Supplementary data for article:

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Supplementary data

Investigation into novel thiophene- and furan-based 4-amino-7-chloroquinolines afforded antimalarials that cure mice

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Figure S1. *In vitro* metabolism of compound **27**.

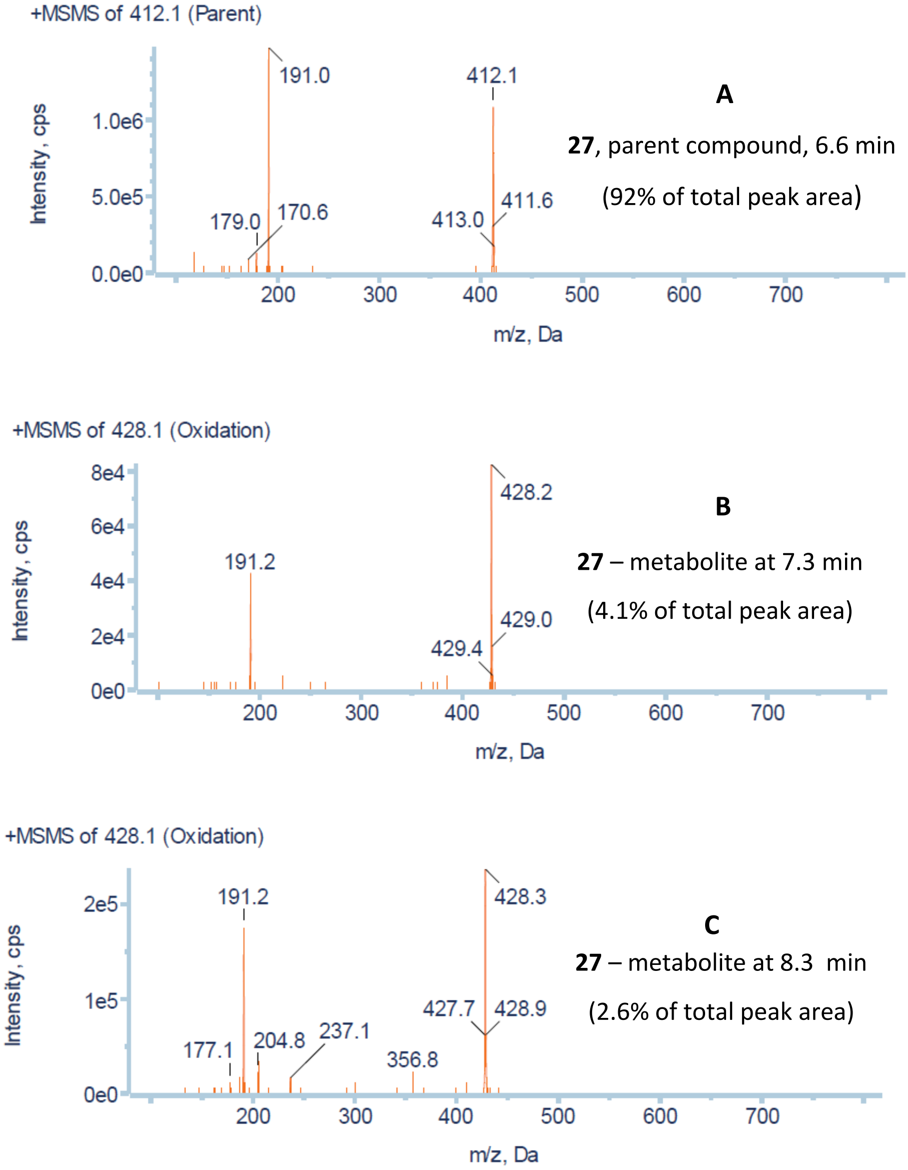
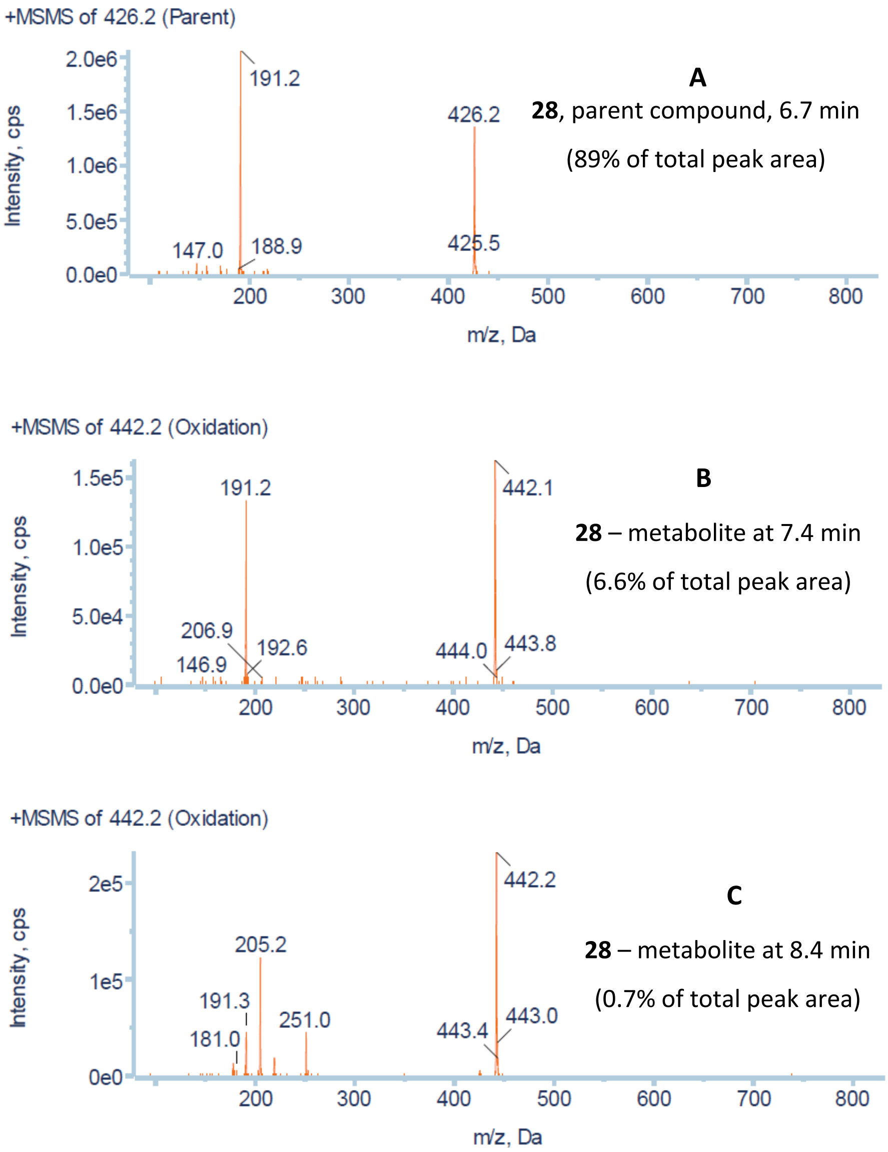
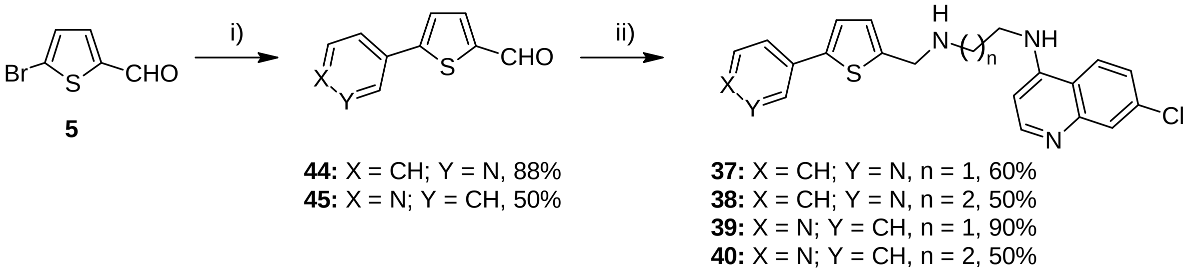


Figure S2. *In vitro* metabolism of compound **28**.



Scheme 1.



i) Pyridineboronic acid, $Pd(OAc)_2$, PPh_3, DME, Na_2CO_3 aq, EtOH, 90 ^oC;
ii) **ACQ**, CH_2Cl_2, MeOH, AcOH, $NaBH_4$, rt, 18 h

5-(Pyridin-3-yl)thiophene-2-carbaldehyde (44).[1] 5-Bromo-2-thiophenecarboxaldehyde (154 μL, 1.3 mmol) and 3-pyridineboronic acid (200 mg, 1.63 mmol) were coupled to afford **44** (216 mg, 88%) using $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and PPh_3 (31.5 mg, 0.12 mmol). The reaction mixture was refluxed for 4 h, and the crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 1/1). **44**: Yellow amorphous powder; mp = 75-81 ^oC. IR (ATR): 3383m, 2921w, 2851w, 1723w, 1661s, 1448m, 1422m, 1384w, 1355w, 1327w, 1252w, 1225s, 1194w, 1130w, 1072m, 1026m, 800m cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 9.93 (s, 1 H), 8.97-8.94 (m, 1 H), 8.68-8.60 (m, 1 H), 7.98-7.90 (m, 1 H), 7.79 (d, J = 4 Hz, 1 H), 7.47 (d, J = 4 Hz, 1 H), 7.44-7.34 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 193.18, 182.71, 150.23, 147.28, 143.58, 137.19, 133.57, 129.16, 125.10, 123.87. GC/MS (*m*/*z* (%)): 189.0 ($[M]^+$, 100), 116.1 (30). (+)ESI-HRMS (m/z): $[M + H]^+$ 190.03239 (error, +1.46 ppm).

5-(Pyridin-4-yl)thiophene-2-carbaldehyde (45). 5-Bromo-2-thiophenecarboxaldehyde (154 μL, 1.3 mmol) and 4-pyridineboronic acid (200 mg, 1.63 mmol) were coupled to afford **45** (123 mg, 50%) using $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and PPh_3 (31.5 mg, 0.12 mmol). The reaction mixture was refluxed for 18 h, and the crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 1/1). **45**: Brown amorphous powder; mp = 107-110 ^oC. IR (ATR): 3445s, 2361m, 1646s, 1543m, 1447m, 1415m, 1228m, 805m, 754w, 704m cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 9.95 (s, 1 H), 8.74-8.64 (m, 2 H), 7.80 (d, J = 4 Hz, 1 H), 7.59 (d, J = 4 Hz, 1 H), 7.56-7.50 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): 182.77, 150.72, 150.10, 144.18, 139.98, 136.90, 126.01, 120.19. (+)ESI-HRMS (m/z): $[M + H]^+$ 190.03231 (error, +1.04 ppm).

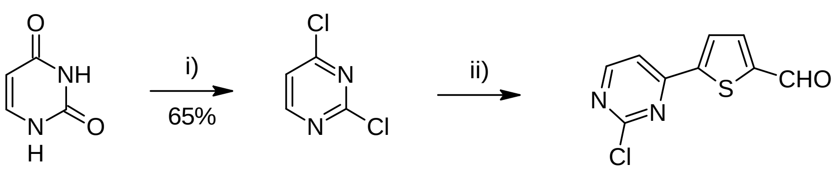
***N*-(7-Chloroquinolin-4-yl)-*N'*-{[5-(pyridin-3-yl)thiophen-2-yl]methyl}ethane-1,2-diamine (37).** 5-(Pyridin-3-yl)thiophene-2-carbaldehyde (92.5 mg, 0.49 mmol) and *N*-(7-chloroquinolin-4-yl)ethane-1,2-diamine (**ACQ2)** (162 mg, 0.73 mmol) were coupled to afford **37** (117 mg, 60%) using AcOH (42 μL, 0.73 mmol) and $NaBH_4$ (110 mg, 2.94 mmol). The crude product was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH = 7/3). **37**: Yellow amorphous powder; mp = 146-149 °C. IR (ATR): 3252m, 3063m, 2816w, 1611m, 1584s, 1491m, 1453m, 1429m, 1374m, 1332m, 1281m, 1250w, 1208m, 1168m, 1139w, 1123w, 1079w, 1024w, 968w, 945m, 901w, 873w, 850m cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ and CD_3OD): 8.79-8.75 (m, 1 H), 8.48-8.42 (m, 1 H), 8.40 (d, *J* = 5.6 Hz, 1 H), 7.90-7.74 (m, 3 H), 7.38-7.28 (m, 2 H), 7.22-7.18 (m, 1 H), 6.97-6.93 (m, 1 H), 6.36 (d, *J* = 5.6 Hz, 1 H), 4.06 (s, 2 H), 3.48-3.28 (m, $CH_2NHCH_2CH_2$NHAr), 3.15-3.00 (m, $CH_2NHCH_2CH_2$NHAr). ^{13}C NMR (50 MHz, $CDCl_3$ and CD_3OD): 151.27, 150.26, 148.30, 147.75, 145.99, 144.44, 139.07, 135.06, 132.91, 130.49, 127.47, 126.47, 125.21, 123.97, 123.79, 121.70, 117.15, 98.74, 47.81, 46.30, 41.93. (+)ESI-HRMS (m/z): $[M + 2H]^{2+}$ 198.05817 (error, −0.26 ppm); $[M + H]^+$ 395.10755 (error, −4.10 ppm). HPLC purity: Method C: RT 1.870, area 96.46 %; method D: RT 1.881, area 96.49 %.

***N*-(7-Chloroquinolin-4-yl)-*N*'-{[5-(pyridin-3-yl)thiophen-2-yl]methyl}propane-1,3-diamine (38).** 5-(Pyridin-3-yl)thiophene-2-carbaldehyde (92.5 mg, 0.49 mmol) and *N*-(7-chloroquinolin-4-yl)propane-1,3-diamine (**ACQ3**) (173 mg, 0.73 mmol) were coupled to afford **38** (101 mg, 50%) using AcOH (42 μL, 0.73 mmol) and $NaBH_4$ (110 mg, 2.94 mmol). The crude product was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH = 7/3). **38**: Pale-yellow amorphous powder; mp = 80-82 °C. IR (ATR): 3257m, 3104m, 2937w, 2869m, 2833m, 1607m, 1582s, 1540m, 1490m, 1473m, 1449m, 1433m, 1416m, 1365m, 1332m, 1287m, 1269m, 1246w, 1220w, 1200m, 1136m, 1122w, 1082m, 1020m, 982m, 953m, 899m, 851m, 820m cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ and CD_3OD): 8.79-8.76 (m, 1 H), 8.48-8.42 (m, 1 H), 8.39 (d, *J* = 5.8 Hz, 1 H), 7.87-7.84 (m, 1 H), 7.82-7.72 (m, 2 H), 7.40-7.16 (m, 3 H), 6.98-6.96 (m, 1 H), 6.35 (d, *J* = 5.8 Hz, 1 H), 4.04 (s, 2 H), 3.48-3.36 (m, $CH_2NHCH_2CH_2CH_2$NHAr), 3.00-2.90 (m, $CH_2NHCH_2CH_2CH_2$NHAr), 2.04-1.88 (m, $CH_2NHCH_2CH_2CH_2$NHAr). ^{13}C NMR (50 MHz, $CDCl_3$ and CD_3OD): 151.21, 150.66, 148.19, 147.70, 145.88, 143.80, 139.09, 134.95, 133.02, 130.49, 127.18, 126.74, 124.92, 123.97, 123.88, 122.21, 117.16, 98.19, 48.29, 47.72, 42.55, 27.30. (+)ESI-HRMS (m/z): $[M + 2H]^{2+}$ 205.06562 (error, −2.12 ppm); $[M + H]^+$ 409.12332 (error, −3.68 ppm). HPLC purity: Method C: RT 2.037, area 98.41 %; method D: RT 1.842, area 96.72 %.

***N*-(7-Chloroquinolin-4-yl)-*N*'-{[5-(pyridin-4-yl)thiophen-2-yl]methyl}ethane-1,2-diamine (39).** 5-(Pyridin-4-yl)thiophene-2-carbaldehyde (50 mg, 0.26 mmol) and **ACQ2** (88 mg, 0.40 mmol) were coupled to afford **39** (92 mg, 90%) using AcOH (23 μL, 0.40 mmol) and $NaBH_4$ (60 mg, 1.56 mmol). The crude product was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH = 7/3). **39**: Yellow amorphous powder; mp = 82-86 °C. IR (ATR): 3266m, 3066m, 1576s, 1536m, 1450m, 1419m, 1368m, 1329m, 1279m, 1243w, 1219w, 1167w, 1137m, 1079m, 995m, 964w, 876m, 848m, 800s cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ and CD_3OD): 8.53-8.44 (m, 2 H), 8.41 (d, *J* = 5.6 Hz, 1 H), 7.90-7.86 (m, 1 H), 7.84 (s, 1 H), 7.42-7.28 (m, 4 H), 7.00-6.94 (m, 1 H), 6.38 (d, *J* = 5.6 Hz, 1 H), 4.08 (s, 2 H), 3.46-3.36 (m, $CH_2NHCH_2CH_2NHAr$), 3.18-3.02 (m, $CH_2NHCH_2CH_2NHAr$). ^{13}C NMR (50 MHz, $CDCl_3$ and CD_3OD): 151.34, 150.26, 149.70, 148.37, 146.02, 141.73, 139.76, 135.15, 127.62, 126.56, 125.41, 125.32, 121.62, 119.59, 117.18, 98.81, 47.89, 46.39, 41.95. (+)ESI-HRMS (m/z): $[M + H]^+$ 395.10815 (error, −2.59 ppm). HPLC purity: Method C: RT 2.172, area 96.33 %; method D: RT 2.044, area 97.98 %.

***N*-(7-Chloroquinolin-4-yl)-*N'*-{[5-(pyridin-4-yl)thiophen-2-yl]methyl}propane-1,3-diamine (40).** 5-(Pyridin-4-yl)thiophene-2-carbaldehyde (50 mg, 0.26 mmol) and **ACQ3** (93 mg, 0.40 mmol) were coupled to afford **40** (53 mg, 50%) using AcOH (23 μL, 0.40 mmol) and $NaBH_4$ (60 mg, 1.56 mmol). The crude product was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH = 7/3). **40**: Pale-yellow amorphous powder; mp = 110-113 °C. IR (ATR): 3244m, 3087m, 2948m, 2917m, 2876m, 2838m, 1578s, 1546m, 1453m, 1426m, 1366m, 1328m, 1283m, 1261w, 1237m, 1185m, 1139m, 1106m, 1081m, 1013w, 991m, 967w, 887m, 845m, 805s cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ and CD_3OD): 8.54-8.50 (m, 2 H), 8.42 (d, *J* = 5.6 Hz, 1 H), 7.90-7.87 (m, 1 H), 7.72 (d, *J* = 9.0 Hz, 1 H), 7.40-7.34 (m, 3 H), 7.21 (dd, *J* = 9.0 Hz, *J* = 2.2 Hz, 1 H), 7.00-6.97 (m, 1 H), 6.35 (d, *J* = 5.6 Hz, 1 H), 4.06 (s, 2 H), 3.48-3.36 (m, $CH_2NHCH_2CH_2CH_2NHAr$), 3.00-2.90 (m, $CH_2NHCH_2CH_2CH_2NHAr$), 2.04-1.90 (m, $CH_2NHCH_2CH_2CH_2NHAr$). ^{13}C NMR (50 MHz, $CDCl_3$ and CD_3OD): 151.47, 150.59, 149.85, 148.43, 145.44, 141.58, 139.89, 134.95, 127.56, 126.81, 125.32, 124.99, 122.14, 119.55, 117.22, 98.32, 48.54, 48.12, 42.90, 27.40. (+)ESI-HRMS (m/z): $[M + H]^+$ 409.12317 (error, −4.04 ppm). HPLC purity: Method C: RT 2.091, area 96.75 %; method D: RT 1.812, area 95.50 %.

Scheme 2.



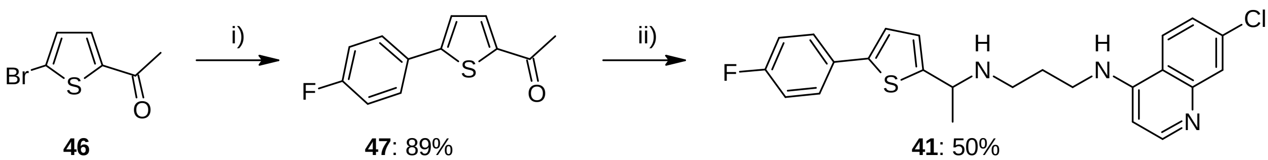
33: 54%

i) $PhNMe_2$, $POCl_3$, 120 °C, 10 min.;
ii) 5-Formyl-2-thienylboronic acid, $Pd(PPh_3)_4$, THF, K_2CO_3 aq, 75 °C, 18 h

2,4-Dichloropyrimidine.[2,3] A mixture of *N*,*N*-dimethylaniline (2.3 mL), $POCl_3$ (2.4 mL, 26.09 mmol) and uracil (2 g, 17.84 mmol) was heated to reflux for 10 min. Upon cooling to rt, the mixture was slowly poured onto an ice/water mixture. The solid was filtered, and filtrate was extracted with Et_2O (2×50 mL). The combined organic fractions were dried over anh. Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to afford 2,4-dichloropyrimidine (1.74 g, 65%) as a white amorphous powder; mp = 60-62 ^oC. IR (ATR): 3093m, 3055m, 2942w, 1733w, 1672w, 1345s, 1538s, 1415s, 1332s, 1206m, 1177m, 1096w, 983w, 866m, 818m cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 8.60-8.50 (m, 1 H), 7.40-7.30 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 162.68, 161.01, 160.08, 120.33.

5-(2-Chloropyrimidin-4-yl)thiophene-2-carbaldehyde (33).[4] To a dry glass flask purged with argon were added 2,4-dichloropyrimidine (1 g, 6.71 mmol), 5-formyl-2-thienylboronic acid (1.05 g, 6.71 mmol), K_2CO_3 (aq) (0.56 M, 24 mL, 13.4 mmol) and dry THF (12 mL). After 10 min a solution of $Pd(PPh_3)_4$ (381 mg, 0.33 mmol) in dry THF (12 mL) was added and reaction mixture was purged with argon and refluxed for 18 h under argon. The solution was cooled to room temperature and carefully evaporated to dryness, and the remaining solid was partitioned between CH_2Cl_2 and brine. The organic fraction was dried over anh. Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was partially purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 4/6) to afford **33** (810 mg, 54%) and was used in the next reactions without further purification.

Scheme 3.



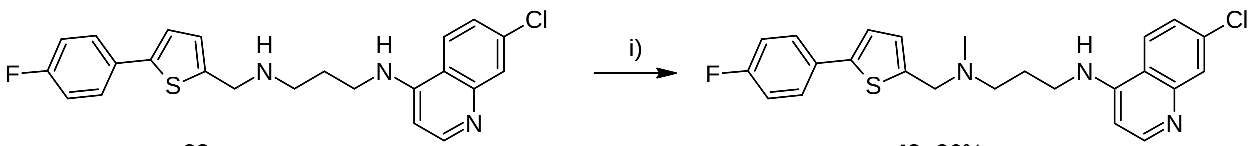
i) 4-fluorophenylboronic acid, $Pd(OAc)_2$, PPh_3, DME, Na_2CO_3 aq, EtOH, 90 ^oC, 2 h;
ii) **ACQ3**, CH_2Cl_2, MeOH, $NaBH_3CN$, $ZnCl_2$, 40 ^oC, 144 h

***N*-(7-chloroquinolin-4-yl)-*N'*-{1-[5-(4-fluorophenyl)thiophen-2-yl]ethyl}propane-1,3-diamine (41).** 2-Acetyl-5-bromothiophene (450 mg, 2.19 mmol) and 4-fluorophenylboronic acid (384 mg, 2.74 mmol) were coupled to afford **47** (430 mg, 89%) using $Pd(OAc)_2$ (16.1 mg, 0.07 mmol) and PPh_3 (75.2 mg, 0.28 mmol). The reaction mixture was refluxed for 2 h followed by partial purification of the crude product by dry-flash chromatography (SiO_2: hexane/EtOAc = 85/15) and was used in the next reactions without further purification.

1-[5-(4-Fluorophenyl)thiophen-2-yl]ethanone (200 mg, 0.90 mmol) and **ACQ3** (237 mg, 1.07 mmol) were coupled to afford **41** (200 mg, 50%) using $ZnCl_2$ (309 mg, 2.27 mmol) and $NaBH_3CN$

(282 mg, 4.48 mmol). The crude product was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH = 9/1) to afford **41** as yellow oil. IR (ATR): 3273m, 3066m, 2965m, 2855m, 1608m, 1582s, 1539m, 1512m, 1474m, 1450m, 1369m, 1332w, 1304w, 1280w, 1233m, 1162w, 1139w, 1104w, 1078w, 900w, 880w cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 8.50 (d, *J* = 5.5 Hz, 1 H), 7.93 (d, *J* = 2.5 Hz , 1 H), 7.74 (d, *J* = 9.0 Hz, 1 H), 7.39-7.34 (m, 2 H), 7.23 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 1 H), 7.13 (N*H*), 7.06-6.99 (m, 3 H), 6.87-6.84 (m, 1 H), 6.33 (d, *J* = 5.5 Hz, 1 H), 4.08 (q, *J* = 6.0 Hz, C*H*(CH_3)NH$CH_2CH_2CH_2$NHAr), 3.47-3.40 (m, CH(CH_3)NHCH_2CH_2C*H*$_2$NHAr), 3.39-3.32 (m, CH(CH_3)NHCH_2CH_2C*H*$_2$NHAr), 2.95-2.90 (m, CH(CH_3)NHC*H*$_2$$CH_2CH_2$NHAr), 2.88-2.82 (m, CH($CH_3$)NHC*H*$_2$$CH_2CH_2$NHAr), 1.93-1.86 (m, CH($CH_3$)NH$CH_2$C*H*$_2$$CH_2$NHAr), 1.69 (N*H*), 1.56 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 162.21 (d, *J* = 245.4 Hz), 152.11, 150.36, 149.18, 141.63, 134.65, 130.52 (d, *J* = 3.6 Hz), 128.55, 127.05 (d, *J* = 7.2 Hz), 124.83, 124.81, 122.25, 122.09, 117.55, 115.82 (d, *J* = 21.8 Hz), 98.53, 54.57, 47.03, 43.58, 27.91, 24.72. (+)ESI-HRMS (m/z): $[M + H]^+$ 440.13634 (error, +1.22 ppm). HPLC purity: Method A: RT 7.591, area 98.83 %; method B: RT 8.954, area 98.28 %.

Scheme 4.



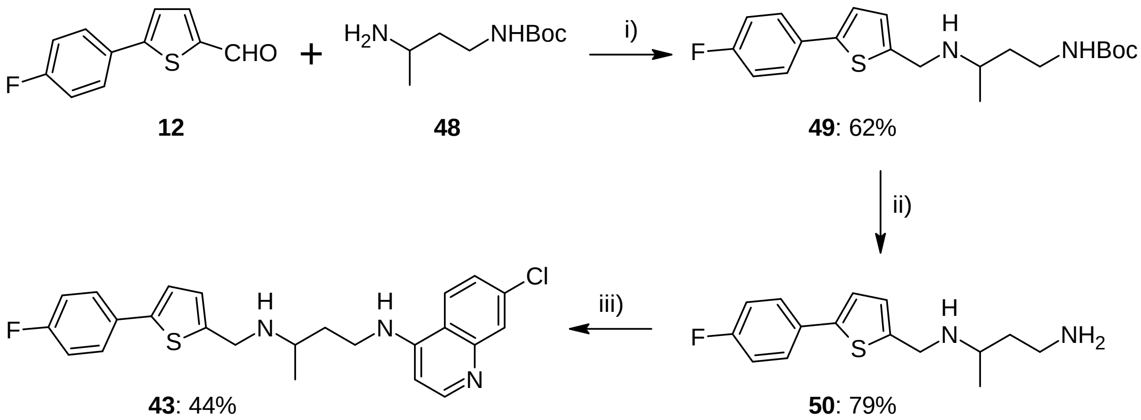
28 **42:** 36%

i) HCHO, MeOH, $NaBH_3CN$, $ZnCl_2$, rt, 1 h

***N'*-(7-chloroquinolin-4-yl)-*N*-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}-*N*-methylpropane-1,3-diamine (42).** *N*-(7-Chloroquinolin-4-yl)-*N'*-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}propane-1,3-diamine (270 mg, 0.63 mmol) and formaldehide (93µL, 1.26 mmol, 37% aq solution) were coupled to afford **42** (100 mg, 36%) using $ZnCl_2$ (171 mg, 1.26 mmol) and $NaBH_3CN$ (158 mg, 2.52 mmol). The crude product was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH = 9/1). **42**: Yellow amorphous powder; mp = 113-115°C. IR (ATR): 3440w, 3239m, 3068w, 2955m, 2873w, 2837w, 2804w, 2765w, 1609m, 1582s, 1544m, 1511m, 1466m, 1429w, 1363m, 1333m, 1280w, 1229m, 1162w, 1138w, 1079w, 1022w, 902w, 872w cm^{-1}. ^{1}H NMR (500 MHz; $CDCl_3$): 8.51 (d, *J* = 5.5 Hz, 1 H), 7.92 (d, *J* = 2.0 Hz, 1 H), 7.56 (d, *J* = 9.5 Hz, 1 H), 7.37-7.32 (m, 2 H), 7.14 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 1 H), 7.07-7.00 (m, 4 H), 6.88-6.85 (m, 1 H), 6.35 (d, *J* = 5.5 Hz, 1 H), 3.77 (s, 2 H), 3.43-3.38 (m, CH_2N(CH_3)CH_2CH_2C*H*$_2$NHAr), 2.72-

2.66 (m, $CH_2N(CH_3)CH_2CH_2CH_2NHAr$), 2.43 (s, 3 H), 1.99-1.93 (m, $CH_2N(CH_3)CH_2C\mathit{H}_2CH_2NHAr$), 1.89 (N*H*). ^{13}C NMR (125 MHz, $CDCl_3$): 162.27 (d, *J* = 245.5 Hz), 152.09, 150.44, 149.18, 143.06, 140.85, 134.63, 130.36 (d, *J* = 2.8 Hz), 128.50, 127.56, 127.04 (d, *J* = 7.2 Hz), 124.95, 122.26, 121.93, 117.57, 115.86 (d, *J* = 21.6 Hz), 98.65, 57.51, 56.48, 43.60, 41.96, 24.72. (+)ESI-HRMS (m/z): $[M + H]^+$ 440.13581 (error, +0.01 ppm). HPLC purity: Method A: RT 7.583, area 95.11 %; method B: RT 8.797, area 95.14 %.

Scheme 5.



i) CH_2Cl_2, MeOH, AcOH, $NaBH_4$, rt, 24 h; ii) TFA, CH_2Cl_2, rt, 18 h;
iii) 4,7-dichloroquinoline, phenol, 150 °C, 48 h

***tert*-butyl [3-({[5-(4-fluorophenyl)thiophen-2-yl]methyl}amino)butyl]carbamate (49).** 5-(4-Fluorophenyl)thiophene-2-carbaldehyde (450 mg, 2.18 mmol) and amine **48** (452 mg, 2.40 mmol) were coupled to afford **49** (512 mg, 62%) using AcOH (137 µL, 2.40 mmol) and $NaBH_4$ (494 mg, 13.06 mmol). The crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc = 4/6) to afford **49** as yellow oil. IR (ATR): 3352w, 3071w, 2974m, 2931m, 1708s, 1601w, 1512s, 1473m, 1389w, 1368m, 1275m, 1234s, 1173s, 1099w, 1077w, 1045w, 836m, 806m cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.55-7.48 (m, 2 H), 7.07-7.02 (m, 3 H), 6.89-6.87 (m, 1 H), 5.39 (N*H*), 4.07-4.01 (m, 1 H), 3.94-3.89 (m, 1 H), 3.34-3.26 (m, $-CH_2NHCH(CH_3)CH_2C\mathit{H}_2NHBoc$), 3.24-3.16 (m, $-CH_2NHCH(CH_3)CH_2C\mathit{H}_2NHBoc$), 2.88-2.82 (m, $-CH_2NHC\mathit{H}(CH_3)CH_2CH_2NHBoc$), 1.67-1.51 (m, $-CH_2NHCH(CH_3)C\mathit{H}_2CH_2NHBoc$), 1.49 (N*H*), 1.43 (s, 9 H), 1.14 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 162.16 (d, *J* = 245.5 Hz), 156.06, 144.14, 142.06, 130.88 (d, *J* = 2.8 Hz), 127.25 (d, *J* = 7.2 Hz), 125.60, 122.53, 115.71 (d, *J* = 21.6 Hz), 78.86, 51.04, 45.92, 38.26, 36.32, 28.44, 20.29. (+)ESI-HRMS (m/z): $[M + H]^+$ 379.18554 (error, +1.42 ppm).

***N*^3-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}butane-1,3-diamine (50).** To a solution of **49** (480 mg, 1.27 mmol) in dry CH_2Cl_2 (20 mL) TFA (1.5 mL) was added and the reaction mixture was vigorously stirred for 18 h at r.t. Solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with 3M NaOH (10 mL). The layers were separated and water layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine and dried over anh. Na_2SO_4. Finally, the solvent was removed under reduced pressure, and crude product was used without further purification. Yield 280 mg (79%). **50** :Yellow oil, IR (ATR): 3364w, 3285w, 3067w, 2960m, 2925m, 2868m, 1600w, 1550w, 1511s, 1471m, 1374w, 1304w, 1231s, 1160m, 1098w, 1049w, 953w, 835s, 806s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 7.55-7.49 (m, 2H), 7.08-7.02 (m, 3H), 6.87-6.85 (m, 1H), 4.06-4.02 (m, 1H), 3.96-3.92 (m, 1H), 2.90-2.81 (m, -$CH_2NHCH(CH_3)CH_2C\mathit{H}_2NH_2$), 2.80-2.73 (m, -$CH_2NHC\mathit{H}(CH_3)CH_2CH_2NH_2$), 1.64-1.49 (m, -$CH_2NHCH(CH_3)C\mathit{H}_2CH_2NH_2$ and N*H*), 1.12 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 162.13 (d, *J* = 245.5 Hz), 144.52, 141.95, 130.87, 127.19 (d, *J* = 7.2 Hz), 125.48, 122.48, 115.72 (d, *J* = 21.8 Hz), 50.51, 45.91, 40.62, 39.41, 20.42. (+)ESI-HRMS (m/z): $[M + H]^+$ 279.13246 (error, −0.40 ppm).

***N*^1-(7-chloroquinolin-4-yl)-*N*^3-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}butane-1,3-diamine (43).** A solution of 4,7-dichloroquinoline (36 mg, 0.18 mmol), amine **50** (50 mg, 0.18 mmol) in phenol (51 mg, 0.54 mmol) was heated in an oil-bath to 150 °C for 48 h. After the reaction mixture was cooled to room temperature, 15% NaOH (5 mL) was added, and desired product was extracted with CH_2Cl_2 (4×20 mL). Combined organic layers were washed with brine, dried over anh. Na_2SO_4 and evaporated to dryness. The crude product was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH = 9/1) to afford **43** (35 mg, 44%) as yellow oil. IR (ATR): 3267m, 3067w, 2962m, 2927m, 1610s, 1583s, 1539m, 1511s, 1470m, 1452m, 1369m, 1332w, 1281w, 1231s, 1160w, 1141w, 1097w, 1079w, 905w cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 8.47 (d, *J* = 5.5 Hz, 1 H), 7.94-7.92 (m, 1 H), 7.60-7.56 (m, 1 H), 7.45-7.41 (m, 2 H), 7.10-7.03 (m, 4 H), 6.92-6.89 (m, 1 H), 6.32 (d, *J* = 5.5 Hz, 1 H), 4.18-4.13 (m, 1 H), 4.02-3.97 (m, 1 H), 3.54-3.47 (m, $CH_2NHCH(CH_3)CH_2C\mathit{H}_2NHAr$), 3.40-3.34 (m, $CH_2NHCH(CH_3)CH_2C\mathit{H}_2NHAr$), 3.14-3.07 (m, $CH_2NHC\mathit{H}(CH_3)CH_2CH_2NHAr$), 2.18 (N*H*), 2.04-1.97 (m, $CH_2NHCH(CH_3)C\mathit{H}_2CH_2NHAr$), 1.81-1.72 (m, $CH_2NHCH(CH_3)C\mathit{H}_2CH_2NHAr$), 1.27 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): 162.33 (d, *J* = 245.5 Hz), 151.16, 150.74, 148.16, 142.63 (d, *J* = 6.2 Hz), 135.02, 130.40 (d, *J* = 3.6 Hz), 127.65, 127.19 (d, *J* = 8.1 Hz), 126.51, 125.05, 122.58, 122.34, 117.30, 115.92 (d, *J* = 21.6 Hz), 98.28, 52.62, 46.11, 41.70, 33.59, 20.06. (+)ESI-HRMS (m/z): $[M + H]^+$ 440.13479 (error, −2.29 ppm). HPLC purity: Method A: RT 7.587, area 97.27 %; method B: RT 8.869, area 96.92 %.

Table 1. *In vitro* antimalarial activity (IC_{90}).

Compd.	Antimalarial activity (IC_{50} and IC_{90}, nM)					
	W2[a]		D6[b]		TM91C235[c]	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}
15	14.93	30.60	2.49	4.04	5.06	11.94
16	38.85	104.89	22.69	30.51	43.05	92.68
17	15.20	23.53	5.15	11.28	20.59	73.54
18	37.92	68.72	13.03	33.18	37.92	85.31
19	30.66	113.22	4.95	7.31	18.40	73.12
20	13.70	20.55	6.62	13.24	22.83	50.23
21	29.66	48.35	5.18	7.68	10.46	21.11
22	104.03	162.71	13.96	19.12	43.10	86.42
23	19.13	31.40	9.12	13.47	10.83	16.95
24	70.17	88.31	16.35	28.95	27.80	49.98
26	174.12	231.38	19.37	34.10	65.79	105.40
27	18.92	26.73	8.09	10.95	9.85	14.76
28	26.00	45.56	13.62	16.38	15.93	25.07
29	23.87	74.00	15.28	31.03	12.65	35.80
30	8.39	26.84	2.49	3.27	8.89	18.49
31	38.07	46.04	8.61	12.94	16.26	38.95
32	11.57	17.20	3.64	5.99	5.99	13.85
34	32.53	85.98	6.27	11.85	32.53	139.42
35	164.19	313.45	40.30	164.19	134.33	283.59
36	228.07	358.39	260.65	423.55	456.13	749.36
37	10.38	19.67	6.73	15.36	15.31	30.56
38	24.67	67.30	9.04	11.25	20.07	44.37
39	13.93	22.56	8.77	10.16	21.08	24.99
40	35.89	58.75	4.23	5.99	12.32	23.30
41	242.51		145.91		160.23	
42	422.96		306.14		319.55	
43	47.73		22.73		36.36	
CQ[i]	595.02 (5)	869.01 (5)	14.72 (6)	19.92 (6)	206.01 (5)	487.07 (5)
MFQ[j]	6.56 (5)	20.71 (5)	22.76 (6)	48.15 (6)	54.90 (5)	169.23 (5)

[a]*P. falciparum* Indochina W2 clone. [b]*P. falciparum* African D6 clone. [c]*P. falciparum* multidrug resistant C235 strain (Thailand).

β-Hematin inhibition: Plots of the dose-dependent inhibition of β-hematin formation by studied compounds.

