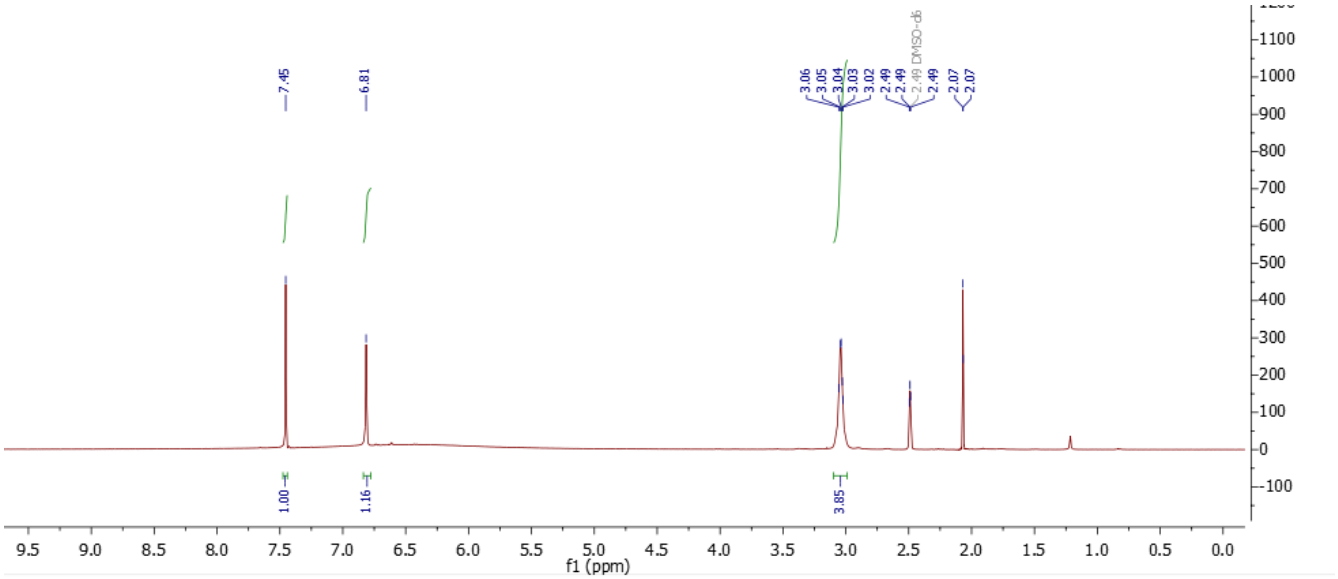
^{1}H NMR of **2c**[S2]



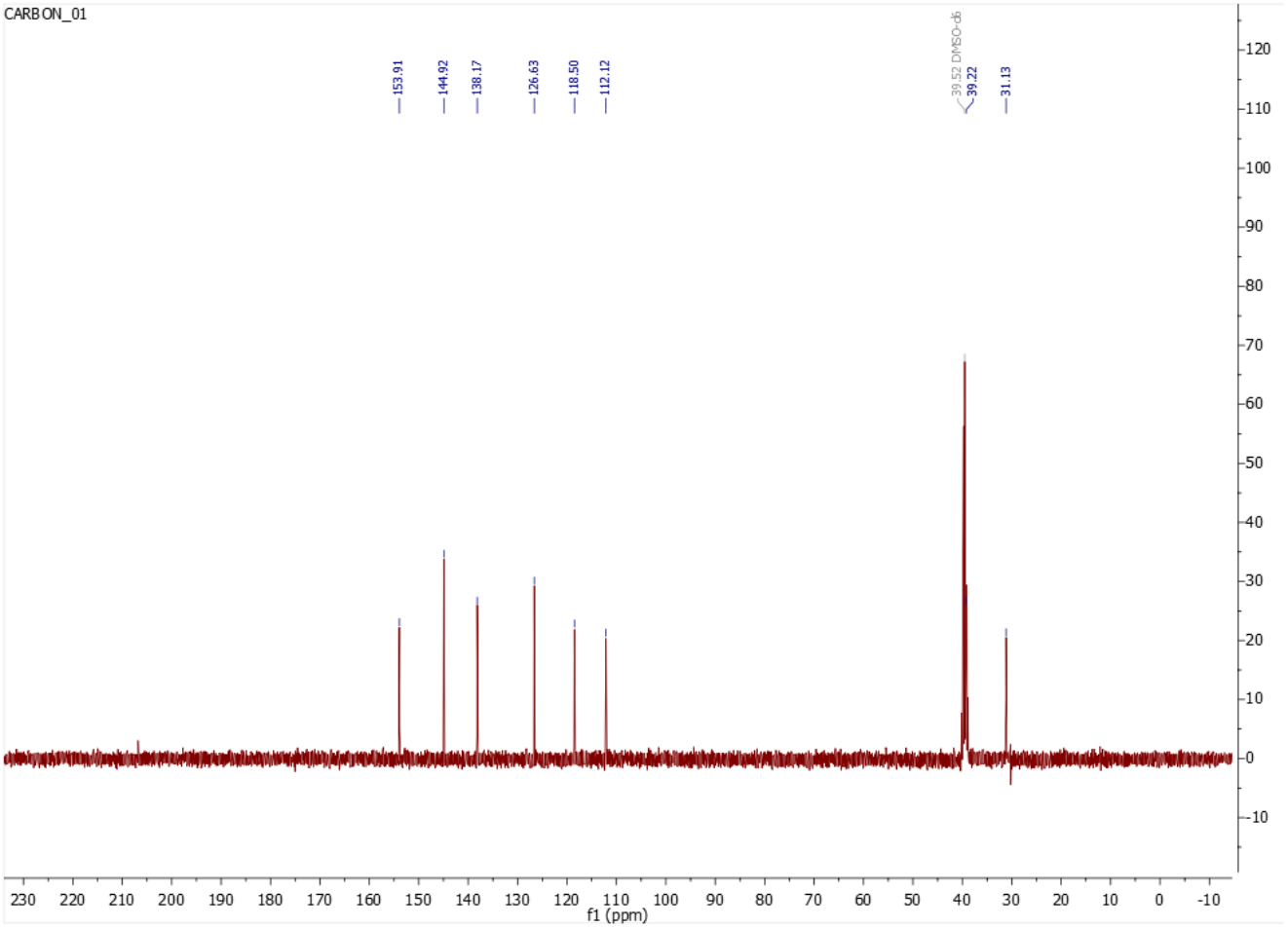
^{1}H NMR of **2d**



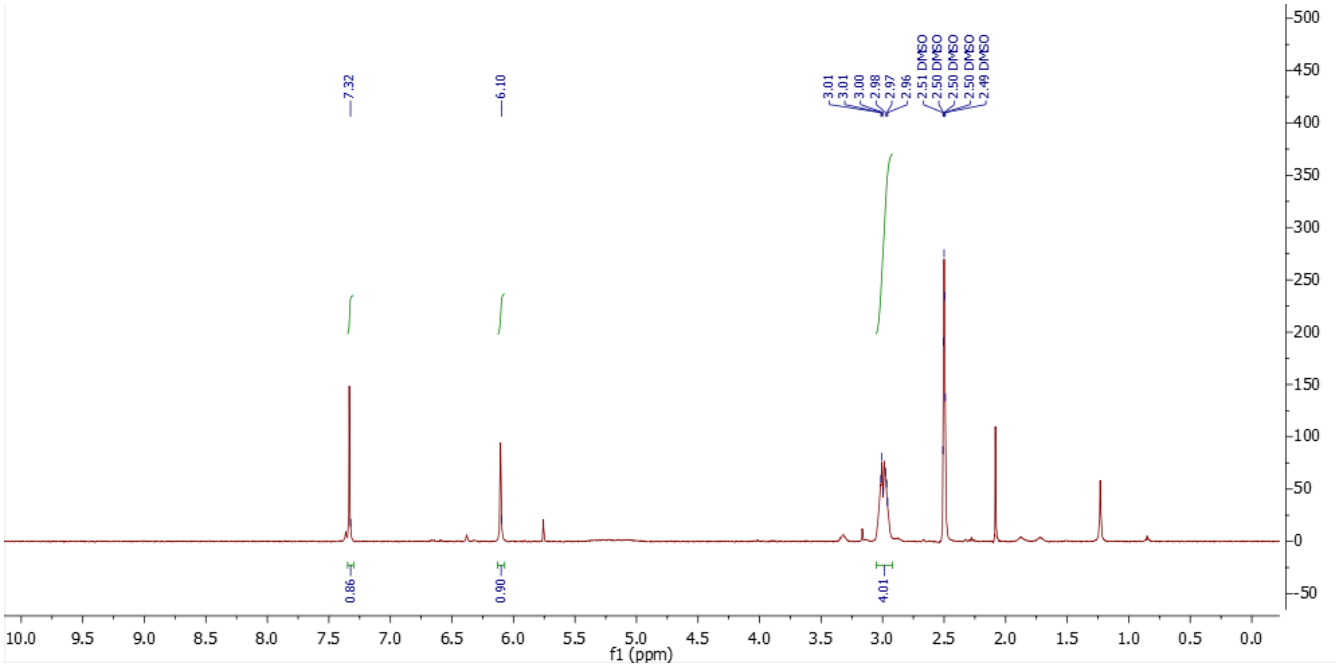
^{1}H NMR of **2e**



^{1}H NMR of **2f**[S2]

