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Synthesis and cytotoxic activity of new hexaazadibenzotetracenes derived from *trans*-1,2-diaminocyclohexane

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Table of contents

General information S1

Synthesis procedure and analytical data for compounds **2a–h** S2

NMR and MS spectra of compounds **2a–h** S7

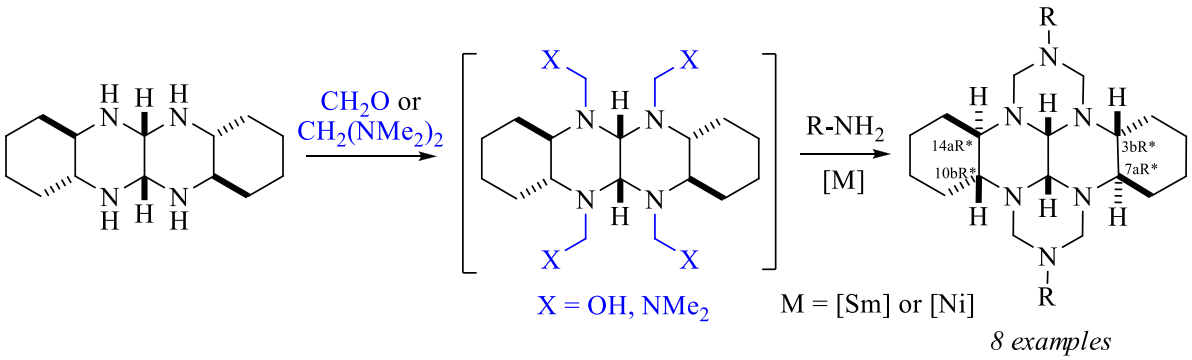
Cytotoxicity assay S23

General information

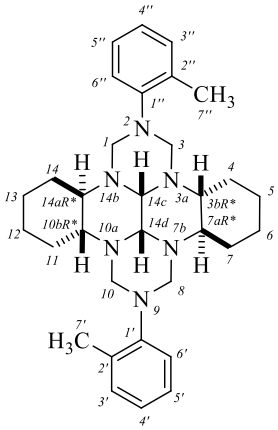
The ^{1}H and ^{13}C NMR spectra, including two dimensional homo- (COSY) and heteronuclear (HSQC, HMBC) spectra, were recorded on a Bruker Avance 500 spectrometer (500.17 MHz for ^{1}H and 125.78 MHz for ^{13}C) or a Bruker Avance 400 spectrometer (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) according to standard Bruker protocols using $CDCl_3$ as solvent and TMS as internal standard. The high-resolution mass spectra were recorded on a Bruker MaXis Impact instrument (TOF mass analyzer, electrospray ionization). The melting points were measured on a PHMK 80/2617 melting point apparatus. Commercially available reagents used in this work were purchased from Sigma–Aldrich and Acros Organics.

Multicomponent condensation of perhydro-1,6,7,12-tetraazatetracene 1 with formaldehyde and substituted anilines (general procedure, method A). A round-bottom flask mounted on a magnetic stirrer was charged with a solution of (±)-*trans*-cyclohexane-1,2-diamine (0.23 g, 2.00 mmol) in methanol (5 ml), and a solution of 40% aqueous glyoxal (0.14 g, 1.00 mmol) in methanol (5 ml) was added. The mixture was stirred at 70°C for 3 h and cooled, and a solution of 37% aqueous formaldehyde (0.45 ml, 4.00 mmol) in methanol (5 ml) and $Sm(NO_3)_3 \cdot 6H_2O$ (0.022 g, 0.05 mmol) were added. The mixture was stirred at room temperature (~20°C) for 30 min, and a solution of the corresponding amine (2.00 mmol) in methanol (5 ml) was added. The mixture was stirred at room temperature for 2.5 h and concentrated, and the solid product was filtered off and washed with methanol (2×10 ml). Pure compounds **2a–h** were thus isolated as powders.

Heterocyclization of 1,6,7,12-tetraazaperhydrotetracene 1 with *N,N,N′,N′*-tetramethylmethanediamine and substituted anilines (general procedure, method B). The reaction was conducted similarly to method A, using tetramethylmethanediamine (0.41 g, 4.00 mmol) and $NiCl_2 \cdot 6H_2O$ (0.012 g, 0.05 mmol).

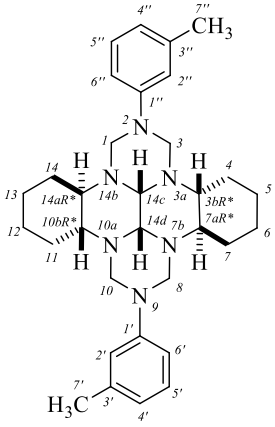


Analytical data for compounds 2a–h

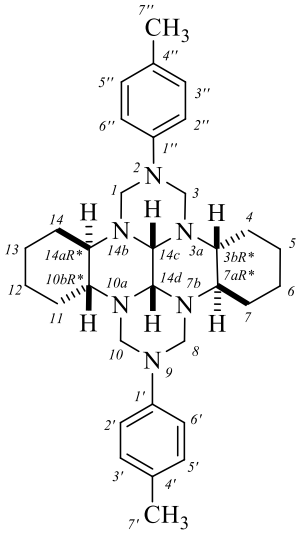


(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(2-methylphenyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (2a).** White powder, 0.24 g (47% yield, method A), 0.20 g (39% yield, method B), mp 220-222 °C, R_f 0.58 (MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.98 br. s (4H, CH_2, H_a-4,7,11,14), 1.19–1.31 m (4H, CH_2, H_a-5,6,12,13), 1.62 br. s (2H, CH_2, H_b-4,11), 1.73 d (2H, CH_2, H_b-5,12; $^2J_{ba}$ = 11.6 Hz), 1.85 br. s (2H, CH, H-7a,14a), 2.01 br. s (2H, CH_2, H_b-7,14), 2.12 d (2H, CH_2, H_b-6,13; $^2J_{ba}$ = 9.6 Hz), 2.33 br. s (6H, CH_3, H-7′,7″), 3.23 d (2H, CH, H-3b,10b; 2H, CH_2, H_a-1,8; $^2J_{ab}$ = 9.2 Hz), 3.52 br. s (2H, CH, H-14c,14d), 3.89 d (2H, CH_2, H_a-3,10;

$^2J_{ab}$ = 12.8 Hz), 4.90 d (4H, CH_2, H_b-1,3,8,10; $^2J_{ba}$ = 11.2 Hz), 6.71 d (2H, CH, H-5′,5″; J = 6.8 Hz), 6.80–6.84 m (4H, CH, H-4′,4″,6′,6″), 7.14 t (2H, CH, H-3′,3″; J = 7.4 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.7 (C-7′,7″), 24.2 (C-4,11), 24.6 (C-5,12), 27.1 (C-6,13), 28.6 (C-7,14), 55.1 (C-3b,10b), 63.6 (C-7a,14a), 66.7 (C-3,10), 70.1 (C-1,8), 77.9 (C-14c,14d), 114.4 (C-6′,6″), 118.1 (C-4′,4″), 121.2 (C-5′,5″), 128.9 (C-3′,3″), 138.7 (C-2′,2″), 149.5 (C-1′,1″). HRMS, *m/z*: 511.3544 $[M - H]^+$, 535.3516 $[M + Na]^+$. $C_{32}H_{44}N_6$. Calculated: *M* – H 511.3549, *M* + Na 535.3525.

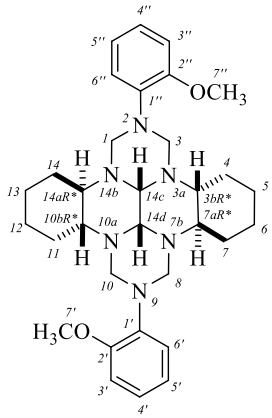


(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(3-methylphenyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (2b).** White powder, 0.28 g (55% yield, method A), 0.23 g (45% yield, method B), mp 224-225 °C, R_f 0.62 (MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.96–1.01 m (4H, CH_2, H_a-4,7,11,14), 1.19–1.29 m (4H, CH_2, H_a-5,6,12,13), 1.62 br. s (2H, CH_2, H_b-4,11), 1.74 d (2H, CH_2, H_b-5,12; $^2J_{ba}$ = 12 Hz), 1.82–1.87 m (2H, CH, H-7a,14a), 2.02 br. s (2H, CH_2, H_b-7,14), 2.13 d (2H, CH_2, H_b-6,13; $^2J_{ba}$ = 12 Hz, 2.33 br. s (6H, CH_3, H-7′,7″), 3.23 d (2H, CH, H-3b,10b; 2H, CH_2, H_a-1,8; $^2J_{ab}$ = 10 Hz), 3.52 br. s (2H, CH, H-14c,14d), 3.89 d (2H, CH_2, H_a-3,10; $^2J_{ab}$ = 13.2 Hz), 4.91 d (4H, CH_2, H_b-1,3,8,10; $^2J_{ba}$ = 11.6 Hz), 6.71 d (2H, CH, H-4′,4″; J = 7.6 Hz), 6.80 br. s (2H, CH, H-2′,2″), 6.83 d (2H, CH, H-6′,6″; J = 8.4 Hz), 7.14 t (2H, CH, H-5′,5″; J = 7.6 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.7 (C-7′,7″), 24.2 (C-4,11), 24.6 (C-5,12), 27.1 (C-6,13), 28.6 (C-7,14), 55.1 (C-3b,10b), 63.7 (C-7a,14a), 66.7 (C-3,10), 70.1 (C-1,8), 77.9 (C-14c,14d), 114.5 (C-6′,6″), 118.1 (C-2′,2″), 121.2 (C-4′,4″), 128.9 (C-5′,5″), 138.7 (C-3′,3″), 149.5 (C-1′,1″). HRMS, *m/z*: 513.3464 $[M + H]^+$. $C_{32}H_{44}N_6$. Calculated: *M* + H 513.3706.

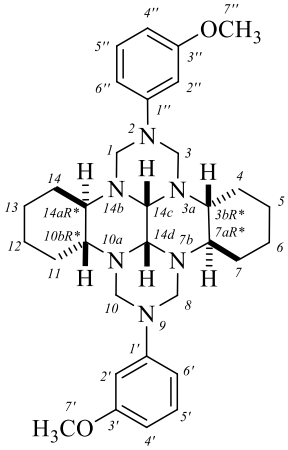


(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(4-methylphenyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (2c).** White powder, 0.42 g (82% yield, method A), 0.31 g (61% yield, method B), mp 226-228 °C, R_f 0.60 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.96 br. s (4H, CH_2, H_a-4,7,11,14), 1.20–1.29 m (4H, CH_2, H_a-5,6,12,13), 1.61 br. s (2H, CH_2, H_b-4,11), 1.71 d (2H, CH_2, H_b-5,12; $^2J_{ba}$ = 10 Hz), 1.83 br. s (2H, CH, H-7a,14a), 1.98 br. s (2H, CH_2, H_b-7,14), 2.09 br. s (2H, CH_2, H_b-6,13), 2.29 br. s (6H, CH_3, H-7′,7″), 3.23 br. s (2H, CH, H-3b,10b; 2H, CH_2, H_a-1,8), 3.51 br. s (2H, CH, H-14c,14d), 3.88 d (2H, CH_2, H_a-3,10; $^2J_{ab}$ = 12.5 Hz), 4.85 d (4H,

CH_2, H_b-1,3,8,10; $^2J_{ba}$ = 9.5 Hz), 6.94 d(4H, CH, H-2′,2″,6′,6″; J = 7 Hz), 7.06 d(4H, CH, H-3′,3″,5′,5″; J = 7 Hz). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 20.5 (C-7′,7″), 24.2 (C-4,11), 24.6 (C-5,12), 27.1 (C-6,13), 28.5 (C-7,14), 55.2 (C-3b,10b), 63.6 (C-7a,14a), 67.0 (C-3,10), 70.4 (C-1,8), 77.9 (C-14c,14d), 117.7 (C-2′,2″,6′,6″), 129.5 (C-3′,3″,5′,5″), 129.8 (C-4′,4″), 147.3 (C-1′,1″). HRMS, *m/z*: 513.3718 [*M* + H]$^+$, 535.3542 [*M* + Na]$^+$. $C_{32}H_{44}N_6$. Calculated: *M* + H 513.3706, *M* + Na 535.3525.

