Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Organocatalytic alkynylation of heterocyclic compounds using hypervalent iodine reagent

M. Kamlar, I. Císařová[b] and J. Veselý[a]

[a] Department of Organic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030, 128 43 Praha 2, Czech Republic, e-mail: jxvesely@natur.cuni.cz, fax: +42-221951226.
[b] Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030, 128 43, Praha 2, Czech Republic.

1 General procedure

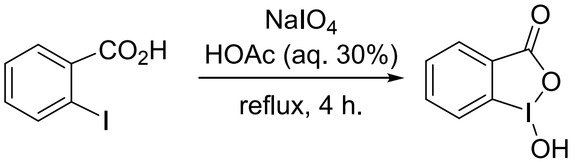
Chemicals and solvents were either purchased (puriss p.A.) from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdenic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of p-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Flash chromatography was performed by using silica gel Merck 60 (particle size 0.040–0.063 mm). ^1H and ^{13}C NMR spectra were measured on FT-NMR spectrometer Bruker AVANCE III 600 MHz. Chemical shifts are given in ppm relative and coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature and served as internal standard (δ = 7.26 ppm) for ^1H NMR and (δ = 77.0 ppm) for ^{13}C NMR. IR DRIFT spectras were recorded with Nicolet AVATAR 370 FT-IR in cm^{-1}. Chiral HPLC was carried out using a LC20AD Shimadzu liquid chromatograph with SPD-M20A diode array detector with columns Daicel Chiralpak® IA, Daicel Chiralpak® IB, Daicel Chiralpak® AD. High-resolution mass spectroscopic data were obtained at Institute of Organic Chemistry and Biochemistry, Academy of Science, v.v.i.

2 Preparation of Reagents and Substrates

2.1 Preparation of alkynyl hypervalent iodine compouds

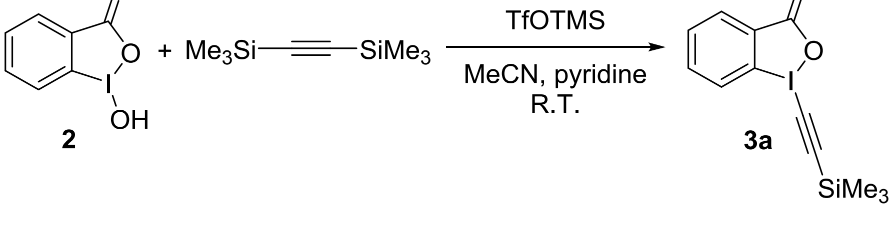
1-hydroxy-1λ³-benzo[*d*][1,2]iodaoxol-3(*1H*)-one (1)



2

Following the reported procedure[1], $NaIO_4$ (1.05 eq., 31 mmol, 6.7 g) and 2-iodobenzoic acid (1.00 eq., 30 mmol, 7.4 g) were suspended in 30% (w:w) aq. HOAc (45 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to r.t, protecting it from light. After 1 h, the crude product was filtered, the filter cake was washed with ice water (3x) and acetone (3x), dried on the air in the dark to affored the pure product **1** in 91% yield as white solid. NMR data fit with that published in the literature.

1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(*1H*)-one (3a)

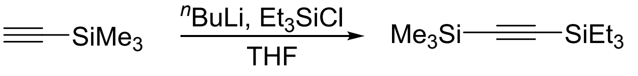


---

[1] L. Kraszkiewicz, L. Skulski, *Arkivoc*, 2003, **6**, 120.

According to a slight modified reported procedure[2], to a stirred solution of 2-iodosylbenzoic acid **2** (1 eq., 11.4 mmol, 3 g) in dry MeCN was added trimethylsilyl triflate (1.3 eq., 15 mmol, 2.8 mL). After stirring 15 min the bis(trimethylsilyl)acetylene (**2**) (1.1 eq., 12.5 mmol, 2.14 g) was added. The reaction mixture was stirred for next 20 min, and then pyridine (1.1 eq., 12.5 mmol, 1.2 mL) was added and the solvent was evaporated. The residual crude oil was washed with water, saturated solution of $NaHCO_3$. Organic layer was dried over $MgSO_4$, filtered and evaporated to afford a white solid, which was recrystallized from acetonitrile to get pure product **3a** (65 %).

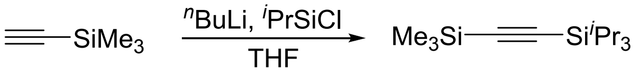
Triethyl((trimethylsilyl)ethynyl)silane (4)



4

Following the reported procedure[3], to a stirred solution of ethynyltrimethylsilane (1.0 eq., 30 mmol, 4.2 mL) in THF was dropped ⁿBuLi (1.6M in hexane, 1 eq., 30 mmol, 18.70 mL) at -70°C. The reaction mixture was allowed to reach 0°C and stirred for 5 min a then cooled again to -70°C. Triethylsilyl chloride (1.0 eq., 30 mmol, 3.8 mL) was then added dropwise and reaction mixture was stirred overnight at RT. To a solution was poured saturated solution of NH_4Cl and organic layer was extracted with Et_2O (2x) and washed with brine (2x) and dried over $MgSO_4$ followed by filtration and evaporation to affored crude product **4**, which was purrified by vacuum distillation (1 mbarr at 70°C) affording pure **4** in 65% yield.

Triisopropyl((trimethylsilyl)ethynyl)silane (5)



5

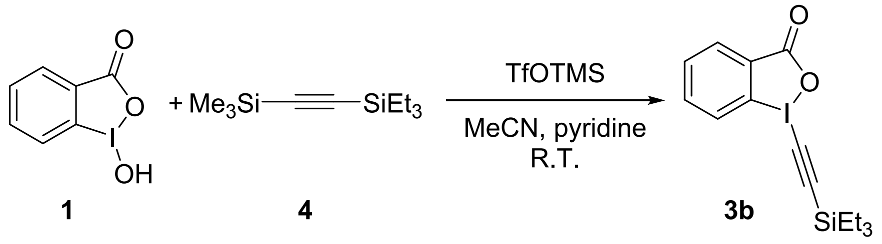
Following the reported procedure[3], to a stirred solution of ethynyltrimethylsilane (1.0 eq., 30 mmol, 4.2 mL) in THF was dropped ⁿBuLi (1.6M in hexane, 1 eq., 30 mmol, 18.70 mL) at -70°C. The reaction mixture was allowed to reach 0°C and stirred for 5 min a then cooled again to -70°C. Triisopropylsilyl chloride (1.0 eq., 30 mmol, 6.4 mL) was then added dropwise and reaction mixture was stirred overnight at RT. To a solution was poured saturated solution of NH_4Cl and organic layer was extracted with Et_2O (2x) and washed with brine (2x) and dried over $MgSO_4$ followed by filtration and evaporation to affored crude product **5**, which was purrified by vacuum distillation (1 mbarr at 70°C) affording pure **5** in 73% yield.

---

[2] V. V. Zhdankin , C. J. Kuehl , A. P. Krasutsky , J. T. Bolz and A. J. Simonsen, *J. Org. Chem.*, 1996, **61**, 6547-6551.

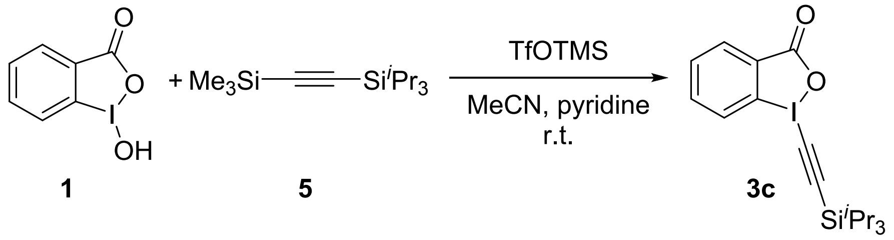
[3] C. J. Helal , P. A. Magriotis and E. J. Corey, *J. Am. Chem. Soc.* 1996, **118**, 10938-10939.

1-[(Triethylsilyl)ethynyl]-1,2-benziodoxol-3(*1H*)-one (3b)



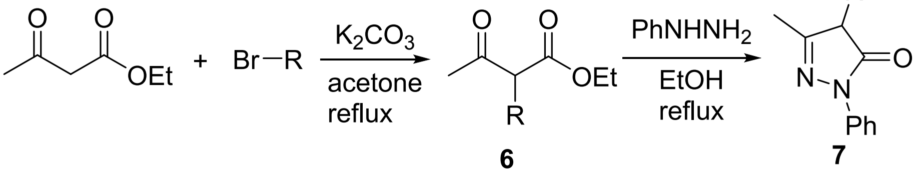
According to a described reported procedure[4], to a stirred solution of 2-iodosylbenzoic **1** acid (1 eq., 3 mmol, 792 mg) in dry MeCN was added trimethylsilyl triflate (1.1 eq., 3.3 mmol, 0.6 mL). After 15 minutes of stirring the triethyl((trimethylsilyl)ethynyl)silane **4** (1.1 eq., 3.3 mmol, 700 mg) was added. The reaction mixture was stirred for next 20 min, and then pyridine (1.1 eq., 3.3 mmol, 0.3 mL) was added and the solvent was evaporated. The residual crude oil was washed with water and saturated solution of $NaHCO_3$. Organic layer was dried over $MgSO_4$, filtered and evaporated affording a white, solid product **3b**, which was recrystallized from acetonitrile (59% yield).

1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(*1H*)-one (3c)



According to a slightly modified reported procedure[1], to a stirred solution of 2-iodosylbenzoic **1** acid (1 eq., 2.9 mmol, 766 mg) in dry MeCN was added trimethylsilyl triflate (1.1 eq., 3.2 mmol, 0.6 mL). After 15 minutes of stirring the triisopropyl((trimethylsilyl)ethynyl)silane **5** (1.1 eq., 3.2 mmol, 821 mg) was added. The reaction mixture was stirred for next 20 min, and then pyridine (1.1 eq., 3.2 mmol, 0.3 mL) was added and the solvent was evaporated. The residual crude oil was washed with water and saturated solution of $NaHCO_3$. Organic layer was dried over $MgSO_4$, filtered and evaporated affording a white, solid product **3c**, which was recrystallized from acetonitrile (70% yield). NMR data fit with data published in the literature.

2.2 Preparation of pyrazolones (7)



R = Me, Bn, p-$BrC_6H_4CH_2$, p-$ClC_6H_4CH_2$, p-$CNC_6H_4CH_2$
p-$NO_2C_6H_4CH_2$, m-$NO_2C_6H_4CH_2$, o-$NO_2C_6H_4CH_2$, napthyl

---

[4] J. P. Brand, C. Chevalley, C.; R. Scopelliti, J. Waser, *Chem. Eur. J.*, **2012**, *18*, 5655-5666.

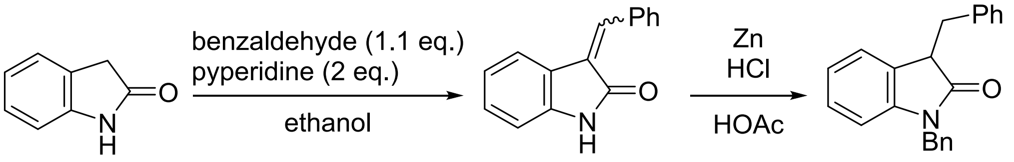
Preparation of α-alkylated acetoacetate (6)

According a published procedure[5], a mixture of acetoacetate (1.0 equiv) and anhydrous K_2CO_3 (1.3 equiv) in dry acetone was stirred under argon atmosphere for five minutes. Then, methyl iodide or corresopnding benzyl bromide (1.3 equiv) was added carefully. The reaction was refluxed overnight and after filtrartion and the solvent evaporation was the crude mixture purified by flash chromatography on silica gel with mixture of hexane/ethyl acetate affording corresponding pure compound **6**. NMR data fit with data published in the literature.

Preparation of corresonding pyrazolones (7)

According to a published procedure[6], a mixture of alkylated acetoacetate (1eq.) and phenylhydrazine (1 eq.) was refluxed in EtOH until full conversion. The solvent was removed a residue was crystalized from Et_2O. Solid material was filtered affording corresponding product. NMR data fit with data published in the literature.

2.3 1,3-Dibenzyl-1,3-dihydroindol-2-one (9)



8 **9**

3-Benzylideneindolin-2-one (8). According to a published procedure[7], to a solution of a oxindole (1 eq., 3.8 mmol, 0.5 g) in ethanol (30 mL) were added benzaldehyde (1.1 eq., 4.2 mmol, 0.43 mL) and piperidine (2 eq., 7.6 mmol, 0.75 mL). The solution was heated at 80 °C for 3 hours and then allowed to cool to room temperature. The precipitate was filtered, washed with ethanol and dried affording corresponding product **8** as a yellow solid (560 mg, 67% yield). The spectral data correspond with previously reported in the literature.

1,3-Dibenzylindolin-2-one (9). To a solution of **8** (2.5 mmol, 560 mg) in DMF (10 mL) was added a 60% dispersion of NaH (1.1 eq., 2.75 mmol, 110 mg) at room temperature. After stirring for 15 min, benzyl bromide (1.1 eq., 2.75 mmol, 0.33 mL) was added. After 3 h, was the reaction mixture quenched with H_2O and washed with MTBE. The organic layers was dried over Na_2SO_4,filtered and concentrated affording an orange residue (quant. yield), which was directly used without further purification.

To a orange residue in acetic acid were added zinc powder (excess) and concentrated HCl. The reaction was stirred overnight and then filtered through celite. The filter cake was washed with EtOAc and the filtrate was washed with solution of saturated aqueous $NaHCO_3$, than with brine and combined organic layers were dried over Na_2SO_4, filtered, and concentrated affording a brown-green residue. After column chromatography was the compound **9** obtained in 51% yield (400 mg) as yellowish solid. The spectral data correspond with data published in literature.

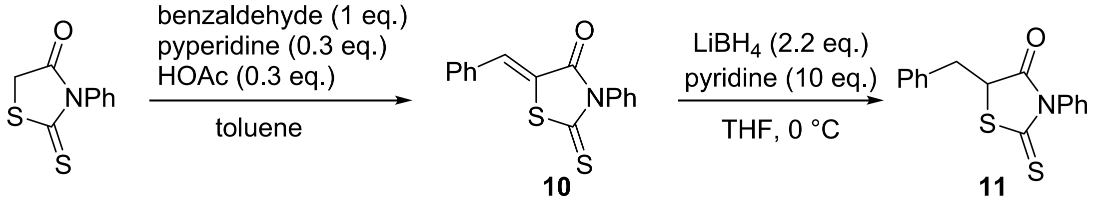
---

[5] A. Rioz-Martínez, A. Cuetos, C. Rodriguéz, G. de Gonzalo, I. Lavandera, M. W. Fraaije, W. Gotor, *Angew. Chem. Int. Ed.,* 2011, **50**, 8387-8390.

[6] H. Nakagawa, R. Ohyama, A. Kimata, T. Suzuki, N. Miyata, *Bioorg. Med. Chem. Lett.* 2006, **16**, 5939-5942.

[7] A. Huang, J. J. Kodanko, L. E. Overman, *J. Am. Chem. Soc.*, 2004, **126**, 14043-14053.

2.4 Preparation of benzylated *N*-Phenylrhodanine (11)

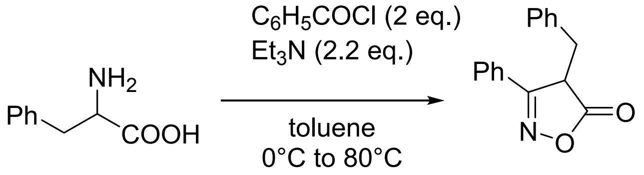


5-Benzylidene-2-thioxothiazolidin-4-one (10). According to a desribed procedure[8], to a solution N-phenylfhodanine (1eq., 2.4 mmol, 0.5 g) in toluene were added benzlaldehyde (1 eq., 2.4 mmol, 0.25 mL), pyperidine (0.3 eq., 0.07 mmol, 6 mg) and acetic acid (0.3 eq., 0.07 mmol, 4 mg). Reaction mixture was then refluxed overnight and after cooling to the room temperature precipitated the product **10** as yellow solid (700 mg, 90% yield). Spectral data correspondes with data published in the literature.[9]

5-benzyl-2-thioxothiazolidin-4-one (11). According to a modified procedure[8], to a solution of **10** (2.36 mmol, 700 mg) and pyridine (23.6 mmol, 1.9 mL) in THF (10 mL) was dropwise added 2M solution of $LiBH_4$ in THF (5.19 mmol, 2.6 mL) at 0 °C. Full conversion was reached after 10 minutes of stirring at the same temperature. Reaction mixture was then quickly washed with 0.1M HCl and brine. Organic layer was then dried over Na_2SO_4, filltered, concentrated and purrified by column chromatography. Compound **11** was obtained as yellow solid in 56% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.52 – 7.44 (m, 3H), 7.39 – 7.32 (m, 5H), 7.30 (dd, J = 5.0, J' = 3.1 Hz, 2H), 7.00 (d, J = 4.0 Hz, 2H), 4.67 (dd, J = 8.6, J' = 3.9 Hz, 1H), 3.53 (dd, J = 14.0, J' = 3.8 Hz, 1H), 3.35 (dd, J = 14.0, J' = 8.6 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 200.27, 175.39, 135.10, 135.00, 129.68, 129.54 (2C), 128.84 (2C), 128.27 (2C), 127.84, 53.27, 38.42 ppm; IR (KBr): v = 3060, 2905, 1736, 1497, 1344, 1239, 1180 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{13}NOS_2$ [M+Na]+ = 322.0331, found = 322.0331.

2.5 Preparation of 4-Benzyl-2-phenyloxazol-5(4*H*)-one (12)



12

According to desribed procedure[10], to the solution of Phenyl alanine (1 eq., 0.5 g, 3.03 mmol) in toluene (10 mL) cooled to 0 °C was added benzoyl chloride (2.0 eq., 6.06 mmol, 0.7 mL). After stirring for 2 h at the same temperature was the reaction mixture placed into a oilbath, pre-warmed to 80 °C. Et_3N (2.2 eq., 6.67 mmol, 0.93 mL) was added dropwise and the resulting mixture was stirred at 80 °C for 10 h. After cooling to room temperature was the reaction mixture washed twice with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$ and once with brine.

---

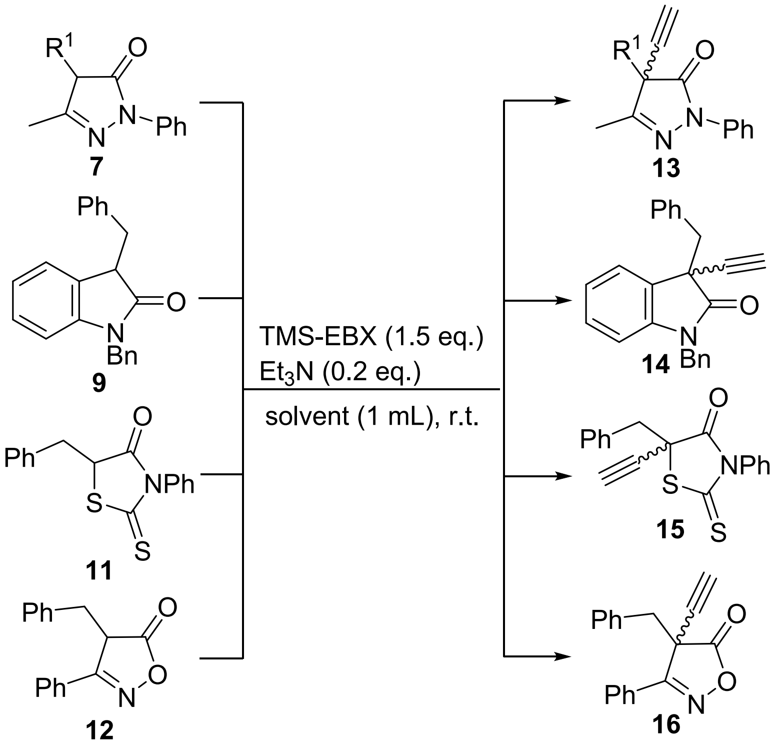
[8] R. G. Giles, N. J. Lewis, J. K. Quick, M. J. Sasse and J. W. J. Urquhart, L. Youssef, *Tetrahedron*, 2000, **56**,4531-4537.

[9] K. A. Kandeel, A. M. Youssef, H. M. El-Bestawy and M. T. Omar, *Monatshefte für Chemie*, 2002, **133**, 1211.

[10] M. Weber, S. Jautze,W. Frey, R. Peters, *Chem. Eur. J.*, 2012, **18**,14792-14804.