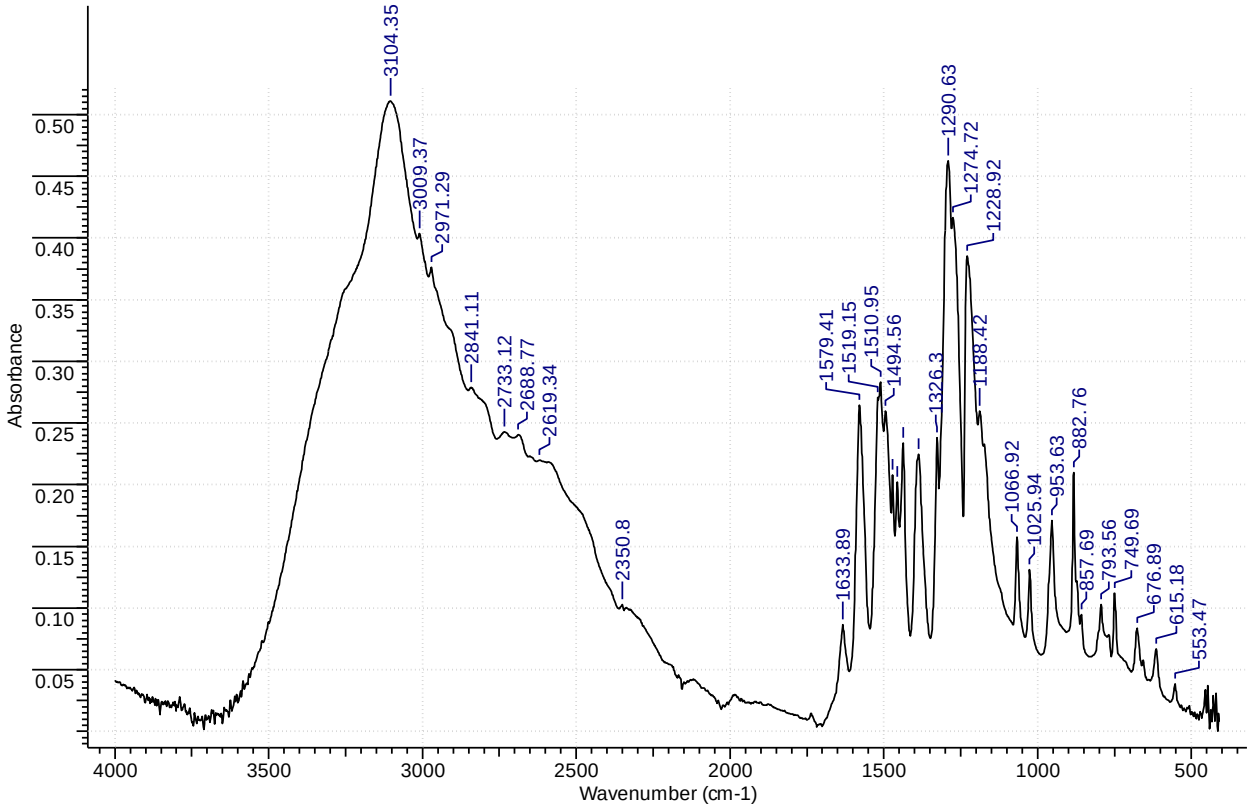


^{13}C NMR of **2f**

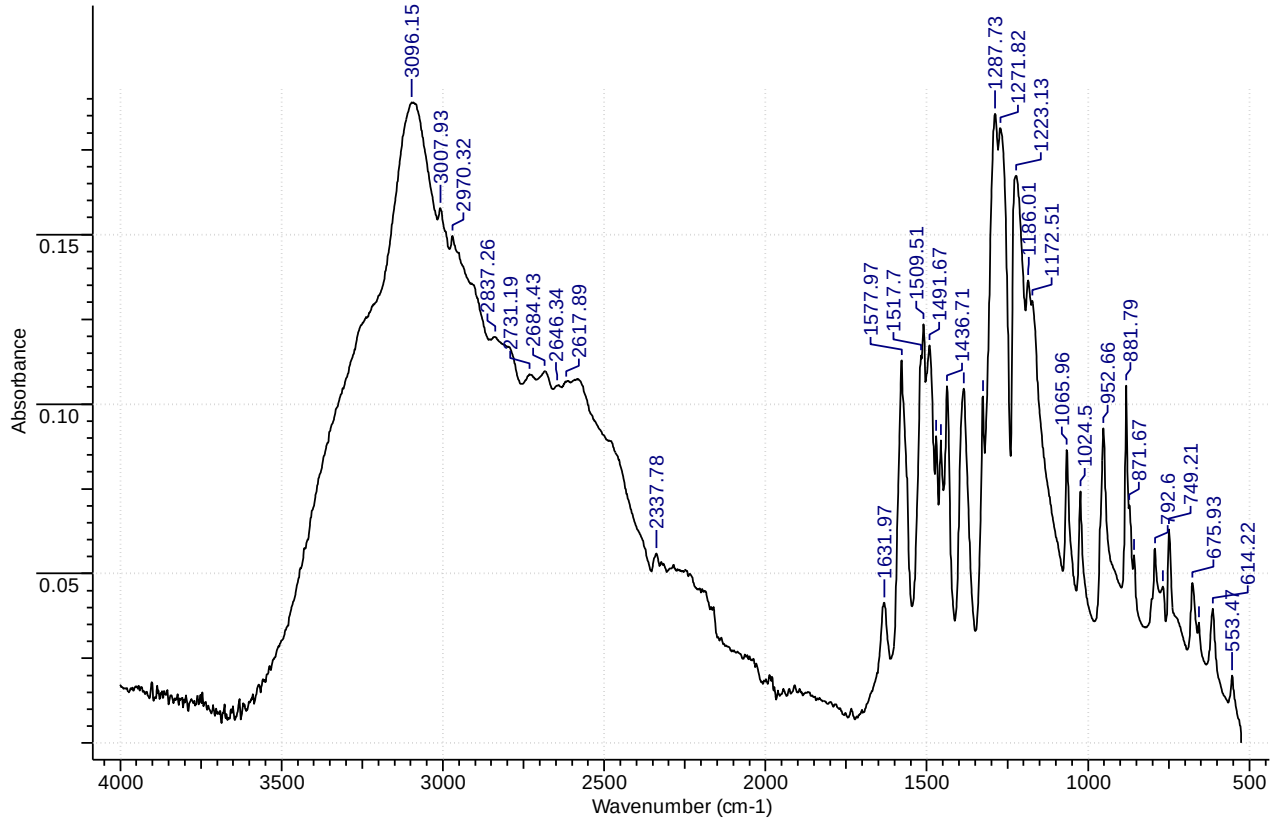


^{1}H NMR of **2f** + $NaHCO_3$

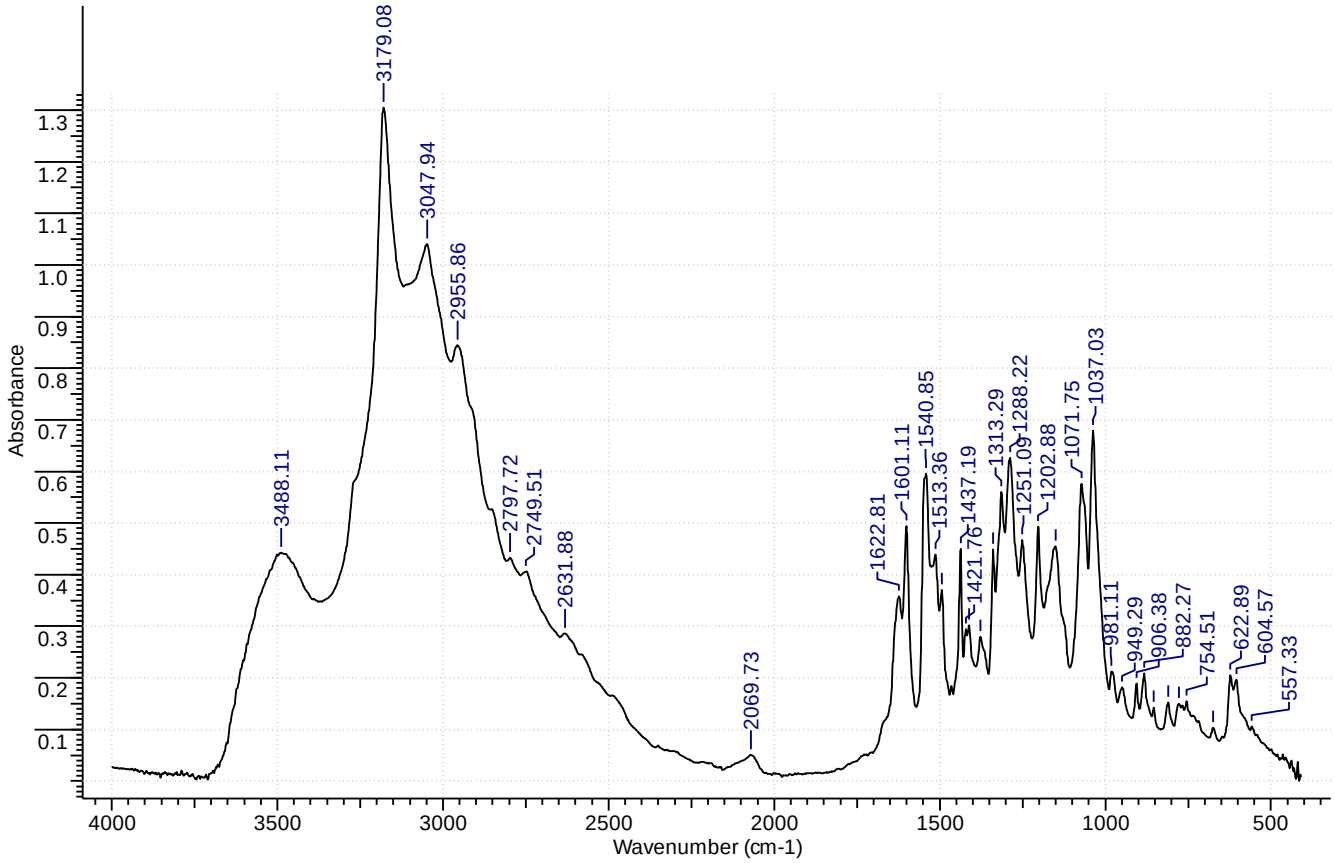
IR-spectroscopy of samples from gram-scale synthesis