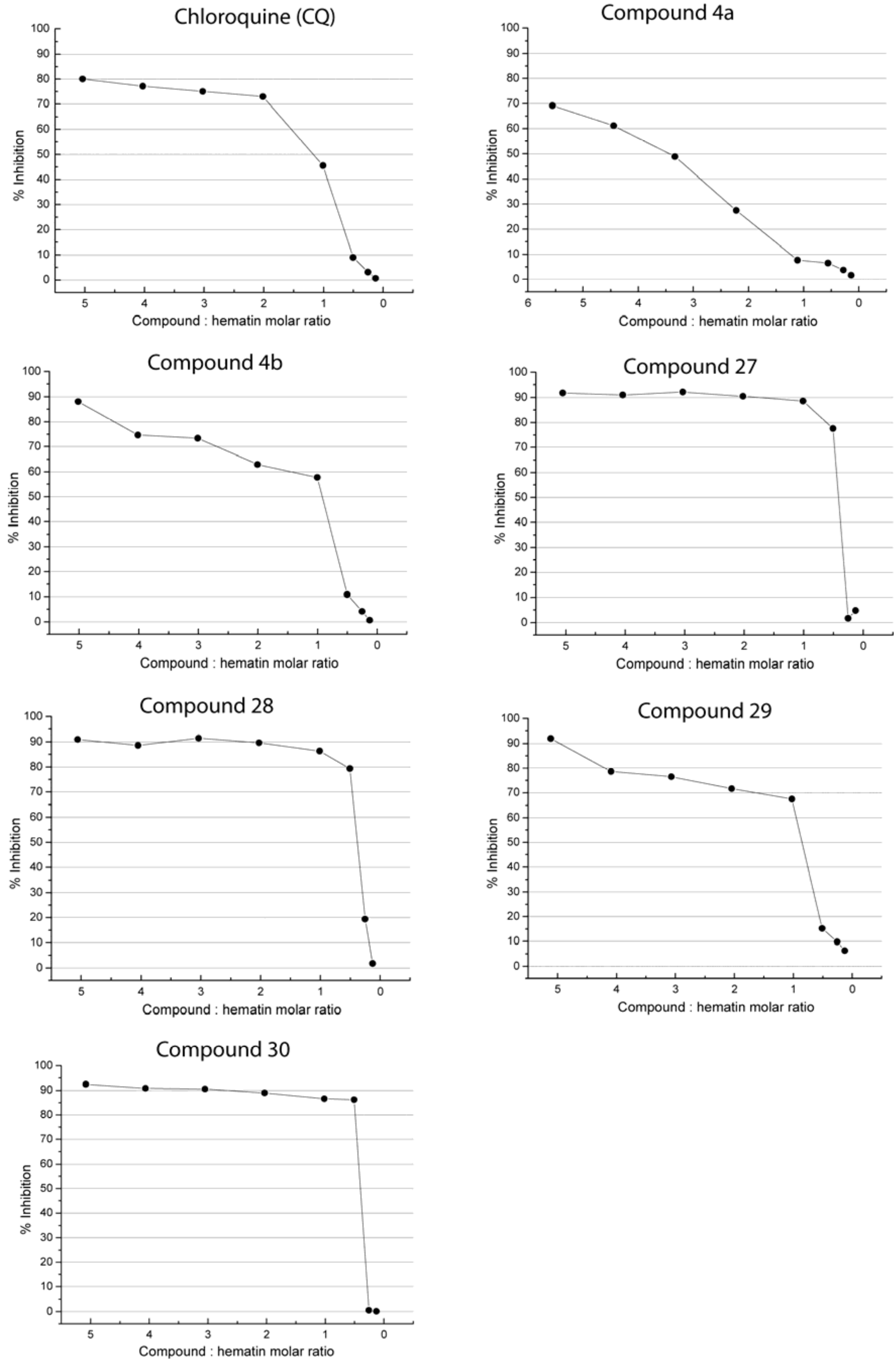
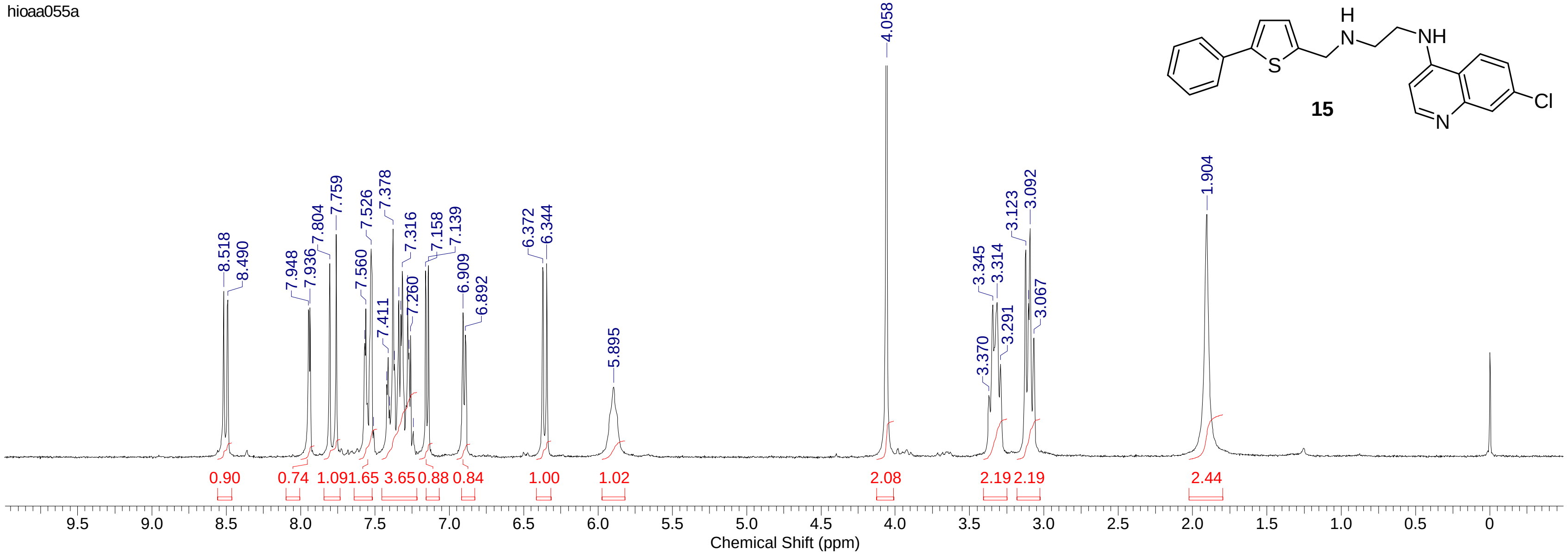


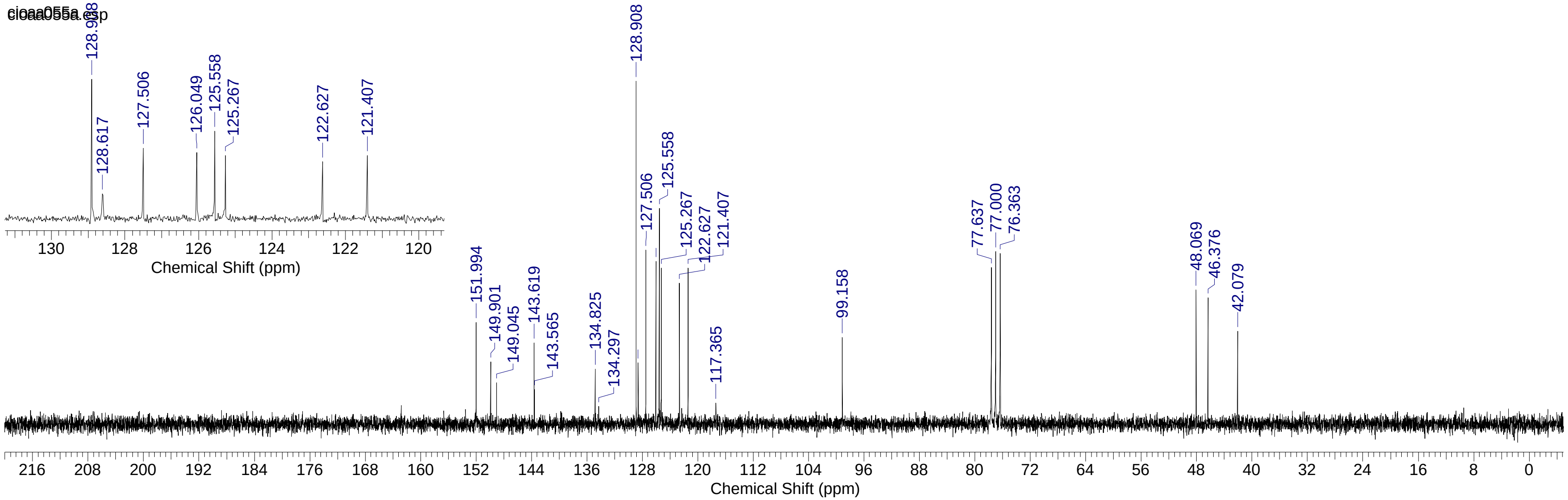
Figure. Plots of the dose-dependent inhibition of β-hematin formation by studied compounds

^{1}H and ^{13}C NMR spectra of representative products.

N-(7-chloroquinolin-4-yl)-N'-[(5-phenylthiophen-2-yl)methyl]ethane-1,2-diamine (15)

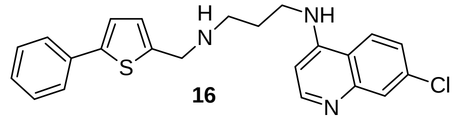
hioaa055a





N-(7-chloroquinolin-4-yl)-*N*'-[(5-phenylthiophen-2-yl)methyl]propane-1,3-diamine (16)

hioaa057.esp



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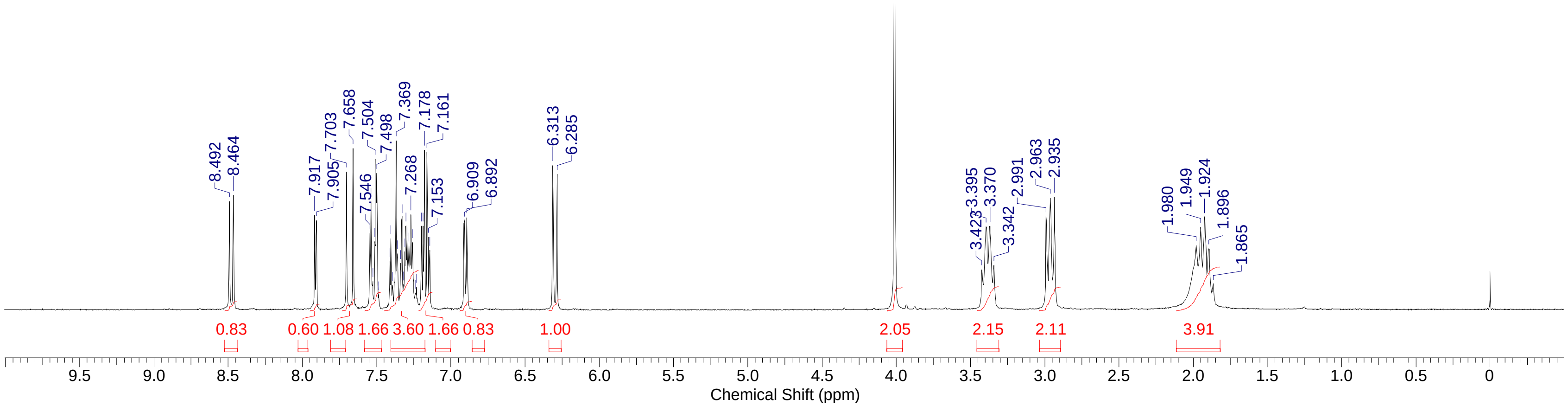

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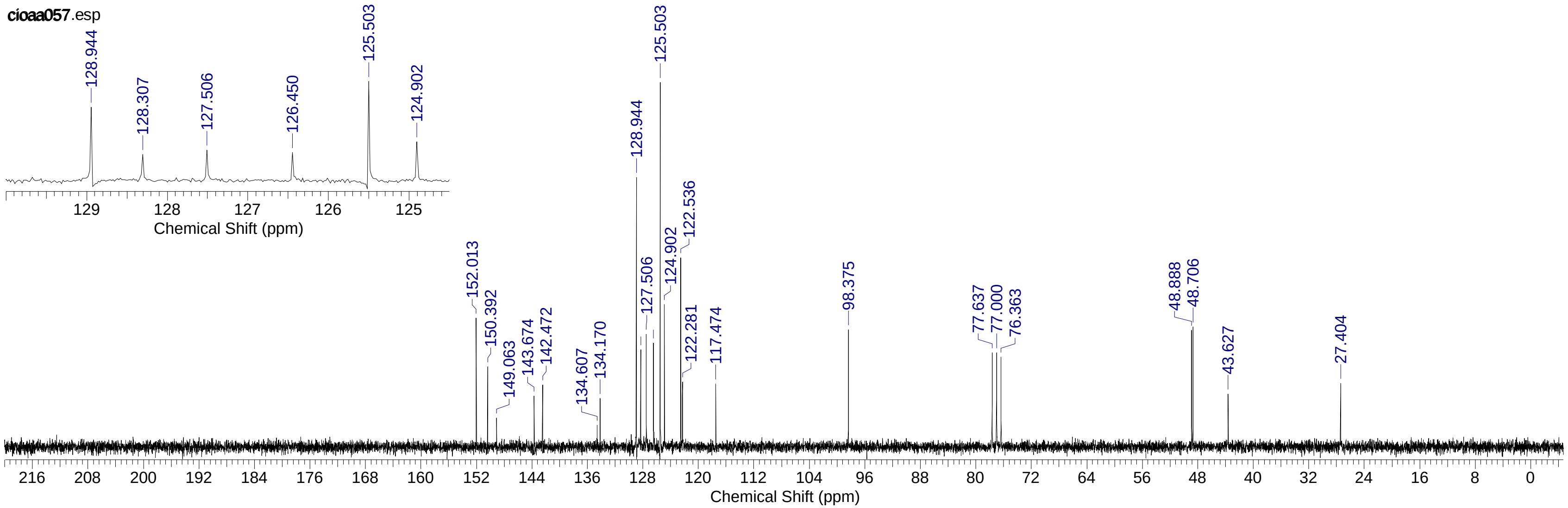

N-(7-chloroquinolin-4-yl)-N'-{[5-(4-methylphenyl)thiophen-2-yl]methyl}ethane-1,2-diamine (17)

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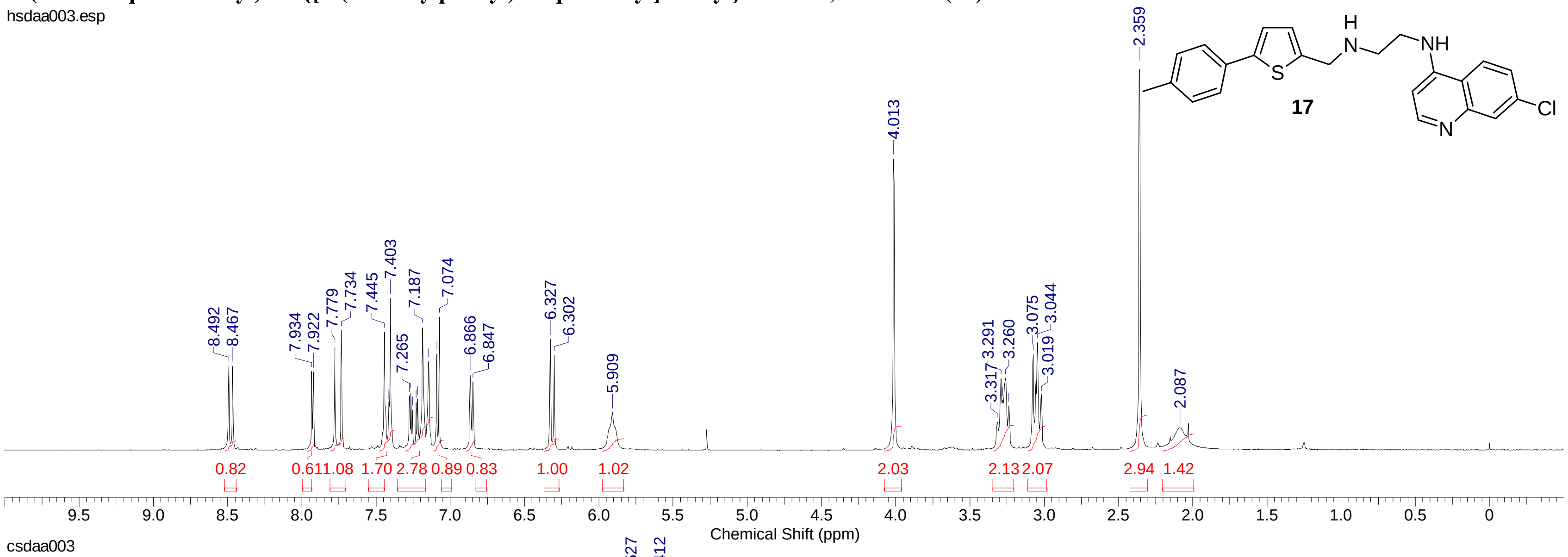

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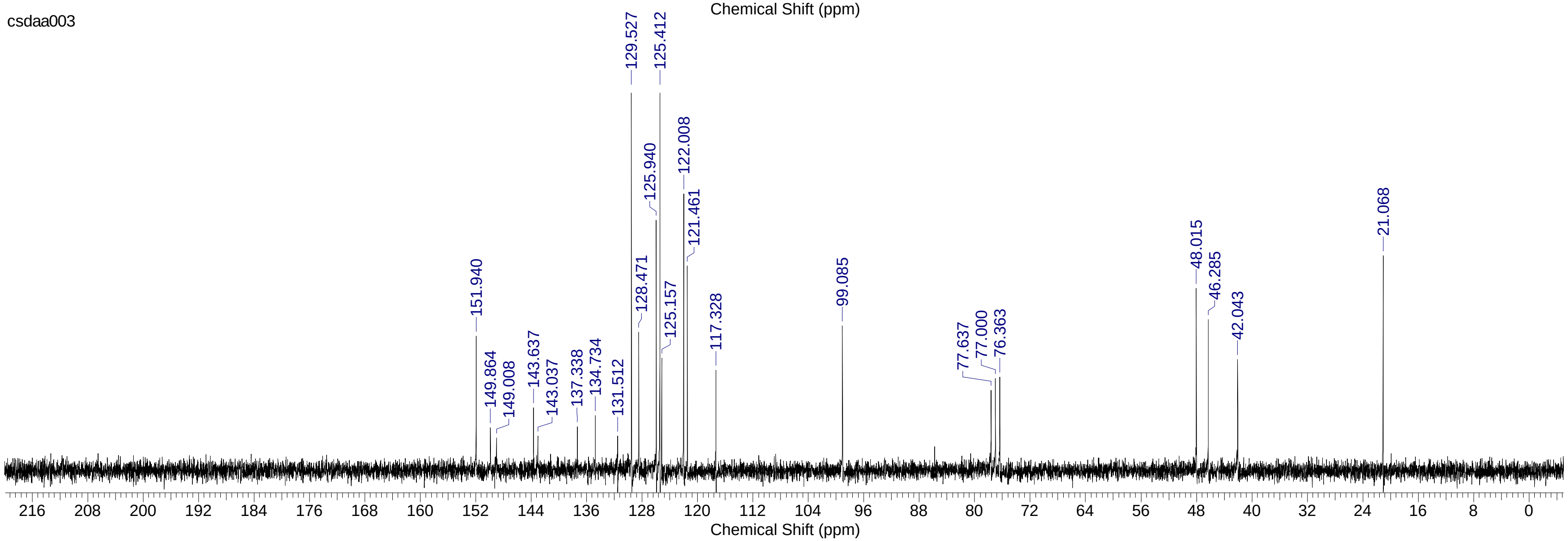
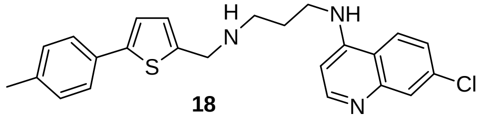


N-(7-chloroquinolin-4-yl)-N'-{[5-(4-methylphenyl)thiophen-2-yl]methyl}propane-1,3-diamine (18)

hsdaa004



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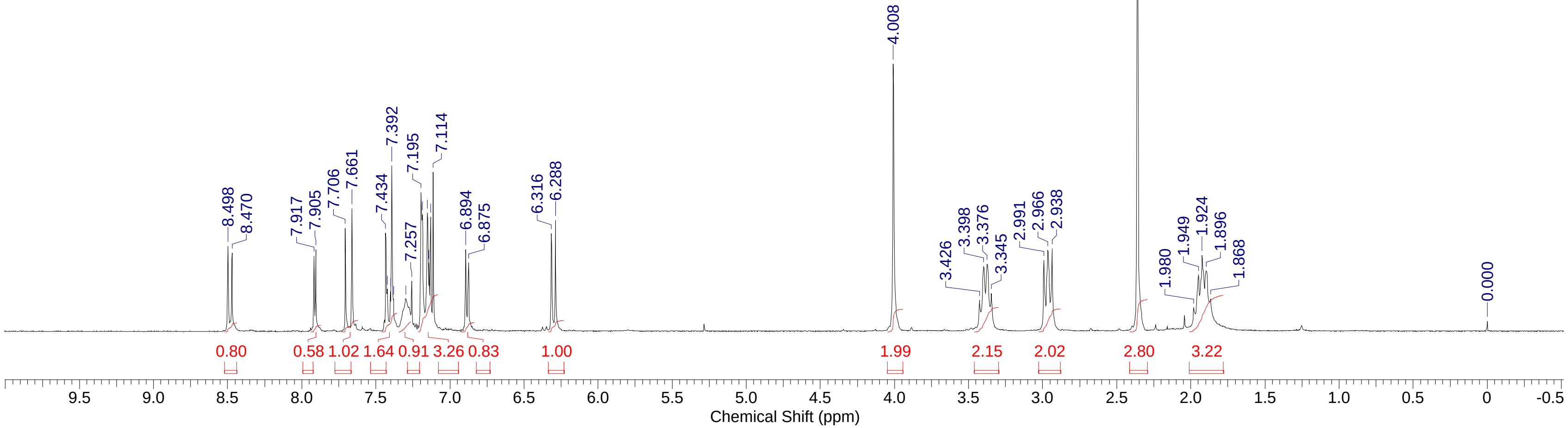
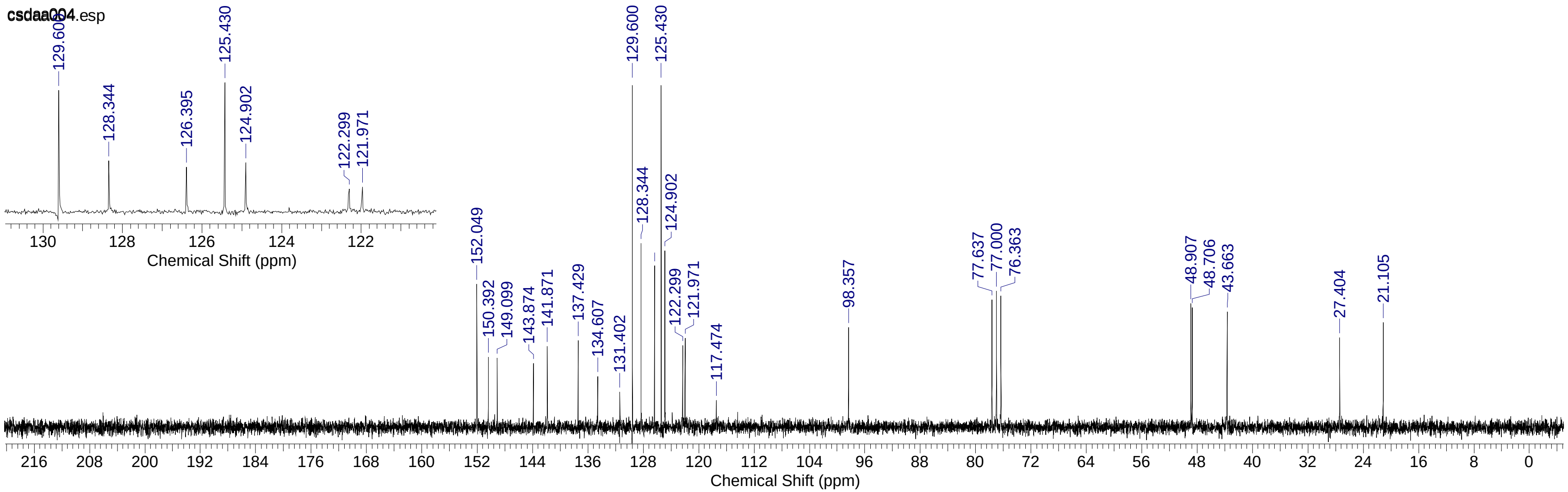
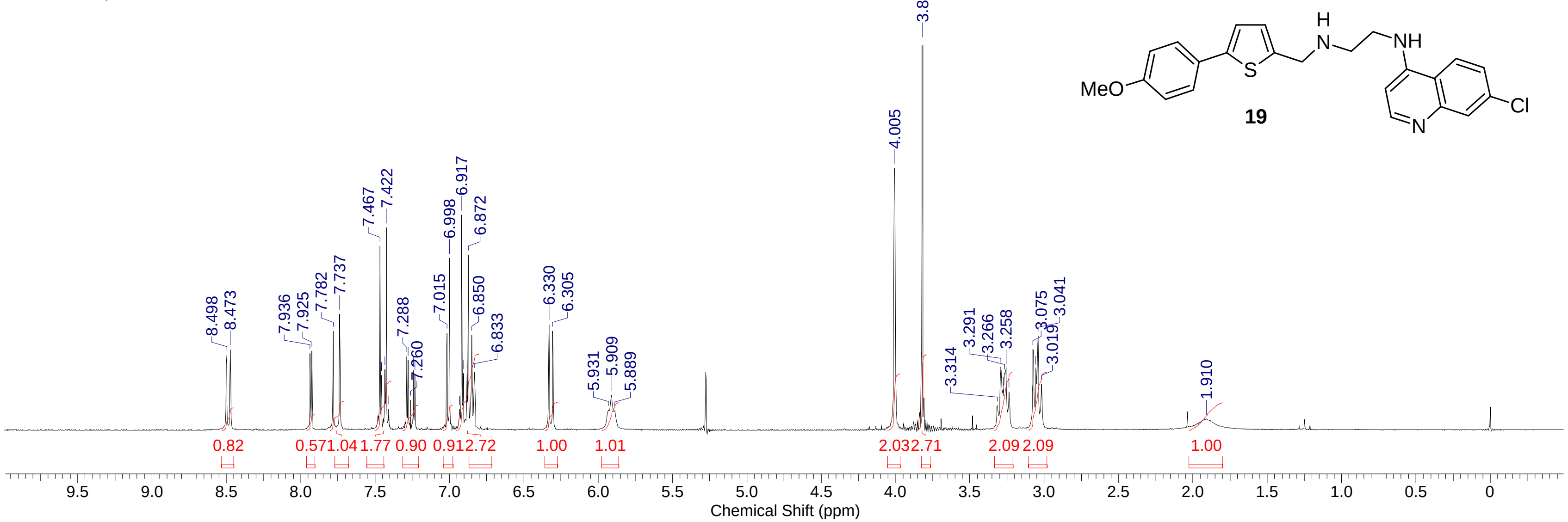




_N_-(7-chloroquinolin-4-yl)-_N'_-{[5-(4-methoxyphenyl)thiophen-2-yl]methyl}ethane-1,2-diamine (19)

hsdaa006a.esp



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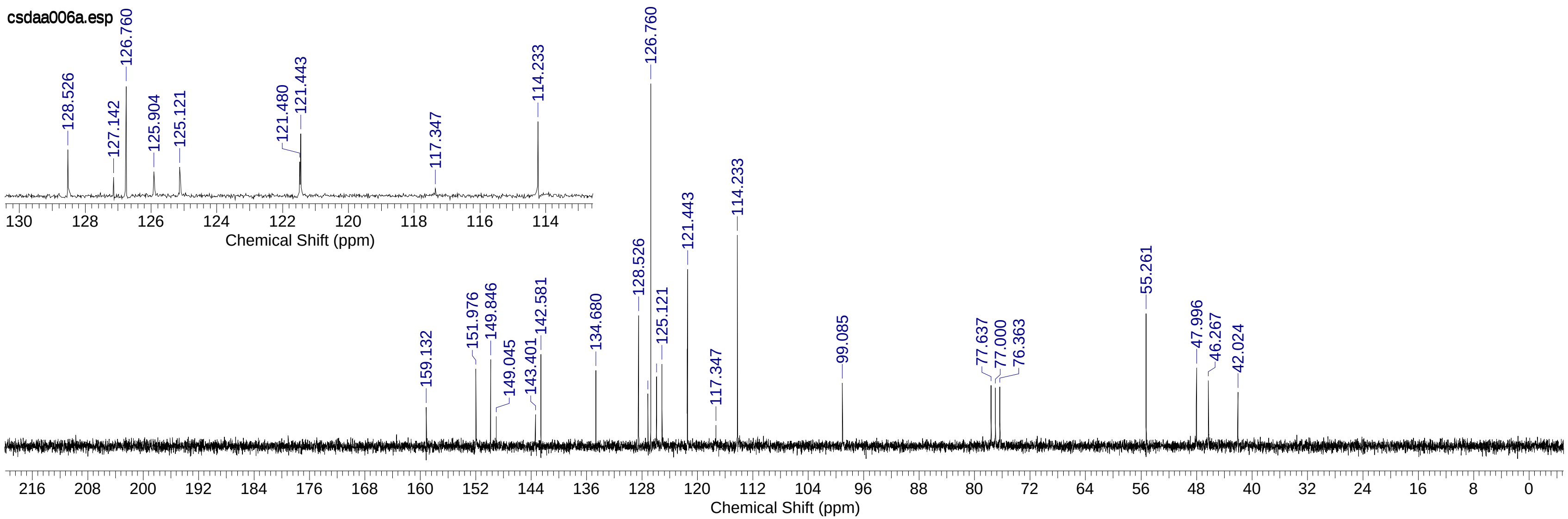
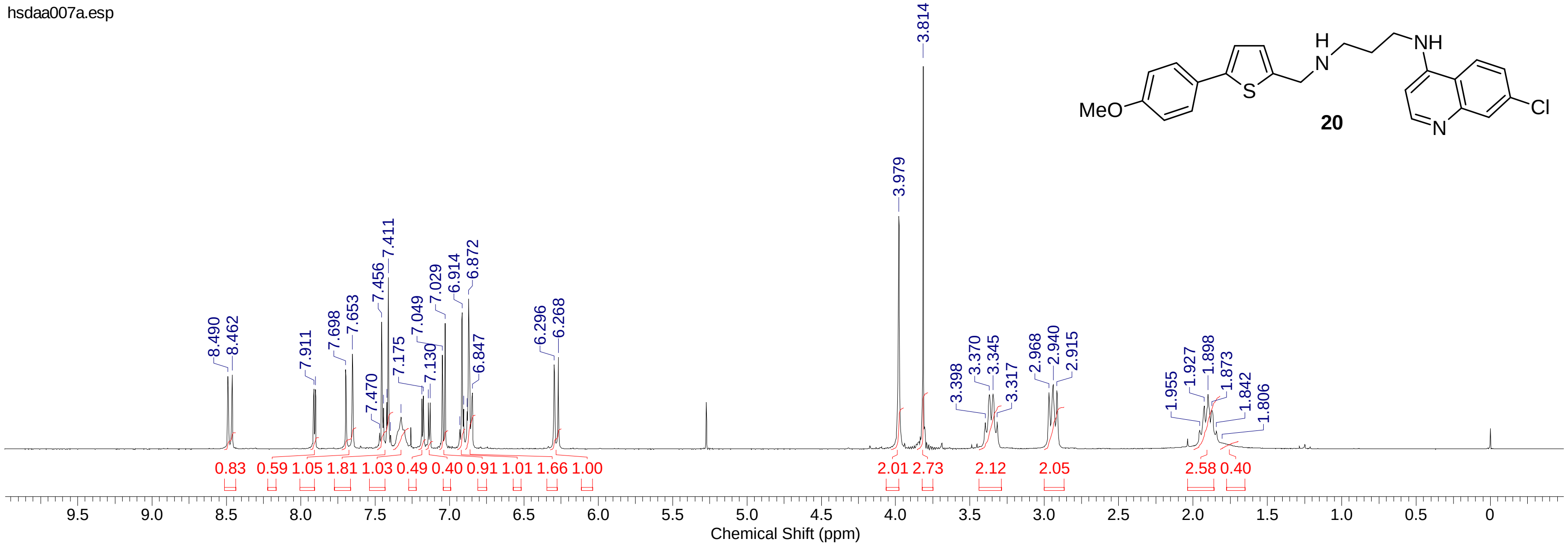
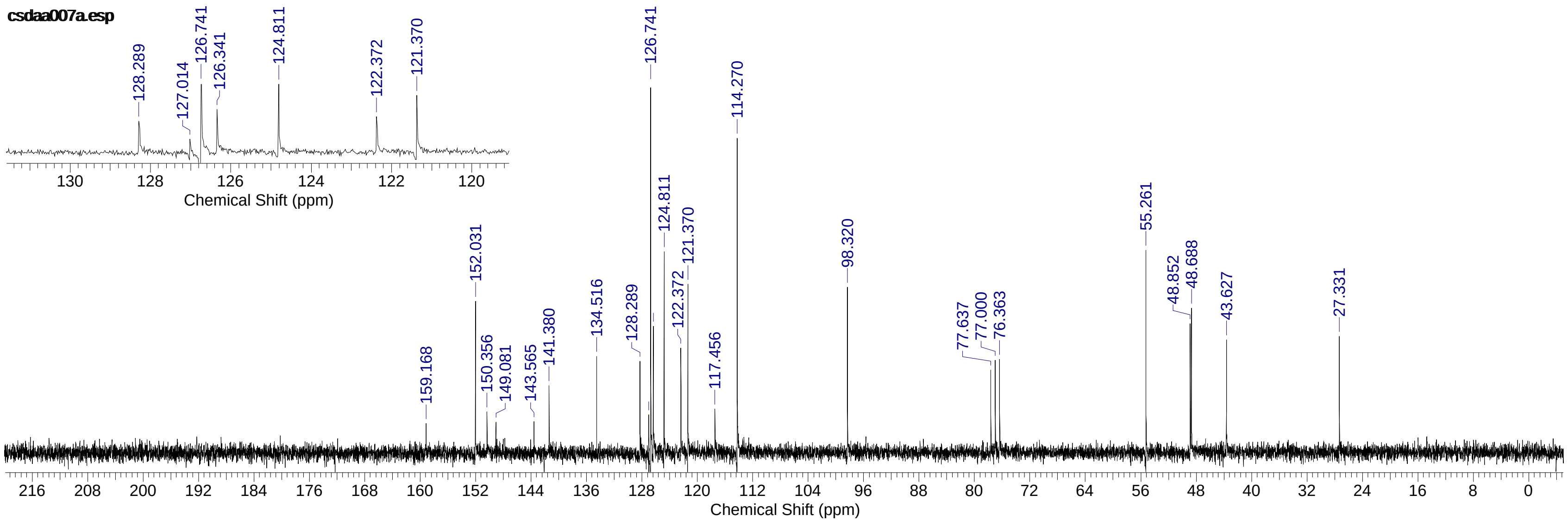
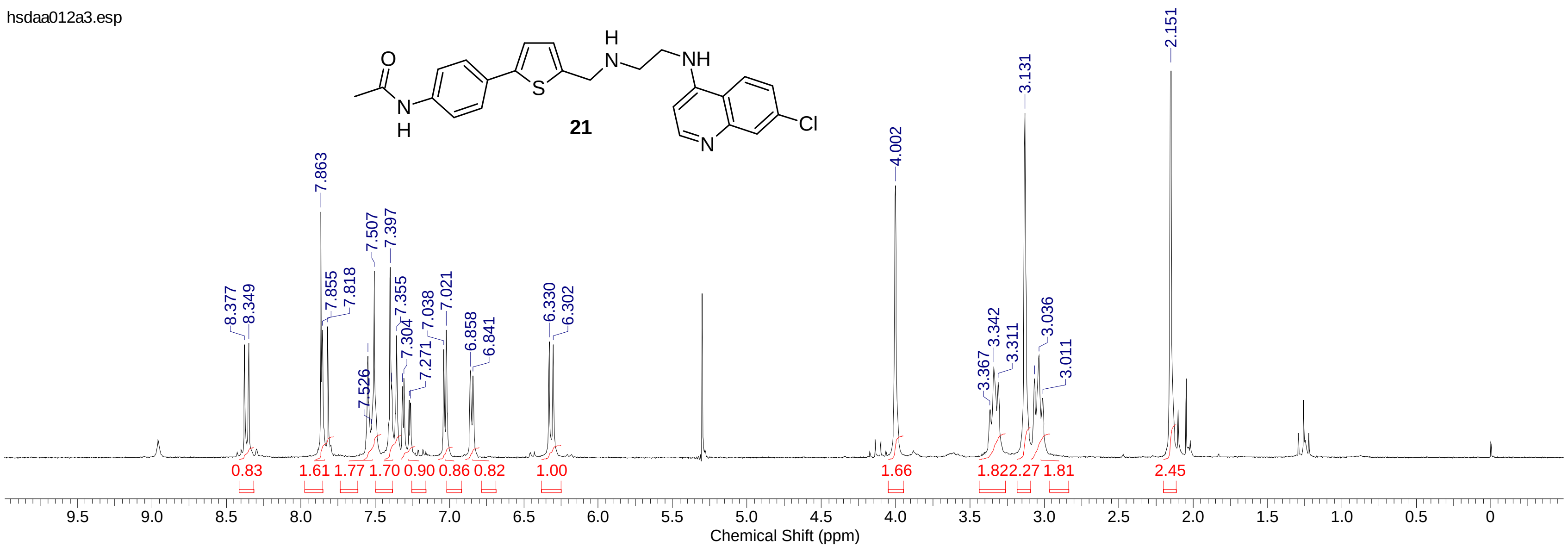


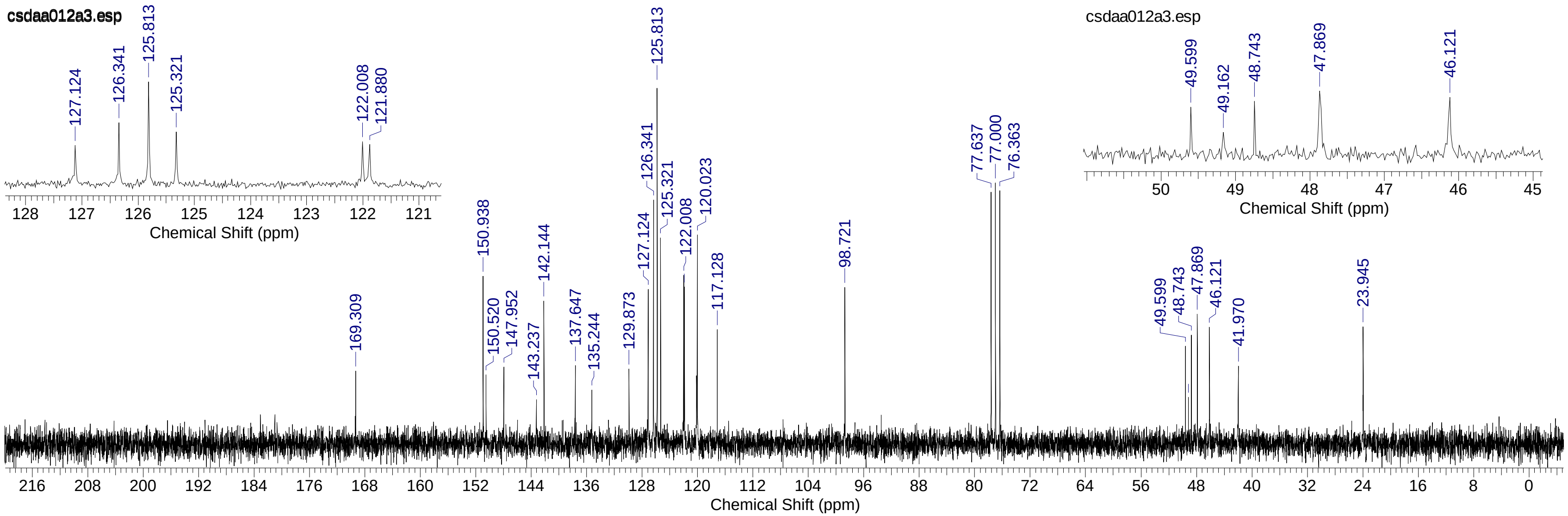
N-(7-chloroquinolin-4-yl)-N'-{[5-(4-methoxyphenyl)thiophen-2-yl]methyl}propane-1,3-diamine (20)



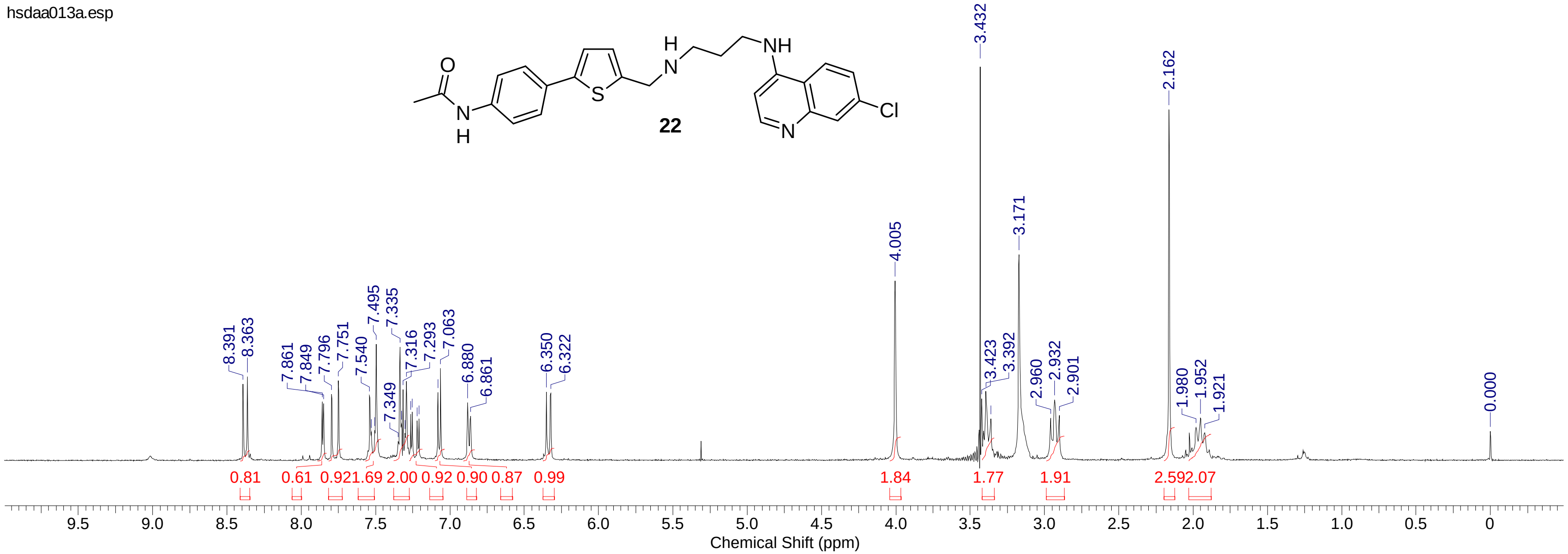


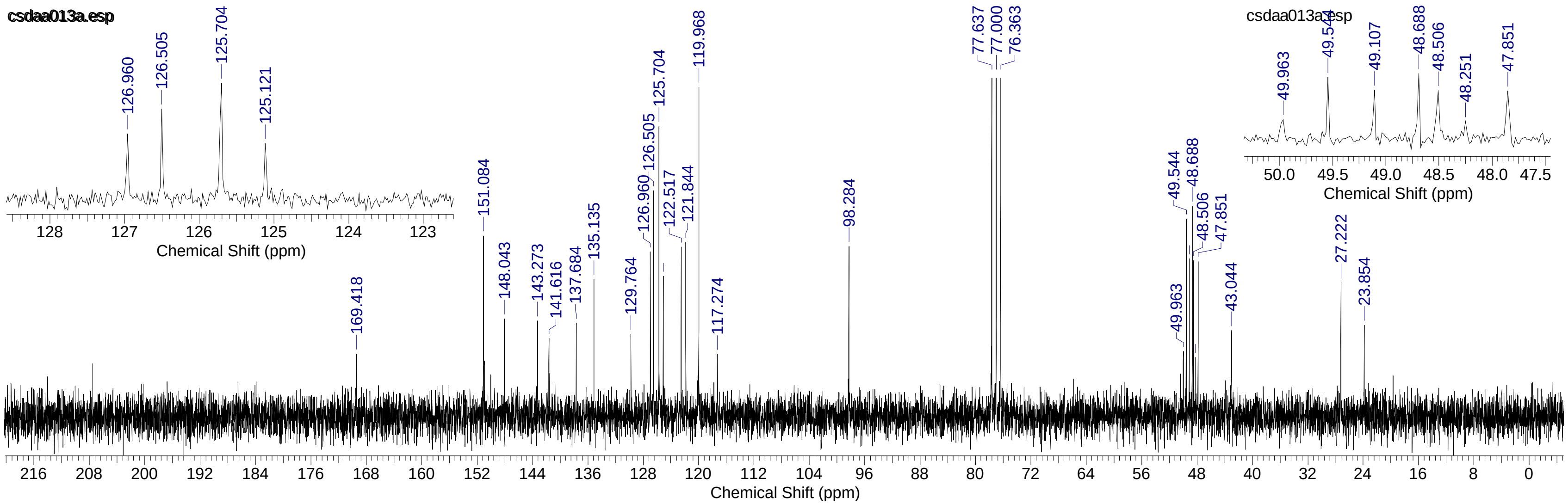
_N_-(4-{5-[({2-[(7-chloroquinolin-4-yl)amino]ethyl}amino)methyl]thiophen-2-yl}phenyl)acetamide (21)