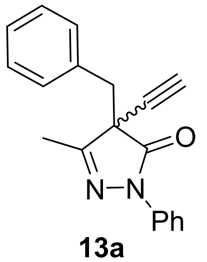
After drying over $MgSO_4$, filtration and concentration was the residue purrified by column chromatography yielding pure compound **12** as a yiellowish solid (162 mg, 21%). The spectral data correspond with data published in the literature.

2.6 Organocatalytic alkynylation



To a stirred solution of Et_3N (0.020 mmol) and heterocycle (**7**, **9**, **11**, **12**) (0.10 mmol) in solvent (1 mL) was added TMS-EBX (**3**) (0.15 mmol) at room temperature. After completion of the reaction was the crude reaction mixture purified by column chromatography (Hex/EtOAc mixtures) afording corresponding compound **13-16**.

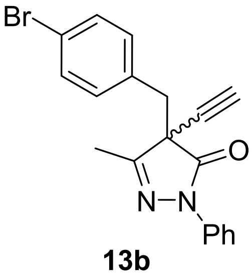
4-Benzyl-4-ethynyl-3-methyl-1-phenyl-1,4-dihydro-1*H*-pyrazol-5-one



13a

Yellowish oil, yield 82 %. ^1H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.62-7.60 (m, 2H), 7.34-7.31 (m, 2H), 7.21–7.14 (m, 5H), 3.49 (d, J = 13.7 Hz, 1H), 3.27 (d, J = 13.7 Hz, 1H), 2.53 (s, 1H), 2.21 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): $\delta =$ 170.21, 158.10, 137.34, 133.12, 129.41 (2C), 128.70 (2C), 128.42 (2C), 127.88, 125.47, 119.44 (2C), 77.27, 74.54, 54.52, 42.44, 14.49 ppm; IR (KBr): v = 3276, 3258, 3084, 3060, 3052, 3031, 2920, 2851, 1709, 1488, 1362, 1332, 764 cm^{-1}; HRMS (TOF) m/z calcd for $C_{19}H_{16}N_2O$ $[M+H]^+$ = 289.1341, found = 289.1339.

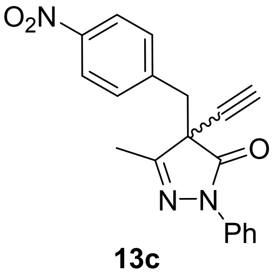
4-(4-Bromobenzyl)-4-ethynyl-3-methyl-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



13b

Yellowish oil, yield 70 %. ^1H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.63–7.62 (m, 2H), 7.36-7.33 (m, 4H), 7.19-7.17 (m, 1H), 7.10–7.04 (m, 2H), 3.42 (d, J = 13.7 Hz, 1H), 3.21 (d, J = 13.7 Hz, 1H), 2.54 (s, 1H), 2.21 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): $\delta =$ 169.93, 157.89, 137.15, 132.07, 131.58 (2C), 131.11 (2C), 128.80 (2C), 125.63, 122.06, 119.30 (2C), 76.79 (overlapped with residual solvent peak), 74.88, 54.18, 41.56, 14.50 ppm; IR (KBr): *v* = 3279, 3105, 3043, 2926, 1793, 1712, 1595, 1488, 1443, 1392, 1362, 1278, 1272 cm^{-1}; HRMS (TOF) m/z calcd for $C_{19}H_{16}N_2OBr$ [M+H]$^+$ = 367.0446, found = 367.0443.

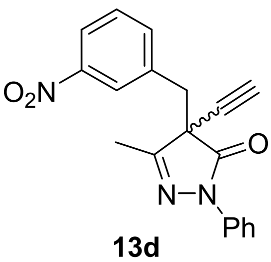
4-Ethynyl-3-methyl-4-(4-nitrobenzyl)-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



13c

Yellowish oil, yield 85 %. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.10 (m, 2H), 7.64-7.62 (m, 2H), 7.37–7.32 (m, 4H), 7.19–7.16 (m, 1H), 3.54 (d, *J* = 13.6 Hz, 1H), 3.32 (d, *J* = 13.6 Hz, 1H), 2.58 (s, 1H), 2.24 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 169.45, 157.52, 147.56, 140.45, 136.98, 130.56 (2C), 128.87 (2C), 125.77, 123.55 (2C), 119.02 (2C) 76.28, 75.47, 53.96, 41.42, 14.44 ppm; IR (KBr): *v* = 3282, 3105, 3075, 2920, 2854, 1715, 1592, 1521, 1503, 1368, 1344, 1278 cm^{-1}; HRMS (TOF) m/z calcd for $C_{19}H_{15}N_3O_3$ [M+H]$^+$ = 334.1192, found = 334.1203.

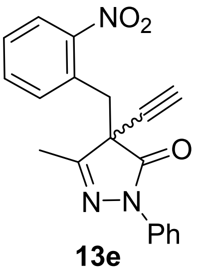
4-Ethynyl-3-methyl-4-(3-nitrobenzyl)-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



13d

Yellowish oil, yield 76 %. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.10–8.08 (m, 2H), 7.64-7.62 (m, 2H), 7.54-7.62 (m, 1H), 7.41–7.39 (m, 1H), 7.35-7.32 (m, 2H), 7.18-7.16 (m, 1H), 3.54 (d, *J* = 13.7 Hz, 1H), 3.33 (d *J* = 13.7 Hz, 1H), 2.59 (s, 1H), 2.26 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 169.49, 157.58, 147.99, 136.99, 135.80, 134.99, 129.42, 128.84 (2C), 125.70, 124.43, 123.01, 119.06 (2C), 76.21, 75.55, 53.98, 41.37, 14.46 ppm; IR (KBr): *v* = 3264, 3111, 3069, 3037, 2122, 1975, 1709, 1595, 1535, 1503, 1488, 1398, 1362, 1347, 1308, 1272 cm^{-1}; HRMS (TOF) m/z calcd for $C_{19}H_{15}N_3O_3$ [M+H]$^+$ = 334.1192, found = 334.1187.

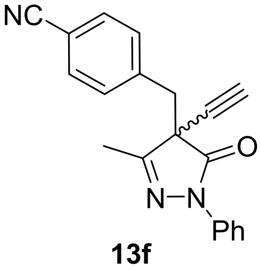
4-Ethynyl-3-methyl-4-(2-nitrobenzyl)-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



13e

Yellowish oil, yield 82 %. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.00–7.99 (m, 1H), 7.75-7.74 (m, 2H), 7.57-7.53 (m, 2H), 7.46–7.43 (m, 1H), 7.38-7.35 (m, 2H), 7.19-7.17 (m, 1H), 3.76 (d, *J* = 13.7 Hz, 1H), 3.68 (d, *J* = 13.7 Hz, 1H), 2.51 (s, 1H), 2.19 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 169.52, 158.12.149.65, 137.36 133.68, 132.80, 128.96, 128.80 (2C), 128.24, 125.47, 125.10, 119.11 (2C), 76.21, 75.88, 52.97, 37.12, 13.93 ppm; IR (KBr): *v* = 3273, 3105, 3075, 2914, 2116, 1700, 1529, 1503, 1491, 1362, 1344, 1287, 1245 cm^{-1}; HRMS (TOF) m/z calcd for $C_{19}H_{15}N_3O_3$ [M+H]$^+$ = 334.1192, found = 334.1187.

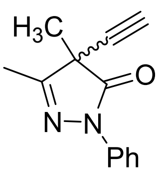
4-((4-Ethynyl-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)methyl)benzonitrile



13f

Yellowish oil, yield 94 %. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 2H), 7.52-7.50 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.28 (m, 2H), 7.19-7.17 (m, 1H), 3.49 (d, *J* = 13.6 Hz, 1H), 3.28 (d, *J* = 13.6 Hz, 1H), 2.57 (s, 1H), 2.23 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 169.49, 157.53, 138.40, 136.96, 132.12 (2C), 130.33 (2C), 128.85 (2C), 125.76, 119.07 (2C), 118.31, 111.93, 76.33, 75.34, 53.99, 41.80, 14.42 ppm; IR (KBr): *v* = 3258, 3072, 2956, 2926, 2226, 1736, 1709, 1595, 1503, 1398, 1371, 1278, 1248 cm^{-1}; HRMS (TOF) m/z calcd for $C_{20}H_{15}N_3O$ [M+H]$^+$ = 314.1293, found = 314.1292.

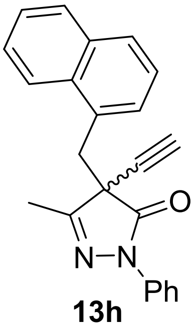
4-Ethynyl-3,4-dimethyl-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



13g

Yellowish oil, yield 95 %. ^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.90–7.88 (m, 2H), 7.42-7.38 (m, 2H), 7.21-7.18 (m, 1H), 2.43 (s, 1H), 2.23 (s, 3H), 1.63 (s, 3H) ppm; ^{13}C NMR (151 MHz, CDCl$_3$): δ = 171.12, 159.95, 137.73, 128.82 (2C), 125.24, 118.77 (2C), 77.72, 73.46, 48.60, 22.03, 13.43 ppm; IR (KBr): *v* = 3395, 3222, 3072, 3031, 2989, 2932, 2116, 1709, 1631, 1598, 1500, 1488, 1374, 1296, 1153 cm^{-1}; HRMS (TOF) m/z calcd for $C_{13}H_{12}N_2O$ $[M+H]^+$ = 213.1028, found = 213.1022.

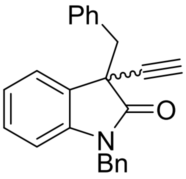
4-Ethynyl-3-methyl-4-(naphthalen-1-yl)-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



13h

Yellowish oil, yield 90 %. ^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.14 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.65–7.63 (m, 2H), 7.54–7.45 (m, 3H), 7.36–7.32 (m, 3H), 7.17–7.15 (m, 1H), 3.92 (d, *J* = 14.3 Hz, 1H), 3.81 (d, *J* = 14.3 Hz, 1H), 2.54 (s, 1H), 1.97 (s, 1H) ppm; ^{13}C NMR (151 MHz, CDCl$_3$): δ = 170.64, 158.80, 137.45, 133.81, 132.08, 129.73, 128.85, 128.73 (2C), 128.64, 128.43, 128.19, 126.12, 125.73, 125.39, 125.17, 125.00, 123.62, 119.21 (2C), 77.43, 75.12, 54.47, 38.04, 14.90 ppm; IR (KBr): *v* = 3261, 3090, 3049, 3010, 2968, 2920, 1715, 1595, 1494, 1398, 1365, 1278, 1123 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{18}ON_2$ $[M+Na]^+$ = 361.1311, found = 361.1312.

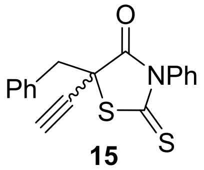
1,3-dibenzyl-3-ethynylindolin-2-one



14

Yellowish oil, yield 85 %. ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.28 – 7.25 (m, 1H), 7.20 – 7.12 (m, 2H), 7.11 – 7.06 (m, 2H), 7.04 (td, *J* = 7.5, 1.1 Hz, 1H), 6.96 – 6.91 (m, 1H), 6.75 – 6.70 (m, 1H), 6.43 – 6.42 (m, 1H), 4.93 (d, *J* = 16.0 Hz, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 3.45 (q, *J* = 13.1 Hz, 1H), 2.41 (s, 1H) ppm; ^{13}C NMR (151 MHz, CDCl$_3$) δ = 174.43, 142.39, 135.12, 134.47, 130.72 (2C), 129.25, 129.08, 128.85 (2C), 128.14 (2C), 127.53, 127.38, 126.94 (2C), 124.53, 123.04, 109.76, 81.99, 72.28, 48.77, 44.68, 44.24 ppm; IR (KBr): *v* = 3291, 3087, 3031, 1793, 1721, 1488 cm^{-1}; HRMS (TOF) m/z calcd for $C_{24}H_{19}NO$ [M+H]+ = 338.1545, found = 338.1544.

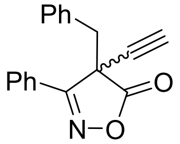
5-benzyl-5-ethynyl-3-phenyl-2-thioxothiazolidin-4-one



15

Colorless oil, yield 94 %. ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.48 – 7.43 (m, 3H), 7.41 – 7.33 (m, 5H), 6.84 (s, 2H), 3.65 (d, *J* = 13.7 Hz, 1H), 3.51 (d, *J* = 13.7 Hz, 1H), 2.82 (s, 1H) ppm; ^{13}C NMR (151 MHz, CDCl$_3$) δ = 197.42, 172.75, 134.85, 132.73, 130.92 (2C), 129.86, 129.56 (2C), 128.63 (2C), 128.50, 128.25 (2C), 78.50, 77.32, 56.60, 45.90 ppm; IR (KBr): ν = 3267, 2920, 1793, 1730, 1350, 1251, 1072 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{13}NOS_2$ $[M+H]^+$ = 324.0511, found = 324.0511.

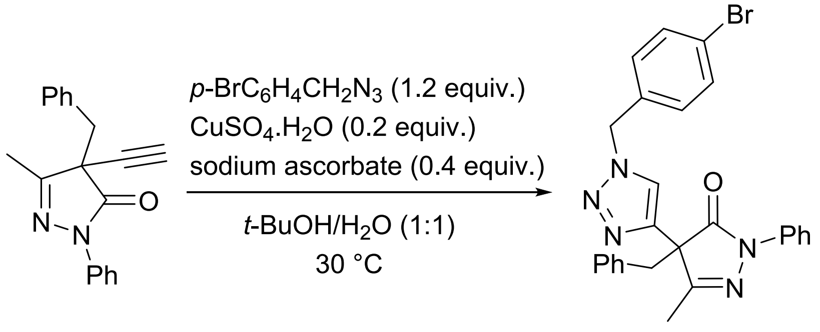
4-benzyl-4-ethynyl-3-phenylisoxazol-5(*4H*)-one



16

Colorless oil, yield 85 %. ^{1}H NMR (600 MHz, CDCl$_3$) δ = 7.92 – 7.85 (m, 2H), 7.59 – 7.53 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.24 – 7.16 (m, 5H), 3.51 (d, *J* = 13.6 Hz, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 2.65 (s, 1H) ppm; ^{13}C NMR (151 MHz, CDCl$_3$) δ = 174.32, 161.86, 133.17, 132.57, 130.51 (2C), 128.73 (2C), 128.22 (2C), 128.10 (2C), 127.80, 125.01, 77.73, 75.03, 67.40, 44.85 ppm; IR (KBr): *v* = 3234, 2932, 1823, 1652, 1458 cm^{-1}; HRMS (TOF) m/z calcd for $C_{18}H_{13}NO_2$ [M+H]+ = 276.1025, found = 276.1028.

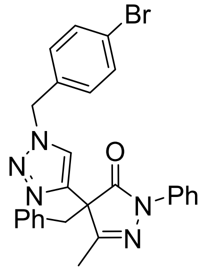
2.7 Preparation of 4-(1-(4-bromobenzyl)-*1H*-1,2,3-triazol-4-yl)-3-methyl-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



13a **17**

According to desribed procedure[11], to a solution of pyrazolone derivative **13a** (0.12 mmol, 1 eq.) and 1-(azidomethyl)-4-bromobenzene (0.14 mmol, 1.2 eq.) in solution of *t*-BuOH/H_2O (1:1, 2 mL) was added copper(II) sulphate (0.024 mmol, 0.2 eq.) and sodium ascorbate (0.05 mmol, 0.4 eq.). Reaction mixture was stirred at 30 °C overnight and then washed with EtOAc and organic phase was washed with brine and dried over $MgSO_4$, filtered a purified with column chromatography yielding the corresponding product **17** as colorless oil (92% yield).

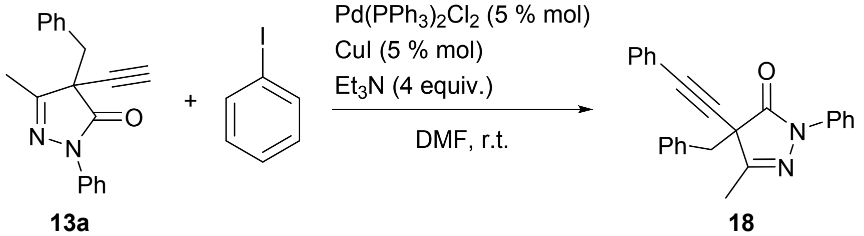
4-(1-(4-bromobenzyl)-*1H*-1,2,3-triazol-4-yl)-3-methyl-1-phenyl-1,4-dihydro-*1H*-pyrazol-5-one



17

White solid, yield 92 %, m. p. 120-121 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.64 – 7.61 (m, 2H), 7.56 (s, 1H), 7.52-7.50 (m, 2H), 7.32-7.31 (m, 2H), 7.19 – 7.15 (m, 8H), 5.46 (s, 2H), 3.53 (dd, J = 36.0, J' = 13.6 Hz, 2H), 2.39 (s, 3H) ppm; ^{13}C NMR (151 MHz, CDCl3) δ = 172.11, 160.12, 143.36, 136.87, 133.35, 132.64, 131.95 (2C), 129.45 (2C), 128.78 (2C), 128.26 (2C), 127.95 (2C), 127.17, 124.97, 122.71, 121.29, 118.98 (2C), 58.68, 53.02, 41.44, 15.30 ppm; IR (KBr): ν = 3031, 2923, 1709, 1592, 1497, 1368 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{22}N_5OBr$ $[M+Na]^+$ = 522.0900, found = 522.0900.

2.8 Preparation of 4-benzyl-3-methyl-1-phenyl-4-(phenylethynyl)-1,4-dihydro-3*H*-pyrazol-5-one



13a **18**

According to desribed procedure[12], to a solution of iodobenzene (0.13 mmol, 1 eq.) in dry DMF was added $Pd(PPh_3)_2Cl_2$ (0.007 mmol, 0.05 eq.), CuI (0.007 mmol, 0.05 eq.) and Et3N (0.52 mmol, 4 eq.) and pyrazolone derivative **13a**. Reaction mixture was stirred for 2 hours

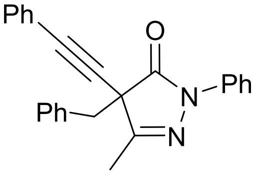
---

[11] Ch. Menendez, A. Chollet, F. Rodriguez, C. Inard, M. R. Pasca, Ch. Lherbet and M. Baltas, *E. J. Med. Chem.*, **2012**, *52*, 275.

[12] M. Toyota, Ch. Komori and M. Ihara, *J. Org. Chem.*, **2000**, *65*, 7110.

and then flashed through celite and then diluted in Et_2O. Organic layer was washed with water, brine and then dried over $MgSO_4$. After evaporation of the solvent was the residue purrified with column chromatography affording corresponding product **18** as yellow oil in 56% yield.

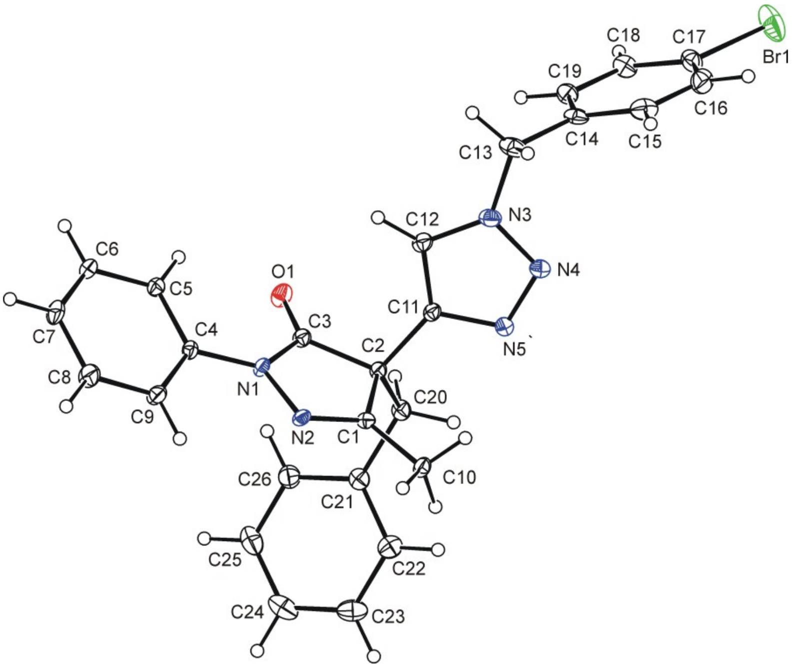
4-benzyl-3-methyl-1-phenyl-4-(phenylethynyl)-1,4-dihydro-*3H*-pyrazol-5-one



18

Colorless oil, yield 56 %.^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.70 – 7.68 (m, 2H), 7.53-7.51 (m, 2H), 7.39-7.36 (m, 5H), 7.27-7.25 (m, 5H), 7.21 – 7.19 (m, 1H), 3.59 (d, *J* = 13.6 Hz, 1H), 3.39 (d, *J* = 13.6 Hz, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.63, 158.74, 137.41, 133.41, 131.97, 129.63, 129.51 (2C), 128.87, 128.72 (2C), 128.41 (2C), 128.31 (2C), 127.81, 125.41, 121.92, 119.41 (2C), 86.23, 82.15, 55.28, 42.51, 14.74. ppm; IR (KBr): ν = 2926, 2848, 1715, 1598, 1500, 1362 cm-1; IR (KBr): ν = 2926, 2848, 1715, 1598, 1500, 1362 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{20}N_2O$ $[M+H]^+$ = 365.1648, found = 365.1649.