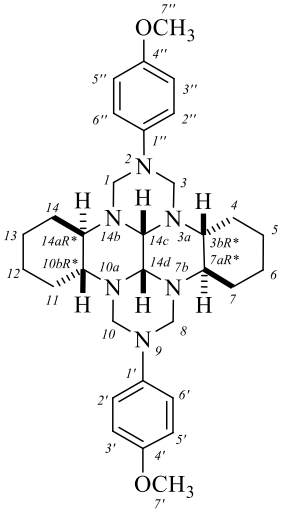


(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(2-methoxyphenyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (2d).** White powder, 0.33 g (61% yield, method A), 0.29 g (53% yield, method B), mp 230-232 °C, R_f 0.64 (MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.80–0.90 m (4H, CH_2, H_a-4,7,11,14), 1.15–1.27 m (4H, CH_2, H_a-5,6,12,13), 1.55 d (2H, CH_2, H_b-4,11; $^2J_{ba}$ = 12 Hz, 1.67 d (2H, CH_2, H_b-5,12; $^2J_{ba}$ = 12.4 Hz), 1.77 br. s (2H, CH, H-7a,14a), 1.87 d (2H, CH_2, H_b-7,14; $^2J_{ba}$ = 10 Hz), 2.11 d (2H, CH_2, H_b-6,13; $^2J_{ba}$ = 11.6 Hz), 3.30–3.35 m (2H, CH, H-3b,10b), 3.42 d (2H, CH_2, H_a-1,8; $^2J_{ab}$ = 10.4 Hz), 3.56 br. s (2H, CH, H-14c,14d), 3.87 br. s (2H, CH_2, H_a-3,10; 6H, CH_3, H-7′,7″), 4.79 d (2H, CH_2, H_b-1,8; $^2J_{ba}$ = 10 Hz), 5.99 d (2H, CH_2, H_b-3,10; $^2J_{ba}$ = 13.6 Hz), 6.85 d (2H, CH, H-3′,3″; J = 8 Hz), 6.91–6.97 m (4H, CH, H-4′,4″,5′,5″), 7.41 d (2H, CH, H-6′,6″; J = 7.2 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 24.4 (C-4,11), 24.6 (C-5,12), 27.3 (C-6,13), 28.1 (C-7,14), 55.5 (C-7′,7″), 55.9 (C-3b,10b), 63.6 (C-7a,14a), 65.2 (C-3,10), 71.2 (C-1,8), 78.1 (C-14c,14d), 111.1 (C-3′,3″), 119.7 (C-6′,6″), 121.3 (C-5′,5″), 122.6 (C-4′,4″), 139.4 (C-1′,1″), 151.7 (C-2′,2″). HRMS, *m/z*: 545.3564 [*M* + H]$^+$, 567.3380 [*M* + Na]$^+$. $C_{32}H_{44}N_6O_2$. Calculated: *M* + H 545.3604, *M* + Na 567.3423.

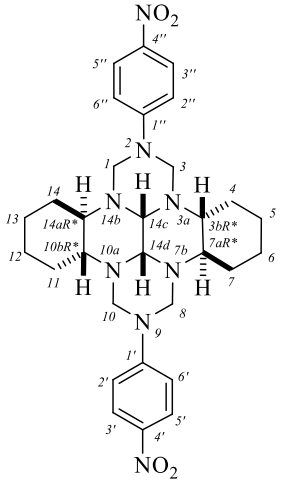


(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(3-methoxyphenyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (2e).** White powder, 0.27 g (50% yield, method A), 0.23 g (42% yield, method B), mp 231-233 °C, R_f 0.61 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.95 br. s (4H, CH_2, H_a-4,7,11,14), 1.20–1.29 m (4H, CH_2, H_a-5,6,12,13), 1.62 br. s (2H, CH_2, H_b-4,11), 1.71 d (2H, CH_2, H_b-5,12; $^2J_{ba}$ = 12 Hz), 1.82 br. s (2H, CH, H-7a,14a), 1.99 br. s (2H, CH_2, H_b-7,14), 2.11 d (2H, CH_2, H_b-6,13; $^2J_{ba}$ = 10.5 Hz), 3.18 br. s (2H, CH, H-3b,10b), 3.25 d (2H, CH_2, H_a-1,8; $^2J_{ab}$ = 10.5 Hz), 3.52 br. s (2H, CH, H-14c,14d), 3.81 br. s (6H, CH_3, H-7′,7″), 3.92 d (2H, CH_2,

H_a-3,10; $^2J_{ab}$ = 13 Hz), 4.88–4.93 m (4H, CH_2, H_b-1,3,8,10), 6.44 d and 6.45 d (2H, CH, H-4′,4″; J = 8 Hz), 6.57 br. s (2H, CH, H-2′,2″), 6.63 d (2H, CH, H-6′,6″; J = 8 Hz), 7.16 d (2H, CH, H-5′,5″; J = 8 Hz). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.2 (C-4,11), 24.6 (C-5,12), 27.2 (C-6,13), 28.6 (C-7,14), 55.1 (C-3b,10b), 55.2 (C-7′,7″), 63.6 (C-7a,14a), 66.5 (C-3,10), 69.8 (C-1,8), 77.9 (C-14c,14d), 103.8 (C-2′,2″), 104.9 (C-4′,4″), 110.2 (C-6′,6″), 129.7 (C-5′,5″), 151.0 (C-1′,1″), 160.4 (C-3′,3″). HRMS, *m/z*: 545.3608 $[M + H]^+$, 567.3430 $[M + Na]^+$. $C_{32}H_{44}N_6O_2$. Calculated: *M* + H 545.3604, *M* + Na 567.3423.

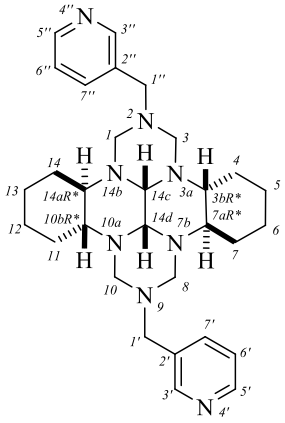


(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(4-methoxyphenyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg,op*]tetracene (2f).** White powder, 0.46 g (85% yield, method A), 0.33 g (62% yield, method B), mp 228-229 °C, R_f 0.63 (MeOH). ^{1}H NMR (500.17 MHz, $CDCl_3$): δ = 0.96 br. s (4H, CH_2, H_a-4,7,11,14), 1.19–1.28 m (4H, CH_2, H_a-5,6,12,13), 1.60 br. s (2H, CH_2, H_b-4,11), 1.71 d (2H, CH_2, H_b-5,12; $^2J_{ba}$ = 10.5 Hz), 1.81 br. s (2H, CH, H-7a,14a), 1.95 br. s (2H, CH_2, H_b-7,14), 2.09 d (2H, CH_2, H_b-6,13; $^2J_{ba}$ = 9 Hz), 3.23 br. s (2H, CH, H-3b,10b; 2H, CH_2, H_a-1,8), 3.50 br. s (2H, CH, H-14c,14d), 3.78 br. s (6H, CH_3, H-7′,7″), 3.86 d (2H, CH_2, H_a-3,10; $^2J_{ab}$ = 12.5 Hz), 4.74–4.79 m (4H, CH_2, H_b-1,3,8,10), 6.82 d (4H, CH, H-2′,2″,6′,6″; J = 7 Hz), 7.01 d (4H, CH, H-3′,3″,5′,5″; J = 7 Hz). ^{13}C NMR (125.78 MHz, $CDCl_3$): δ = 24.3 (C-4,11), 24.6 (C-5,12), 27.2 (C-6,13), 28.4 (C-7,14), 55.3 (C-3b,10b), 55.6 (C-7′,7″), 63.6 (C-7a,14a), 67.6 (C-3,10), 71.0 (C-1,8), 77.8 (C-14c,14d), 114.3 (C-2′,2″,6′,6″), 119.6 (C-3′,3″,5′,5″), 143.7 (C-1′,1″), 154.1 (C-4′,4″). HRMS, *m/z*: 545.3572 $[M + H]^+$, 567.3394 $[M + Na]^+$. $C_{32}H_{44}N_6O_2$. Calculated: *M* + H 545.3604, *M* + Na 567.3423.



(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(4-nitrophenyl)octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg,op*]tetracene (2g).** Orange powder, 0.51 g (89% yield, method A), 0.36 g (63% yield, method B), mp 202-203 °C, R_f 0.58 (MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.81 br. s (2H, CH_2, H_a-4,11), 0.99 d (2H, CH_2, H_a-7,14; $^2J_{ba}$ = 11.2 Hz), 1.23 br. s (4H, CH_2, H_a-5,6,12,13), 1.63 br. s (2H, CH_2, H_b-4,11), 1.74 br. s (2H, CH_2, H_b-5,12), 1.87 br. s (2H, CH, H-7a,14a; 2H, CH_2, H_b-7,14), 2.12 br. s (2H, CH_2, H_b-6,13), 2.89 br. s (2H, CH, H-3b,10b), 3.39 d (2H, CH_2, H_a-1,8; $^2J_{ab}$ = 10 Hz), 3.58 br. s (2H, CH, H-14c,14d), 4.10 d (2H, CH_2, H_a-3,10; $^2J_{ab}$ = 12.8 Hz), 5.01 d (2H, CH_2, H_b-1,8; $^2J_{ba}$ = 9.6 Hz), 5.10 d (2H, CH_2, H_b-3,10; $^2J_{ba}$ = 12.8 Hz), 6.95 br. s (4H, CH,

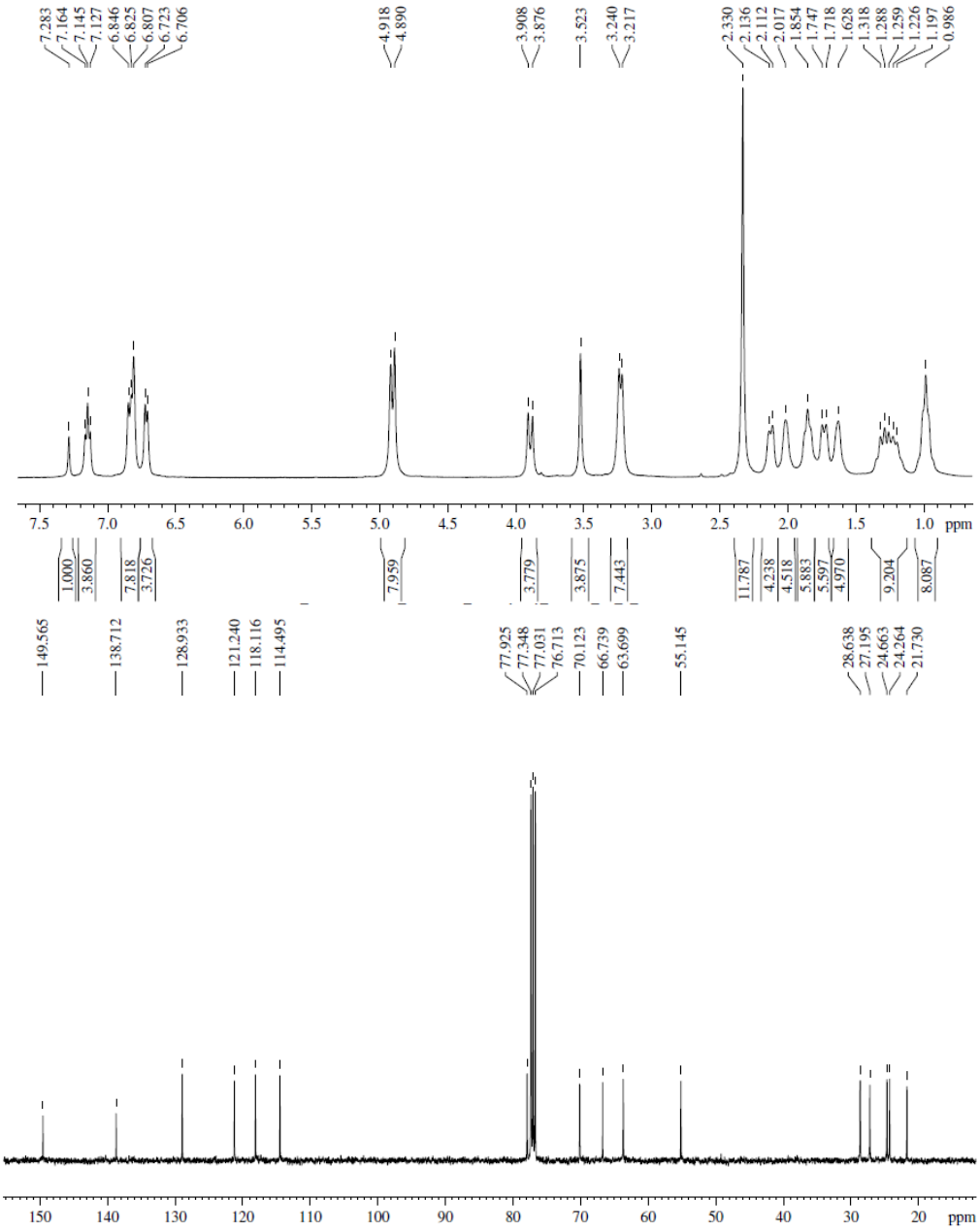
H-2′,2″,6′,6″), 8.15 br. s (4H, CH, H-3′,3″,5′,5″). ^{13}C NMR (100.62 Hz, $CDCl_3$): δ = 24.1 (C-4,11), 24.3 (C-5,12), 27.1 (C-6,13), 28.6 (C-7,14), 54.9 (C-3b,10b), 63.3 (C-7a,14a), 65.1 (C-3,10), 67.9 (C-1,8), 77.9 (C-14c,14d), 114.5 (C-2′,2″,6′,6″), 125.8 (C-3′,3″,5′,5″), 139.5 (C-4′,4″), 154.2 (C-1′,1″). HRMS, *m/z*: 573.2984 [*M* – H]$^+$, 597.3815 [*M* + Na]$^+$. $C_{30}H_{38}N_8O_4$. Calculated: *M* – H 573.2938, *M* + Na 597.2914.

