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Synthesis of 3,4-diarylisoxazoline *N*-oxides from nitrostilbenes and nitroacetates

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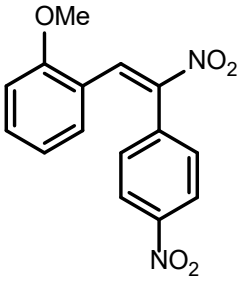
^{1}H and ^{13}C NMR spectra were recorded on Bruker-AM 300, Bruker-DRX 500. Chemical shift values (δ) are given in parts per million (ppm). The values of the spin-spin coupling constants (J) are expressed in hertz (Hz). Low resolution mass spectrum (m/z) was recorded on a Finnigan MAT/INCOS50 mass spectrometer at 70 eV using direct probe injection. High resolution mass spectrum (HRMS) was measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). Melting points were measured using a Boetius melting point apparatus. All solvents and reagents were purified according to standard procedures.

***(E)-1-Methoxy-2-[2-nitro-2-(4-nitrophenyl)vinyl]benzene* 1c**



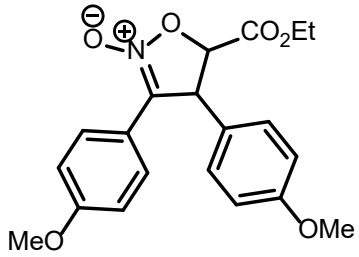
A mixture of 2-methoxybenzaldehyde (3.15 mmol, 1.05 eq.) and 1-nitro-4-(nitromethyl)benzene (3 mmol, 1 eq.) and ammonium acetate (1 mmol, 0.33 eq.) in toluene (4 mL) was stirred under reflux for 6 h. After completion (consumption of starting 1-nitro-4-(nitromethyl)benzene) the mixture was evaporated under reduced pressure, dissolved in CH_2Cl_2 (10 mL) and washed with water (3x10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Further purification by column chromatography on silica gel (10% EtOAc in hexanes) provided pure (*E*)-1-methoxy-2-(2-nitro-2-(4-nitrophenyl)vinyl)benzene **1c**. Yield 62%. Yellow-green crystals; m.p. 118-120°C (EtOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.71 (s, 1H, =CH), 8.28 (d, J=8.3 Hz, 2H, ArH), 7.53 (d, J=8.3 Hz, 2H, ArH), 7.36-7.32 (m, 1H, ArH), 6.93 (d, J=8.2 Hz, 1H, ArH), 6.68-6.64 (m, 2H, ArH), 3.89 (s, 3H, OMe).**^{13}C NMR** (126 MHz, $CDCl_3$) δ: 158.97, 148.35, 147.00, 137.55, 133.09, 132.36, 132.05, 130.31, 124.07, 120.55, 119.42, 111.21, 55.71.

HRMS (ESI) m/z $[M+Na]^+$ calc. for $C_{15}H_{12}N_2NaO_5$ 323.0638, found 323.0638

General procedure for synthesis of 3,4-diarylisoxazoline-N-oxides **3a-3d:**

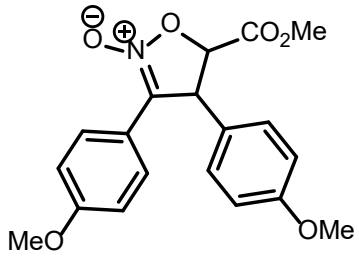
Nitrostilbene **1a-c** (0.5 mmol) and nitroacetate **2a,b** (0.55 mmol) were dissolved in acetonitrile (2 ml), then triethylamine (1 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 h until completion (consumption of starting nitrostilbene **1a-c**). Then the reaction mixture was evaporated under reduced pressure, dissolved in CH_2Cl_2 (5 mL) and washed with water (3x10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Further purification by column chromatography on silica gel 20% EtOAc in hexanes provided pure 3,4-diarylisoxazoline-N-oxides **3a-d**

5-Ethoxycarbonyl-3,4-bis(4-methoxyphenyl)-4,5-dihydroisoxazole 2-oxide **3a**



Yield 74%. White solid. m.p. 125-126°C (EtOH) (lit. [1] m.p. 124-125°C). **^{1}H NMR** (300 MHz, DMSO-d_6) δ: 7.85 (d, *J* = 8.9 Hz, 4H, ArH), 7.29 (d, *J* = 8.6 Hz, 2H, ArH), 7.02-6.93 (m, 4H, ArH), 5.32 (d, *J* = 2.6 Hz, 1H, H5), 5.03 (d, *J* = 2.6 Hz, 1H, H4), 4.26 (q, *J* = 7.1 Hz, 2H, O$\underline{CH_2}CH_3$), 3.77 (s, 3H, OMe), 3.74 (s, 3H, OMe), 1.28 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$).

5-Methoxycarbonyl-3,4-bis(4-methoxyphenyl)-4,5-dihydroisoxazole 2-oxide **3b**

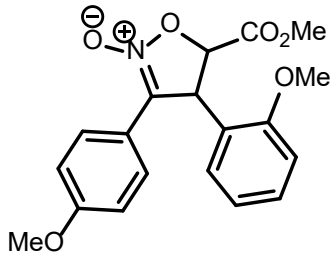


Yield 77%. White solid. m.p. 147-149°C (EtOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.82 (d, J = 8.6 Hz, 2H, ArH), 7.25 (m, 2H, ArH), 6.88 (d, J = 8.6 Hz, 2H, ArH), 6.86 (d, J = 8.9 Hz, 2H, ArH), 4.99 (d, J = 1.8 Hz, 1H, H5), 4.77 (d, J = 1.8 Hz, 1H, H4), 3.87 (s, 3H, OMe), 3.79 (s, 6H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 169.89, 160.44, 159.76, 130.27, 128.55, 128.39, 117.87, 114.95, 114.65, 114.27, 78.77, 55.36, 54.00, 53.22

Mass spectrum m/z (%): 357 $[M]^+$ (42), 239 (100), 165 (23), 135 (36), 121 (48), 77 (23), 59 (29), 29 (38), 15 (32).

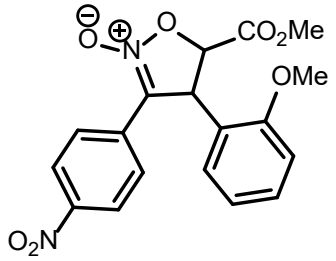
Found (%): C 63.69; H 5.47; N 3.83. $C_{19}H_{19}NO_6$. Calculated (%): C 63.86; H 5.36; N 3.92

***5-Methoxycarbonyl-4-(2-methoxyphenyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole 2-oxide* 3c**



Yield 68%. White solid, m.p. 131-133°C (EtOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.86 (d, J = 9.0 Hz, 2H),7.32 (m, 1H, ArH), 7.13 (d, J=8.2 Hz, 1H, ArH), 6.96 (d, J=8.2 Hz, 1H, ArH), 6.92-6.86 (m, 3H, ArH), 5.47 (d, J = 2.5 Hz, 1H), 4.81 (d, J = 2.5 Hz, 1H), 3.95 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.81 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 169.71, 160.37, 156.17, 129.79, 128.42, 128.24, 125.80, 121.14, 118.12, 114.58, 114.18, 110.95, 78.19, 55.71, 55.31, 53.05, 48.05.
HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{20}NO_6$ 358.1285, found 358.1275.