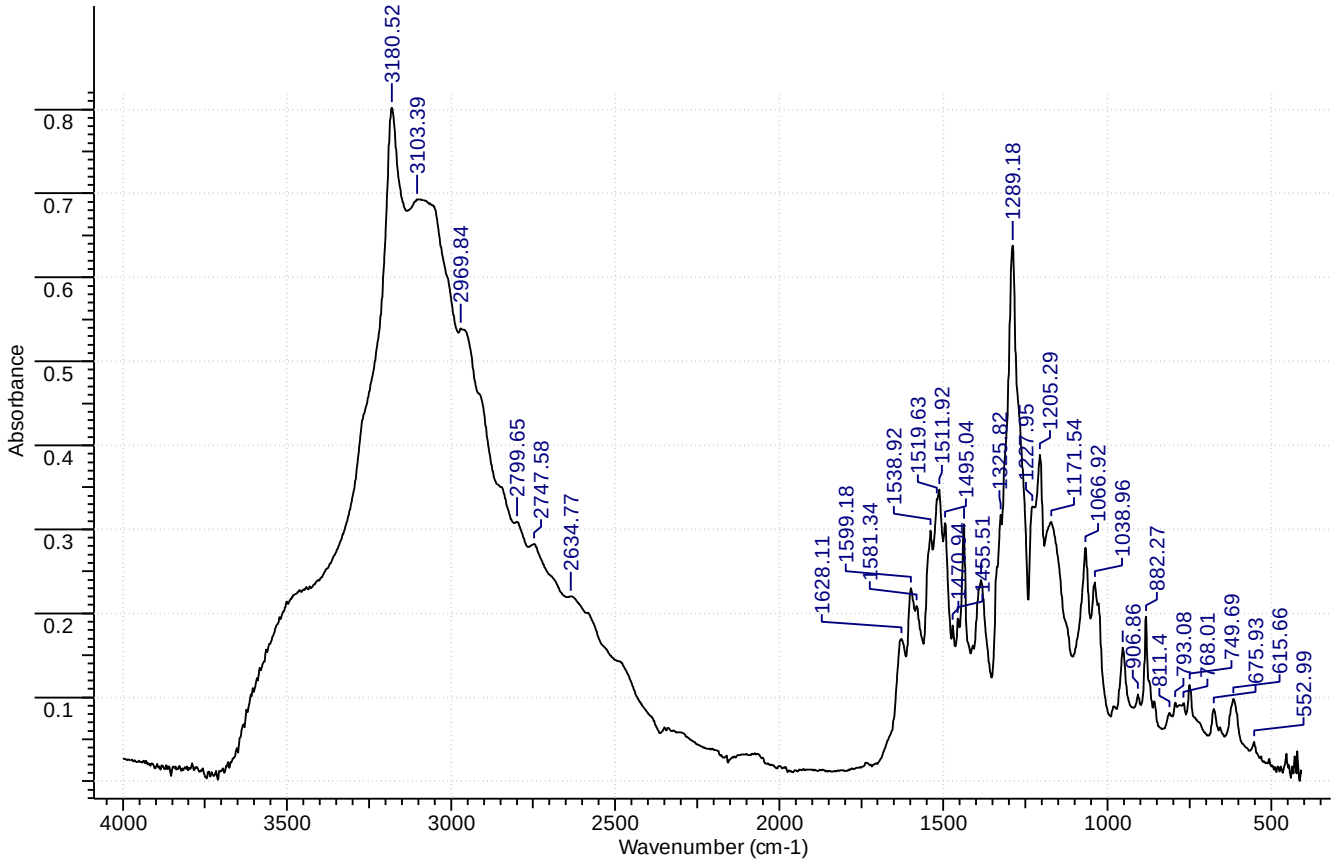
IR spectrum of **2a**



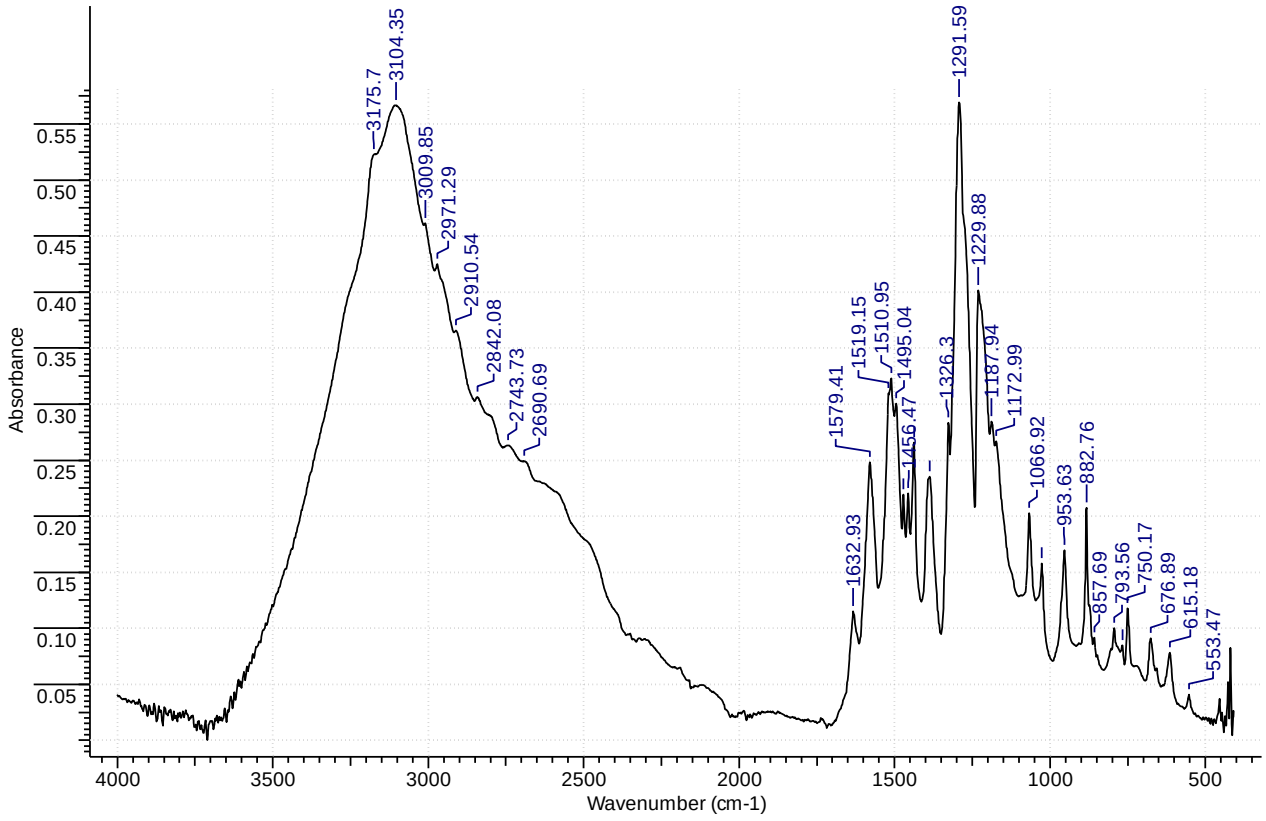
IR spectrum of **2b**



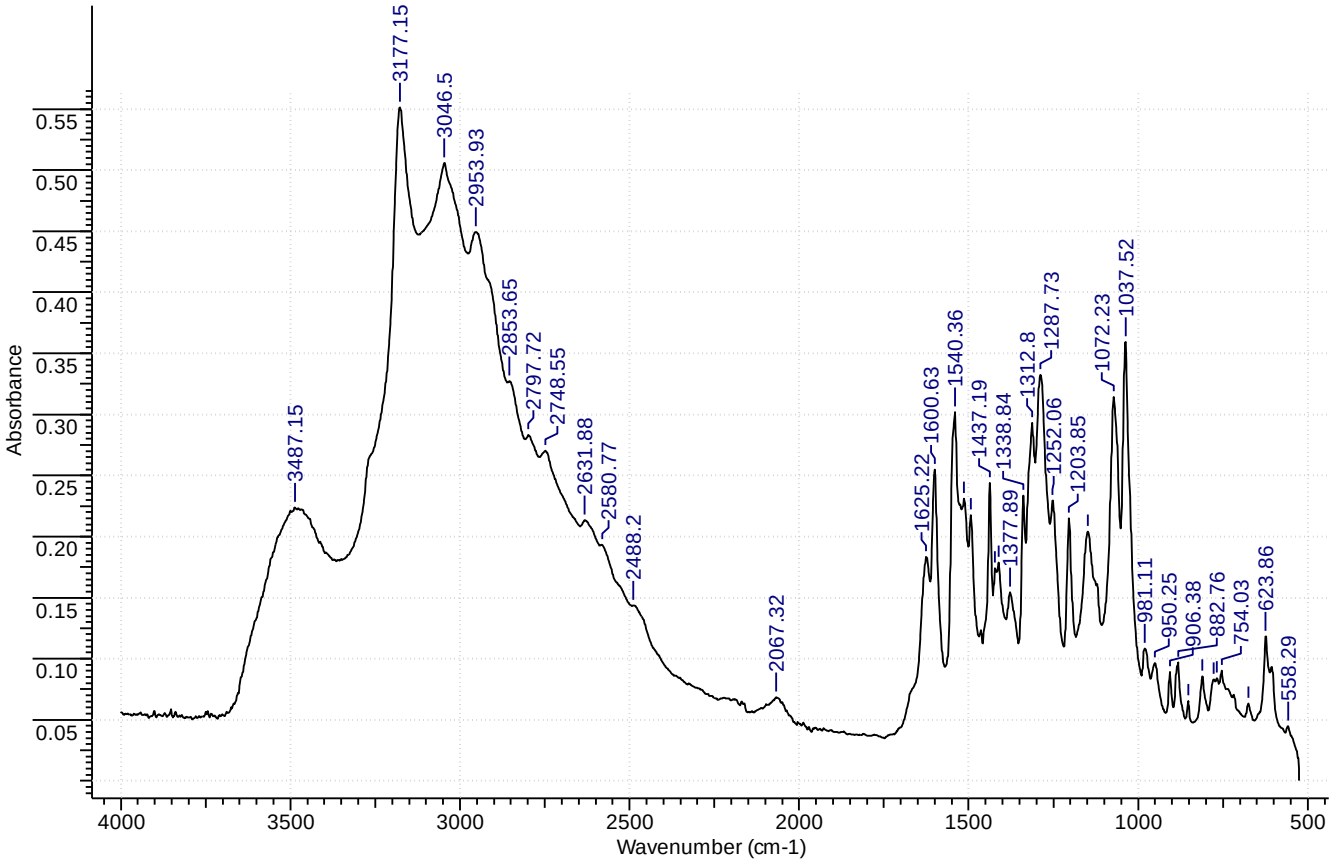