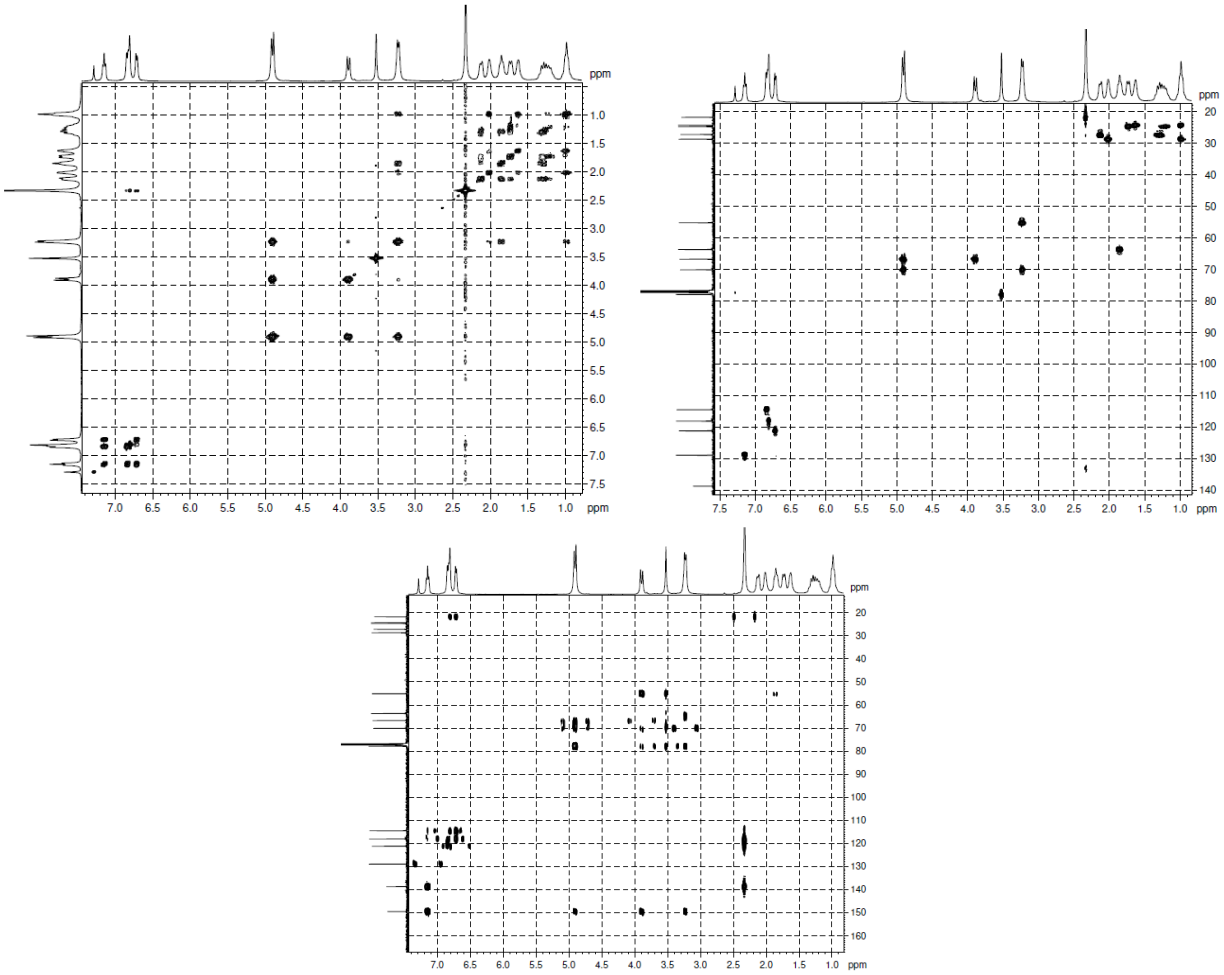


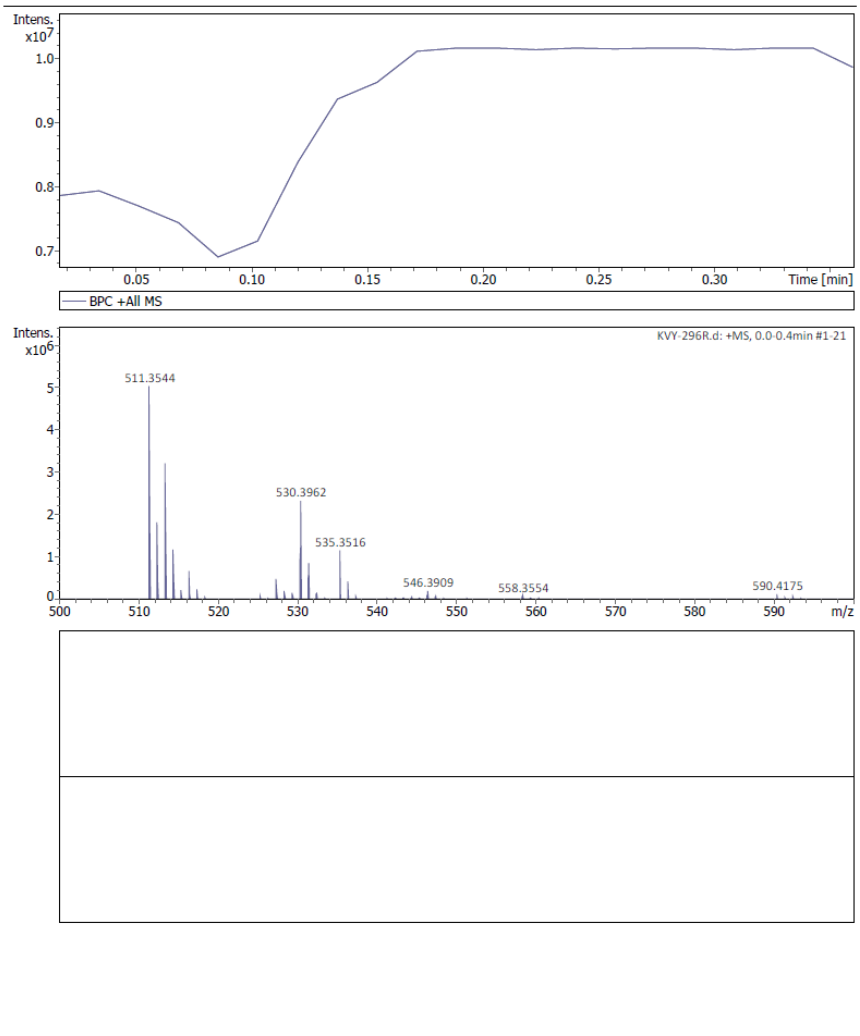
(3b*R,7a*R**,10b*R**,14a*R**,*cis*-14c,14d)-2,9-Bis(pyridin-3-ylmethyl)-octadecahydro-1*H*,8*H*-2,3a,7b,9,10a,14b-hexaazadibenzo[*fg*,*op*]tetracene (2h).** White powder, 0.23 g (45% yield, method A), 0.19 g (37% yield, method B), mp 260-262 °C, R_f 0.65 (MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.77–0.86 m (2H, CH_2, H_a-7,14), 1.15–1.18 m (2H, CH_2, H_a-4,11), 1.22–1.29 m (4H, CH_2, H_a-5,6,12,13), 1.63–1.77 m (2H, CH, H-7a,14a; 6H, CH_2, H_b-4,5,7,11,12,14), 1.87 d (2H, CH_2, H_b-6,13; $^2J_{ba}$ = 11.6 Hz), 2.48 d (2H, CH_2, H_a-1,8; $^2J_{ab}$ = 8 Hz), 3.07 d (2H, CH_2, H_a-3,10; $^2J_{ab}$ = 12 Hz), 3.34 br. s (2H, CH, H-14c,14d), 3.36–3.39 m (2H, CH, H-3b,10b), 3.49 d (4H, CH_2, H-1′,1″; ^2J = 13.6 Hz), 4.01 d (2H, CH_2, H_b-3,10; $^2J_{ba}$ = 11.6 Hz), 4.20 d (2H, CH_2, H_b-1,8; $^2J_{ba}$ = 7.6 Hz), 7.24–7.28 m (2H, CH, H-6′,6″), 7.73 d (2H, CH, H-7′,7″; J = 7.6 Hz), 8.52 d (4H, CH, H-3′,3″,5′,5″; J = 8 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 24.2 (C-4,11), 24.6 (C-5,12), 26.9 (C-6,13), 28.2 (C-7,14), 54.4 (C-1′,1″), 55.4 (C-3b,10b), 63.9 (C-7a,14a), 68.6 (C-3,10), 74.4 (C-1,8), 77.4 (C-14c,14d), 123.3 (C-6′,6″), 133.6 (C-2′,2″), 136.3 (C-7′,7″), 148.9 (C-5′,5″), 150.0 (C-3′,3″).

NMR and MS spectra of compounds 2a–h

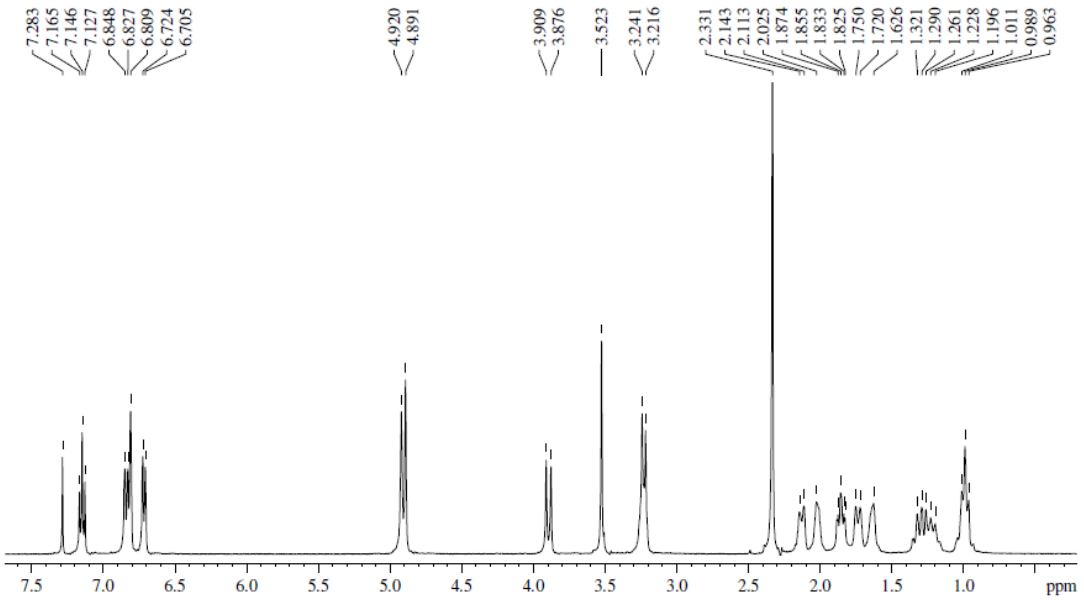
FigureS1. NMR and MS spectra of compound **2a**

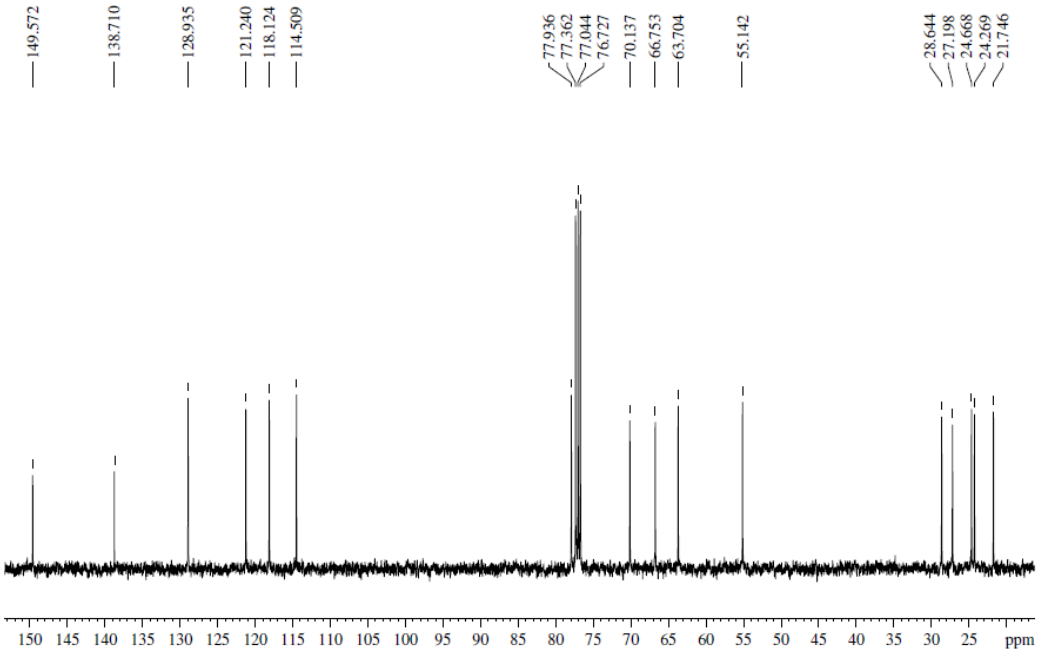


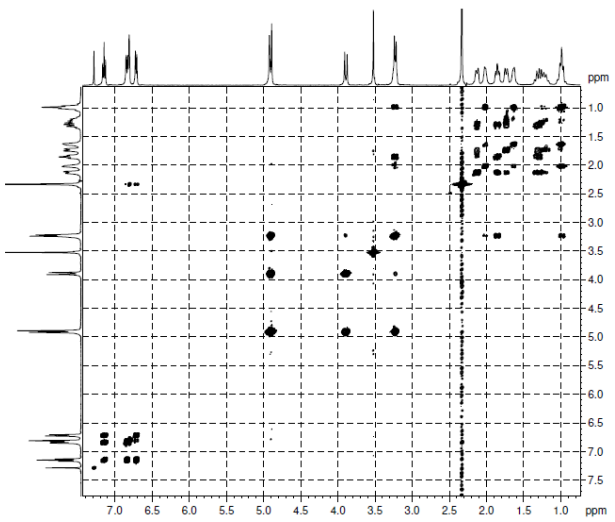

ppm
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

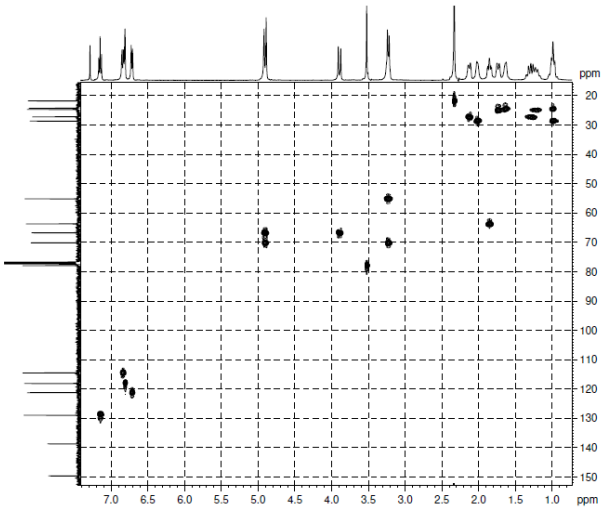

Intens.
x10^7
1.0
0.9
0.8
0.7
0.05 0.10 0.15 0.20 0.25 0.30 Time [min]
BPC +All MS
Intens.
x10^6
KVY-296R.d: +MS, 0.0-0.4min #1-21
511.3544
530.3962
535.3516
546.3909
558.3554
590.4175
500 510 520 530 540 550 560 570 580 590 m/z

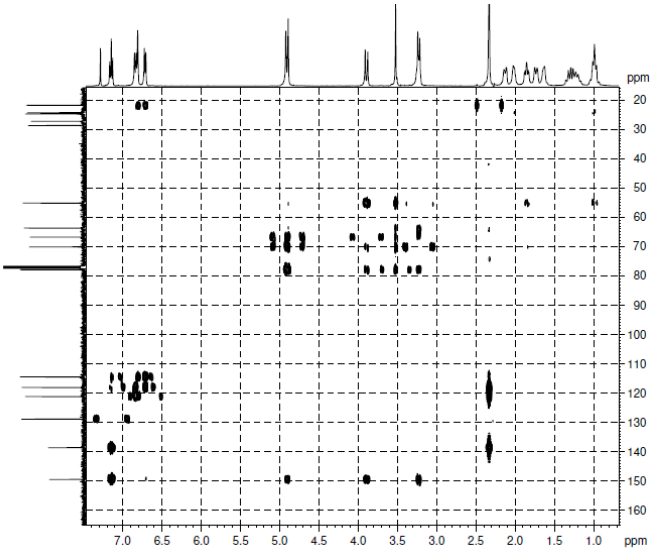
FigureS2. NMR and MS spectra of compound **2b**

