

Supporting Information

Synthesis of 3-amino-thiochromanes from 4-benzyl 2-thiazolines, via an unprecedented intramolecular electrophilic aromatic substitution

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General Information:

NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts (δ) are reported in ppm (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad) and are indicated in ppm using TMS as internal standard. Coupling constants (J) are given in Hertz.

Mass spectra were obtained on a GC/MS Saturn 2000 spectrometer and HRMS on a Waters QTOF micro spectrometer. IR spectra were recorded with a Perkin Elmer 16 PC FT-IR instrument. Analytical data were obtained using a THERMOQUEST NA 2500 instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

X-ray diffraction experiments were performed with graphite-monochromatized MoK α radiation on a Bruker-Nonius Kappa CCD area detector diffractometer.

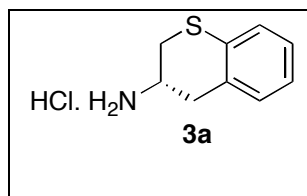
Preparation of the starting materials: Thiazolines **1a** and **1b** were prepared according to: G. Mercey, D. Brégeon, A.-C. Gaumont, J. Levillain, M. Gulea, *Tetrahedron Lett.*, 2008, **49**, 6553. Thiazolinium salts **4a-e** and disulfides **5b-d** were prepared according to: G. Mercey, J.-F. Lohier, A.-C. Gaumont, J. Levillain, M. Gulea, *Eur. J. Org. Chem.* 2009, 4357.

Preparation of the 3-amino-thiochromanes **3a,b** and **6a-e**. *General procedure:*

1 mmol of starting material (thiazoline **3**, thiazolinium salt **4**, or disulfide **2** or **5**) was placed in aqueous 5N HCl (5 mL) and heated at 100°C, in air, until reaction completion. After

evaporation under vacuum, the residue was washed with acetone and the resulting solid filtrated and dried to afford the 3-amino-thiochromane as a hydrochloride.

(S)-3-Aminothiochromane hydrochloride **3a**



Prepared from thiazoline **1a** (150 mg, 0.86 mmol); reaction time = 5 days; yield = 86%.

Prepared from disulfide **2a** (50 mg, 0.28 mmol); reaction time = 4 days; yield = 88%.

Formula: C₉H₁₂NSCl

Molecular weight: 201.72 g.mol⁻¹

Aspect: red powder

[α]_D²⁰ - 17 (c = 0.45, MeOH); for the (*R*)-**3a**: [α]_D²⁰ + 18 (c = 1.00, MeOH)

mp 214 °C

¹H NMR (250 MHz, D₂O) δ (ppm) 2.96 (dd, *J* = 6.1, 17.1 Hz, 1H), 3.08 (dd, *J* = 6.4, 13.6 Hz, 1H), 3.20 (dd, *J* = 4.3, 17.1 Hz, 1H), 3.33 (dd, *J* = 3.1, 13.6 Hz, 1H), 4.02 – 4.09 (m, 1H), 7.07 – 7.17 (m, 4H).

¹³C NMR (63 MHz, D₂O) δ (ppm) 28.8, 32.1, 44.7, 125.5, 126.5, 127.6, 129.0, 130.2, 131.1.

HMRS (ESI) calcd. for C₉H₁₂NS, 166.0690; found, 166.0698.

Elemental analysis : Calc. for C₉H₁₂NSCl + 0.3 HCl: H 5.83, C 50.83, N 6.59; found: H 5.69, C 50.77, N 6.65.

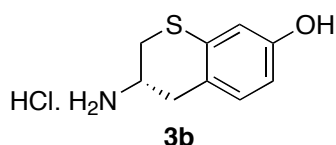
See reference for the racemic compound: RN [103659-74-1], B. Trivedi, Eur. Pat. Appl. (1986), EP 181109 A2 19860514.

X-ray crystallographic data

Single crystals of aminothiochromane (*S*)-**3a** suitable for X-ray crystallographic analysis were obtained by slow evaporation of methanol. X-ray diffraction experiments for monocystal of **3a** were performed at 291 K with graphite-monochromatized Mo K α radiation on an Bruker–Nonius Kappa CCD area detector diffractometer. Formula C₉H₁₂CINS, *M* = 201.71, crystal system orthorhombic, space group *P*2₁2₁2₁ (no. 19), *a* = 5.3668(11) Å, *b* = 6.2152(12) Å, *c* = 29.035(6) Å, *U* = 968.5(3) Å³, *T* = 291 K, *Z* = 4, calculated density = 1.383 g/cm³, μ = 0.55 mm⁻¹, 15838 reflections measured, 2871 unique (*R*_{int} = 0.069) which were used in all calculations. The final *wR*(*F*₂) was 0.141 (all data).

Single crystals of aminothiochromane (*R*)-**3a** suitable for X-ray crystallographic analysis were obtained by slow evaporation of methanol. X-ray diffraction experiments for monocrystal of **3a** were performed at 291 K with graphite-monochromatized Mo K α radiation on an Bruker–Nonius Kappa CCD area detector diffractometer. Formula C₉H₁₂ClNS, *M* = 201.71, crystal system orthorhombic, space group *P*2₁2₁2₁ (no. 19), *a* = 5.3436(12) Å, *b* = 6.2291(19) Å, *c* = 29.214(8) Å, *U* = 972.4(4) Å³, *T* = 291 K, *Z* = 4, calculated density = 1.378 g/cm³, μ = 0.55 mm⁻¹, 39910 reflections measured, 4476 unique (*R*_{int} = 0.021) which were used in all calculations. The final *wR*(*F*₂) was 0.085 (all data).

(*S*)-3-Amino-7-hydroxythiochromane hydrochloride **3b**



Prepared from thiazoline **1b** (150 mg, 0.86 mmol); reaction time = 10 days; yield = 36%.