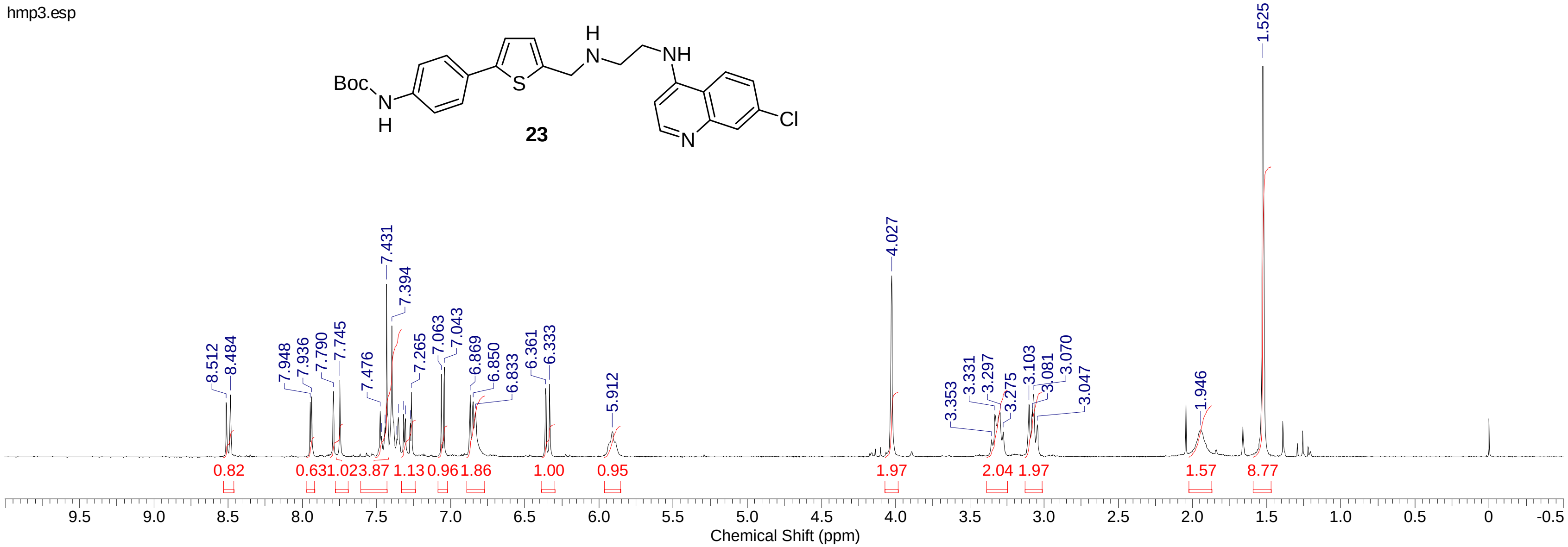


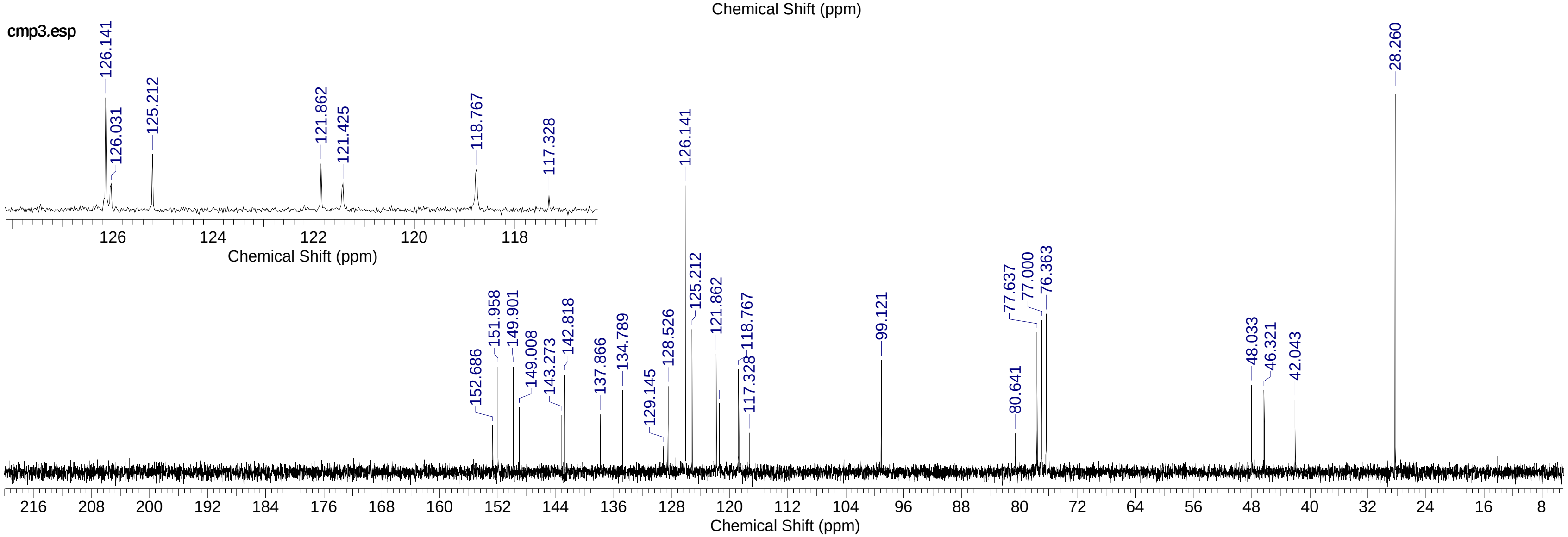
_N_-(4-{5-[({3-[(7-chloroquinolin-4-yl)amino]propyl}amino)methyl]thiophen-2-yl}phenyl)acetamide (22)



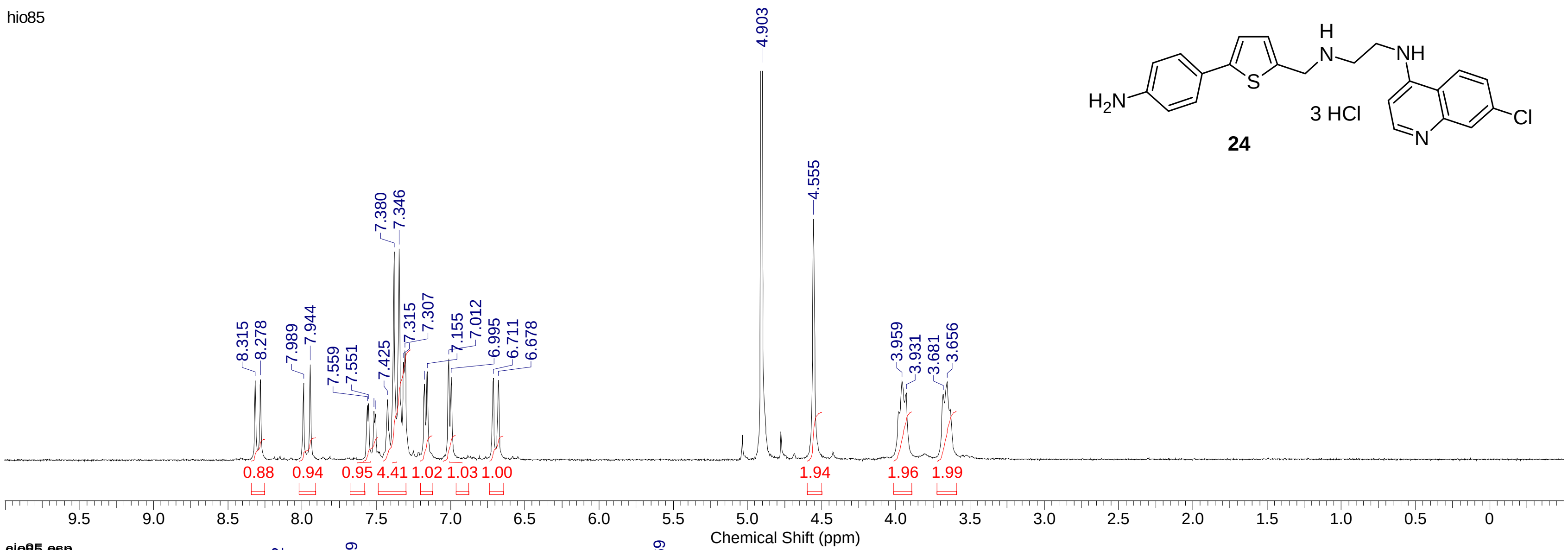


***tert*-Butyl (4-{5-[({2-[(7-chloroquinolin-4-yl)amino]ethyl}amino)methyl]thiophen-2-yl}phenyl)carbamate (23)**





N-{[5-(4-Aminophenyl)thiophen-2-yl]methyl}-N'-(7-chloroquinolin-4-yl)ethane-1,2-diamine trihydrochloride (24)



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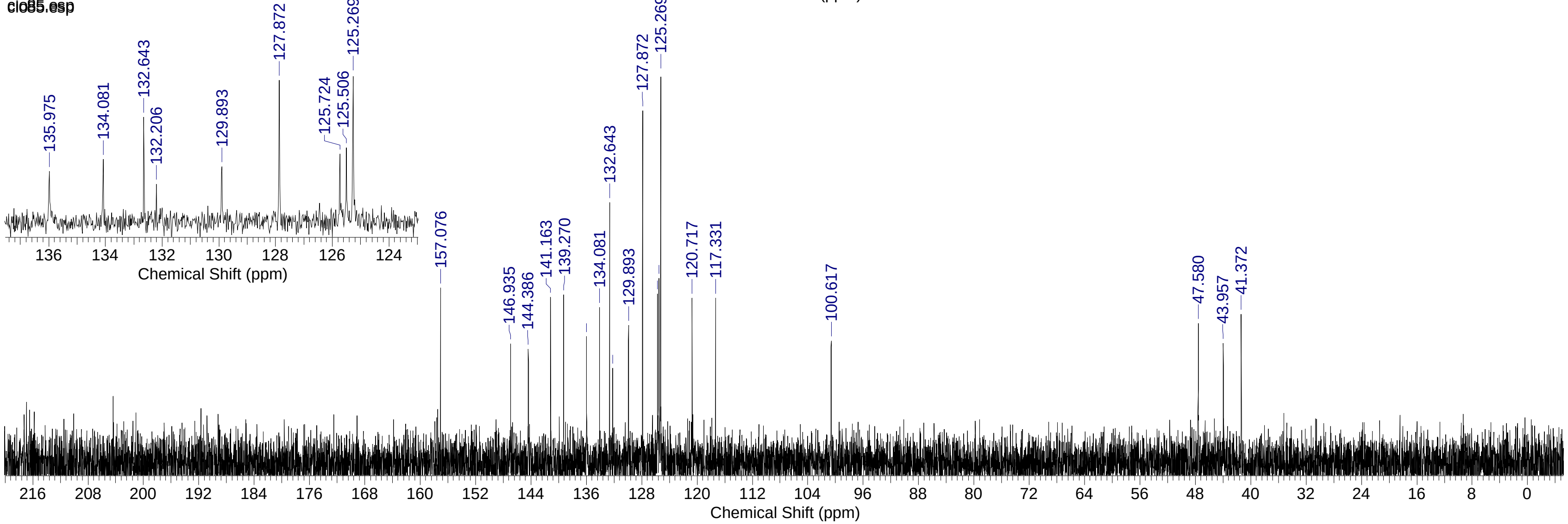
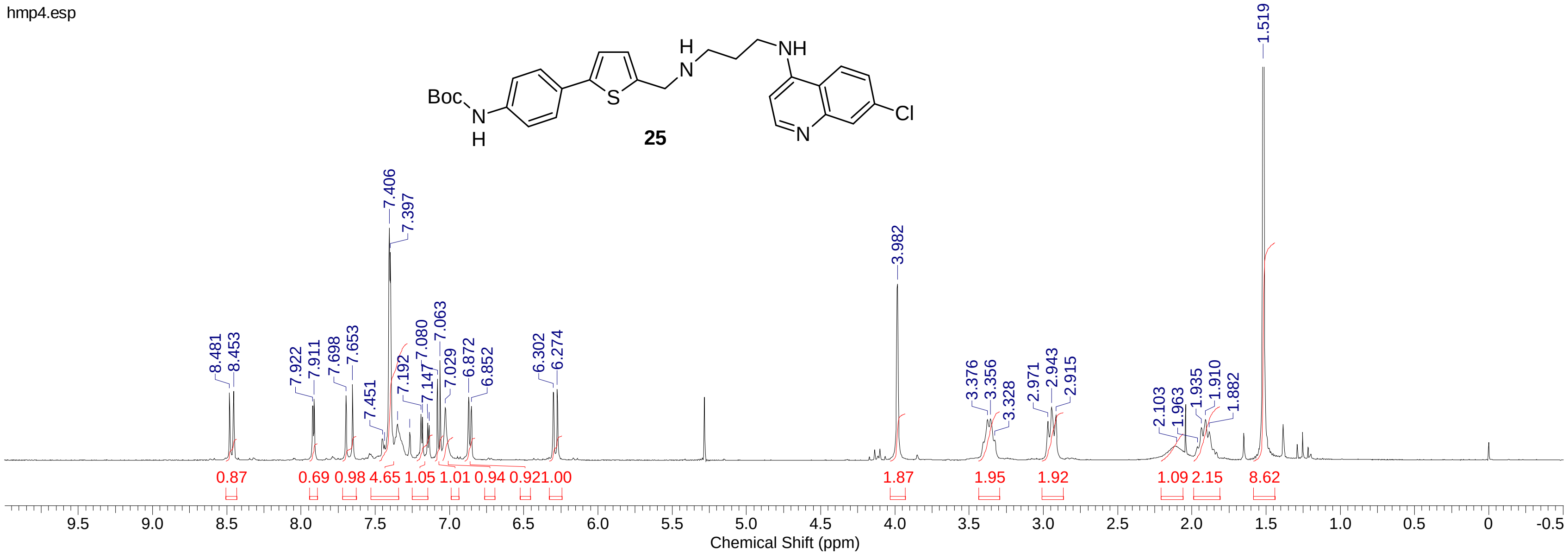
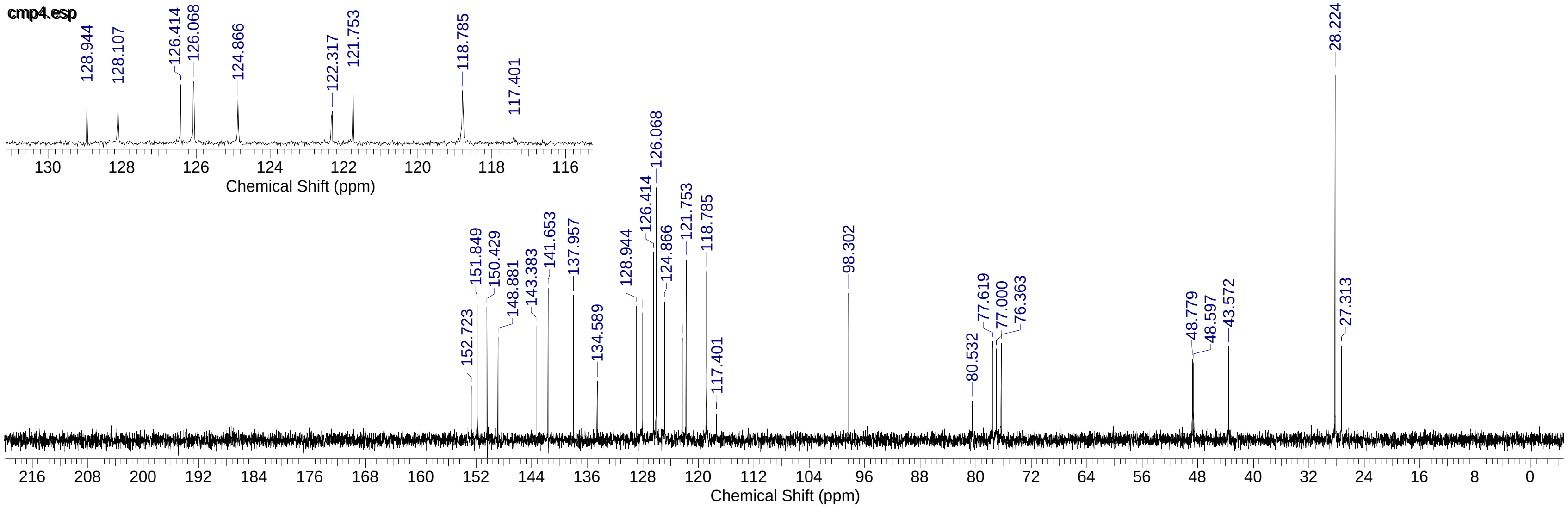
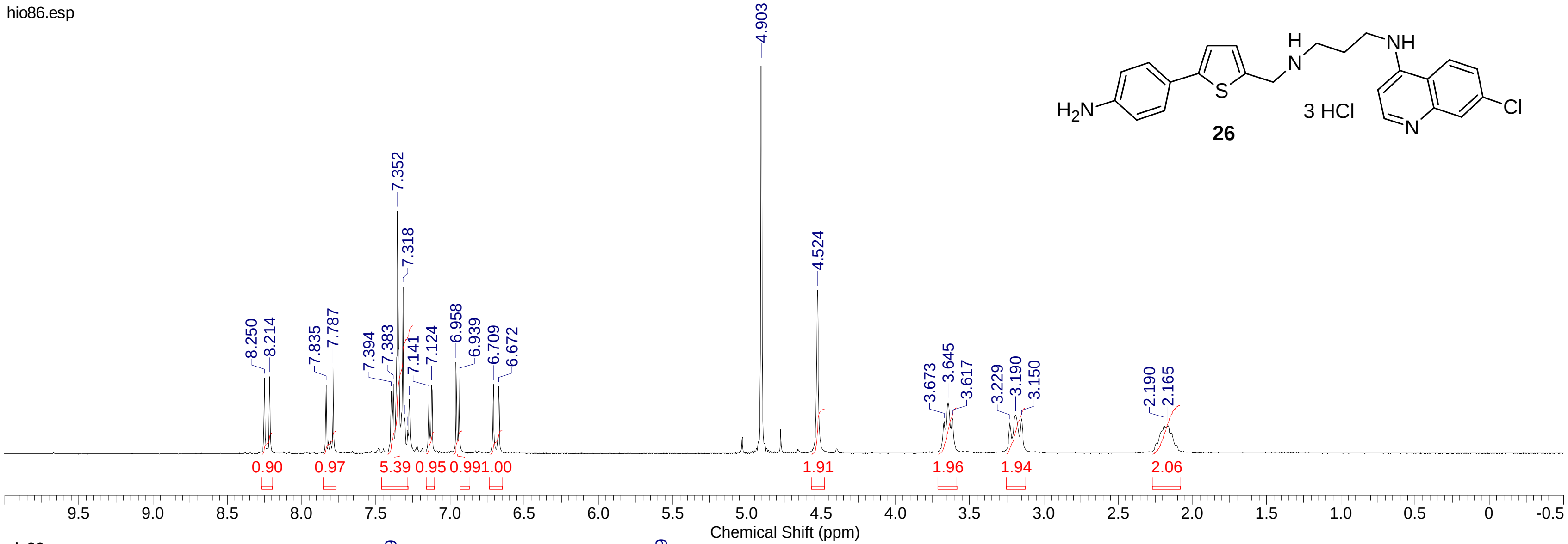


tert-Butyl (4-{5-[({3-[(7-chloroquinolin-4-yl)amino]propyl}amino)methyl]thiophen-2-yl}phenyl)carbamate (25)





***N*-{[5-(4-Aminophenyl)thiophen-2-yl]methyl}-*N'*-(7-chloroquinolin-4-yl)propane-1,3-diamine trihydrochloride (26)**



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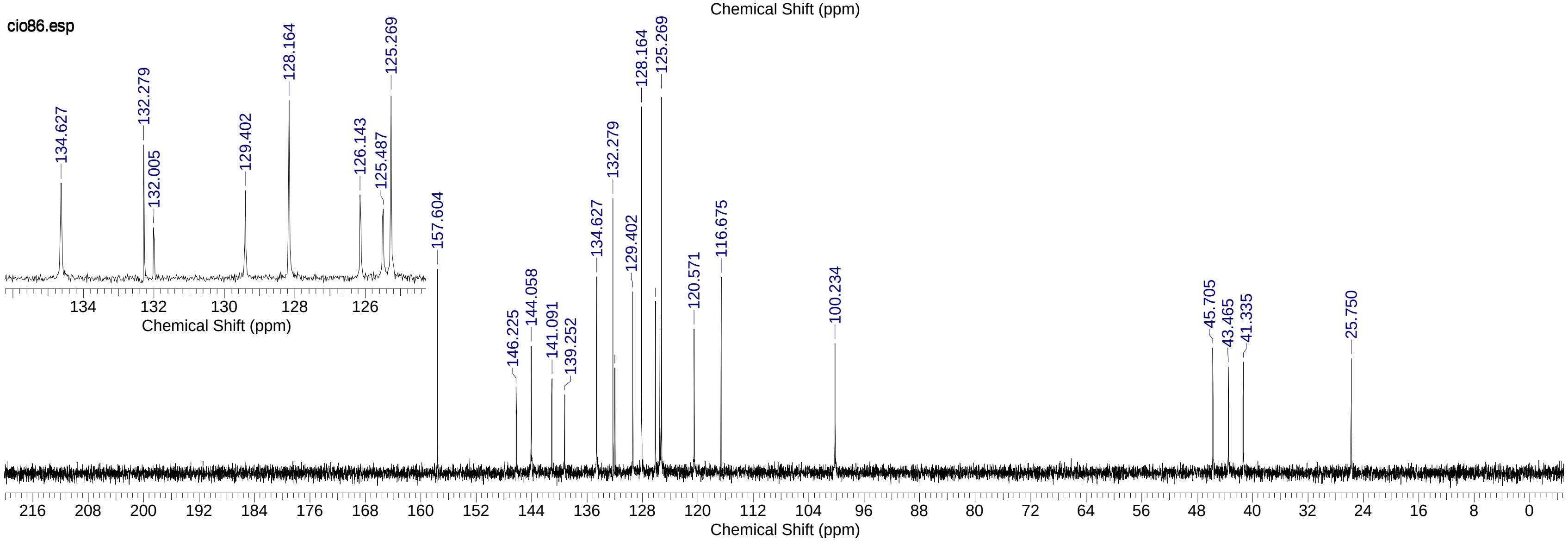
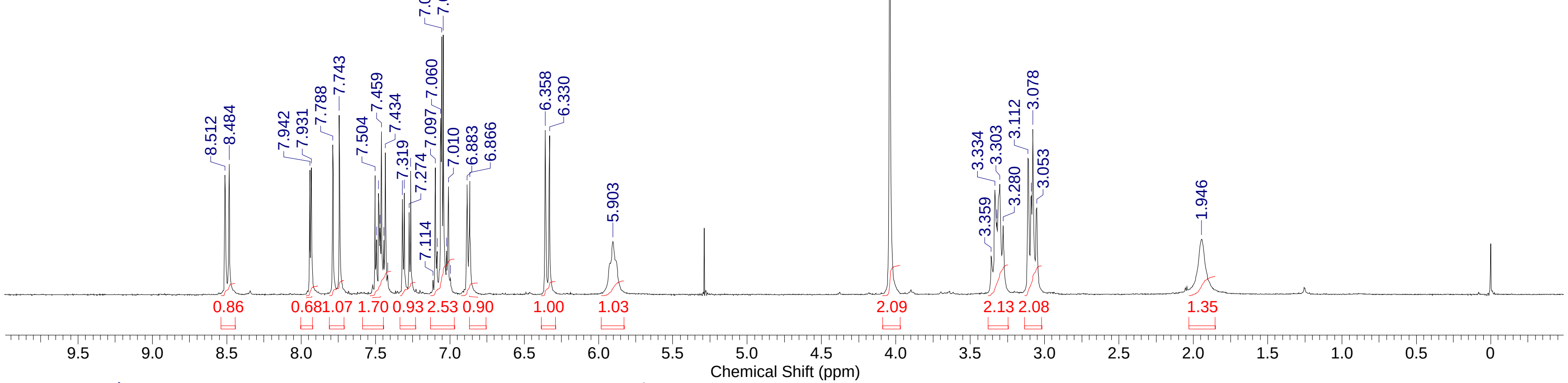
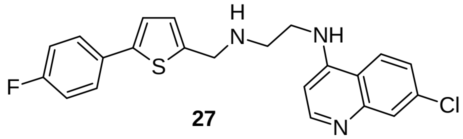


N-(7-Chloroquinolin-4-yl)-*N*'-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}ethane-1,2-diamine (27)





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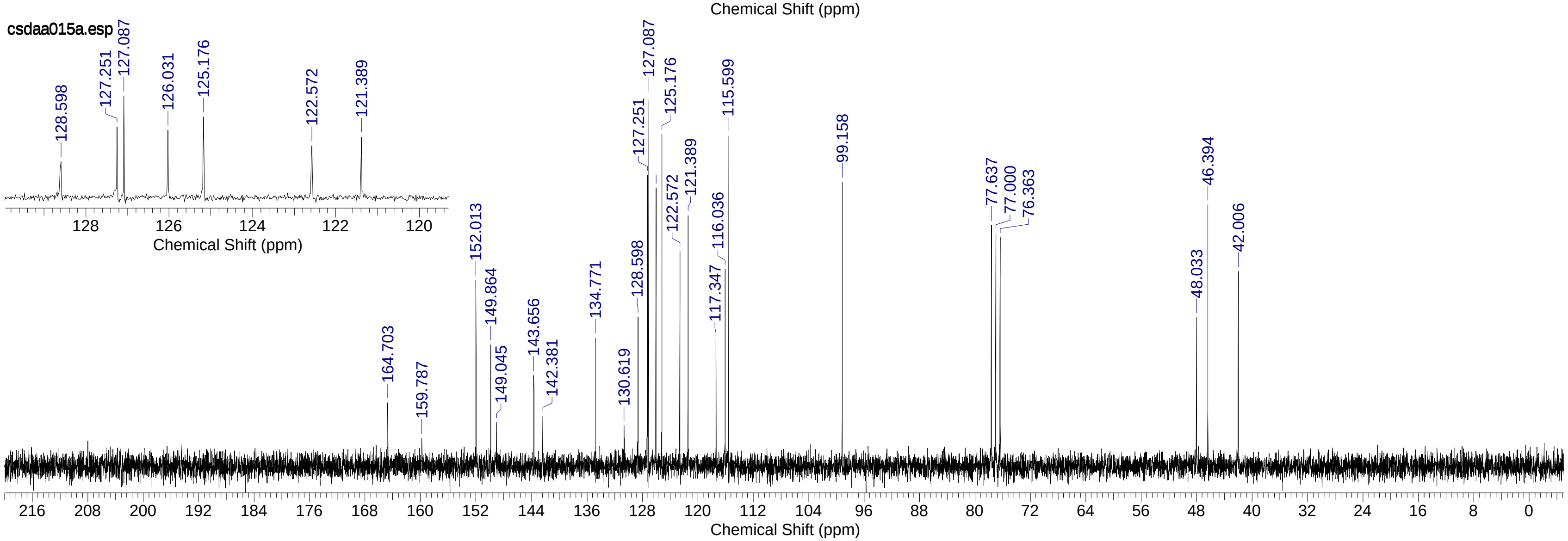
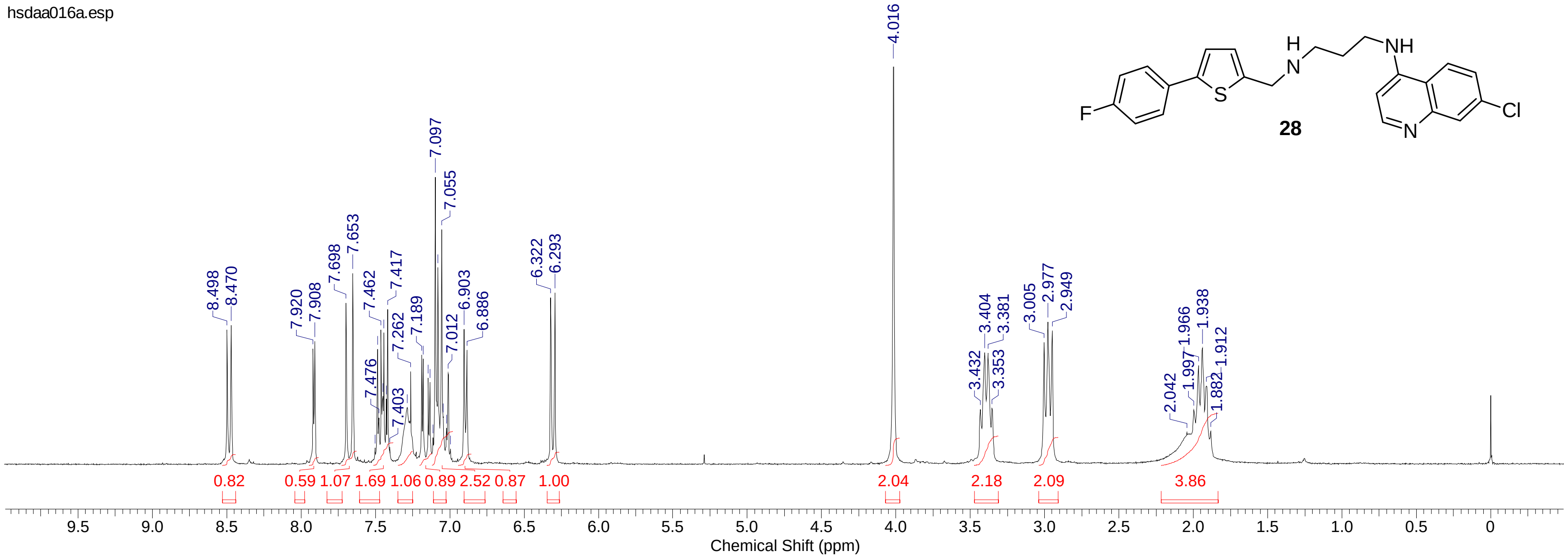
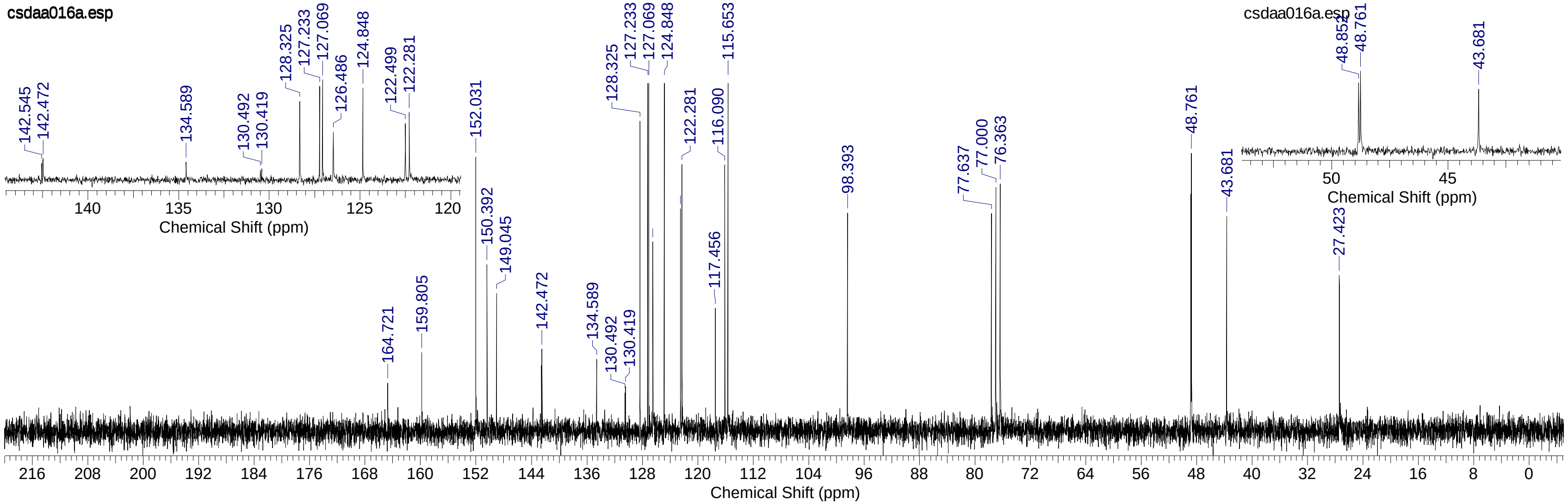
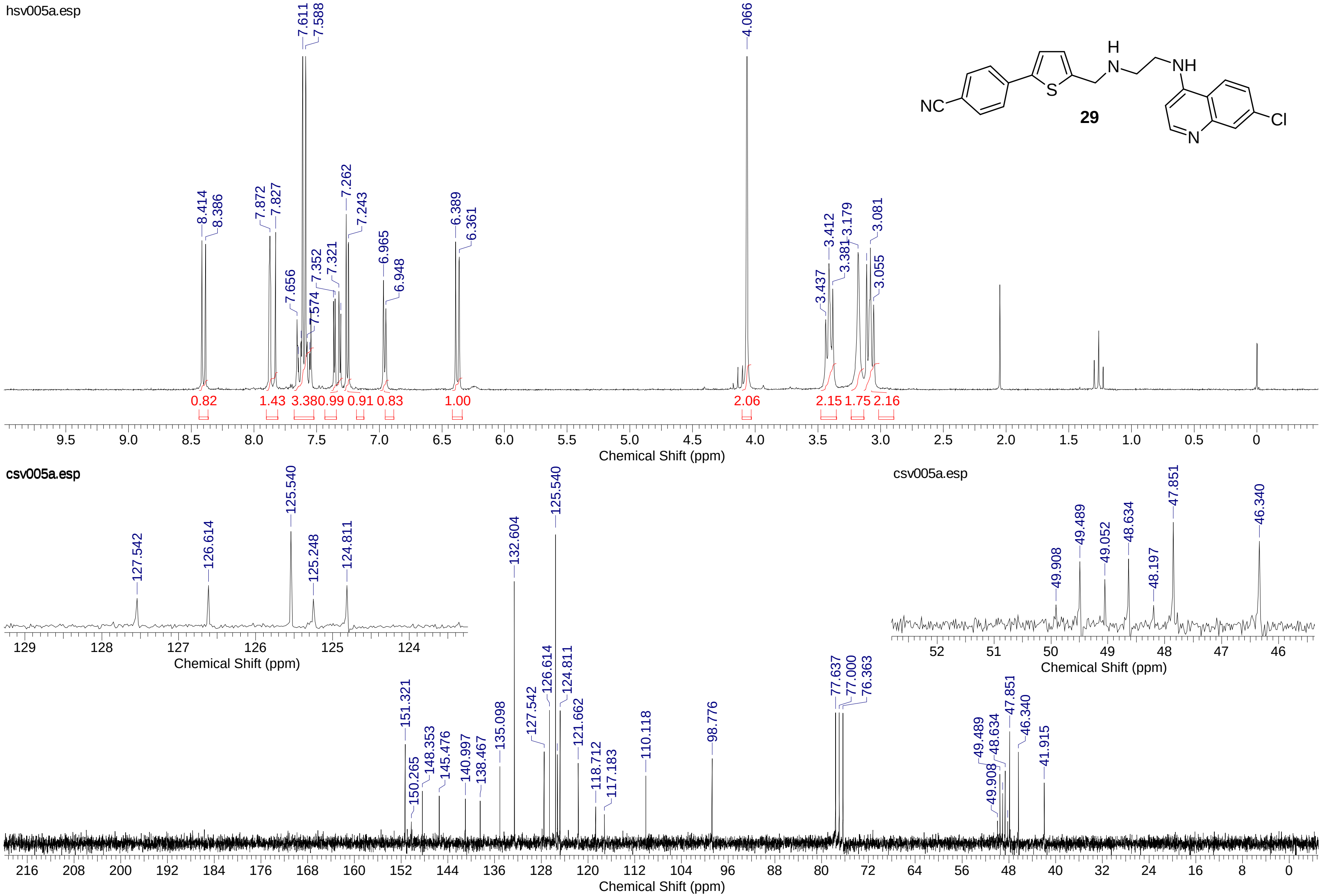


N-(7-Chloroquinolin-4-yl)-*N*'-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}propane-1,3-diamine (28)

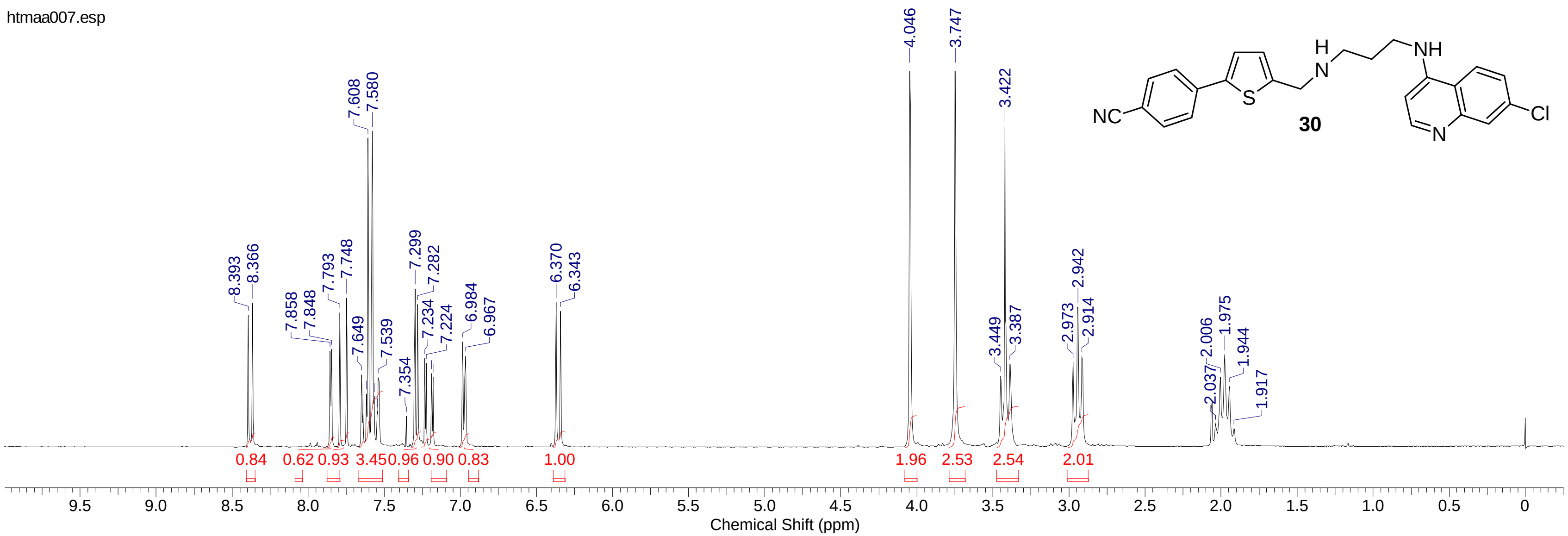


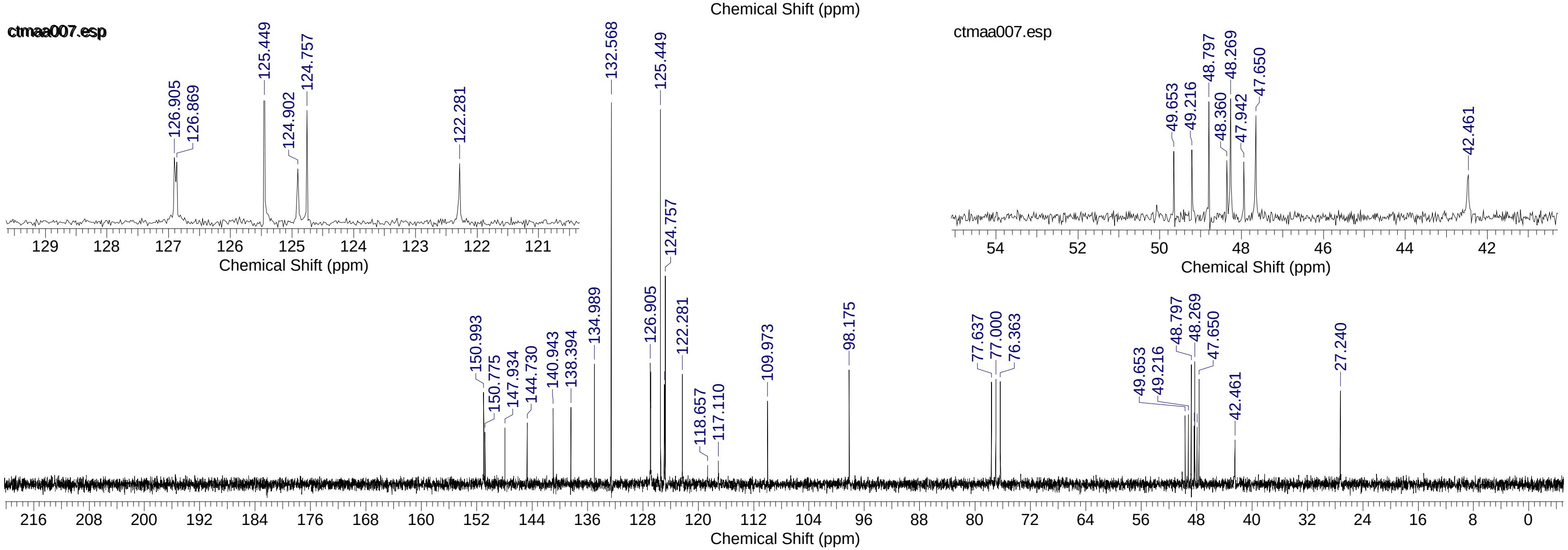


4-{5-[({2-[(7-Chloroquinolin-4-yl)amino]ethyl}amino)methyl]thiophen-2-yl}benzonitrile (29)