***5-Methoxycarbonyl-4-(2-methoxyphenyl)-3-(4-nitrophenyl)-4,5-dihydroisoxazole 2-oxide* 3d**

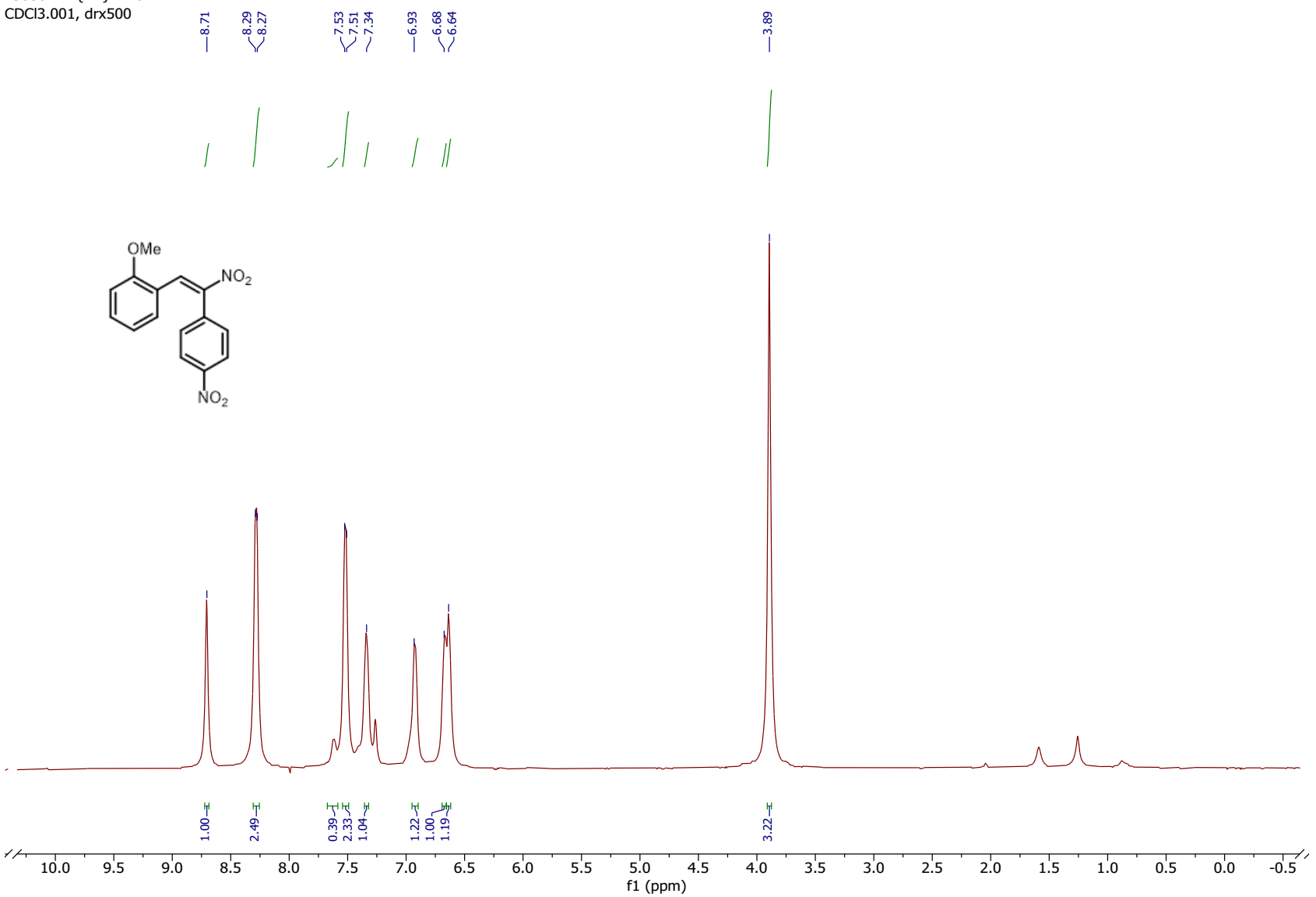


Yield 70%. White solid. m.p. 178-180°C (EtOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 8.18 (d, J=8.7 Hz, 2H, ArH), 8.03 (d, J=8.8 Hz, 2H, ArH), 7.33 (t, J=7.3 Hz, 1H, ArH), 7.10 (d, J=7.5 Hz, 1H, ArH), 6.97 (d, J=8.3 Hz, 1H, ArH), 6.91 (t, J=7.5 Hz, 1H, ArH), 5.50 (d, J=2.9 Hz, 1H, H5), 4.90 (d, J=2.8 Hz, 1H, H4), 3.94 (s, 3H, OMe), 3.88 (s, 3H, OMe). **^{13}C NMR** (126 MHz, $CDCl_3$) δ: 169.07, 156.23, 147.34, 131.99, 130.38, 128.16, 127.09, 124.90, 123.92, 121.43, 114.05, 111.27, 78.50, 55.82, 53.28, 47.76.
HRMS (ESI) m/z $[M+H]^+$ calc. for $C_{18}H_{17}N_2O_7$ 373.1030, found 373.1021.