Formula: C₉H₁₂NOSCl

Molecular weight: 217.72 g.mol⁻¹

Aspect: red powder

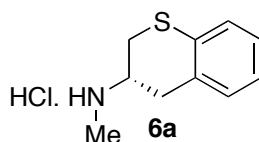
[α]_D²⁰ + 61 (*c* = 0.23, MeOH)

¹H NMR (500 MHz, D₂O) δ (ppm) 2.78 (dd, *J* = 5.2, 13.5 Hz, 1H), 2.96 (dd, *J* = 4.5, 10.5 Hz, 1H), 2.99 (dd, *J* = 3.8, 13.5 Hz, 1H), 3.20 (dd, *J* = 2.5, 10.5 Hz, 1H), 3.90 – 3.95 (m, 1H), 6.47 – 6.90 (m, 4H).

¹³C NMR (125 MHz, D₂O) : δ (ppm) 28.6, 31.3, 44.7, 112.4, 113.0, 120.6, 131.2, 132.2, 154.4.

HMRS (ESI) calcd. for C₉H₁₂NOS, 182.0640; found, 182.0646.

(*S*)-3-(Methylamino)thiochromane hydrochloride **6a**



Prepared from thiazolinium salt **4a** (50 mg, 0.08 mmol); reaction time = 5 days; yield = 69%.

Formula: C₁₀H₁₄NSCl

Molecular weight: 215.74 g.mol⁻¹

Aspect: white powder

$[\alpha]_{\text{D}}^{20}$ - 36 (c = 0.10, MeOH)

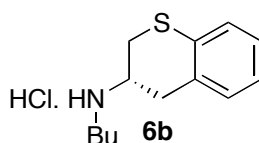
mp 191 °C

^1H NMR (400 MHz, D_2O) δ (ppm) 2.74 (s, 3H), 3.05 (dd, J = 5.0, 17.3 Hz, 1H), 3.15 (dd, J = 5.8, 13.8 Hz, 1H), 3.23 (dd, J = 4.3, 17.3 Hz, 1H), 3.40 (dd, J = 3.1, 13.8 Hz, 1H), 3.89 – 3.95 (m, 1H), 7.07 – 7.17 (m, 4H).

^{13}C NMR (125 MHz, D_2O) δ (ppm) 27.2, 30.4, 30.6, 52.0, 125.5, 126.6, 127.7, 128.4, 130.3, 131.1.

HMRS (ESI) calc. for $\text{C}_{10}\text{H}_{14}\text{NS}$, 180.0847; found, 180.0847.

(S)-3-(Butylamino)thiochromane hydrochloride **6b**



Prepared from thiazolinium salt **4b** (50 mg, 0.18 mmol); reaction time = 5 days; yield = 87%.

Prepared from disulfide **5b** (30 mg, 0.06 mmol); reaction time = 3 days; yield = 84%.

Formula: $\text{C}_{13}\text{H}_{20}\text{NSCl}$

Molecular weight: 257.82 $\text{g}\cdot\text{mol}^{-1}$

Aspect: white powder

$[\alpha]_{\text{D}}^{20}$ + 26 (c = 0.40, MeOH).

mp 194 °C.

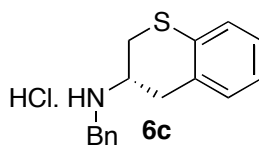
^1H NMR (400 MHz, D_2O) δ (ppm) 0.77 (t, J = 7.2 Hz, 3H), 1.25 (sx, J = 7.2 Hz, 2H), 1.48 – 1.58 (m, 2H), 2.94 (dd, J = 6.2, 17.3 Hz, 1H), 2.98 – 3.09 (m, 3H), 3.16 (dd, J = 4.5, 17.3 Hz, 1H), 3.27 (dd, J = 2.7, 13.6 Hz, 1H), 3.84 – 3.90 (m, 1H), 6.98 – 7.08 (m, 4H).

^{13}C NMR (63 MHz, D_2O) δ (ppm) 12.6, 19.2, 27.4, 31.0, 45.2, 51.3, 125.6, 126.6, 127.6, 129.0, 130.5, 131.0.

HMRS (ESI) calcd. for $\text{C}_{13}\text{H}_{20}\text{NS}$, 222.1316; found, 222.1326.

Elemental analysis : Calc. for $\text{C}_{13}\text{H}_{20}\text{NSCl}$ + 1.4 HCl: H 6.98, C 50.55, N 4.53; found: H 7.00, C 50.29, N 4.63.

(S)-3-(Benzylamino)thiochromane hydrochloride **6c**



Prepared from thiazolinium salt **4c** (100 mg, 0.28 mmol); reaction time = 14 days; yield = 89%. Prepared from disulfide **5c** (25 mg, 0.07 mmol); reaction time = 4 days; yield = 98%.

Formula: C₁₆H₁₈NSCl

Molecular weight: 291.84 g.mol⁻¹

Aspect: light blue powder

[α]_D²⁰ + 33 (c = 0.32, MeOH)

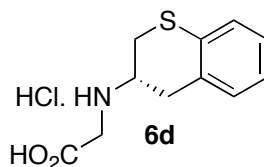
¹H NMR (400 MHz, D₂O) δ (ppm) 3.04 (dd, *J* = 5.9, 17.1 Hz, 1H), 3.17 (ddd, *J* = 1.0, 6.7, 13.6 Hz, 1H), 3.25 (dd, *J* = 4.6, 17.1 Hz, 1H), 3.36 (dd, *J* = 2.8, 13.6 Hz, 1H), 3.96 – 4.01 (m, 1H), 4.27 – 4.37 (m, 2H), 7.08 – 7.16 (m, 4H), 7.44 (s, 5H).