3 X-Ray of compound 18



Single-crystal X-ray diffraction data for compound **8** were obtained from Bruker ApexII-CCD diffractometer by monochromatized MoKα radiation ($\lambda = 0.71073$ Å) at 150(2)K. The structure was solved by direct methods (SHELXS, Sheldrik, 2008) and refined by full-matrix least squares based on F^2 (SHELXL97). The hydrogen atoms were fixed into idealised positions (riding model) and assigned temperature factors $H_{\mathrm{iso}}(\mathrm{H}) = 1.2\ U_{\mathrm{eq}}$(pivot atom).

Crystal data for **18**: $C_{26}H_{22}BrN_5O$, $M_r = 500.40$, Monoclinic, $P2_1/n$ (No 14), $a = 9.6625$ (2) Å, $b = 23.9818$ (6) Å, $c = 10.8059$ (2) Å, $V = 2255.29$ (8) Å^3, Z = 4, $D_x = 1.474$ Mg m^{-3}, colourless crystal of dimensions 0.27 × 0.21 × 0.18 mm, numerical absorption correction (μ = 1.85 mm^{-1}) , $T_{min} = 0.634$, $T_{max} = 0.738$; a total of 29307 measured reflections (θ_{max}= 27.5°), from which 5177 were unique ($R_{int} = 0.038$) and 3951 observed according to the $I > 2\sigma(I)$ criterion. The refinement converged ($\Delta/\sigma_{\mathrm{max}} < 0.001$) to $R = 0.050$ for observed reflections and $wR(F^2) = 0.126$, $GOF = 1.06$ for 299 parameters and all 5177 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{\mathrm{max}} = 2.01$, $\Delta\rho_{\mathrm{min}}$ -1.39 e.Å^{-3}).

Crystallographic data (excluding structure factors) for the structures has been deposited with the Cambridge Crystallographic Data Centre with CCDC number 1038569. Copies of the data can be obtained, free of charge, on application to Cambridge Crystallographic Data Centre, 12

Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

Literature:

G.M. Sheldrick, *Acta Cryst*., 2008, **A64**, 112-122.

4 Detection of EBX using low temperature ^{1} H NMR experiment

Figure 1: Generation and decomposition of EBX at -30 °C during 30 minutes time period. Signals of EBX are highlighted by *. ^{1} H NMR (CD_2Cl_2): $\delta = 8.36$ (d, $J = 8.05$ Hz, 1H), 8.22 (dd, $J = 7.3$ Hz, $J' = 1.7$ Hz, 1 H), 7.74 (m, 2H), 3.49 (s, 1H) ppm. ^{1}H NMR spectrum correspondes with data published by Waser et al.[13]

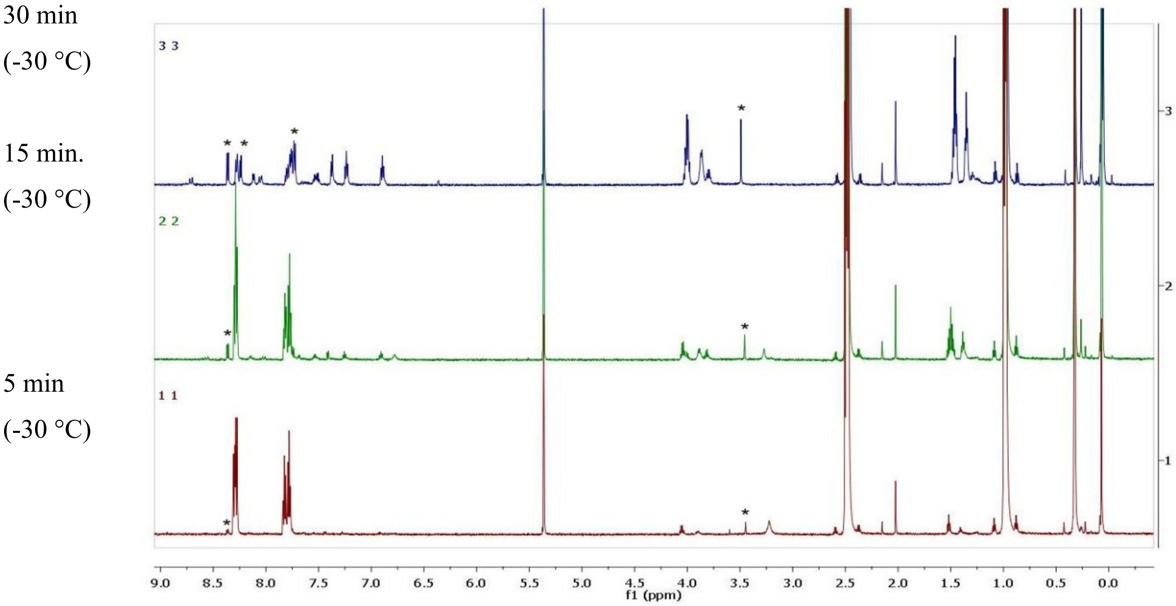
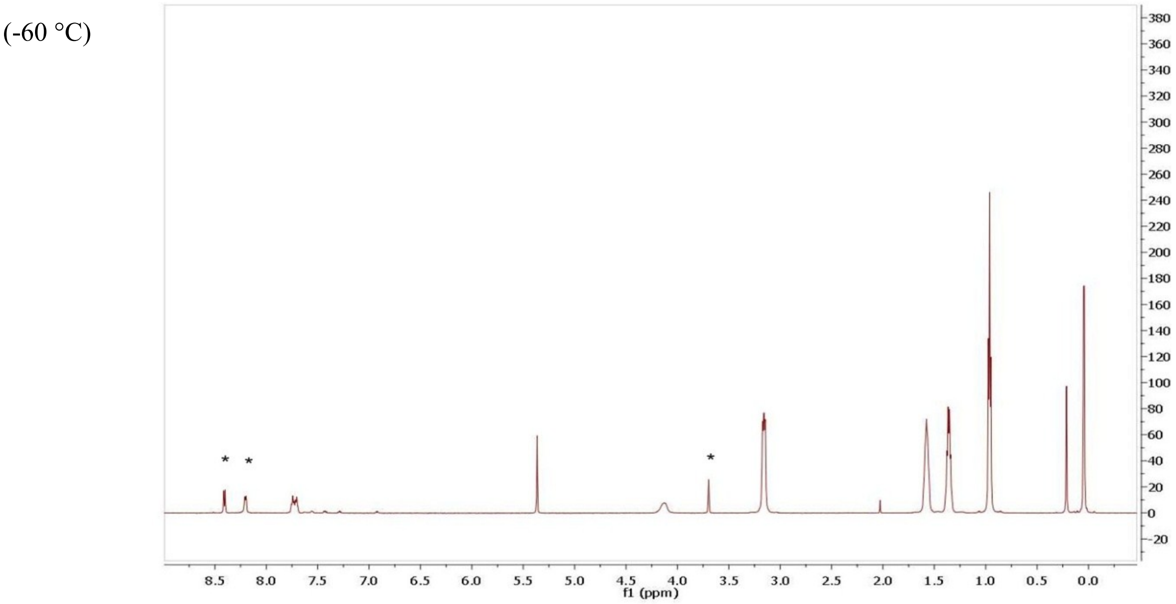


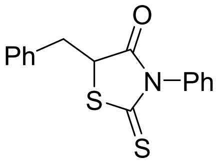
Figure 2: Control experiment with TMS-EBX and TBAF·$3H_2O$.



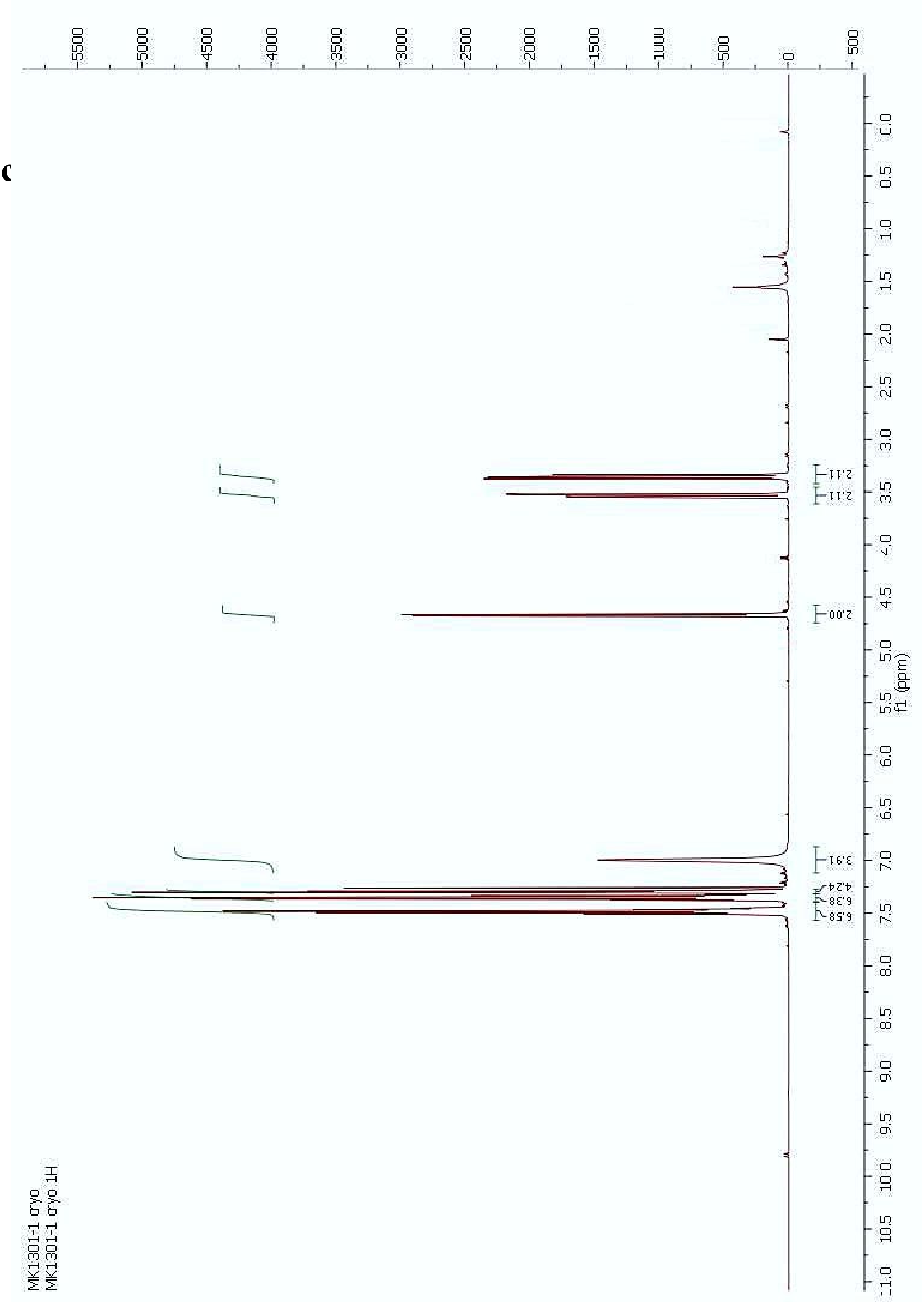
---

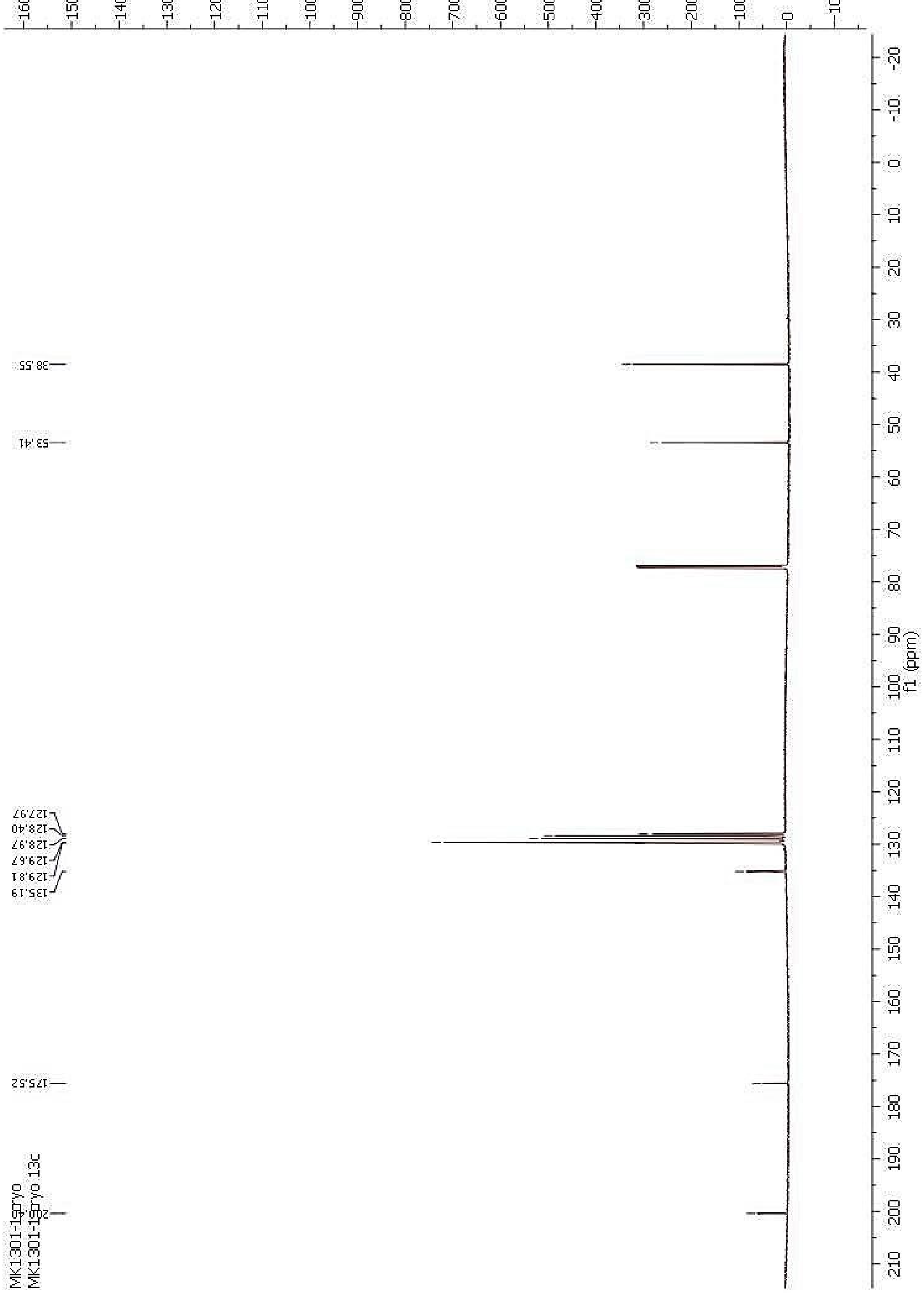
[13] D. F. González, J. P. Brand and J. Waser, *Chem. Eur. J.*, 2010, **16**, 9457-9461

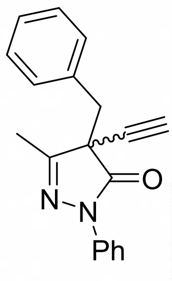
5 NMR spec


Ph
O
N−Ph
S
S

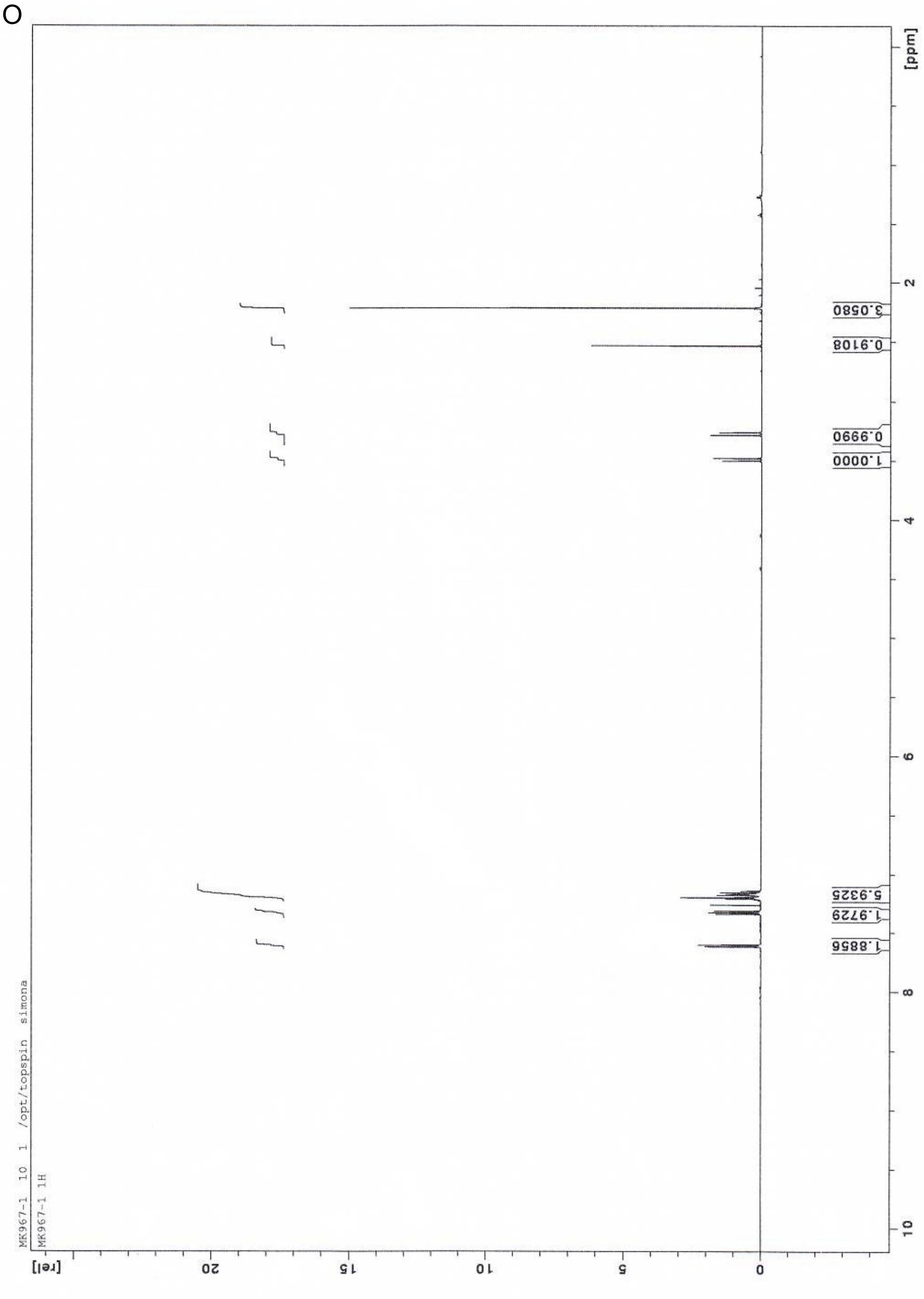
11

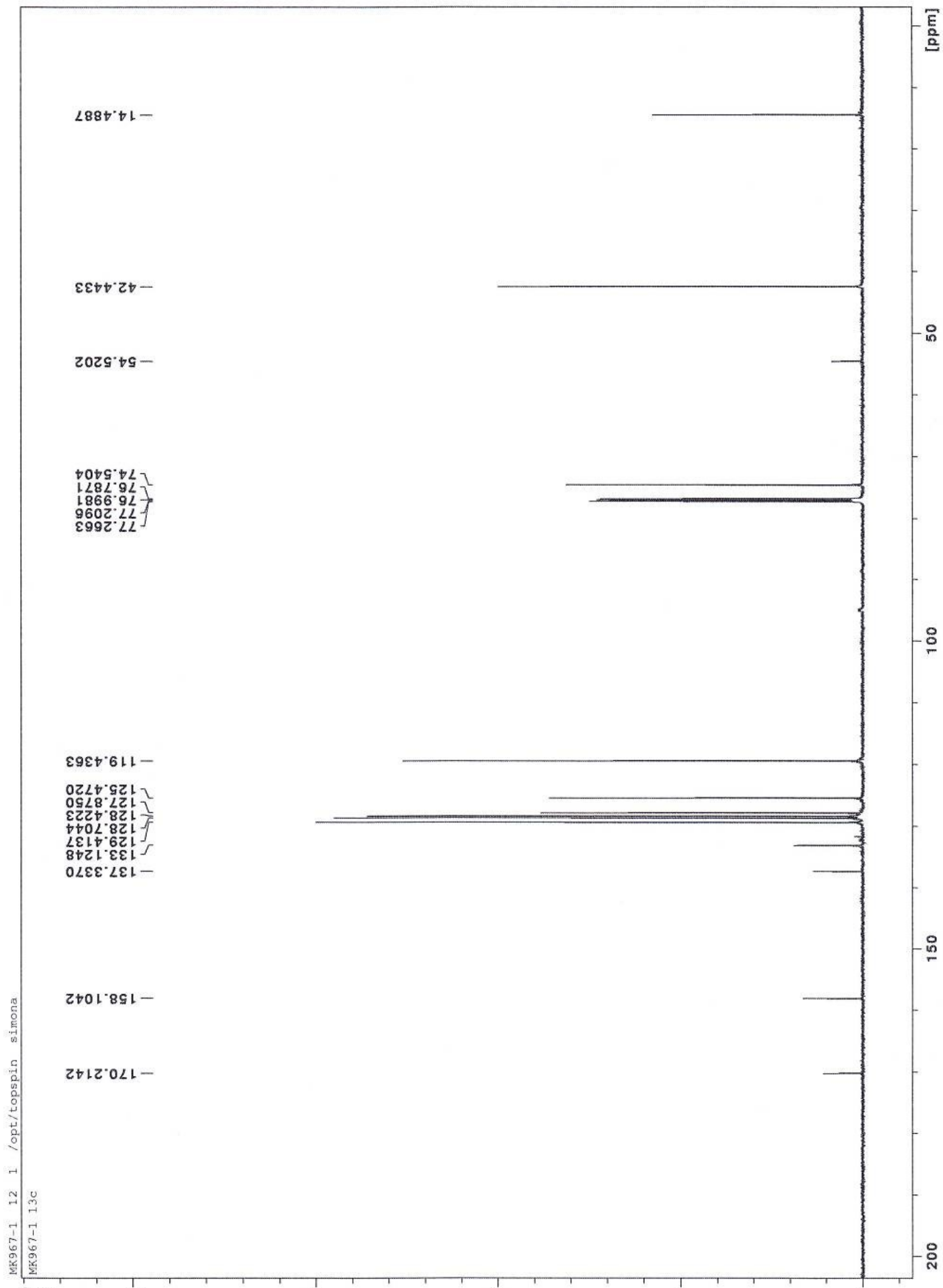

5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
f1 (ppm)
2.11
2.11
2.00
3.91
4.24
6.38
6.58
MK1301-1 cryo
MK1301-1 cryo 1H

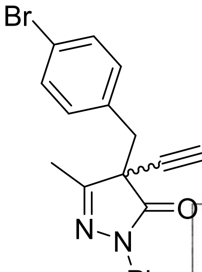

MK1301-1-cryo
MK1301-1-cryo.13c
38.55
53.41
127.97
128.40
128.97
129.67
129.81
135.19
175.52
f1 (ppm)
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600


N
N
O
Ph

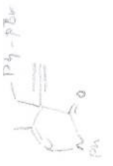
13a

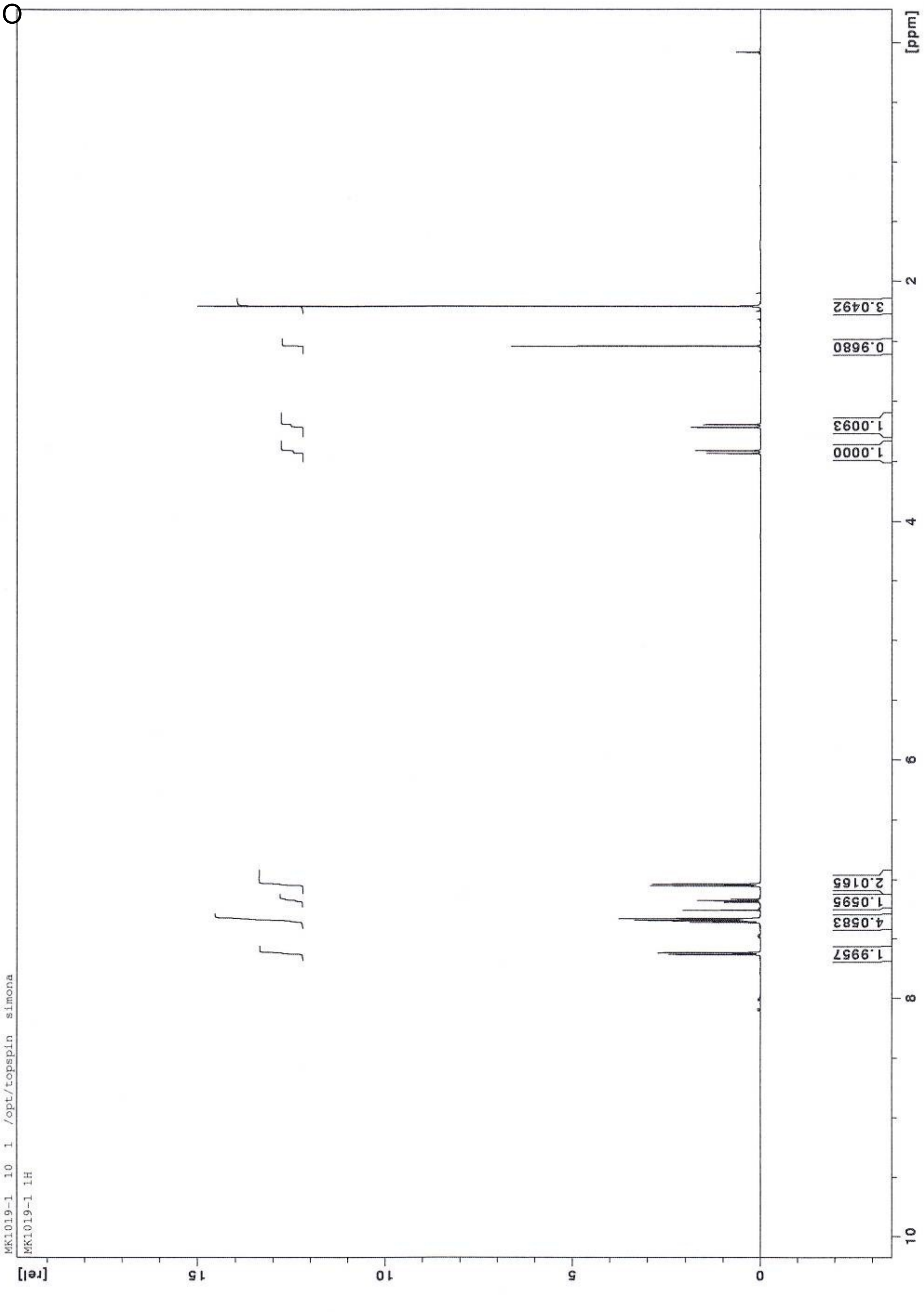

MK967-1 10 1 /opt/topspin simona
MK967-1 1H
[ppm]
2
4
6
8
10
[rel]
20
15
10
5
0
3.0580
0.9108
0.9990
1.0000
5.9325
1.9729
1.8856

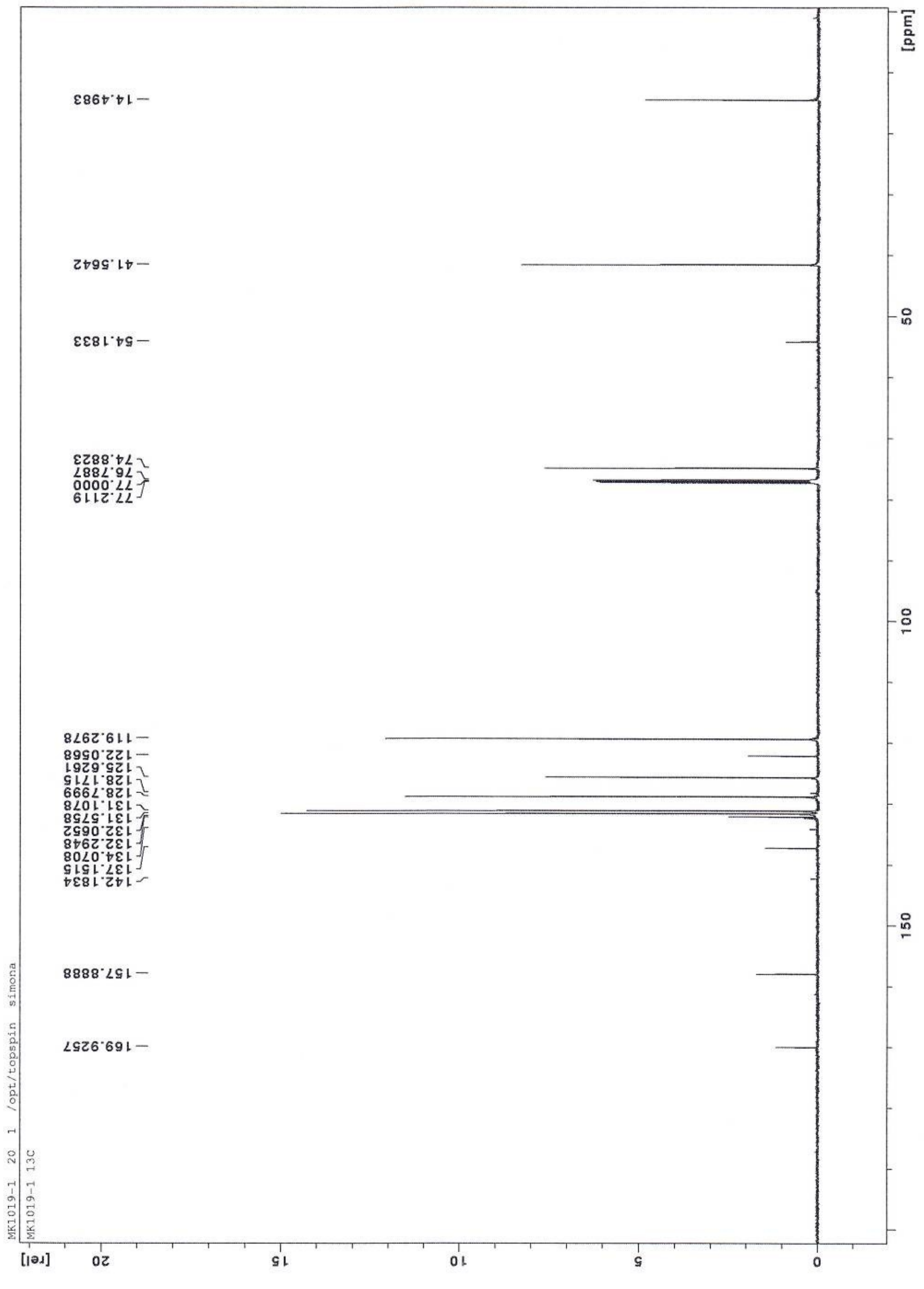

MK967-1 12 1 /opt/topspin simona
MK967-1 13c
170.2142
158.1042
137.3370
133.1248
129.4137
128.7044
128.4223
127.8750
125.4720
119.4363
77.2663
77.2096
76.9981
76.7871
74.5404
54.5202
42.4433
14.4887
[rel]
20
15
10
5
0
200
150
100
50
[ppm]

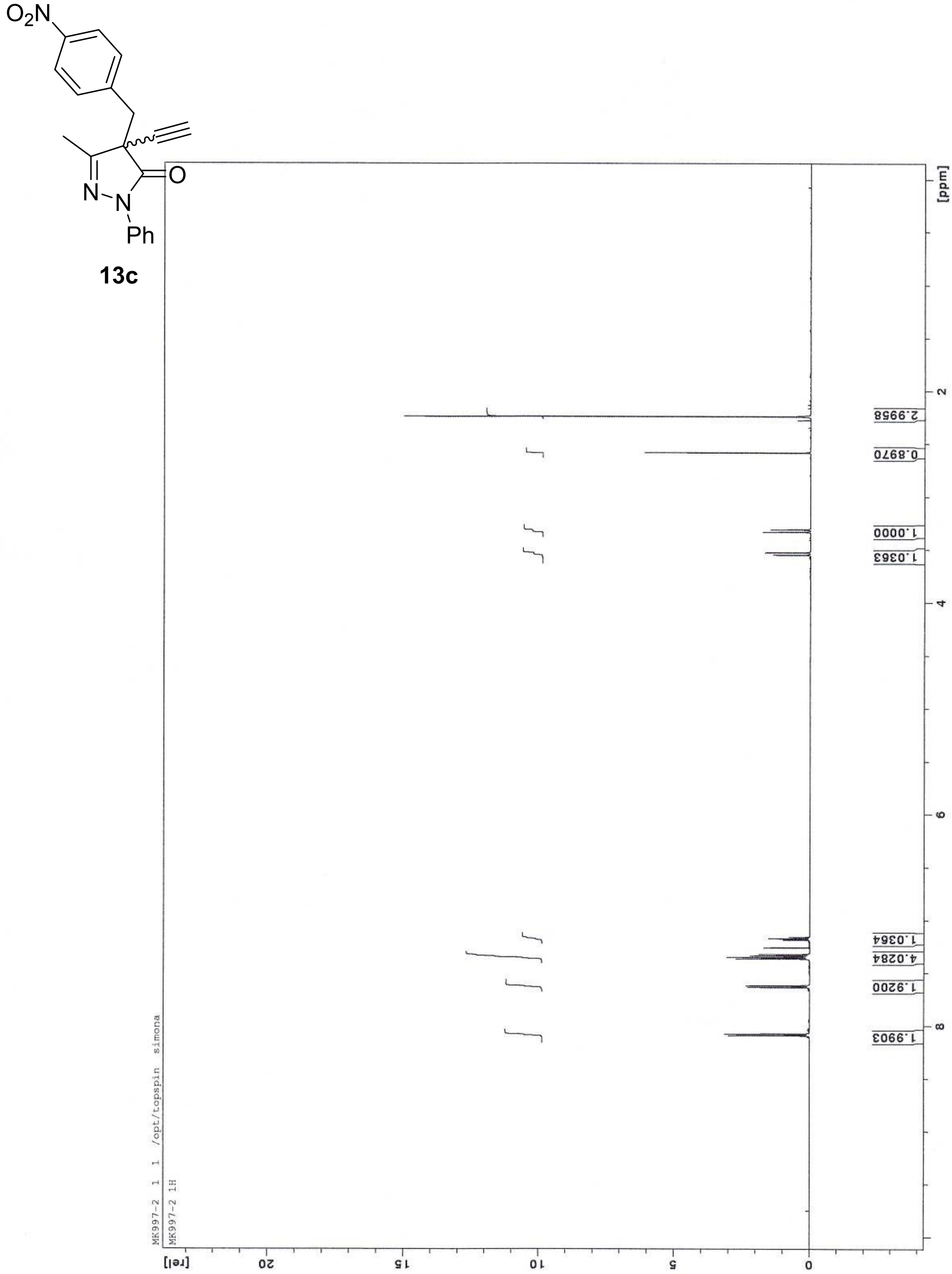


13b

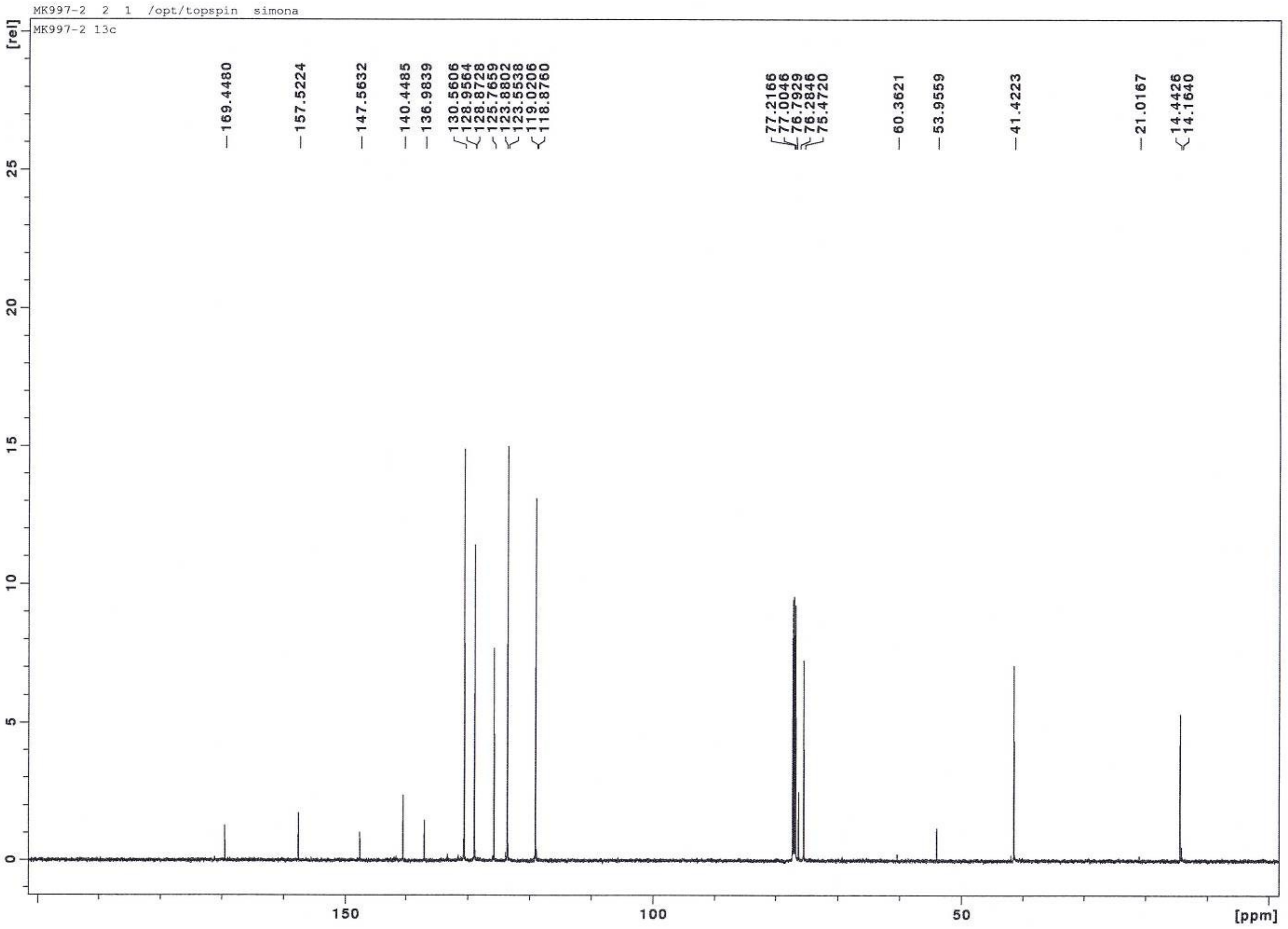

Ph-pBr

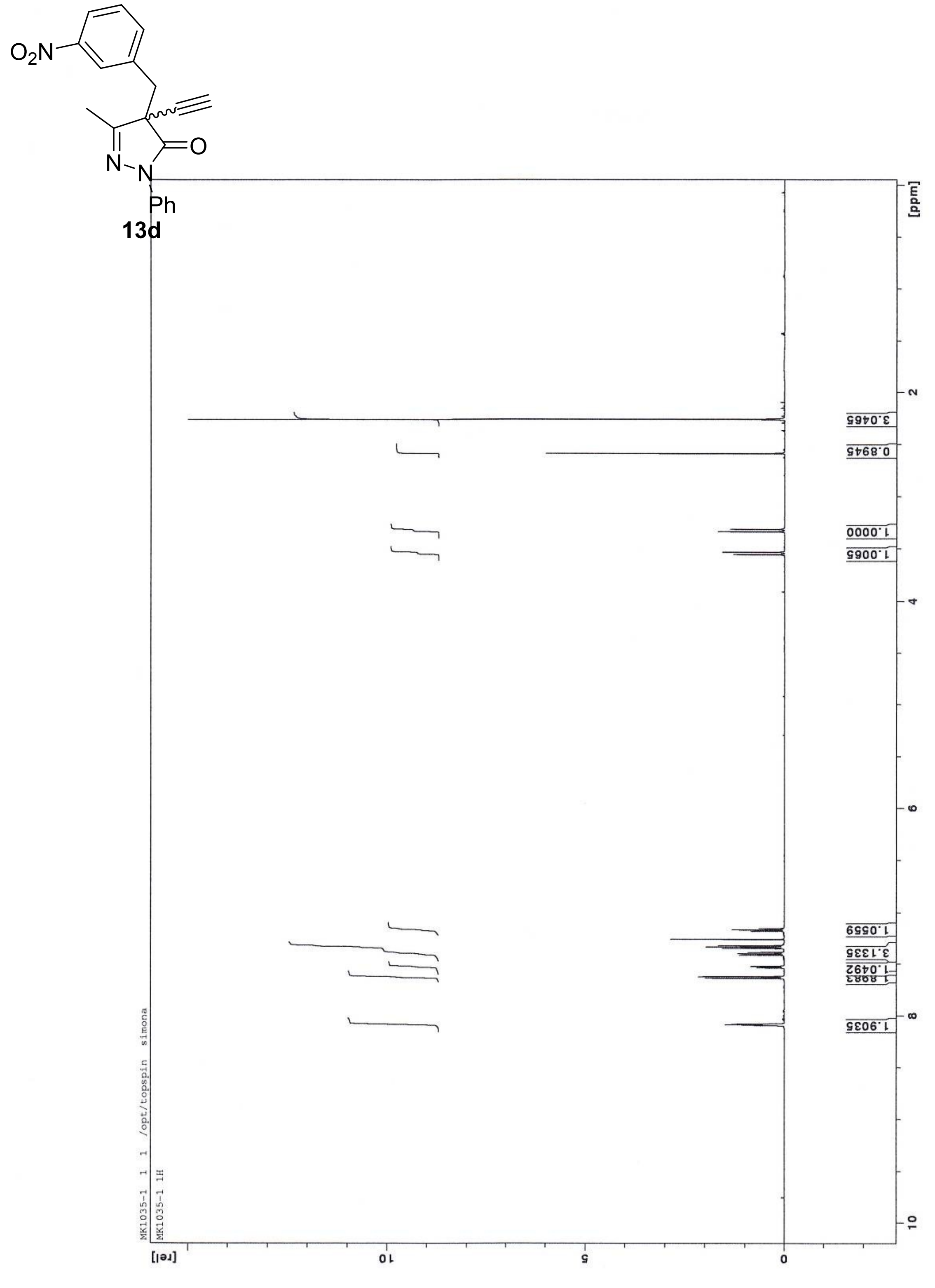

[ppm]
2
4
6
8
10
3.0492
0.9680
1.0093
1.0000
2.0165
1.0595
4.0583
1.9957
[rel]
15
10
5
0
MK1019-1 10 1 /opt/topspin simona
MK1019-1 1H