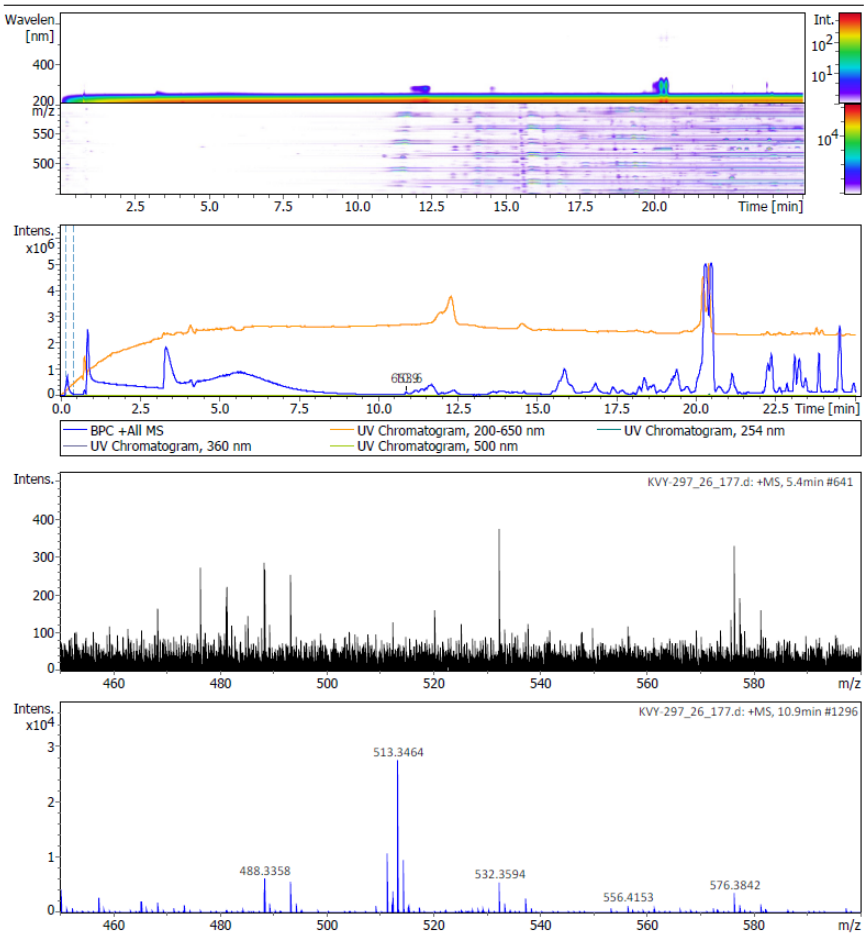




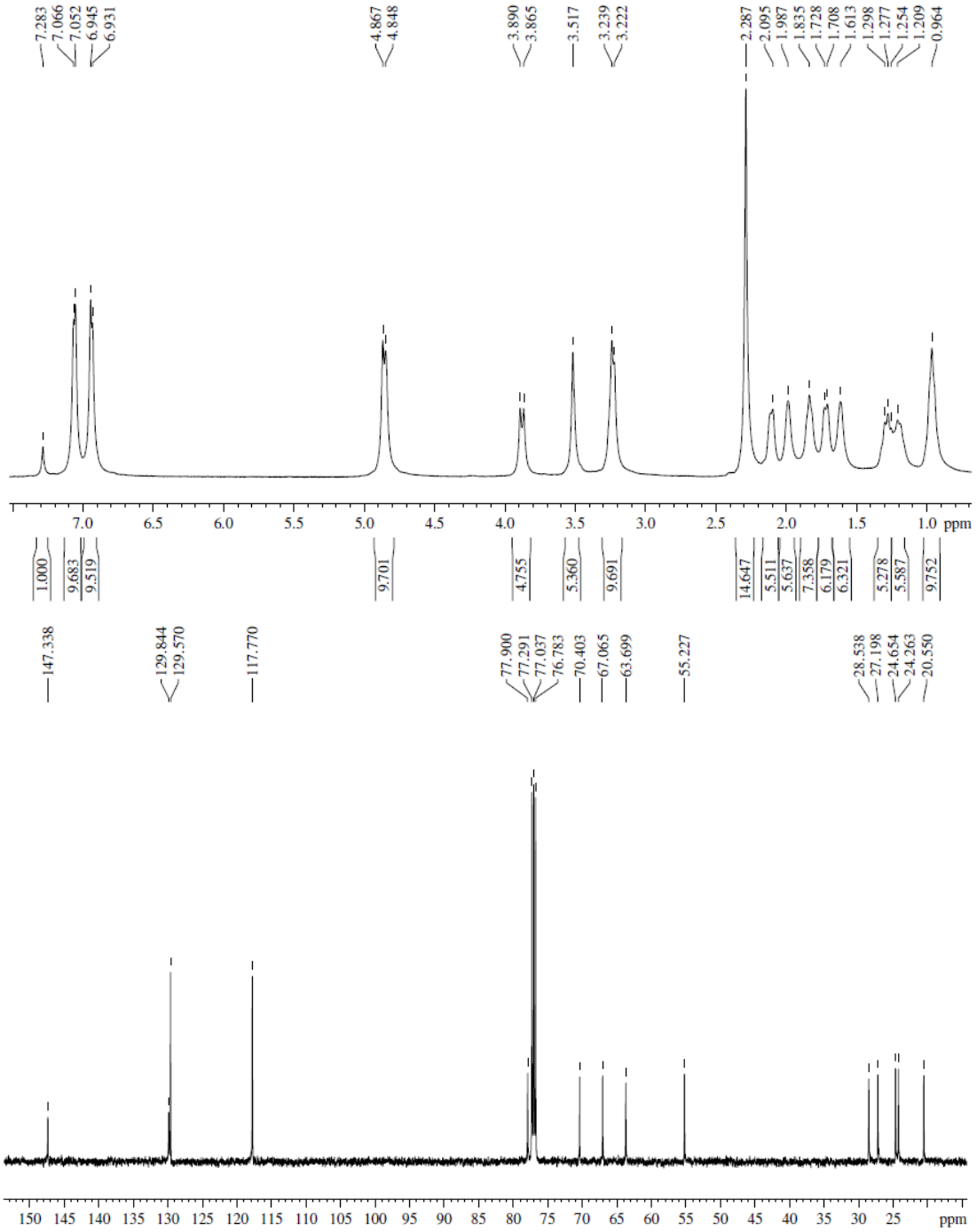


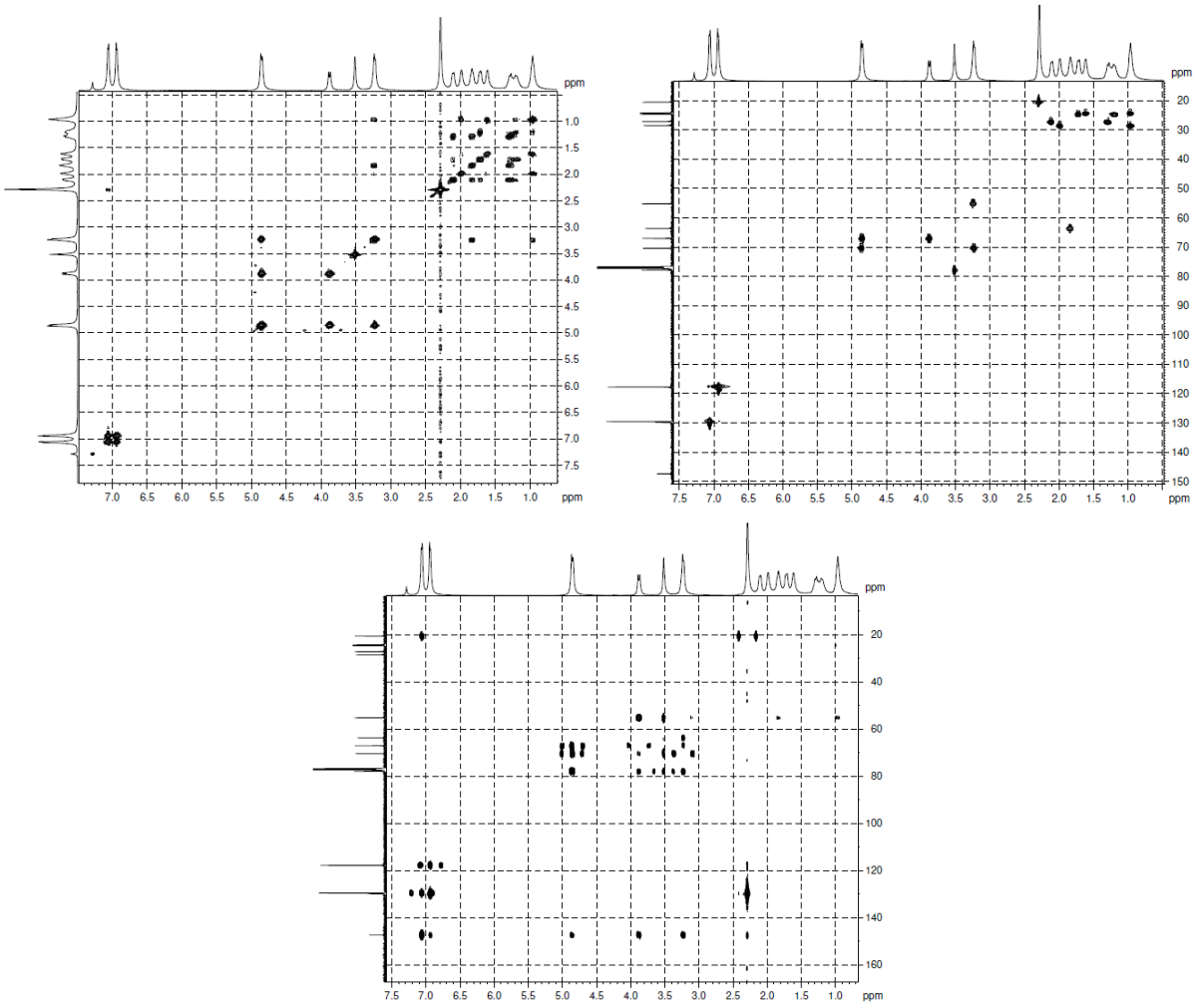



ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

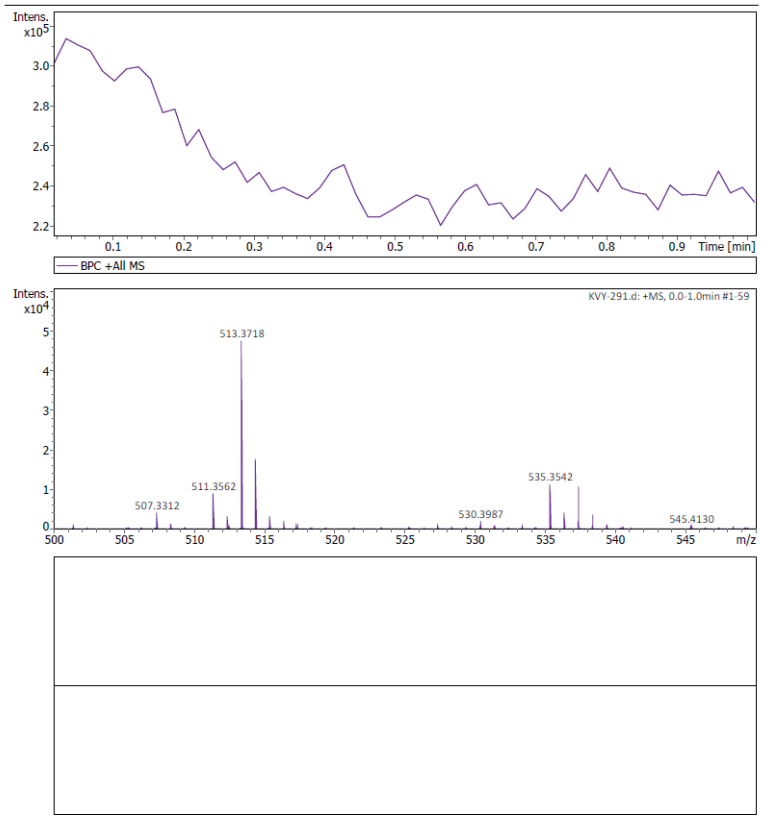

Wavelen. [nm]
400
200
m/z
550
500
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
Time [min]
Int.
10^2
10^1
10^4
Intens.
x10^6
5
4
3
2
1
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
Time [min]
BPC +All MS
UV Chromatogram, 360 nm
UV Chromatogram, 200-650 nm
UV Chromatogram, 500 nm
UV Chromatogram, 254 nm
Intens.
KVY-297_26_177.d: +MS, 5.4min #641
400
300
200
100
0
460
480
500
520
540
560
580
m/z
Intens.
x10^4
KVY-297_26_177.d: +MS, 10.9min #1296
3
2
1
0
513.3464
488.3358
532.3594
556.4153
576.3842
460
480
500
520
540
560
580
m/z

FigureS3. NMR and MS spectra of compound **2c**

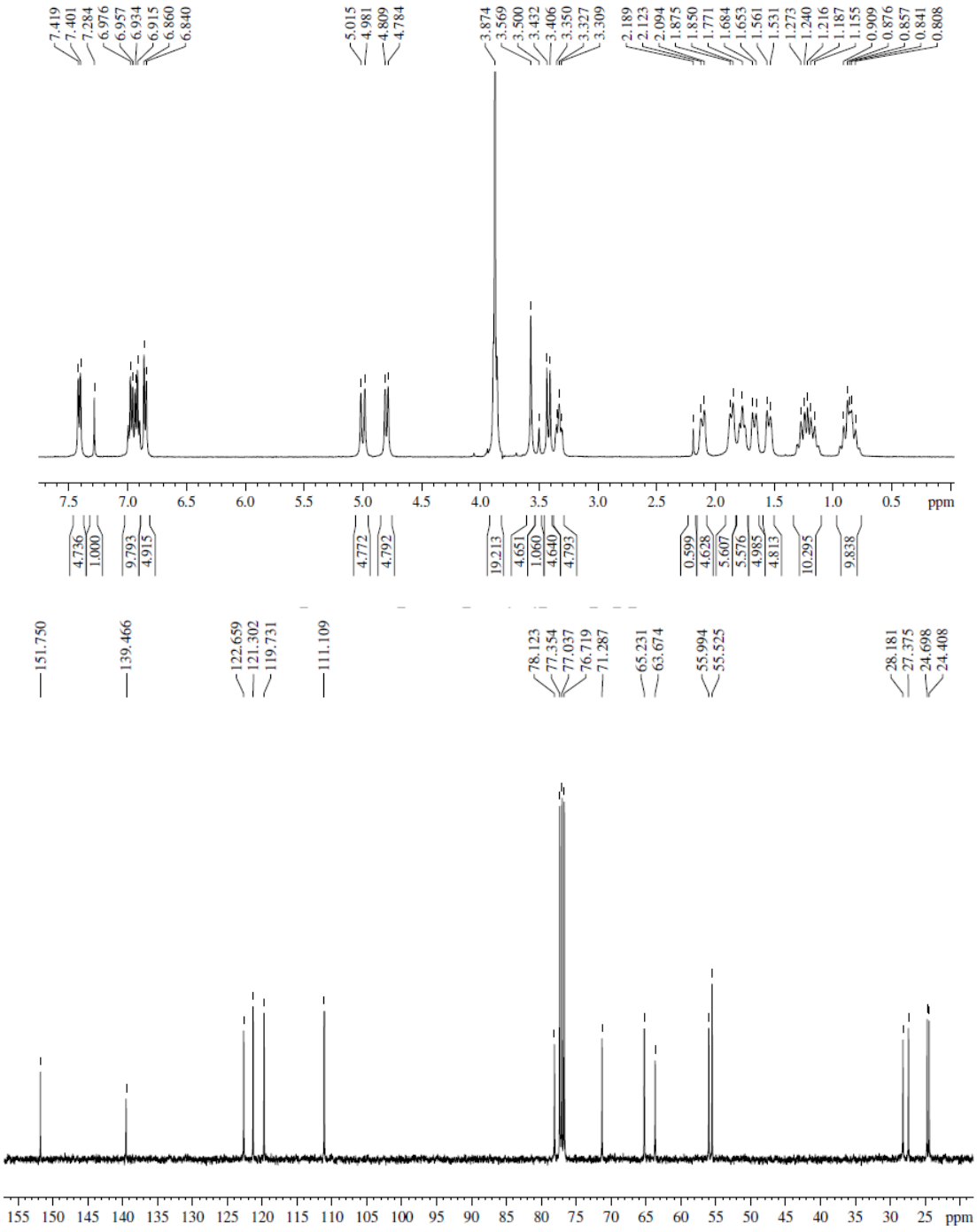


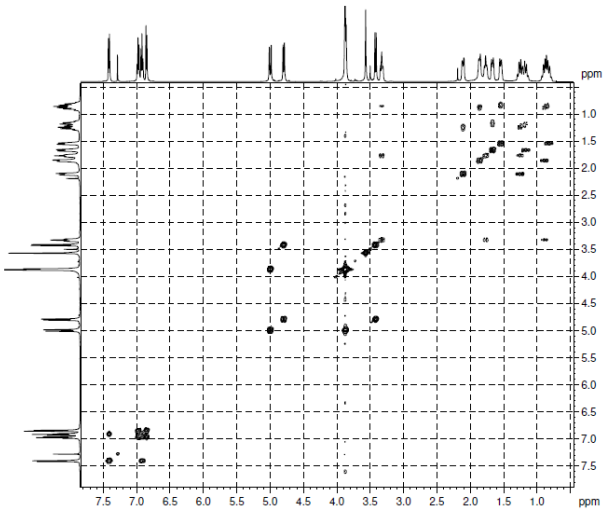

ppm
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

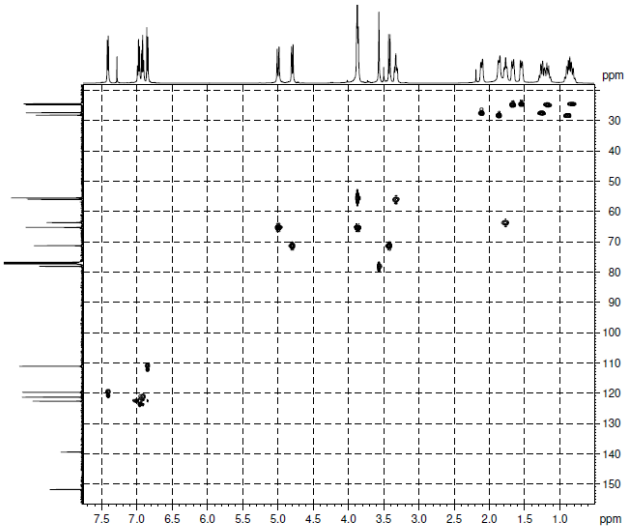
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

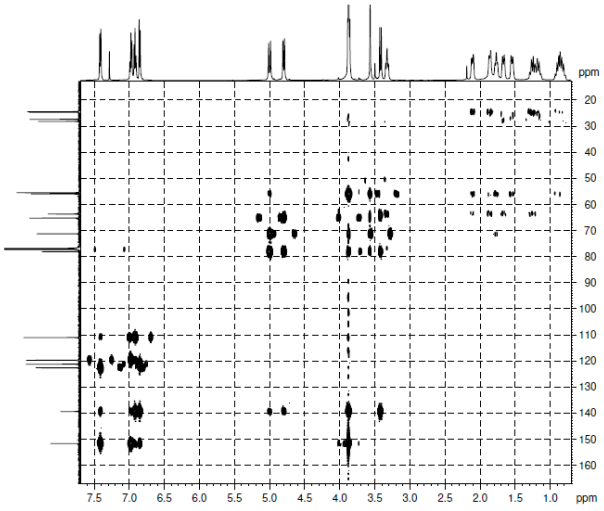

Intens.
x10^5
3.0
2.8
2.6
2.4
2.2
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 Time [min]
BPC +All MS
Intens.
x10^4
KVY-291.d: +MS, 0.0-1.0min #1-59
513.3718
511.3562
507.3312
535.3542
530.3987
545.4130
500 505 510 515 520 525 530 535 540 545 m/z

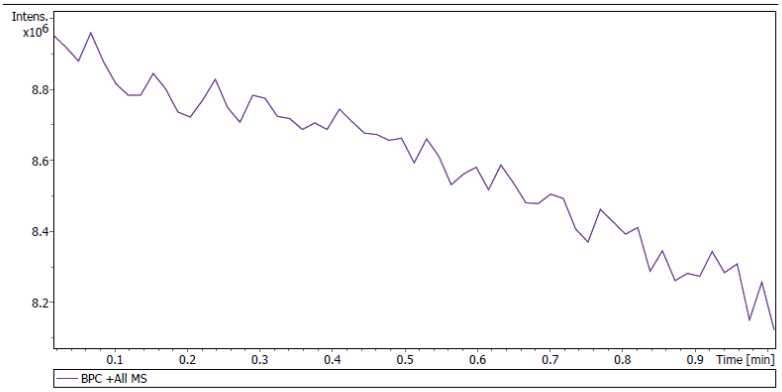
FigureS4. NMR and MS spectra of compound **2d**

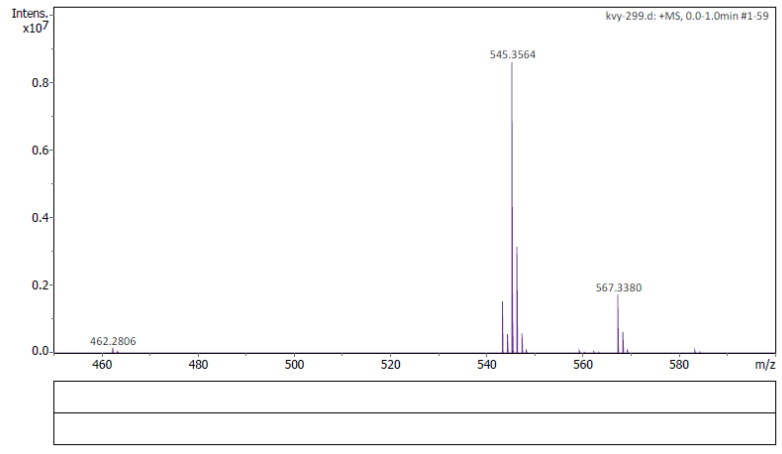



ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

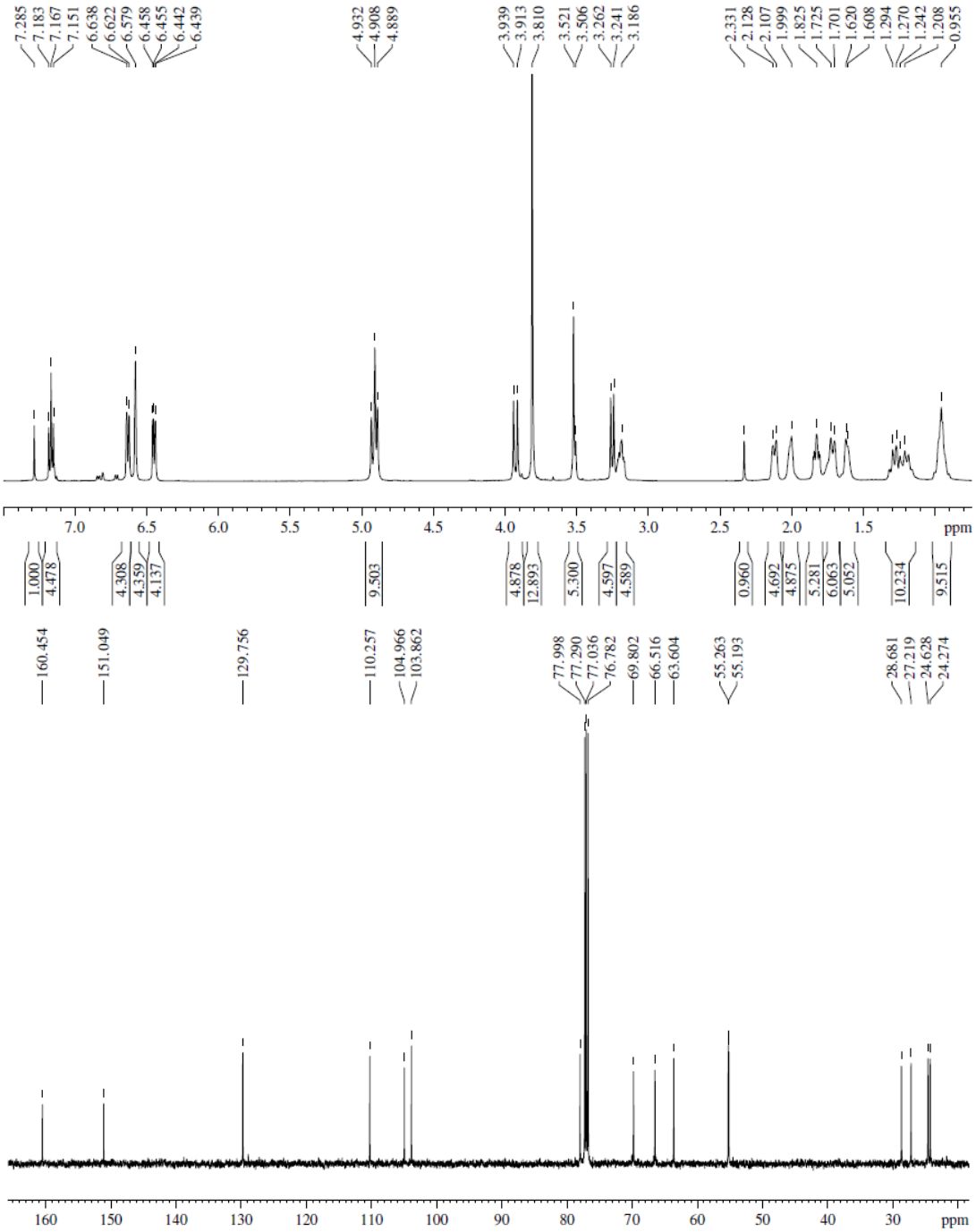

ppm
30 40 50 60 70 80 90 100 110 120 130 140 150
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

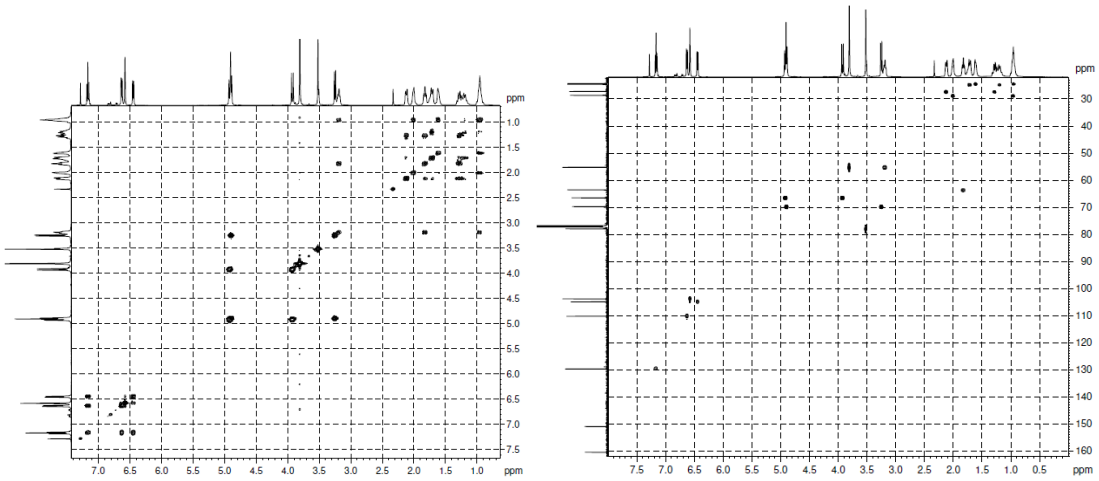

ppm
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

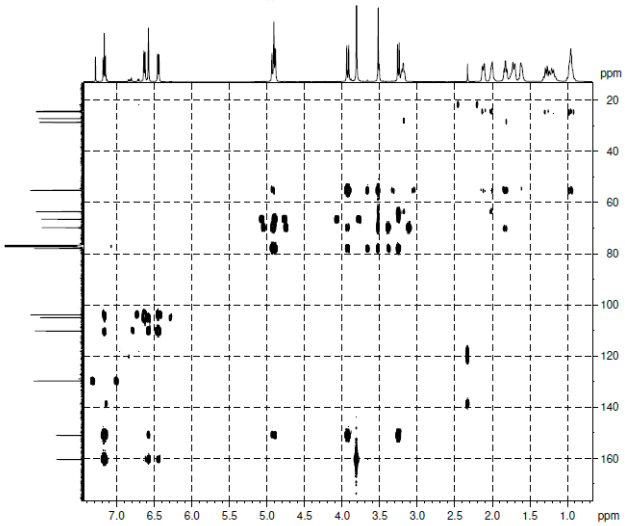

Intens.
x10^6
8.8
8.6
8.4
8.2
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 Time [min]
BPC +All MS

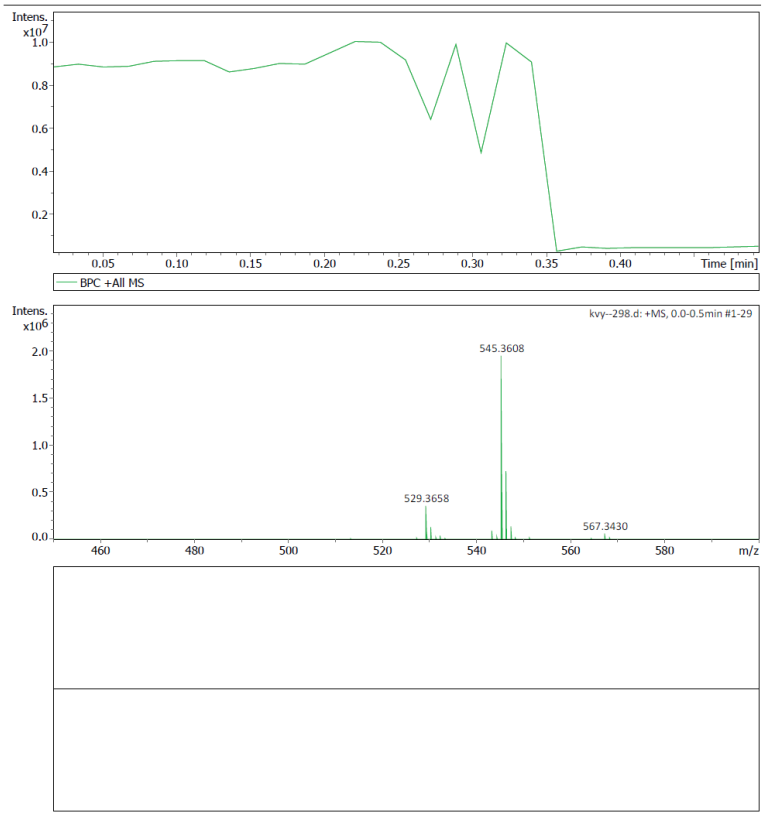

Intens.
x10^7
kvy-299.d: +MS, 0.0-1.0min #1-59
545.3564
567.3380
462.2806
0.8
0.6
0.4
0.2
0.0
460 480 500 520 540 560 580 m/z

FigureS5. NMR and MS spectra of compound **2e**

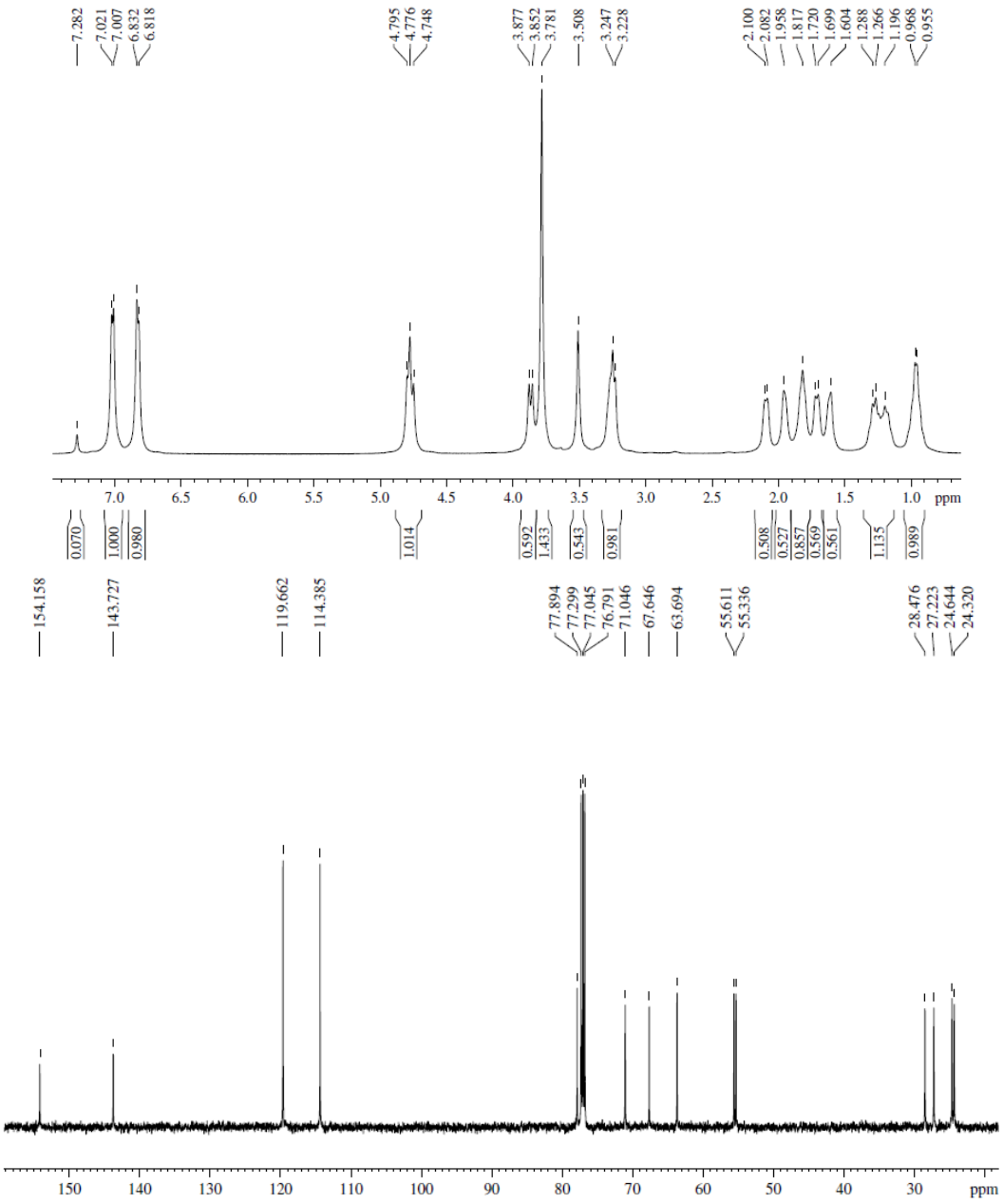


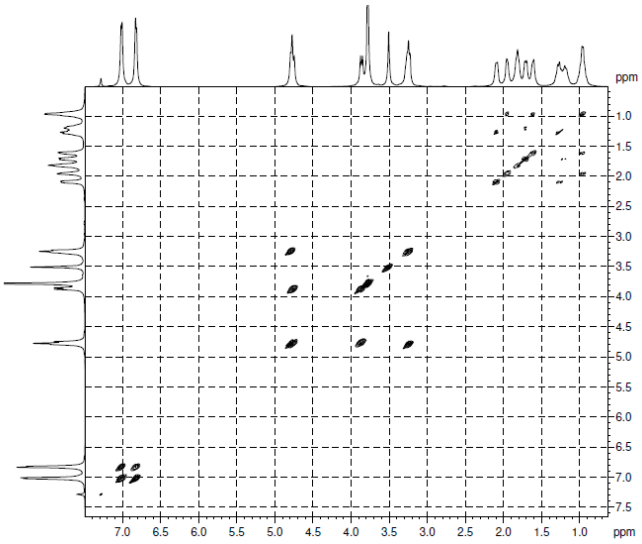

ppm
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

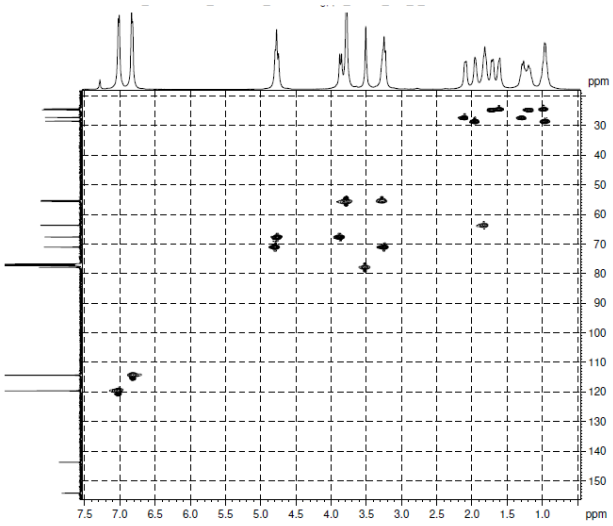

ppm
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

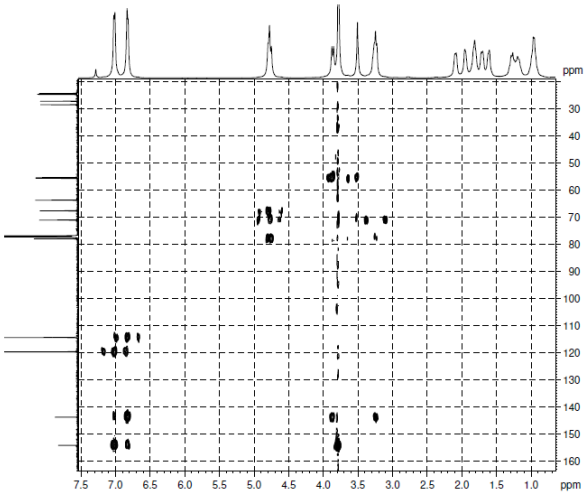

Intens.
x10^7
1.0
0.8
0.6
0.4
0.2
0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 Time [min]
BPC +All MS
Intens.
x10^6
kvy--298.d: +MS, 0.0-0.5min #1-29
2.0
1.5
1.0
0.5
0.0
545.3608
529.3658
567.3430
460 480 500 520 540 560 580 m/z

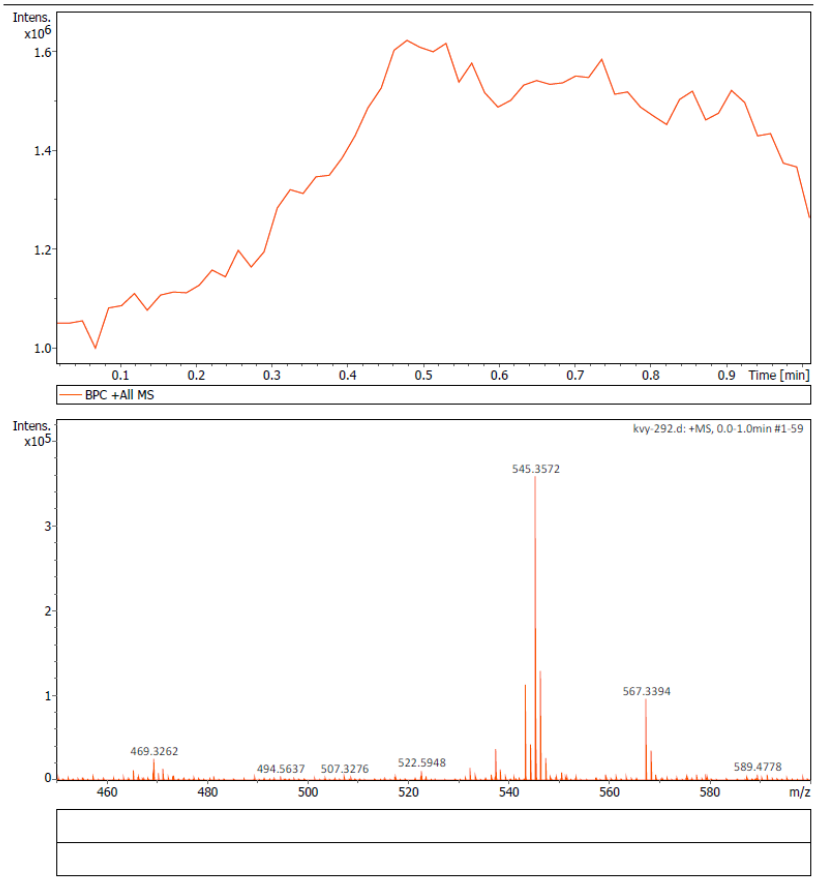
FigureS6. NMR and MS spectra of compound **2f**



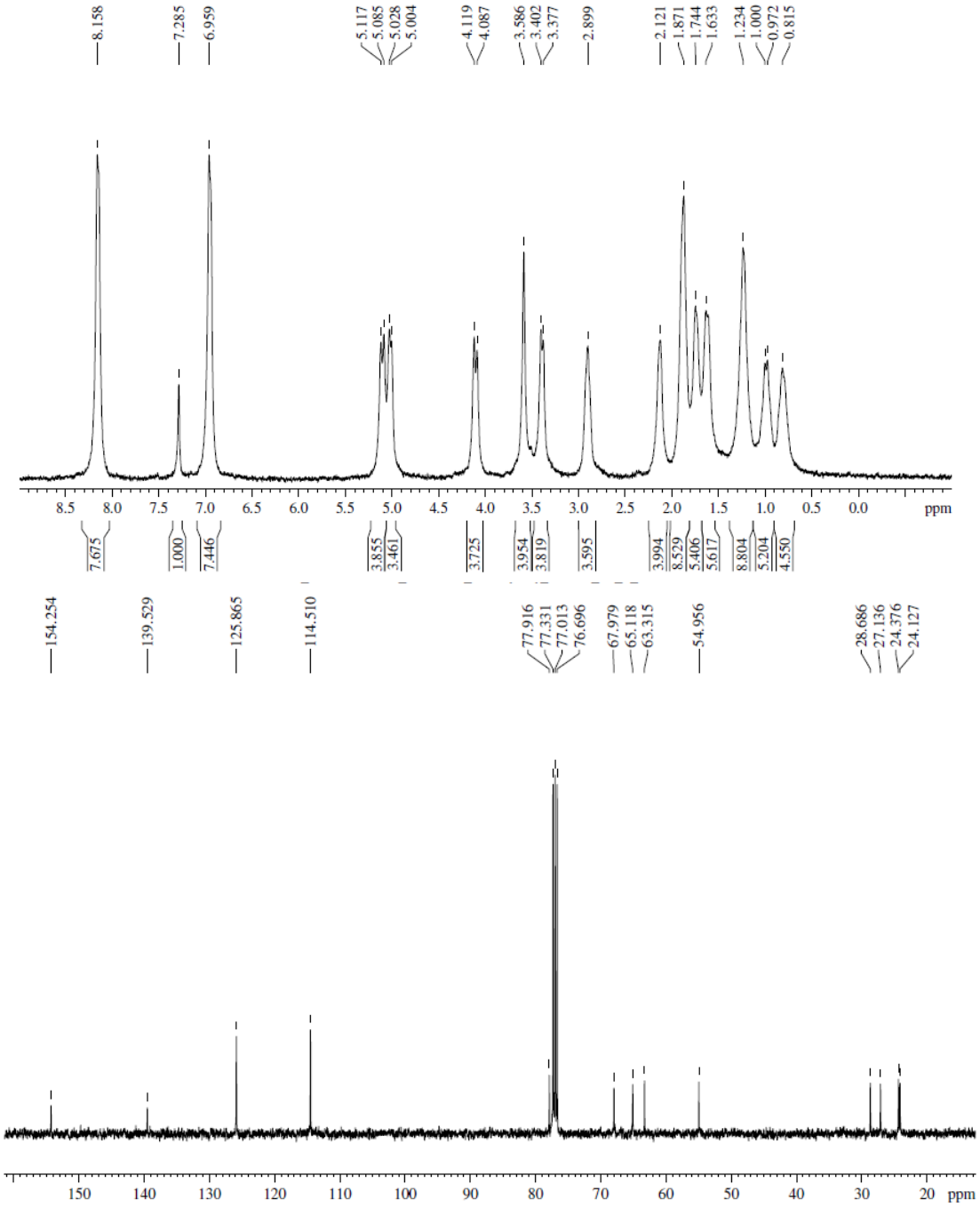

ppm
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5

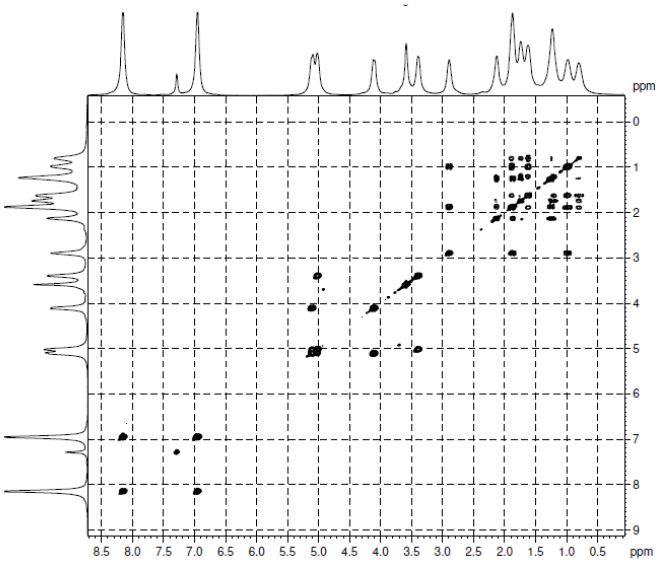

ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
30 40 50 60 70 80 90 100 110 120 130 140 150

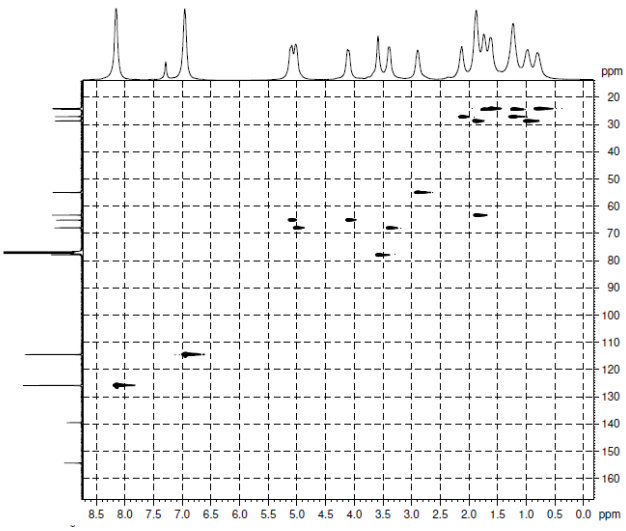

ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
30 40 50 60 70 80 90 100 110 120 130 140 150 160

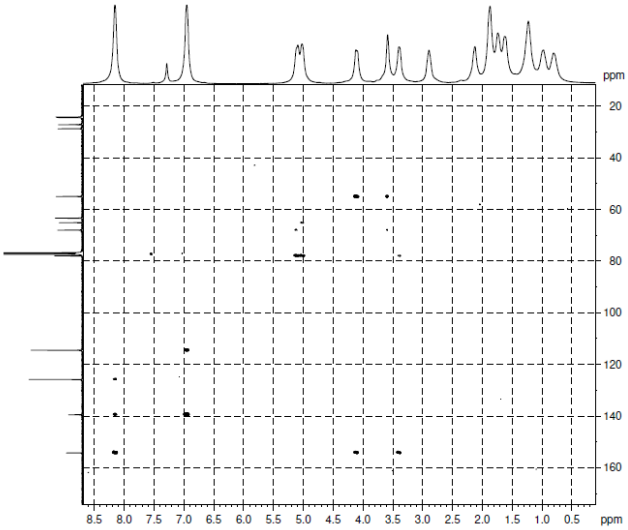

Intens.
x10^6
1.6
1.4
1.2
1.0
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 Time [min]
BPC +All MS
Intens.
x10^5
kvy-292.d: +MS, 0.0-1.0min #1-59
545.3572
567.3394
469.3262
494.5637
507.3276
522.5948
589.4778
3
2
1
0
460 480 500 520 540 560 580 m/z