¹³C NMR (63 MHz, D₂O) δ (ppm) 27.6, 31.1, 48.8, 51.0, 125.6, 126.7, 127.7, 129.0, 129.3, 129.8, 129.9, 130.3, 130.5, 131.0.

HMRS (ESI) calcd. for C₁₆H₁₈NS, 256.1160; found, 256.1154.

Elemental analysis : Calc. for C₁₆H₁₈NSCl + 2 HCl: H 5.53, C 52.68, N 3.84; found: H 5.01, C 52.31, N 3.83.

(S)-2-(thiochromane-3)aminoacetic acid hydrochloride **6d**



Prepared from thiazolinium salt **4d** (170 mg, 0.42 mmol); reaction time = 5 days; yield = 83%. Prepared from disulfide **5d** (100 mg, 0.28 mmol); reaction time = 4 days; yield = 68%.

Formula: C₁₁H₁₄NO₂SCl

Molecular weight: 259.75 g.mol⁻¹

Aspect: light brown powder

[α]_D²⁰ + 14.8 (c = 0.40, MeOH).

mp 209 °C.

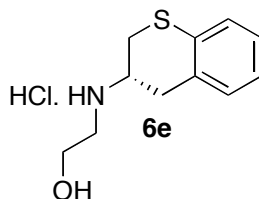
¹H NMR (400 MHz, D₂O) δ (ppm) 3.07 (dd, *J* = 6.4, 16.8 Hz, 1H), 3.17 (dd, *J* = 7.0, 13.9 Hz, 1H), 3.25 (dd, *J* = 4.0, 16.8 Hz, 1H), 3.36 (dd, *J* = 2.9, 13.9 Hz, 1H), 3.89 (AB, *J* = 16.8

Hz, 1H), 3.95 (AB, $J = 16.8$ Hz, 1H), 4.01 – 4.07 (m, 1H), 7.07 – 7.11 (m, 1H), 7.12 – 7.17 (m, 3H).

^{13}C NMR (63 MHz, D_2O) δ (ppm) 27.6, 30.9, 45.8, 52.1, 125.6, 126.6, 127.7, 129.0, 130.4, 131.0, 169.4.

Elemental analysis : Calc. for $\text{C}_{11}\text{H}_{14}\text{NSO}_2\text{Cl} + 0.6 \text{HCl}$: H 5.23, C 46.91, N 4.97; found: H 5.23, C 46.78, N 5.20.

(S)-3-(2-Hydroxyethyl)aminothiochromane hydrochloride 6e



Prepared from thiazolinium salt **4e** (100 mg, 0.32 mmol); reaction time = 7 days; yield = 82%.

Formula: $\text{C}_{11}\text{H}_{16}\text{NSCl}$

Molecular weight: $245.77 \text{ g}\cdot\text{mol}^{-1}$

Aspect: light brown powder

$[\alpha]_{\text{D}}^{20} -1.1$ ($c = 1.0$, MeOH).

mp $203 \text{ }^\circ\text{C}$.

^1H NMR (500 MHz, D_2O) δ (ppm) 3.02 (dd, $J = 6.0, 17.2$ Hz, 1H), 3.14 (dd, $J = 6.7, 13.5$ Hz, 1H), 3.20 - 3.27 (m, 3H), 3.34 (dd, $J = 3.0, 13.5$ Hz, 1H), 3.78 (t, $J = 5.2$ Hz, 1H), 3.96 - 4.01 (m, 1H), 7.04 – 7.14 (m, 4H).

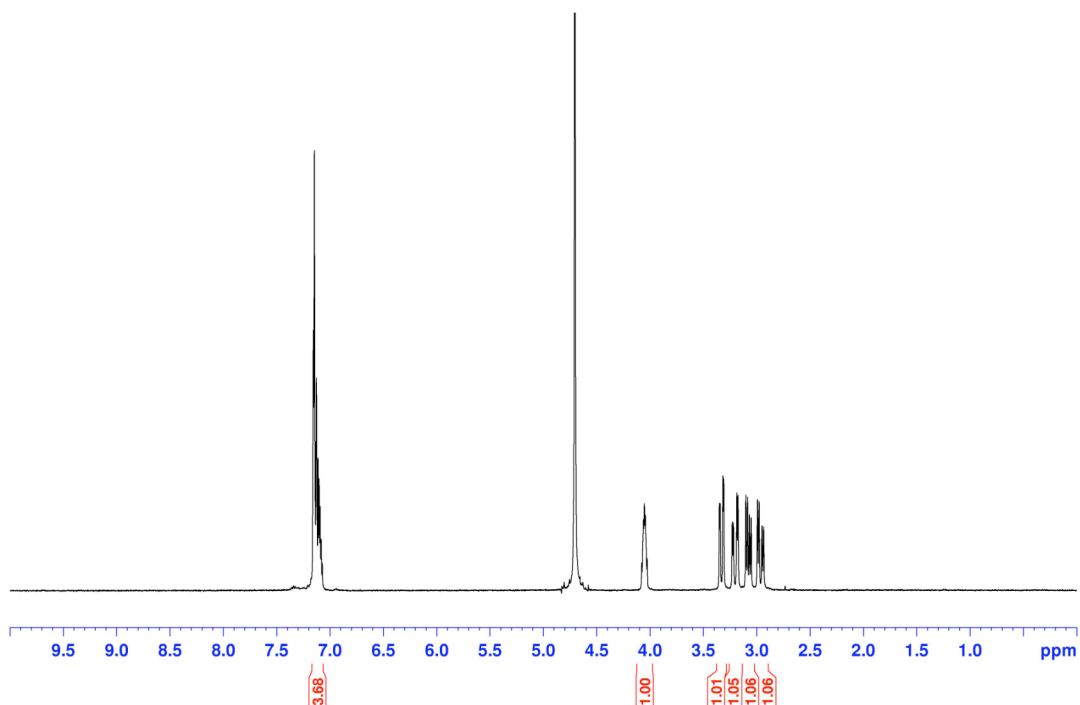
^{13}C NMR (125 MHz, D_2O) δ (ppm) 27.4, 31.0, 46.8, 51.5, 56.5, 125.6, 126.6, 127.6, 129.0, 130.4, 131.0.