MK1019-1 20 1 /opt/topspin simona
MK1019-1 13C
169.9257
157.8888
142.1834
137.1515
134.0708
132.2948
132.0652
131.5758
131.1078
128.7999
128.1715
125.6261
122.0568
119.2978
77.2119
77.0000
76.7887
74.8823
54.1833
41.5642
14.4983
[ppm]
50
100
150
[rel]
20
15
10
5
0


O2N
N
N
O
Ph
MK997-2 1 1 /opt/topspin simona
MK997-2 1H
[ppm]
2
4
6
8
2.9958
0.8970
1.0000
1.0363
1.0364
4.0284
1.9200
1.9903
[rel]
20
15
10
5
0

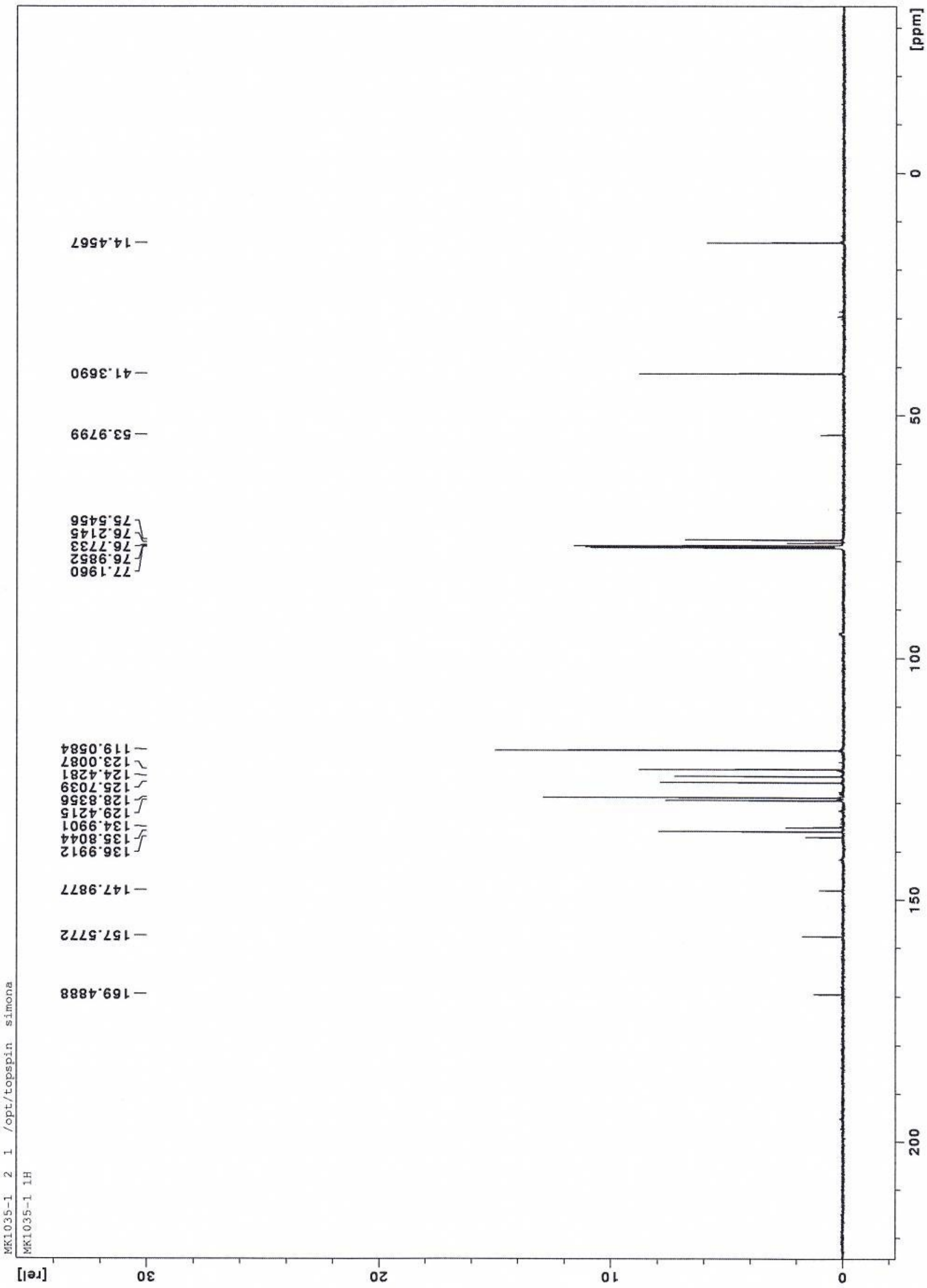
13c

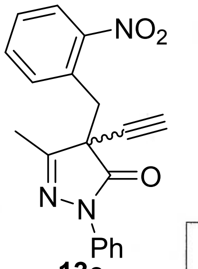

MK997-2 2 1 /opt/topspin simona
MK997-2 13c
169.4480
157.5224
147.5632
140.4485
136.9839
130.5606
128.9564
128.8728
125.7659
123.8802
123.5538
119.0206
118.8760
77.2166
77.0046
76.7929
76.2846
75.4720
60.3621
53.9559
41.4223
21.0167
14.4426
14.1640
[rel]
0
5
10
15
20
25
150
100
50
[ppm]



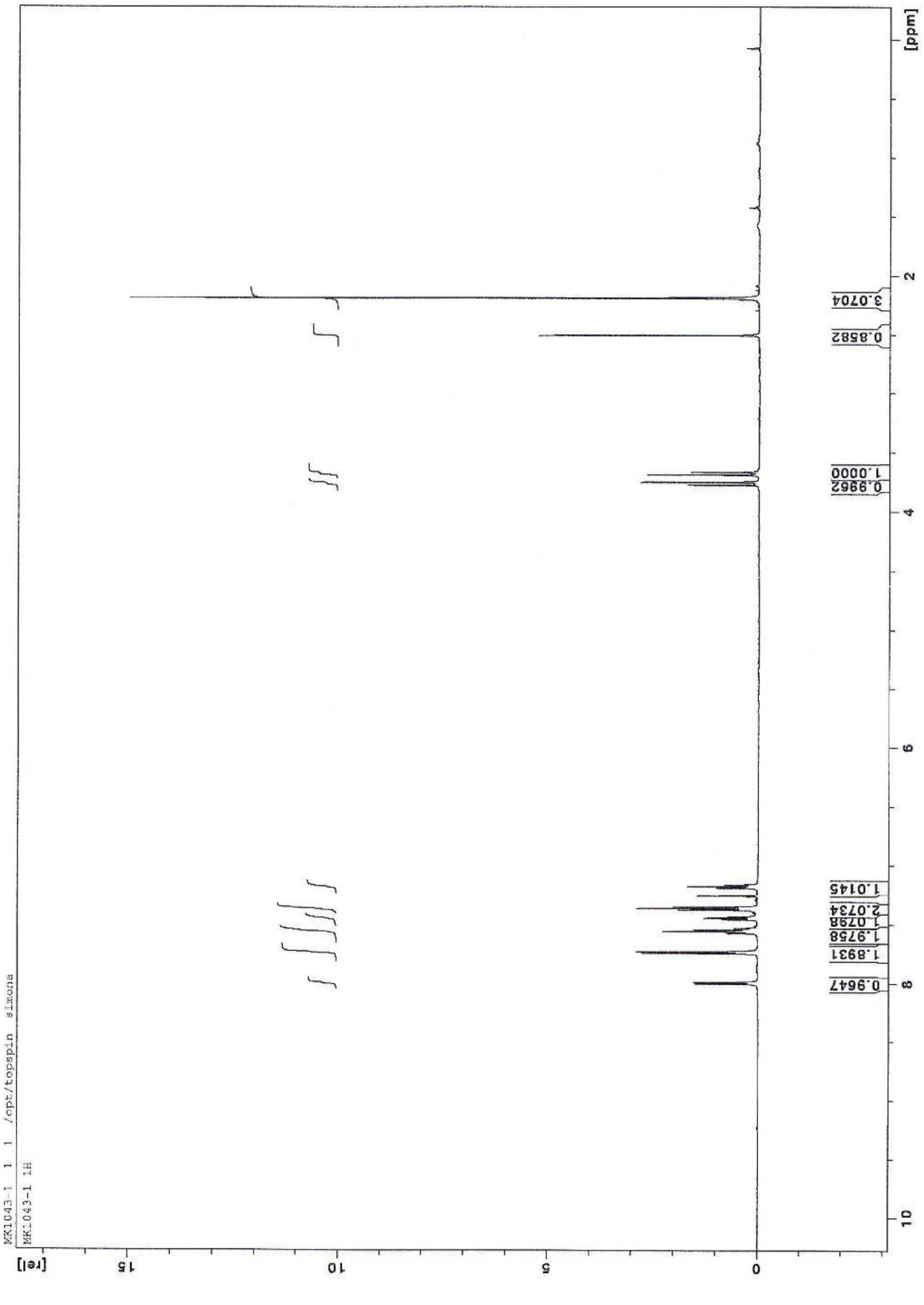
13d

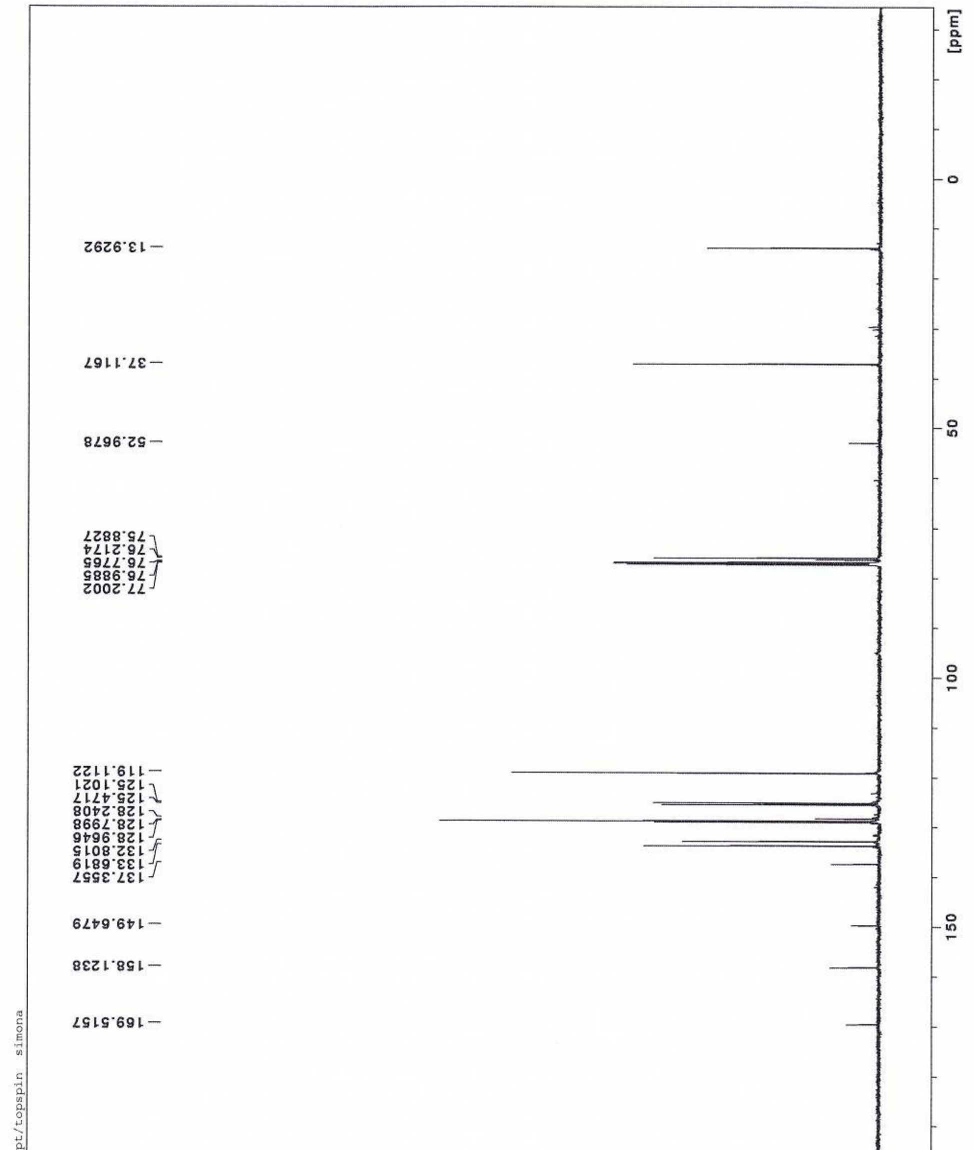
O_2N
N
N
O
Ph
MK1035-1 1 1 /opt/topspin simona
MK1035-1 1H
[rel]
10
5
0
[ppm]
2
4
6
8
10
3.0465
0.8945
1.0000
1.0065
1.0559
3.1335
1.0492
1.8983
1.9035

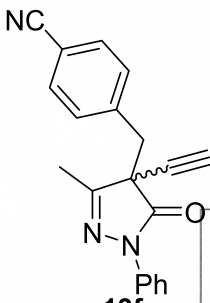

MK1035-1 2 1 /opt/topspin simona
MK1035-1 1H
169.4888
157.5772
147.9877
136.9912
135.8044
134.9901
129.4215
128.8356
125.7039
124.4281
123.0087
119.0584
77.1960
76.9852
76.7733
76.2145
75.5456
53.9799
41.3690
14.4567
200
150
100
50
0
[ppm]
30
20
10
0
[rel]