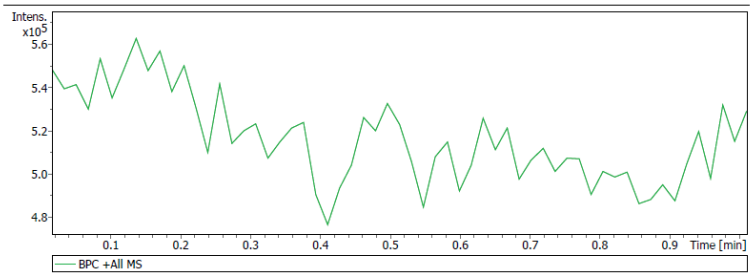
FigureS7. NMR and MS spectra of compound **2g**

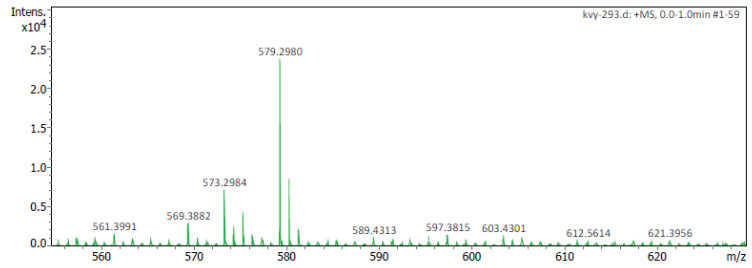



ppm
0
1
2
3
4
5
6
7
8
9
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

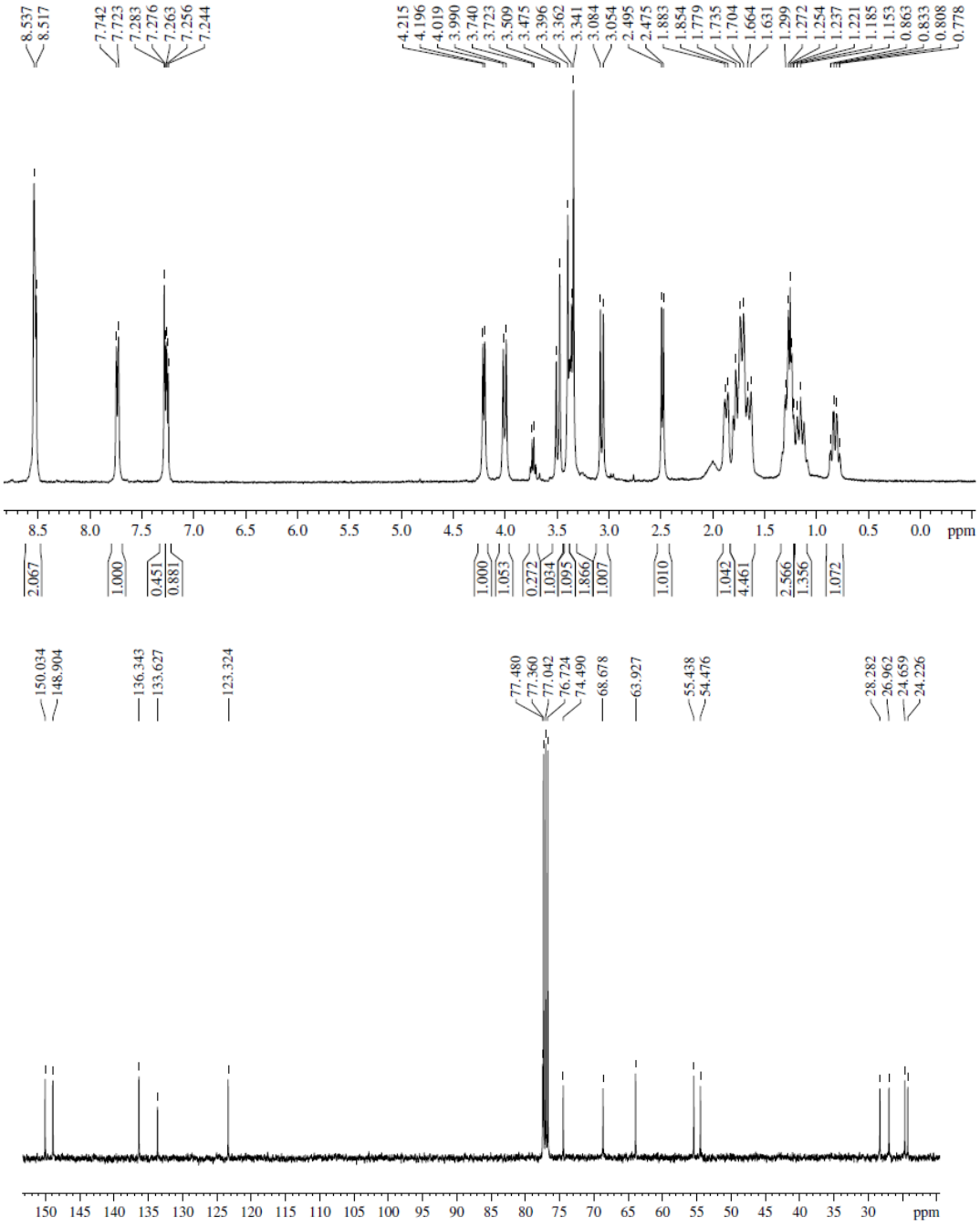

ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

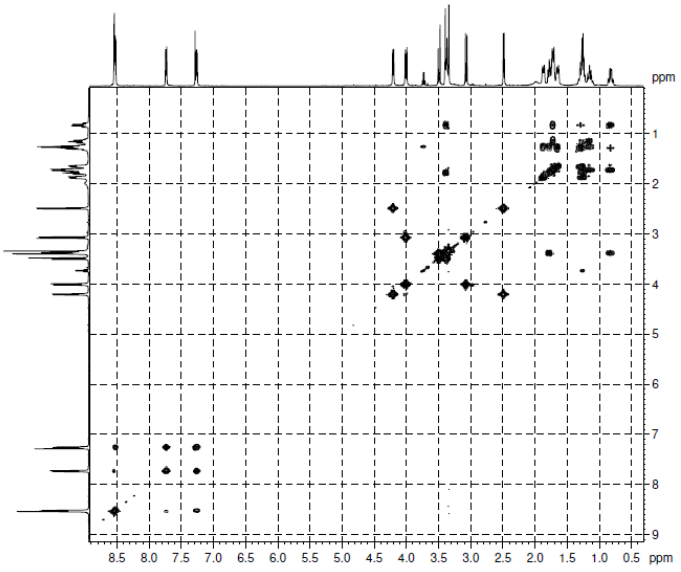

ppm
20
40
60
80
100
120
140
160
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


Intens.
x10^5
5.6
5.4
5.2
5.0
4.8
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 Time [min]
BPC +All MS


kvy-293.d: +MS, 0.0-1.0min #1-59
Intens.
x10^4
2.5
2.0
1.5
1.0
0.5
0.0
579.2980
573.2984
569.3882
561.3991
589.4313
597.3815
603.4301
612.5614
621.3956
560 570 580 590 600 610 620 m/z

FigureS8. NMR spectra of compound **1h**

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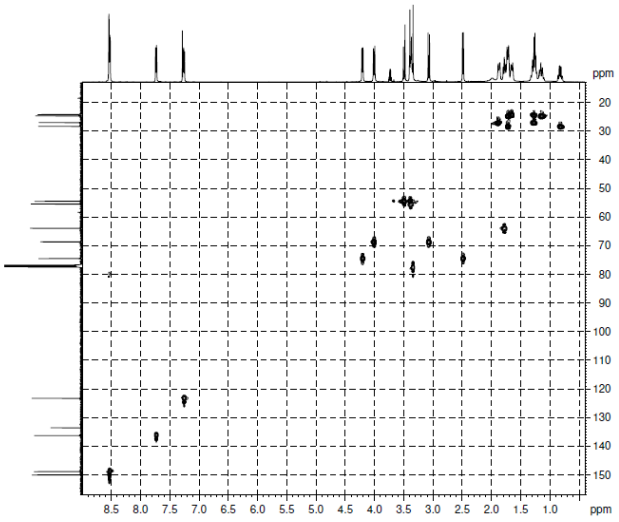
2
3
4
5
6
7
8
9
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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50
60
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140
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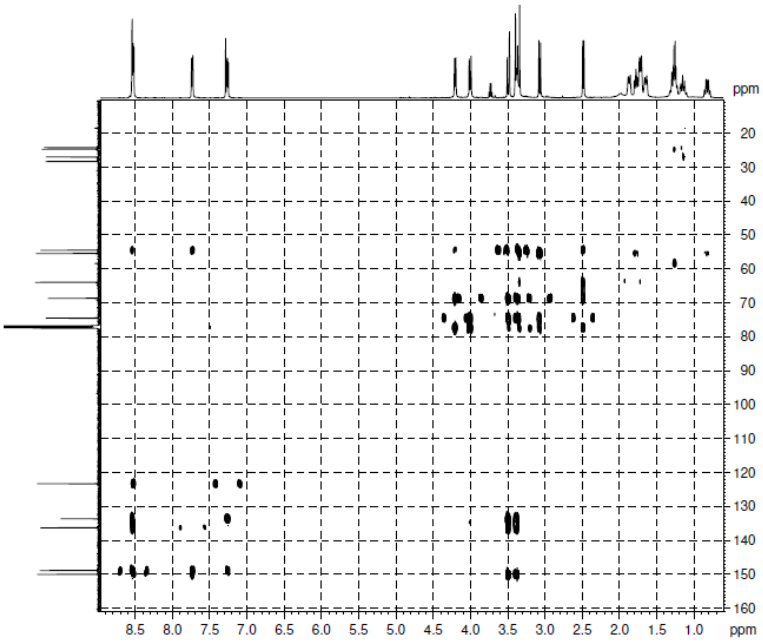
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160
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

Cytotoxicity assay

Culture conditions and treatments

HEK293 (human embryonic kidney 293 cells), A549 (human lung carcinoma), MCF-7 (human breast adenocarcinoma), SH-SY5Y (human neuroblastoma), HepG2 (human hepatocellular carcinoma), HTC116 (human colon cancer), Jurkat (Human leukaemic T cell lymphoblast), THP-1 (human leukemia monocytic) cell lines were purchased from the Russian Cell Culture Collection (Institute of Cytology Russian Academy of Science, Saint Petersburg, Russia). HEK293, A-549, MCF-7, HepG2, HTC116 and SH-SY5Y cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen, USA) supplemented with 2 mM *L*-glutamine (Sigma-Aldrich, UK), 10% fetal bovine serum (FBS; Invitrogen, USA), 50 μg ml^{-1} gentamicin sulfate (Invitrogen, USA). Jurkat and THP-1 cells were grown in RPMI 1640 medium (Invitrogen, USA) supplemented with 10% FBS, 50 μg ml^{-1} gentamicin sulfate and 2 mM L-glutamine. All cells were cultured and maintained at 37°C with 5% CO_2 and 95% wet condition. Compounds were dissolved in 100% DMSO (Sigma-Aldrich, UK) to 100 mM stock solutions and diluted in completed DMEM or RPMI immediately before addition to the assay plates. DMSO was maintained at a final concentration of 0.1%.

Cell viability assay

Cells were cultured at appropriate density in 96-well plates (3×10^4 cells/well for HEK293; 1.2×10^4 cells/well for A-549; 1.2×10^4 cells/well for MCF-7; 3×10^4 cells/well for SH-SY5Y; 1.5×10^4 cells/well for HepG2; 1×10^4 cells/well for HTC116; 5×10^4 cells/well for Jurkat; 2×10^4 cells/well for THP-1) and allowed to grow for 24 h in an appropriate culture media. Thereafter, cells were treated with compounds at a final concentrations of 1, 10, 100 μM for 48 hours and cell viability was measured by conventional MTT assay following manufacturer's instruction (Thermo Fisher Scientific, USA) using «2300 EnSpire® Multimode Plate Reader» (Perkin Elmer, USA) at 590 nm. The concentration of the compound that inhibited 50% cell viability (IC_{50} value) was calculated using nonlinear regression analysis (GraphPad Prism v.5.02; GraphPad Software Inc., USA). The viability of control group (cells treated with 0.1% DMSO) was set at 100%, and viability of treated groups was determined through the comparison of its optical density with control. Data were expressed as mean ± S.E.M. calculated from two independent experiments, performed in triplicate. Under similar conditions, cells were treated with 5-fluorouracil as a positive control for the MTT assay.