HMRS (ESI) calc. for $\text{C}_{11}\text{H}_{16}\text{NSO}$, 210.0953; found, 210.0943.

Elemental analysis : Calc. for $\text{C}_{11}\text{H}_{16}\text{NSOCl} + 2 \text{HCl}$: H 5.69, C 41.46, N 4.40; found: H 5.62, C 41.29, N 4.55.

^1H NMR and ^{13}C NMR spectra of 3-amino-thiochromanes **3a,b** and **6a-e**:

3a:

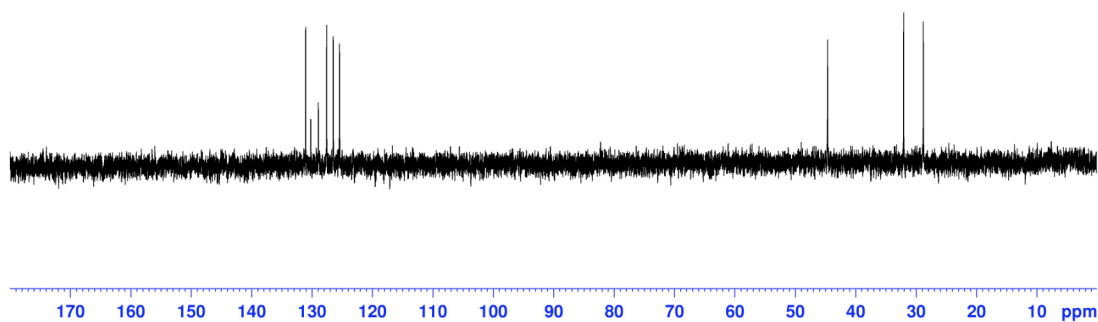


131.08
130.23
127.61
126.52
125.48

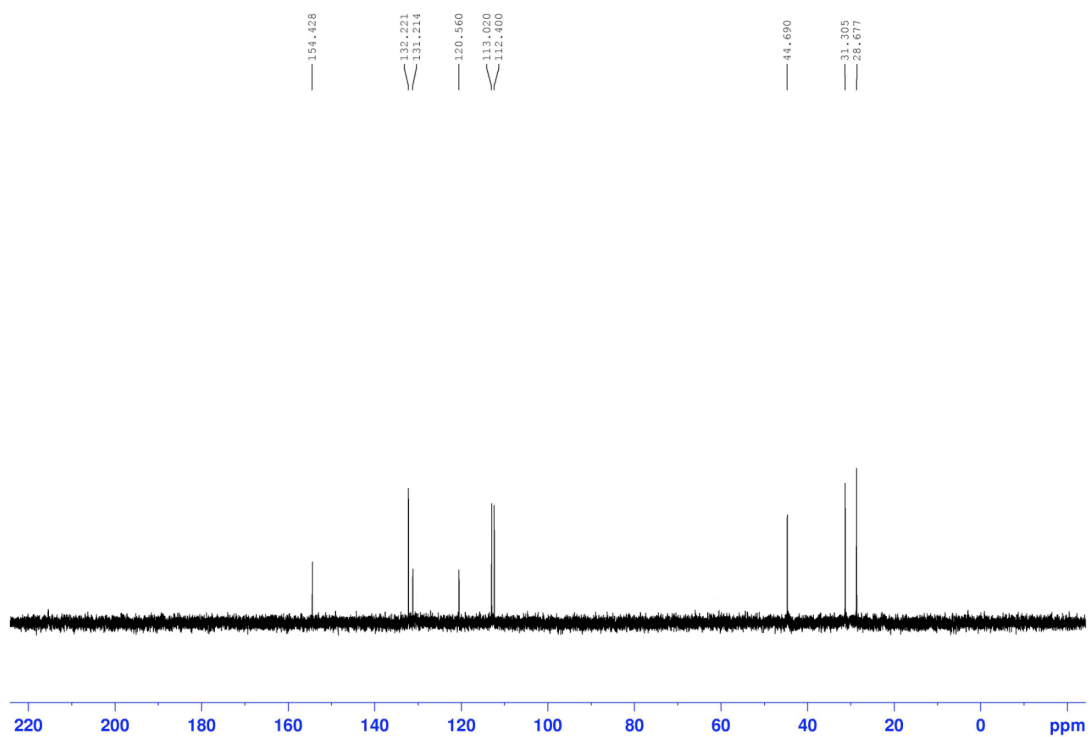
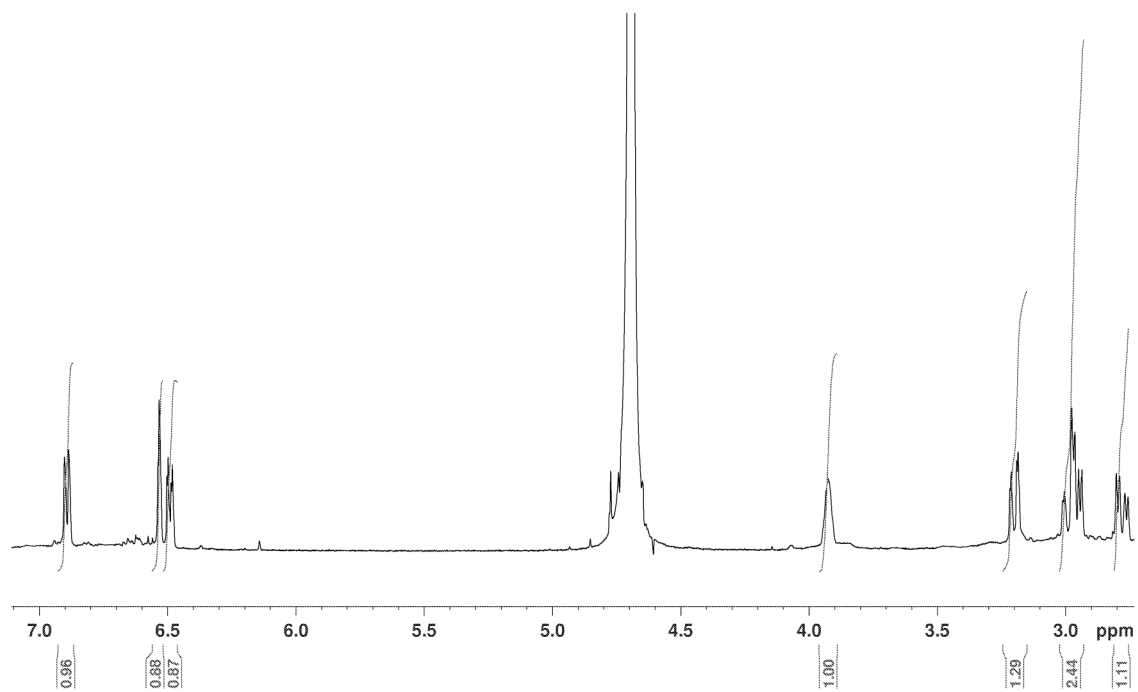
44.67