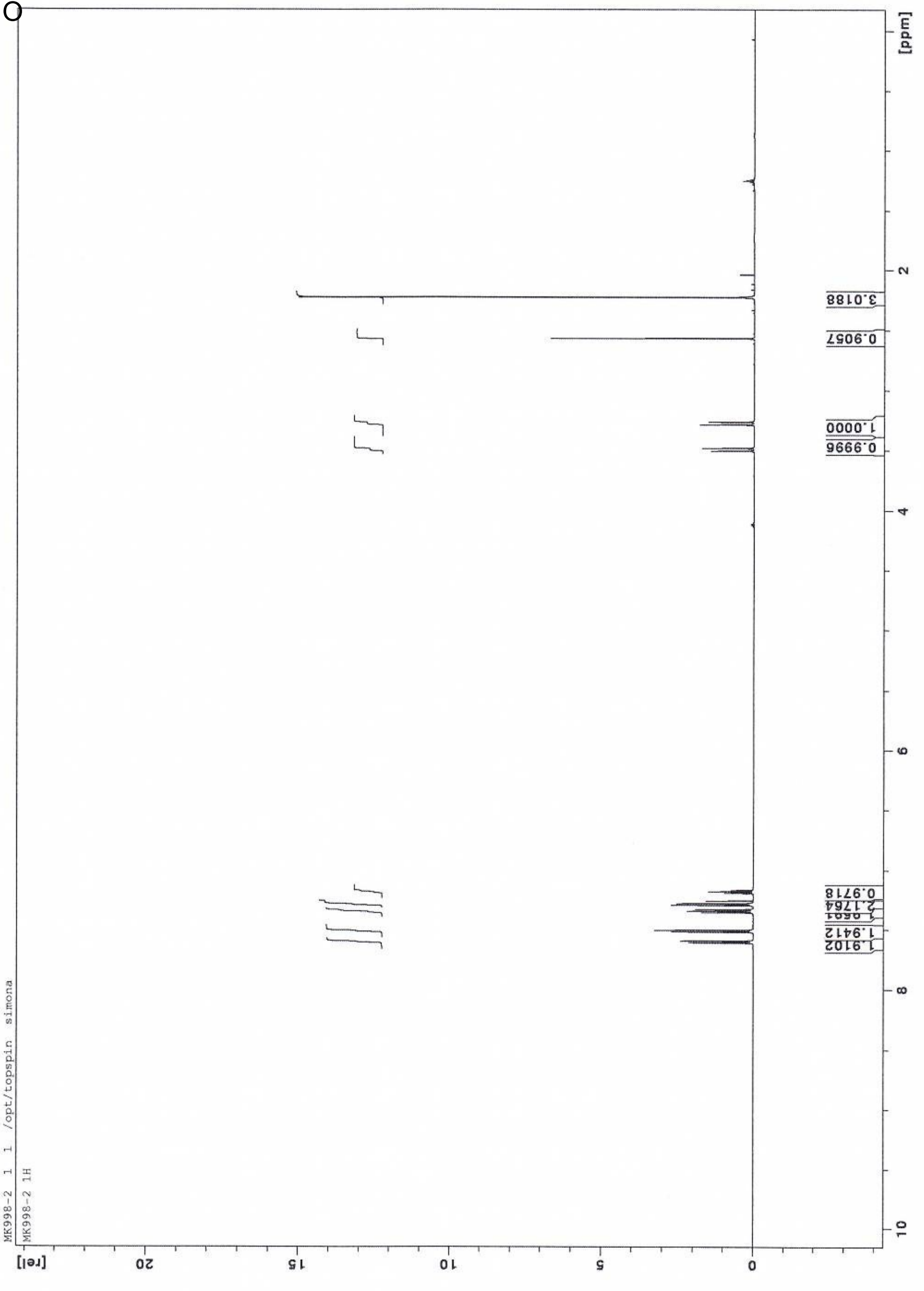
13e

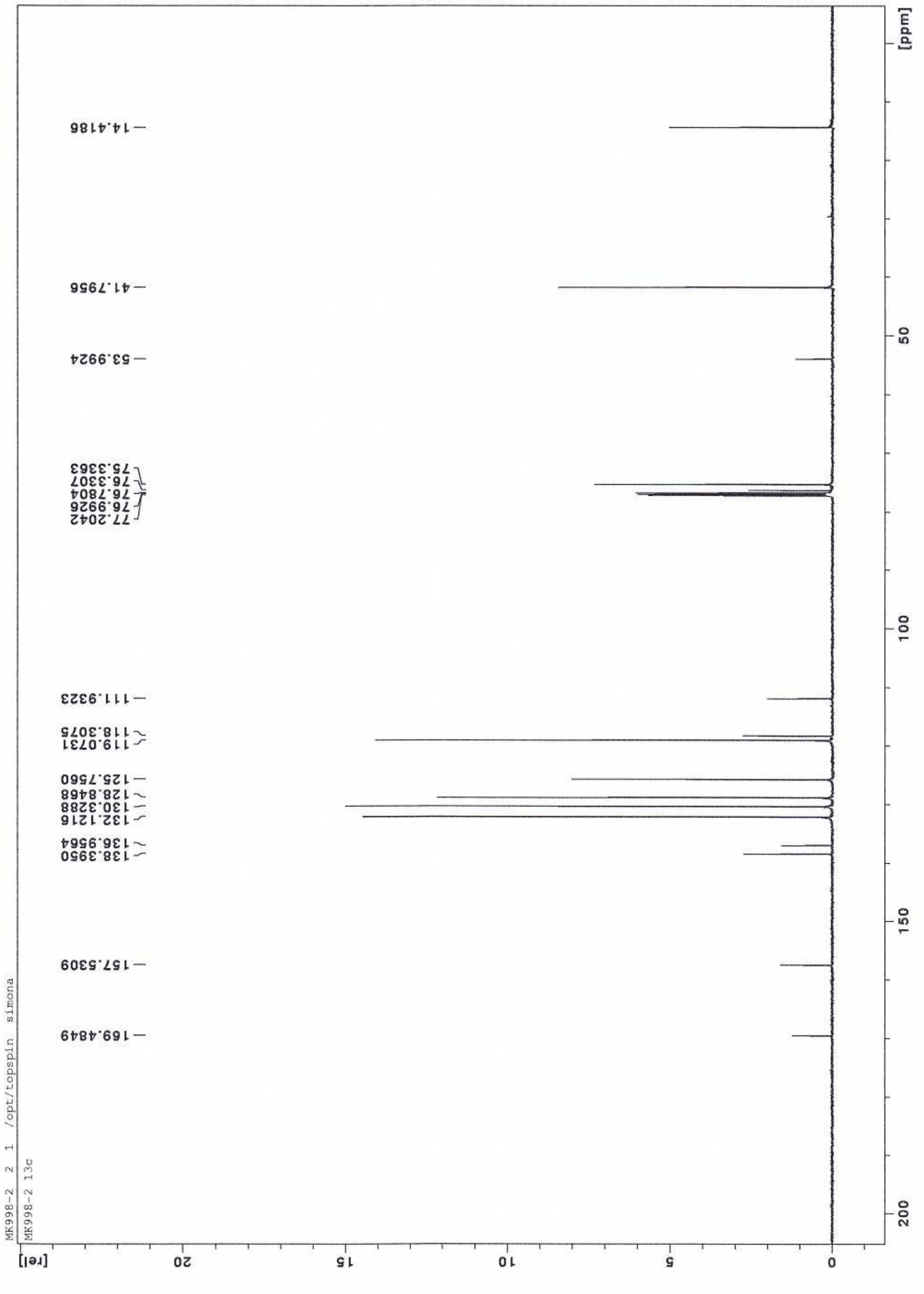

MK1043-1 1 1 /opt/topspin simona
MK1043-1 1H
[ppm]
2
4
6
8
10
3.0704
0.8582
1.0000
0.9962
1.0145
2.0734
1.0798
1.9758
1.8931
0.9647
[rel]
15
10
5
0

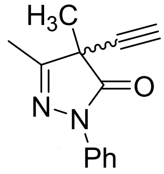

MK1043-1 2 1 /opt/topspin simona
MK1043-1 1H
169.5157
158.1238
149.6479
137.3557
133.6819
132.8015
128.9646
128.7998
128.2408
125.4717
125.1021
119.1122
77.2002
76.9885
76.7765
76.2174
75.8827
52.9678
37.1167
13.9292
200
150
100
50
0
[ppm]
[rel]
25
20
15
10
5
0


NC
N
N
O
Ph

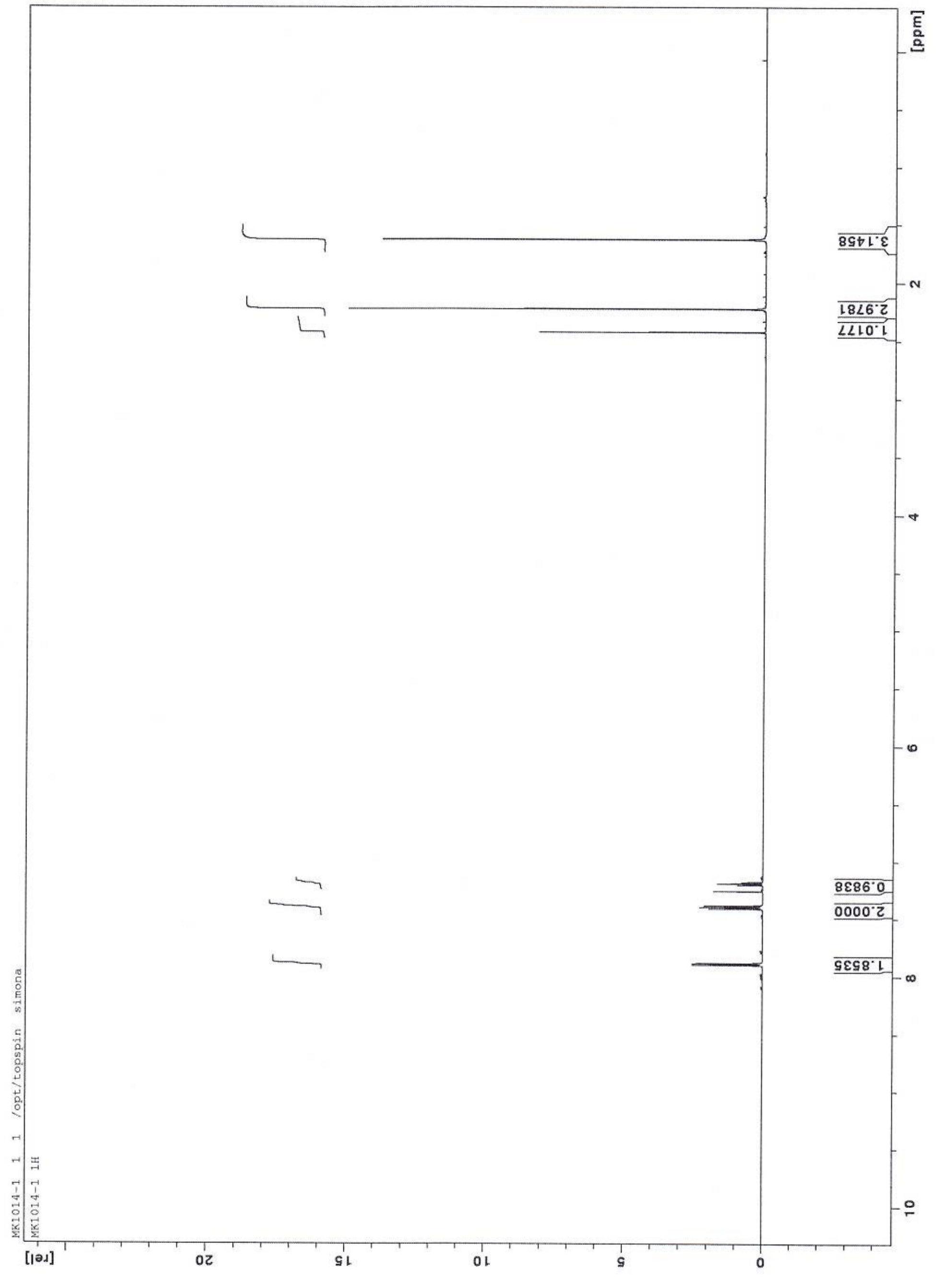
13f

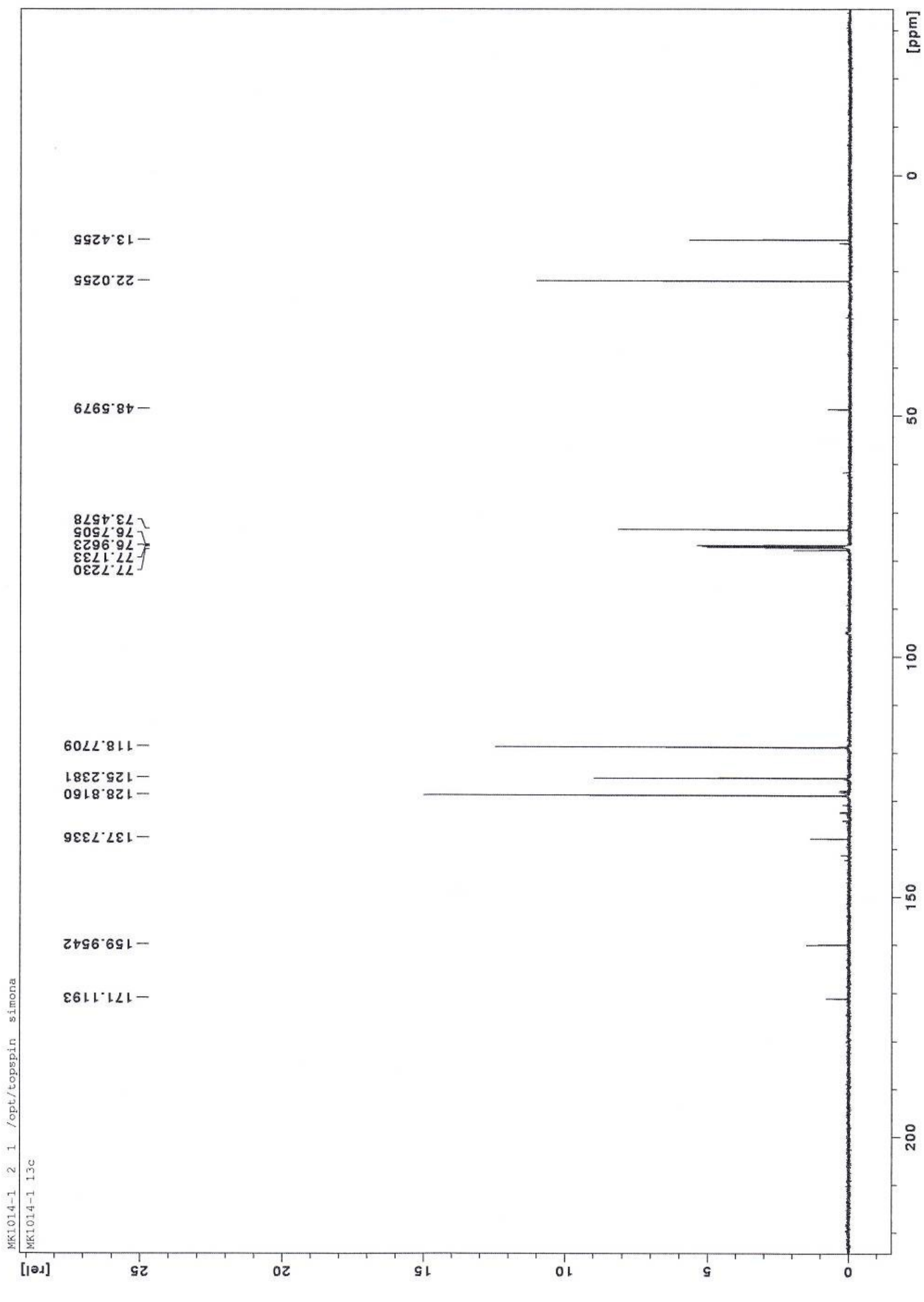

MK998-2 1 1 /opt/topspin simona
MK998-2 1H
[ppm]
2
4
6
8
10
[rel]
20
15
10
5
0
3.0188
0.9057
1.0000
0.9996
0.9718
2.1764
1.9412
1.9102

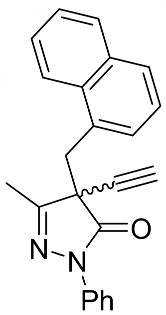

MK998-2 2 1 /opt/topspin simona
MK998-2 13c
169.4849
157.5309
138.3950
136.9564
132.1216
130.3288
128.8468
125.7560
119.0731
118.3075
111.9323
77.2042
76.9926
76.7804
76.3307
75.3363
53.9924
41.7956
14.4186
[ppm]
200
150
100
50
[rel]
20
15
10
5
0


H$_3$C
O
N
N
Ph

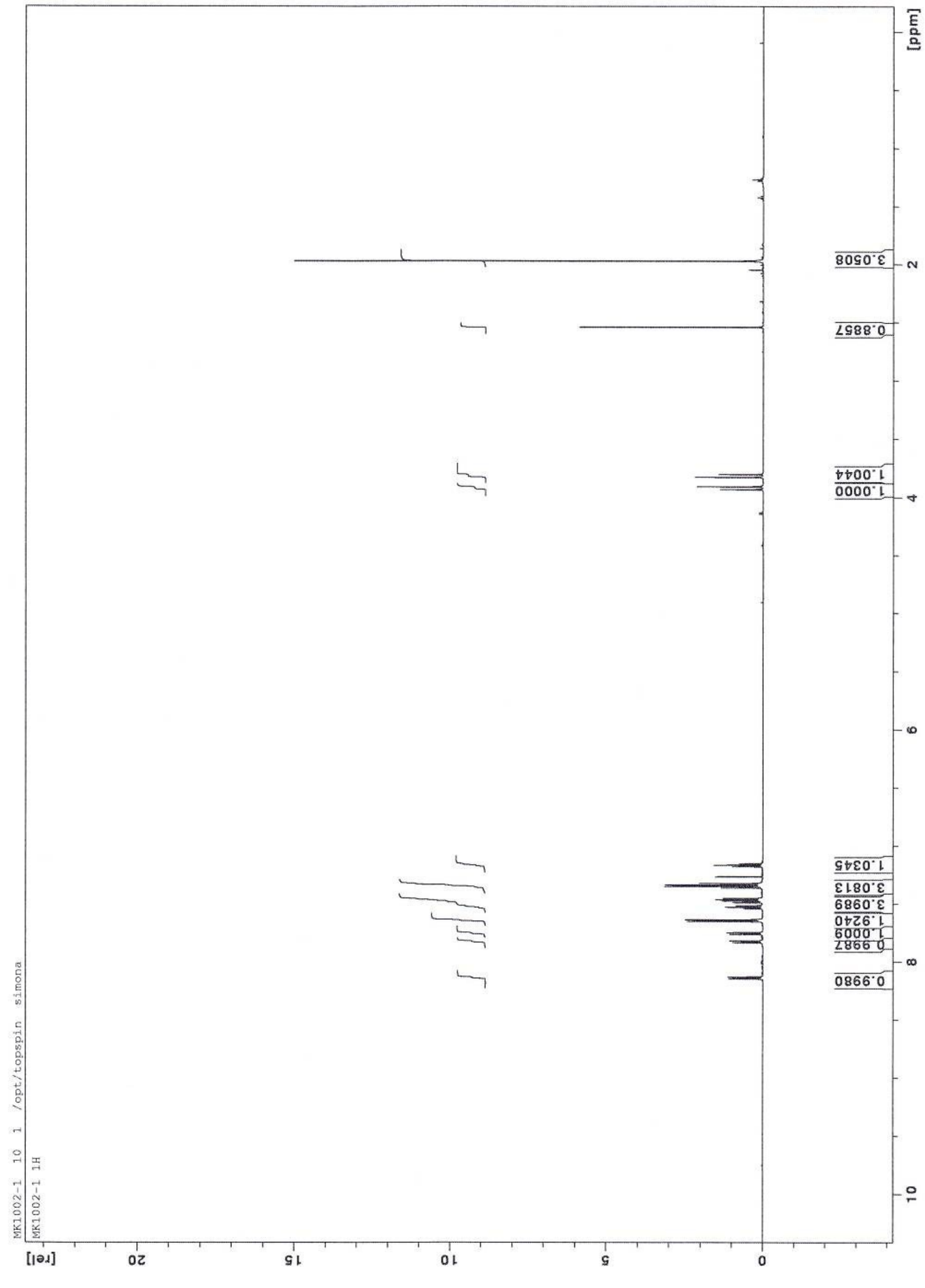
13g

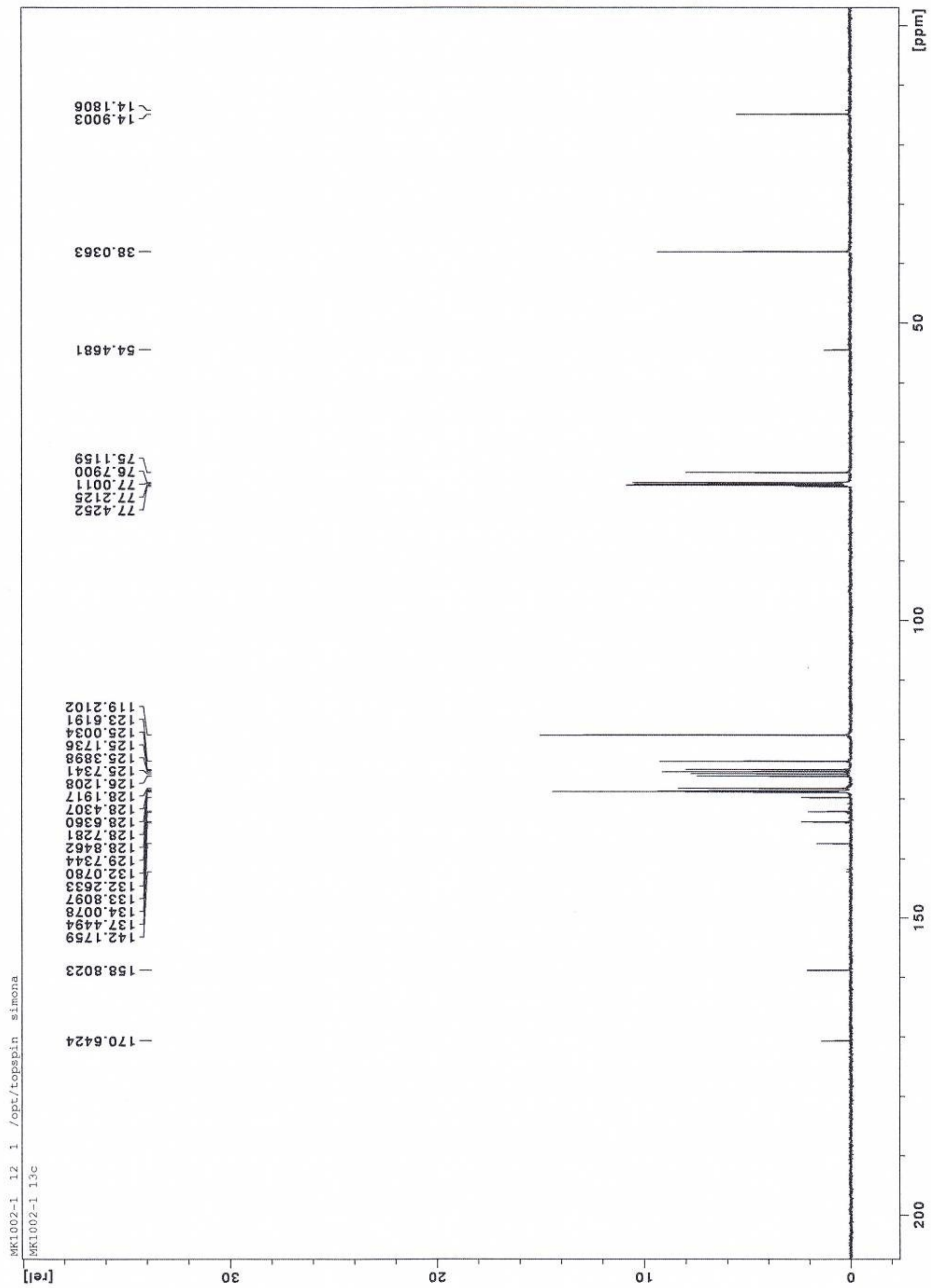

MK1014-1 1 1 /opt/topspin simona
MK1014-1 1H
[ppm]
2
4
6
8
10
[rel]
0
5
10
15
20
3.1458
2.9781
1.0177
0.9838
2.0000
1.8535

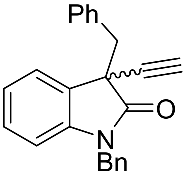

MK1014-1 2 1 /opt/topspin simona
MK1014-1 13c
171.1193
159.9542
137.7336
128.8160
125.2381
118.7709
77.2230
77.1733
76.9623
76.7505
73.4578
48.5979
22.0255
13.4255
[ppm]
0
50
100
150
200
[rel]
0
5
10
15
20
25



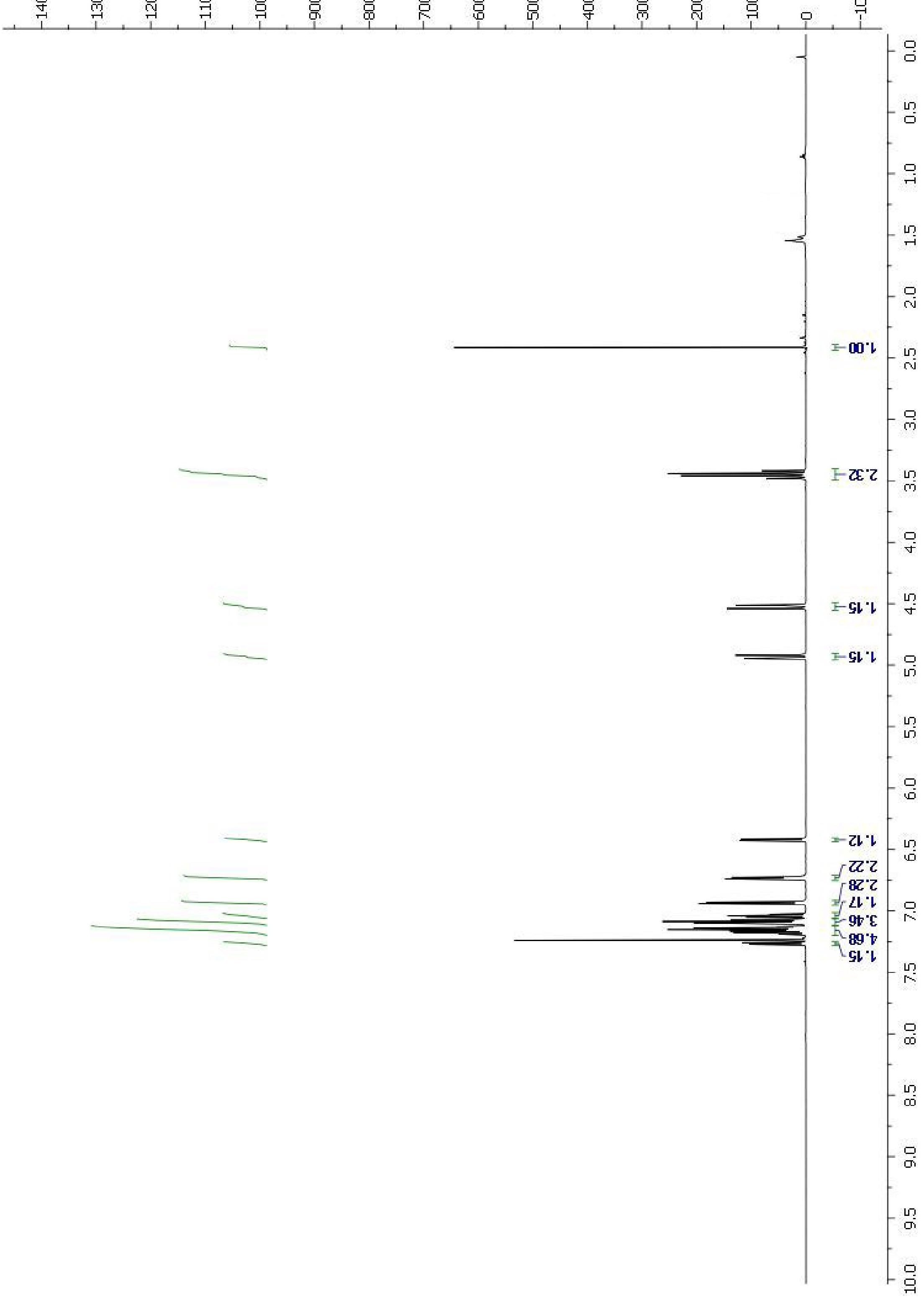
13g


MK1002-1 10 1 /opt/topspin simona
MK1002-1 1H
3.0508
0.8857
1.0044
1.0000
1.0345
3.0813
3.0989
1.9240
1.0009
0.9987
0.9980
[ppm]
2
4
6
8
10
[rel]
0
5
10
15
20

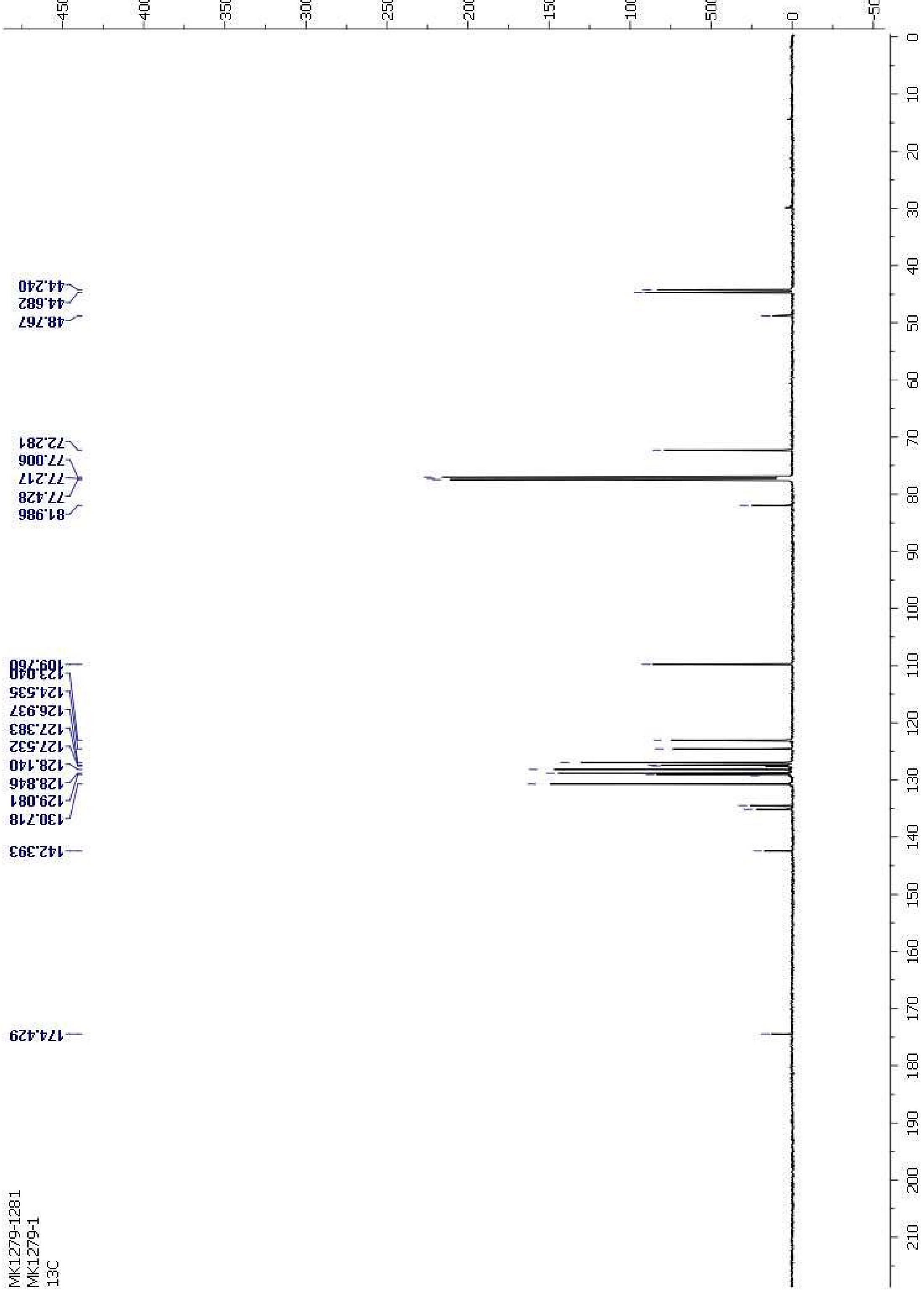

MK1002-1 12 1 /opt/topspin simona
MK1002-1 13c
170.6424
158.8023
142.1759
137.4494
134.0078
133.8097
132.2633
132.0780
129.7344
128.8462
128.7281
128.6360
128.4307
128.1917
126.1208
125.7341
125.3898
125.1736
125.0034
123.6191
119.2102
77.4252
77.2125
77.0011
76.7900
75.1159
54.4681
38.0363
14.9003
14.1806
200
150
100
50
[ppm]
[rel]
30
20
10
0

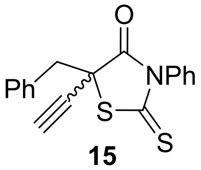


14

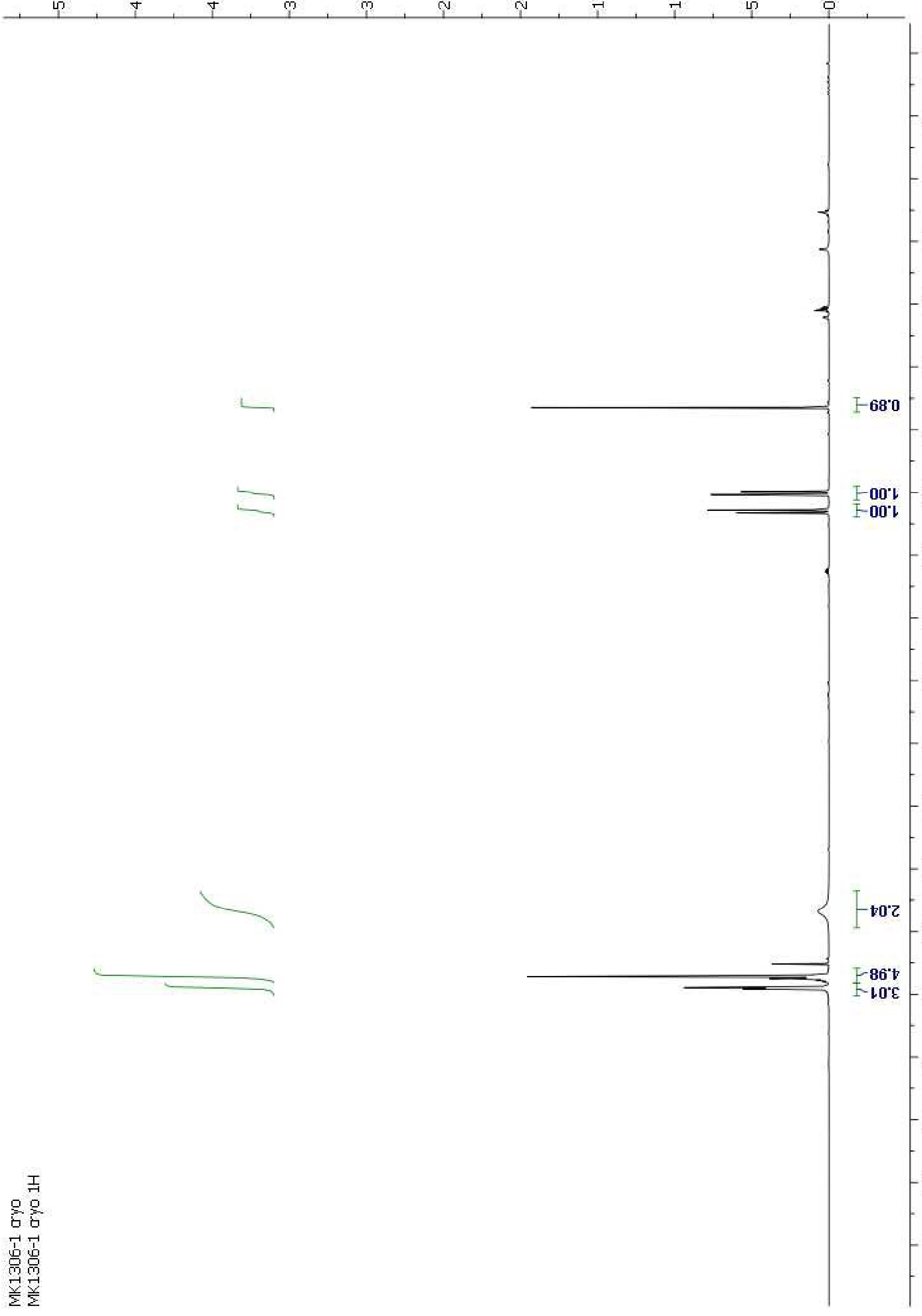


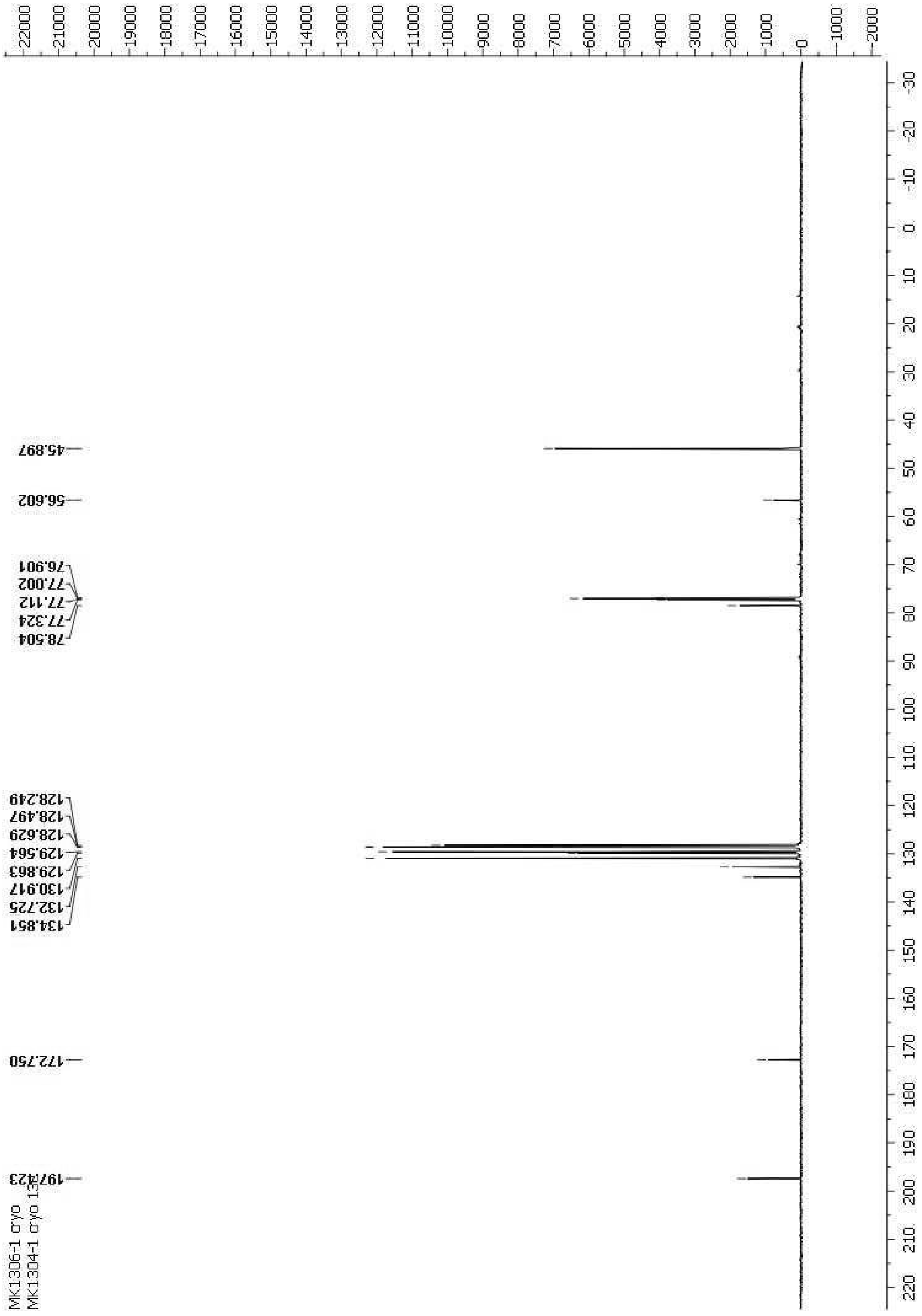
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-10
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
1.00
2.32
1.15
1.15
1.12
2.22
2.28
1.17
3.46
4.68
1.15


MK1279-1281
MK1279-1
13C
174.429
142.393
130.718
129.081
128.846
128.140
127.532
127.383
126.937
124.535
123.940
109.760
81.986
77.428
77.217
77.006
72.281
48.767
44.682
44.240
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
450
400
350
300
250
200
150
100
50
0
-50

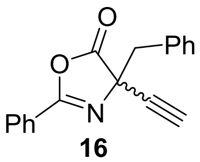

O
Ph
NPh
S
S

15

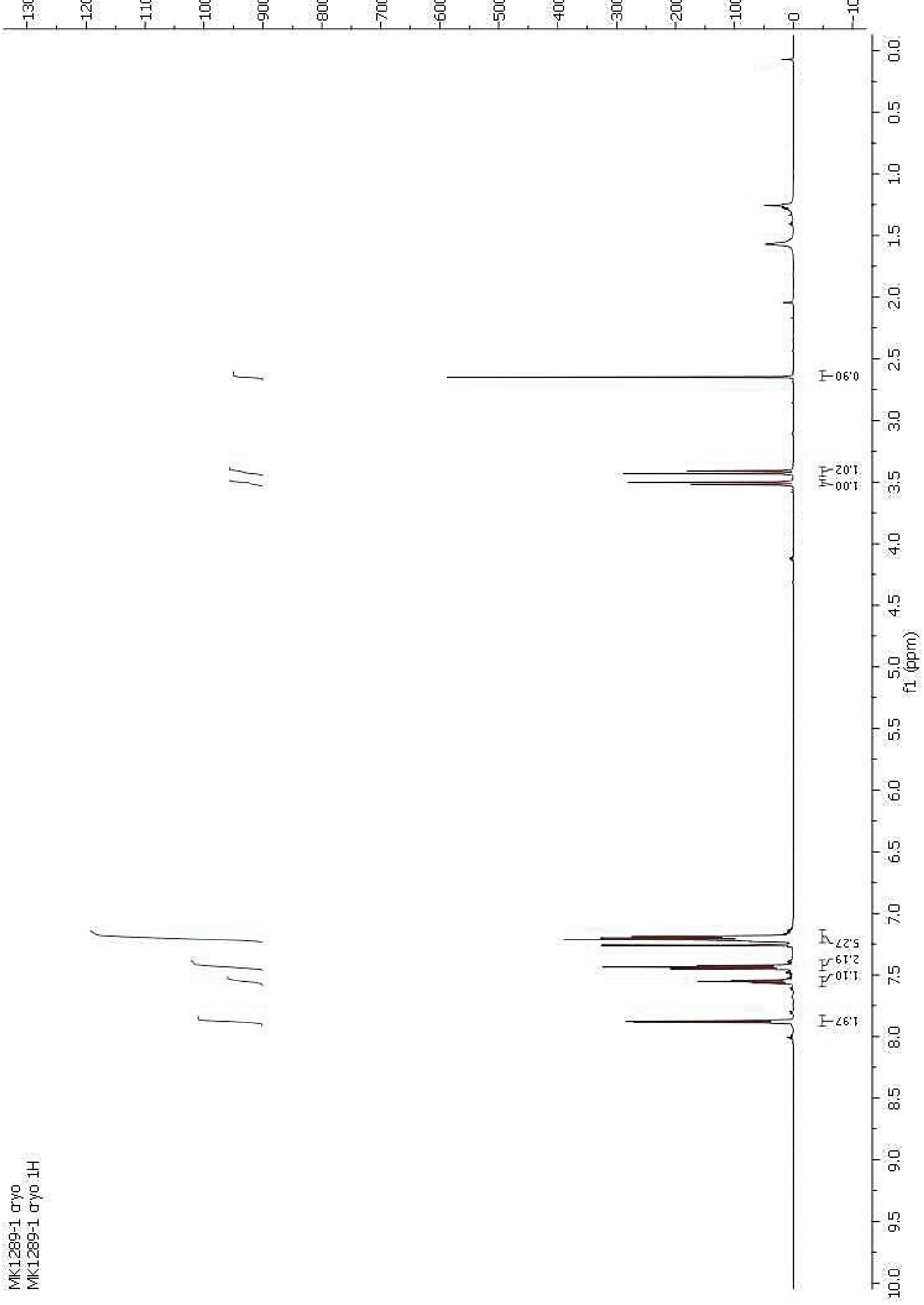

MK1306-1 dryo
MK1306-1 dryo 1H
0.89
1.00
1.00
2.04
4.98
3.01
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
500
450
400
350
300
250
200
150
100
50
0

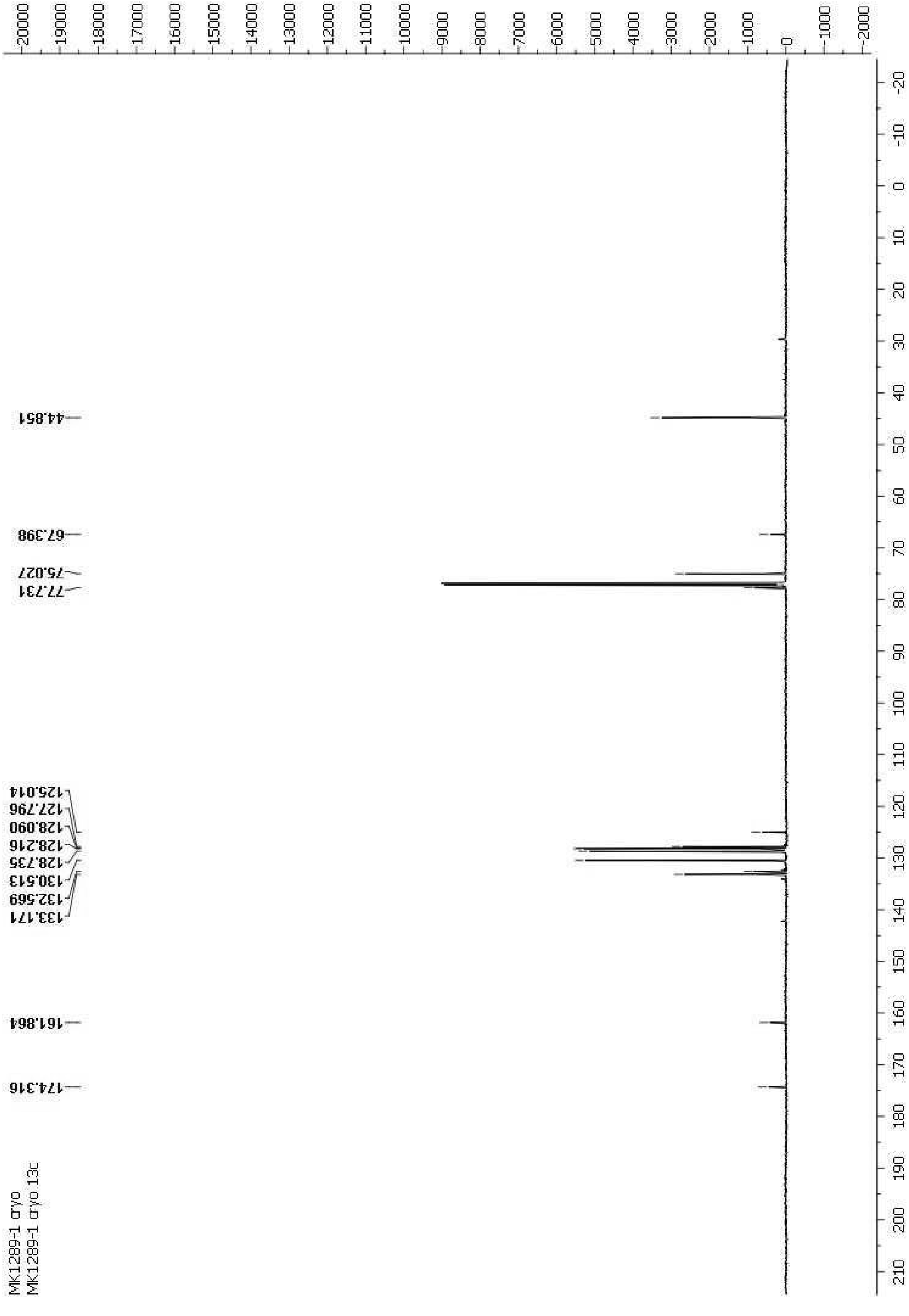


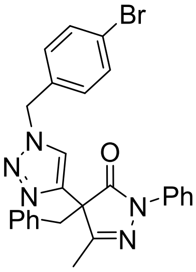
MK1306-1 cryo
MK1304-1 cryo 13
45.897
56.602
76.901
77.002
77.112
77.324
78.504
128.249
128.497
128.629
129.564
129.863
130.917
132.725
134.851
172.750
197.423
-30
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000


O
Ph
O
N
Ph

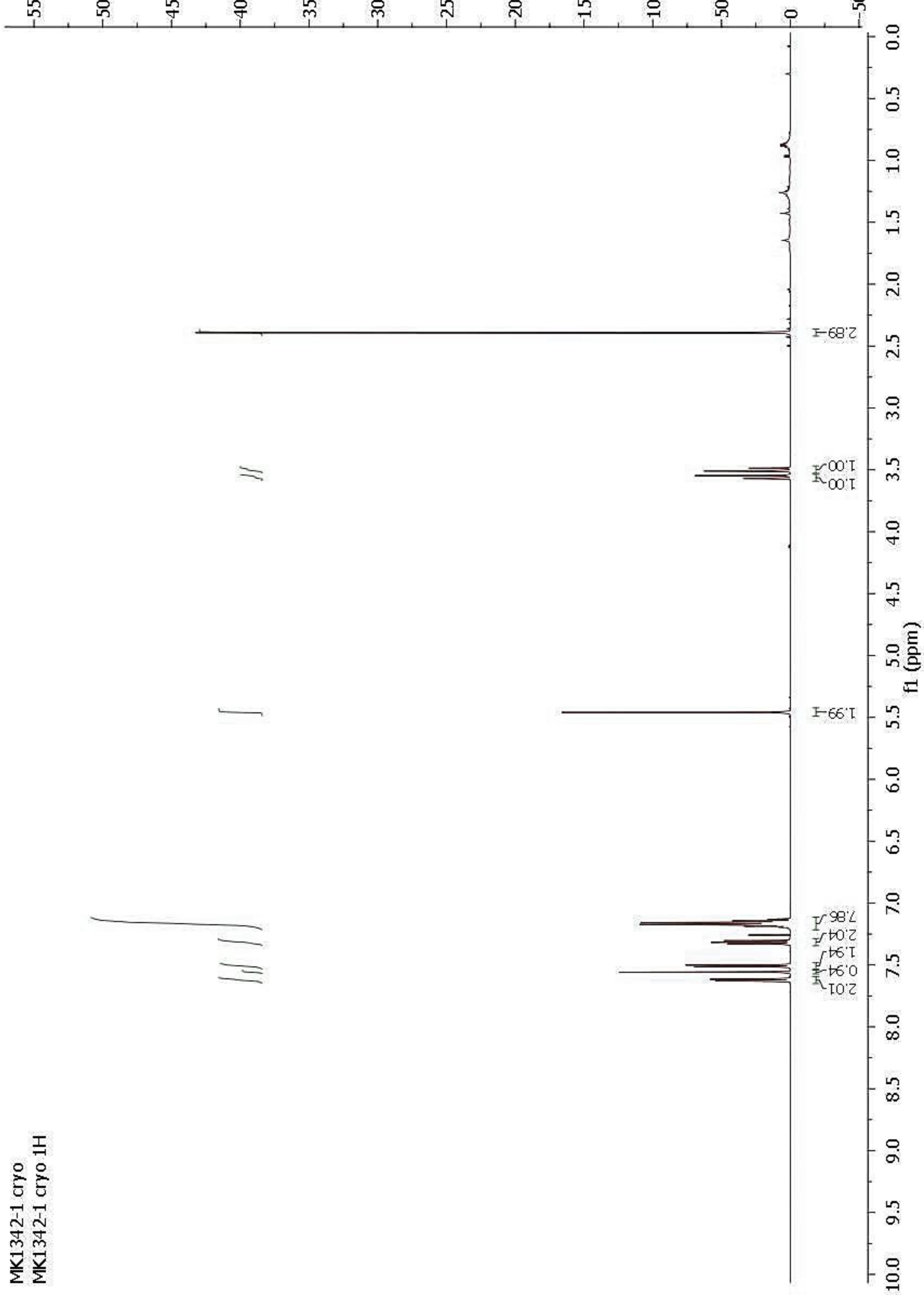
16

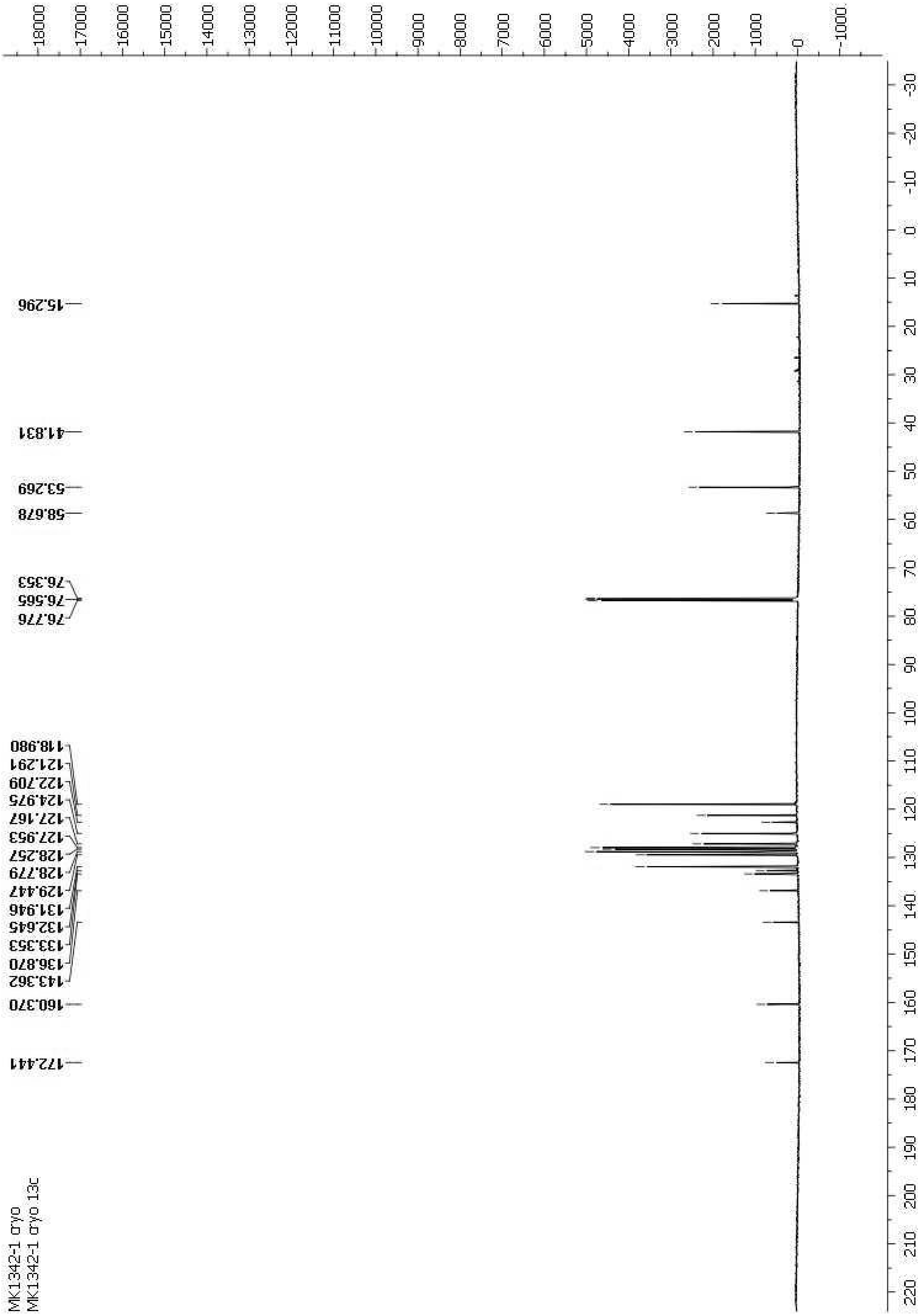

1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
f1 (ppm)
0.90
1.02
1.00
5.27
2.19
1.10
1.97
MK1289-1 aryo
MK1289-1 aryo.1H

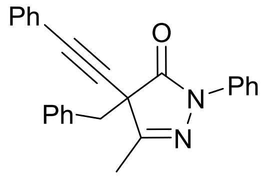

MK1289-1 cryo
MK1289-1 cryo 13c
174.316
161.864
133.171
132.569
130.513
128.735
128.216
128.090
127.796
125.014
77.231
75.027
67.398
44.851
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210



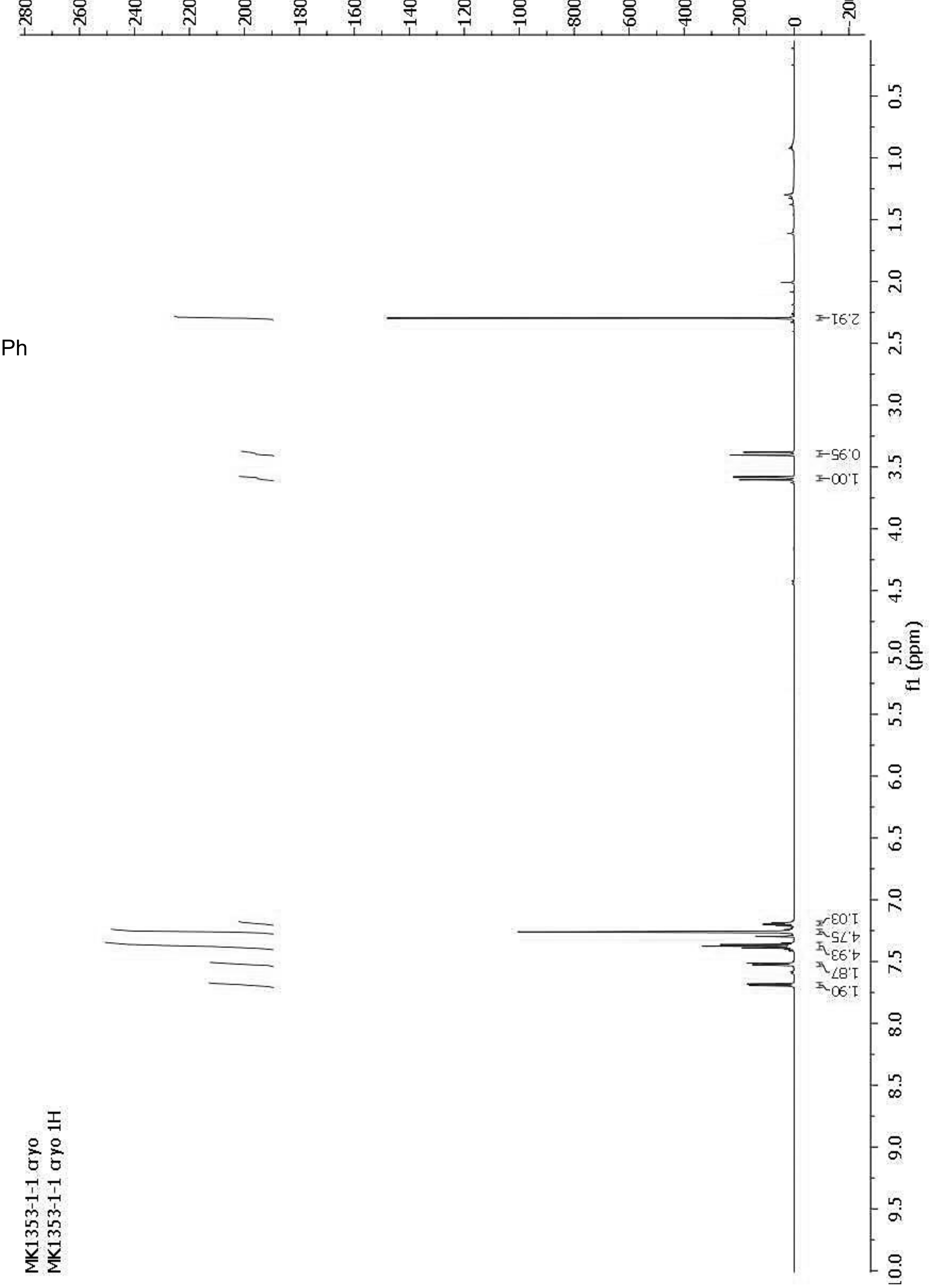
17

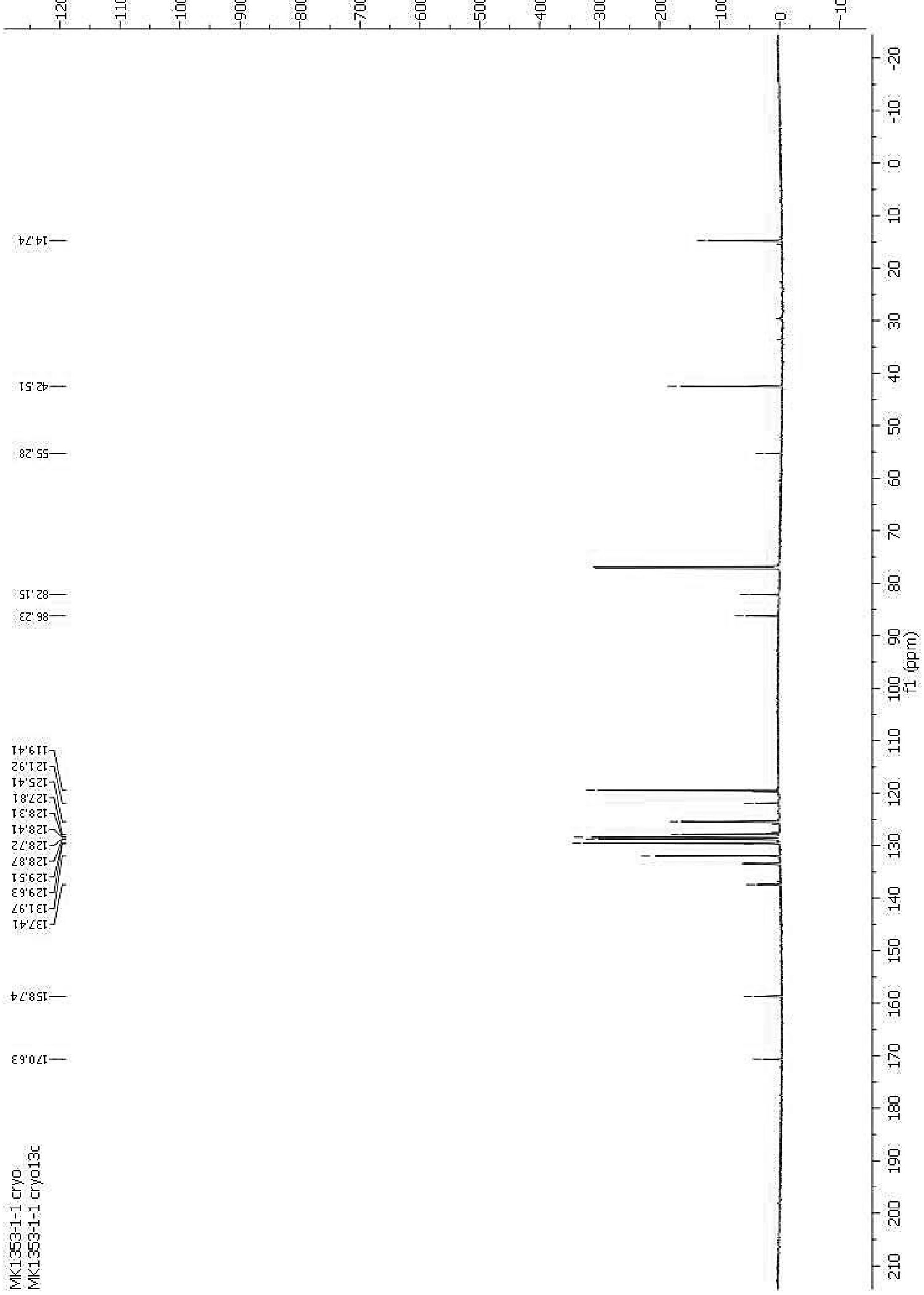

MK1342-1 cryo
MK1342-1 cryo 1H
f1 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
2.89
1.00
1.00
1.99
7.86
2.04
1.94
0.94
2.01
-50
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
5500


MK1342-1 cryo
MK1342-1 cryo 13c
172.441
160.370
143.362
136.870
133.353
132.645
131.946
129.447
128.779
128.257
127.953
127.167
124.975
122.709
121.291
118.980
76.776
76.565
76.353
58.678
53.269
41.831
15.296
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-30
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220


Ph
O
N
Ph
Ph
N

18


MK1353-1-1 cryo
MK1353-1-1 cryo 1H
2.91
0.95
1.00
1.03
4.75
4.93
1.87
1.90
f1 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0


MK1353-1-1 cryo
MK1353-1-1 cryo13c
170.63
158.74
137.41
131.97
129.63
129.51
128.87
128.72
128.41
128.31
127.81
125.41
121.92
119.41
86.23
82.15
55.28
42.51
14.74
f1 (ppm)