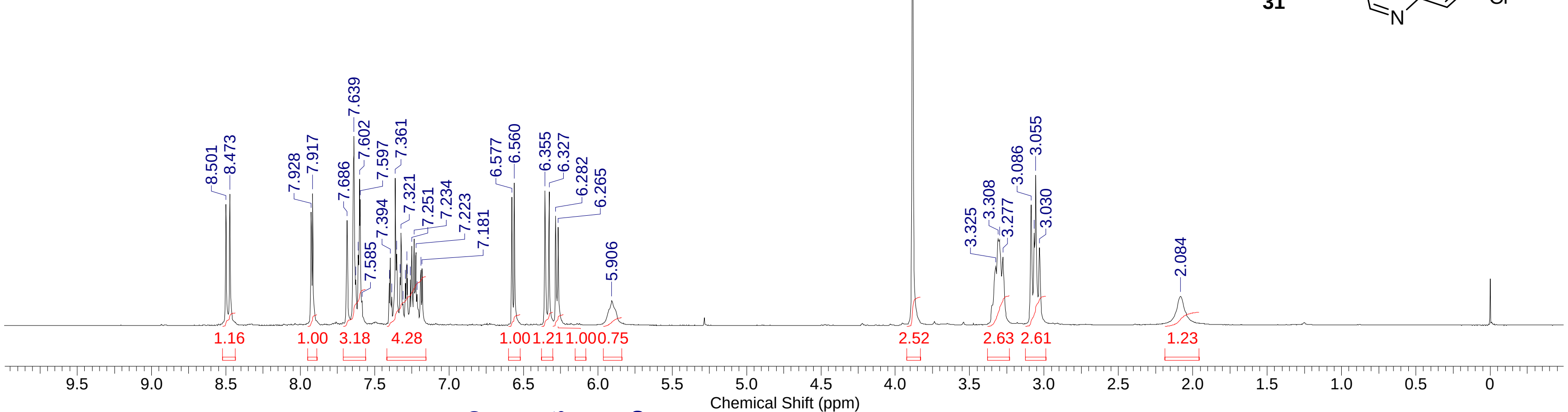


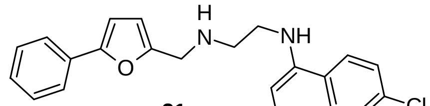
4-{5-[({3-[(7-Chloroquinolin-4-yl)amino]propyl}amino)methyl]thiophen-2-yl}benzonitrile (30)





N-(7-chloroquinolin-4-yl)-*N'*-[(5-phenylfuran-2-yl)methyl]ethane-1,2-diamine (31)





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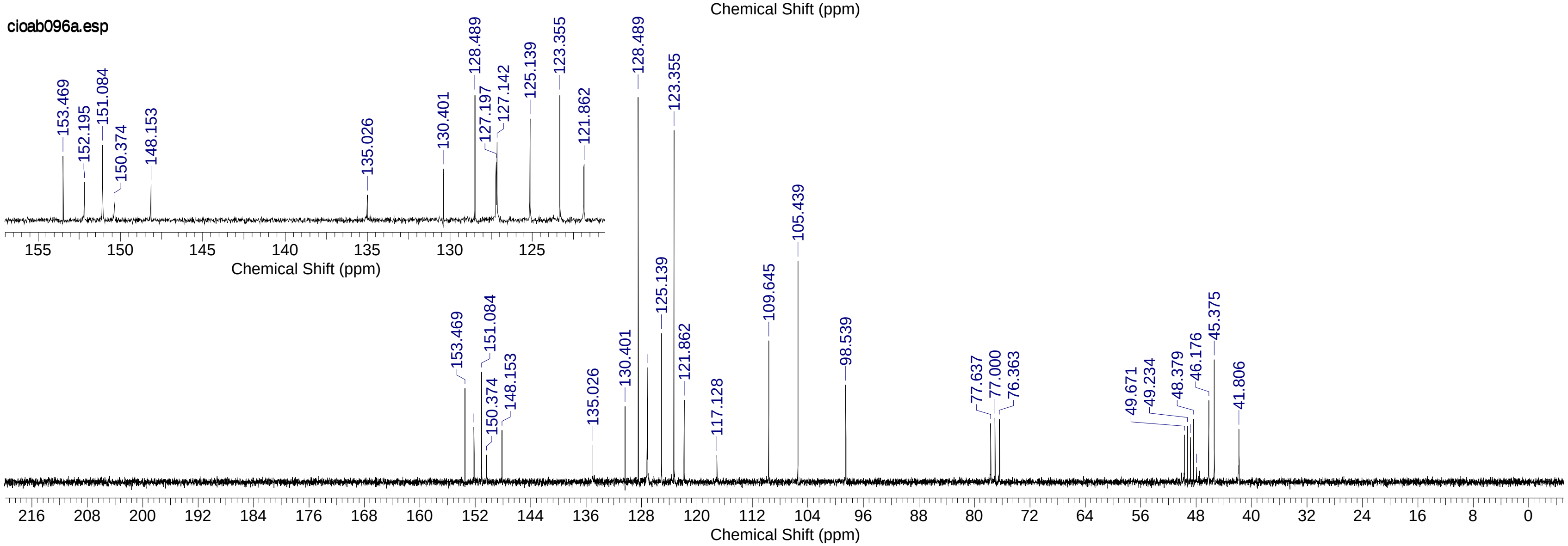
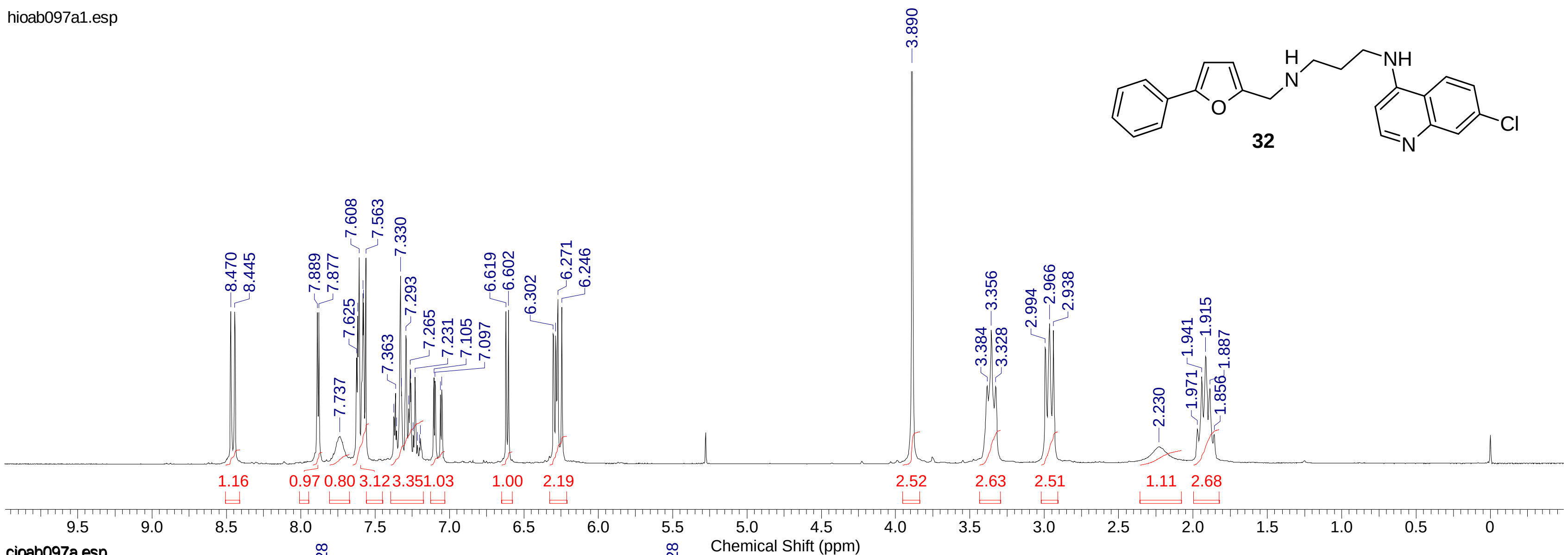
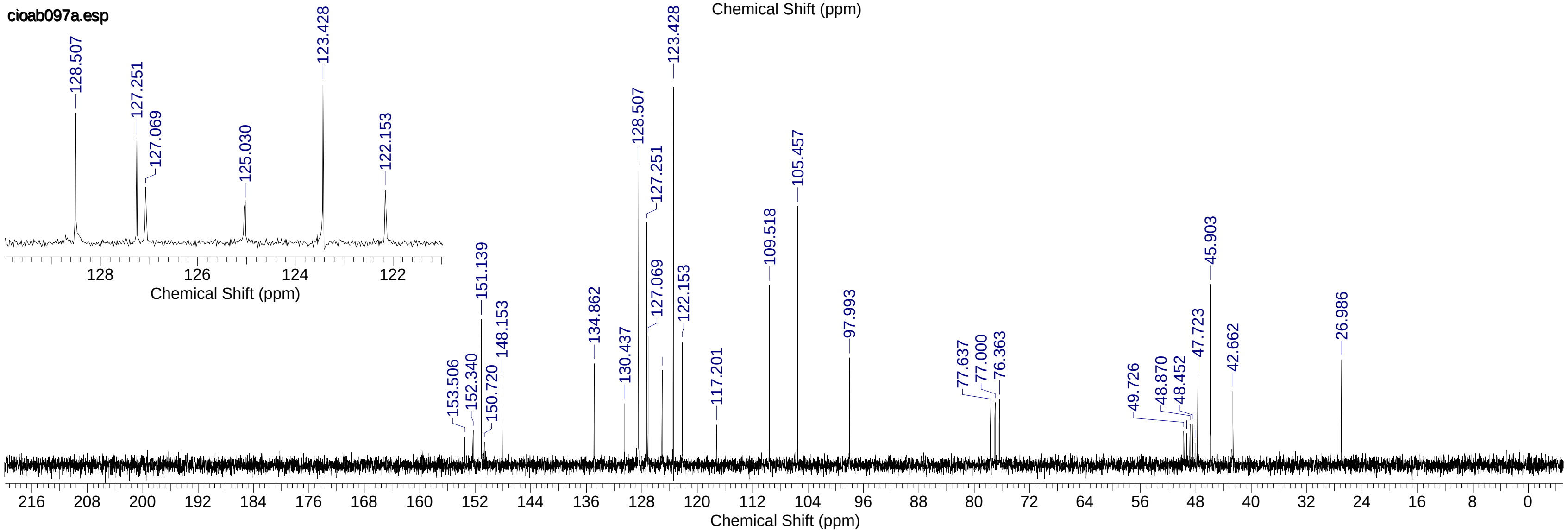
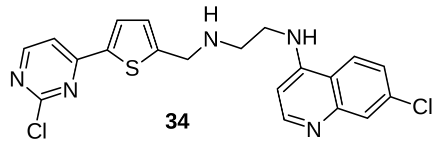


***N*-(7-chloroquinolin-4-yl)-*N'*-[(5-phenylfuran-2-yl)methyl]propane-1,3-diamine (32)**

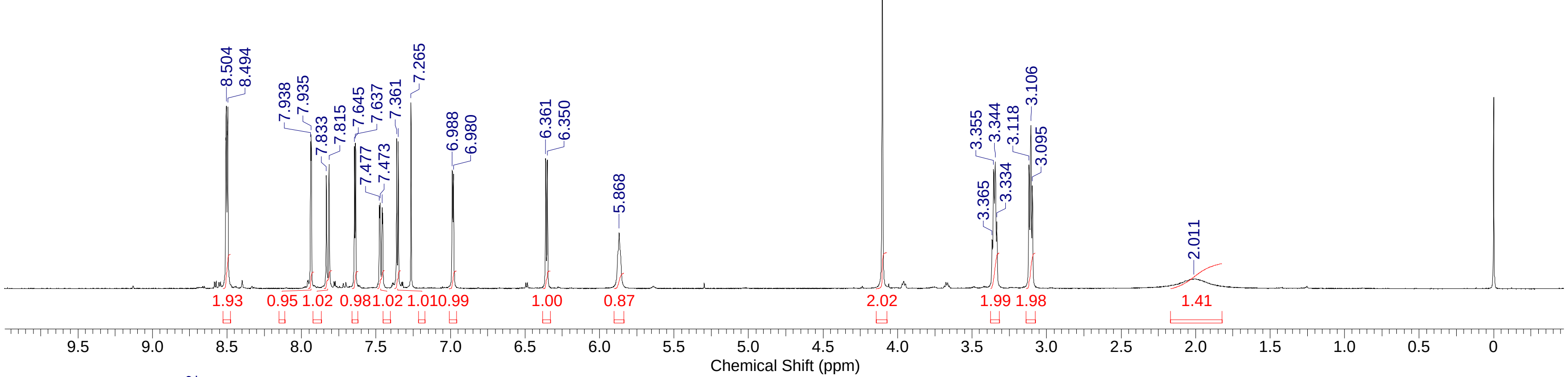


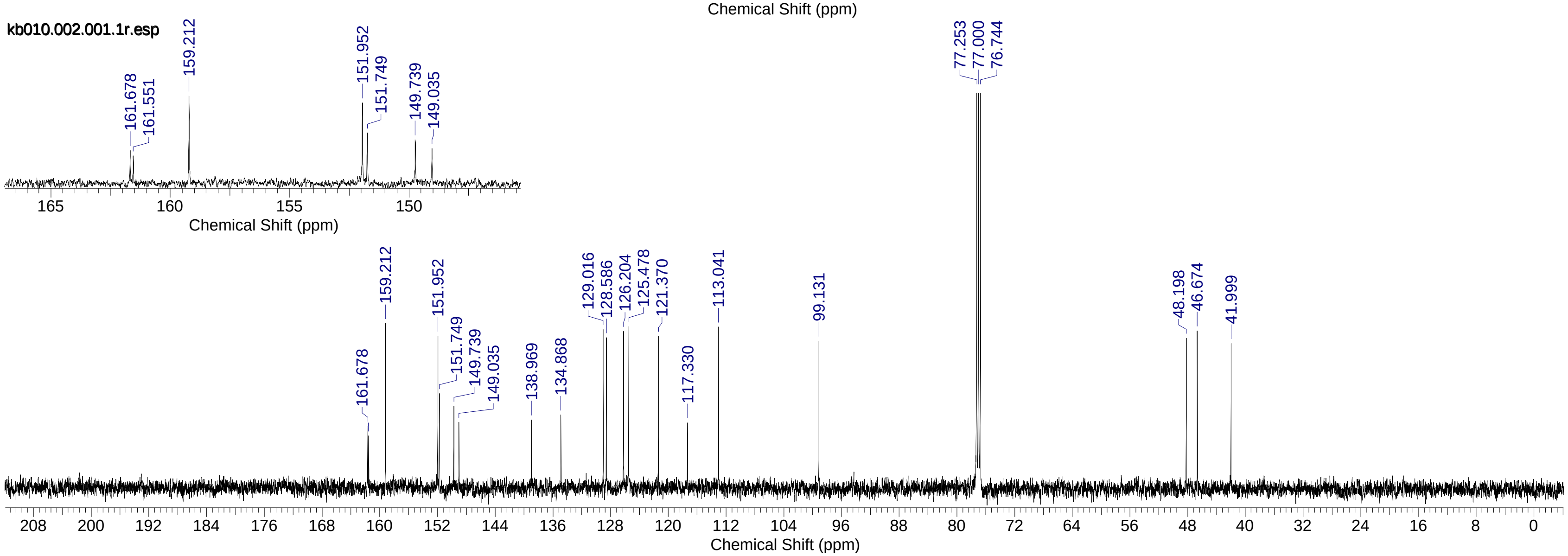


N-{[5-(2-Chloropyrimidin-4-yl)thiophen-2-yl]methyl}-*N*'-(7-chloroquinolin-4-yl)ethane-1,2-diamine (34)

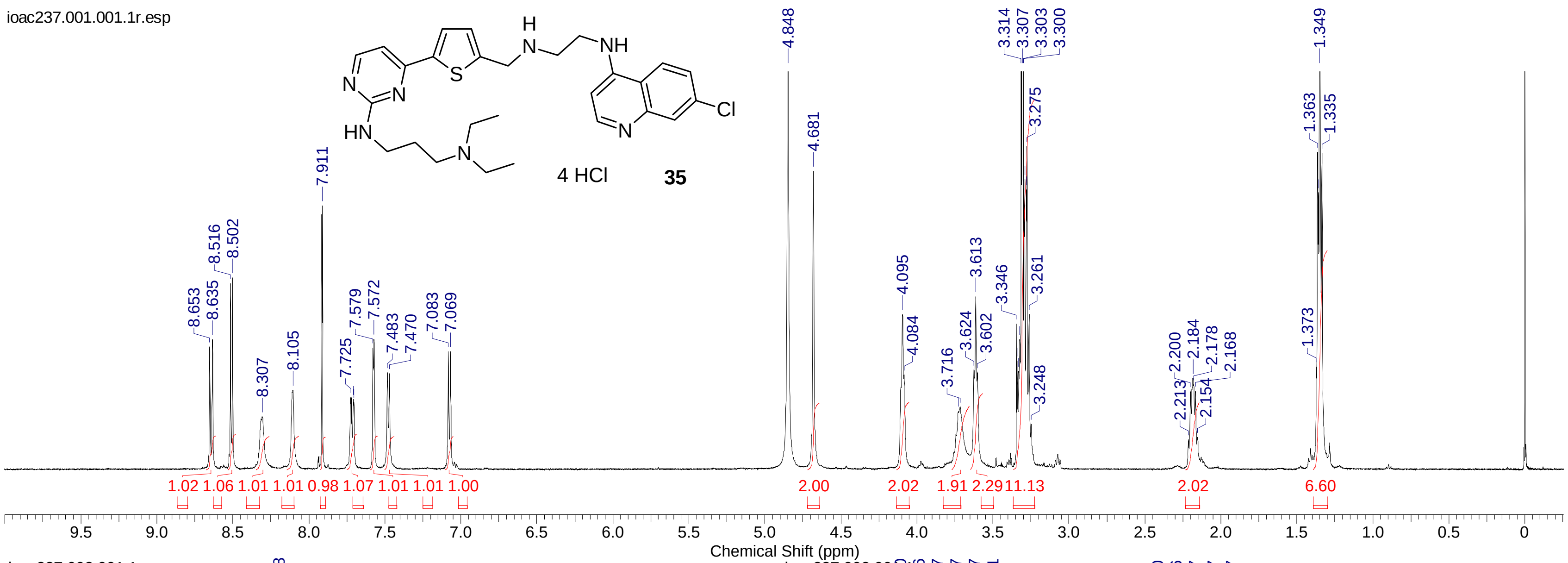


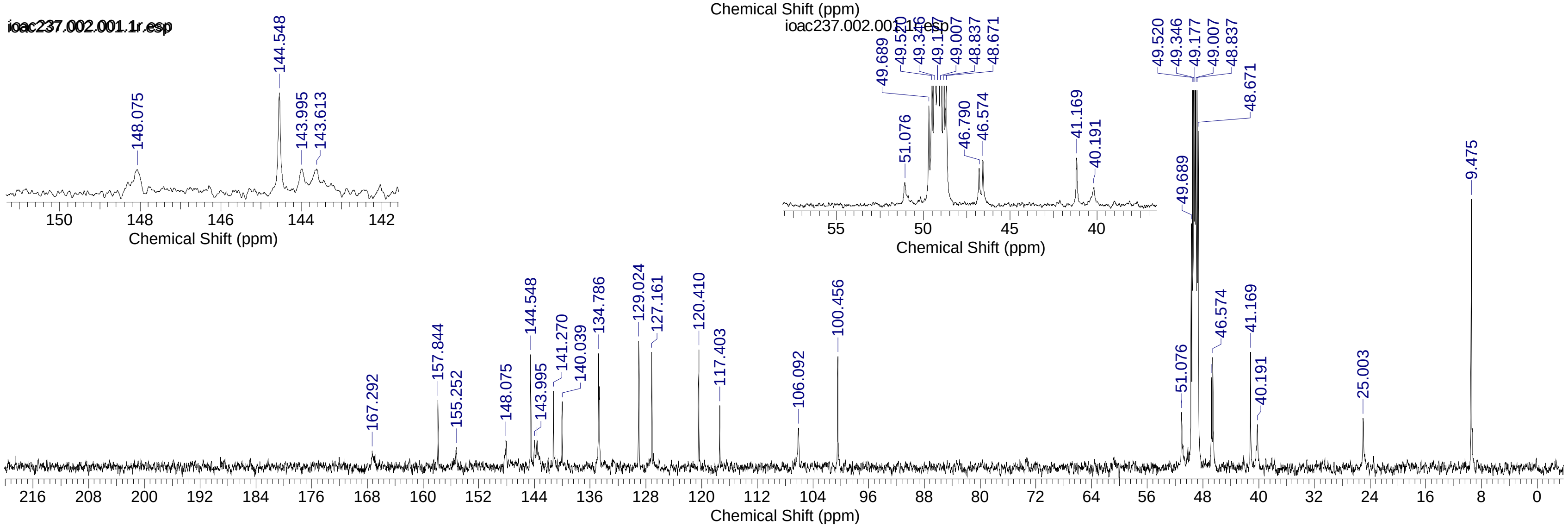
34



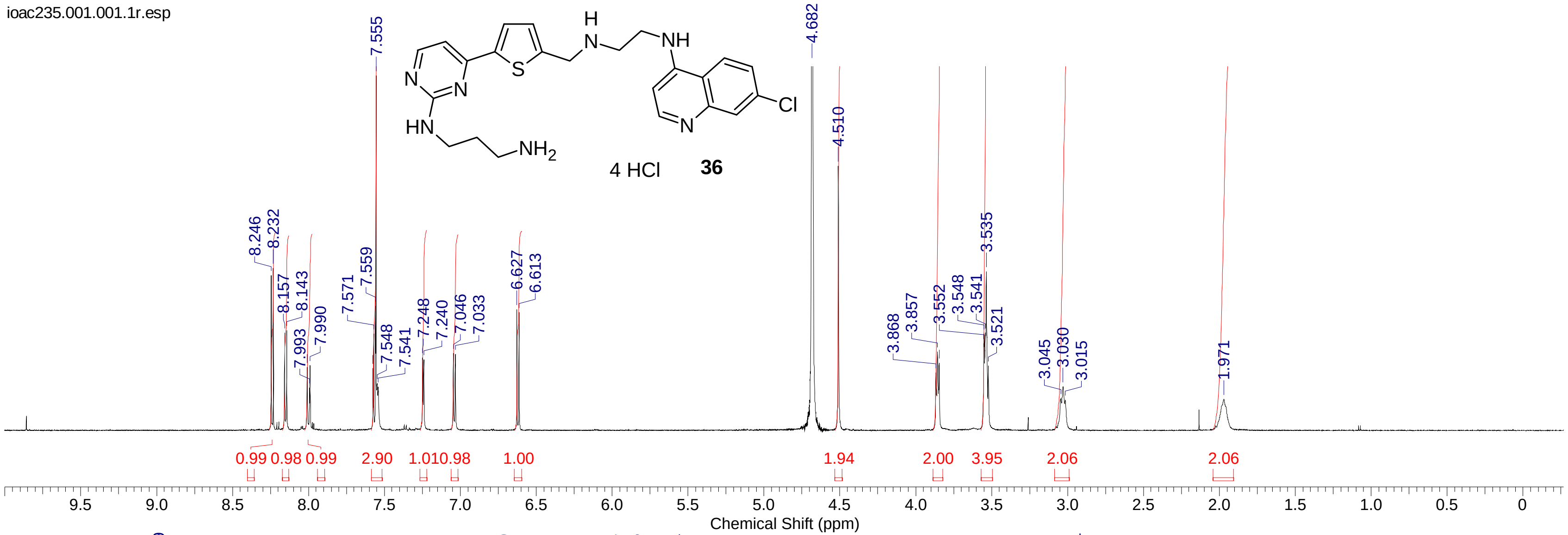


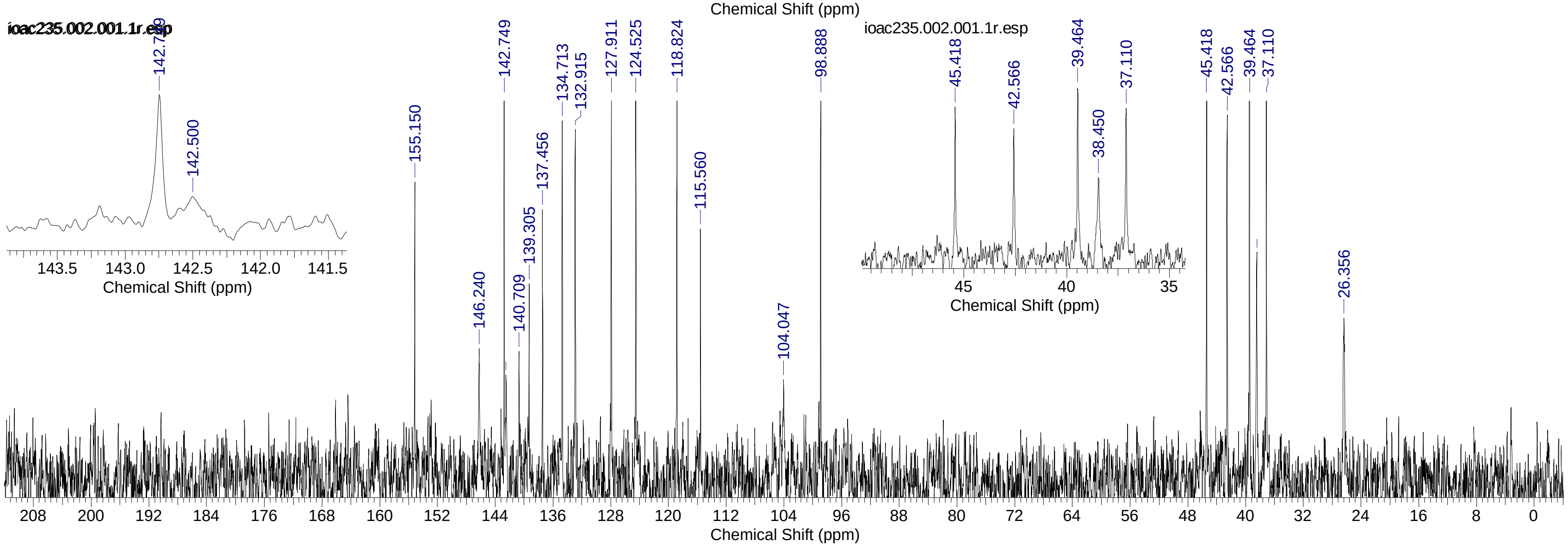
_N'_-(4-{5-[({2-[(7-chloroquinolin-4-yl)amino]ethyl}amino)methyl]thiophen-2-yl}pyrimidin-2-yl)-_N_,_N_-diethylpropane-1,3-diamine tetrahydrochloride (35)



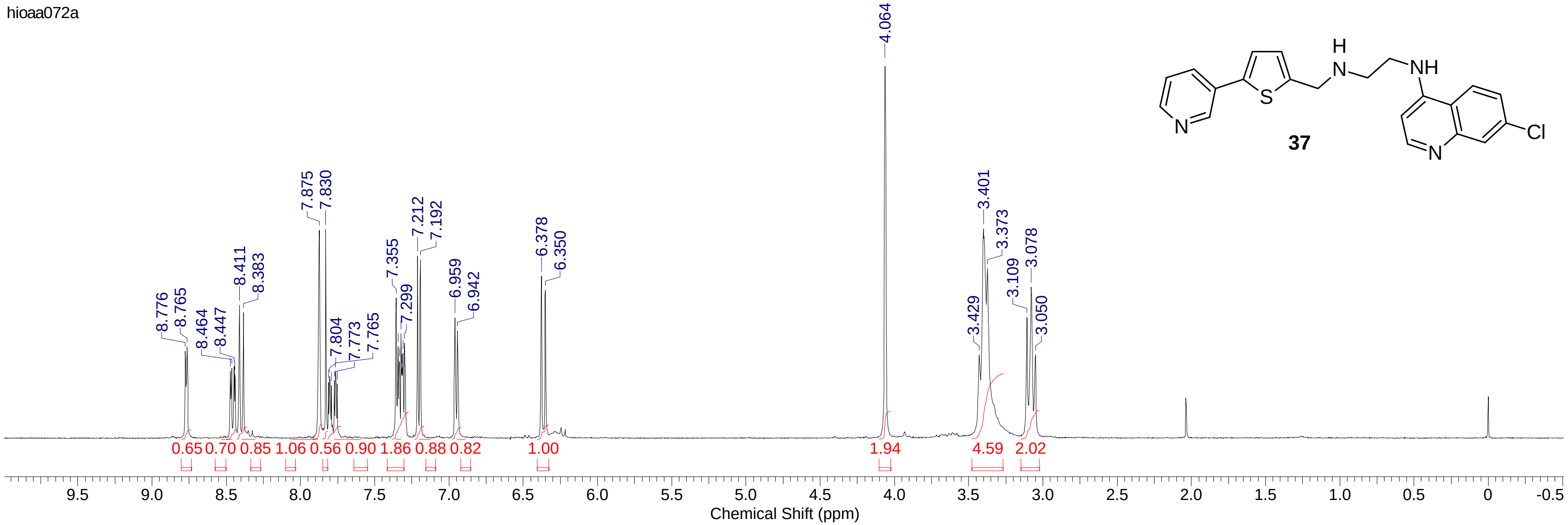


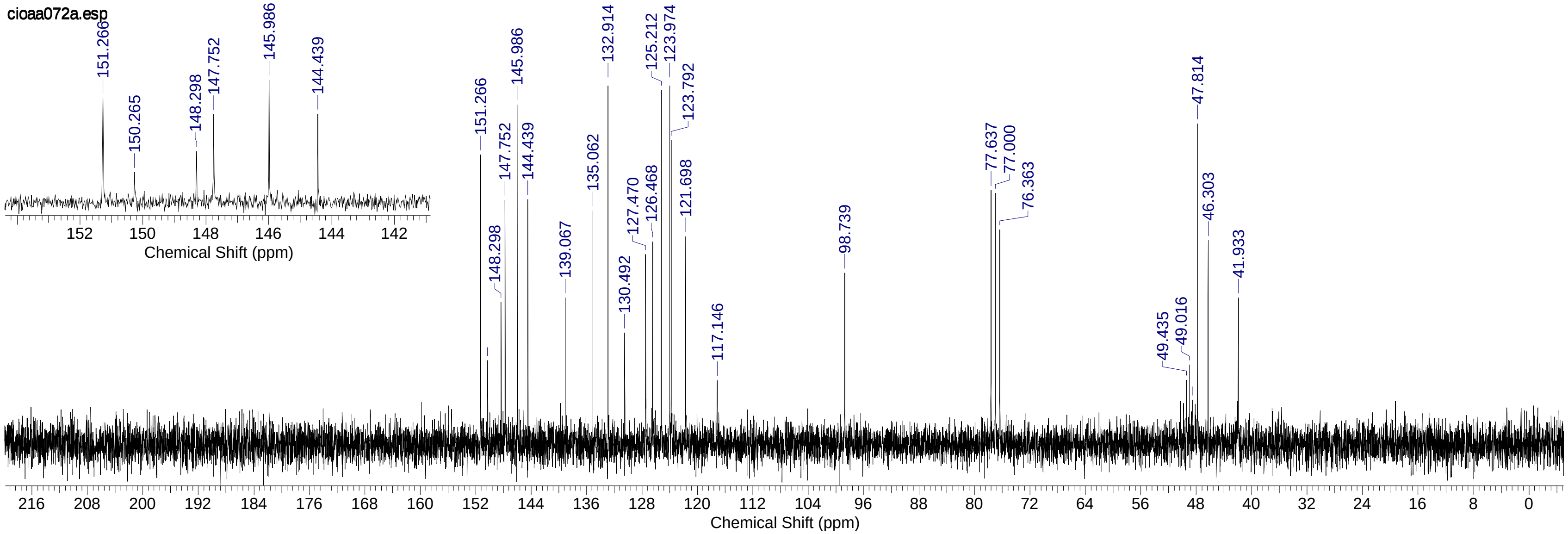
***N*-(4-{5-[({2-[(7-chloroquinolin-4-yl)amino]ethyl}amino)methyl]thiophen-2-yl}pyrimidin-2-yl)propane-1,3-diamine tetrahydrochloride (36)**



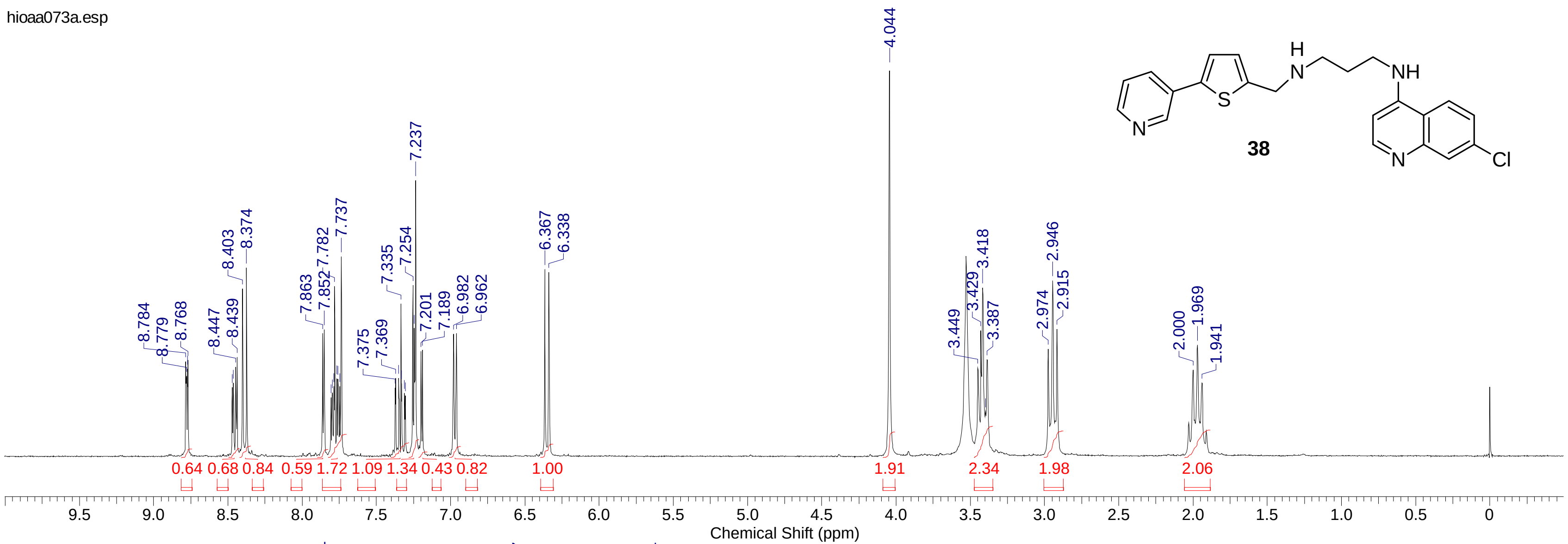


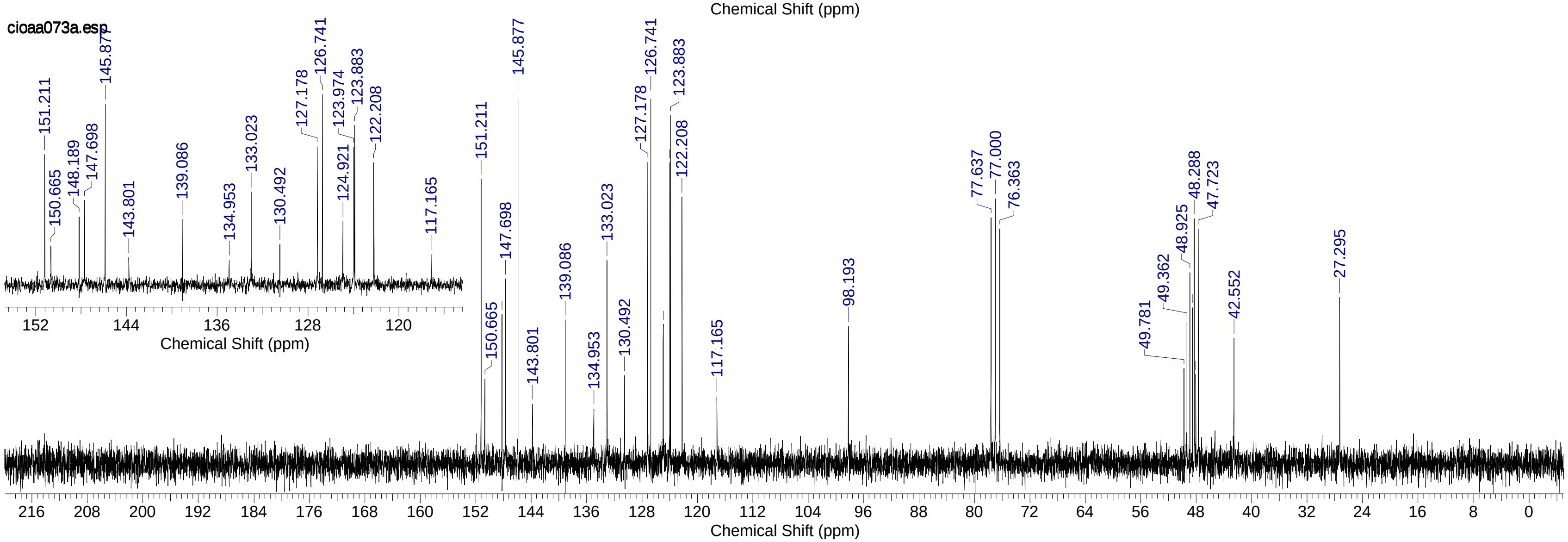
N-(7-Chloroquinolin-4-yl)-*N*'-{[5-(pyridin-3-yl)thiophen-2-yl]methyl}ethane-1,2-diamine (37)



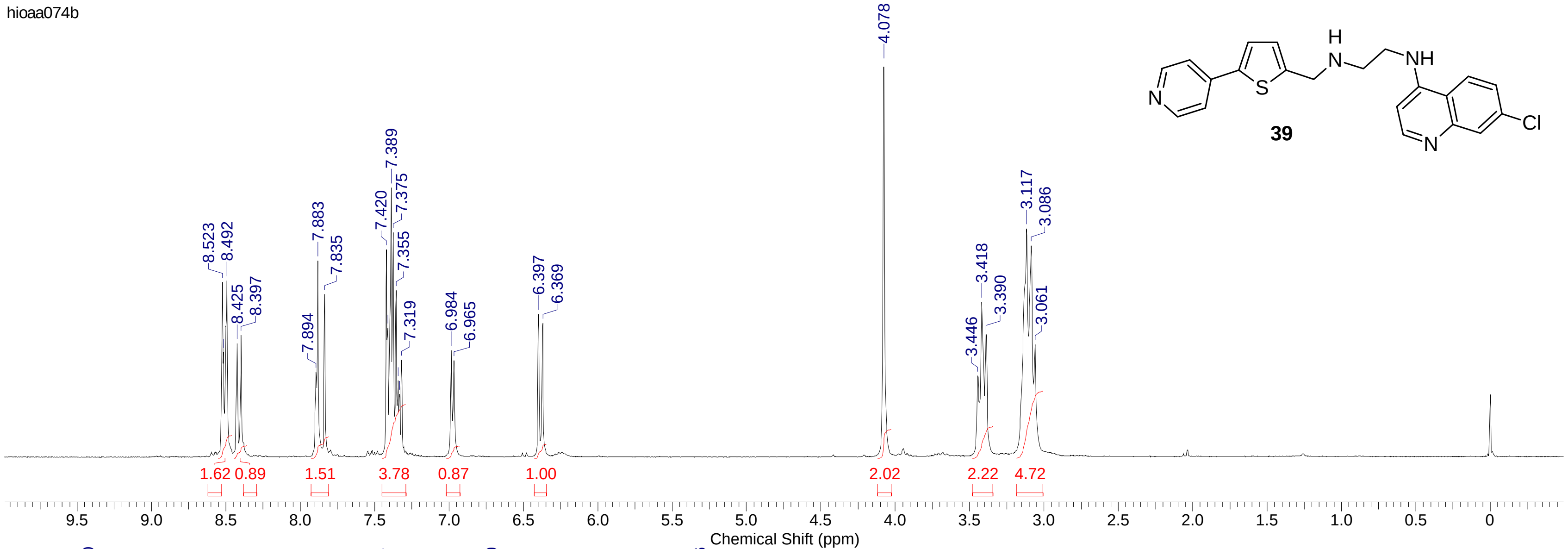


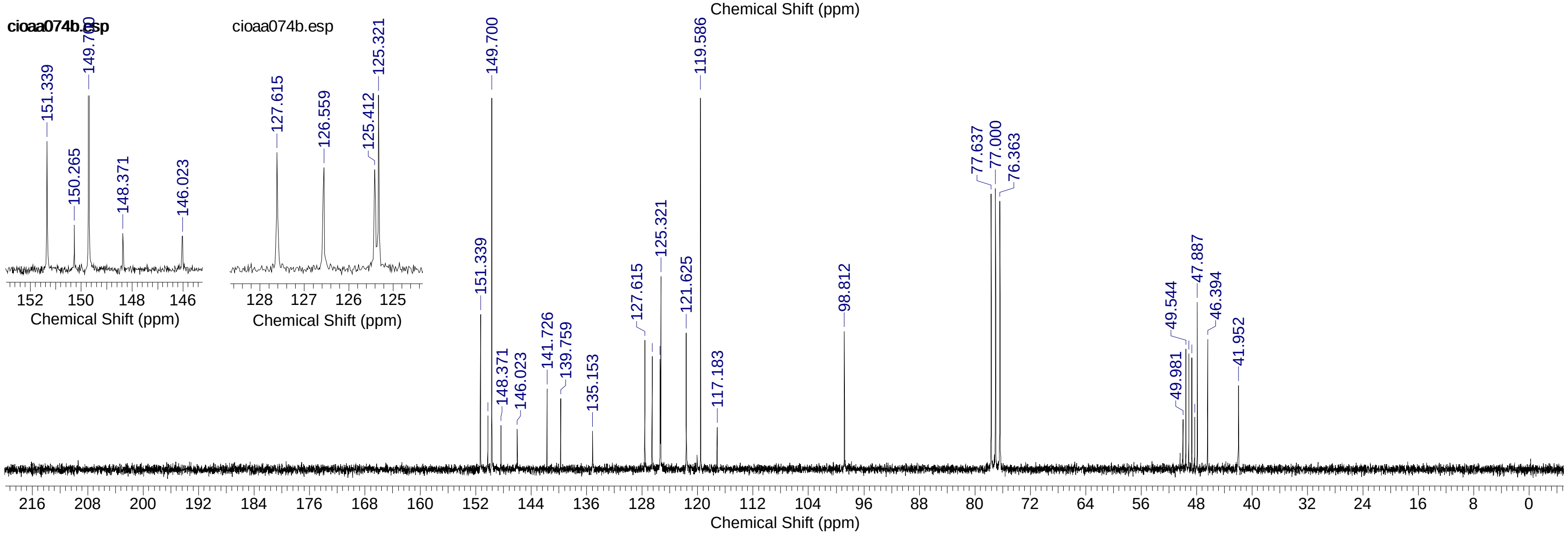
***N*-(7-Chloroquinolin-4-yl)-*N'*-{[5-(pyridin-3-yl)thiophen-2-yl]methyl}propane-1,3-diamine (38)**



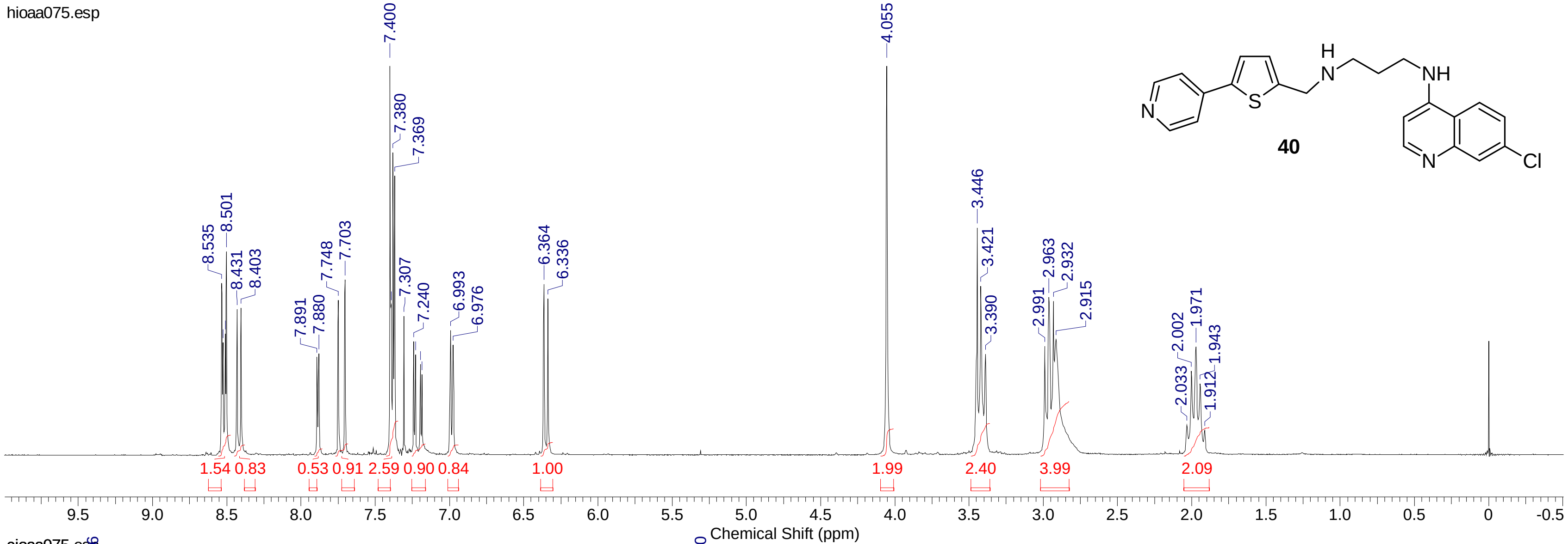


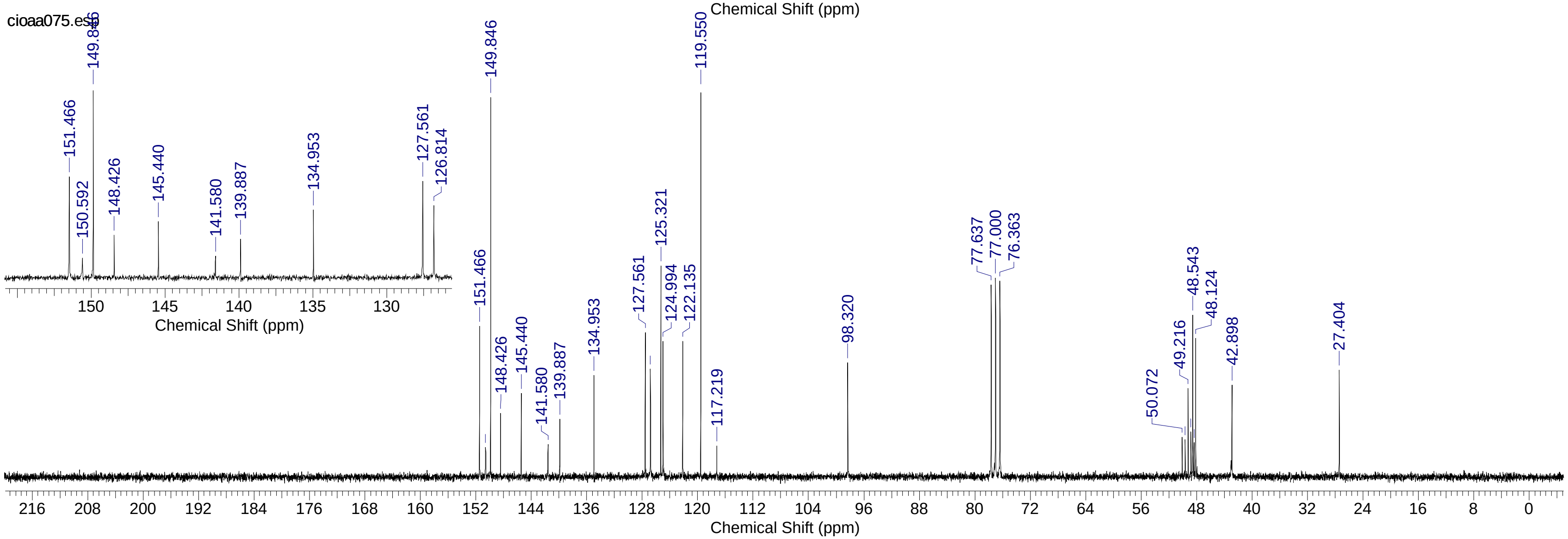
_N_-(7-Chloroquinolin-4-yl)-_N'_-{[5-(pyridin-4-yl)thiophen-2-yl]methyl}ethane-1,2-diamine (39)





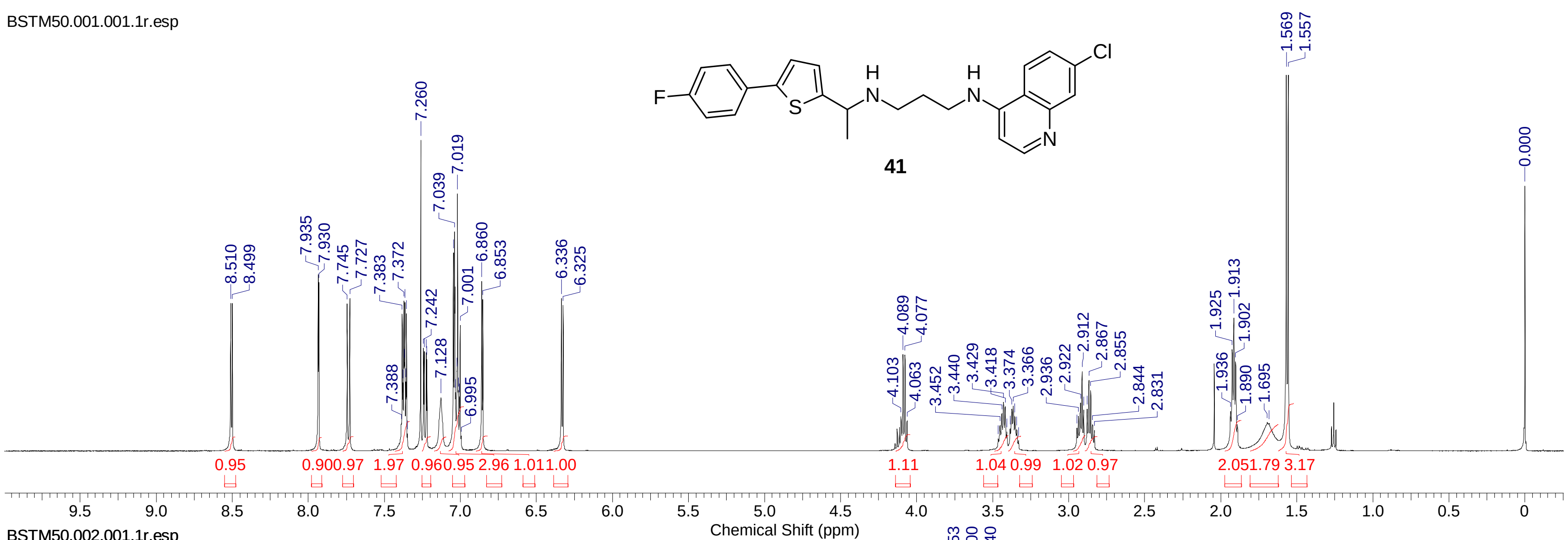
***N*-(7-Chloroquinolin-4-yl)-*N'*-{[5-(pyridin-4-yl)thiophen-2-yl]methyl}propane-1,3-diamine (40)**



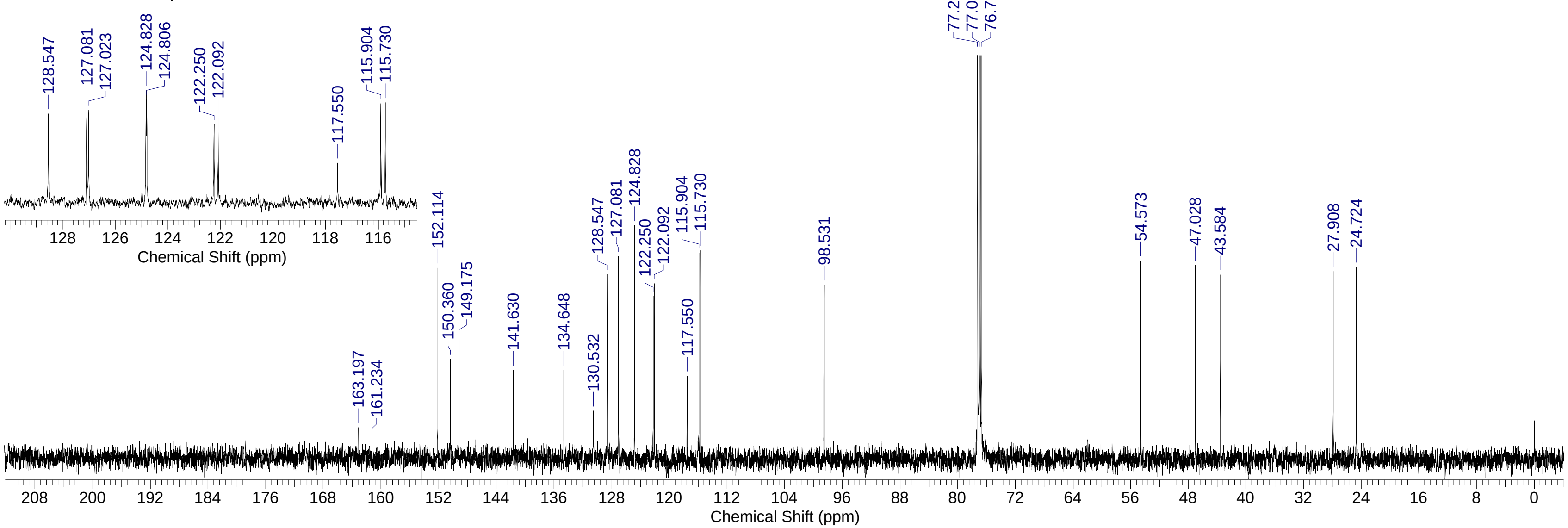


_N_-(7-chloroquinolin-4-yl)-_N'_-{1-[5-(4-fluorophenyl)thiophen-2-yl]ethyl}propane-1,3-diamine (41)

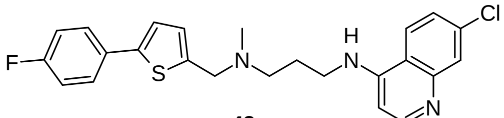
BSTM50.001.001.1r.esp



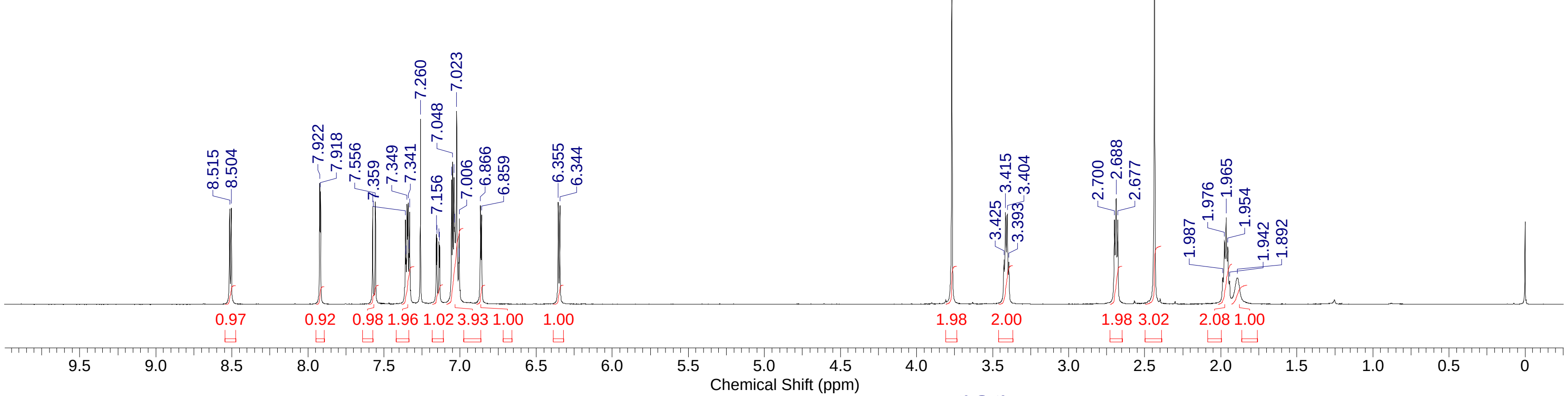
BSTM50.002.001.1r.esp

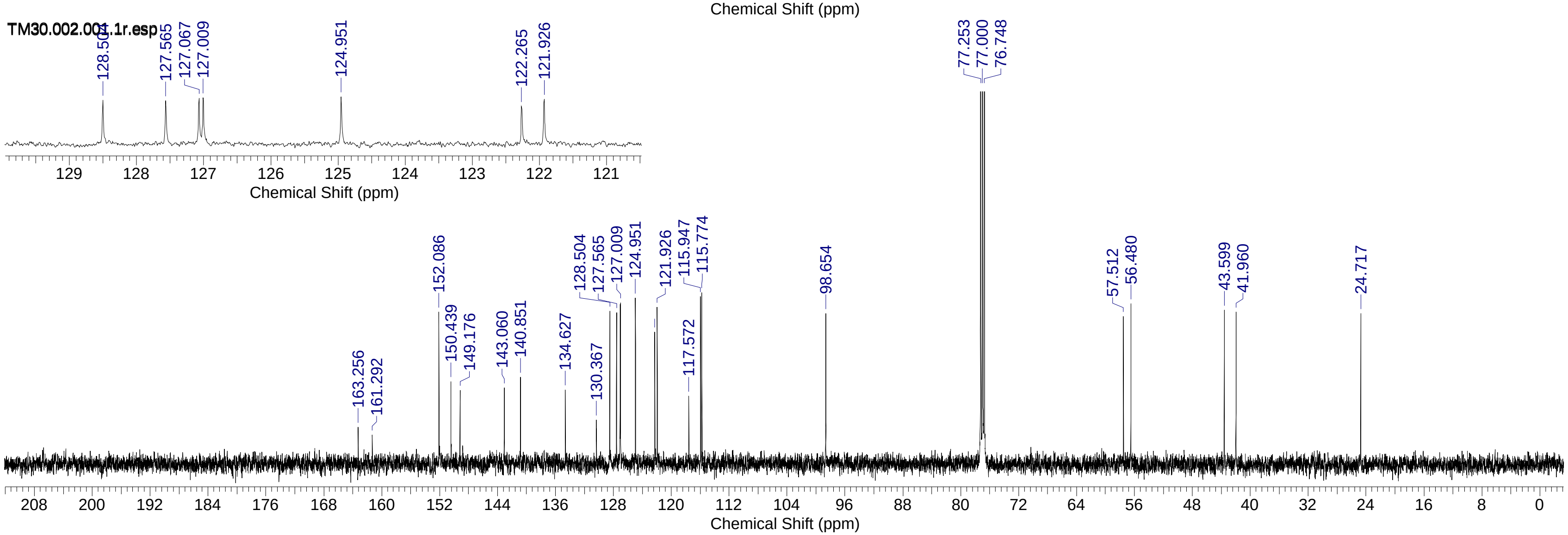


N'-(7-chloroquinolin-4-yl)-N-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}-N-methylpropane-1,3-diamine (42)

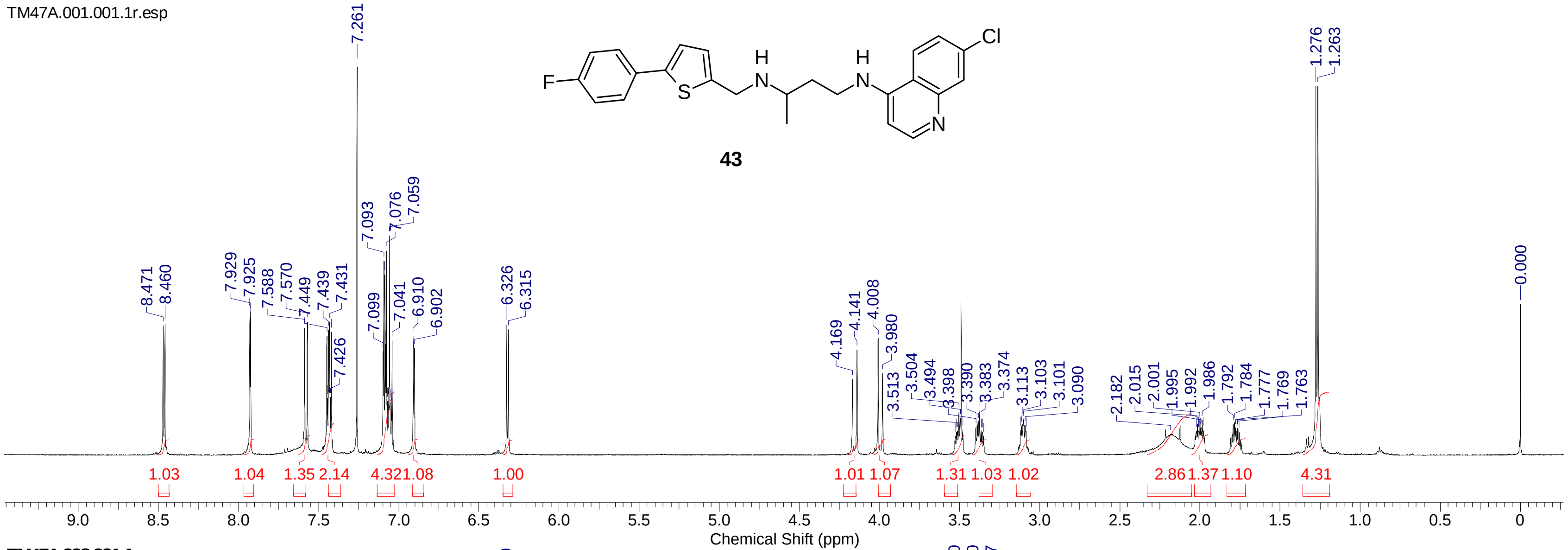


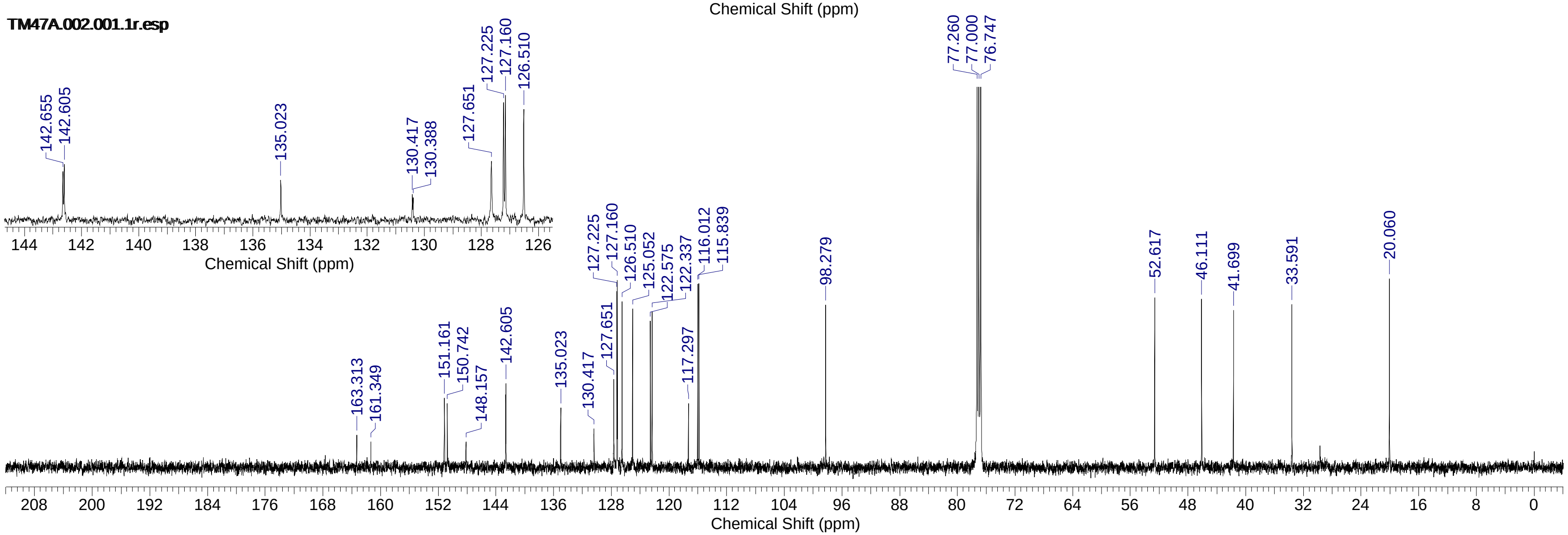
42





N^1-(7-chloroquinolin-4-yl)-N^3-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}butane-1,3-diamine (43)





HPLC analyses for purity

Compounds **15**, **17**, **18**, **19, 21**, **22**, **27**, **28**, **29**, **34**, **35**, **36**, **41**, **42**, **43** were analyzed for purity (HPLC) using a Agilent 1200 HPLC system equipped with Quat Pump (G1311B), Injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and Detector 1260 DAD VL+ (G1315C). HPLC analysis was performed in two diverse systems:

METHOD A

Zorbax Eclipse Plus C18 4.6 x 150 mm, 1.8μ, S.N. USWKY01594 was used as the stationary phase. Eluent was made from the following solvents: 0.2% formic acid in water (A) and acetonitrile (B). The analysis were performed at the UV max of the compounds (at 254, 270 or 330 nm) to maximize selectivity. Compounds were dissolved in mixture containing dichloromethane and methanol, final concentrations were ~ 1 mg/mL. Flow rate was 0.5mL/min.

Compounds were eluted using gradient protocol: 0 – 1.5 min 95% A, 1.5 - 5 min 95% A→ 5% A, 5 - 16 min 5% A, 16 – 18 min 5% A→ 95% A.

METHOD B

Zorbax Eclipse Plus C18 4.6 x 150 mm, 1.8μ, S.N. USWKY01594 was used as the stationary phase. Eluent was made from the following solvents: 0.2% formic acid in water (A) and methanol (B). The analysis were performed at the UV max of the compounds (at 254, 270 or 330 nm) to maximize selectivity. Compounds were dissolved in mixture containing dichloromethane and methanol, final concentrations were ~ 1 mg/mL. Flow rate was 0.5 mL/min.

Compounds were eluted using gradient protocol: 0 – 1.5 min 95% A, 1.5 - 5 min 95% A→ 5% A, 5 - 16 min 5% A, 16 – 18 min 5% A→ 95% A.

Compounds **16**, **20**, **23**, **24**, **25**, **26**, **30**, **31**, **32**, **37**, **38**, **39**, **40** were analyzed for purity (HPLC) using a Waters 1525 HPLC dual pump system equipped with an Alltech, Select degasser system, and dual λ 2487 UV-VIS detector. HPLC analysis was performed in two diverse systems:

METHOD C

Octadecylsilica was used as the stationary phase (Symmetry C18 analytical column, 4.6 mm _ 150 mm, 5 μm, series no. 021336278136 37). Compounds **16**, **20**, **23**, **25**, **30**, **31**, **32**, **37**, **38**, **39**, **40** were dissolved in mixture containing dichloromethane and methanol; compounds **24**, **26** were dissolved in ultra pure water, final concentrations were 0.1-0.5 mg/mL and injection volume was 10 μL. Eluent was made from the following solvents: 0.2% formic acid in water (A) and methanol (B). The analysis were performed at the UV max of the compounds (at 254 nm for compounds **16**, **20**, **31**,

32, **37**, **38**, **39**, **40**, and at 330 nm for compounds **23**, **24**, **25**, **26, 30**) to maximize selectivity. For data processing, Empower software was used.

Compound **25** was eluted using gradient protocol: 0-3 min 6% A, 3-6 min 6% A→ 94 % A, 6-9 min 94% A, 9-12 min 94% A→ 6 % A, 12-13 min 6% A.

Compounds **16**, **20**, **23**, **24**, **26, 30**, **31**, **32**, **37**, **38**, **39**, **40** were eluted using gradient protocol: 0-3 min 10% A, 3-6 min 10% A→ 90 % A, 6-9 min 90% A, 9-12 min 90% A→ 10 % A, 12-13 min 10% A.

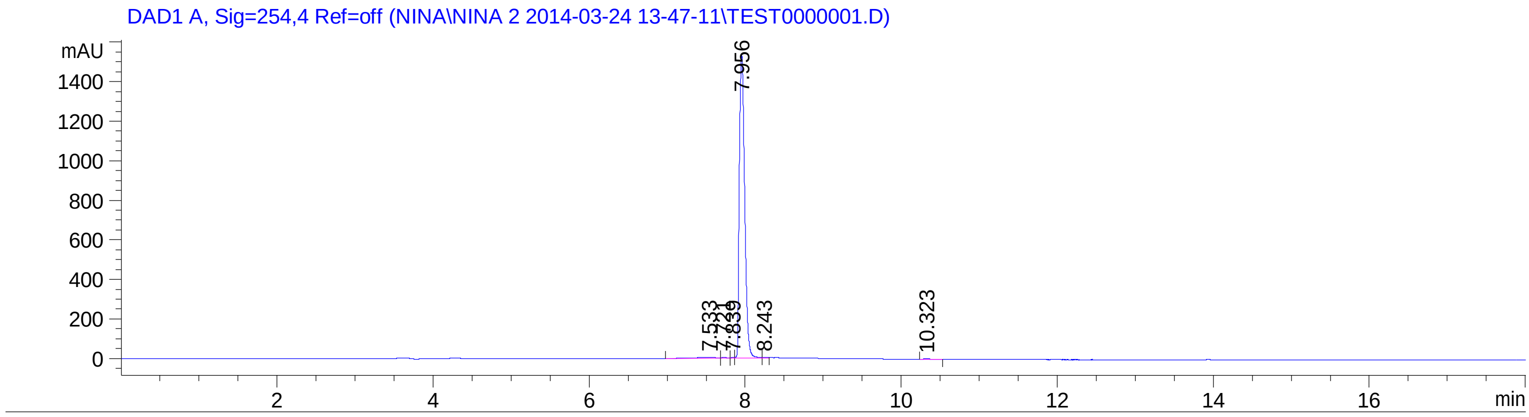
METHOD D

Octadecylsilica was used as the stationary phase (Nucleosil C18 analytical column, 4 mm _ 150 mm, 5 μm). Compounds **16**, **20**, **23**, **25**, **30**, **31**, **32**, **37**, **38**, **39**, **40** were dissolved in mixture containing dichlormethane and methanol; compounds **24**, **26** were dissolved in ultra-pure water, final concentrations were 0.1-0.5 mg/mL and injection volume was 10 μL. Eluent was made from the following solvents: 0.2% formic acid in water (A) and methanol (B). The analysis were performed at the UV max of the compounds (at 254 nm for compounds **16**, **20**, **31**, **32**, **37**, **38**, **39**, **40**, and at 330 nm for compounds **23**, **24**, **25**, **26**, **30**) to maximize selectivity. For data processing, Empower software was used.

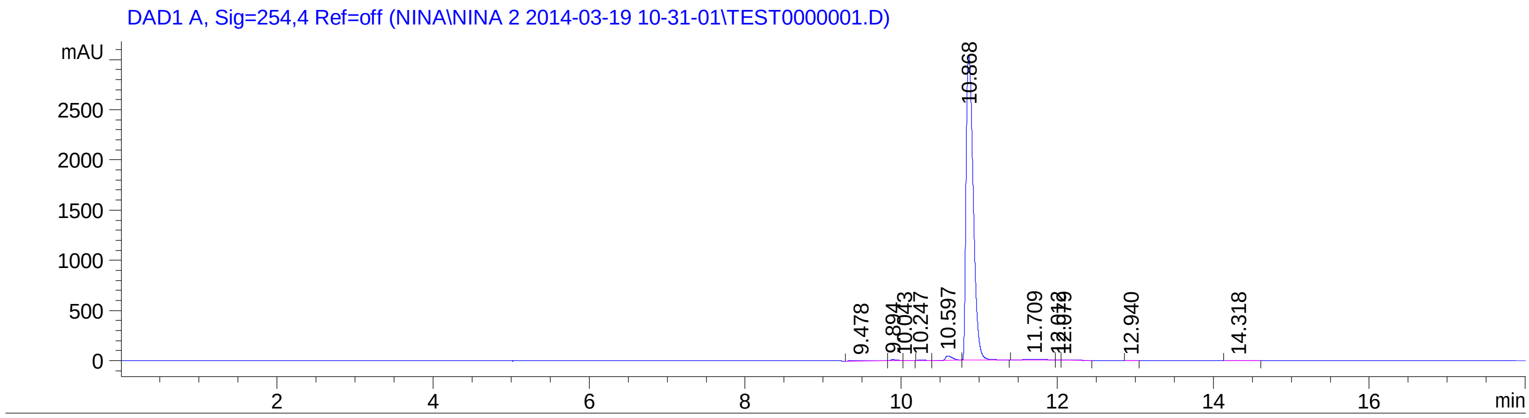
Compound **25** was eluted using gradient protocol: 0-3 min 6% A, 3-6 min 6% A→ 94 % A, 6-9 min 94% A, 9-12 min 94% A→ 6 % A, 12-13 min 6% A.

Compounds **16**, **20**, **23**, **24**, **26**, **30**, **31**, **32**, **37**, **38**, **39**, **40** were eluted using gradient protocol: 0-3 min 10% A, 3-6 min 10% A→ 90 % A, 6-9 min 90% A, 9-12 min 90% A→ 10 % A, 12-13 min 10% A.

Sample Name: 15

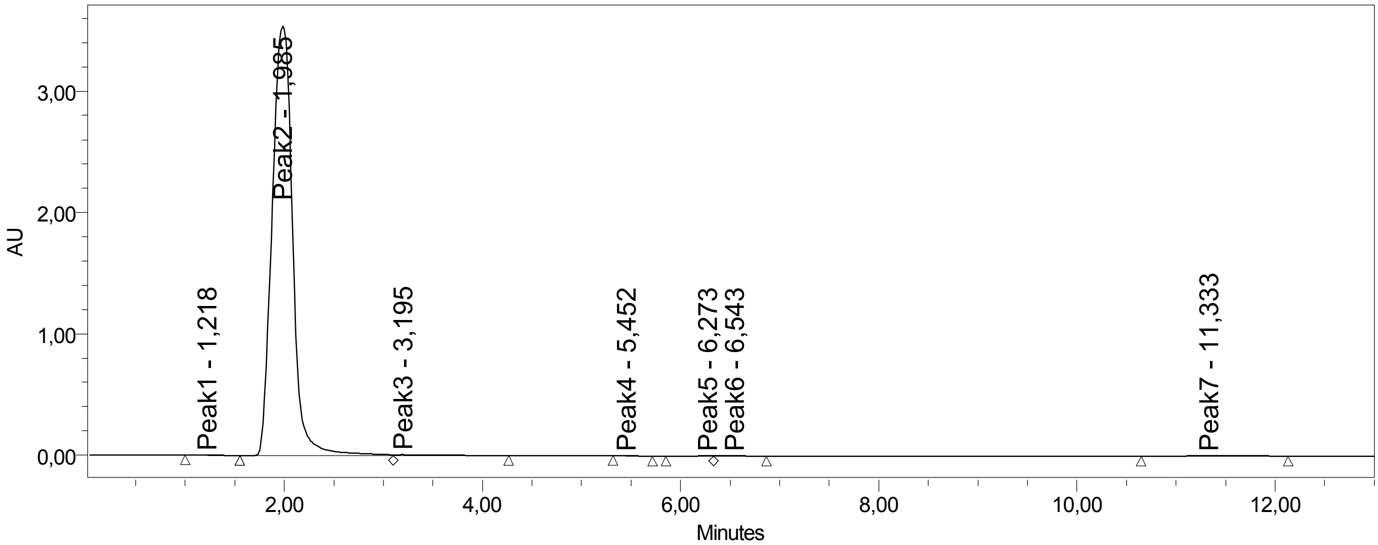


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.533	BB	0.2197	86.45097	4.71970	1.1674
2	7.721	BB	0.0515	17.99755	5.18105	0.2430
3	7.839	BV	0.0379	7.61829	3.24328	0.1029
4	7.956	VV	0.0762	7264.30176	1533.99573	98.0960
5	8.243	VV	0.0573	9.25065	2.19120	0.1249
6	10.323	BB	0.0661	19.67621	4.40596	0.2657

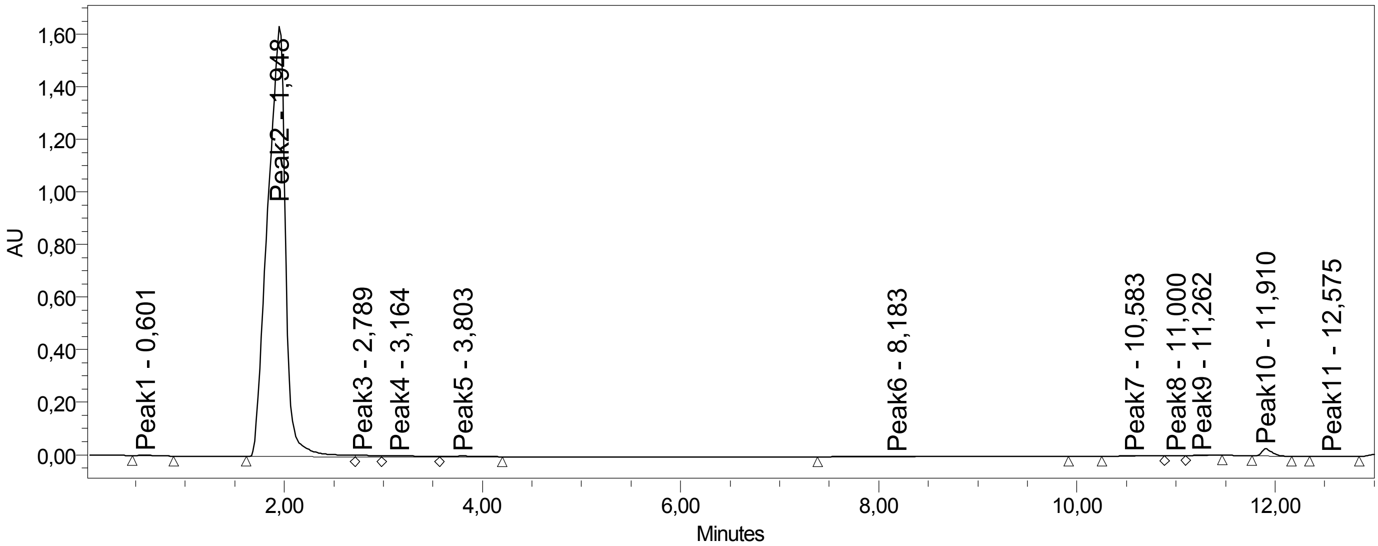


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.478	BV	0.2214	116.12550	6.16106	0.5767
2	9.894	VV	0.0996	73.08664	11.19750	0.3630
3	10.043	VB	0.0625	10.85100	2.22071	0.0539
4	10.247	BB	0.0784	37.67653	7.04214	0.1871
5	10.597	BV	0.0967	279.72247	44.89317	1.3892
6	10.868	VB	0.1008	1.94143e4	3026.83813	96.4155
7	11.709	BV	0.2377	117.31232	5.80714	0.5826
8	12.012	VV	0.0559	15.95224	3.76646	0.0792
9	12.079	VB	0.1238	42.63982	4.11804	0.2118
10	12.940	VB	0.0689	9.58395	1.91584	0.0476
11	14.318	BB	0.1291	18.82424	1.82069	0.0935

Sample Name: 16

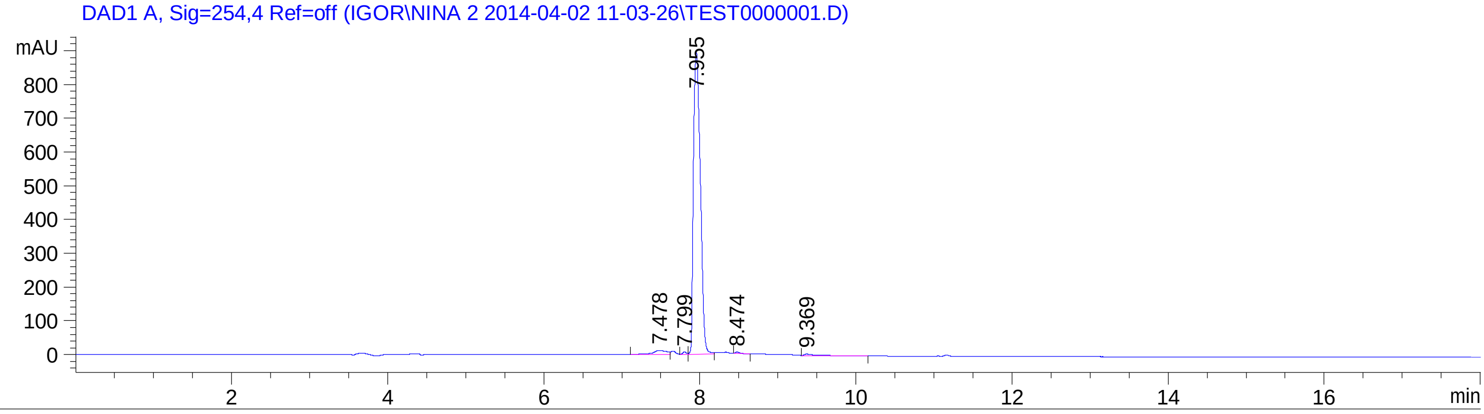


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,218	19524	0,04	1141
2	Peak2	1,985	50937029	99,10	3539734
3	Peak3	3,195	233818	0,45	6730
4	Peak4	5,452	10191	0,02	817
5	Peak5	6,273	20493	0,04	1341
6	Peak6	6,543	36388	0,07	2050
7	Peak7	11,333	142169	0,28	2750

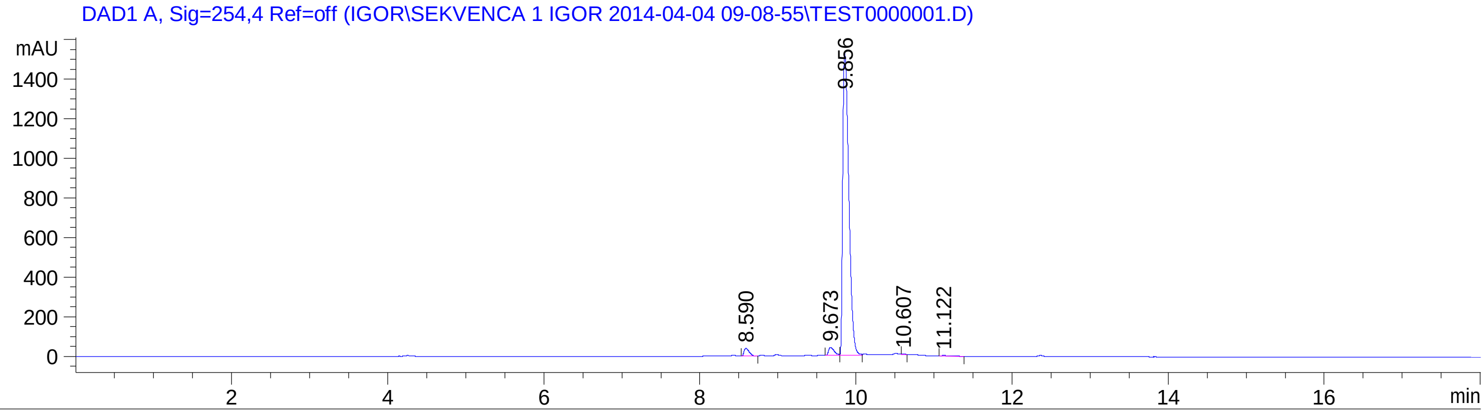


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,601	23227	0,11	3327
2	Peak2	1,948	20480667	97,38	1636603
3	Peak3	2,789	64451	0,31	5038
4	Peak4	3,164	79921	0,38	3638
5	Peak5	3,803	42020	0,20	2426
6	Peak6	8,183	82230	0,39	1012
7	Peak7	10,583	20719	0,10	832
8	Peak8	11,000	4694	0,02	401
9	Peak9	11,262	13928	0,07	1447
10	Peak10	11,910	195706	0,93	27022
11	Peak11	12,575	24873	0,12	1541

Sample Name: 17

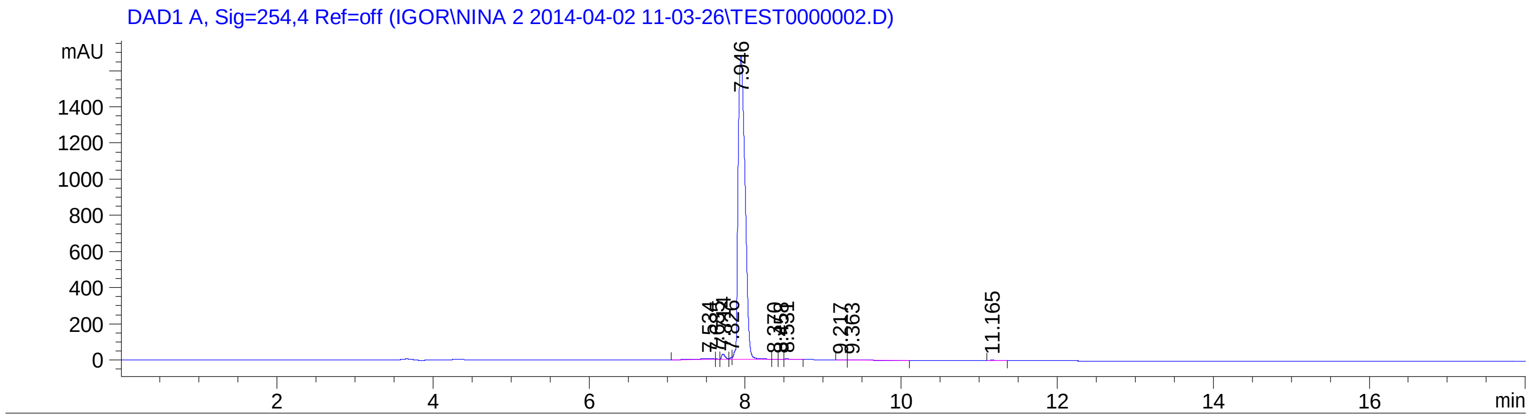


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.478	BV	0.1629	144.61624	11.97045	2.5249
2	7.799	BV	0.0500	23.89814	7.06340	0.4172
3	7.955	VV	0.1059	5482.37646	895.97748	95.7169
4	8.474	BB	0.0602	20.38374	4.88483	0.3559
5	9.369	BB	0.1670	56.42309	4.41691	0.9851

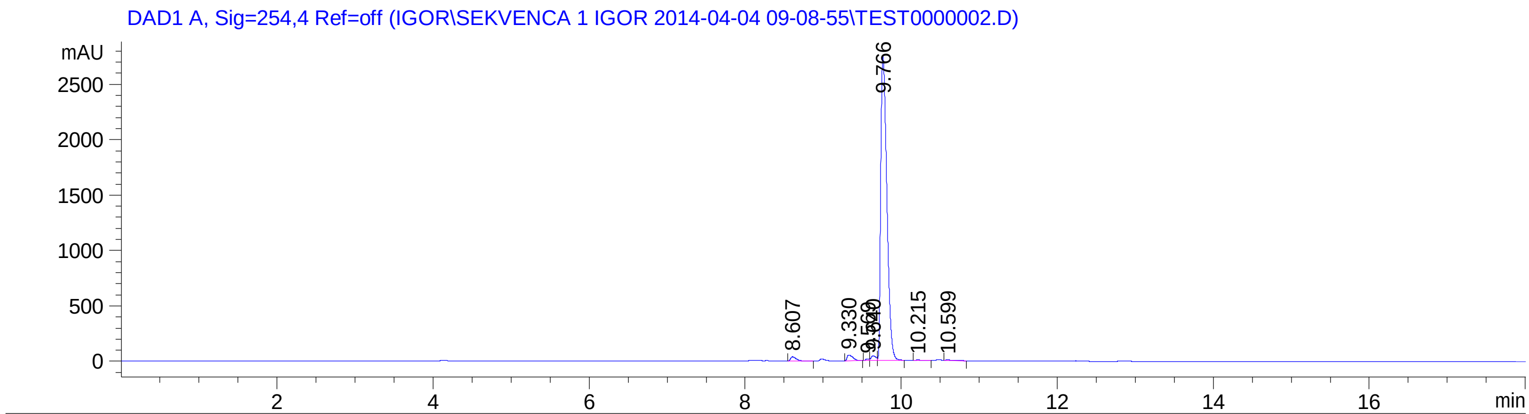


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.590	VV	0.0735	185.68053	39.71957	2.1379
2	9.673	BV	0.0806	203.54221	39.16151	2.3436
3	9.856	VV	0.0856	8270.13965	1528.85974	95.2223
4	10.607	VB	0.0396	9.44567	3.54358	0.1088
5	11.122	BB	0.0738	16.28110	3.12592	0.1875

Sample Name: 18

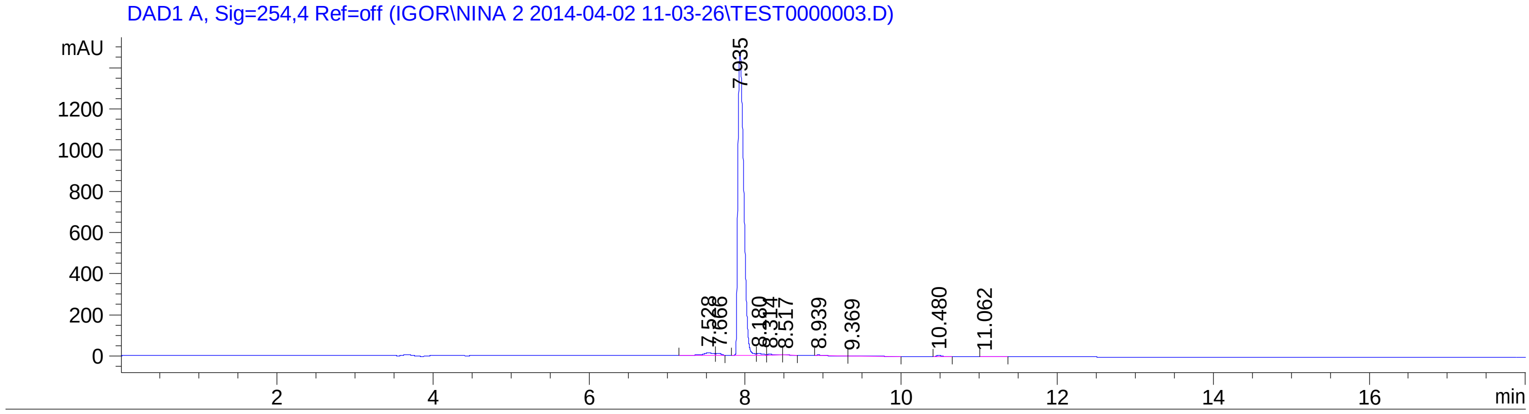


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.534	BV	0.1819	61.36889	3.97928	0.5784
2	7.635	VB	0.0361	6.35067	2.63794	0.0599
3	7.714	BB	0.0476	91.72213	30.06849	0.8645
4	7.826	BV	0.0262	17.86364	11.17172	0.1684
5	7.946	VV	0.1054	1.03462e4	1678.63684	97.5170
6	8.370	VV	0.0566	10.69652	2.32921	0.1008
7	8.458	VV	0.0508	10.04359	2.47901	0.0947
8	8.531	VB	0.0752	18.27568	3.34685	0.1723
9	9.217	BB	0.0741	6.09676	1.01397	0.0575
10	9.363	BB	0.1322	23.00384	2.22413	0.2168
11	11.165	VB	0.0711	18.01242	3.88608	0.1698

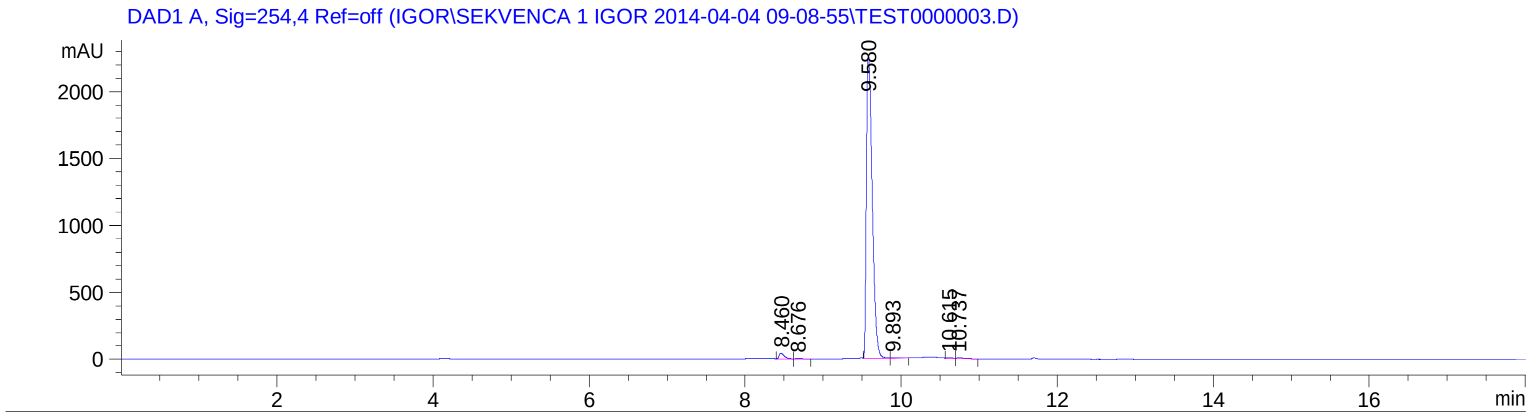


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.607	VB	0.0779	187.46317	37.79242	1.1924
2	9.330	BB	0.0814	267.72449	52.61611	1.7029
3	9.569	BV	0.0507	43.27514	13.74033	0.2753
4	9.640	VV	0.0733	184.65002	40.38219	1.1745
5	9.766	VB	0.0862	1.49707e4	2742.65918	95.2243
6	10.215	VV	0.1202	22.13623	2.35495	0.1408
7	10.599	VB	0.1002	45.56642	5.64042	0.2898

Sample Name: 19

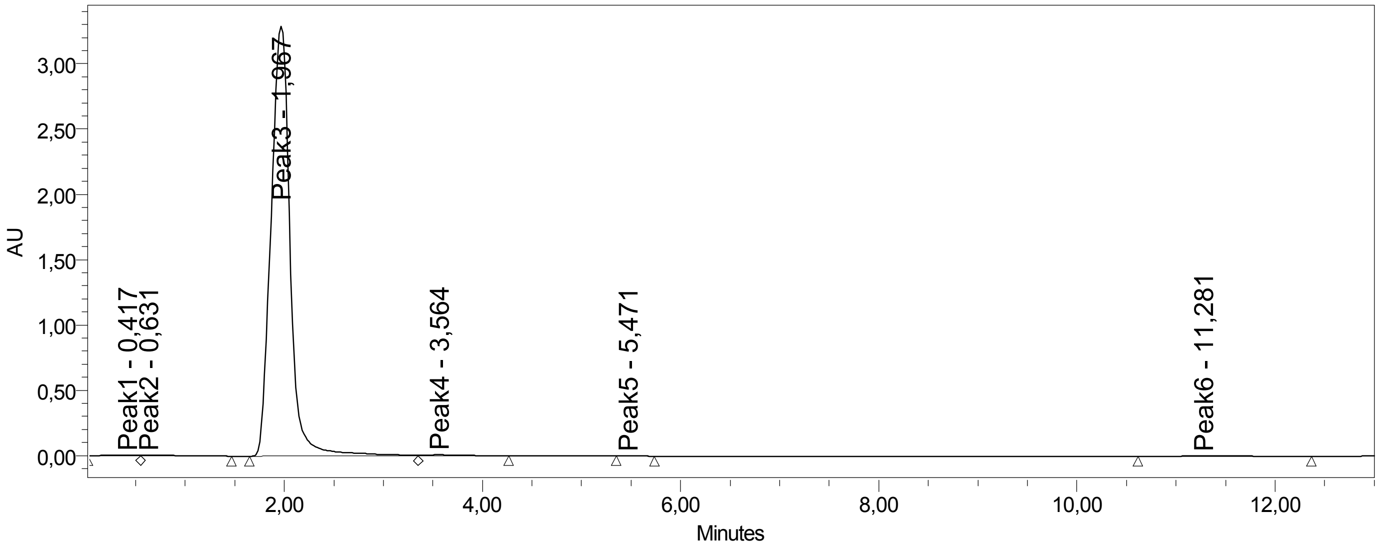


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.528	BV	0.1369	124.41763	12.52797	1.5551
2	7.666	VB	0.0609	47.40432	10.76180	0.5925
3	7.935	BV	0.0851	7646.54736	1472.66321	95.5756
4	8.180	VV	0.0795	48.53087	8.08368	0.6066
5	8.314	VB	0.0780	25.58833	4.35552	0.3198
6	8.517	BB	0.0575	6.88196	1.67244	0.0860
7	8.939	VB	0.1183	35.64691	3.89500	0.4456
8	9.369	BB	0.1543	25.85496	2.08312	0.3232
9	10.480	VB	0.0628	28.36738	6.71906	0.3546
10	11.062	VB	0.0993	11.28195	1.38789	0.1410

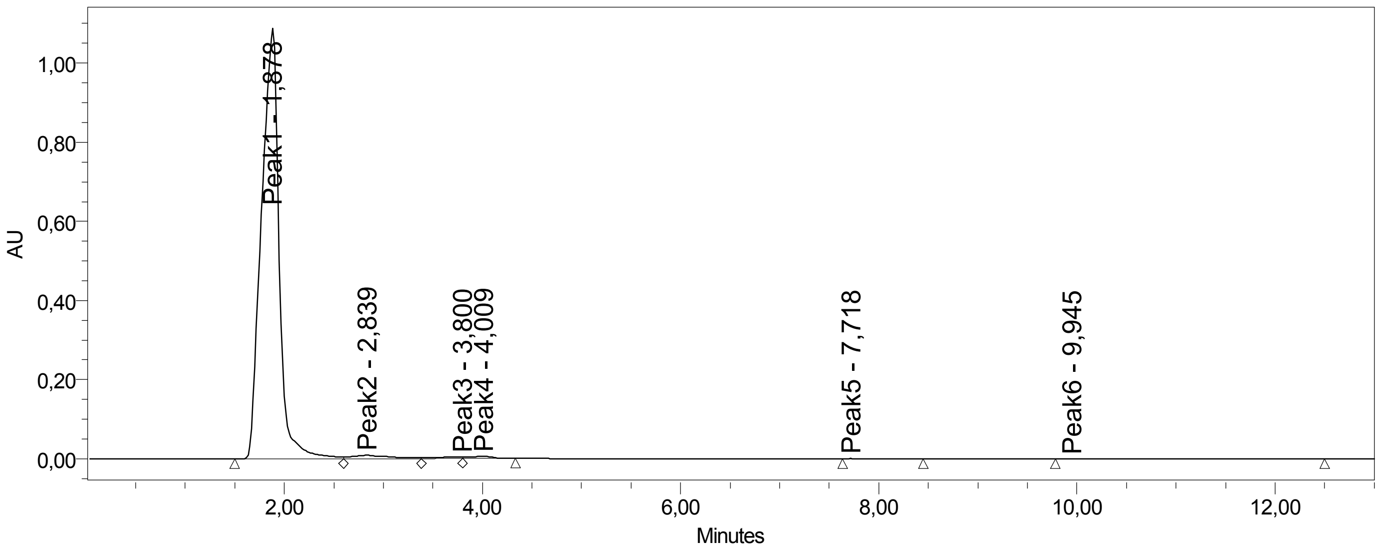


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.460	VV	0.0748	202.68483	42.37138	1.6697
2	8.676	VB	0.0751	19.46282	3.65547	0.1603
3	9.580	VV	0.0818	1.18188e4	2266.69751	97.3604
4	9.893	VB	0.0973	32.21076	4.23353	0.2653
5	10.615	VV	0.0837	25.72016	4.21503	0.2119
6	10.737	VB	0.0879	40.35468	6.33153	0.3324

Sample Name: 20

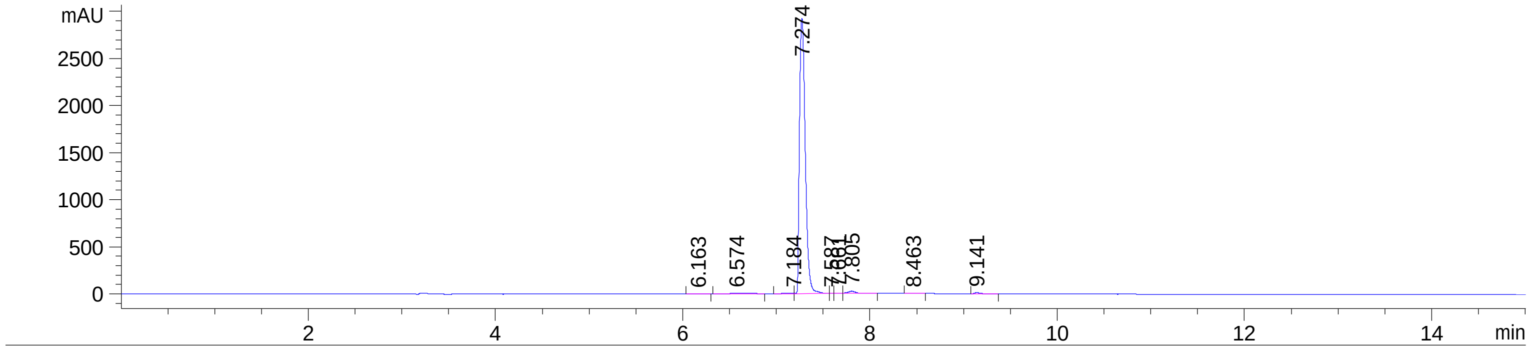


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,417	78297	0,17	3805
2	Peak2	0,631	117704	0,26	4235
3	Peak3	1,967	44155879	98,67	3289620
4	Peak4	3,564	219141	0,49	7671
5	Peak5	5,471	11530	0,03	971
6	Peak6	11,281	170596	0,38	2995

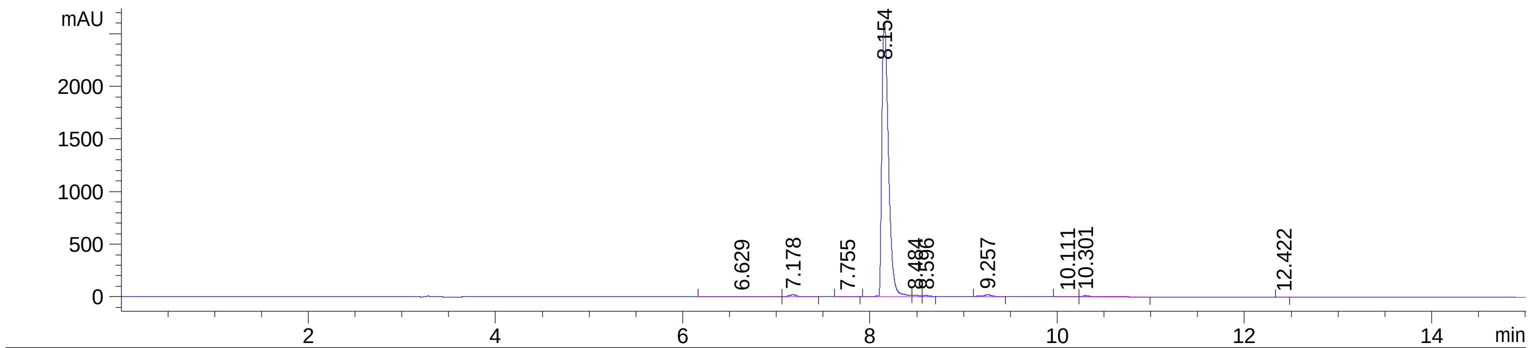


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,878	13489554	97,20	1089391
2	Peak2	2,839	224029	1,61	8333
3	Peak3	3,800	69144	0,50	3397
4	Peak4	4,009	87510	0,63	5848
5	Peak5	7,718	3327	0,02	721
6	Peak6	9,945	5198	0,04	505

Sample Name: 21

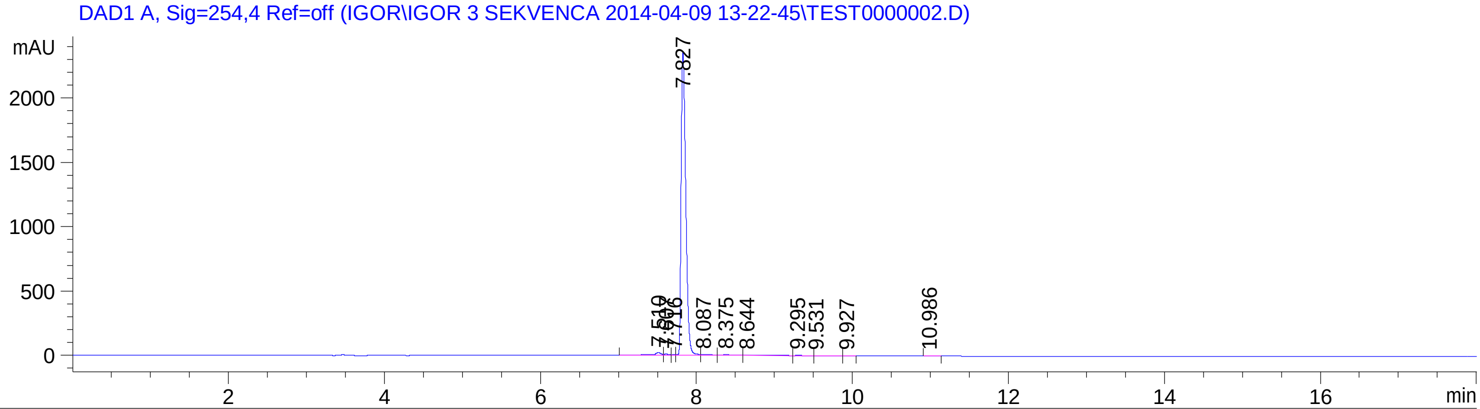


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.163	BB	0.0889	9.31767	1.32722	0.0724
2	6.574	BV	0.1658	58.73492	4.43993	0.4561
3	7.184	BV	0.0618	17.13140	3.74850	0.1330
4	7.274	VV	0.0686	1.25550e4	2924.23511	97.4938
5	7.587	VV	0.0408	11.08234	3.71431	0.0861
6	7.661	VV	0.0608	19.45114	3.85979	0.1510
7	7.805	VB	0.0808	153.13068	26.16061	1.1891
8	8.463	BB	0.0796	6.90219	1.04386	0.0536
9	9.141	BB	0.0606	46.99408	11.76232	0.3649

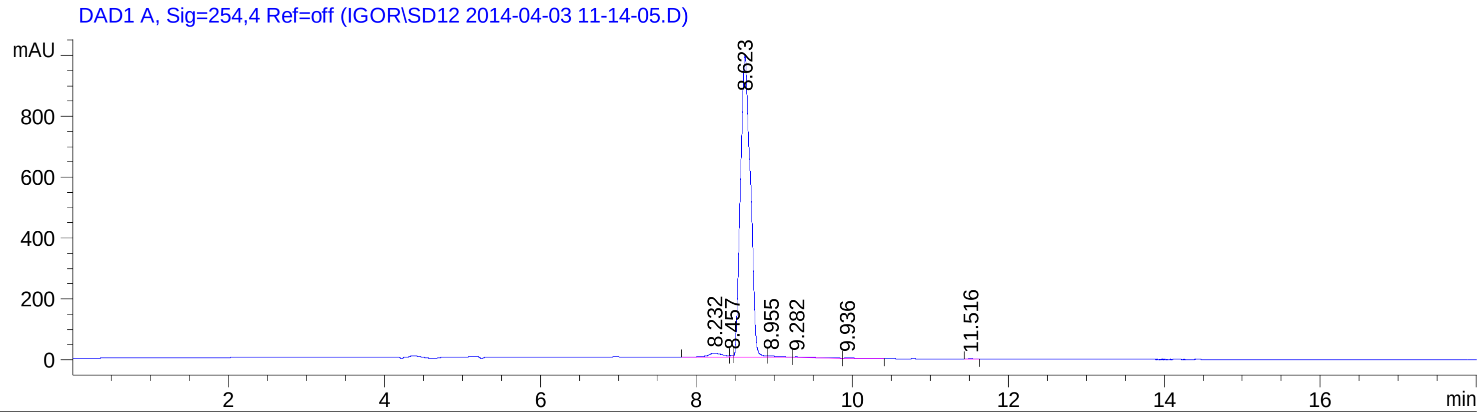


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.629	BV	0.3599	71.65200	2.32928	0.5370
2	7.178	VB	0.0760	117.11697	22.04725	0.8777
3	7.755	BB	0.0603	5.15406	1.09790	0.0386
4	8.154	BV	0.0769	1.28621e4	2612.16138	96.3958
5	8.484	VV	0.0625	61.43609	14.06608	0.4604
6	8.596	VB	0.0604	40.32317	10.02397	0.3022
7	9.257	BB	0.0791	112.84854	19.05113	0.8458
8	10.111	BV	0.0884	10.24258	1.42436	0.0768
9	10.301	VB	0.0760	56.03357	10.63210	0.4199
10	12.422	BV	0.0643	6.09451	1.13259	0.0457

Sample Name: 22

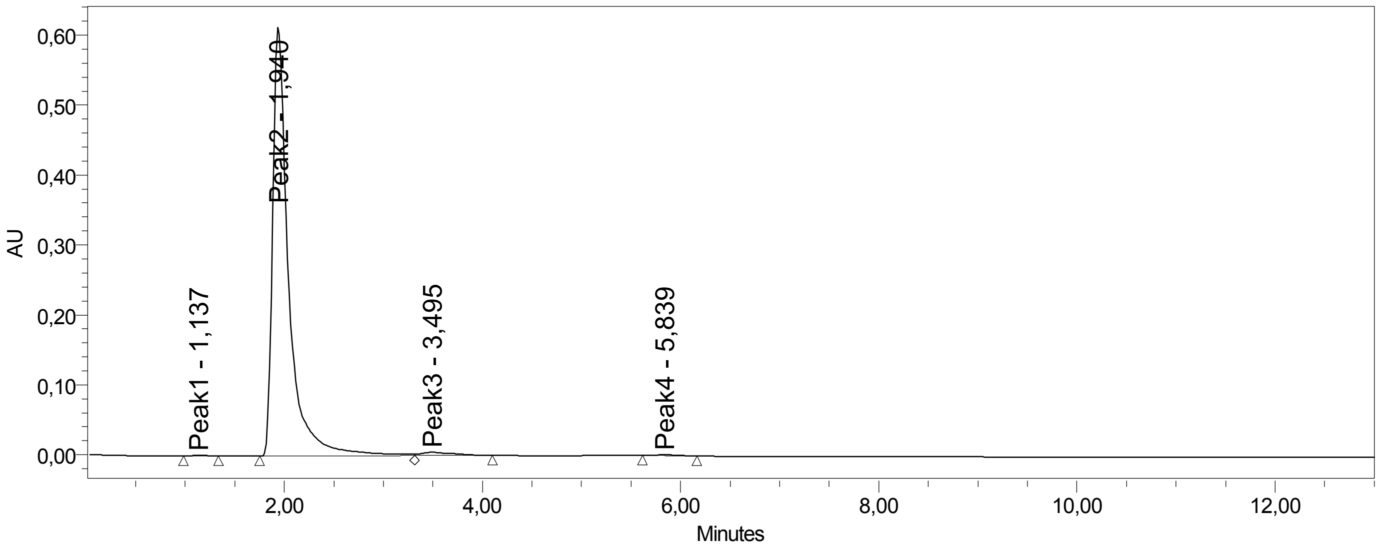


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.510	BV	0.0941	127.49896	19.04073	1.2777
2	7.607	VB	0.0519	24.96962	7.48227	0.2502
3	7.716	BV	0.0344	5.30682	2.34295	0.0532
4	7.827	VV	0.0643	9667.58691	2359.51343	96.8784
5	8.087	VB	0.0743	27.20654	4.78507	0.2726
6	8.375	BV	0.0889	17.71429	2.74016	0.1775
7	8.644	VB	0.2914	47.08648	1.94190	0.4719
8	9.295	BV	0.1218	29.88405	3.13195	0.2995
9	9.531	VV	0.1314	14.40206	1.29393	0.1443
10	9.927	VB	0.0628	5.37479	1.22314	0.0539
11	10.986	BB	0.0677	12.06574	2.69589	0.1209

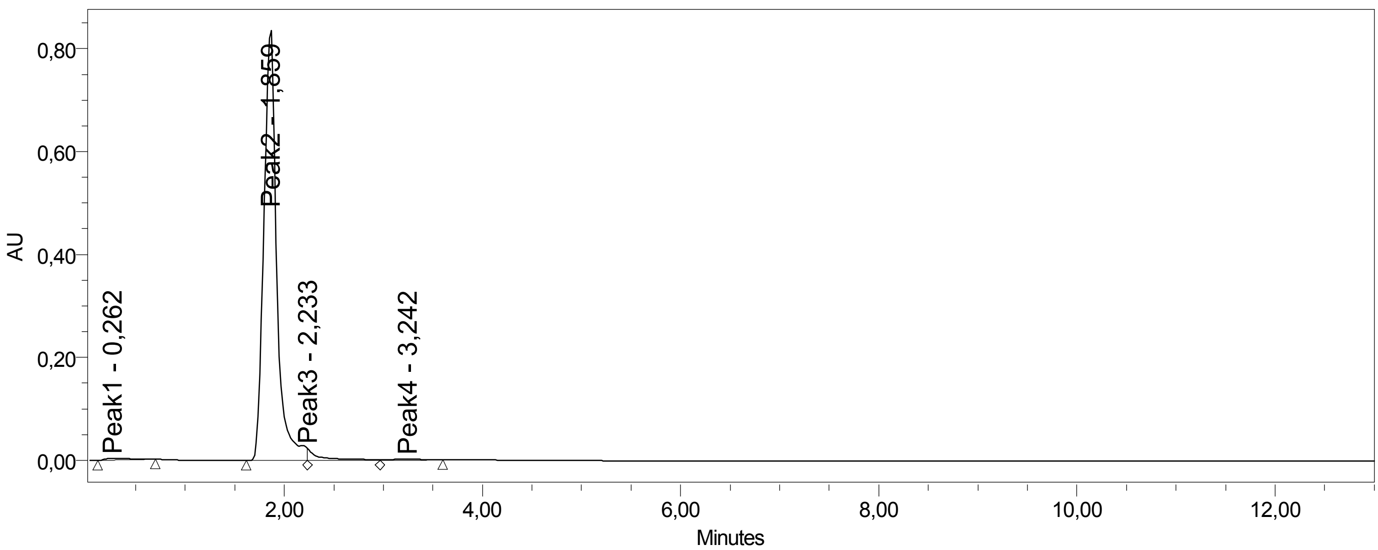


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.232	BV	0.1790	184.96089	13.74807	2.0452
2	8.457	VV	0.0461	18.96677	6.48711	0.2097
3	8.623	VV	0.1219	8735.31738	994.98395	96.5889
4	8.955	VB	0.1086	31.15451	3.39405	0.3445
5	9.282	BB	0.4026	35.34614	1.03835	0.3908
6	9.936	BV	0.1560	29.26387	2.42088	0.3236
7	11.516	BB	0.0720	8.80337	1.83512	0.0973

Sample Name: 23

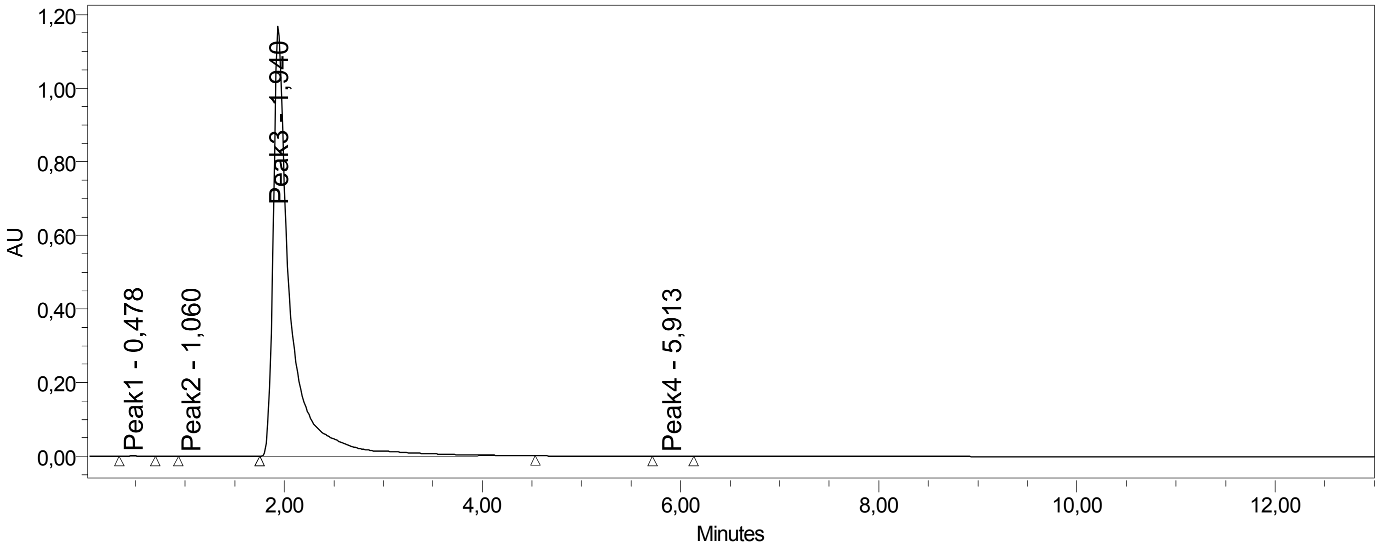


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,137	3975	0,06	342
2	Peak2	1,940	6906922	98,10	615496
3	Peak3	3,495	110164	1,56	4885
4	Peak4	5,839	19868	0,28	1392

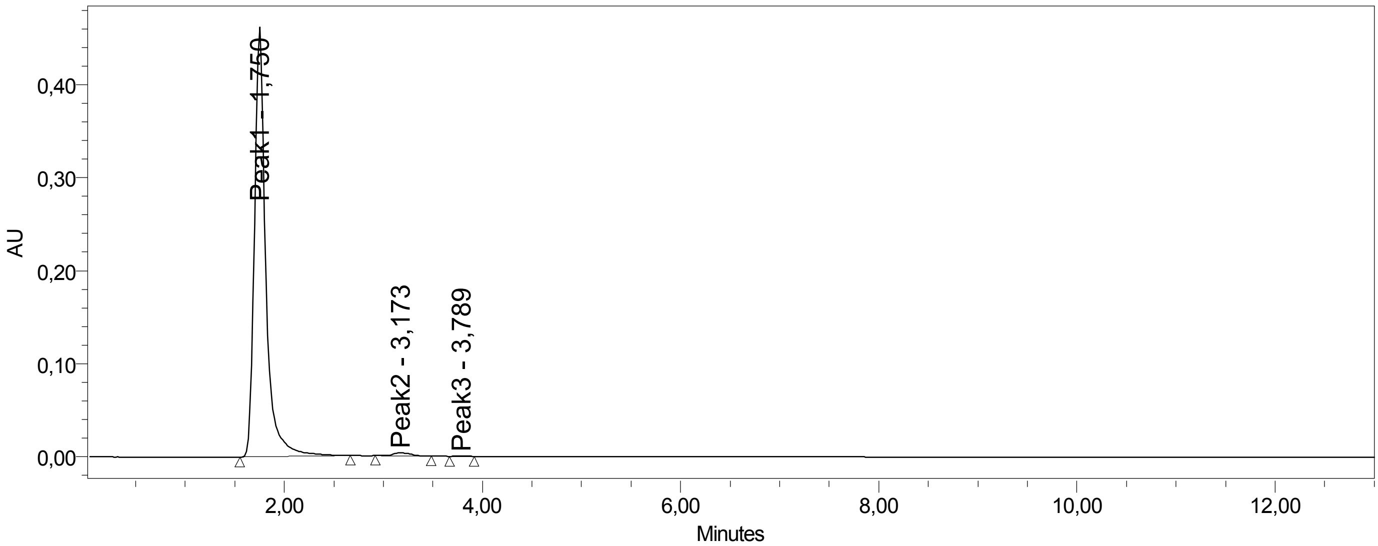


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,262	57296	0,73	3546
2	Peak2	1,859	7586656	96,32	837624
3	Peak3	2,233	189215	2,40	23335
4	Peak4	3,242	43105	0,55	2169

Sample Name: 24

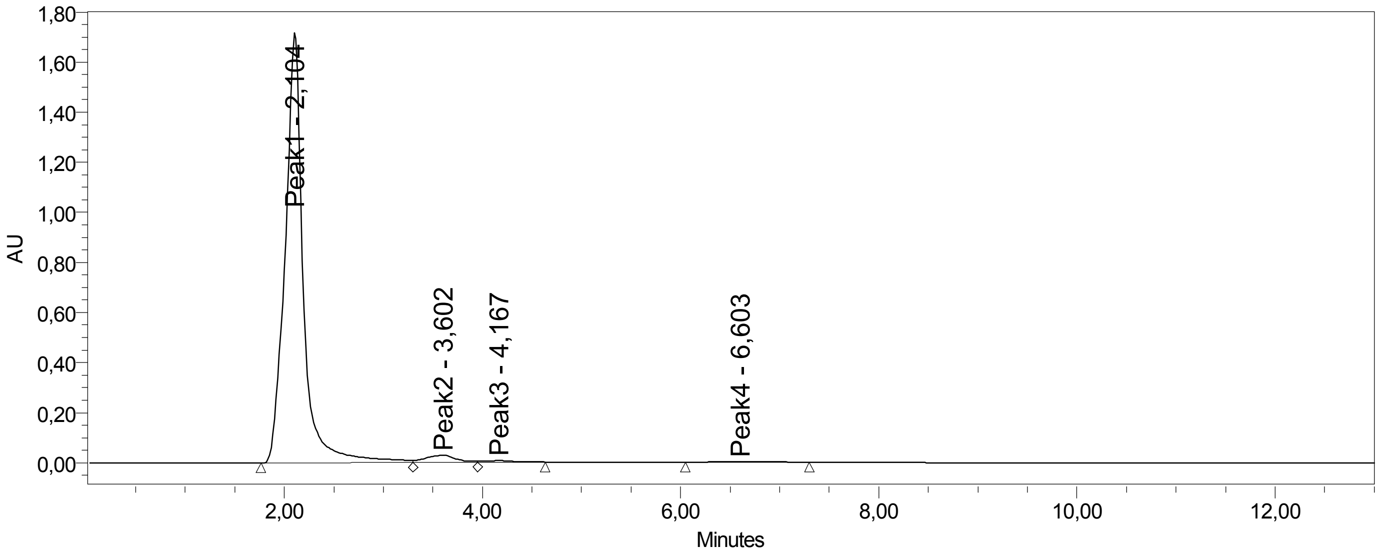


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,478	10999	0,08	1051
2	Peak2	1,060	7550	0,05	406
3	Peak3	1,940	14246728	99,82	1171652
4	Peak4	5,913	6711	0,05	547

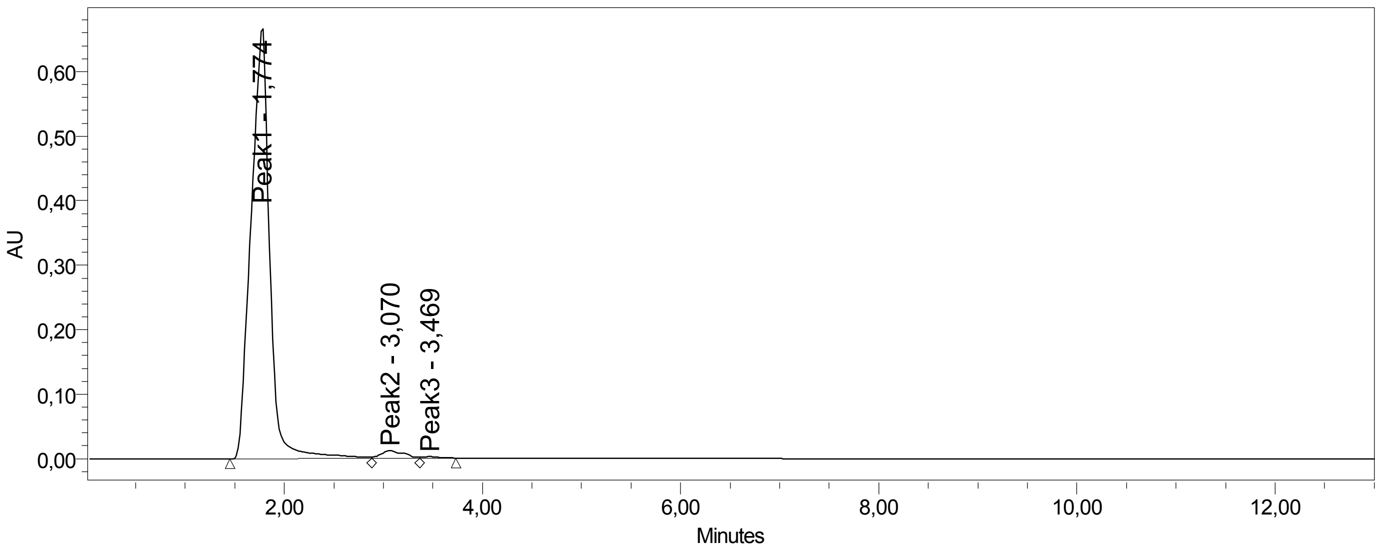


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,750	3668697	98,82	457317
2	Peak2	3,173	40445	1,09	3518
3	Peak3	3,789	3478	0,09	532

Sample Name: 25

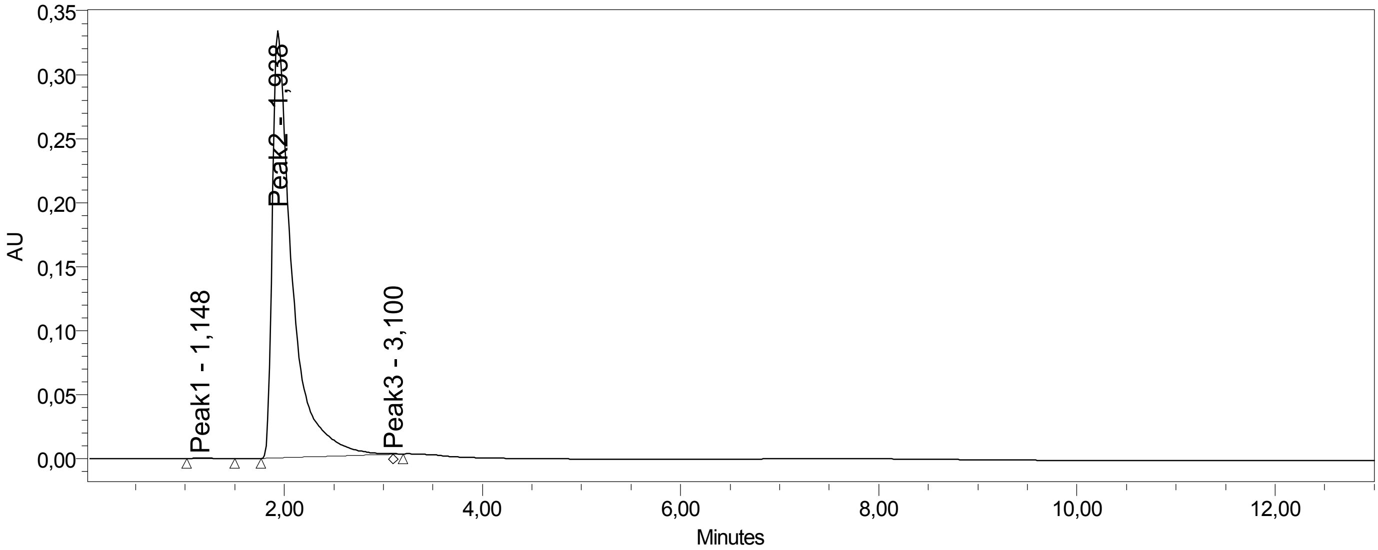


	Peak Name	RT	Area	% Area	Height
1	Peak1	2,104	21894782	96,38	1715367
2	Peak2	3,602	594770	2,62	28950
3	Peak3	4,167	116775	0,51	6464
4	Peak4	6,603	111107	0,49	2902

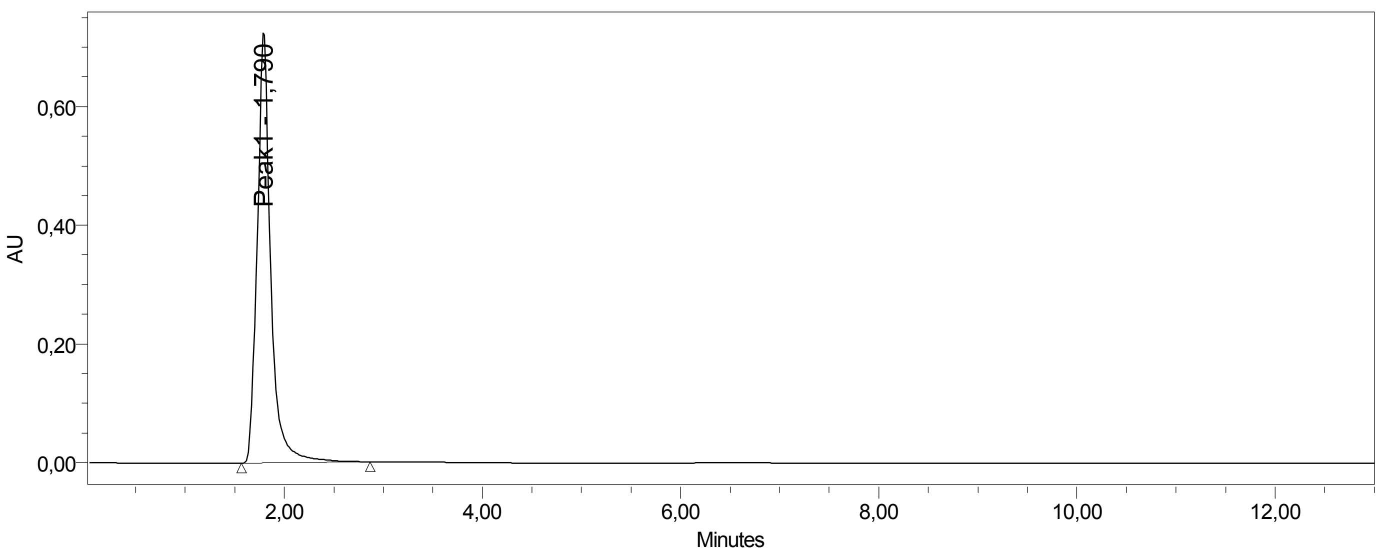


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,774	8729491	97,61	670800
2	Peak2	3,070	187853	2,10	12113
3	Peak3	3,469	26091	0,29	2481

Sample Name: 26

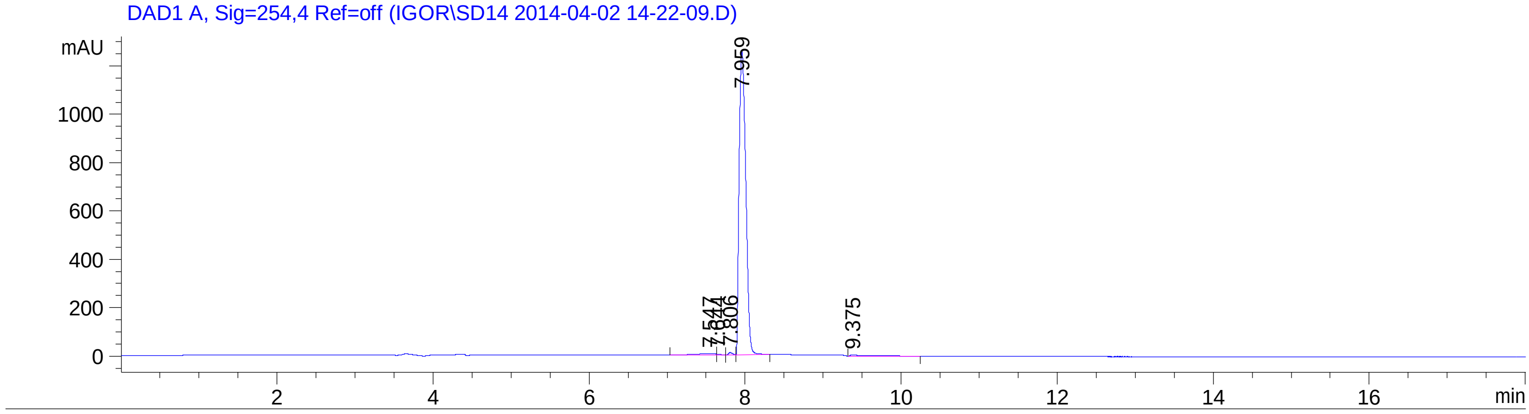


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,148	5062	0,11	475
2	Peak2	1,938	4618978	99,86	334185
3	Peak3	3,100	1225	0,03	473

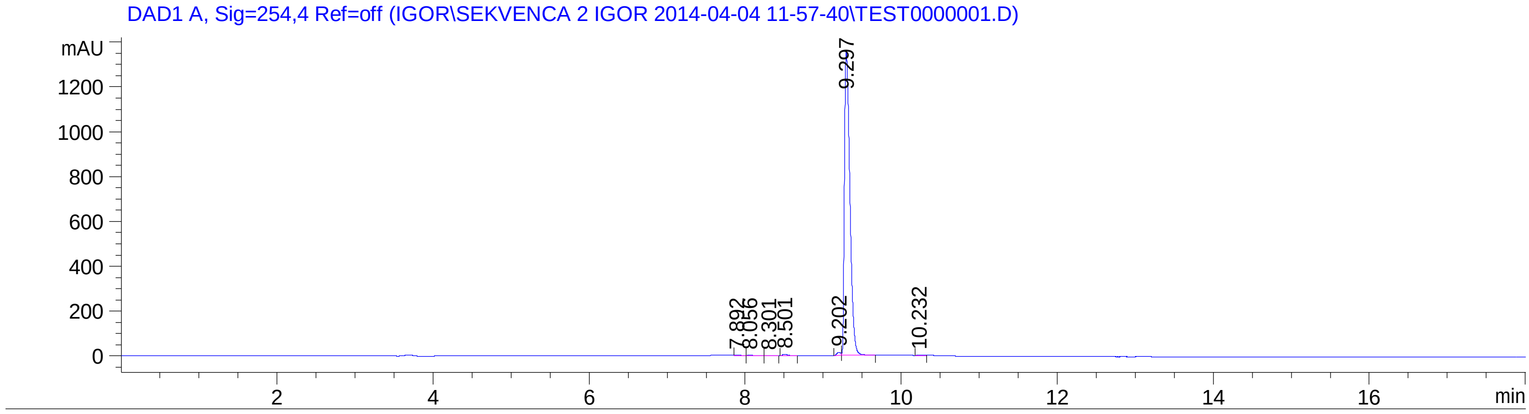


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,790	6903251	100,00	726572

Sample Name: 27

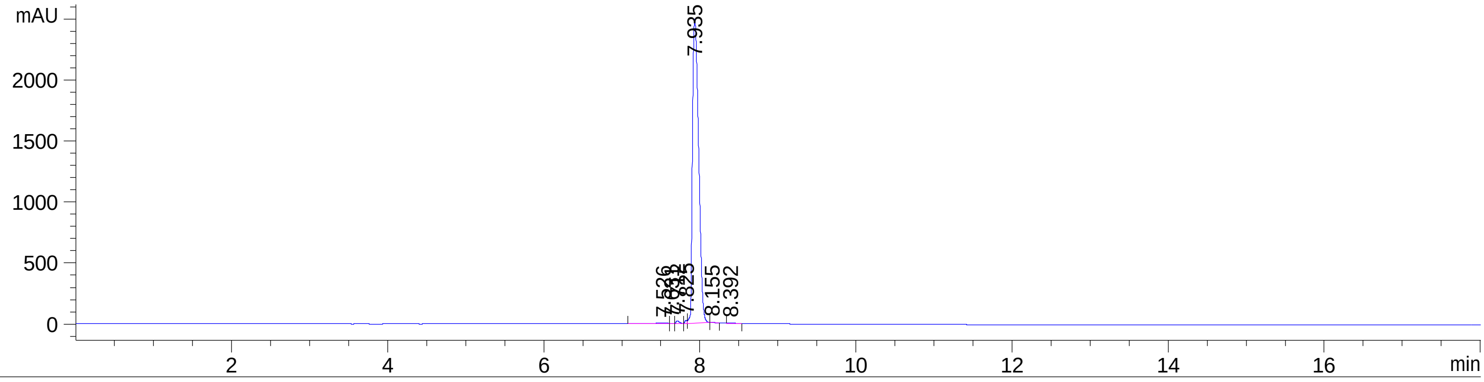


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.547	BV	0.2106	104.19794	5.86929	1.3545
2	7.644	VB	0.0490	16.08813	4.57380	0.2091
3	7.806	BV	0.0541	36.39954	10.32849	0.4732
4	7.959	VB	0.1011	7431.05859	1254.98767	96.6014
5	9.375	BB	0.2284	104.74931	5.68637	1.3617

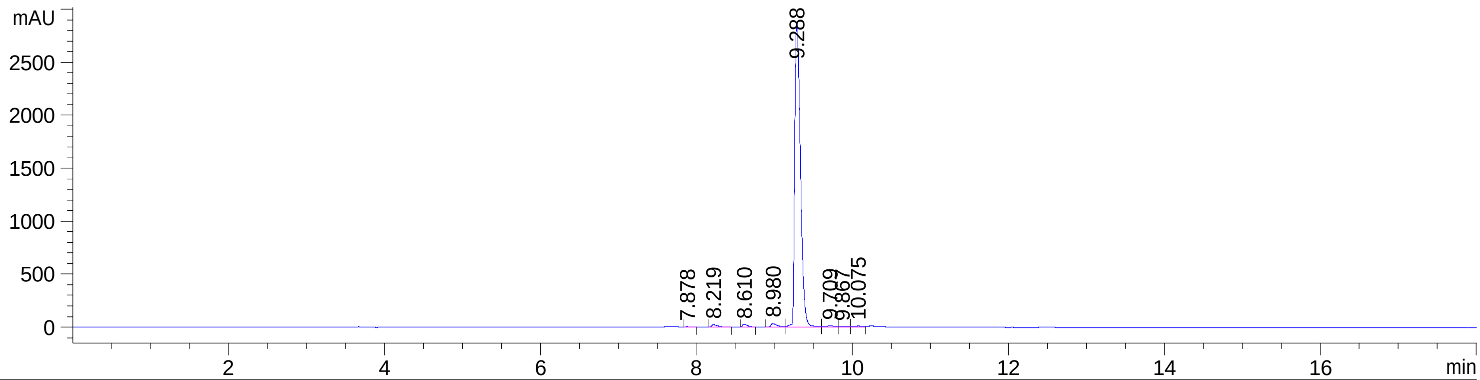


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.892	VV	0.0837	15.89127	2.35541	0.2367
2	8.056	VB	0.0762	13.43715	2.42269	0.2001
3	8.301	BB	0.0610	6.31684	1.44539	0.0941
4	8.501	BB	0.0704	32.20456	7.04132	0.4796
5	9.202	VV	0.0610	47.56428	12.90168	0.7084
6	9.297	VB	0.0767	6570.74414	1351.37634	97.8589
7	10.232	BV	0.0845	28.34934	4.53287	0.4222

Sample Name: 28

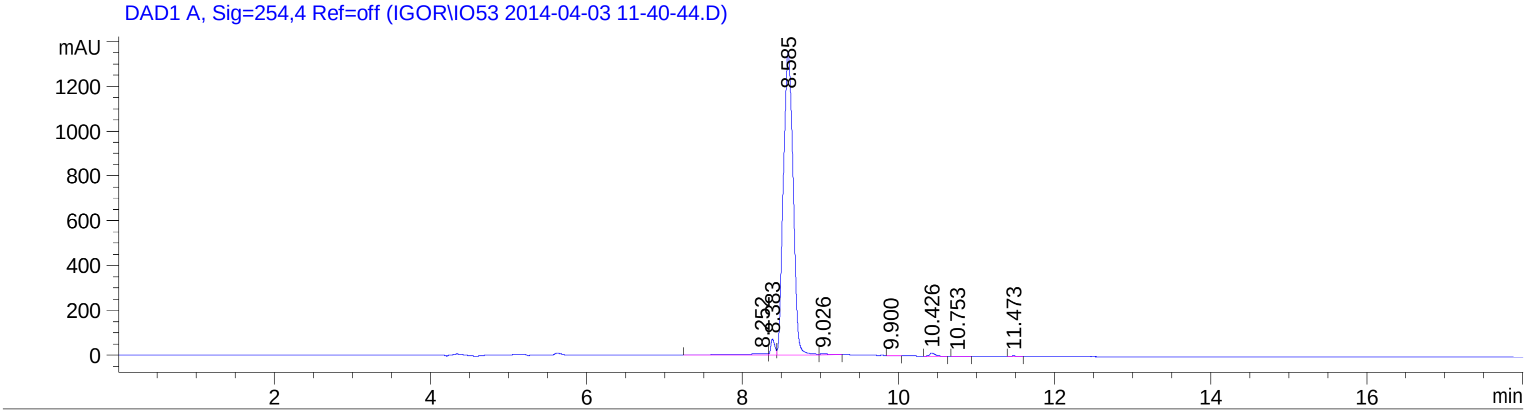


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.526	BV	0.1840	63.33385	4.10444	0.4549
2	7.631	VB	0.0369	6.40645	2.63104	0.0460
3	7.712	BB	0.0470	68.71401	22.92845	0.4935
4	7.825	BV	0.0313	46.63649	23.83233	0.3350
5	7.935	VB	0.0913	1.37150e4	2488.37695	98.5094
6	8.155	BB	0.0530	9.51653	2.81420	0.0684
7	8.392	VB	0.0837	12.92423	1.89169	0.0928

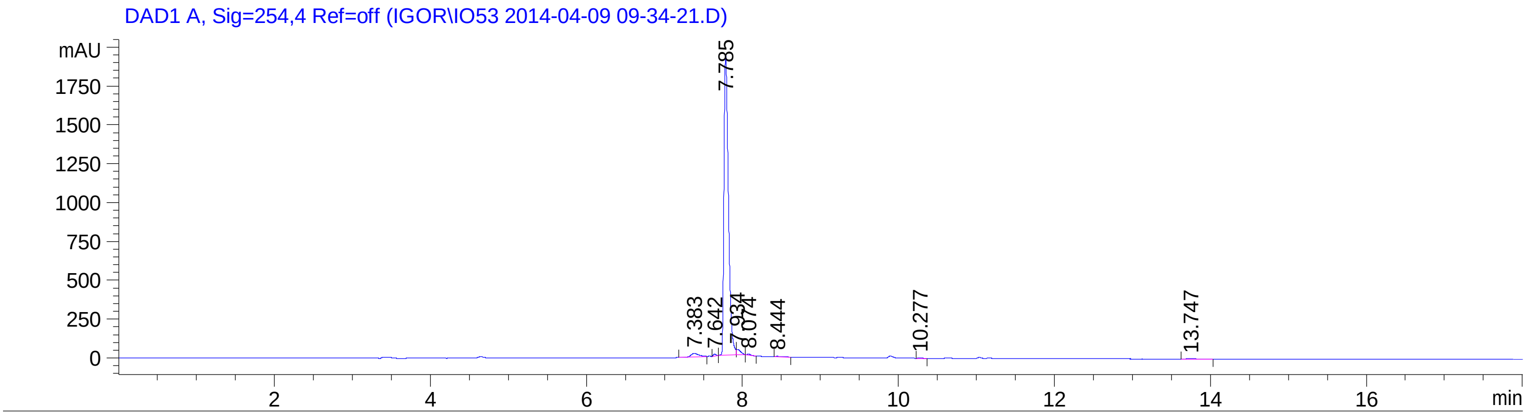


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.878	VV	0.0824	15.09164	2.36773	0.0990
2	8.219	BB	0.0754	105.99377	21.36873	0.6951
3	8.610	BB	0.0720	107.00383	23.79654	0.7017
4	8.980	BV	0.0796	165.02600	32.03164	1.0822
5	9.288	VV	0.0803	1.46227e4	2876.98877	95.8924
6	9.709	VV	0.1234	94.75630	10.58620	0.6214
7	9.867	VV	0.1003	50.97498	6.30364	0.3343
8	10.075	VV	0.1171	87.52140	9.44903	0.5739

Sample Name: 29

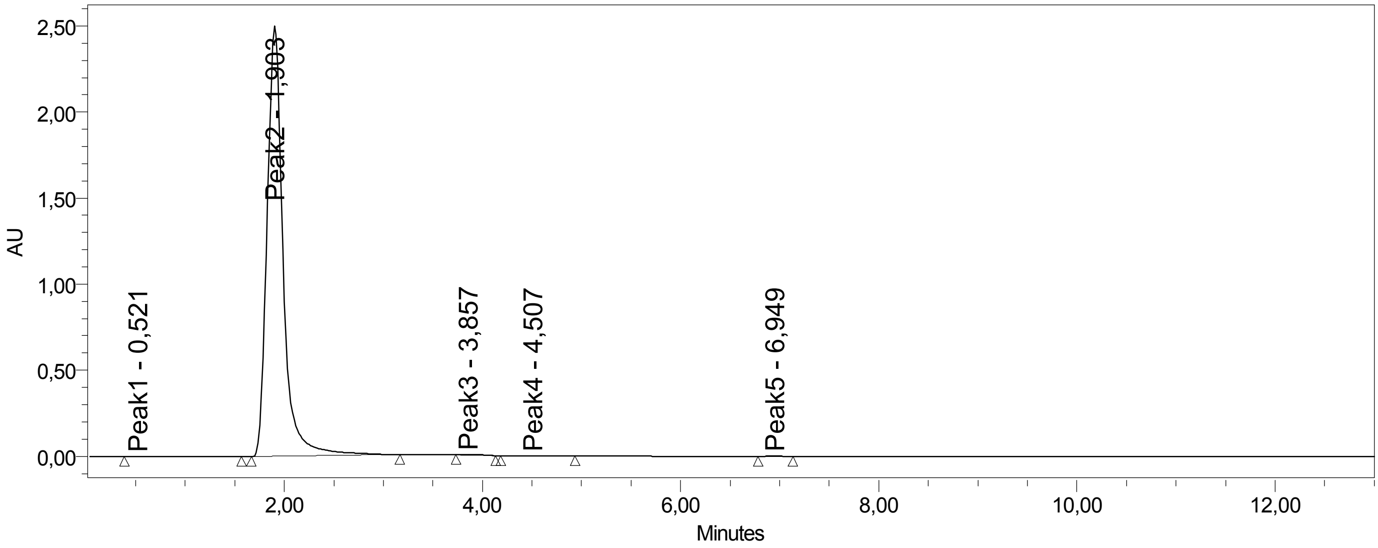


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.252	BV	0.3355	154.97433	5.41331	1.2671
2	8.383	VV	0.0557	247.20737	69.92418	2.0211
3	8.585	VV	0.1322	1.16918e4	1353.95520	95.5909
4	9.026	VB	0.1144	42.24943	4.85879	0.3454
5	9.900	BV	0.0808	10.33165	1.64416	0.0845
6	10.426	BB	0.0673	66.87661	14.23998	0.5468
7	10.753	BB	0.0663	5.71115	1.05228	0.0467
8	11.473	BB	0.0676	11.93638	2.50465	0.0976

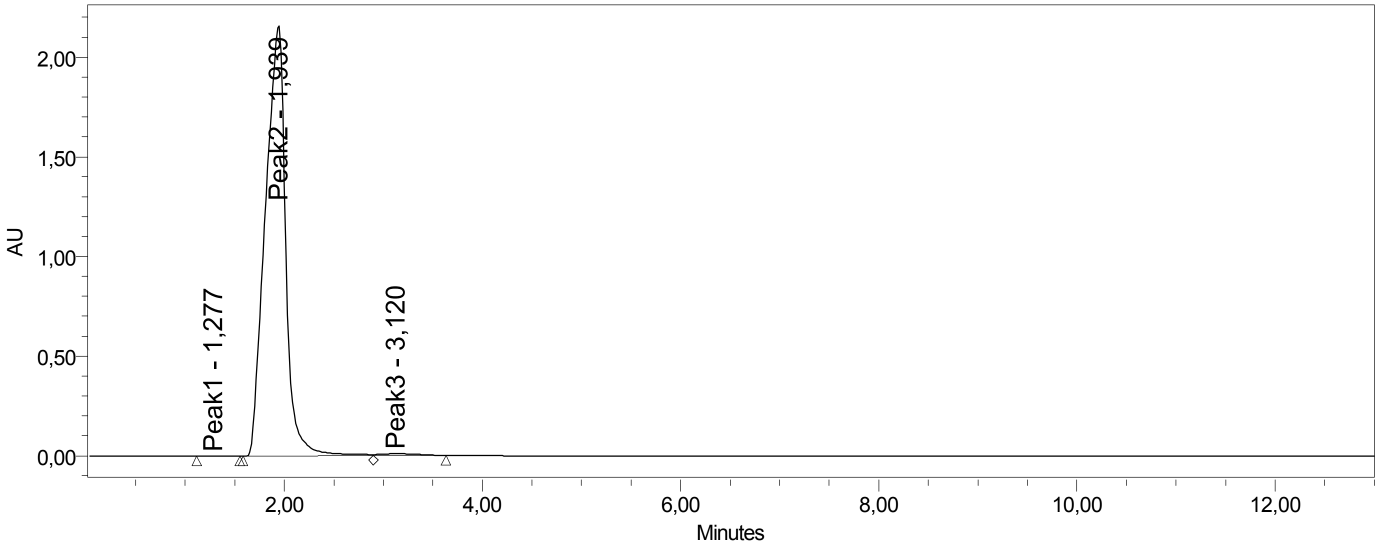


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.383	BV	0.1142	171.20050	22.51560	2.1104
2	7.642	BB	0.0404	30.71502	12.41855	0.3786
3	7.785	BV	0.0621	7724.98584	1935.99902	95.2256
4	7.934	VB	0.0582	132.72450	35.86045	1.6361
5	8.074	BB	0.0482	21.66151	6.53628	0.2670
6	8.444	BB	0.0700	14.14155	2.72489	0.1743
7	10.277	VV	0.0701	6.93675	1.40517	0.0855
8	13.747	BB	0.0944	9.93222	1.51750	0.1224

Sample Name: 30

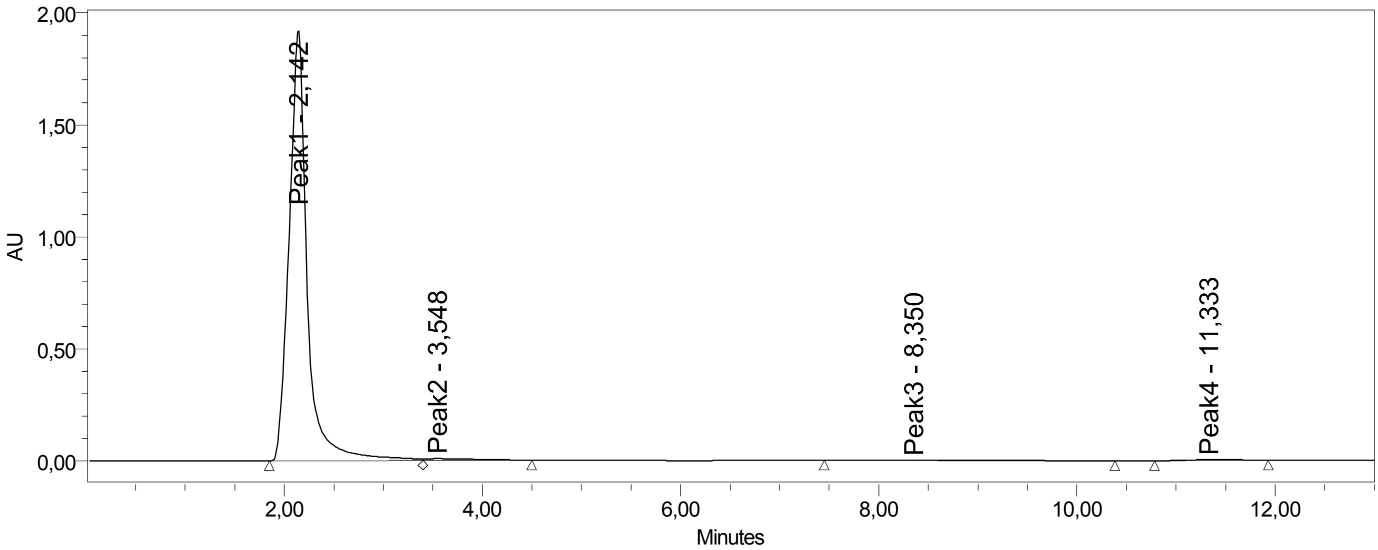


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,521	18370	0,07	490
2	Peak2	1,903	28132926	99,66	2497051
3	Peak3	3,857	48141	0,17	4058
4	Peak4	4,507	26200	0,09	1383
5	Peak5	6,949	4503	0,02	400

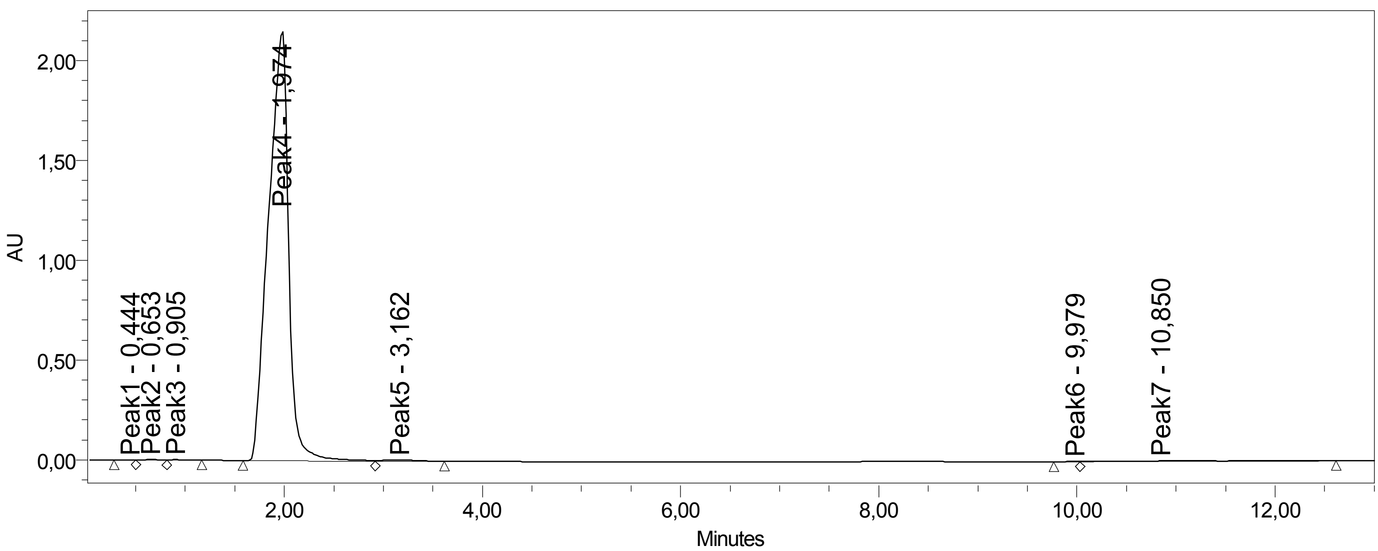


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,277	4748	0,02	454
2	Peak2	1,939	30809330	99,27	2177747
3	Peak3	3,120	222065	0,72	10300

Sample Name: 31

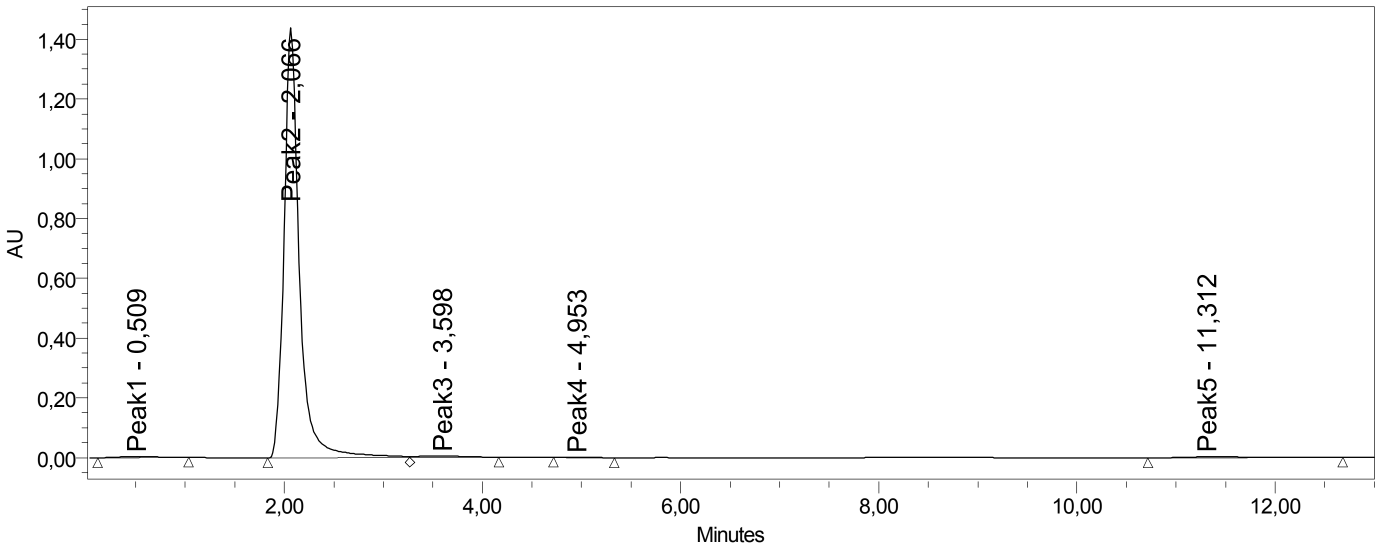


	Peak Name	RT	Area	% Area	Height
1	Peak1	2,142	24320339	97,95	1928548
2	Peak2	3,548	246330	0,99	8145
3	Peak3	8,350	169328	0,68	1742
4	Peak4	11,333	93764	0,38	2487

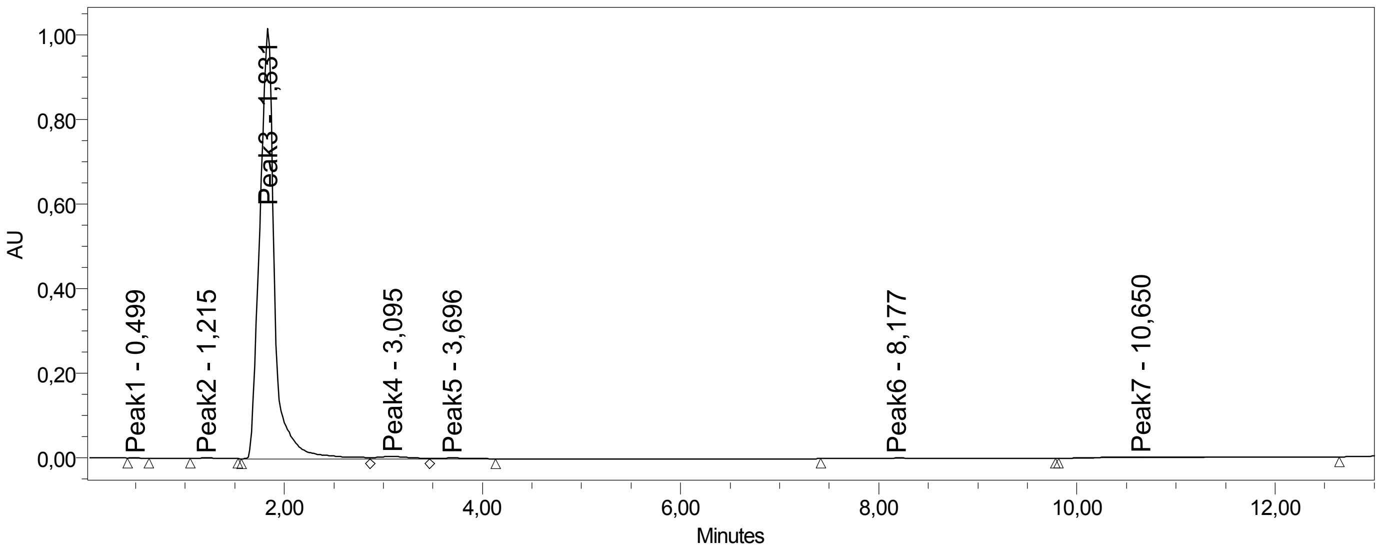


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,444	7447	0,02	1022
2	Peak2	0,653	37513	0,12	2832
3	Peak3	0,905	35329	0,11	2745
4	Peak4	1,974	30438790	98,68	2165735
5	Peak5	3,162	133948	0,43	6048
6	Peak6	9,979	4407	0,01	454
7	Peak7	10,850	189424	0,61	2051

Sample Name: 32

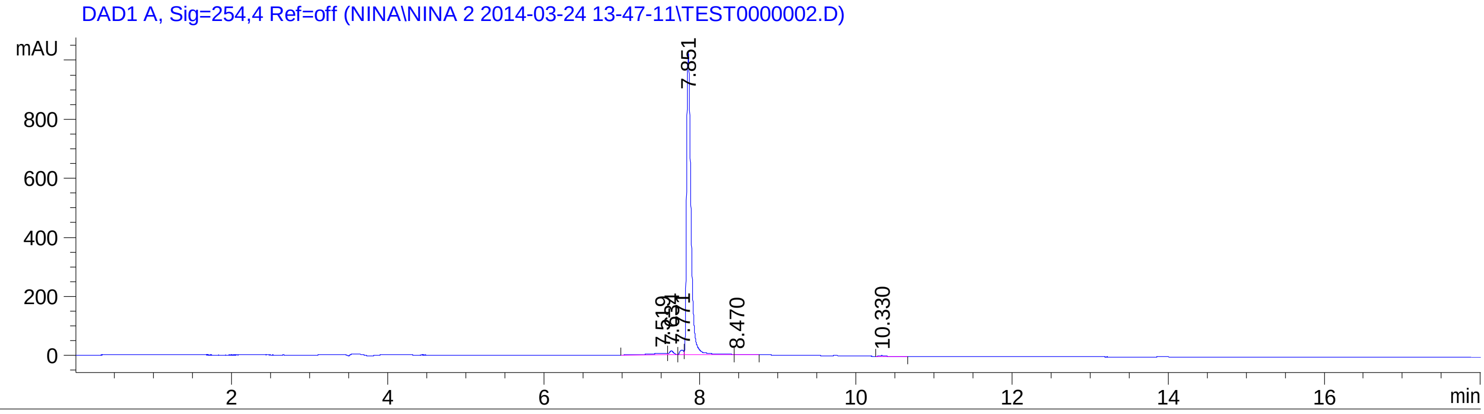


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,509	81917	0,51	2712
2	Peak2	2,066	15533782	97,51	1435321
3	Peak3	3,598	145679	0,91	5251
4	Peak4	4,953	21139	0,13	1293
5	Peak5	11,312	147348	0,92	2552

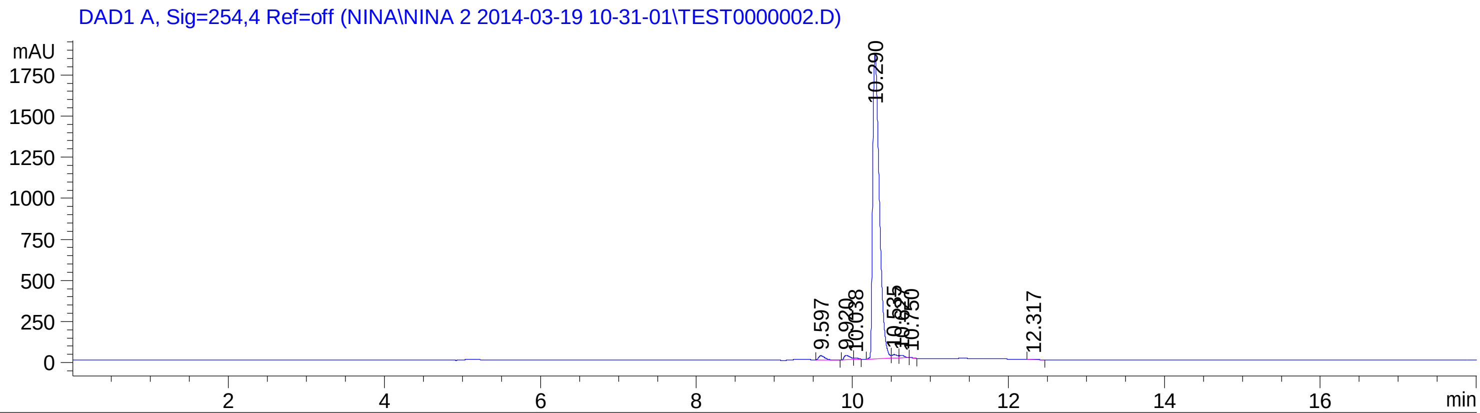


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,499	2505	0,02	412
2	Peak2	1,215	15062	0,14	1744
3	Peak3	1,831	10508149	96,07	1015969
4	Peak4	3,095	114874	1,05	5696
5	Peak5	3,696	36805	0,34	1680
6	Peak6	8,177	78133	0,71	995
7	Peak7	10,650	182562	1,67	1855

Sample Name: 34

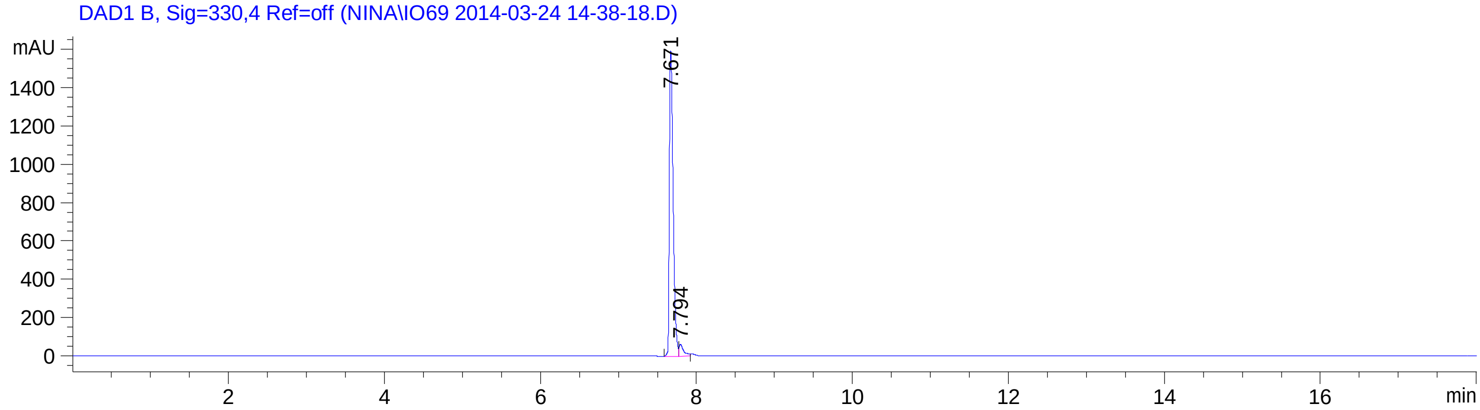


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.519	BV	0.1919	79.05135	4.88288	1.8641
2	7.634	VB	0.0574	51.29633	13.63024	1.2096
3	7.771	BV	0.0547	51.38031	15.29219	1.2116
4	7.851	VV	0.0604	4032.30298	1023.89929	95.0855
5	8.470	VB	0.1132	14.82044	1.55494	0.3495
6	10.330	BB	0.0662	11.86001	2.57595	0.2797

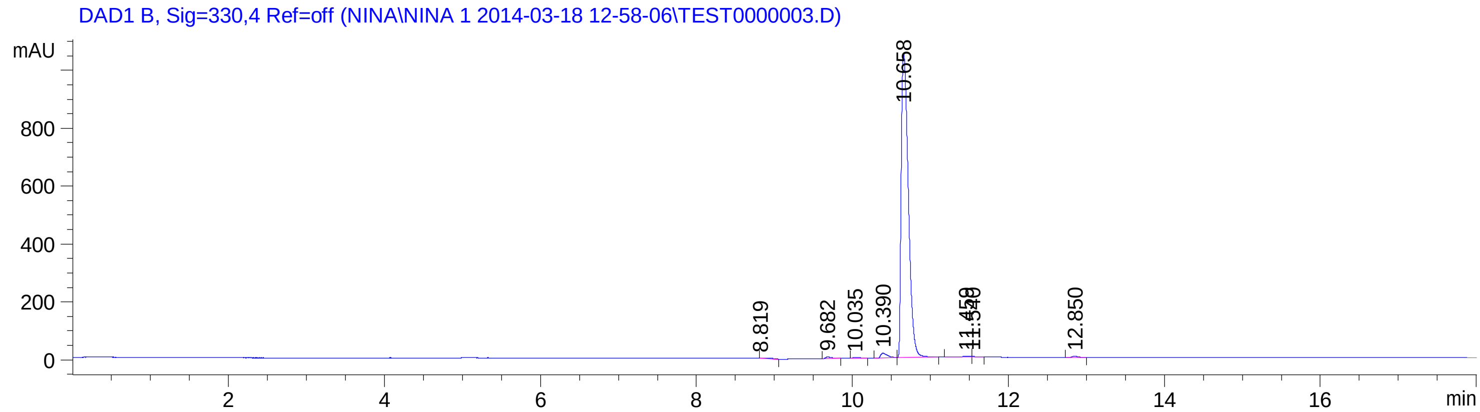


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.597	VB	0.0882	152.19554	26.61145	1.3282
2	9.920	BV	0.0797	139.22368	26.13055	1.2150
3	10.038	VB	0.0545	31.76940	8.52029	0.2772
4	10.290	BV	0.0921	1.09341e4	1846.62122	95.4208
5	10.535	VV	0.0732	113.35368	22.92750	0.9892
6	10.627	VB	0.0734	73.41582	15.89852	0.6407
7	10.750	BB	0.0637	5.61417	1.29065	0.0490
8	12.317	BB	0.0735	9.15296	1.53660	0.0799

Sample Name: 35

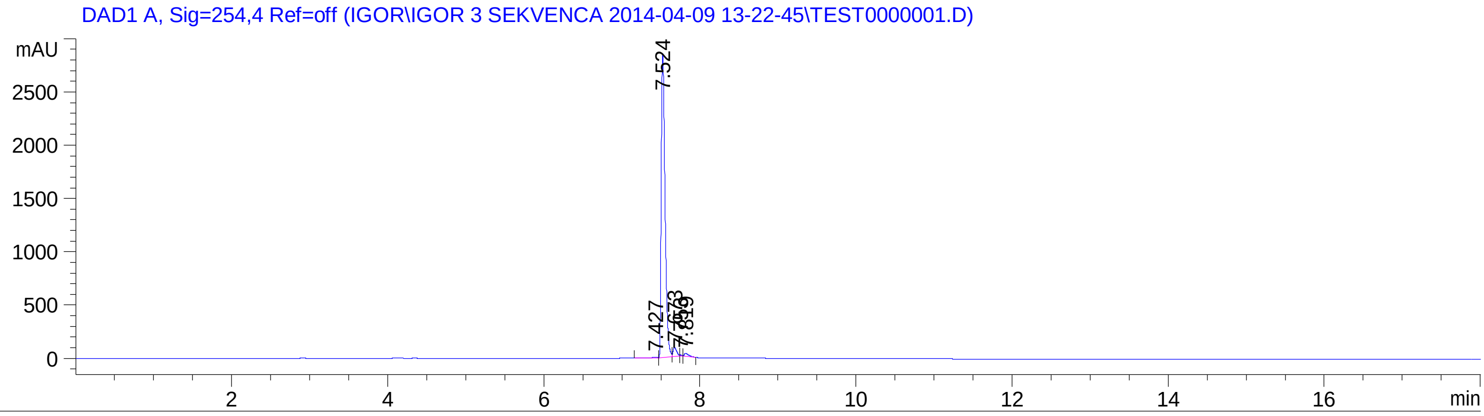


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.671	BV	0.0524	5368.72705	1589.40210	95.1979
2	7.794	VV	0.0628	270.81403	61.55981	4.8021

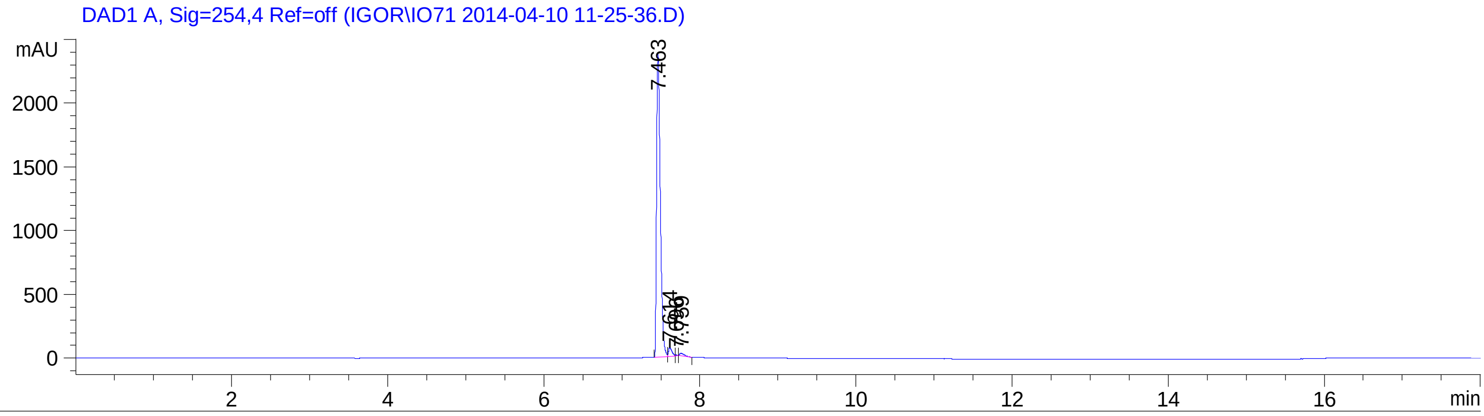


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.819	VB	0.1897	18.39823	1.14379	0.2671
2	9.682	BV	0.0795	30.14439	5.16861	0.4377
3	10.035	BB	0.0715	18.23293	3.40217	0.2647
4	10.390	BV	0.0865	98.56040	16.07614	1.4309
5	10.658	VB	0.1013	6670.11523	1047.63721	96.8401
6	11.459	BV	0.1251	19.35805	1.84223	0.2810
7	11.540	VB	0.0563	6.94603	1.53580	0.1008
8	12.850	BB	0.0719	26.00815	5.02616	0.3776

Sample Name: 36

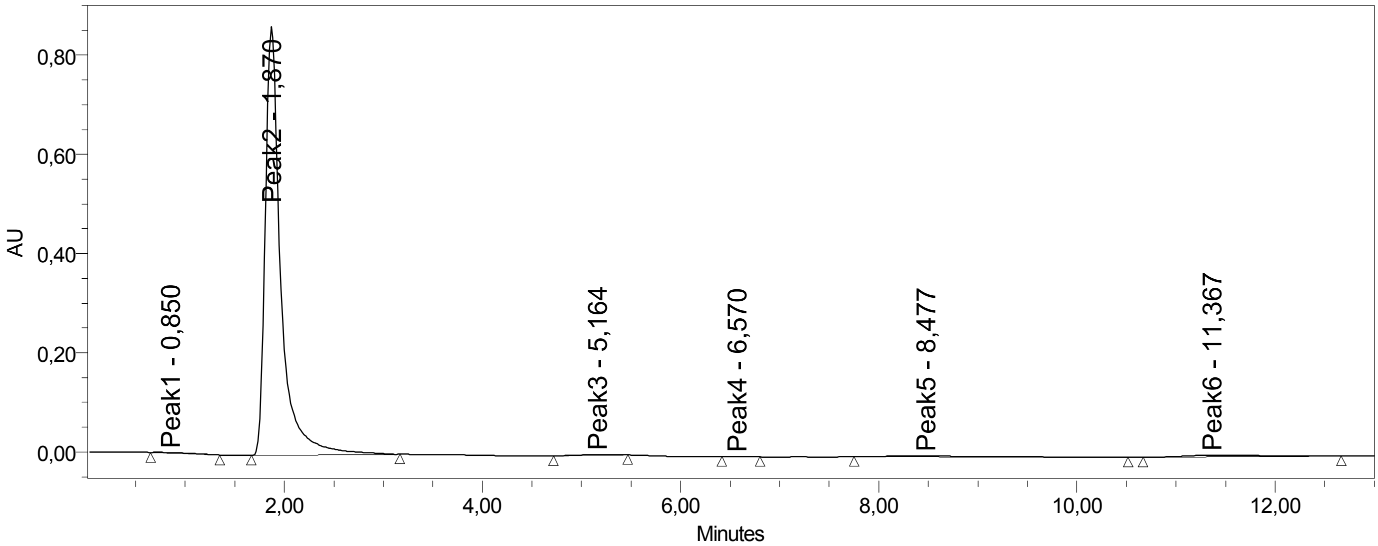


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.427	BB	0.0777	12.00829	1.88830	0.1196
2	7.524	BV	0.0520	9651.10059	2849.38623	96.1079
3	7.673	VV	0.0485	265.23276	83.61145	2.6412
4	7.753	VB	0.0293	15.44356	8.66407	0.1538
5	7.819	BB	0.0550	98.16235	26.04781	0.9775

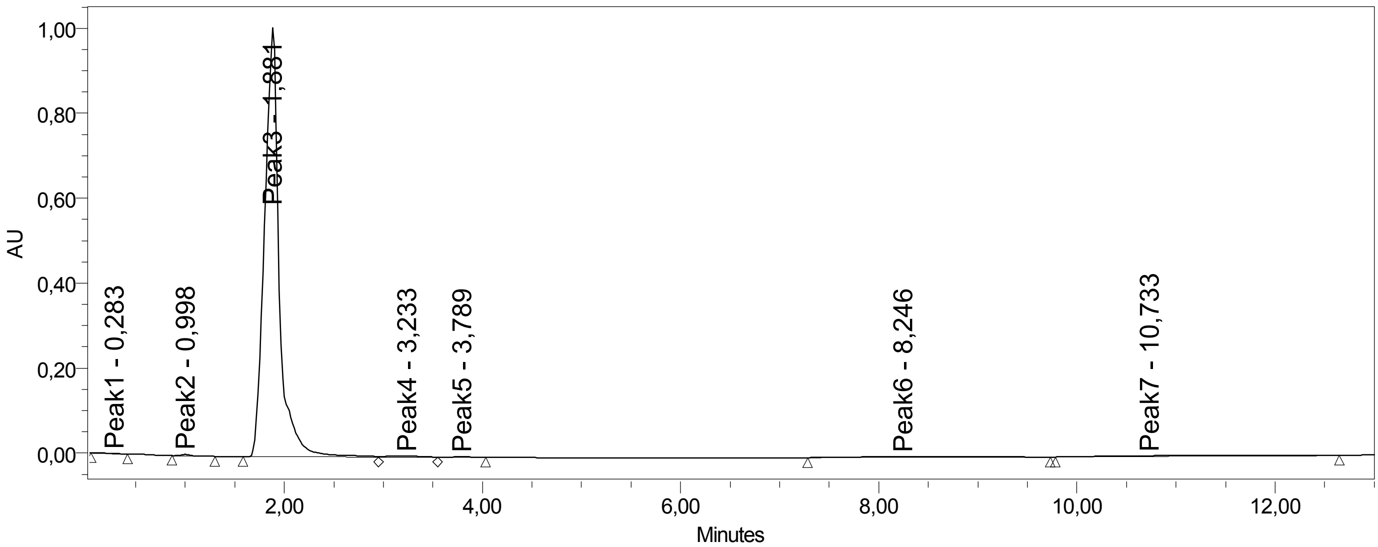


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.463	BV	0.0515	7962.14307	2379.07715	96.2920
2	7.614	VV	0.0469	204.84021	66.53059	2.4773
3	7.696	VB	0.0272	10.18409	6.03438	0.1232
4	7.759	BB	0.0583	91.58028	22.57058	1.1075

Sample Name: 37

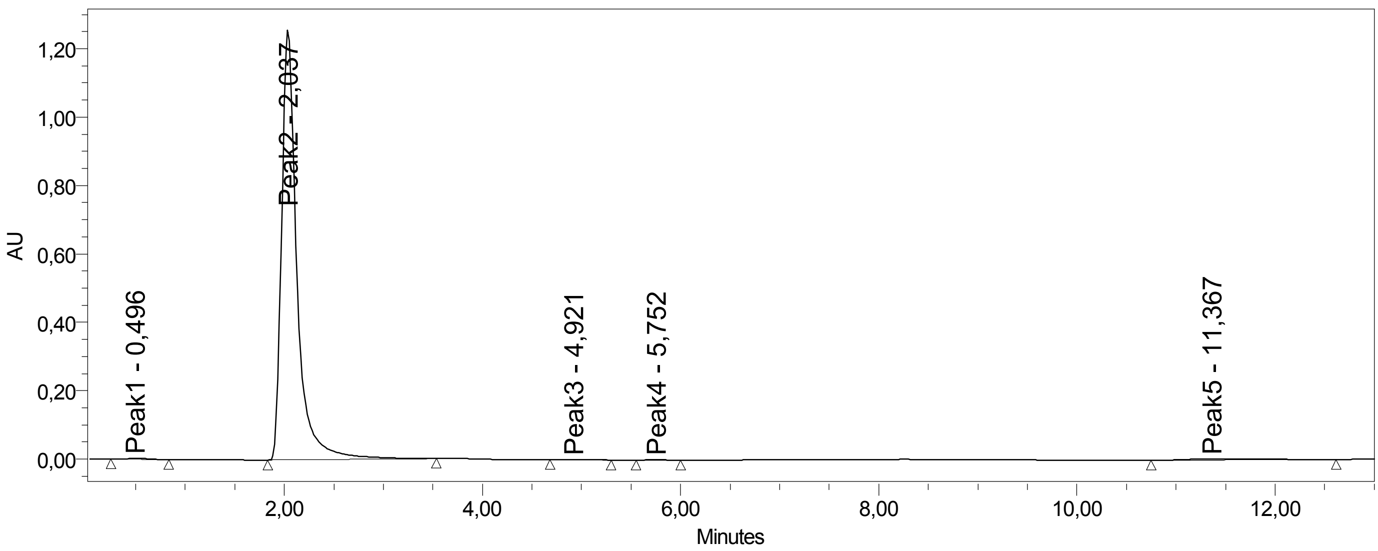


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,850	31848	0,32	1388
2	Peak2	1,870	9487640	96,46	863870
3	Peak3	5,164	37185	0,38	1684
4	Peak4	6,570	4942	0,05	435
5	Peak5	8,477	112081	1,14	1356
6	Peak6	11,367	161910	1,65	2845

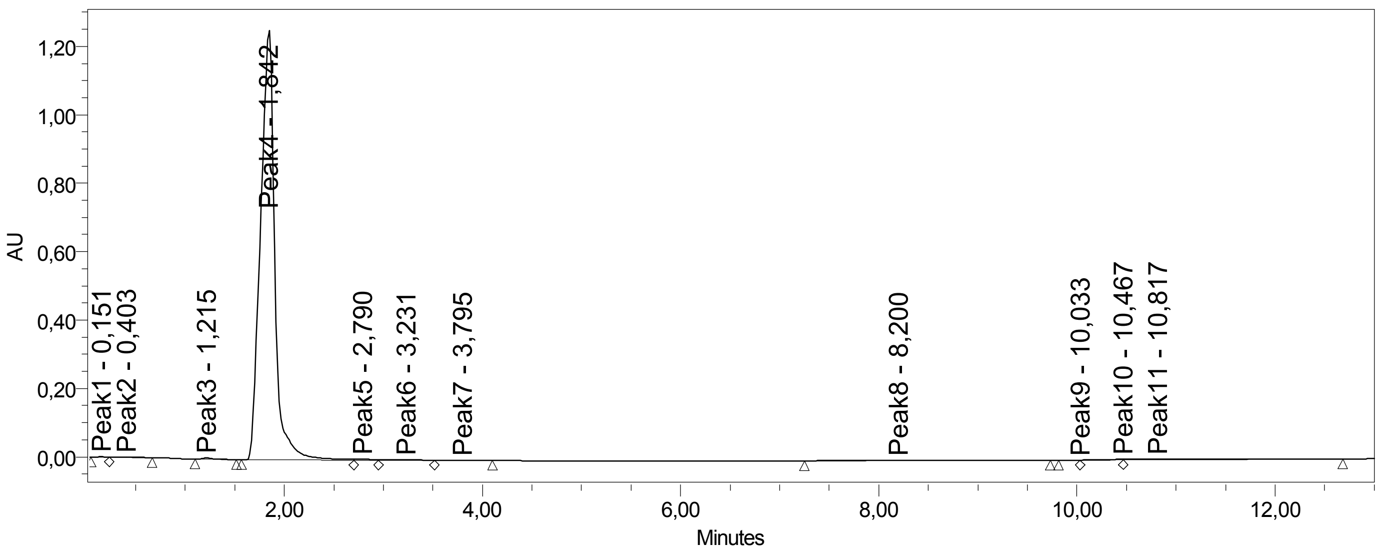


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,283	15314	0,14	1117
2	Peak2	0,998	23831	0,22	3290
3	Peak3	1,881	10468478	96,49	1006243
4	Peak4	3,233	52128	0,48	2346
5	Peak5	3,789	10052	0,09	688
6	Peak6	8,246	98208	0,91	1151
7	Peak7	10,733	180844	1,67	1992

Sample Name: 38

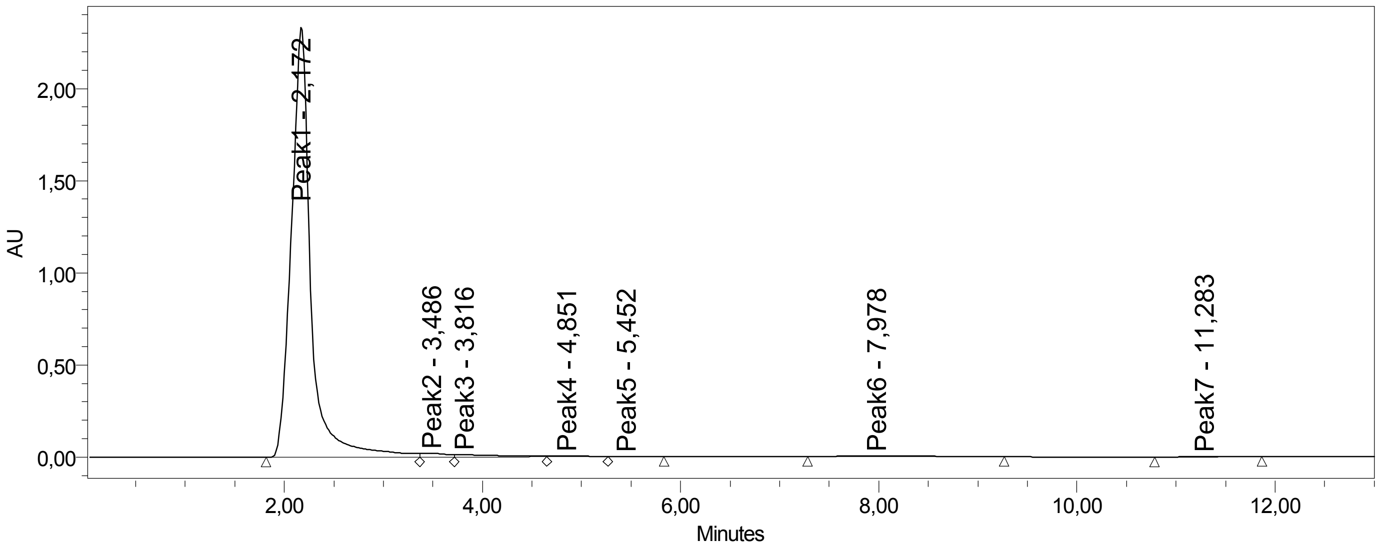


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,496	36770	0,27	2725
2	Peak2	2,037	13561198	98,41	1256271
3	Peak3	4,921	17260	0,13	1005
4	Peak4	5,752	9205	0,07	739
5	Peak5	11,367	156349	1,13	3039

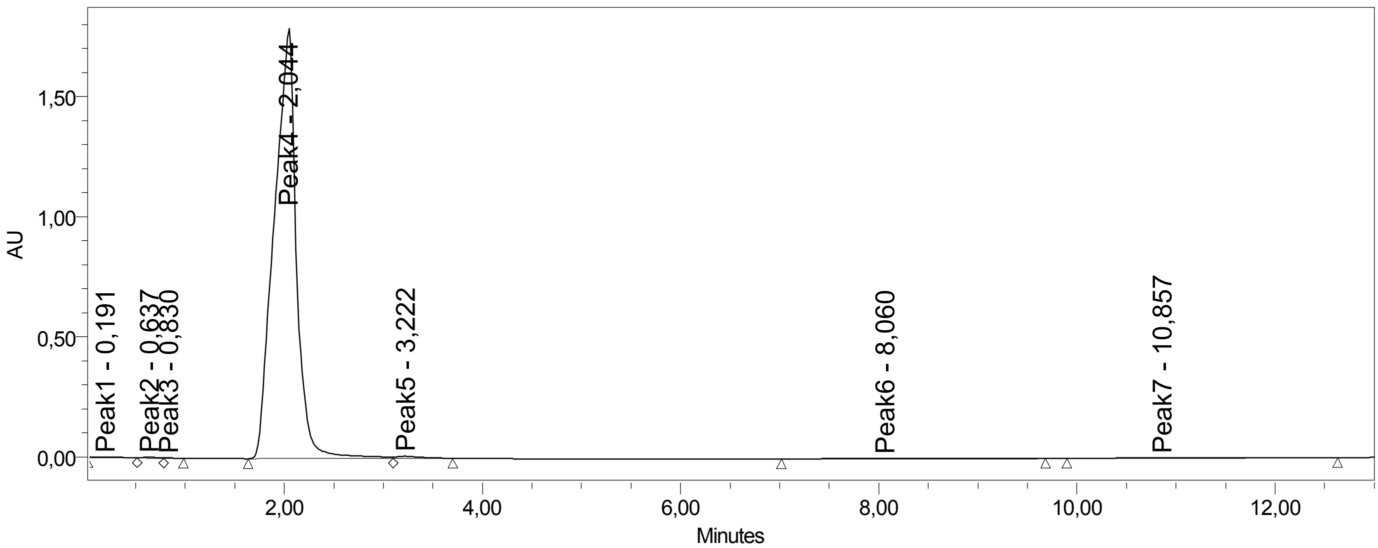


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,151	5746	0,04	892
2	Peak2	0,403	25414	0,20	1523
3	Peak3	1,215	25709	0,20	3641
4	Peak4	1,842	12519565	96,72	1260745
5	Peak5	2,790	29324	0,23	2518
6	Peak6	3,231	44348	0,34	1951
7	Peak7	3,795	17504	0,14	1022
8	Peak8	8,200	99649	0,77	1218
9	Peak9	10,033	1809	0,01	277
10	Peak10	10,467	29897	0,23	1674
11	Peak11	10,817	145772	1,13	1990

Sample Name: 39

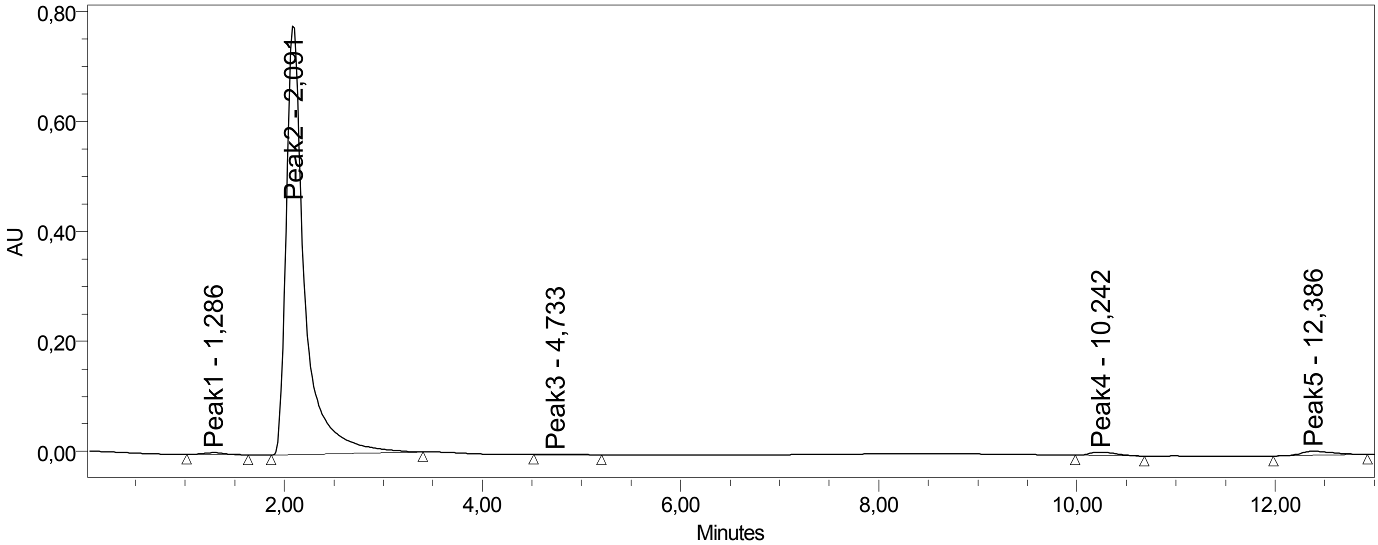


	Peak Name	RT	Area	% Area	Height
1	Peak1	2,172	31975823	96,33	2334572
2	Peak2	3,486	348397	1,05	19760
3	Peak3	3,816	402419	1,21	12752
4	Peak4	4,851	131934	0,40	5361
5	Peak5	5,452	44635	0,13	2222
6	Peak6	7,978	209924	0,63	3152
7	Peak7	11,283	80212	0,24	2284

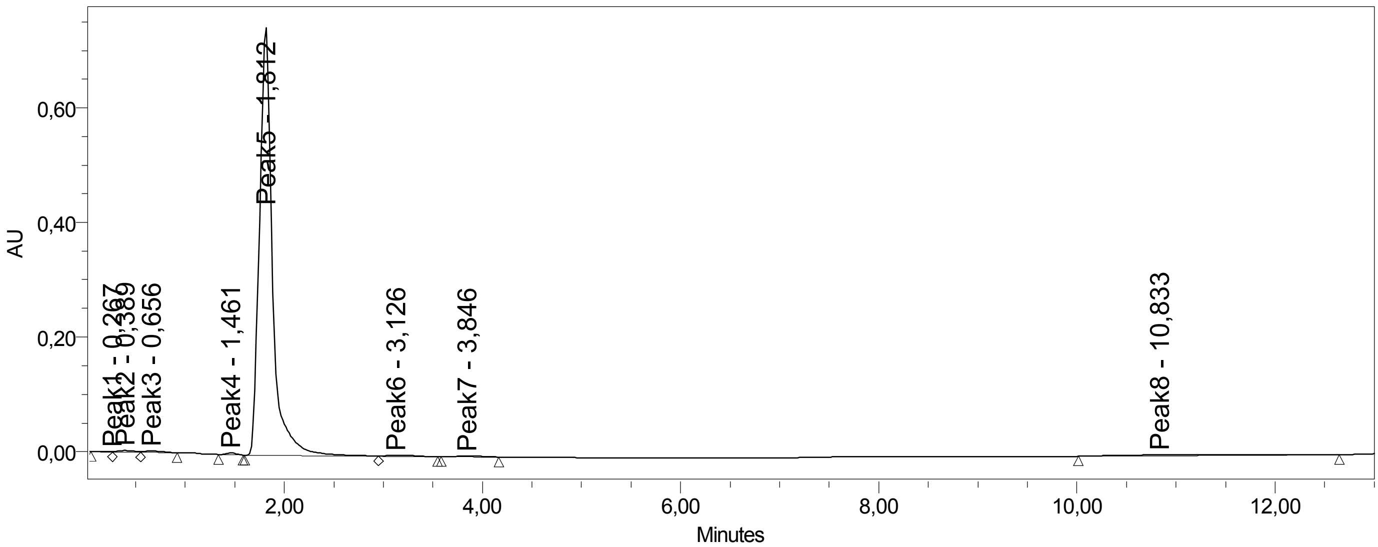


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,191	74145	0,26	3438
2	Peak2	0,637	35997	0,13	4326
3	Peak3	0,830	6704	0,02	1035
4	Peak4	2,044	27814501	97,98	1794182
5	Peak5	3,222	132974	0,47	8814
6	Peak6	8,060	150422	0,53	1662
7	Peak7	10,857	174204	0,61	1876

Sample Name: 40

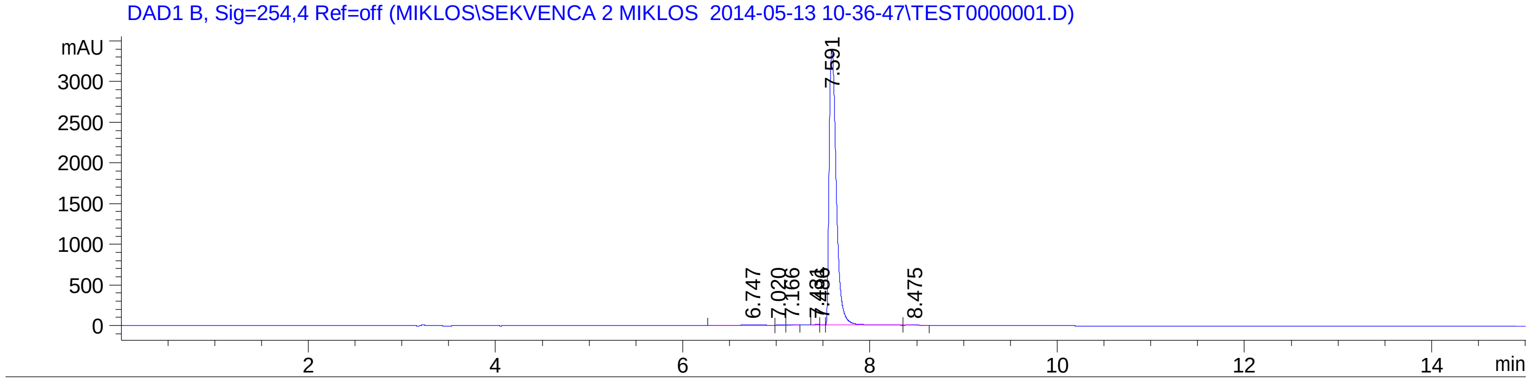


	Peak Name	RT	Area	% Area	Height
1	Peak1	1,286	47229	0,45	3321
2	Peak2	2,091	10161845	96,75	783646
3	Peak3	4,733	26182	0,25	1212
4	Peak4	10,242	104335	0,99	5537
5	Peak5	12,386	163638	1,56	7298

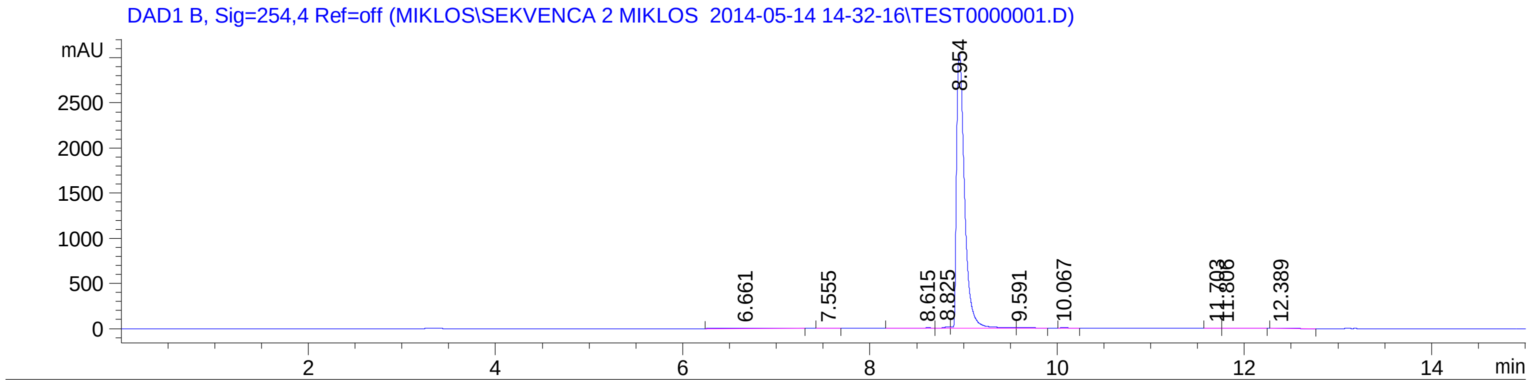


	Peak Name	RT	Area	% Area	Height
1	Peak1	0,267	7058	0,10	925
2	Peak2	0,389	32590	0,46	2643
3	Peak3	0,656	34478	0,48	2623
4	Peak4	1,461	20975	0,29	3441
5	Peak5	1,812	6836725	95,50	744540
6	Peak6	3,126	49972	0,70	2481
7	Peak7	3,846	32306	0,45	2222
8	Peak8	10,833	144957	2,02	1672

Sample Name: 41

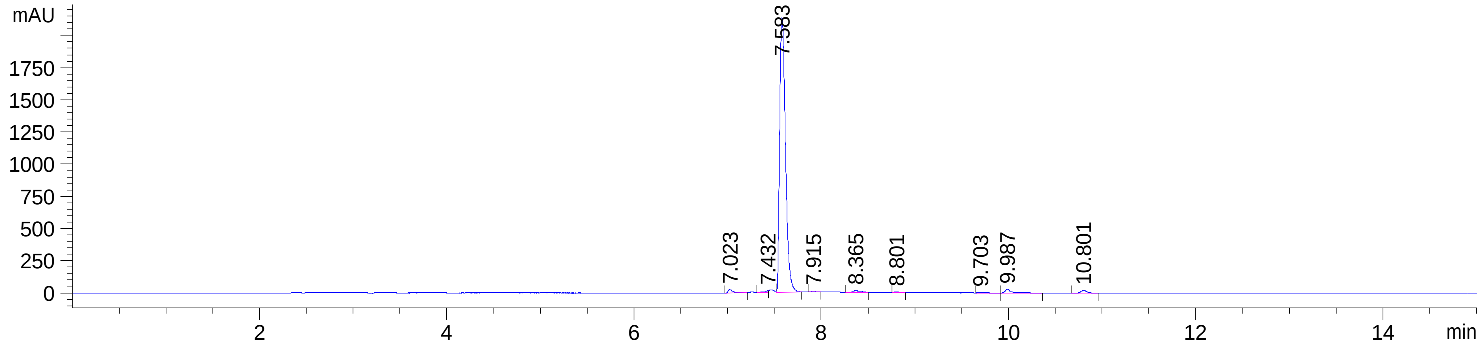


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.747	BB	0.2365	102.24201	5.10901	0.5635
2	7.020	BV	0.0581	26.11293	6.26295	0.1439
3	7.166	VB	0.0686	19.23531	3.64358	0.1060
4	7.431	BV	0.0491	26.78262	8.42363	0.1476
5	7.486	VV	0.0455	17.19991	5.81246	0.0948
6	7.591	VB	0.0729	1.79321e4	3382.27393	98.8345
7	8.475	BB	0.0832	19.89902	3.25880	0.1097

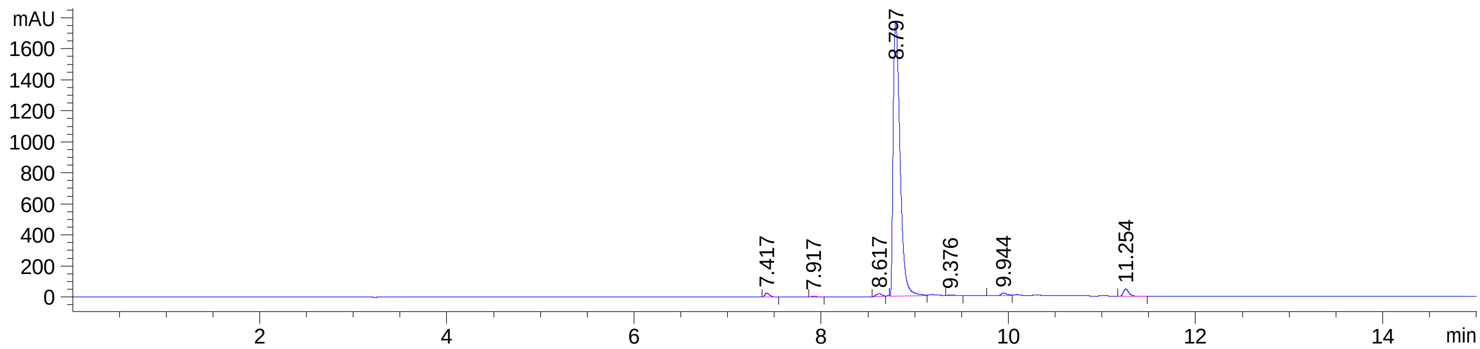


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.661	BB	0.3493	73.13423	2.45294	0.3959
2	7.555	BB	0.0819	16.95400	2.55471	0.0918
3	8.615	BV	0.0887	48.23012	7.33471	0.2611
4	8.825	VV	0.0631	74.17924	16.61006	0.4015
5	8.954	VV	0.0919	1.81575e4	3053.46826	98.2823
6	9.591	VB	0.1178	40.07056	4.33537	0.2169
7	10.067	VB	0.0735	24.12022	4.89036	0.1306
8	11.703	VV	0.0980	9.20056	1.14804	0.0498
9	11.806	VB	0.1082	14.85909	1.85948	0.0804
10	12.389	BB	0.1244	16.59746	1.68496	0.0898

Sample Name: 42

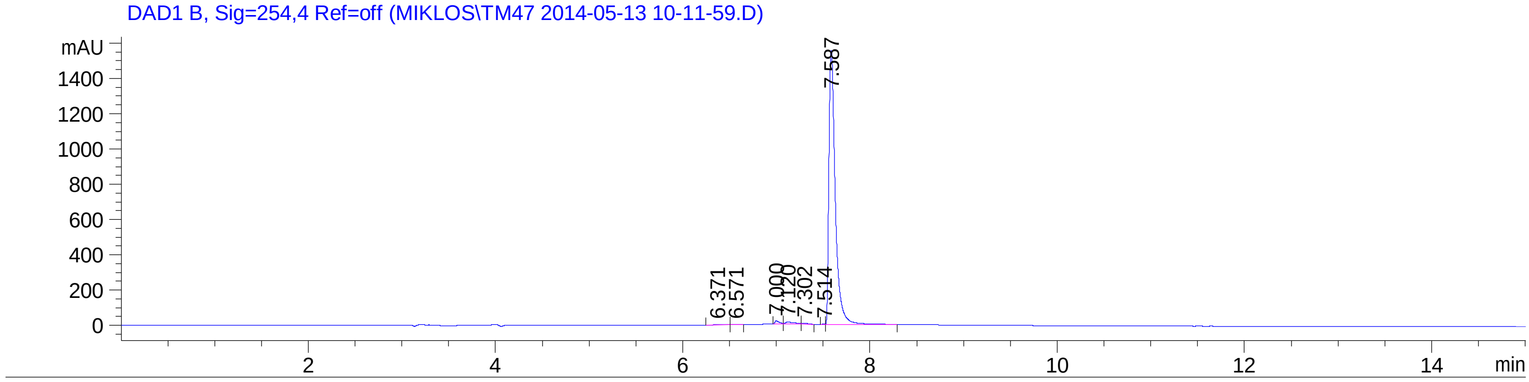


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.023	BB	0.0524	96.71097	26.94332	1.0004
2	7.432	BV	0.0343	29.66064	12.46399	0.3068
3	7.583	VV	0.0683	9194.48730	2130.52783	95.1072
4	7.915	BB	0.0511	21.74875	6.40102	0.2250
5	8.365	BV	0.0754	79.84153	14.34903	0.8259
6	8.801	BV	0.0572	18.95380	5.05888	0.1961
7	9.703	BB	0.0622	13.10441	3.14021	0.1356
8	9.987	BB	0.0678	130.72540	27.83163	1.3522
9	10.801	BB	0.0608	82.26559	20.75148	0.8510

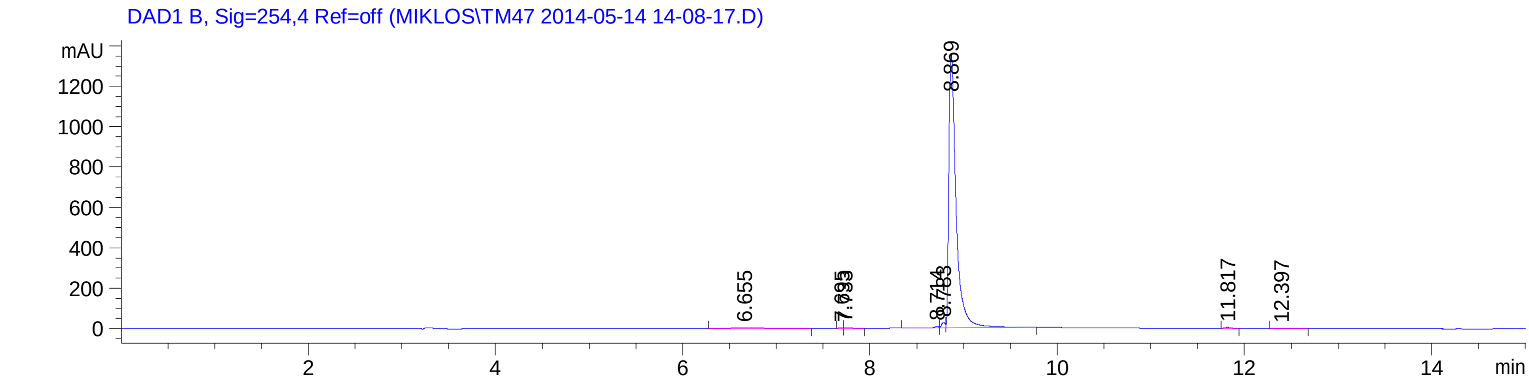


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.417	BB	0.0542	87.52073	24.76833	0.9202
2	7.917	BB	0.0530	20.41072	5.60416	0.2146
3	8.617	BB	0.0527	68.05319	18.59532	0.7155
4	8.797	VV	0.0802	9048.70996	1767.46301	95.1371
5	9.376	BB	0.0555	14.51447	3.89221	0.1526
6	9.944	BV	0.0799	79.47834	15.60193	0.8356
7	11.254	BB	0.0615	192.53976	47.32071	2.0243

Sample Name: 43



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.371	BV	0.0872	23.11329	3.53760	0.3019
2	6.571	VB	0.0584	9.63028	2.34622	0.1258
3	7.000	BV	0.0465	57.45541	17.89169	0.7505
4	7.120	VV	0.0895	87.62866	12.77541	1.1447
5	7.302	VB	0.0657	24.32160	5.13867	0.3177
6	7.514	BV	0.0289	6.69461	3.73645	0.0874
7	7.587	VV	0.0734	7446.55615	1554.86169	97.2719



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.655	BB	0.3571	74.74962	2.45233	0.9865
2	7.695	VV	0.0472	8.20980	2.54317	0.1083
3	7.733	VB	0.0617	10.01465	2.15549	0.1322
4	8.714	BV	0.0650	29.01695	6.38721	0.3829
5	8.783	VV	0.0435	72.94117	26.18888	0.9626
6	8.869	VB	0.0811	7344.33398	1358.27917	96.9215
7	11.817	VB	0.0640	20.91494	4.73846	0.2760
8	12.397	BB	0.1138	17.43189	1.87740	0.2300

References.

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2. Boarland M. P. V.; McOmie, J. F. W. *J. Chem. Soc.* **1951**, 1218.

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