IR spectrum of **2c**



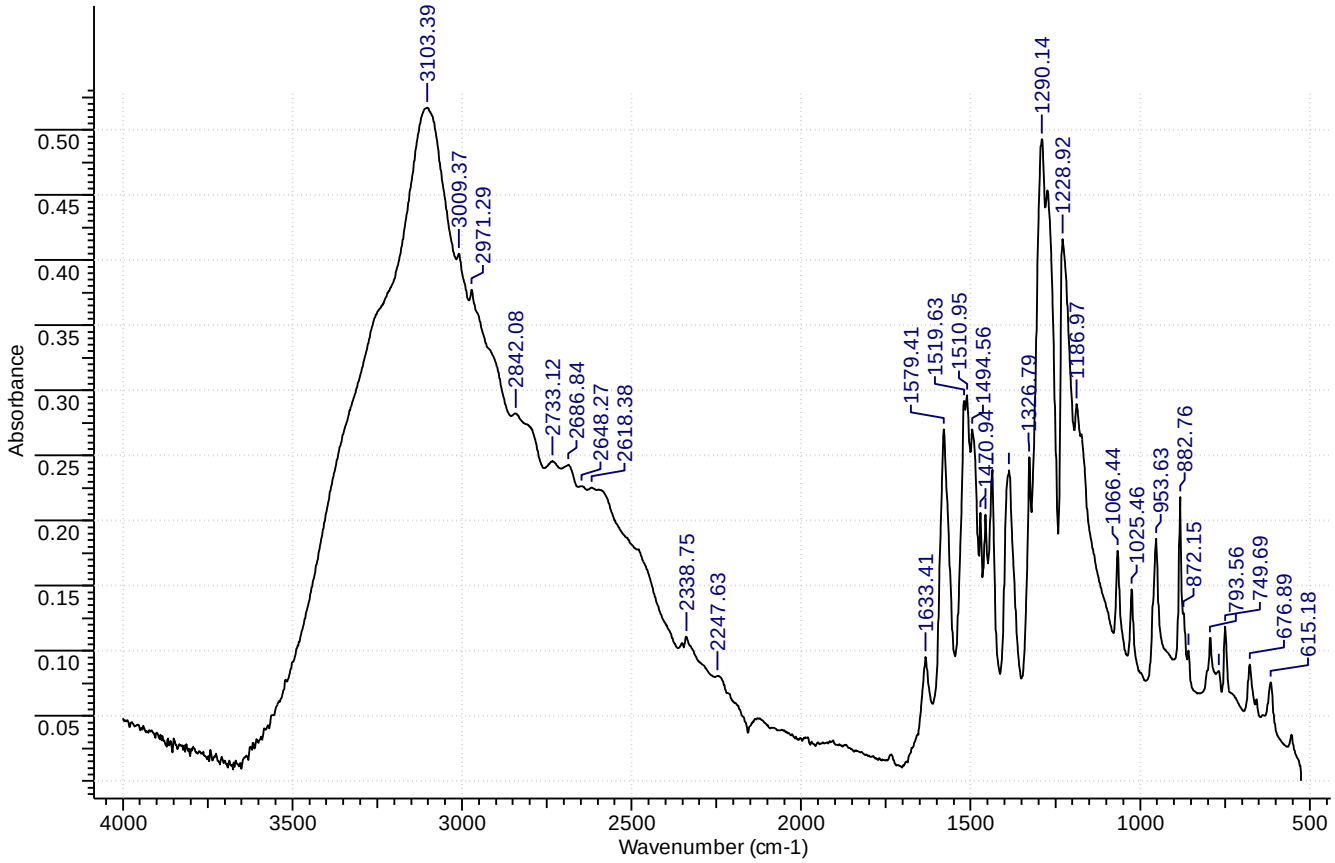
IR spectrum of **2d**



IR spectrum of **2e**

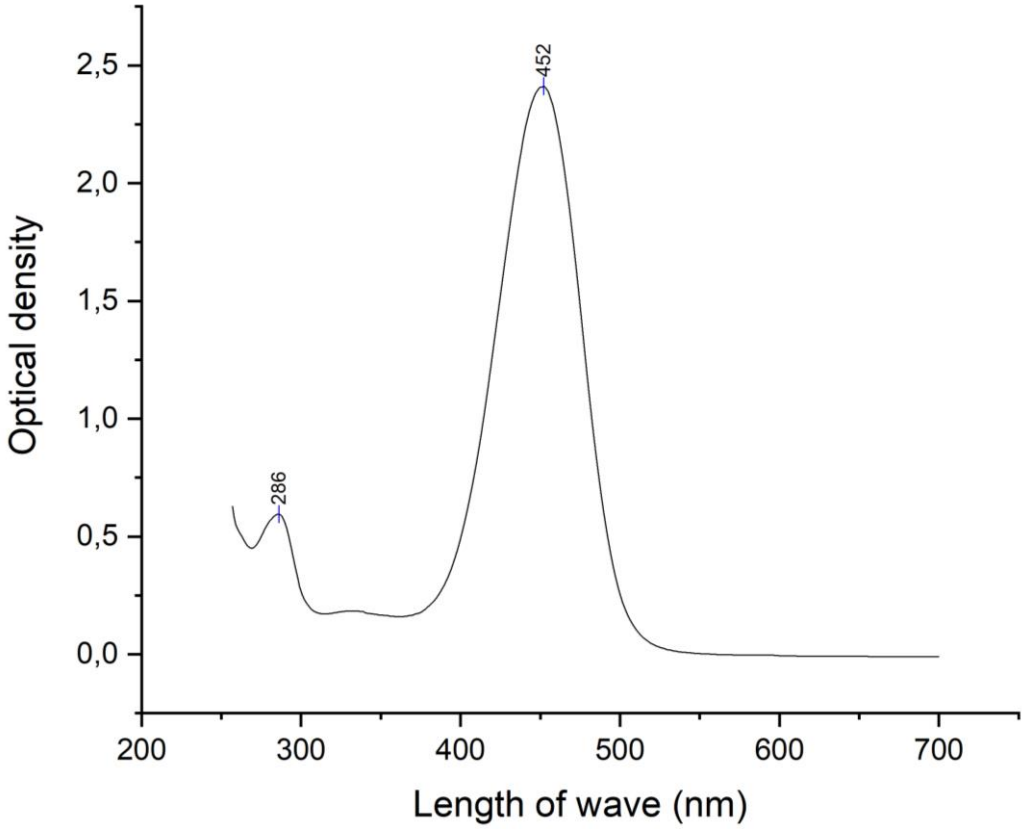


IR spectrum of **2f**

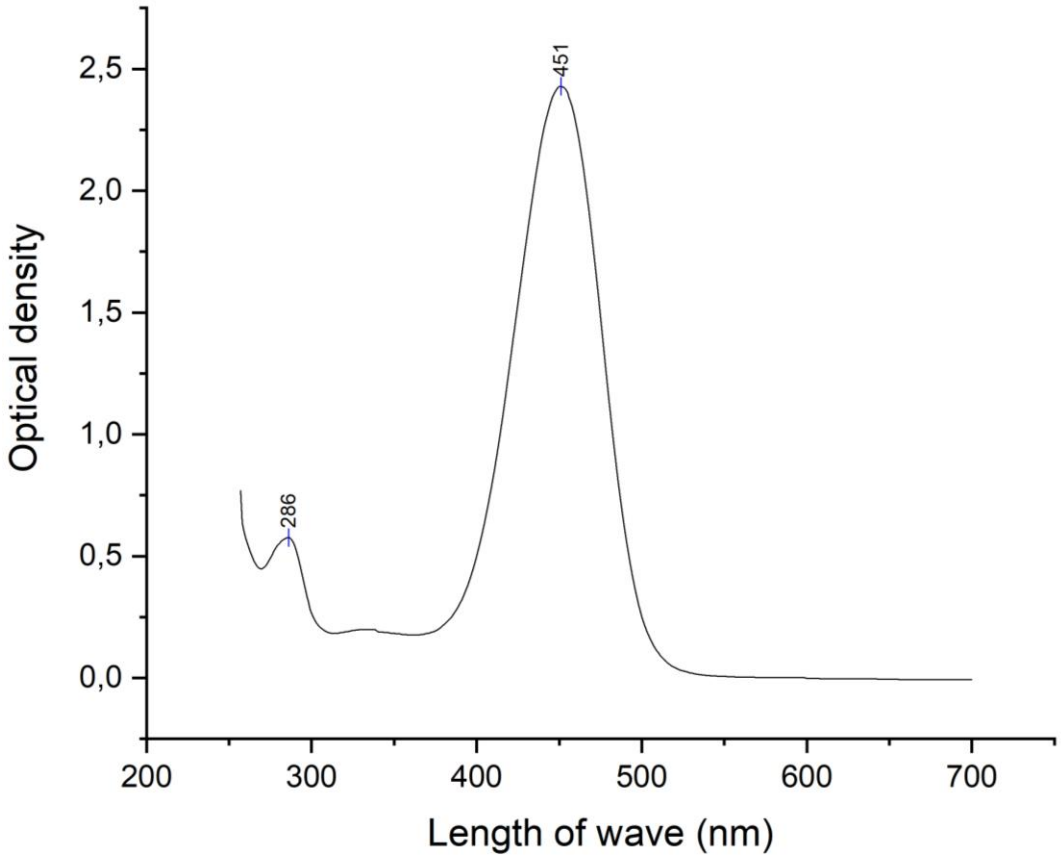


IR spectrum of **2f** + $NaHCO_3$

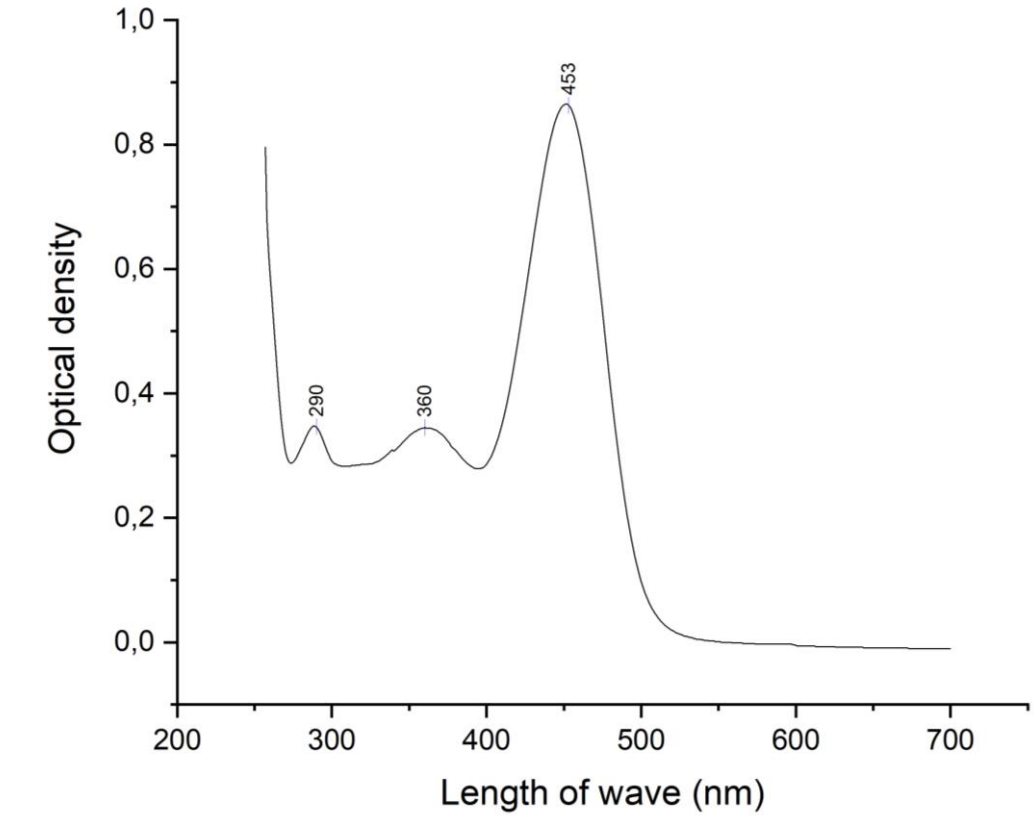
UV-Vis spectroscopy of samples from gram-scale synthesis



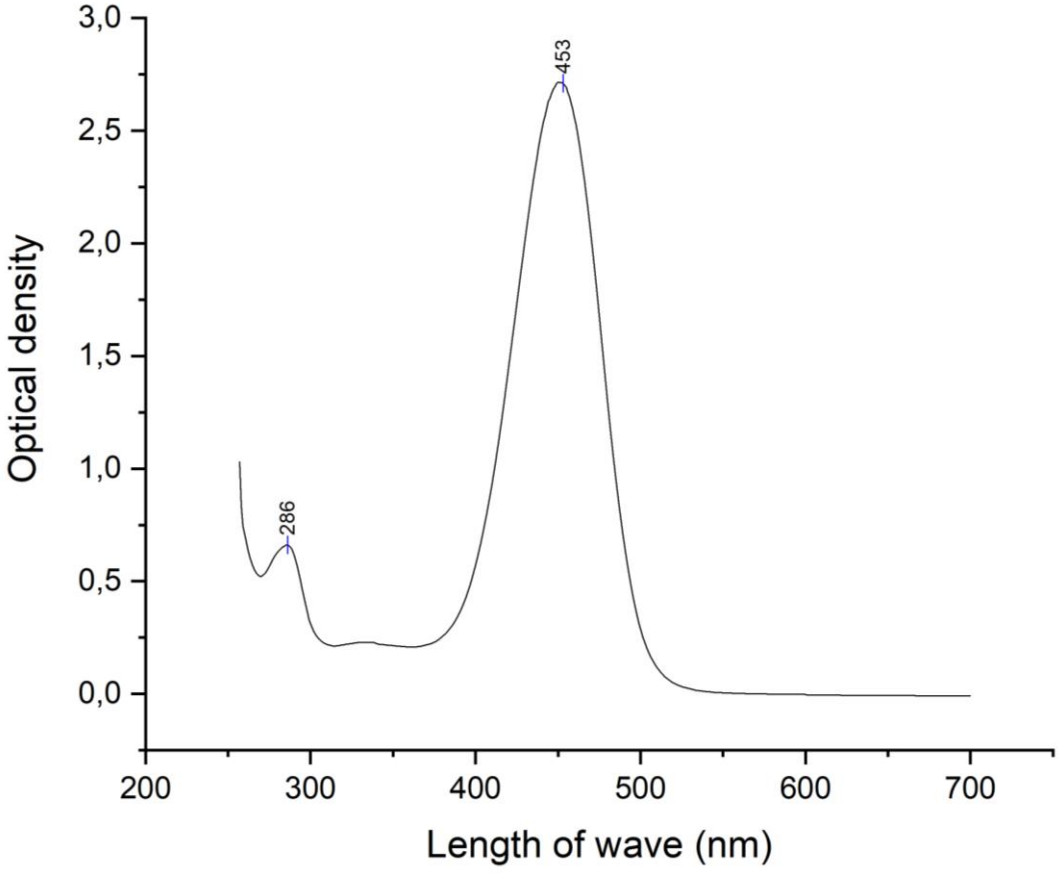
UV-Vis spectrum of sample **2a**



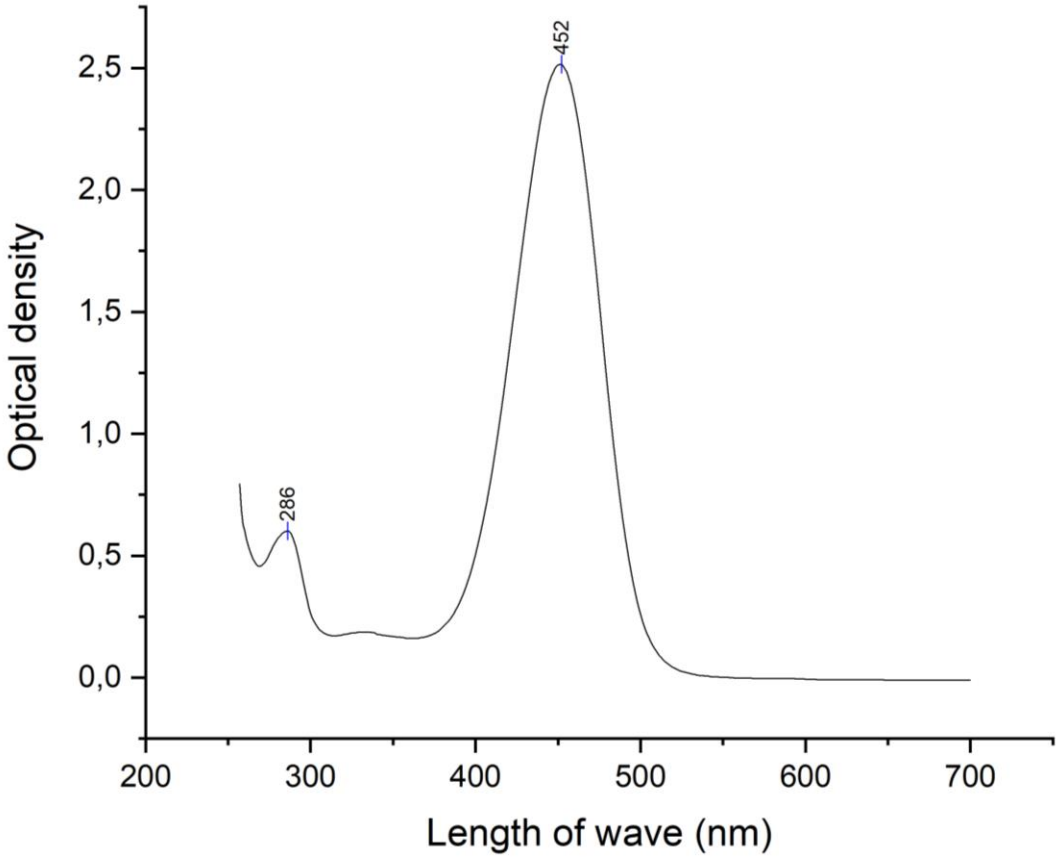
UV-Vis spectrum of **2b**



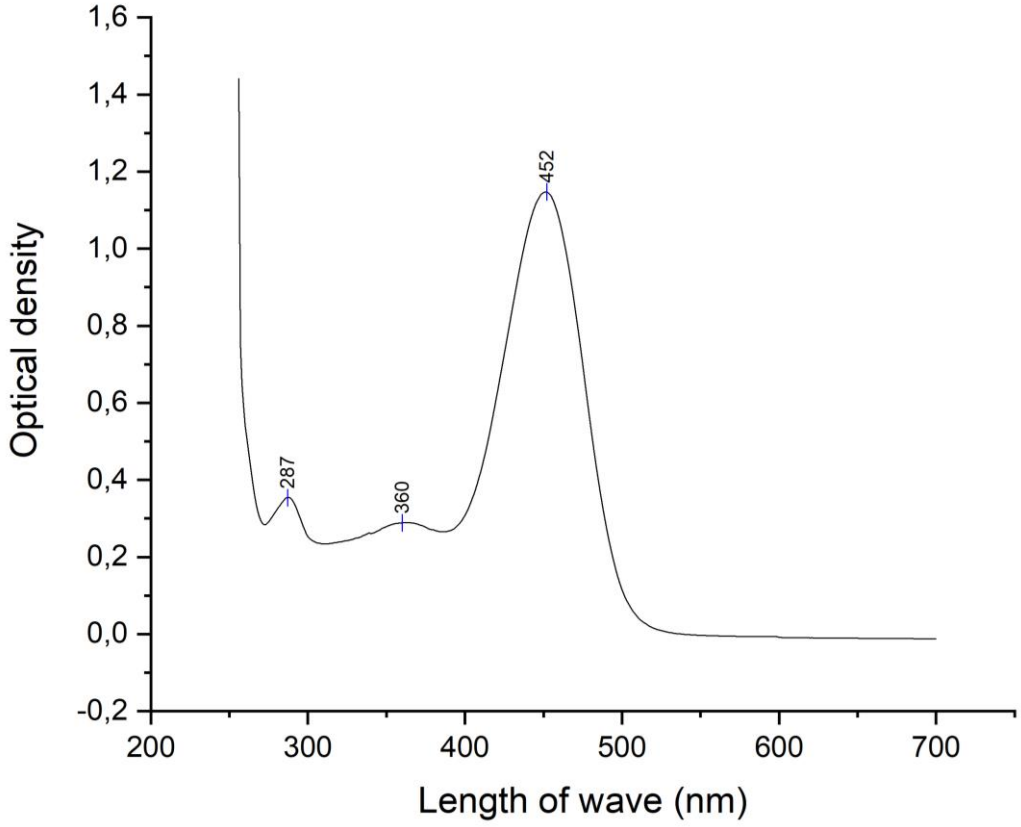
UV-Vis spectrum of **2c**[S2]



UV-Vis spectrum of **2d**

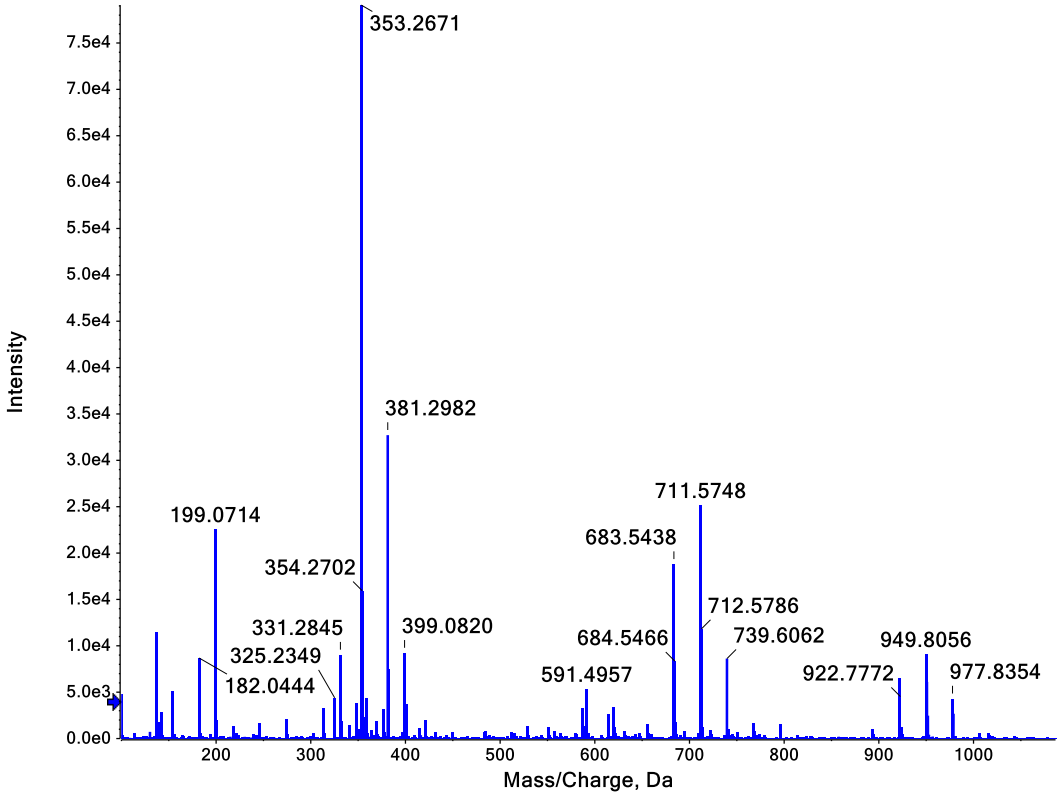


UV-Vis spectrum of **2e**

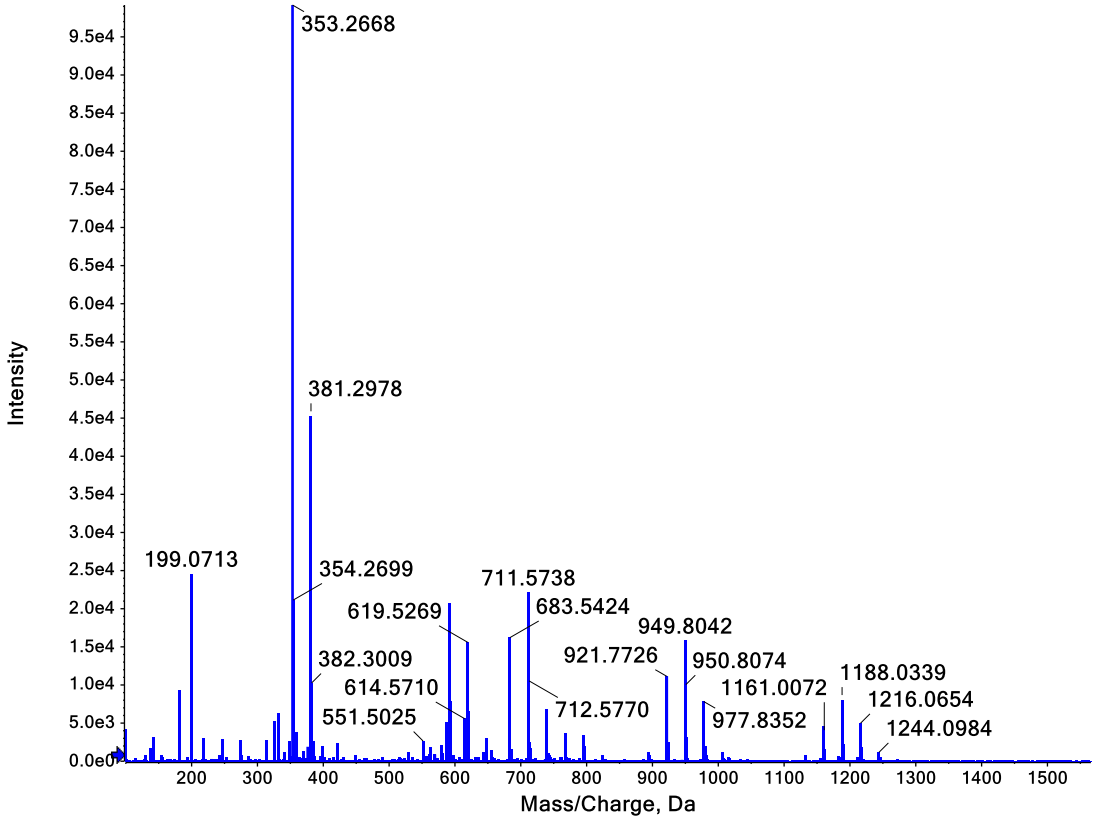


UV-Vis spectrum of **2f**[S2]

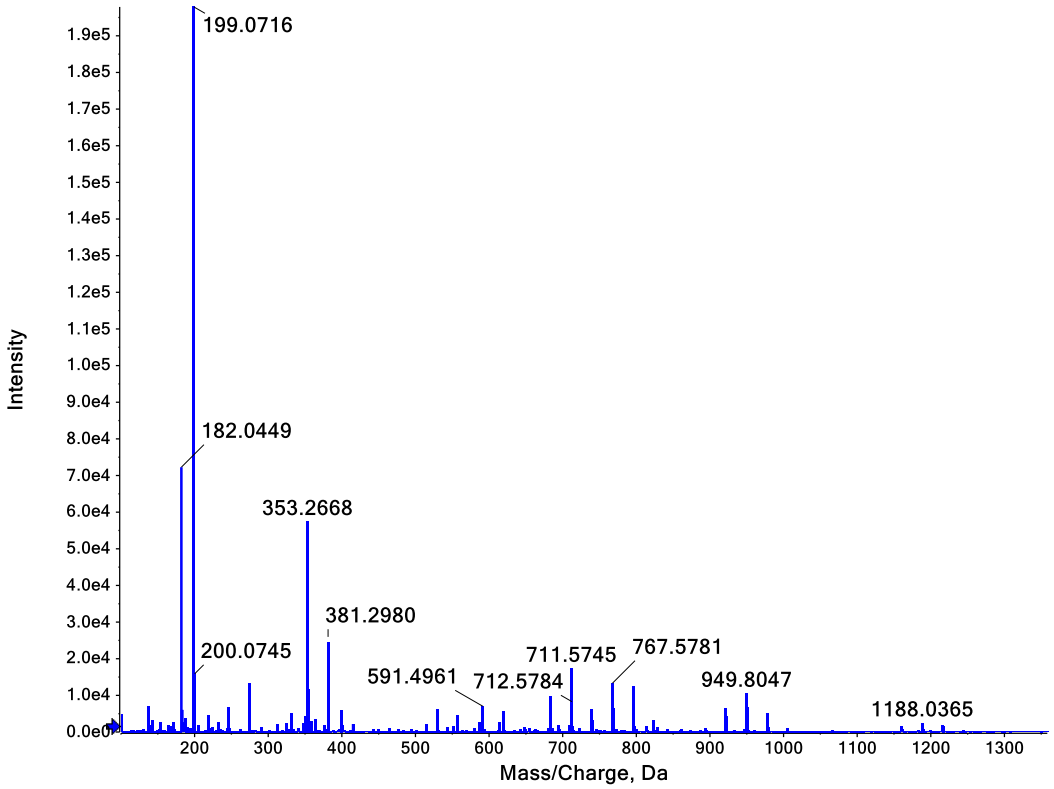
HRMS of samples from gram-scale synthesis



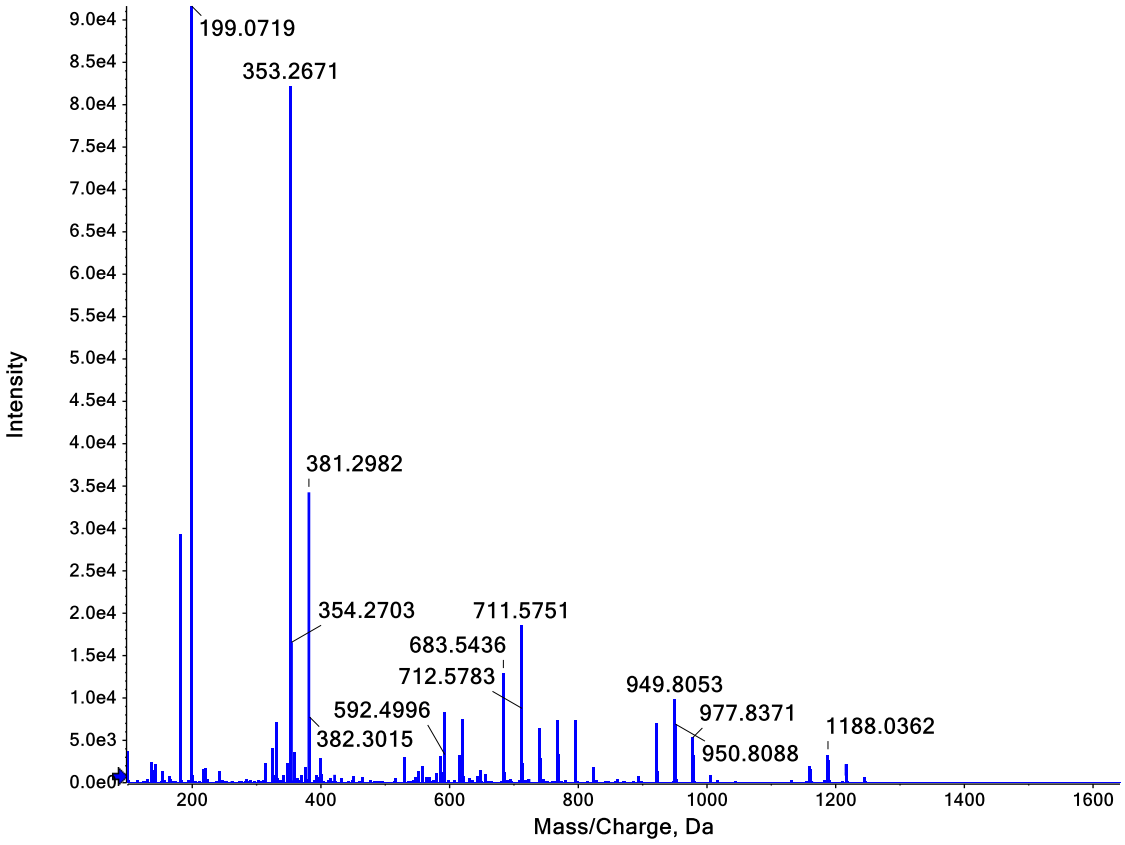
High-resolution mass spectrum measured for sample **2a** using ESI(+)-HRMS



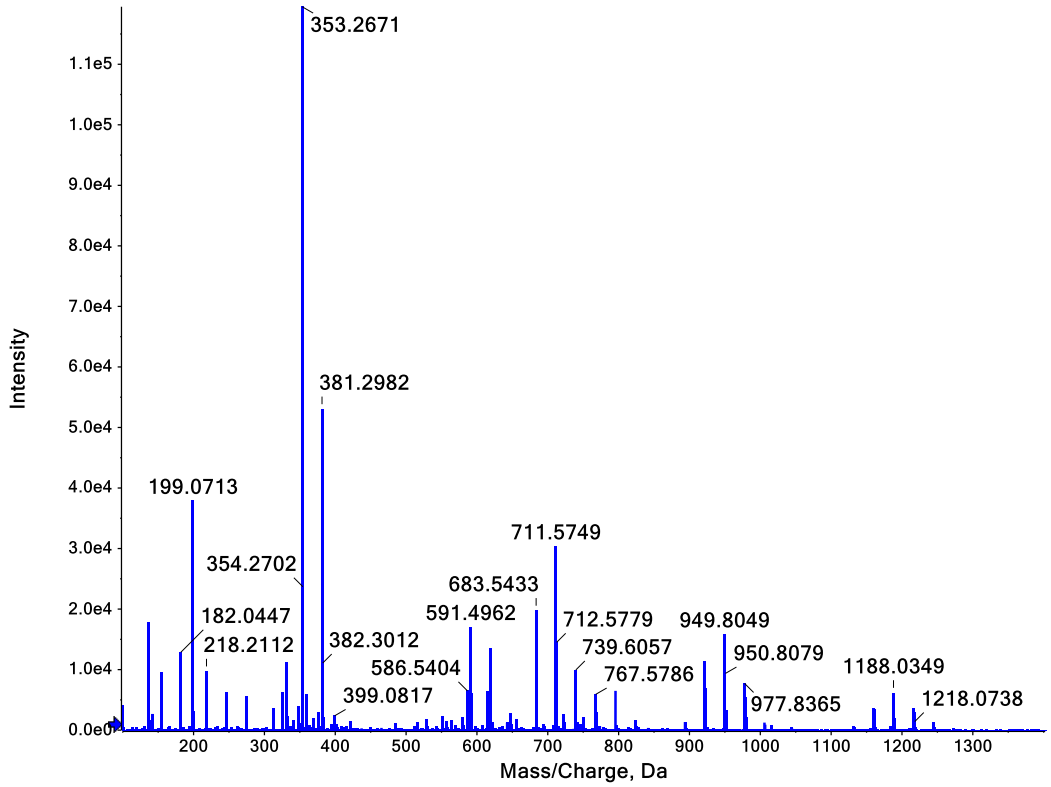
High-resolution mass spectrum measured for sample **2b** using ESI(+)-HRMS



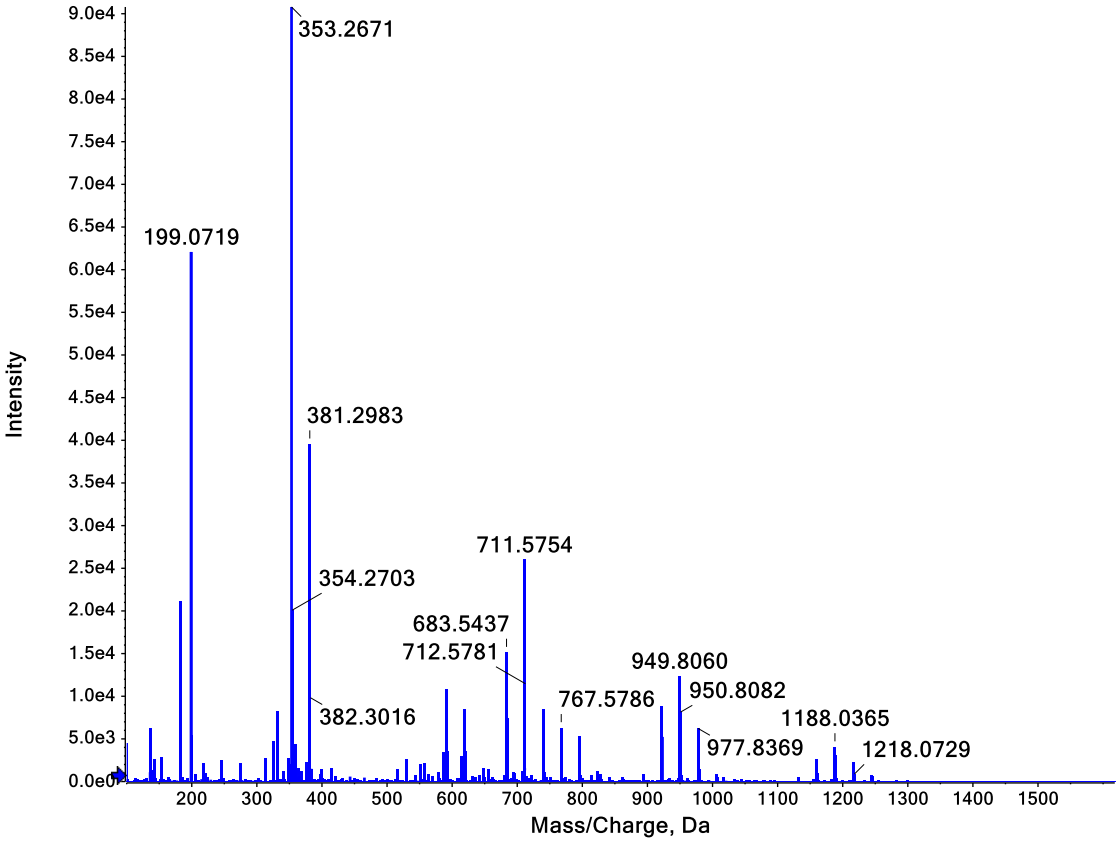
High-resolution mass spectrum measured for sample **2c** using ESI(+)-HRMS



High-resolution mass spectrum measured for sample **2d** using ESI(+)-HRMS



High-resolution mass spectrum measured for sample **2e** using ESI(+)-HRMS



High-resolution mass spectrum measured for sample **2f** using ESI(+)-HRMS

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S2 A. Napolitano, M. d'Ischia, C. Costantini, G. Prota, *Tetrahedron*, 1992, **48**, 8515.

S3 J. C. Rote, S. N. Malkowski, C. S. Cochrane, G. E. Bailey, N. S. Brown, M. Cafiero, L. W. Peterson, *Synth. Commun.*, 2017, **47**, 435.