32.10

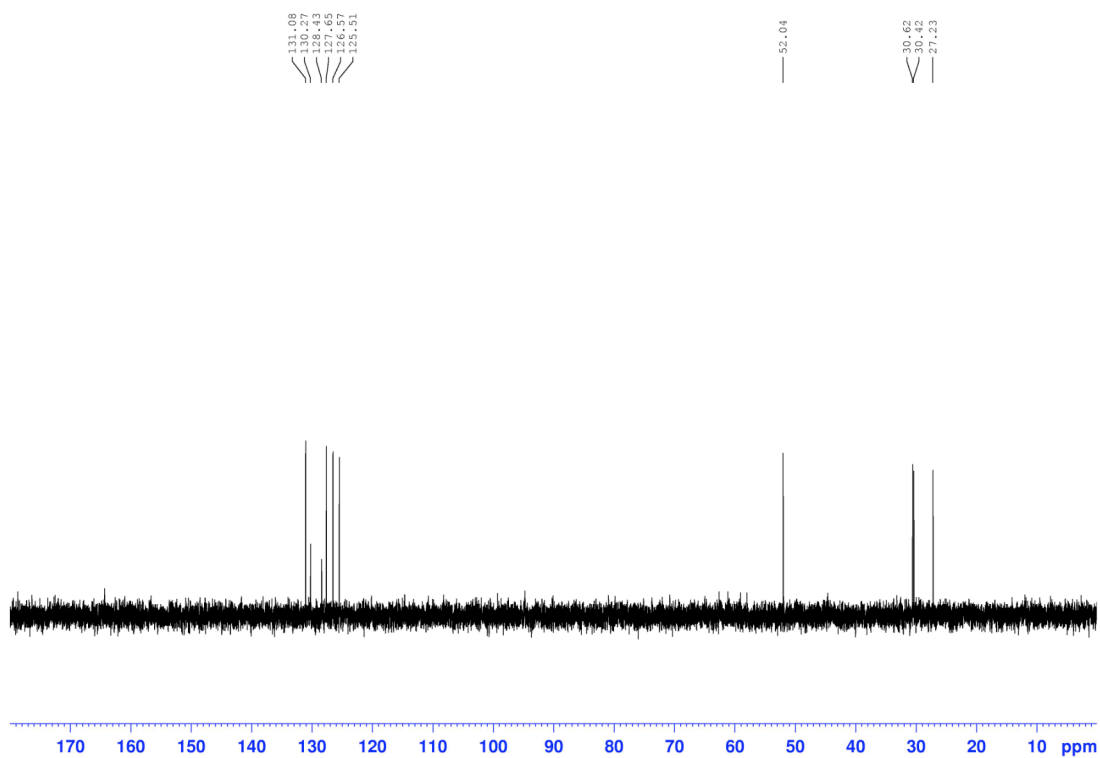
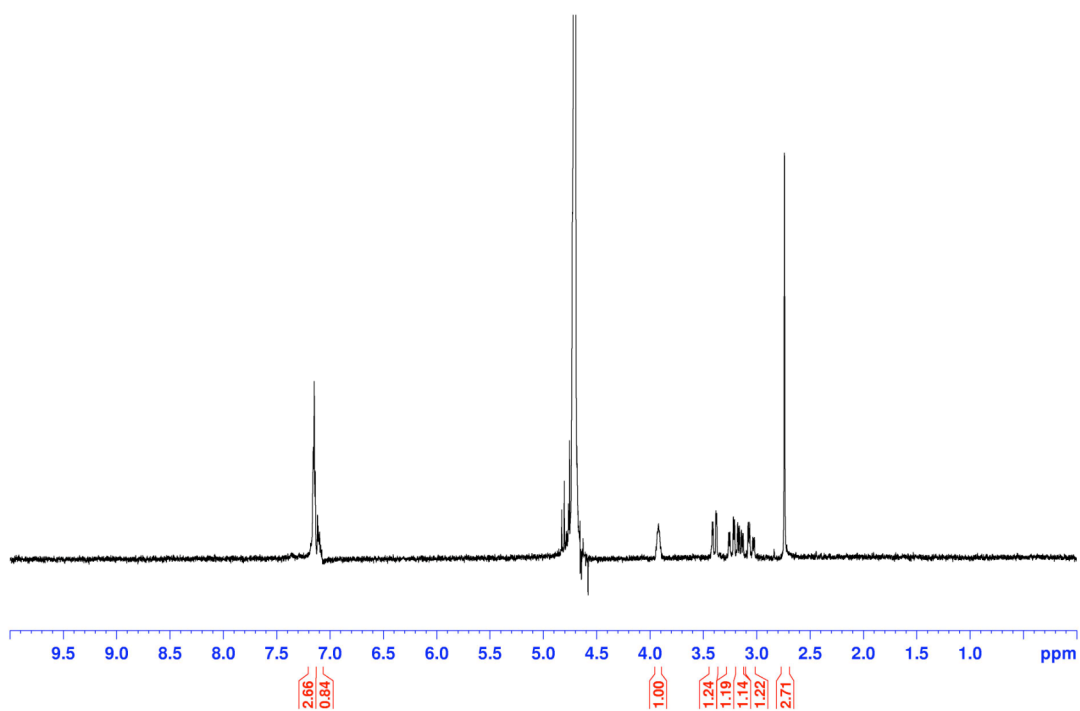
29.83