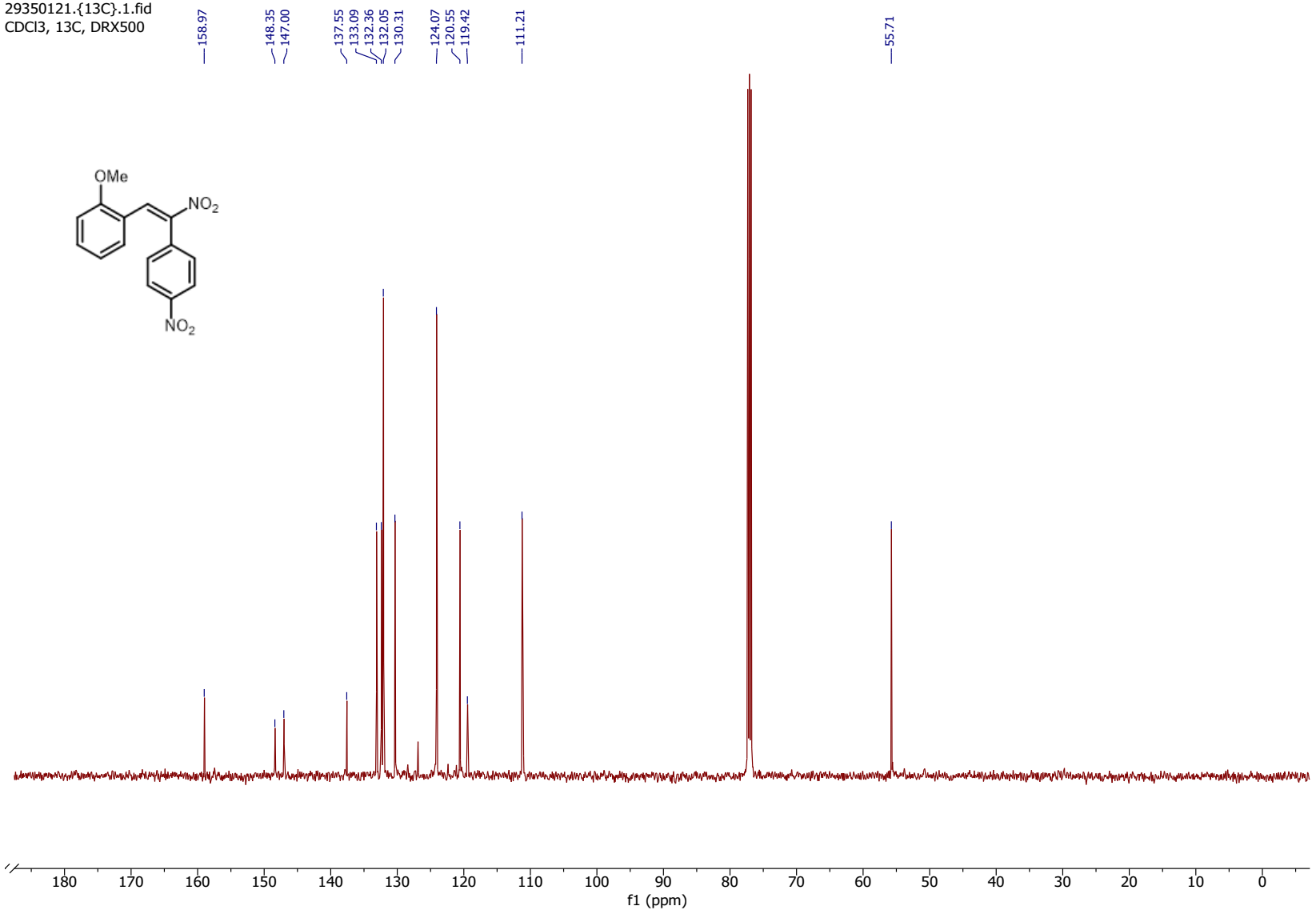
References.

S1. E. A. Silyanova, A. V. Samet and V. V. Semenov, *J. Org. Chem*., 2022, **87**, 6444; https://doi.org/10.1021/acs.joc.2c00312.

^{1}H NMR of compound **1c** ($CDCl_3$)



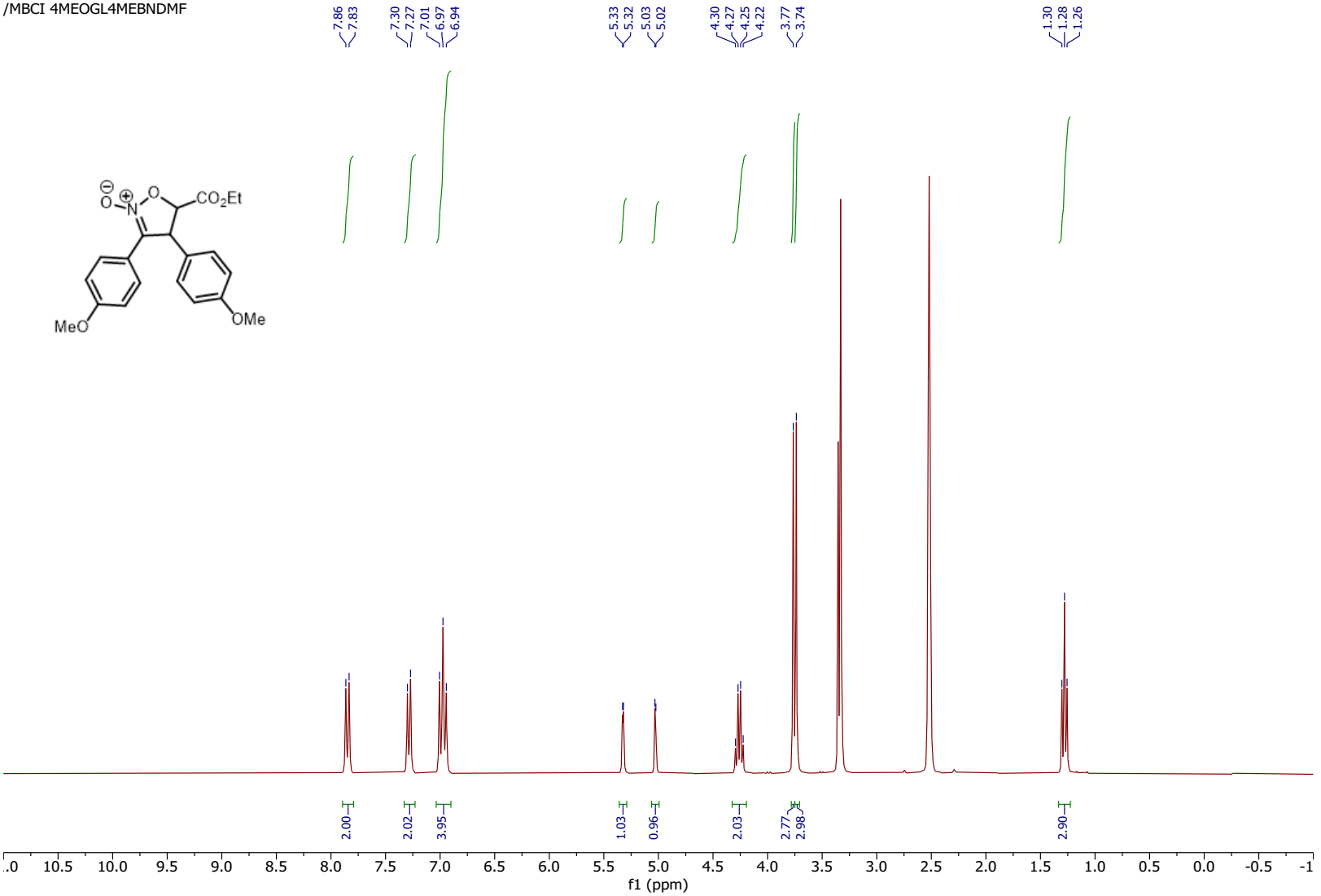
^{13}C NMR of compound **1c** ($CDCl_3$)



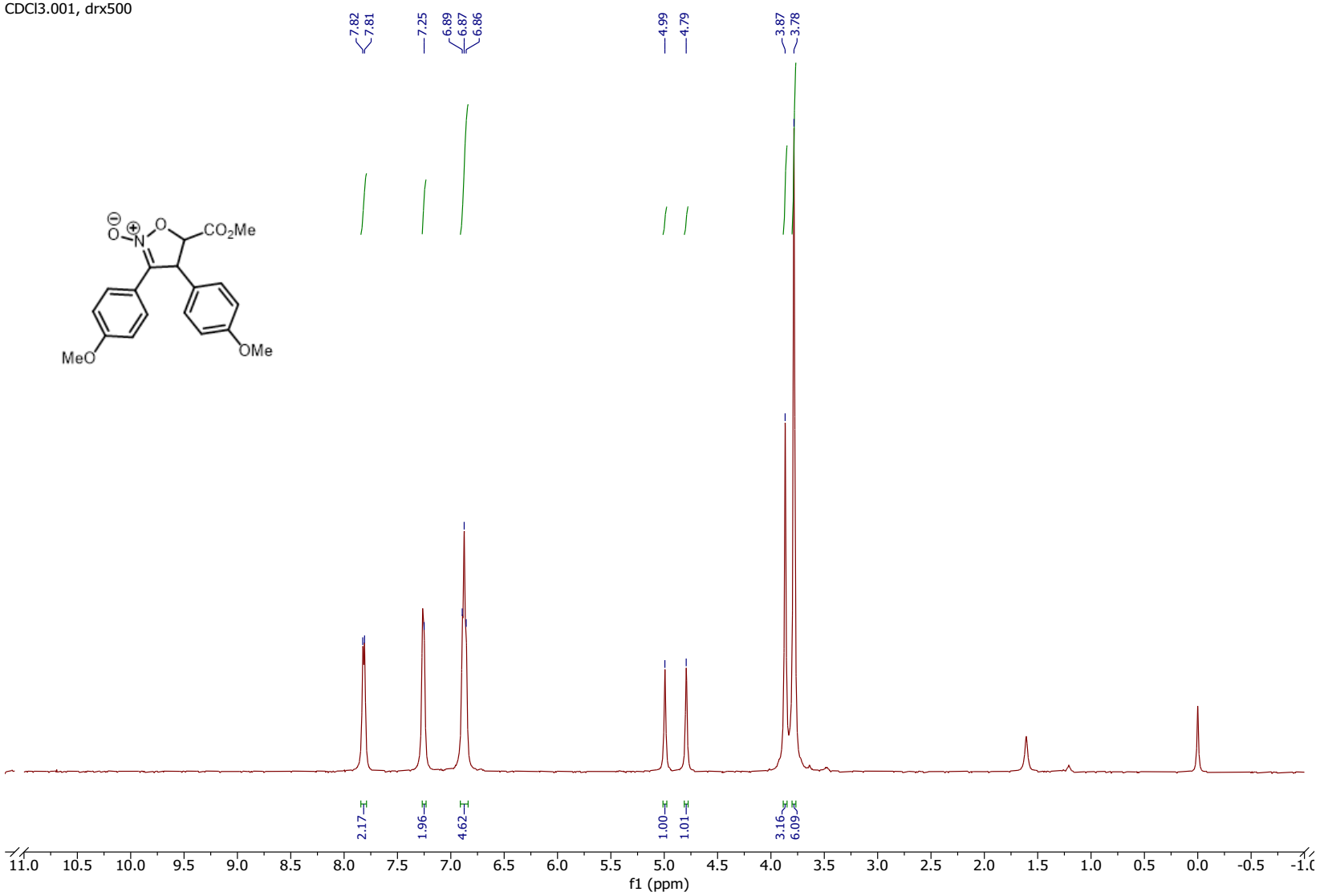
^{1}H NMR of compound **3a** (DMSO-d_6)

50156851.{1H}.1.fid

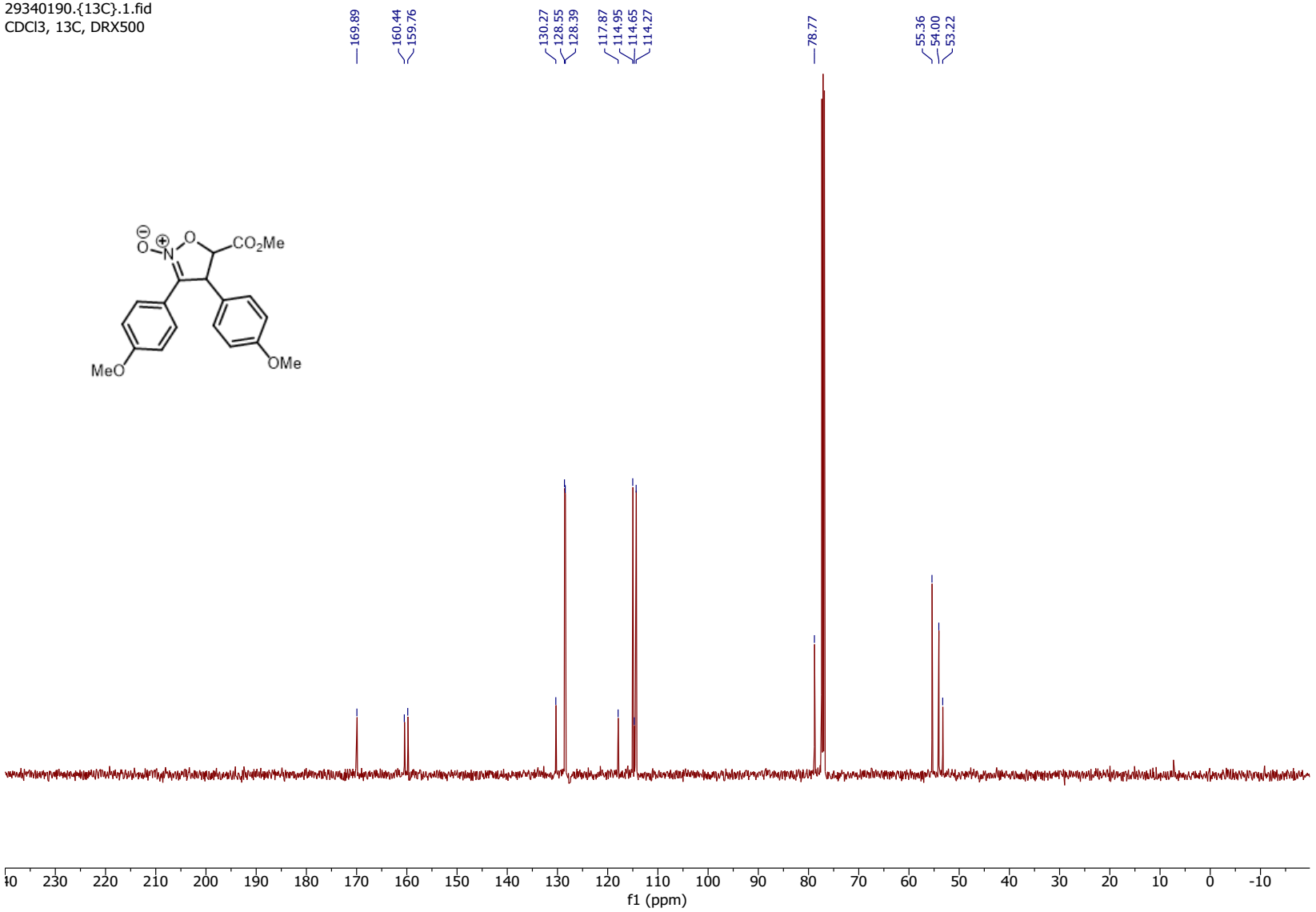
/MBCI 4MEOGL4MEBNDMF



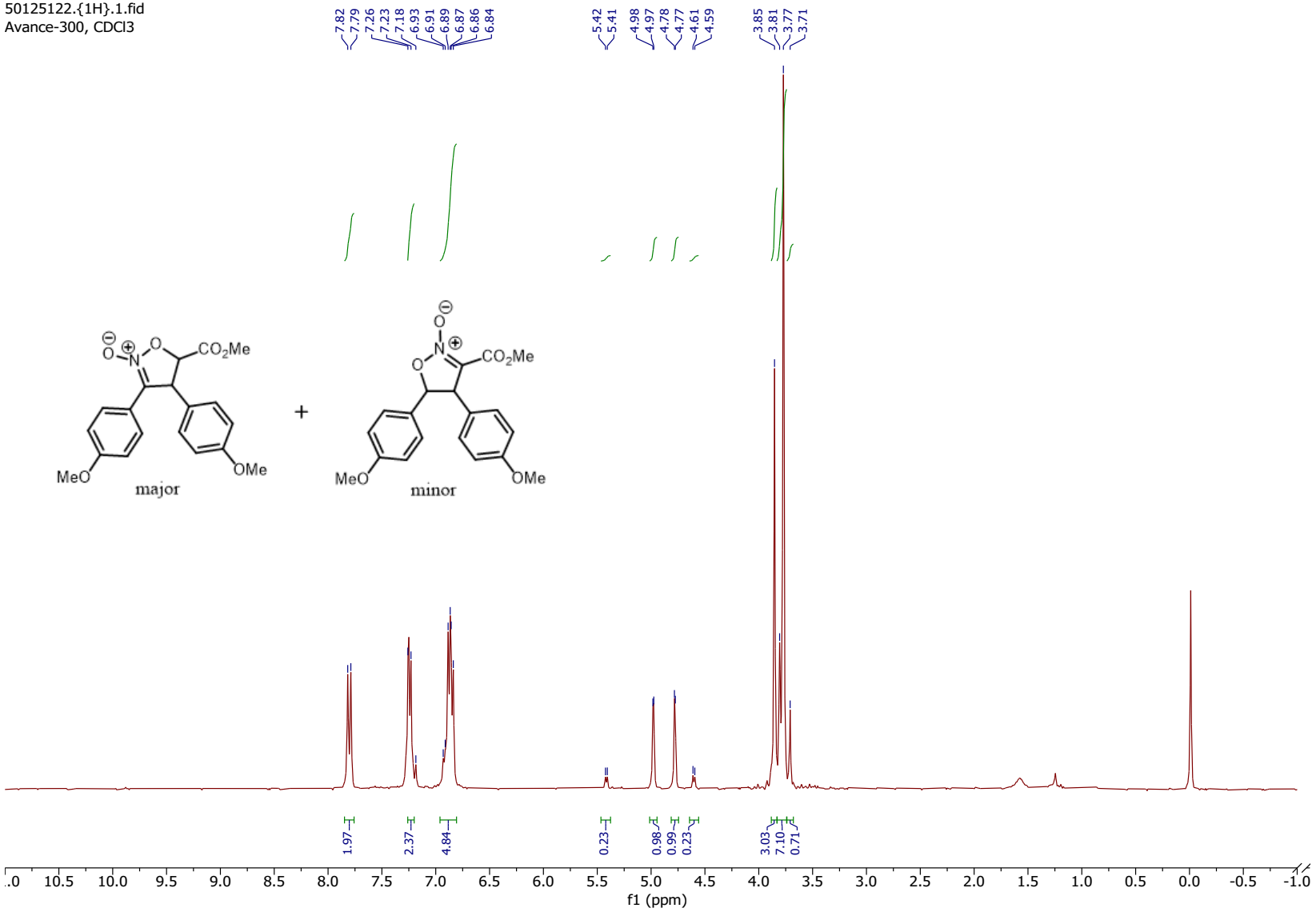
^{1}H NMR of compound **3b** ($CDCl_3$)



^{13}C NMR of compound **3b** ($CDCl_3$)

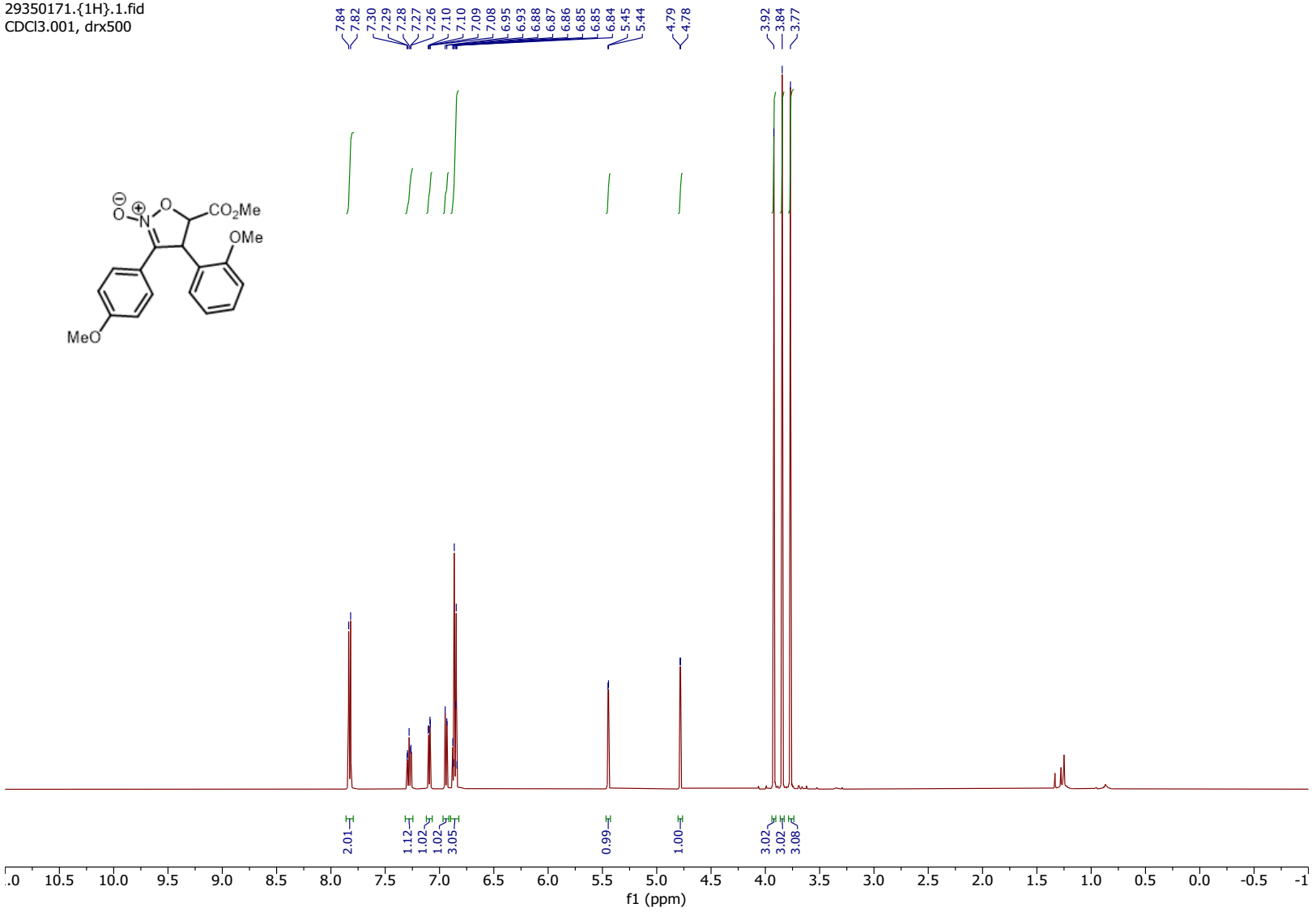


^{1}H NMR of a mixture of **3b** (major) and **3'b** (minor) ($CDCl_3$)



^{1}H NMR of compound **3c** ($CDCl_3$)

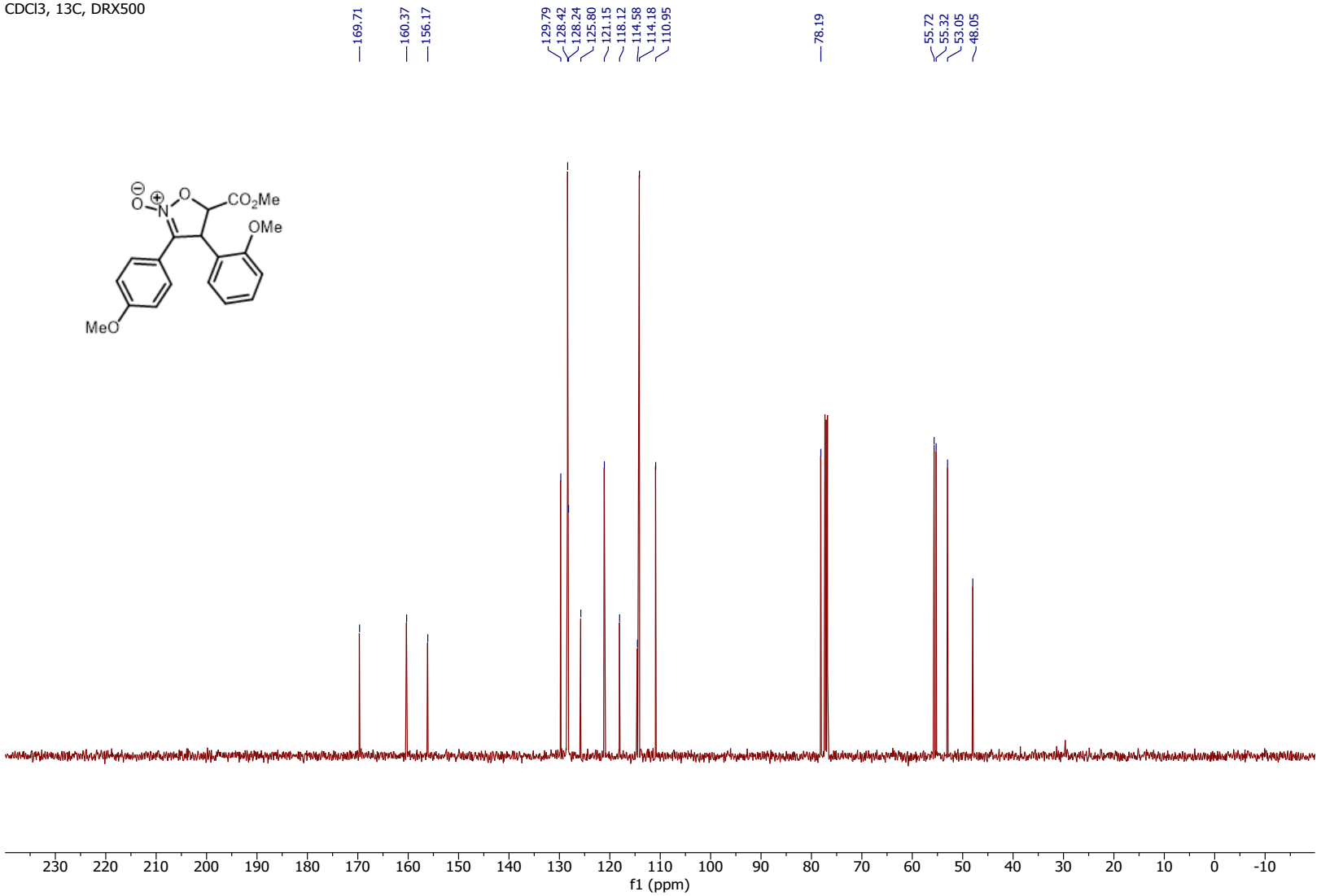
29350171.{1H}.1.fid
CDCl3.001, drx500



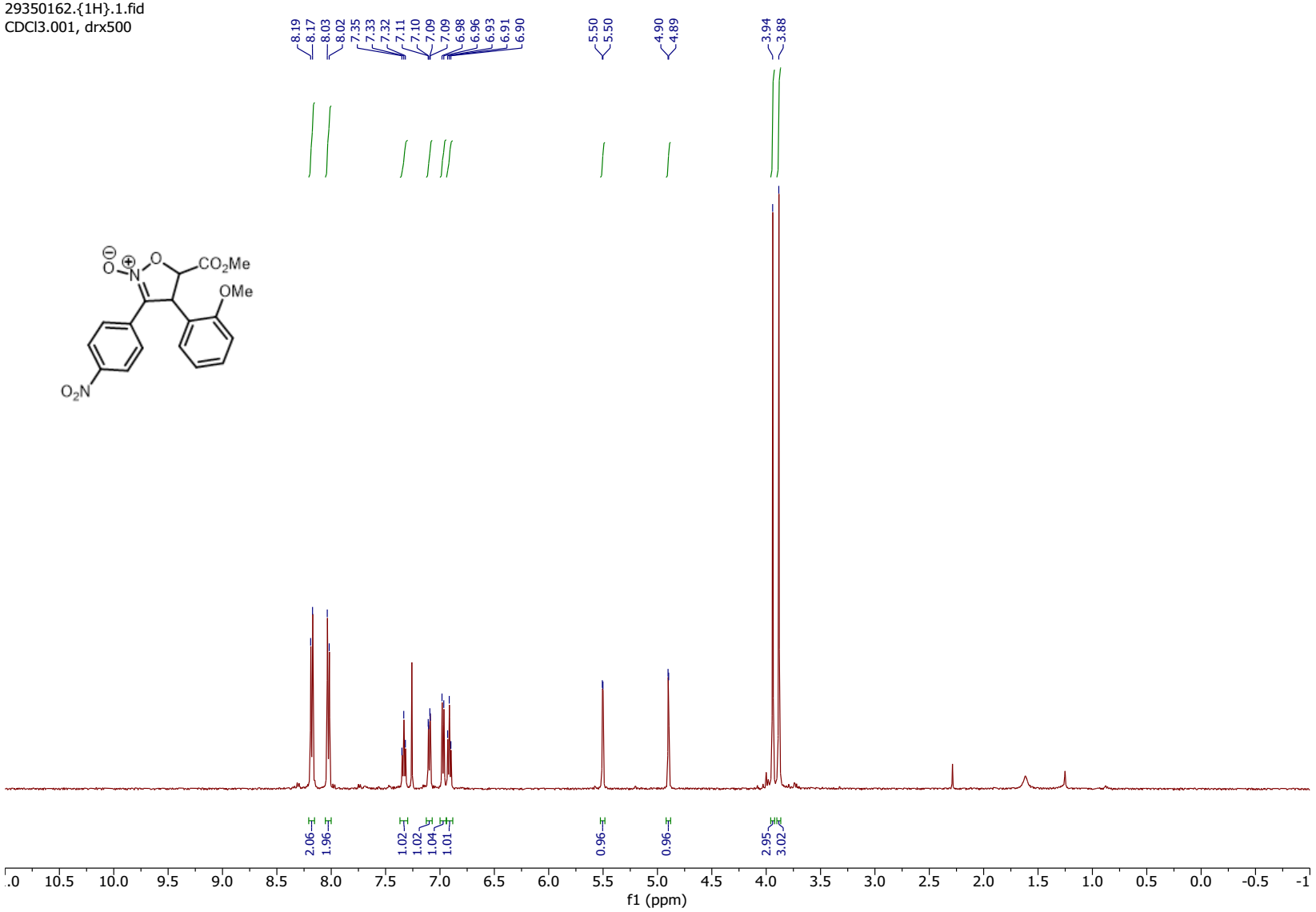
^{13}C NMR of compound **3c** ($CDCl_3$)

29350171.{13C}.1.fid

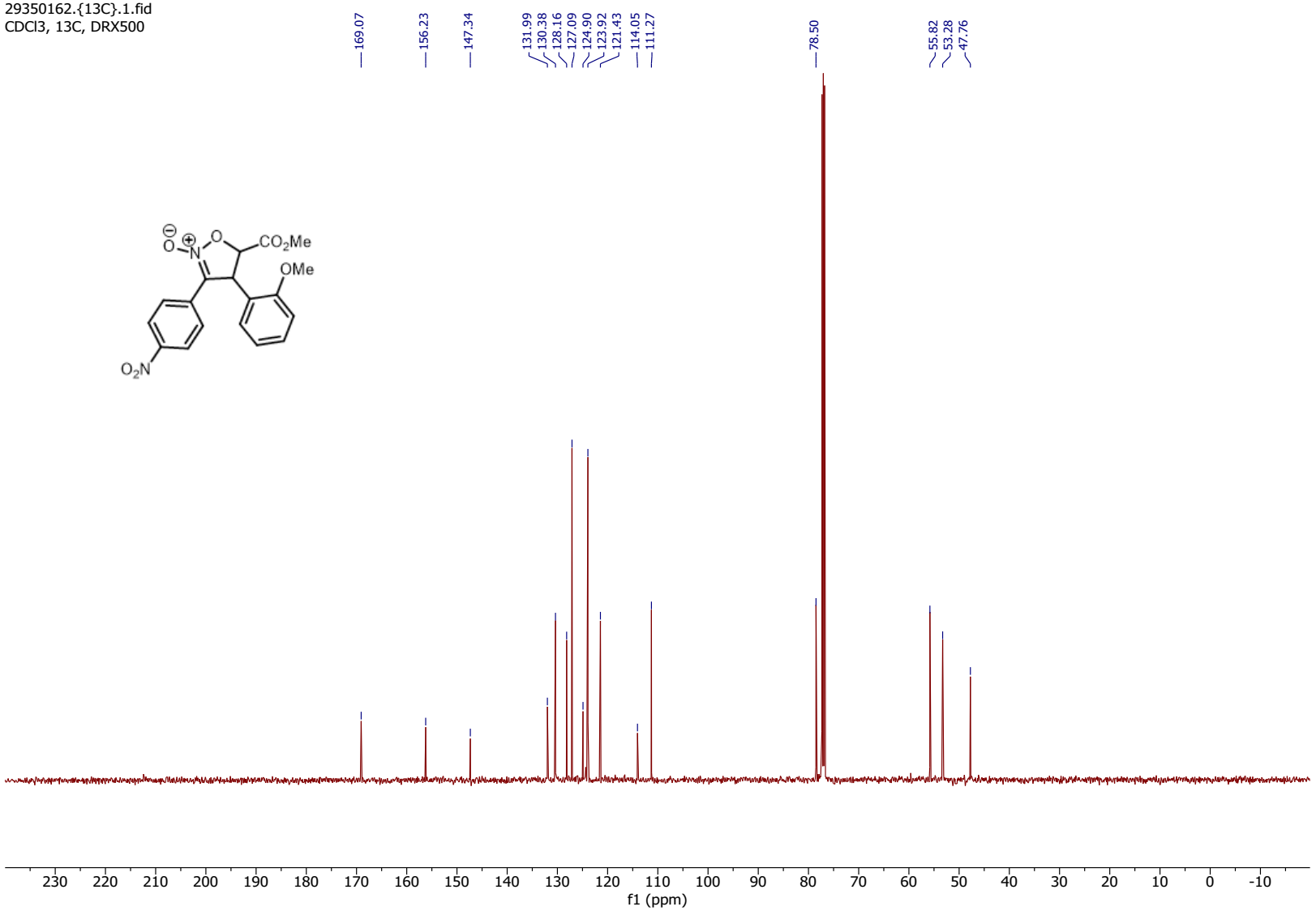
CDCl3, 13C, DRX500



^{1}H NMR of compound **3d** ($CDCl_3$)



^{13}C NMR of compound **3d** ($CDCl_3$)



HRMS of compound **1c**

Display Report

Analysis Info

Analysis Name	D:\Data\Chizhov\Semenov\Kuznetsov\n1_&clblow.d	Acquisition Date	26.01.2024 14:46:13
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Sample Name	/DRUS N1	Instrument / Ser#	micrOTOF 10248
Comment	CH3CN 100 %, dil. 20, low conc. calibrant added		

Acquisition Parameter

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Focus	Not active			Set Dry Heater	180 °C
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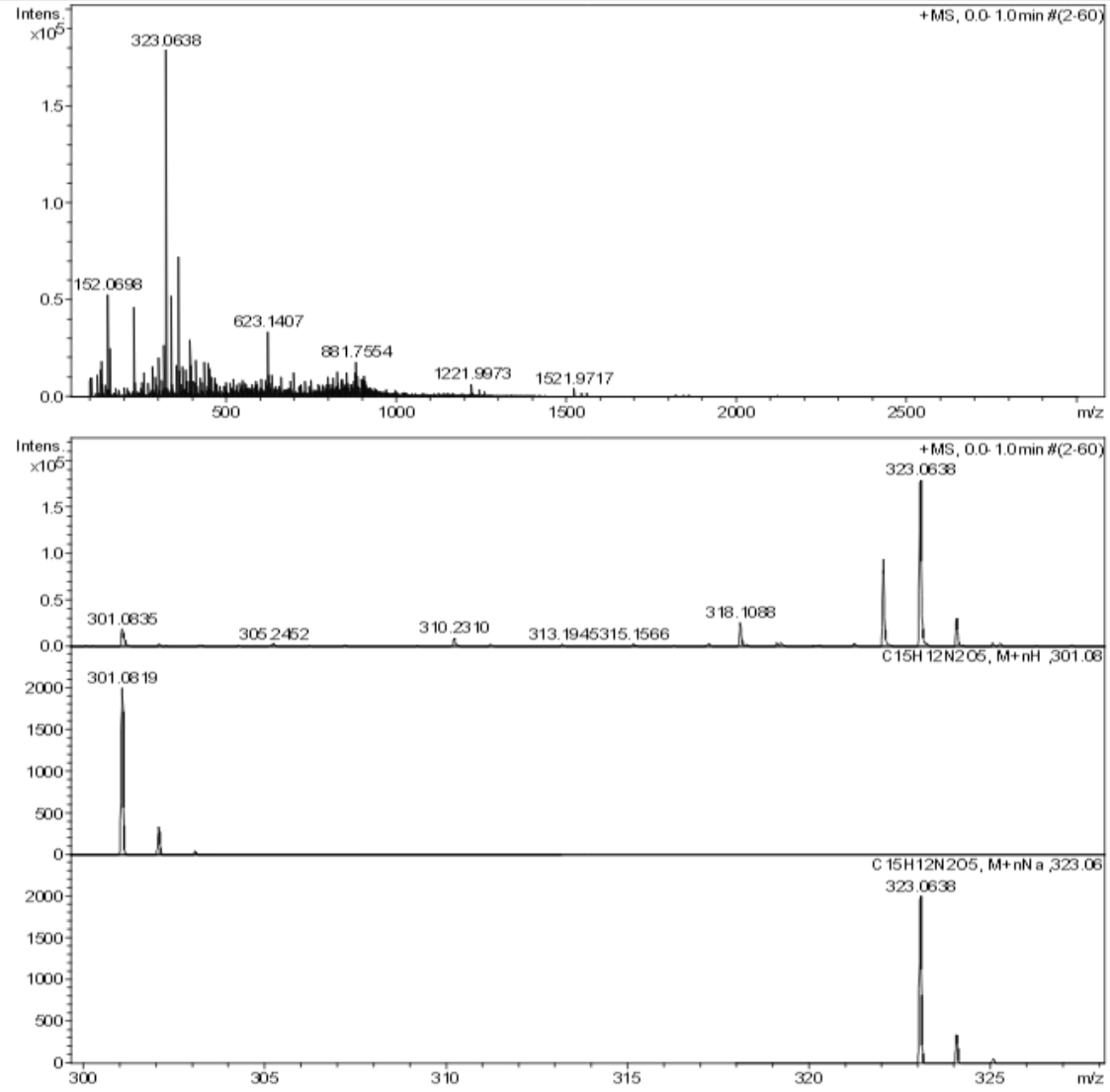
Scan End	3000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



HRMS of compound **3c**

Display Report

Analysis Info

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Sample Name	/DRUS I2	Instrument / Ser#	micrOTOF 10248
Comment	CH3CN 100 %, dil. 200, calibrant added		

Acquisition Parameter

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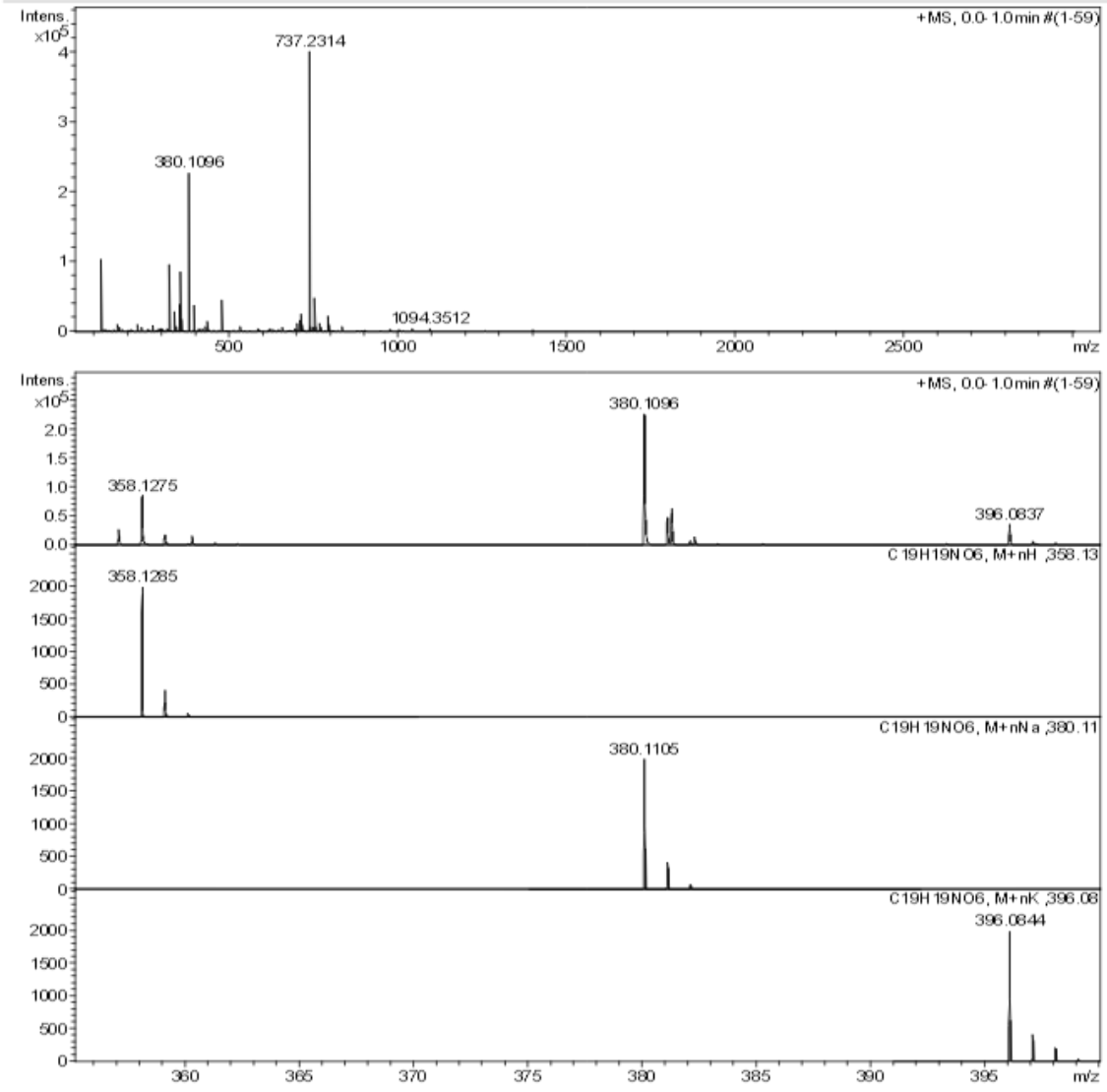
Scan End	3000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste



HRMS of compound **3d**

Display Report

Analysis Info

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Sample Name	/DRUS I1	Instrument / Ser#	micrOTOF 10248
Comment	C18H16N2O7 mH373.1030 calibrant added CH3CN		

Acquisition Parameter

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