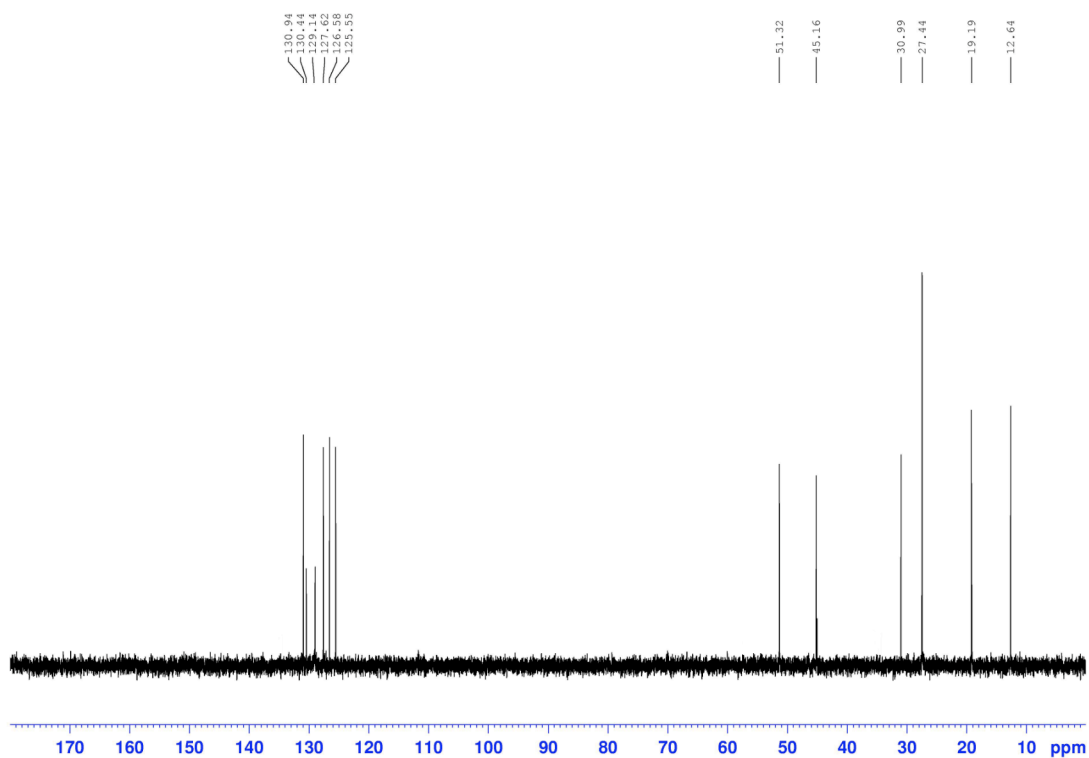
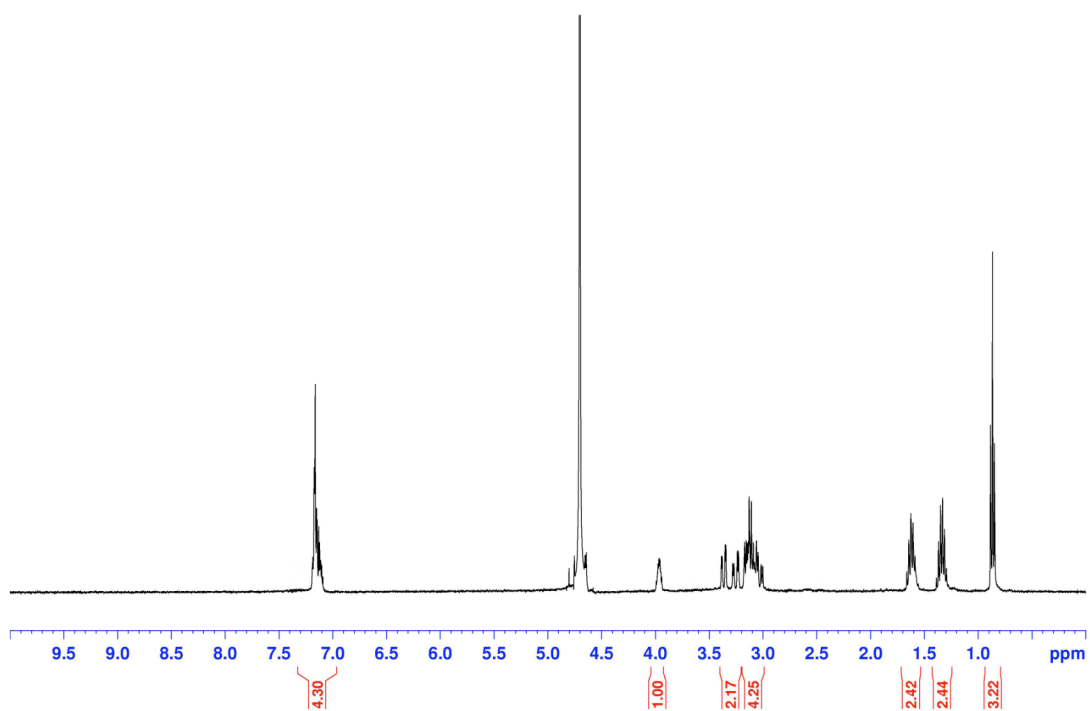
3b:



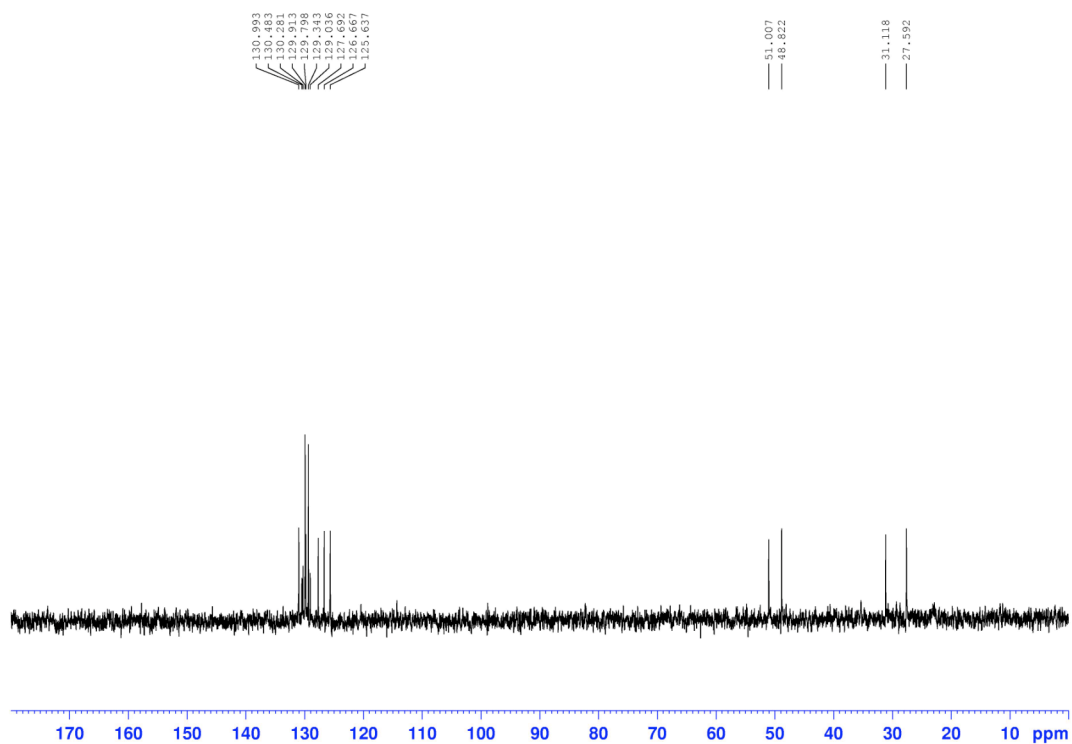
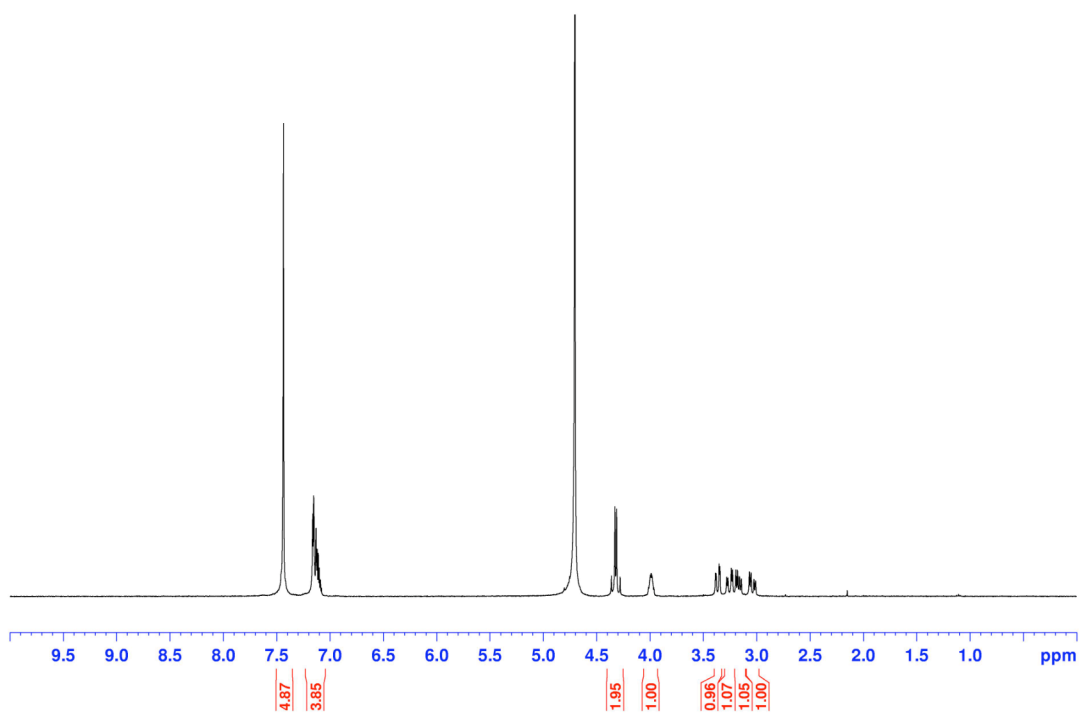
6a:



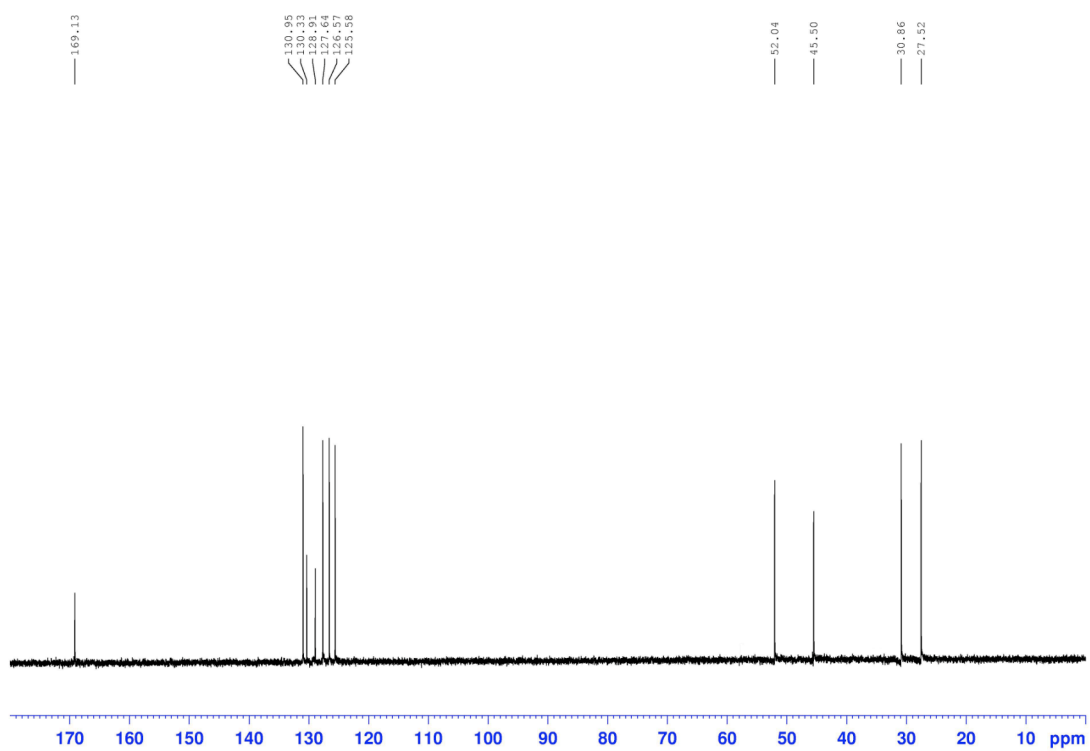
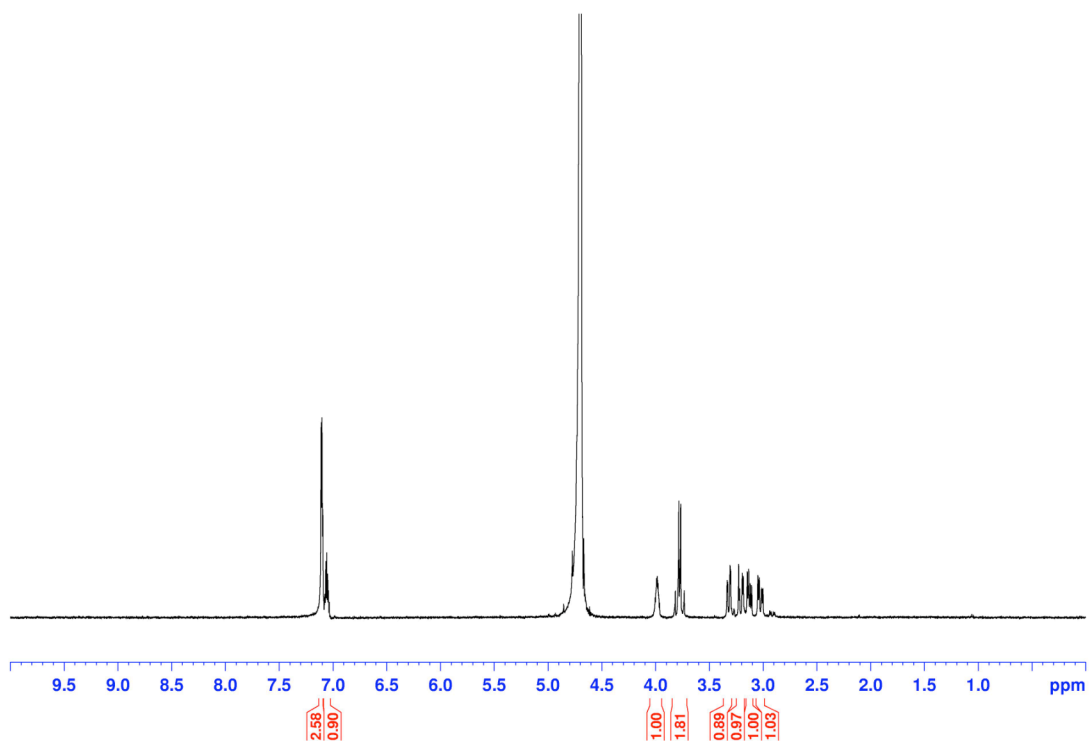
6b:



6c:



6d:



6e:

