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Synthesis and antibacterial evaluation of novel mono- and bis(2*H*-chromen-2-imine) hybrids linked to heteroarene units

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Contents

1. Experimental details.

1.1. Materials

All solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck or Aldrich and used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer. NMR spectra were recorded on Bruker Avance III 400 MHz spectrophotometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS as an internal standard and DMSO-*d*$_6$ as solvent and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series.

1.2. Procedures and spectral data.

Synthesis of 3-heteroaryl-2*H*-chromen-2-imines 3, 4, 6 and 7.

A mixture of 2-hydroxybenzaldehyde derivative **1a,b** (5 mmol) and 2- heteroaryl-acetonitrile, namely, 2-[4-(*p*-tolyl)thiazol-2-yl]acetonitrile **2a**, 2-[4-(4-methoxyphenyl)-thiazol-2-yl]acetonitrile **2b**, 2-(benzo[*d*]thiazol-2-yl)acetonitrile **5a**, 2-(benz[*d*]oxazol-2-yl)acetonitrile **5b** and 2-(1*H*-benz[*d*]imidazol-2-yl)acetonitrile **5c** (5 mmol) in dioxane (20 ml) in the presence of six drops of Et_2NH was heated at reflux for 3 h. The mixture was cooled, filtrated, washed with cold ethanol, and the product was recrystallized from the proper solvent.

3-[4-(*p*-Tolyl)thiazol-2-yl)-6-(*p*-tolylthiomethyl)-2*H*-chromen-2-imine (3a).

Beige soild (dioxane / ethanol mixture, 82%); m.p. 222-225 ^{o}C; IR (υ cm^{-1}): 3225 (NH); ^{1}H-NMR (DMSO-*d*$_6$): δ 2.21 (s, 3H, *p*-CH_3), 2.37 (s, 3H, *p*-CH_3), 4.12 (s, 2H, SCH_2), 7.11 (d, *J* = 8 Hz, 2H, Ar-H's), 7.19 (d, *J* = 8 Hz, 2H, Ar-H's), 7.28 (d, *J* = 8.8 Hz, 2H, Ar-H's), 7.34 (d, *J* = 8.4 Hz, 1H, H7), 7.61 (d, *J* = 8.4 Hz, 1H, H8), 7.74 (s, 1H, H5), 7.80 (d, *J* = 8.8 Hz, 2H, Ar-H's), 7.99 (s, 1H, thiazole-H), 8.50 (s, 1H, H4), 9.97 (s, 1H, NH); ^{13}C-NMR (DMSO-*d*$_6$): δ 20.2 (*p*-*C*H_3), 20.4 (*p*-*C*H_3), 36.3 (S*C*H_2), 113.2, 118.4, 118.7, 123.2, 124.7, 127.0, 128.9, 129.2, 129.8, 131.3, 131.4, 131.7, 132.6, 135.4, 139.5, 144.0, 148.7, 151.2, 158.4, 161.4; Anal. for $C_{27}H_{22}N_2OS_2$ (454.6): C, 71.34; H, 4.88; N, 6.16; found: C, 71.23; H, 5.01; N, 6.27%.

3-[4-(4-Methoxyphenyl)thiazol-2-yl]-6-(*p*-tolylthiomethyl)-2*H*-chromen-2-imine (3b).

Beige soild (dioxane / ethanol mixture, 84%); m.p. 264-265 ^{o}C; IR (υ cm^{-1}): 3222 (NH); ^{1}H-NMR (DMSO-*d*$_6$): δ 2.22 (s, 3H, *p*-CH_3), 3.85 (s, 3H, OCH_3), 4.16 (s, 2H, SCH_2), 6.92 (d, *J* =

8.8 Hz, 2H, Ar-H's), 7.12 (d, *J* = 8 Hz, 2H, Ar-H's), 7.21 (d, *J* = 8 Hz, 2H, Ar-H's), 7.35 (d, *J* = 8.4 Hz, 1H, H7), 7.65 (d, *J* = 8.4 Hz, 1H, H8), 7.72 (s, 1H, H5), 7.78 (d, *J* = 8.4 Hz, 2H, Ar-H's), 7.97 (s, 1H, thiazole-H), 8.38 (s, 1H, H4), 9.62 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 20.3 (*p*-*C*H_3), 36.5 (S*C*H_2), 55.2 (O*C*H_3), 113.6 (*C*8), 114.1 (Ar-*C*), 118.6, 118.8, 123.4, 124.8, 127.1, 129.2, 129.3, 129.7, 131.4, 131.6, 132.4, 135.2, 144.3, 148.8, 150.8, 158.6, 159.5, 161.2; Anal. for $C_{27}H_{22}N_2O_2S_2$ (470.6): C, 68.91; H, 4.71; N, 5.95; found: C, 69.07; H, 4.58; N, 6.03%.

6-Diethylaminomethyl-3-[4-(*p*-tolyl)thiazol-2-yl]-2*H*-chromen-2-imine (4a).

Pale yellow solid (dioxane / ethanol mixture, 79%); m.p. 200 ºC; IR (υ cm^{-1}): 3218 (NH); ^{1}H-NMR (DMSO-d_6): δ 0.97 (t, *J* = 7.2 Hz, 6H, 2 CH_2CH_3), 2.36 (s, 3H, *p*-CH_3), 2.41 (q, *J* = 7.2 Hz, 4H, 2 CH_2CH_3), 3.41 (s, 2H, NCH_2), 7.28 (d, *J* = 8.8 Hz, 2H, Ar-H's), 7.36 (d, *J* = 8.4 Hz, 1H, H7), 7.64 (d, *J* = 8.4 Hz, 1H, H8), 7.76 (s, 1H, H5), 7.82 (d, *J* = 8.8 Hz, 2H, Ar-H's), 7.99 (s, 1H, thiazole-H), 8.47 (s, 1H, H4), 9.88 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 11.2 (CH_2CH_3), 20.4 (*p*-*C*H_3), 46.1 (CH_2CH_3), 55.8 (NCH_2), 113.4, 118.6, 118.9, 123.4, 124.8, 127.1, 128.8, 131.3, 131.5, 132.4, 139.2, 143.7, 148.8, 151.0, 158.7, 161.2; Anal. for $C_{24}H_{25}N_3OS$ (403.5): C, 71.43; H, 6.24; N, 10.41; found: C, 71.30; H, 6.15; N, 10.55%.

6-Diethylaminomethyl-3-[4-(4-methoxyphenyl)thiazol-2-yl]-2*H*-chromen-2-imine (4b).

Pale yellow soild (dioxane / ethanol mixture, 80%); m.p. 212-214 ºC; IR (υ cm^{-1}): 3232 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.01 (t, *J* = 7.2 Hz, 6H, 2 CH_2CH_3), 2.43 (q, *J* = 7.2 Hz, 4H, 2 CH_2CH_3), 3.47 (s, 2H, NCH_2), 3.84 (s, 3H, OCH_3), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-H's), 7.33 (d, *J* = 8.4 Hz, 1H, H7), 7.63 (d, *J* = 8.4 Hz, 1H, H8), 7.74 (s, 1H, H5), 7.79 (d, *J* = 8.8 Hz, 2H, Ar-H's), 7.96 (s, 1H, thiazole-H), 8.44 (s, 1H, H4), 10.04 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 11.3 (CH_2CH_3), 46.4 (CH_2CH_3), 55.3 (OCH_3), 56.1 (NCH_2), 112.8, 114.0, 118.4, 118.6, 123.1, 124.4, 127.2, 129.5, 131.7, 132.8, 144.7, 148.4, 150.6, 158.8, 159.7, 161.4; Anal. for $C_{24}H_{25}N_3O_2S$ (419.5): C, 68.71; H, 6.01; N, 10.02; found: C, 68.85; H, 6.05; N, 10.14%.

3-(Benzo[*d*]thiazol-2-yl)-6-(*p*-tolylthiomethyl)-2*H*-chromen-2-imine (6a).

Pale yellow soild (dioxane, 77%); m.p. 278 ºC; IR (υ cm^{-1}): 3234 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.23 (s, 3H, *p*-CH_3), 4.11 (s, 2H, SCH_2), 7.09 (d, *J* = 8 Hz, 2H, Ar-H's), 7.18 (d, *J* = 8 Hz, 2H, Ar-H's), 7.33 (d, *J* = 8.4 Hz, 1H, H7), 7.39 (t, *J* = 7.6 Hz, 1H, H6′), 7.50 (t, *J* = 7.6 Hz, 1H, H5′), 7.66 (d, *J* = 8.4 Hz, 1H, H8), 7.78 (s, 1H, H5), 7.96 (d, *J* = 7.6 Hz, 1H, H7′), 8.13 (d, *J* = 7.6 Hz, 1H, H4′), 8.42 (s, 1H, H4), 10.32 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 20.3 (*p*-*C*H_3), 35.9 (S*C*H_2), 112.8, 118.4, 121.4, 121.5, 123.6, 124.3, 124.9, 125.9, 129.3, 129.9,

131.5, 131.8, 132.5, 132.9, 135.6, 143.7, 149.4, 150.8, 157.8, 159.3; Anal. for $C_{24}H_{18}N_2OS_2$ (414.5): C, 69.54; H, 4.38; N, 6.76; found: C, 69.45; H, 4.44; N, 6.63%.

3-(Benz[*d*]oxazol-2-yl)-6-(*p*-tolylthiomethyl)-2*H*-chromen-2-imine (6b).

Pale yellow soild (dioxane, 74%); m.p. 262-265 ºC; IR (υ cm^{-1}): 3335 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.21 (s, 3H, *p*-CH_3), 4.15 (s, 2H, SCH_2), 7.11 (d, *J* = 8 Hz, 2H, Ar-H's), 7.19 (d, *J* = 8 Hz, 2H, Ar-H's), 7.23-7.29 (m, 2H, H5′ and H6′), 7.37 (d, *J* = 8.4 Hz, 1H, H7), 7.58-7.62 (m, 2H, H4′ and H7′), 7.69 (d, *J* = 8.4 Hz, 1H, H8), 7.77 (s, 1H, H5), 8.55 (s, 1H, H4), 10.24 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 20.2 (*p*-*C*H_3), 35.8 (S*C*H_2), 112.4, 113.0, 118.2, 118.4, 123.4, 123.9, 124.2, 124.7, 129.2, 129.7, 131.3, 131.6, 132.5, 135.4, 141.8, 143.5, 150.6, 151.8, 157.9, 164.3; Anal. for $C_{24}H_{18}N_2O_2S$ (398.4): C, 72.34; H, 4.55; N, 7.03; found: C, 72.25; H, 4.62; N, 7.14%.

3-(1*H*-Benz[*d*]imidazol-2-yl)-6-(*p*-tolylthiomethyl)-2*H*-chromen-2-imine (6c).

Pale yellow soild (dioxane, 78%); m.p. 284-286 ºC; IR (υ cm^{-1}): 3415, 3220 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.23 (s, 3H, *p*-CH_3), 4.14 (s, 2H, SCH_2), 7.12 (d, *J* = 8 Hz, 2H, Ar-H's), 7.20 (d, *J* = 8 Hz, 2H, Ar-H's), 7.33-7.38 (m, 3H, H5′, H6′ and H7), 7.42 (d, *J* = 7.6 Hz, 1H, H4′), 7.65-7.68 (m, 2H, H8 and H7′), 7.74 (s, 1H, H5), 8.32 (s, 1H, H4), 9.20 (s, 1H, NH), 10.12 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 20.4 (*p*-*C*H_3), 36.2 (S*C*H_2), 113.4, 117.2, 117.7, 118.7, 123.7, 125.0, 125.1, 128.6, 129.2, 129.9, 131.4, 131.5, 132.4, 135.6, 139.9, 140.4, 143.8, 148.5, 151.1, 158.4; Anal. for $C_{24}H_{19}N_3OS$ (397.5): C, 72.52; H, 4.82; N, 10.57; found: C, 72.37; H, 4.90; N, 10.62%.

3-(Benzo[*d*]thiazol-2-yl)-6-diethylaminomethyl-2*H*-chromen-2-imine (7a).

Pale yellow soild (dioxane, 81%); m.p. 255-256 ºC; IR (υ cm^{-1}): 3219 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.00 (t, *J* = 7.2 Hz, 6H, 2 CH_2C*H*$_3$), 2.42 (q, *J* = 7.2 Hz, 4H, 2 C*H*$_2CH_3$), 3.42 (s, 2H, NCH_2), 7.36 (d, *J* = 8.4 Hz, 1H, H7), 7.41 (t, *J* = 7.6 Hz, 1H, H6′), 7.52 (t, *J* = 7.6 Hz, 1H, H5′), 7.68 (d, *J* = 8.4 Hz, 1H, H8), 7.76 (s, 1H, H5), 7.93 (d, *J* = 7.6 Hz, 1H, H7′), 8.10 (d, *J* = 7.6 Hz, 1H, H4′), 8.39 (s, 1H, H4), 10.17 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 11.4 (CH_2*C*H_3), 46.6 (*C*H_2CH_3), 56.3 (N*C*H_2), 113.3, 118.2 , 121.4, 121.6, 123.7, 124.4, 124.7, 125.8, 131.6, 132.4, 132.7, 143.7, 149.2, 151.2, 158.1, 159.2; Anal. for $C_{21}H_{21}N_3OS$ (363.4): C, 69.39; H, 5.82; N, 11.56; found: C, 69.47; H, 5.93; N, 11.45%.

3-(Benz[*d*]oxazol-2-yl)-6-diethylaminomethyl-2*H*-chromen-2-imine (7b).

Pale yellow soild (dioxane, 74%); m.p. 262-265 ºC; IR (υ cm^{-1}): 3335 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.02 (t, *J* = 7.2 Hz, 6H, 2 CH_2C*H*$_3$), 2.45 (q, *J* = 7.2 Hz, 4H, 2 C*H*$_2CH_3$), 3.50 (s, 2H,

NCH_2), 7.25-7.31 (m, 2H, H5′ and H6′), 7.38 (d, *J* = 8.4 Hz, 1H, H7), 7.61-7.65 (m, 2H, H4′ and H7′), 7.70 (d, *J* = 8.4 Hz, 1H, H8), 7.81 (s, 1H, H5), 8.41 (s, 1H, H4), 10.36 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 11.4 (CH_2CH_3), 46.4 (CH_2CH_3), 56.2 (NCH_2), 112.5, 113.2, 118.0, 118.3, 123.6, 123.8, 124.3, 124.5, 131.3, 132.2, 141.6, 143.3, 150.2, 151.6, 157.4, 164.2; Anal. for $C_{21}H_{21}N_3O_2$ (347.4): C, 72.60; H, 6.09; N, 12.10; found: C, 72.71; H, 6.12; N, 12.03%.

3-(1*H*-Benz[*d*]imidazol-2-yl)-6-diethylaminomethyl-2*H*-chromen-2-imine (7c).

Pale yellow soild (dioxane, 76%); m.p. 244 ºC; IR (υ cm^{-1}): 3421, 3237 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.02 (t, *J* = 7.2 Hz, 6H, 2 CH_2CH_3), 2.45 (q, *J* = 7.2 Hz, 4H, 2 CH_2CH_3), 3.48 (s, 2H, NCH_2), 7.29-7.34 (m, 3H, H5′, H6′ and H7), 7.39 (d, *J* = 7.6 Hz, 1H, H4′), 7.61-7.65 (m, 2H, H8 and H7′), 7.70 (s, 1H, H5), 8.28 (s, 1H, H4), 9.32 (s, 1H, NH), 10.20 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 11.3 (CH_2CH_3), 46.2 (CH_2CH_3), 56.0 (NCH_2), 113.2, 117.2, 117.9, 118.6, 123.4, 124.6, 125.0, 128.5, 131.3, 131.9, 139.8, 140.5, 143.3, 148.8, 150.6, 158.6; Anal. for $C_{21}H_{22}N_4O$ (346.4): C, 72.81; H, 6.40; N, 16.17; found: C, 72.65; H, 6.33; N, 16.05%.

Synthesis of bis[3-(thiazol-2-yl)-2*H*-chromen-2-imines] 9 and bis[2-(thiazol-2-yl)-2*H*-benzo[*f*]chromen-3-imines] 11.

A mixture of each of 2-hydroxybenzaldehyde derivatives **1a,b** or 2-hydroxy-1-naphthaldehyde **10** (10 mmol) and bis[2-(thiazol-2-yl)acetonitrile] **8a,b** (5 mmol) in dioxane (20 ml) in the presence of six drops of Et_2NH was heated at reflux for 5 h. The mixture was cooled, filtrated, washed with cold ethanol and the reaction product was recrystallized from the proper solvent.

3,3'-({[Propane-1,3-diylbis(oxy)]bis(4,1-phenylene)}bis(thiazole-4,2-diyl))-bis[6-(*p*-tolylthiomethyl)-2*H*-chromen-2-imine) (9a).

Pale yellow soild (dioxane, 67%); m.p. 282-283 ºC; IR (υ cm^{-1}): 3213 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.18 (quint, *J* = 6.4 Hz, 2H, OCH_2CH_2), 2.25 (s, 6H, 2 *p*-CH_3), 4.17 (t, *J* = 6.4 Hz, 4H, 2 OCH_2), 4.26 (s, 4H, 2 SCH_2), 7.06 (d, *J* = 8 Hz, 4H, Ar-H's), 7.12 (d, *J* = 8 Hz, 4H, Ar-H's), 7.20 (d, *J* = 8 Hz, 4H, Ar-H's), 7.35 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.65 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.72 (s, 2H, 2 H5), 7.91 (d, *J* = 8 Hz, 4H, Ar-H's), 8.00 (s, 2 H, 2 thiazole-H), 8.44 (s, 2H, 2 H4), 9.83 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.2 (*p*-CH_3), 28.3 (OCH_2CH_2), 36.2 (SCH_2), 66.2 (OCH_2), 113.3, 115.2, 118.2, 118.5, 123.1, 124.6, 126.5, 129.2, 129.7, 129.8, 131.5, 131.7, 132.6, 135.4, 144.6, 147.9, 151.2, 158.4, 159.9, 161.0; Anal. for $C_{55}H_{44}N_4O_4S_4$ (953.2): C, 69.30; H, 4.65; N, 5.88; found: C, 69.23; H, 4.74; N, 5.99%.

3,3'-({[Pentane-1,5-diylbis(oxy)]bis(4,1-phenylene)}bis(thiazole-4,2-diyl))-bis[6-(*p*-tolylthiomethyl)-2*H*-chromen-2-imine] (9b).

Pale yellow soild (dioxane, 71%); m.p. 274-277 ºC; IR (υ cm^{-1}): 3218 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.58 (m, 2H, $OCH_2CH_2CH_2$), 1.77 (quint, *J* = 6.4 Hz, 4H, OCH_2CH_2), 2.23 (s, 6H, 2 *p*-CH_3), 4.05 (t, *J* = 6.4 Hz, 4H, 2 OCH_2), 4.27 (s, 4H, 2 SCH_2), 7.05 (d, *J* = 8 Hz, 4H, Ar-H's), 7.11 (d, *J* = 8 Hz, 4H, Ar-H's), 7.19 (d, *J* = 8 Hz, 4H, Ar-H's), 7.37 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.68 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.74 (s, 2H, 2 H5), 7.89 (d, *J* = 8 Hz, 4H, Ar-H's), 8.01 (s, 2H, 2 thiazole-H), 8.39 (s, 2H, 2 H4), 9.70 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.3 (*p*-CH_3), 22.7 ($O(CH_2)_2CH_2$), 28.8 (OCH_2CH_2), 36.3 (SCH_2), 68.1 (OCH_2), 113.5, 115.2, 118.4, 118.6, 123.2, 124.4, 126.5, 129.3, 129.8, 129.9, 131.4, 131.7, 132.4, 135.5, 144.2, 147.6, 151.1, 157.6, 159.7, 160.7; Anal. for $C_{57}H_{48}N_4O_4S_4$ (981.2): C, 69.77; H, 4.93; N, 5.71; found: C, 69.65; H, 5.04; N, 5.82%.

3,3'-({[Propane-1,3-diylbis(oxy)]bis(4,1-phenylene)}bis(thiazole-4,2-diyl))-bis(6-diethylaminomethyl-2*H*-chromen-2-imine) (9c).

Pale yellow soild (dioxane, 72%); m.p. 250-252 ºC; IR (υ cm^{-1}): 3236 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.00 (t, *J* = 7.2 Hz, 12H, 4 CH_2CH_3), 2.21 (quint, *J* = 6.4 Hz, 2H, OCH_2CH_2), 2.42 (q, *J* = 7.2 Hz, 8H, 4 CH_2CH_3), 3.43 (s, 4H, 2 NCH_2), 4.20 (t, *J* = 6.4 Hz, 4H, 2 OCH_2), 7.08 (d, *J* = 8 Hz, 4H, Ar-H's), 7.36 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.62 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.70 (s, 2H, 2 H5), 7.93 (d, *J* = 8 Hz, 4H, Ar-H's), 8.03 (s, 2 H, 2 thiazole-H), 8.55 (s, 2H, 2 H4), 9.98 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 11.3 (CH_2CH_3), 28.4 (OCH_2CH_2), 46.2 (CH_2CH_3), 56.1 (NCH_2), 66.3 (OCH_2), 113.5, 115.1, 118.4, 118.6, 123.4, 124.5, 126.6, 129.6, 131.5, 132.3, 144.2, 147.6, 150.9, 158.2, 159.5, 160.5; Anal. for $C_{49}H_{50}N_6O_4S_2$ (851.1): C, 69.15; H, 5.92; N, 9.87; found: C, 69.06; H, 6.01; N, 9.95%.

3,3'-({[Pentane-1,5-diylbis(oxy)]bis(4,1-phenylene)}bis(thiazole-4,2-diyl))-bis(6-diethylaminomethyl-2*H*-chromen-2-imine) (9d).

Pale yellow soild (dioxane, 66%); m.p. 240 ºC; IR (υ cm^{-1}): 3230 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.01 (t, *J* = 7.2 Hz, 12H, 4 CH_2CH_3), 1.60 (m, 2H, $OCH_2CH_2CH_2$), 1.80 (quint, *J* = 6.4 Hz, 4H, OCH_2CH_2), 2.44 (q, *J* = 7.2 Hz, 8H, 4 CH_2CH_3), 3.49 (s, 4H, 2 NCH_2), 4.09 (t, *J* = 6.4 Hz, 4H, 2 OCH_2), 7.09 (d, *J* = 8 Hz, 4H, Ar-H's), 7.38 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.60 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.68 (s, 2H, 2 H5), 7.91 (d, *J* = 8 Hz, 4H, Ar-H's), 8.00 (s, 2 H, 2 thiazole-H), 8.43 (s, 2H, 2 H4), 9.75 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 11.4 (CH_2CH_3), 22.8 ($O(CH_2)_2CH_2$), 28.9 (OCH_2CH_2), 46.4 (CH_2CH_3), 56.3 (NCH_2), 68.3 (OCH_2), 113.2, 115.2,

118.2, 118.7, 123.6, 124.7, 126.4, 129.5, 131.3, 131.8, 143.6, 147.4, 150.3, 157.6, 159.7, 160.8; Anal. for $C_{51}H_{54}N_6O_4S_2$ (879.1): C, 69.68; H, 6.19; N, 9.56; found: C, 69.76; H, 6.24; N, 9.30%.

2,2'-({[Propane-1,3-diylbis(oxy)]bis(4,1-phenylene)}bis(thiazole-4,2-diyl))-bis(3*H*-benzo[*f*]chromen-3-imine) (11a).

Pale yellow soild (DMF / ethanol mixture, 70%); m.p. above 300 ºC; IR (υ cm^{-1}): 3242 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.21 (quint, *J* = 6.4 Hz, 2H, OCH_2CH_2), 4.21 (t, *J* = 6.4 Hz, 4H, 2 OCH_2), 7.08 (d, *J* = 8 Hz, 4H, Ar-H's), 7.39 (d, *J* = 8.4 Hz, 2H, 2 H5), 7.49-7.56 (m, 4H, 2 H8 and 2 H9), 7.88-7.93 (m, 8H, 2 H6, 2 H7 and Ar-H's), 8.03 (s, 2 H, 2 thiazole-H), 8.12 (d, *J* = 8.4 Hz, 2H, 2 H10), 8.36 (s, 2H, 2 H1), 9.81 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 28.2 (OCH_2CH_2), 66.3 (OCH_2), 115.1, 115.4, 117.1, 118.4, 118.5, 123.1, 126.0, 126.6, 127.8, 128.1, 129.3, 129.5, 130.7, 134.4, 144.6, 147.7, 154.7, 158.4, 159.6, 160.4; Anal. for $C_{47}H_{32}N_4O_4S_2$ (780.9): C, 72.29; H, 4.13; N, 7.17; found: C, 72.17; H, 4.05; N, 7.09%.

2,2'-({[Pentane-1,5-diylbis(oxy)]bis(4,1-phenylene)}bis(thiazole-4,2-diyl))-bis(3*H*-benzo[*f*]chromen-3-imine) (11b).

Pale yellow soild (DMF / ethanol mixture, 68%); m.p. above 300 ºC; IR (υ cm^{-1}): 3238 (NH); ^{1}H-NMR (DMSO-d_6): δ 1.59 (m, 2H, $OCH_2CH_2CH_2$), 1.79 (quint, *J* = 6.4 Hz, 4H, OCH_2CH_2), 4.07 (t, *J* = 6.4 Hz, 4H, 2 OCH_2), 7.10 (d, *J* = 8 Hz, 4H, Ar-H's), 7.37 (d, *J* = 8.4 Hz, 2H, 2 H5), 7.50-7.55 (m, 4H, 2 H8 and 2 H9), 7.86-7.93 (m, 8H, 2 H6, 2 H7 and Ar-H's), 8.05 (s, 2 H, 2 thiazole-H), 8.13 (d, *J* = 8.4 Hz, 2H, 2 H10), 8.43 (s, 2H, 2 H1), 9.65 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 22.7 ($O(CH_2)_2CH_2$), 28.7 (OCH_2CH_2), 68.1 (OCH_2), 115.2, 115.3, 117.4, 118.5, 118.7, 123.3, 125.8, 126.6, 127.7, 128.2, 129.2, 129.3, 130.5, 134.2, 144.8, 147.4, 154.9, 158.6, 159.8, 160.6; Anal. for $C_{49}H_{36}N_4O_4S_2$ (808.9): C, 72.75; H, 4.49; N, 6.93; found: C, 72.66; H, 4.41; N, 7.00%.

Synthesis of bis(3-heteroarly-2*H*-chromen-2-imines) 13 and 14.

A mixture of 1,4-bis[(3-formyl-4-hydroxyphenyl)methyl]piperazine **12** (5 mmol) and hetarylacetonitrile **2a,b** or **5a-c** (10 mmol) in dioxane (20 ml) in the presence of six drops of Et_2NH was heated at reflux for 5 h. The mixture was cooled, filtrated, washed with cold ethanol and the reaction product was recrystallized from the proper solvent.

6,6'-[Piperazine-1,4-diylbis(methylene)]bis{3-[4-(*p*-tolyl)thiazol-2-yl]-2*H*-chromen-2-imine} (13a).

Pale yellow soild (dioxane, 69%); m.p. 266 ºC; IR (υ cm^{-1}): 3238 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.39 (s, 6H, 2 *p*-CH_3), 2.43 (s, 8H, 4 piperazine-CH_2), 3.56 (s, 4H, 2 CH_2), 7.28 (d, *J* = 8.8 Hz, 4H, Ar-H's), 7.37 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.60 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.71 (s, 2H, 2 H5), 7.78 (d, *J* = 8.8 Hz, 4H, Ar-H's), 7.95 (s, 2H, 2 thiazole-H), 8.37 (s, 2H, 2 H4), 9.66 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.3 (*p*-*C*H_3), 52.4 (piprazine-*C*H_2), 60.7 (*C*H_2), 113.0, 118.2, 118.5, 123.6, 124.4, 127.2, 128.8, 131.6, 131.8, 132.8, 139.2, 143.3, 147.4, 150.5, 157.4, 160.7; Anal. for $C_{44}H_{38}N_6O_2S_2$ (746.9): C, 70.75; H, 5.13; N, 11.25; found: C, 70.62; H, 5.07; N, 11.31%.

6,6'-[Piperazine-1,4-diylbis(methylene)]bis{3-[4-(4-methoxyphenyl)thiazol-2-yl]-2*H*-chromen-2-imine} (13b).

Pale yellow soild (dioxane, 72%); m.p. 290-292 ºC; IR (υ cm^{-1}): 3234 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 8H, 4 piperazine-CH_2), 3.56 (s, 4H, 2 CH_2), 3.84 (s, 6H, 2 OCH_3), 6.93 (d, *J* = 8.8 Hz, 4H, Ar-H's), 7.33 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.67 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.72 (s, 2H, 2 H5), 7.79 (d, *J* = 8.8 Hz, 4H, Ar-H's), 7.99 (s, 2H, 2 thiazole-H), 8.40 (s, 2H, 2 H4), 9.75 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 52.3 (piprazine-*C*H_2), 55.4 (O*C*H_3), 60.6 (*C*H_2), 113.3, 114.2, 118.2, 118.7, 122.7, 123.9, 127.1, 129.4, 131.2, 132.1, 143.4, 147.2, 150.4, 157.2, 159.4, 160.1; Anal. for $C_{44}H_{38}N_6O_4S_2$ (778.9): C, 67.85; H, 4.92; N, 10.79; found: C, 67.94; H, 5.02; N, 10.73%.

6,6'-[Piperazine-1,4-diylbis(methylene)]bis[3-(benzo[*d*]thiazol-2-yl)-2*H*-chromen-2-imine] (14a).

Pale yellow soild (DMF / ethanol mixture, 67%); m.p. above 300 ºC; IR (υ cm^{-1}): 3264 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 8H, 4 piperazine-CH_2), 3.54 (s, 4H, 2 CH_2), 7.35 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.40 (t, *J* = 7.6 Hz, 2H, 2 H6′), 7.50 (t, *J* = 7.6 Hz, 2H, 2 H5′), 7.60 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.74 (s, 2H, 2 H5), 7.92 (d, *J* = 7.6 Hz, 2H, 2 H7′), 8.07 (d, *J* = 7.6 Hz, 2H, 2 H4′), 8.32 (s, 2H, 2 H4), 10.09 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 52.5 (piprazine-*C*H_2), 60.5 (*C*H_2), 112.4, 118.0, 121.3, 121.4, 123.3, 124.4, 124.6, 125.8, 131.5, 132.6, 132.7, 143.4, 149.5, 150.4, 157.6, 159.5; Anal. for $C_{38}H_{30}N_6O_2S_2$ (666.8): C, 68.45; H, 4.53; N, 12.60; found: C, 68.53; H, 4.64; N, 12.55%.

6,6'-[Piperazine-1,4-diylbis(methylene)]bis[3-(benzo[*d*]oxazol-2-yl)-2*H*-chromen-2-imine] (14b).

Pale yellow soild (DMF / ethanol mixture, 68%); m.p. above 300 ºC; IR (υ cm^{-1}): 3372 (NH). ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 8H, 4 piperazine-CH_2), 3.56 (s, 4H, 2 CH_2), 7.21-7.27 (m, 4H, 2 H5′ and 2 H6′), 7.34 (d, *J* = 8.4 Hz, 2H, 2 H7), 7.54-7.58 (m, 4H, 2 H4′ and 2 H7′), 7.65 (d, *J* = 8.4 Hz, 2H, 2 H8), 7.72 (s, 2H, 2 H5), 8.46 (s, 2H, 2 H4), 10.02 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 52.4 (piprazine-CH_2), 60.7 (CH_2), 112.5, 113.3, 117.6, 118.3, 123.6, 123.9, 124.3, 124.8, 130.8, 131.9, 141.7, 143.2, 150.1, 151.9, 157.5, 164.2; Anal. for $C_{38}H_{30}N_6O_4$ (634.7): C, 71.91; H, 4.76; N, 13.24; found: C, 72.06; H, 4.82; N, 13.18%.

6,6'-[Piperazine-1,4-diylbis(methylene)]bis[3-(1*H*-benzo[*d*]imidazol-2-yl)-2*H*-chromen-2-imine] (14c).

Pale yellow soild (DMF / ethanol mixture, 72%); m.p. above 300 ºC; IR (υ cm^{-1}): 3421, 3262 (NH); ^{1}H-NMR (DMSO-d_6): δ 2.44 (s, 8H, 4 piperazine-CH_2), 3.58 (s, 4H, 2 CH_2), 7.30-7.35 (m, 6H, 2 H5′, 2 H6′ and 2 H7), 7.41 (d, *J* = 7.6 Hz, 2H, 2 H4′), 7.61-7.64 (m, 4H, 2 H8 and 2 H7′), 7.72 (s, 2H, 2 H5), 8.38 (s, 2H, 2 H4), 9.35 (s, 2H, 2 NH), 10.38 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 52.2 (piprazine-*C*H_2), 60.5 (*C*H_2), 113.2, 117.3, 117.5, 118.7, 123.4, 124.8, 125.2, 128.3, 131.7, 132.5, 139.8, 140.5, 143.7, 148.9, 151.3, 158.8; Anal. for $C_{38}H_{32}N_8O_2$ (632.7): C, 72.13; H, 5.10; N, 17.71; found: C, 72.27; H, 4.98; N, 17.59%.

1.3. Minimum inhibitory concentration (MIC) determination.

The inhibitory activities against three different Gram-positive bacterial strains [*Staphylococcus aureus* (ATCC:6538), *Streptococcus mutans,* (ATCC:25175) and *Enterococcus faecalis* (ATCC:29212)] were selected as well as three different Gram-negative strains [*Escherichia coli* (ATCC:9637), *Pseudomonas aeruginosa* (ATCC:27953) and *Klebsiella pneumonia* (ATCC:10031)] were estimated. MIC values were determined using microbroth serial dilution method [S1] in a sterile 96-well microtiter plate after overnight incubation of tested bacteria at 37°C. This assay was performed in triplicates for consistency in accordance with guidelines provided by CLSI (2012) [S2]. Ciprofloxacin (100 μg susceptibility disc) was used as a standard drug. The concentration of the tested hybrids as well as Ciprofloxacin used in the study ranged from 250 to 0.9 μg ml^{-1}. The sterile Muller-Hinton broth (MHB) was enriched with 2% NaCl before the tested antimicrobial agents were inserted into the well at concentration gradient in a serial dilution. Then the diluted bacterial suspension at final inoculum of 10^6 CFU/ml was added. The tested compound in MHB was used as negative control to ensure medium sterility, while the inoculum in MHB served as positive control to ensure the adequacy of the broth for bacterial growth. To facilitate the observation of the growth of bacteria in each well, 20 μl of 2,3,5-triphenyltetrazolium chloride (TTC) at 2 mg ml^{-1} was added into each well [S3].

2. References.

[S1] A. E. M. Mekky and S. M. H. Sanad, *Bioorg. Chem.*, 2020, **102**, 104094.

[S2] H. Mohammad, P. N. Reddy, D. Monteleone, A. S. Mayhoub, M. Cushman and M. N. Seleem, *Eur. J. Med. Chem.*, 2015, **94**, 306.

[S3] CLSI. 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically-7th edition. Approved standard M07-A9, Clinical and Laboratory Standards Institute Wayne, PA.

3. ^{1}H- and ^{13}C-NMR copies of all new hybrids.

Figure S1. ^{1}H-NMR of compound 3a.

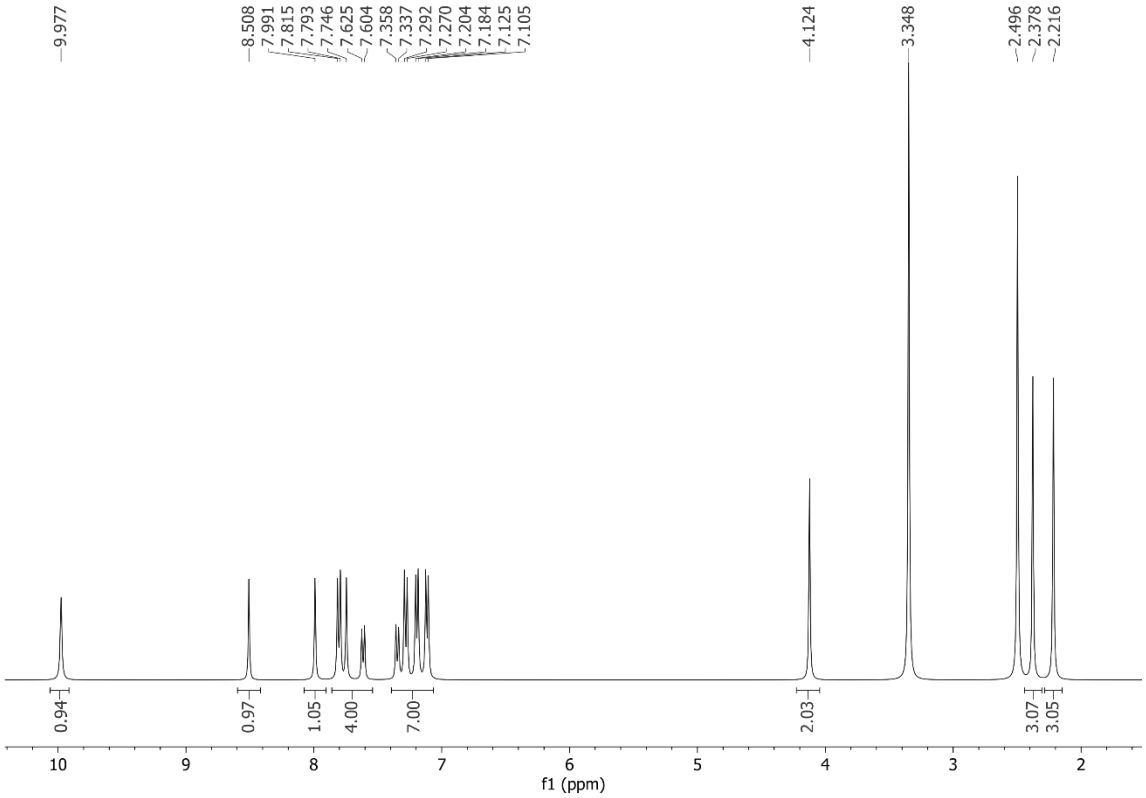

Figure S2. ^{13}C-NMR of compound 3a.

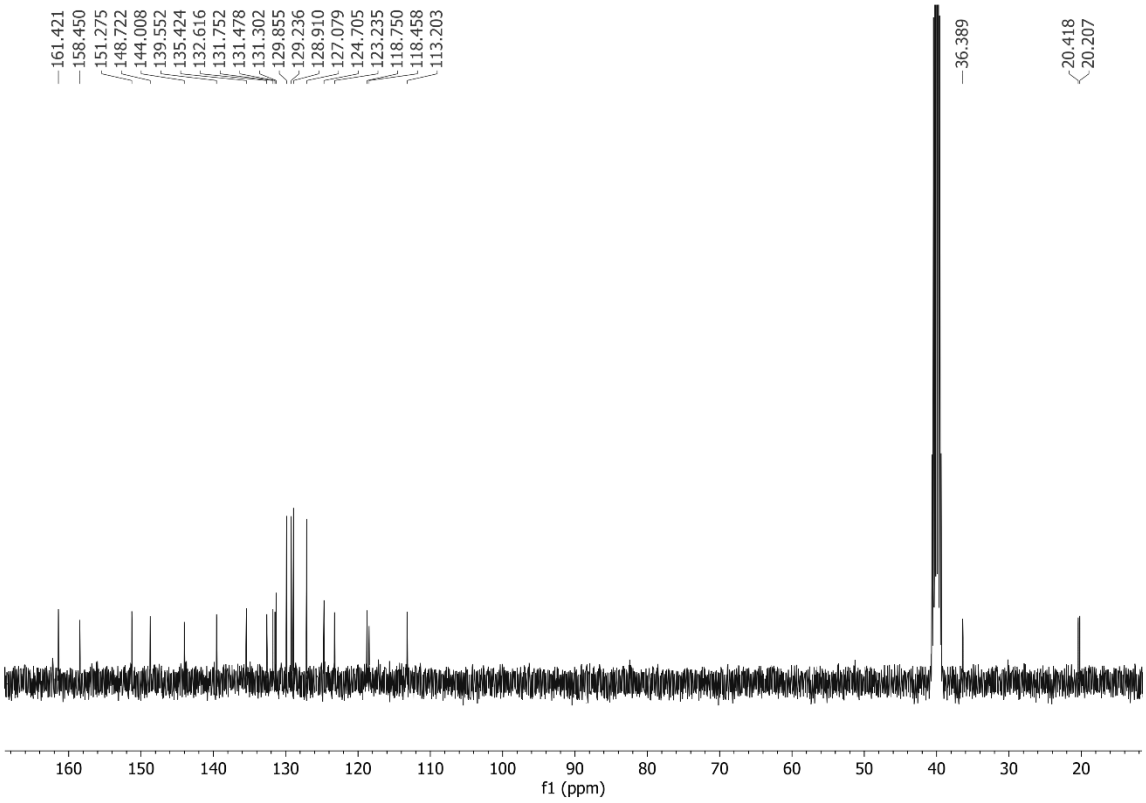

Figure S3. ^{1}H-NMR of compound 3b.

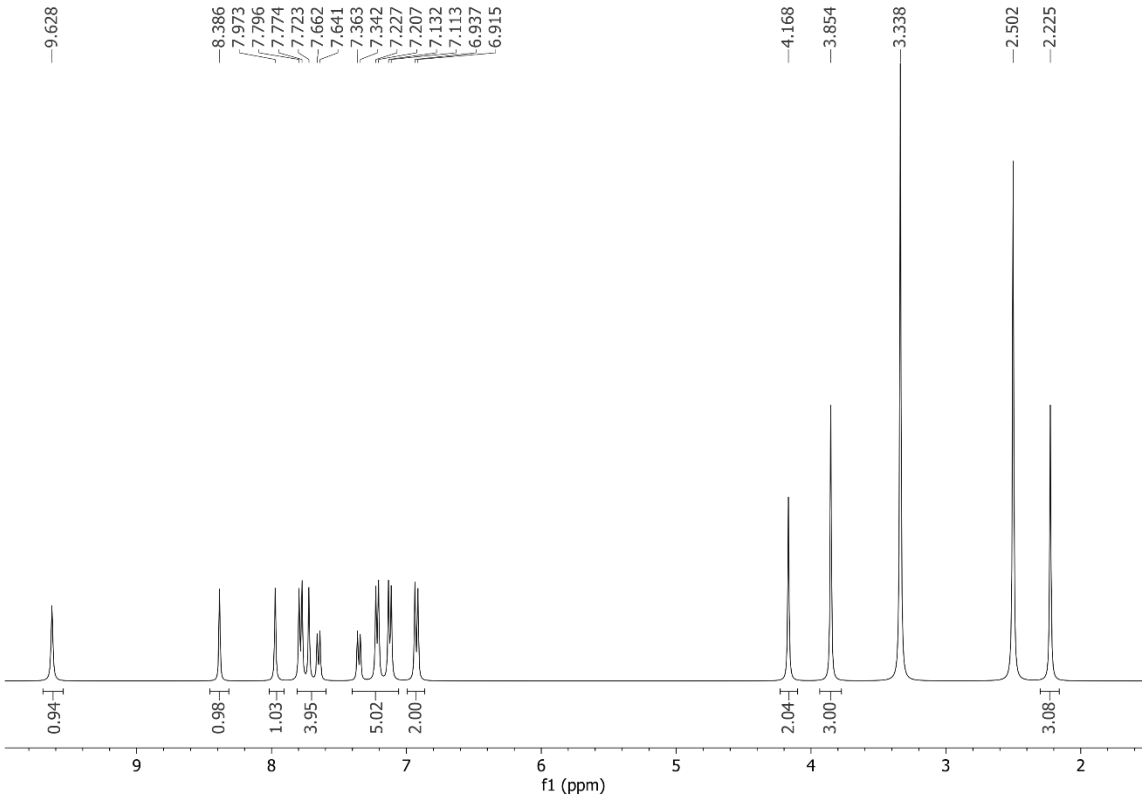

Figure S4. ^{13}C-NMR of compound 3b.

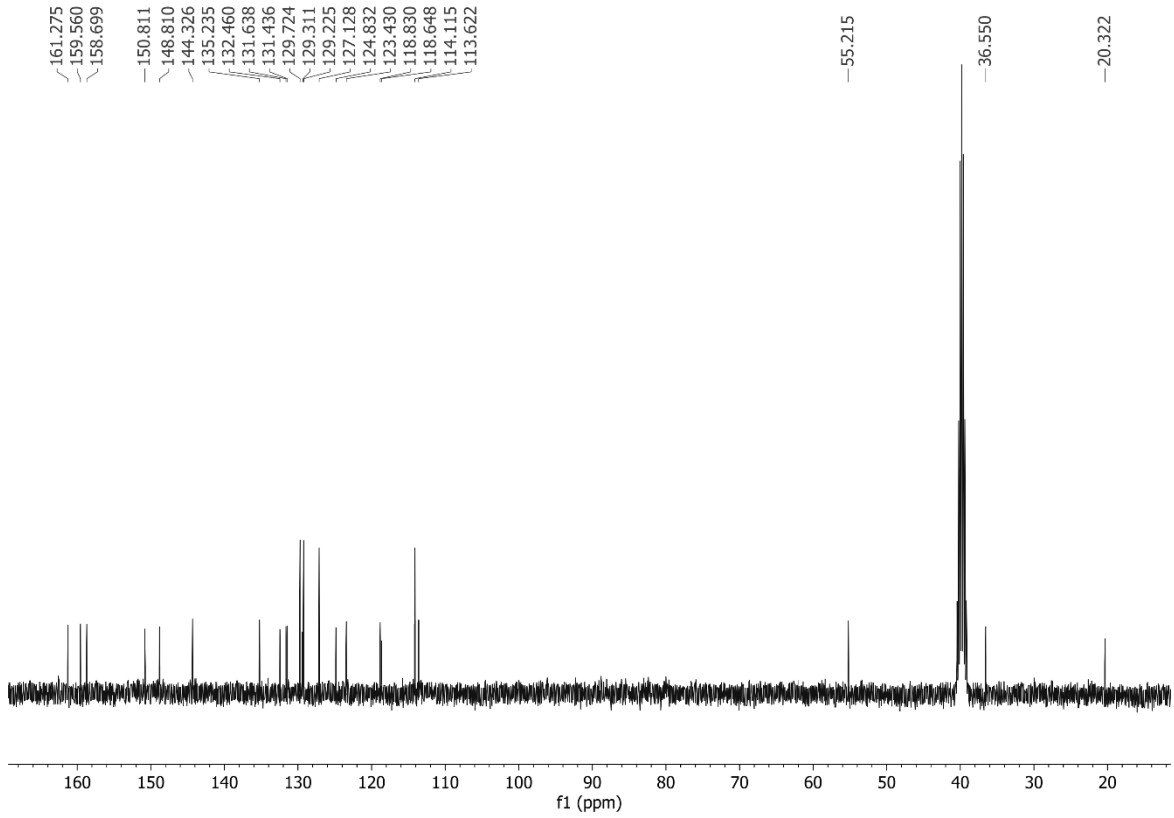

Figure S5. ^{1}H-NMR of compound 4a.

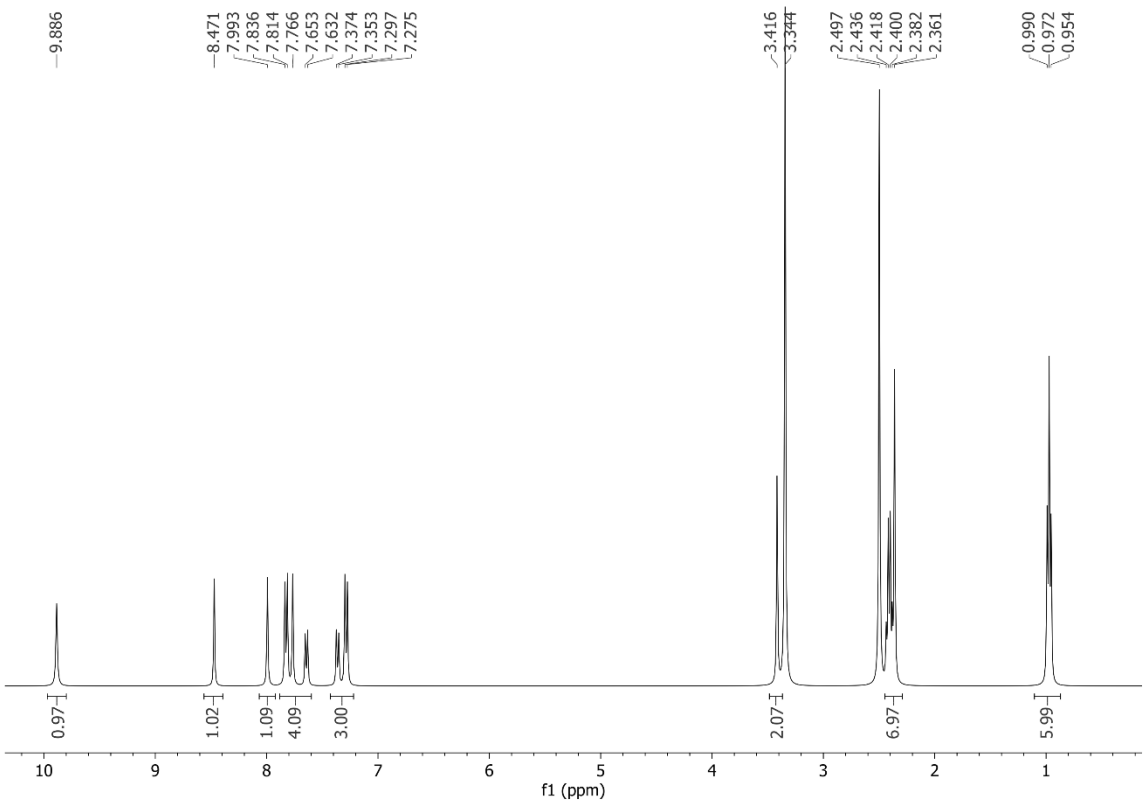

Figure S6. ^{13}C-NMR of compound 4a.

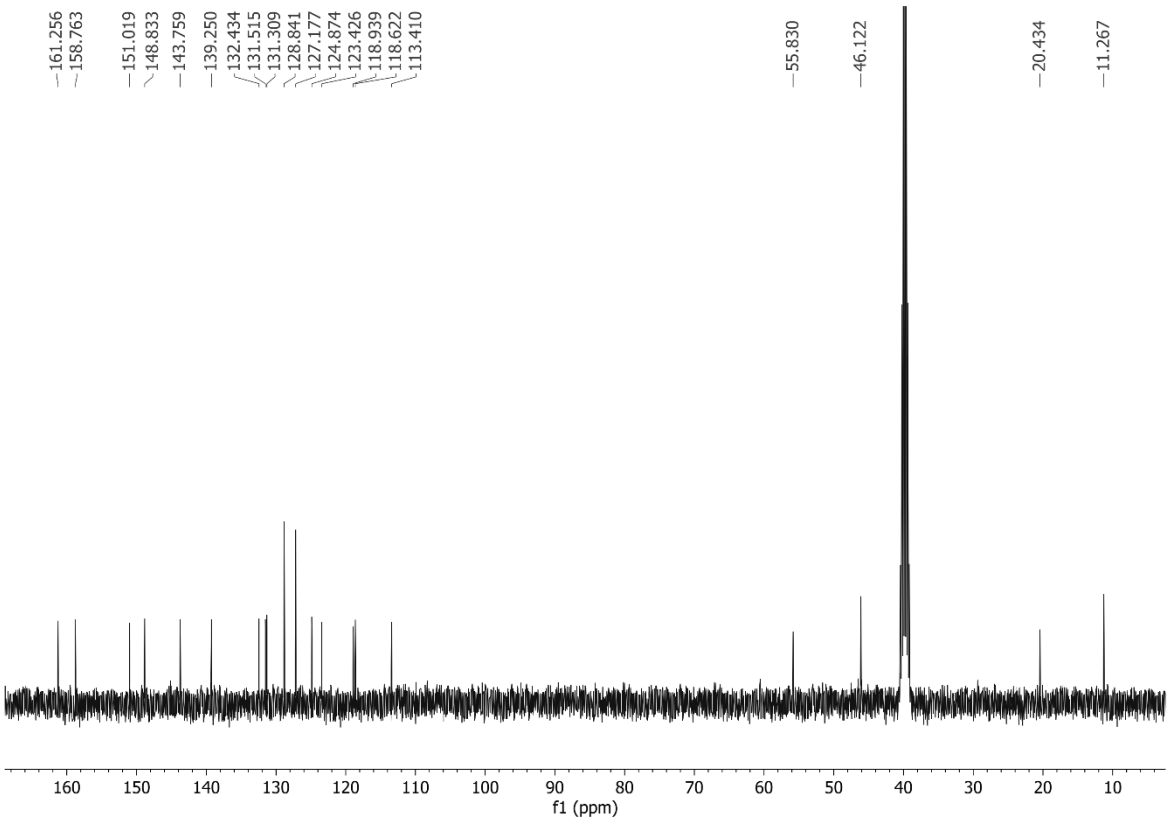

Figure S7. ^{1}H-NMR of compound 4b.

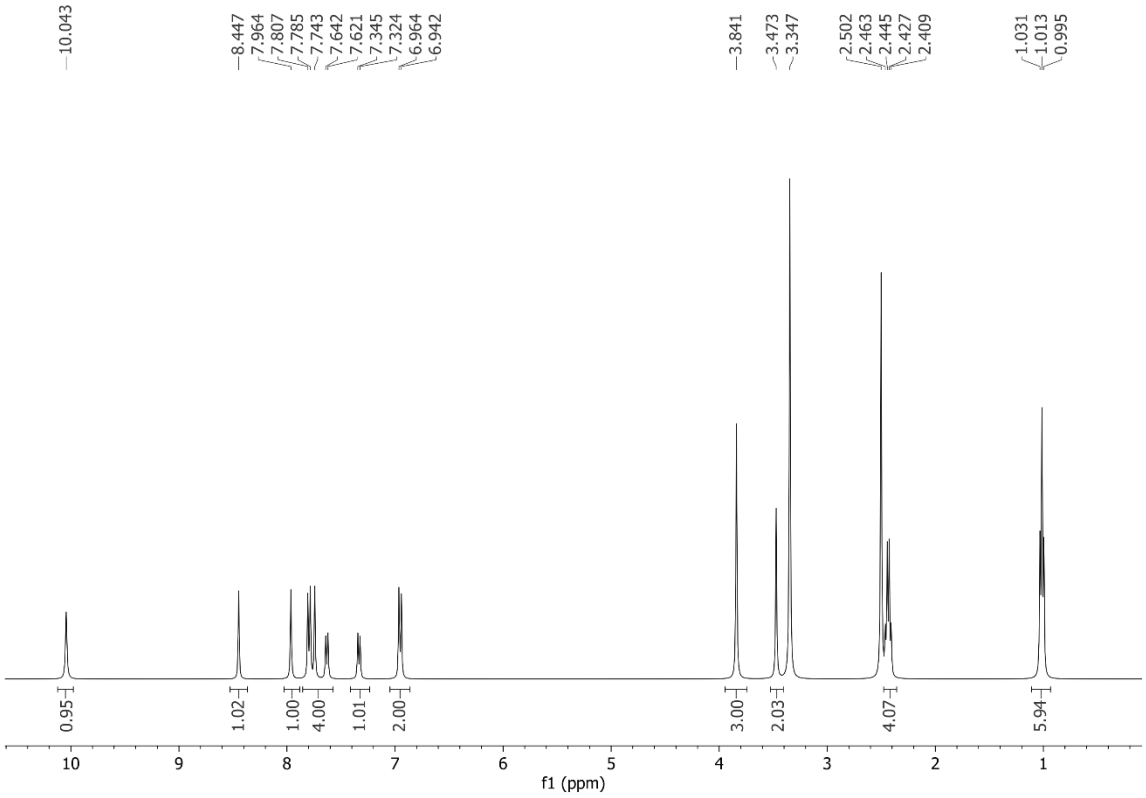

Figure S8. ^{13}C-NMR of compound 4b.

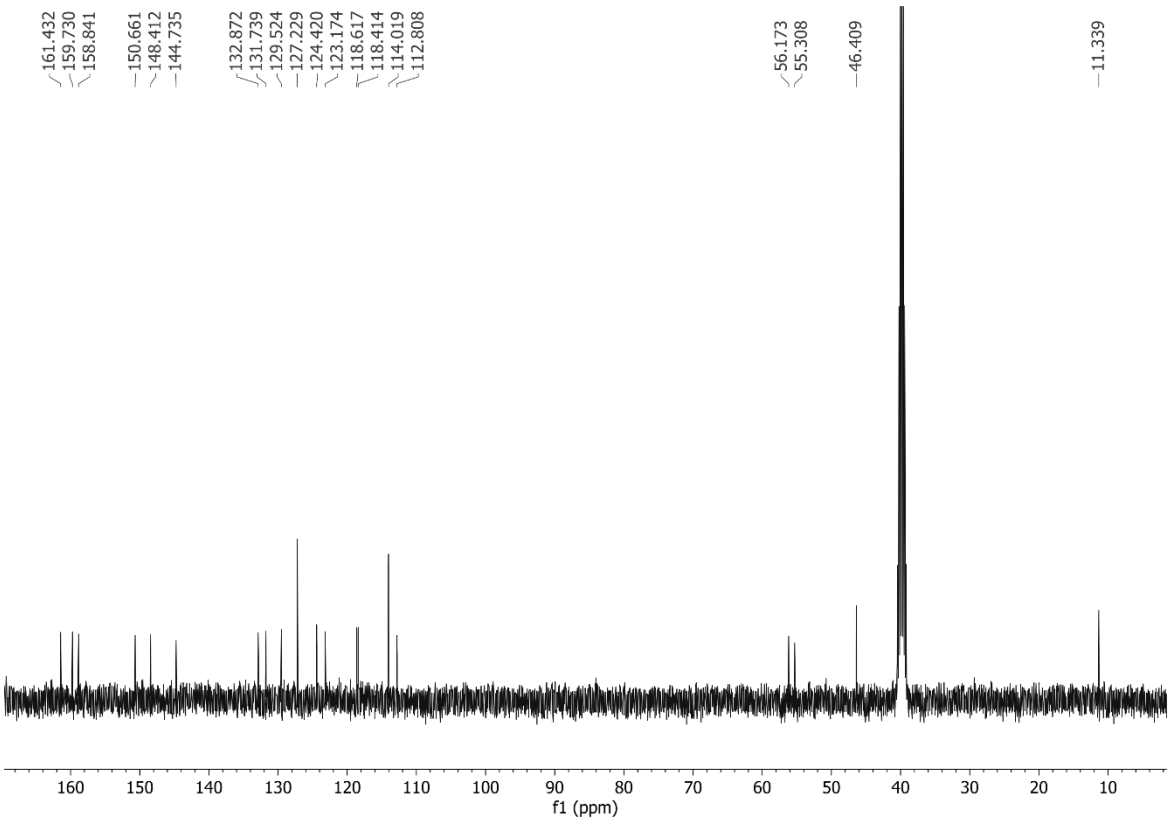

Figure S9. ^{1}H-NMR of compound 6a.

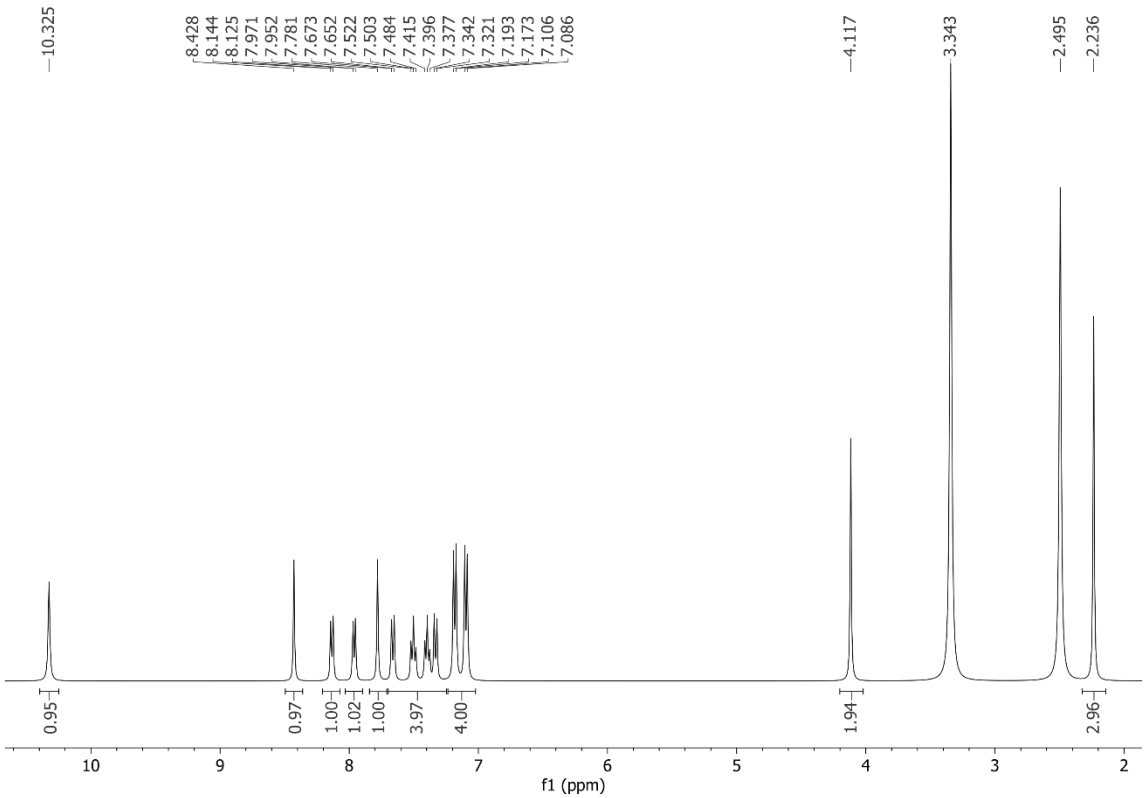

Figure S10. ^{13}C-NMR of compound 6a.

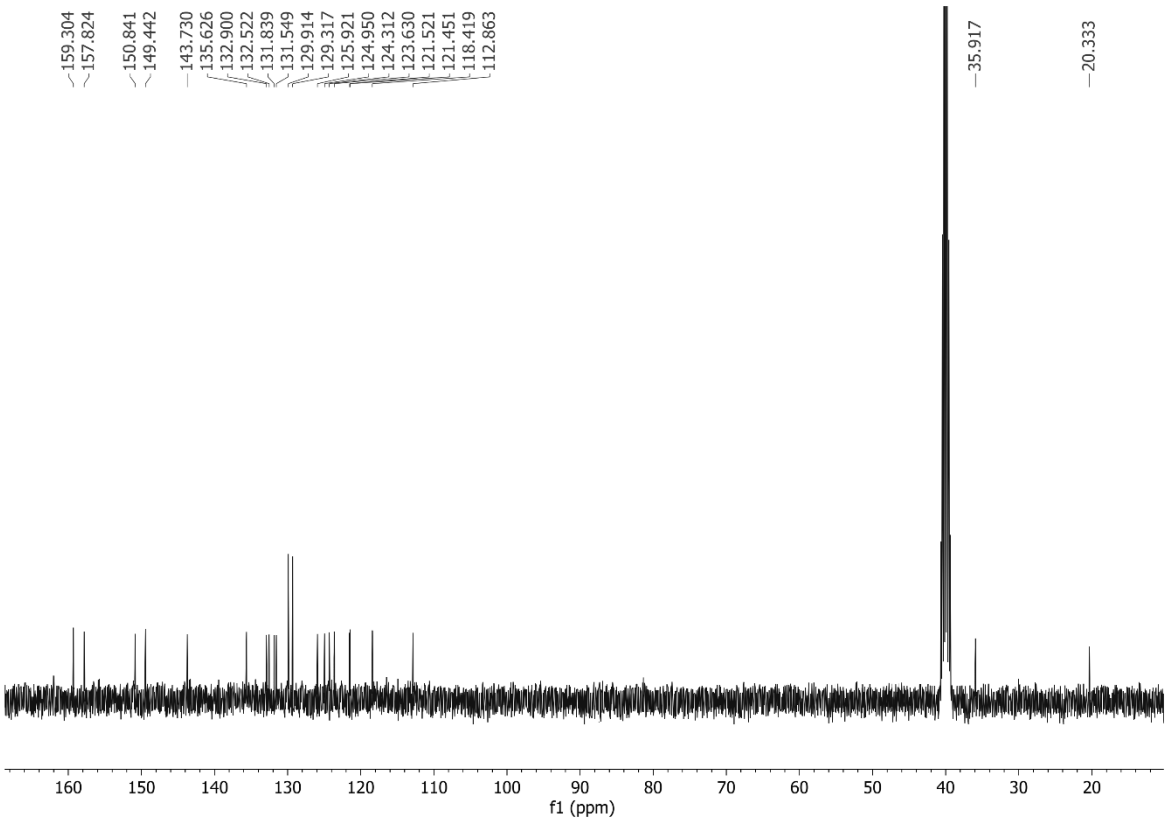

Figure S11. ^{1}H-NMR of compound 6b.

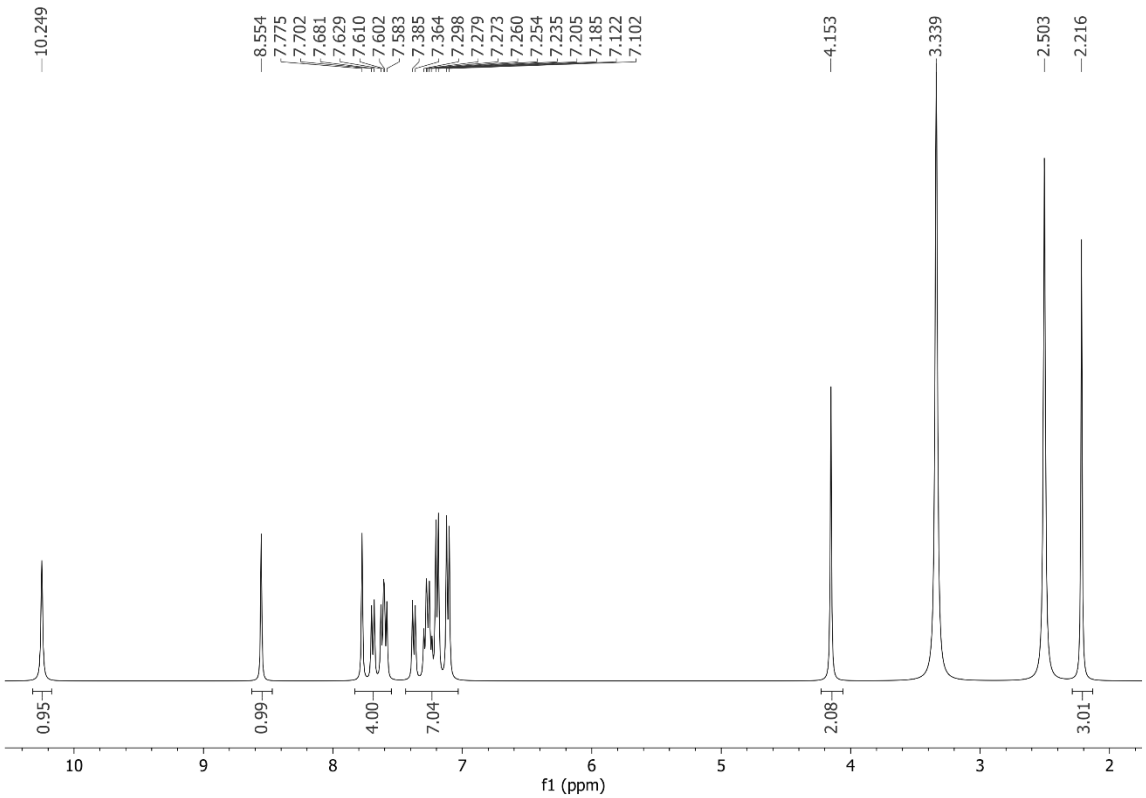

Figure S12. ^{13}C-NMR of compound 6b.

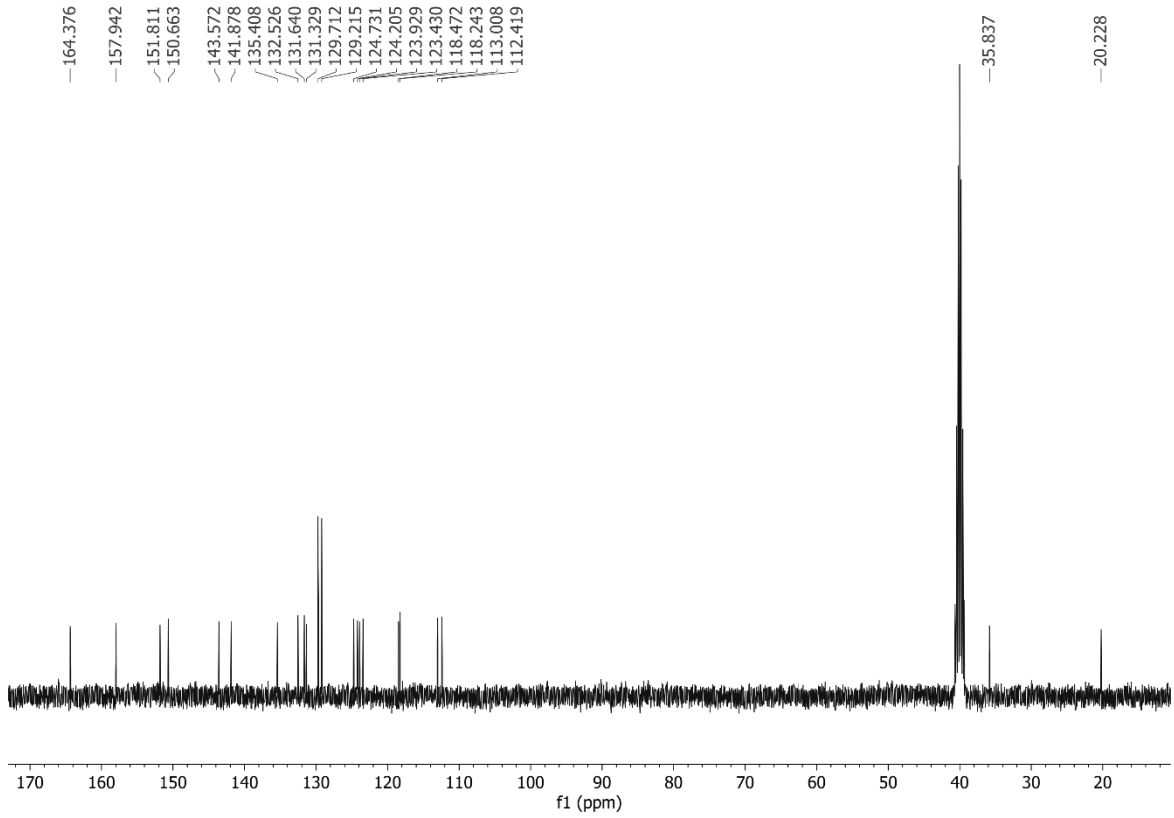

Figure S13. ^{1}H-NMR of compound 6c.

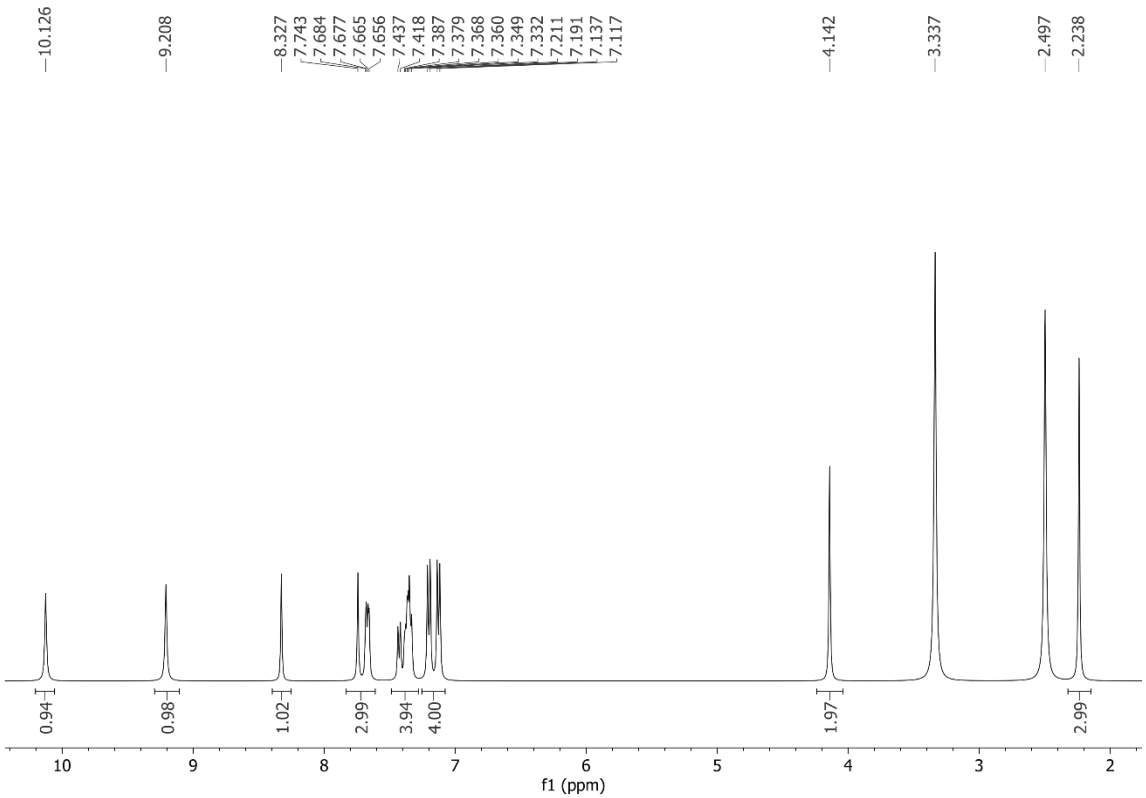

Figure S14. ^{13}C-NMR of compound 6c.

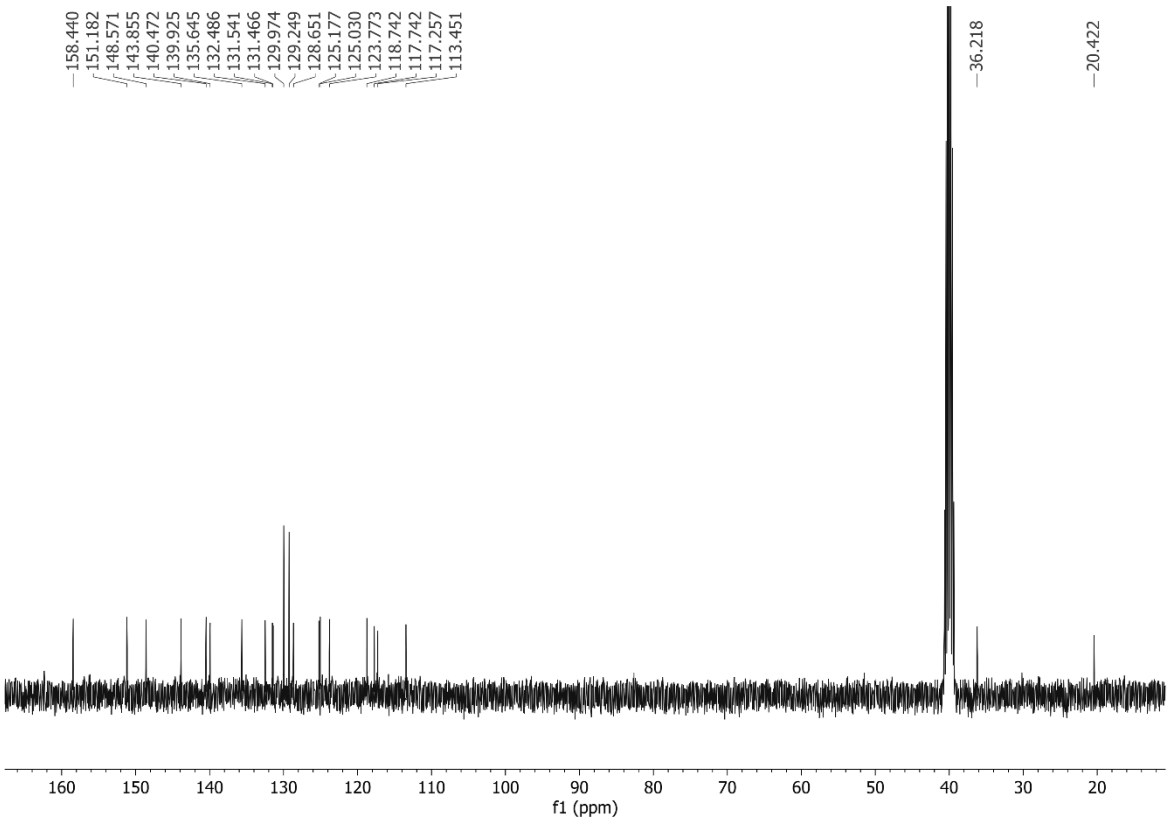

Figure S15. ^{1}H-NMR of compound 7a.

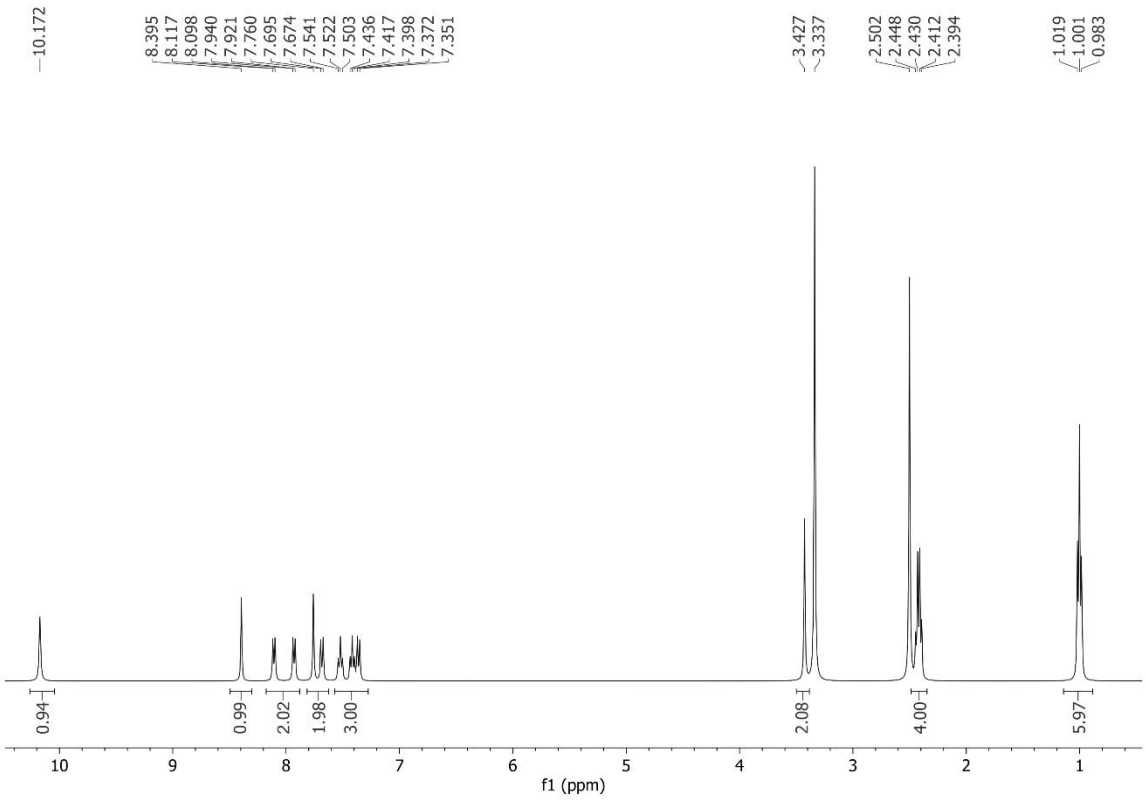

Figure S16. ^{13}C-NMR of compound 7a.

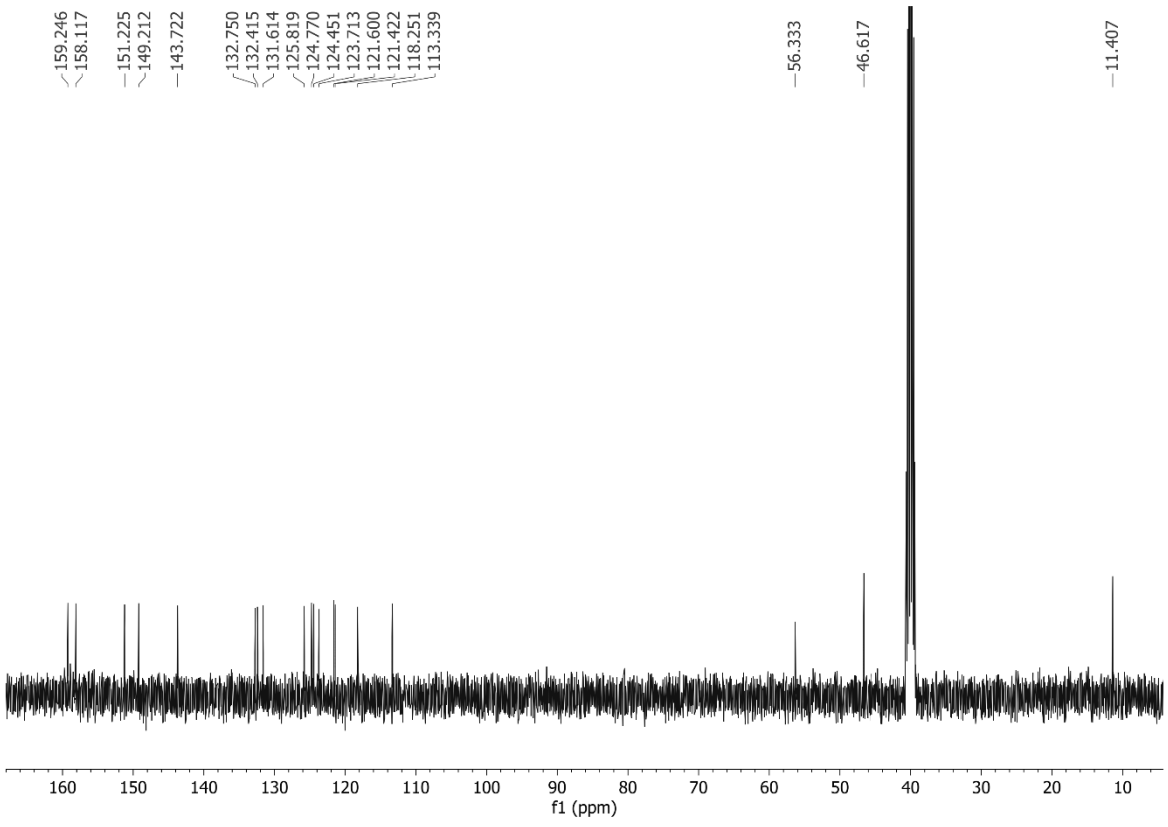

Figure S17. ^{1}H-NMR of compound 7b.

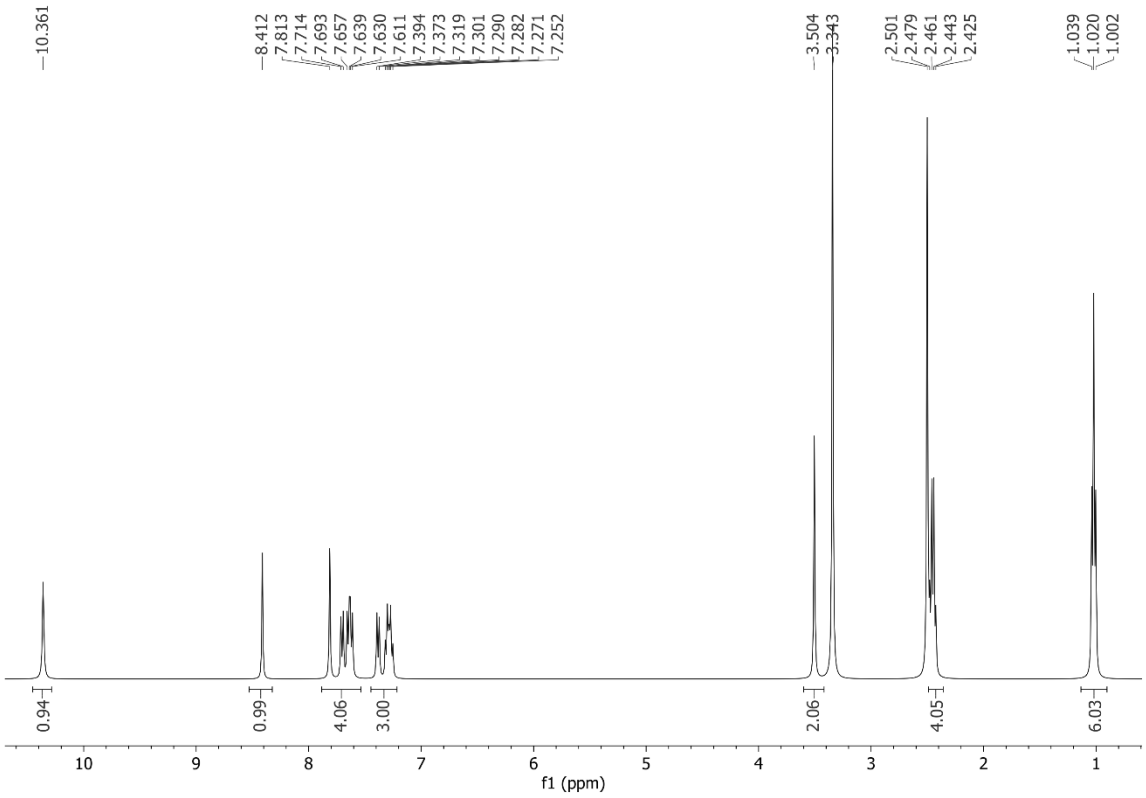

Figure S18. ^{13}C-NMR of compound 7b.

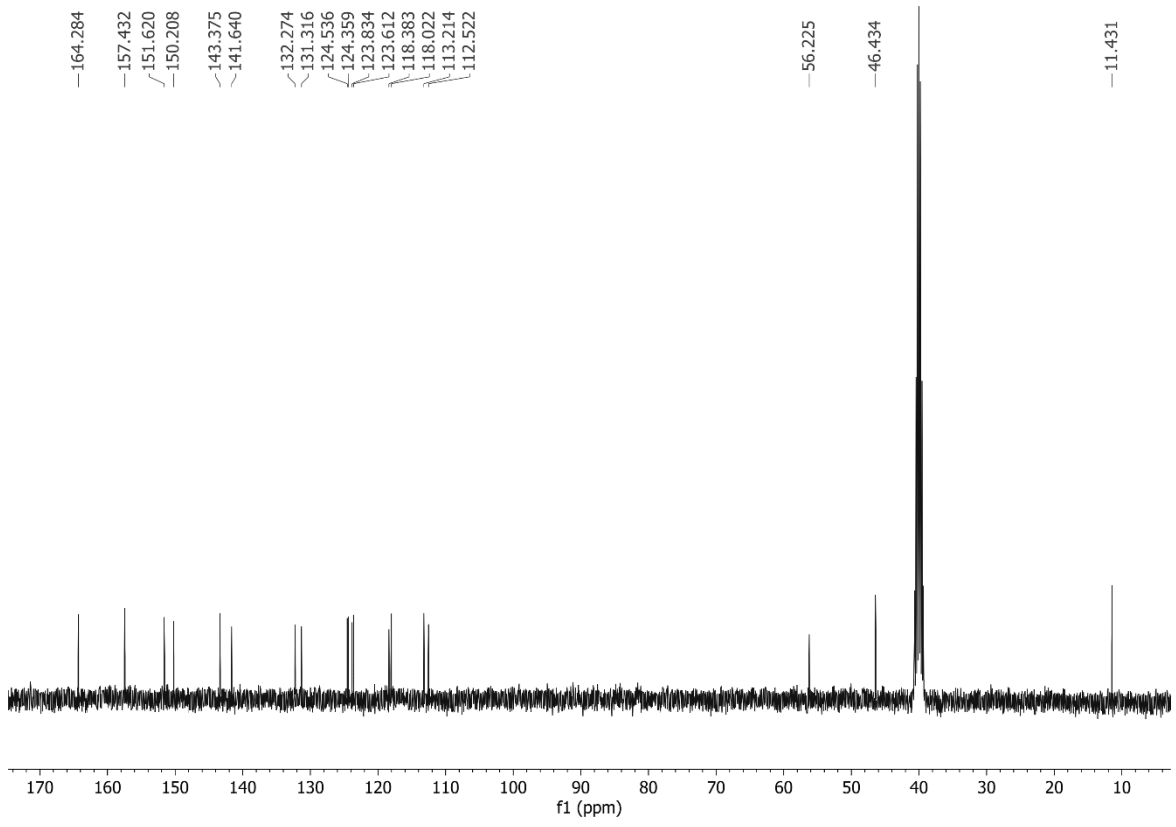

Figure S19. ^{1}H-NMR of compound 7c.

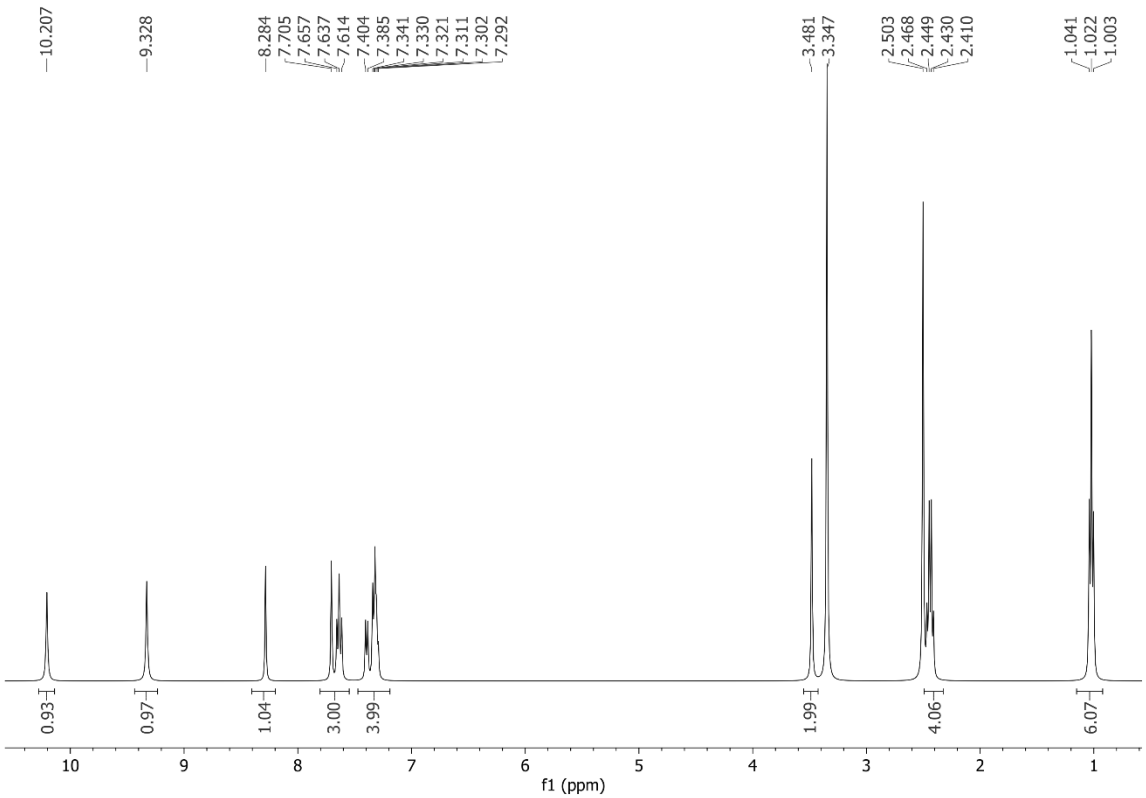

Figure S20. ^{13}C-NMR of compound 7c.

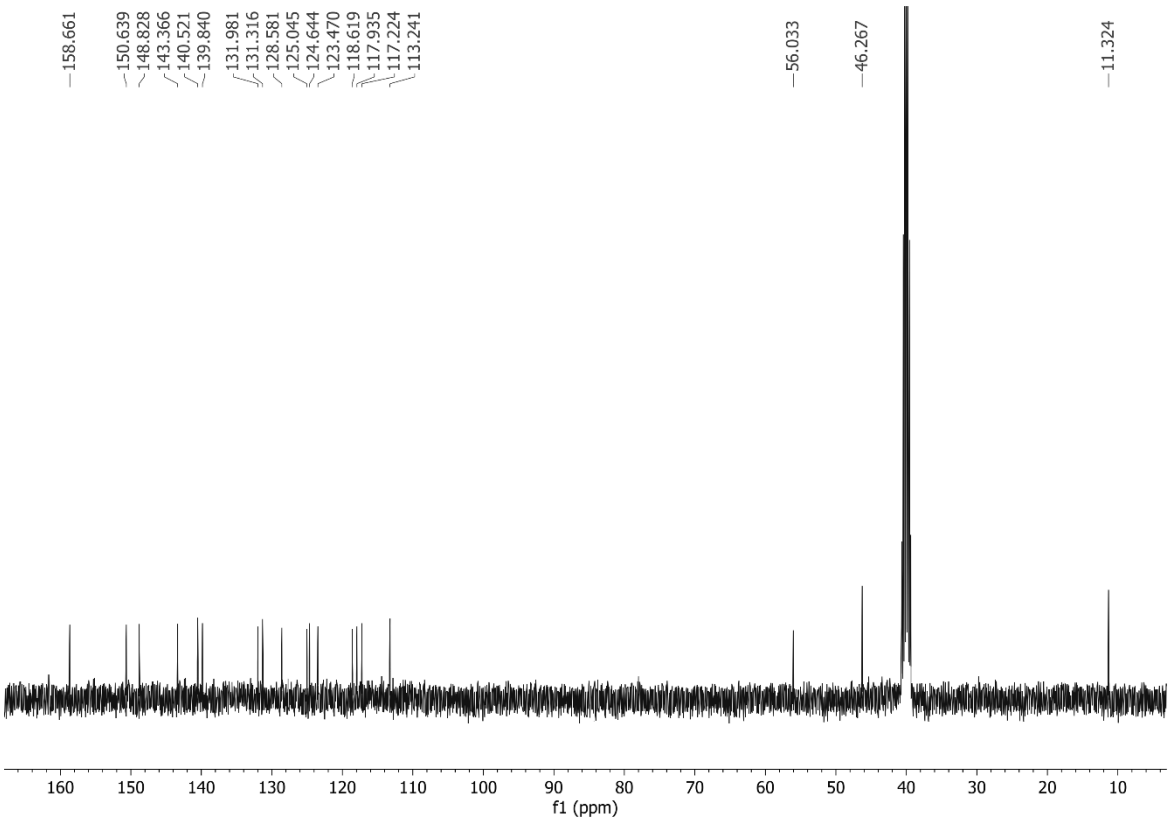

Figure S21. ^{1}H-NMR of compound 9a.

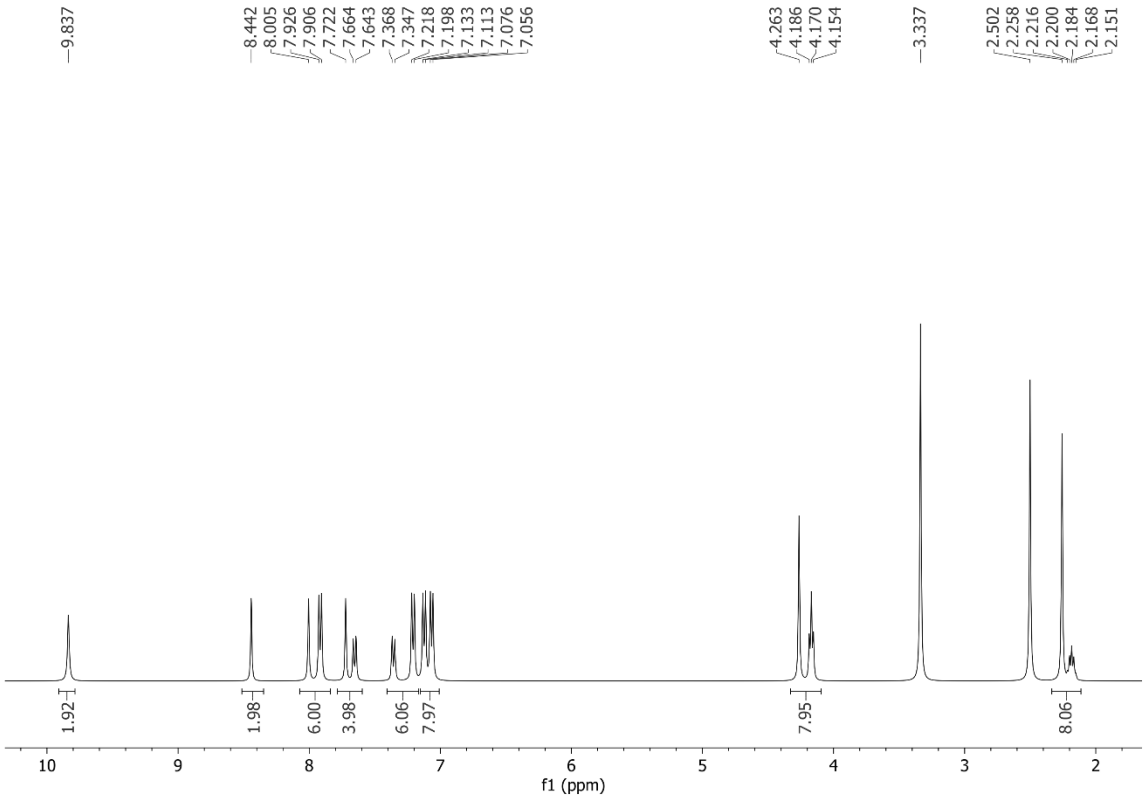

Figure S22. ^{13}C-NMR of compound 9a.

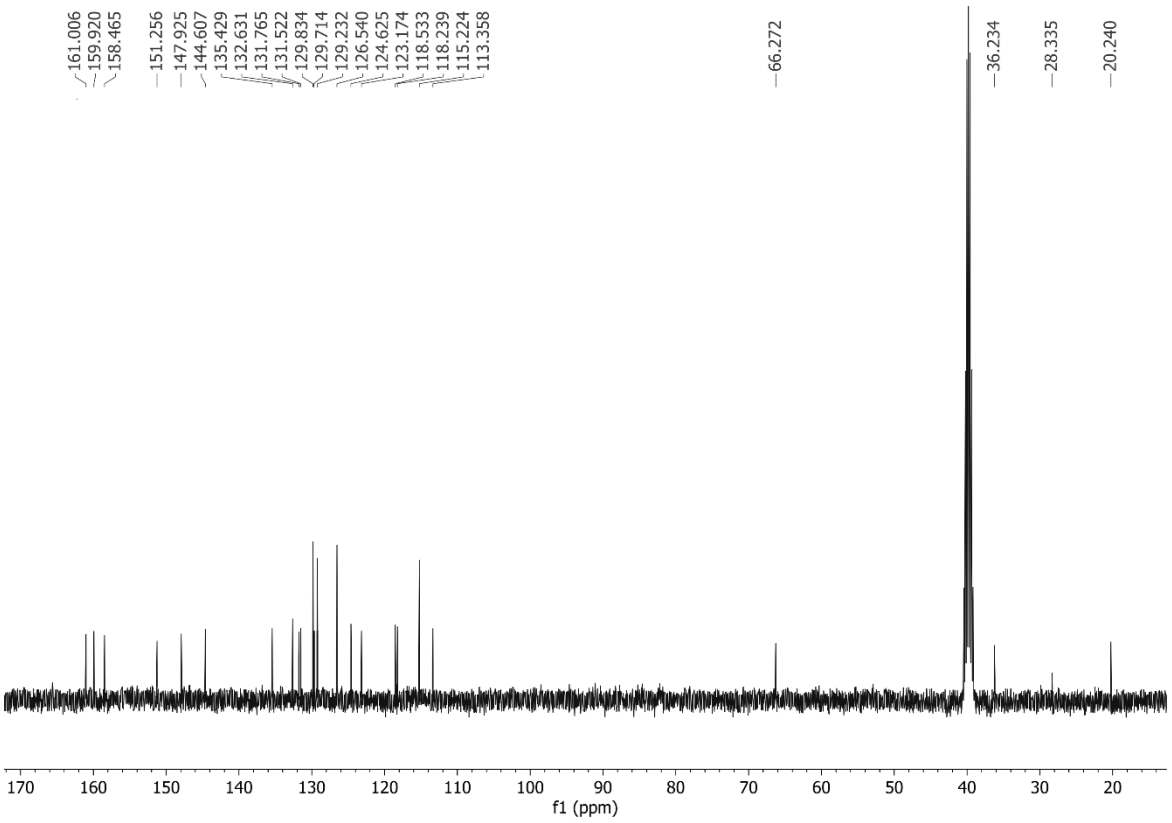

Figure S23. ^{1}H-NMR of compound 9b.

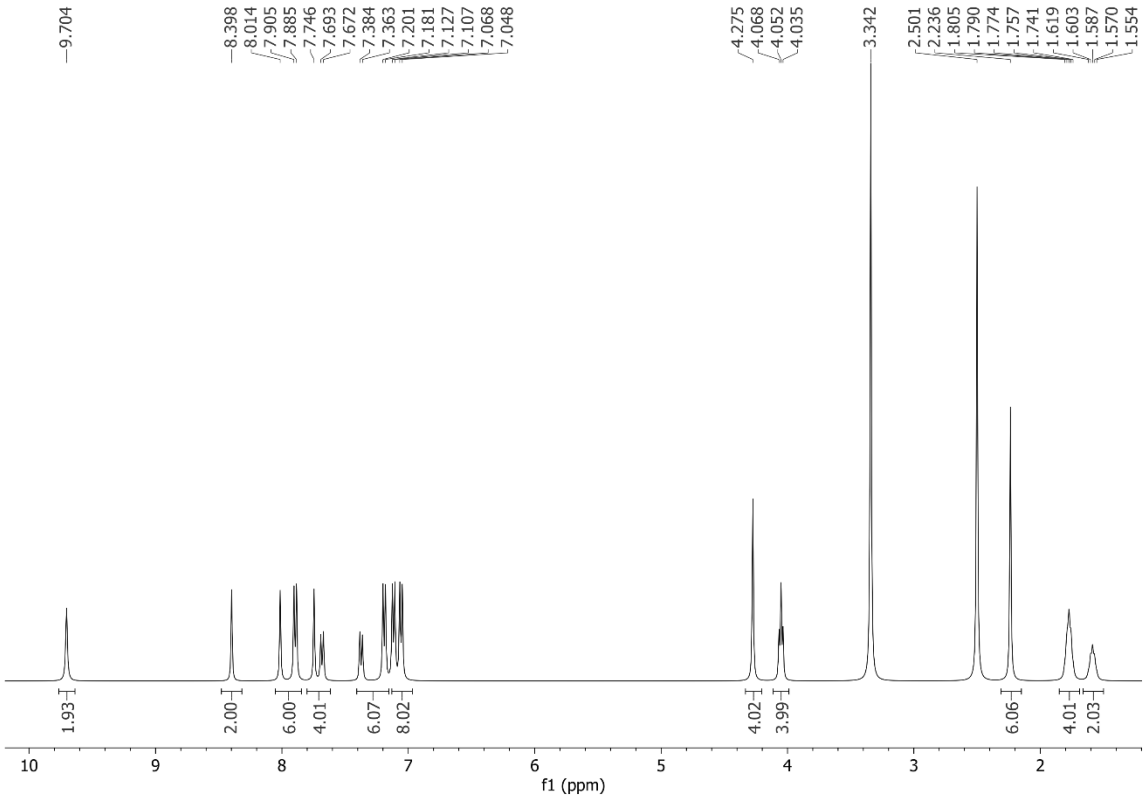

Figure S24. ^{13}C-NMR of compound 9b.

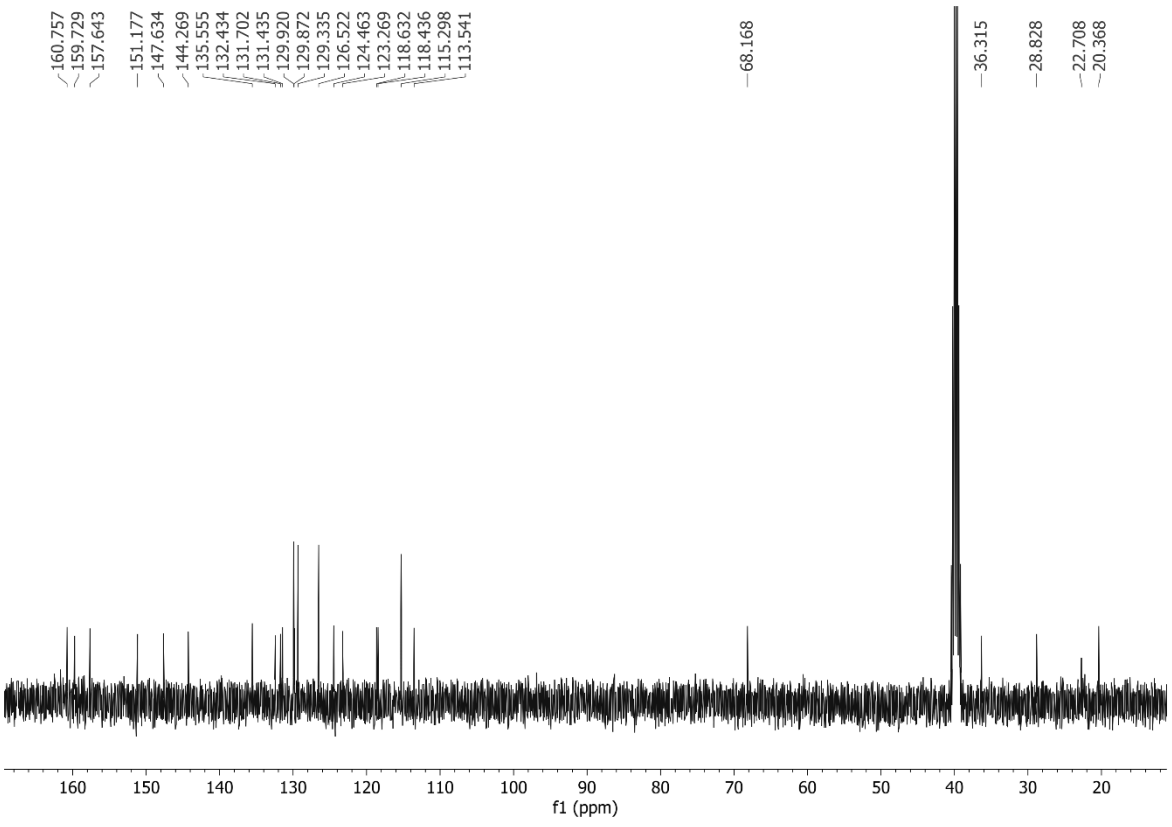

Figure S25. ^{1}H-NMR of compound 9c.

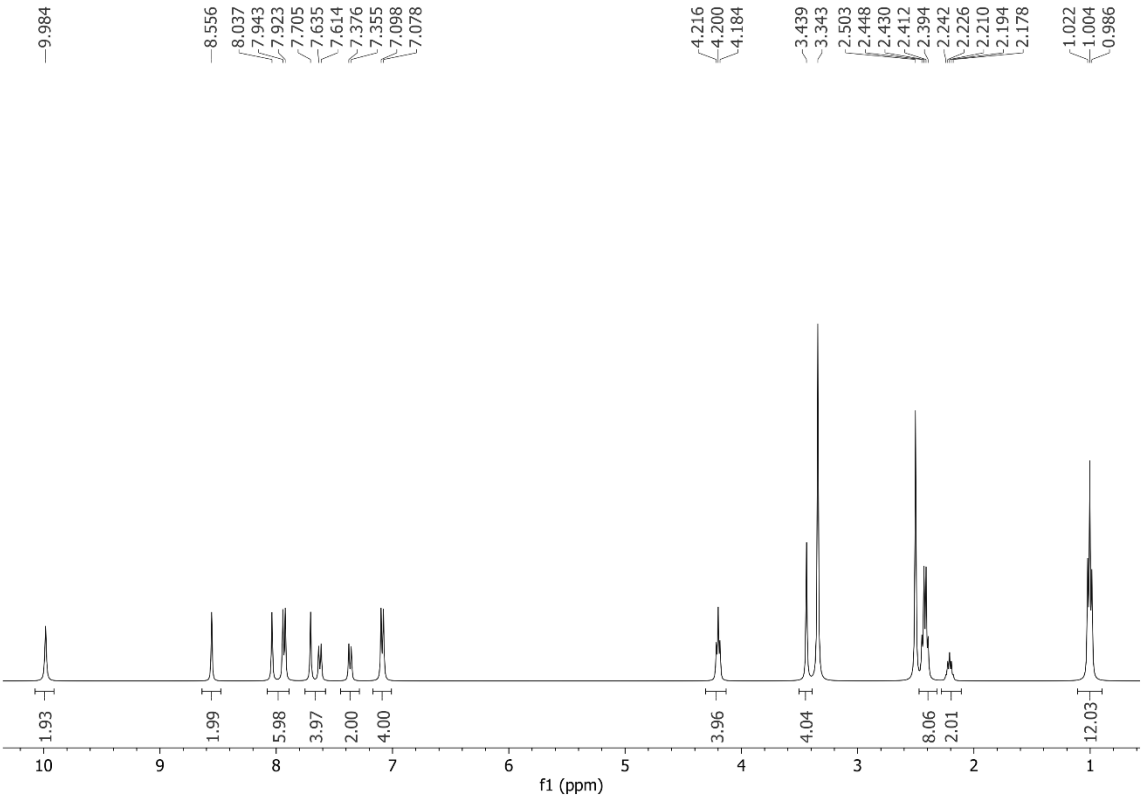

Figure S26. ^{13}C-NMR of compound 9c.

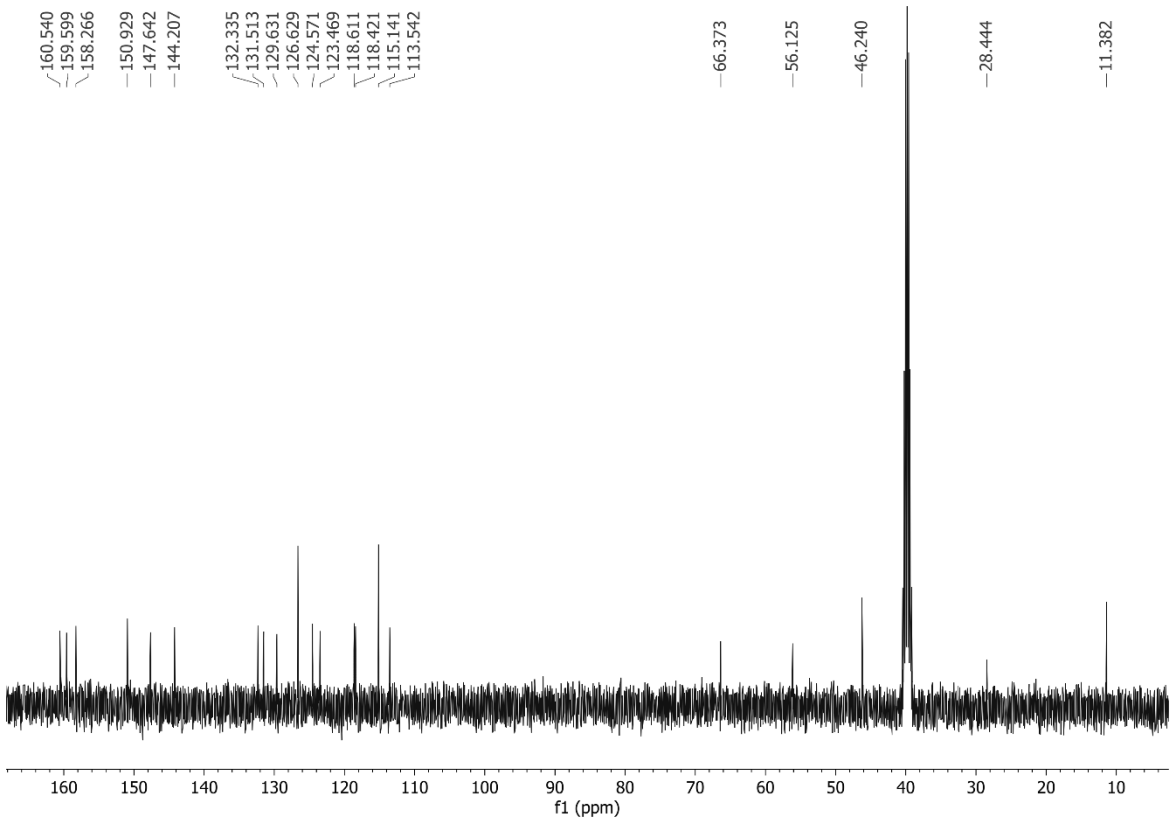

Figure S27. ^{1}H-NMR of compound 9d.

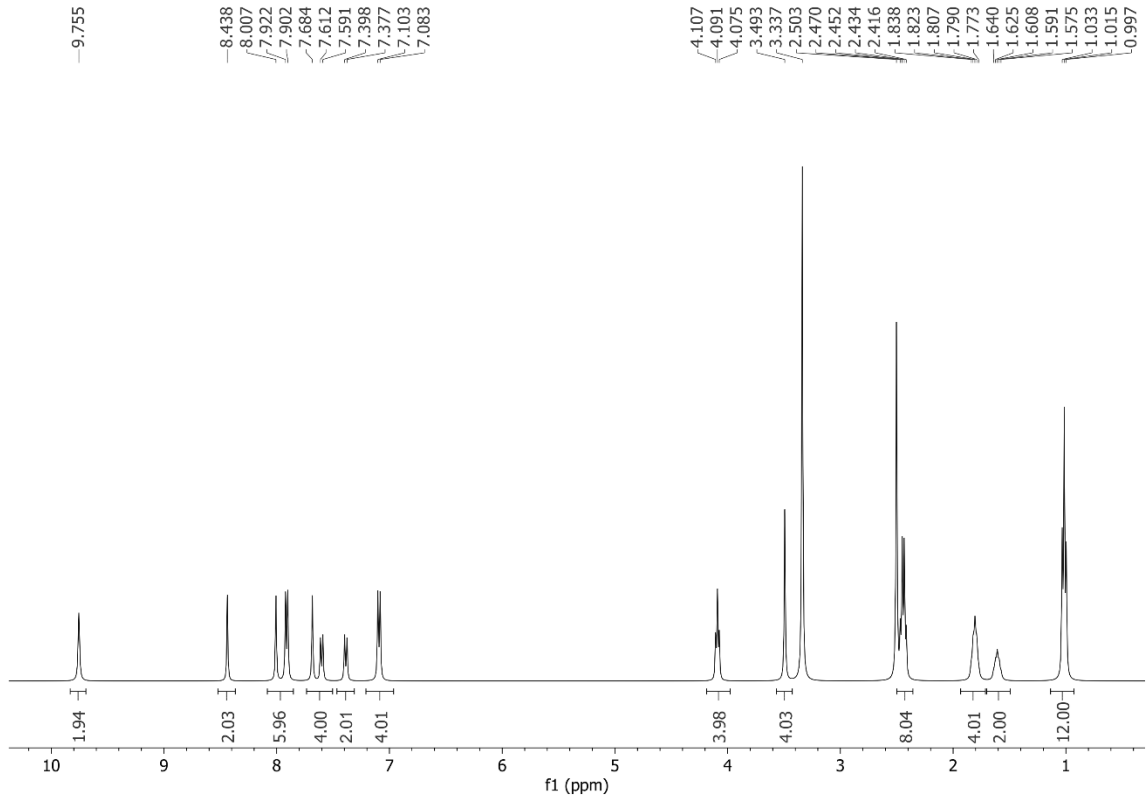

Figure S28. ^{13}C-NMR of compound 9d.

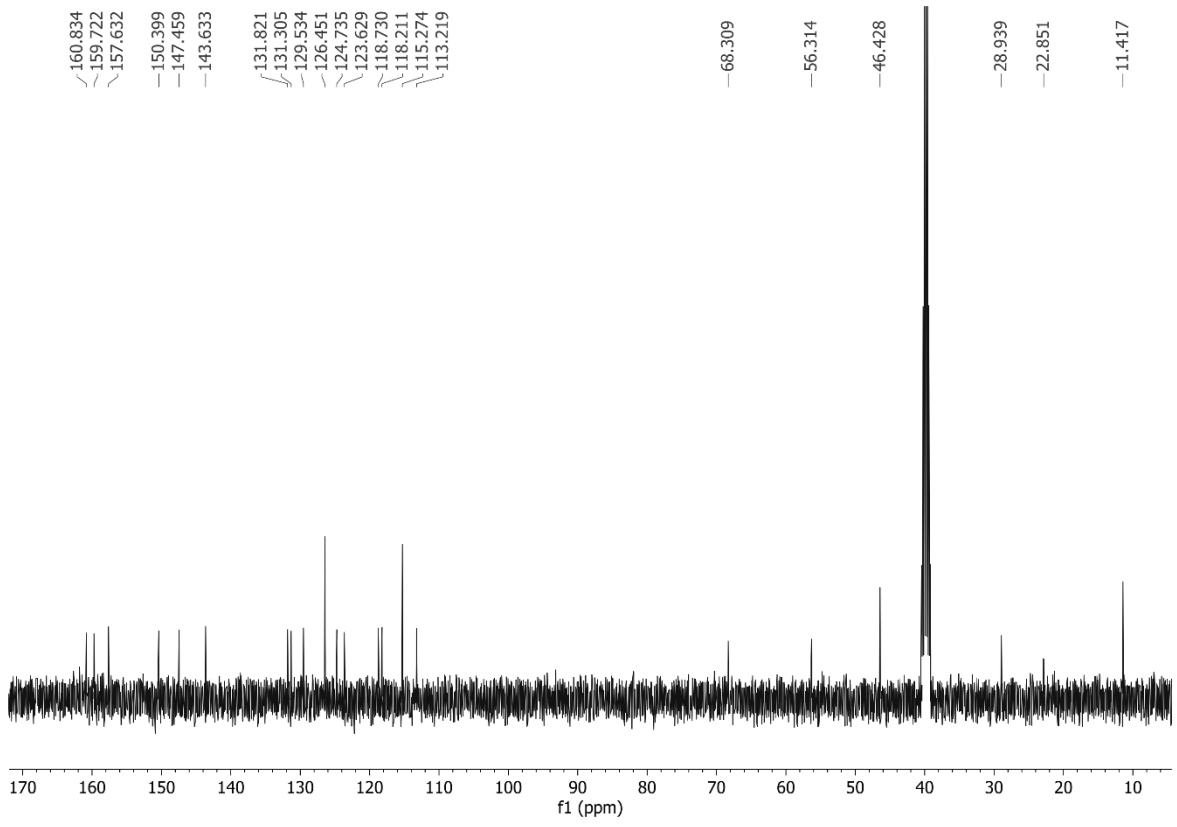

Figure S29. ^{1}H-NMR of compound 11a.

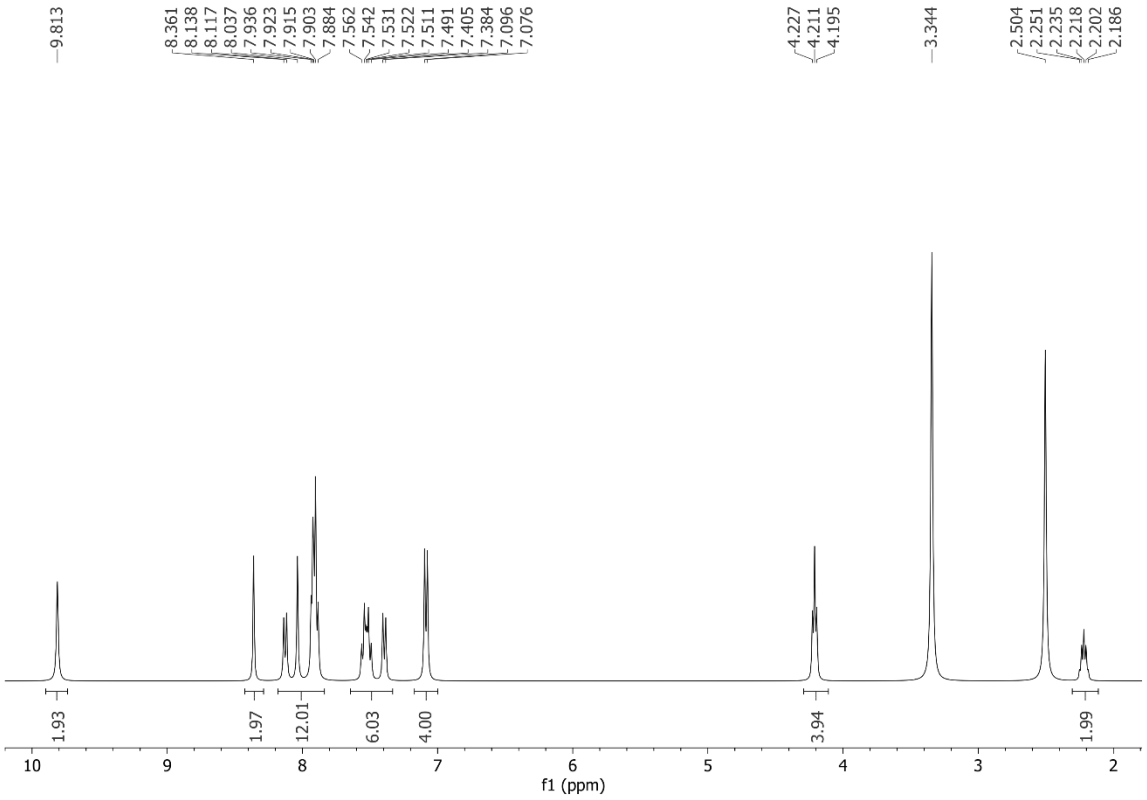

Figure S30. ^{13}C-NMR of compound 11a.

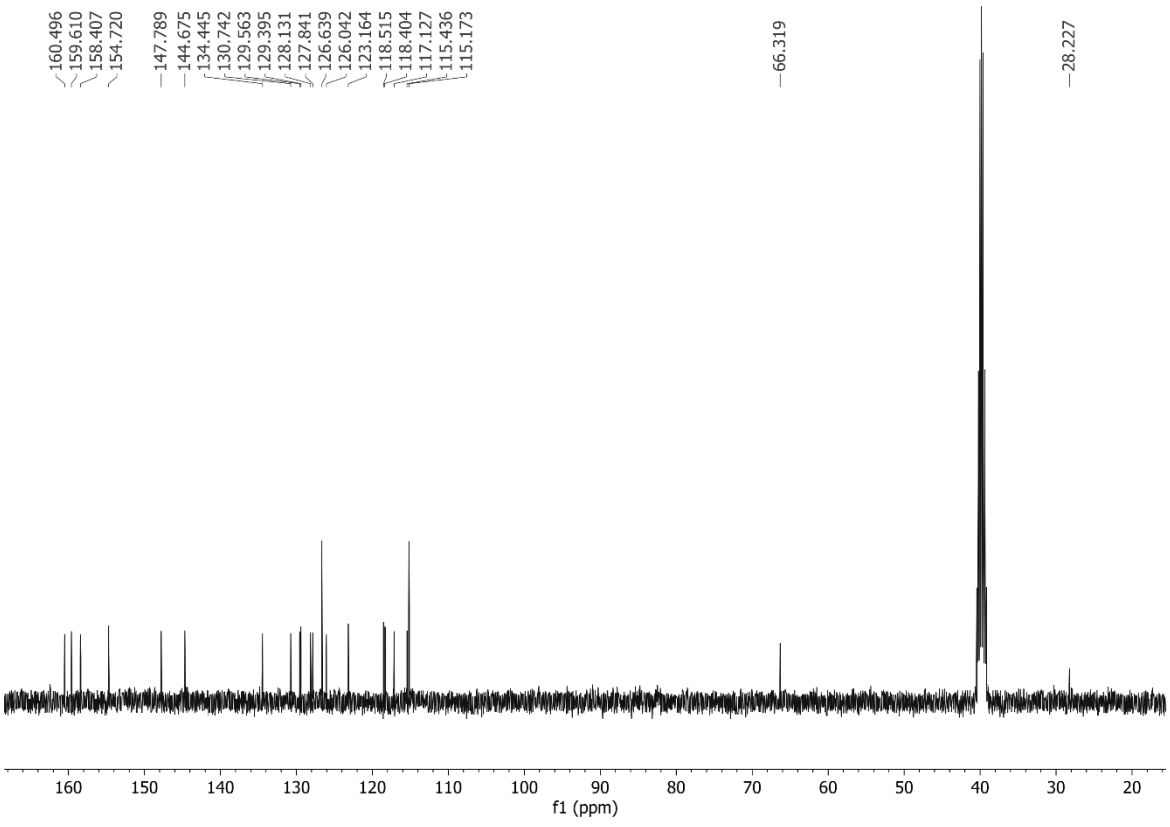

Figure S31. ^{1}H-NMR of compound 11b.

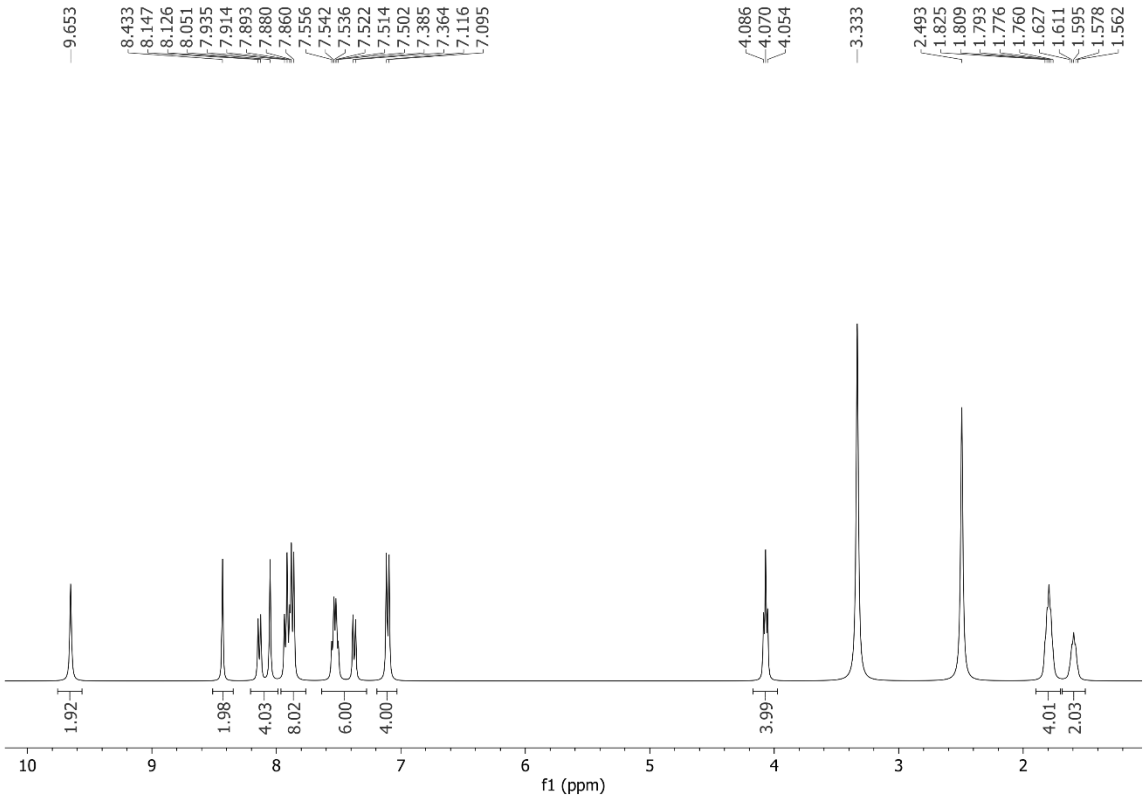

Figure S32. ^{13}C-NMR of compound 11b.

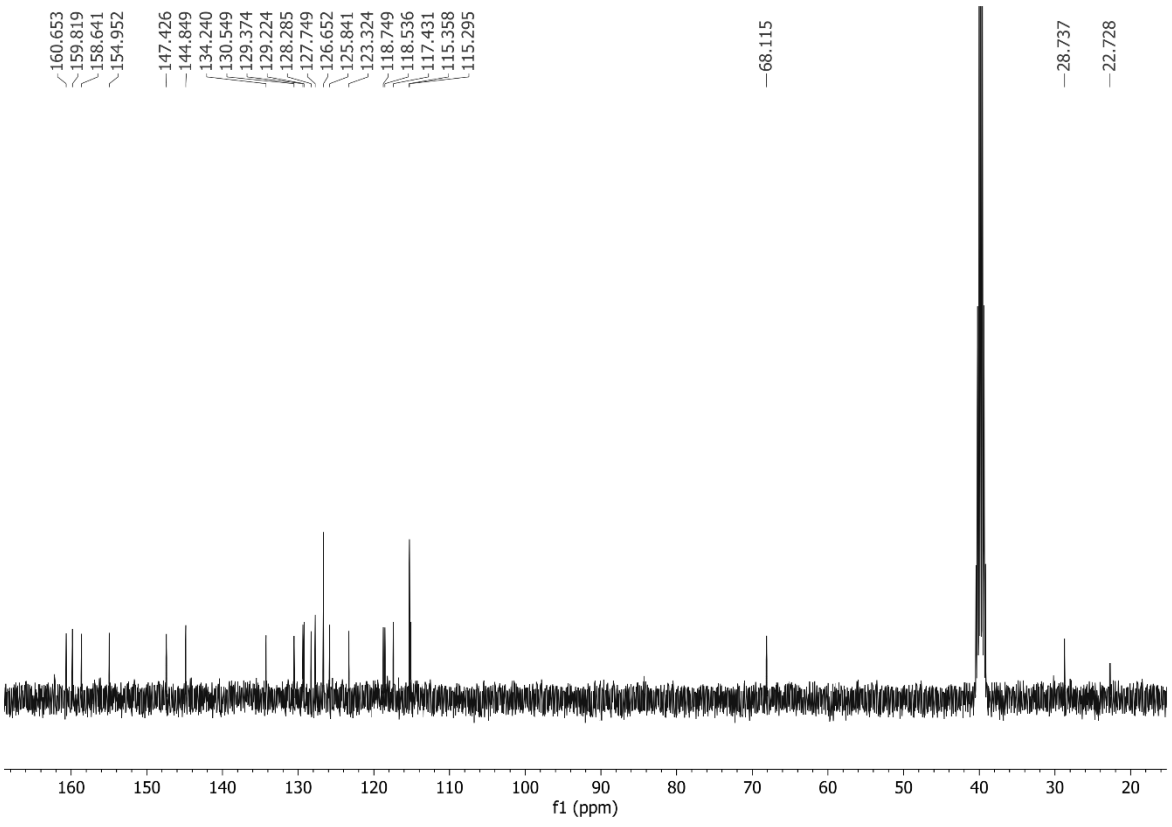

Figure S33. ^{1}H-NMR of compound 13a.

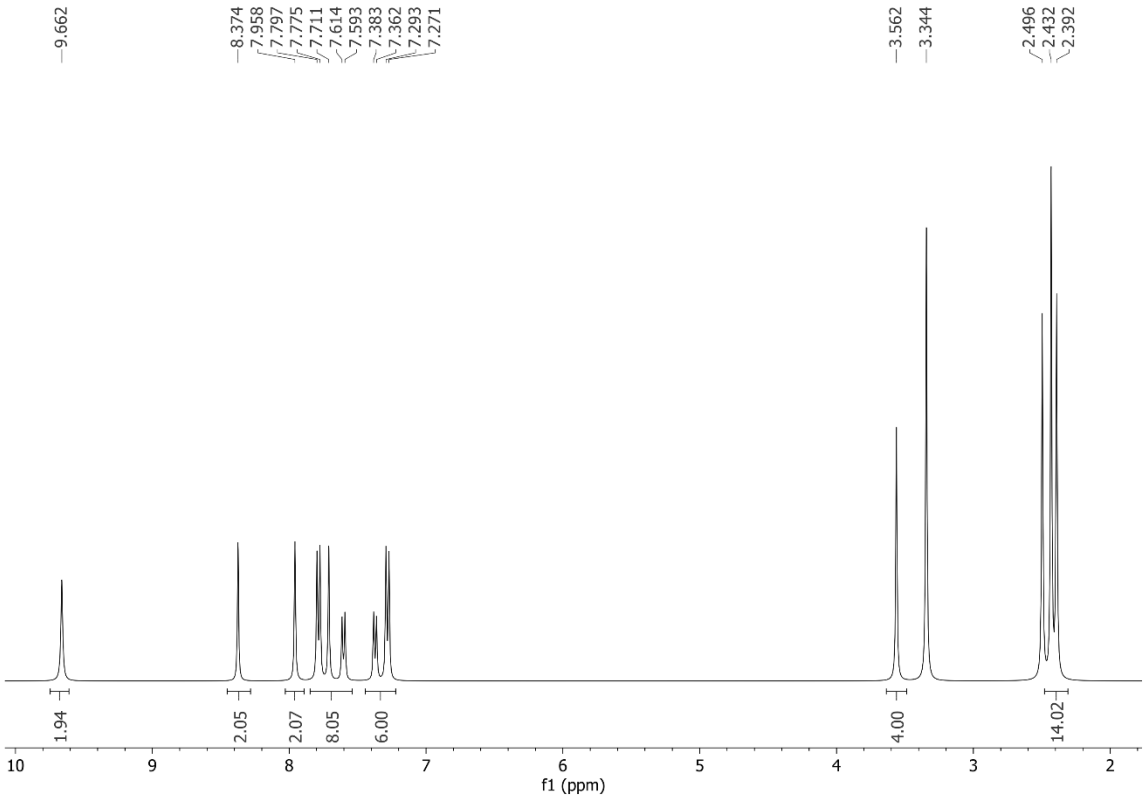

Figure S34. ^{13}C-NMR of compound 13a.

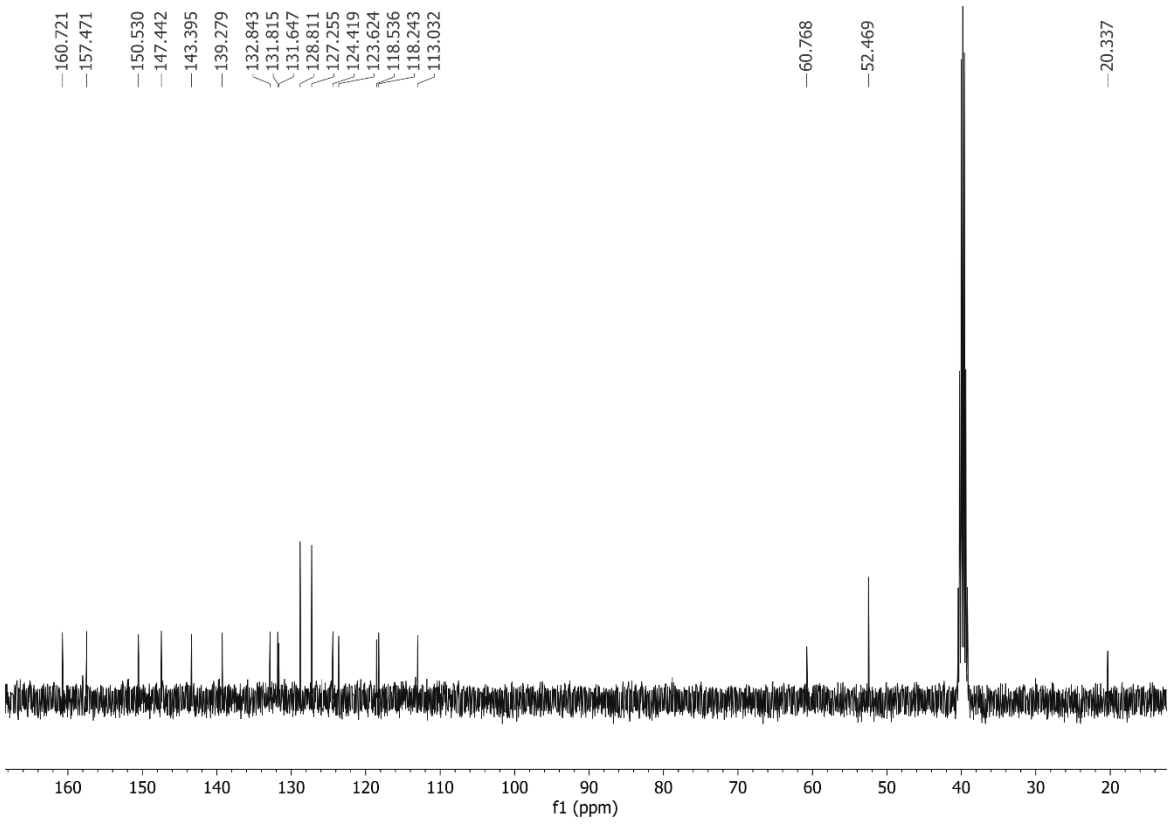

Figure S35. ^{1}H-NMR of compound 13b.

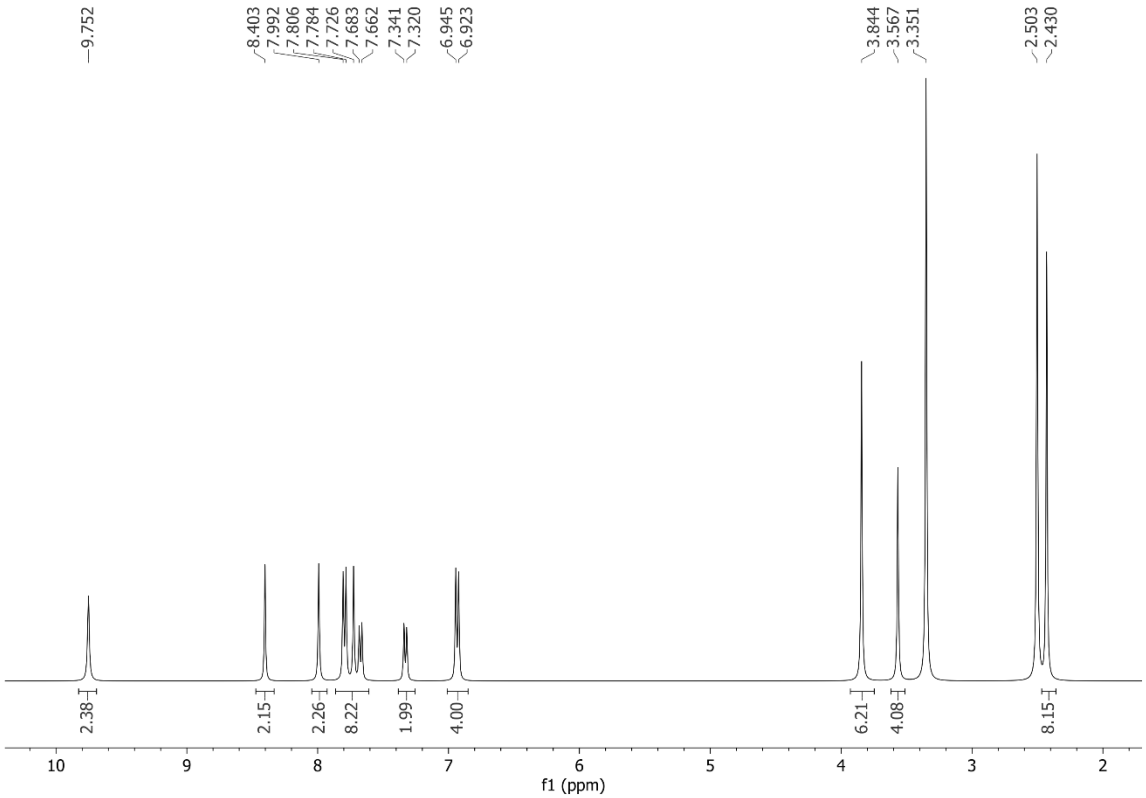

Figure S36. ^{13}C-NMR of compound 13b.

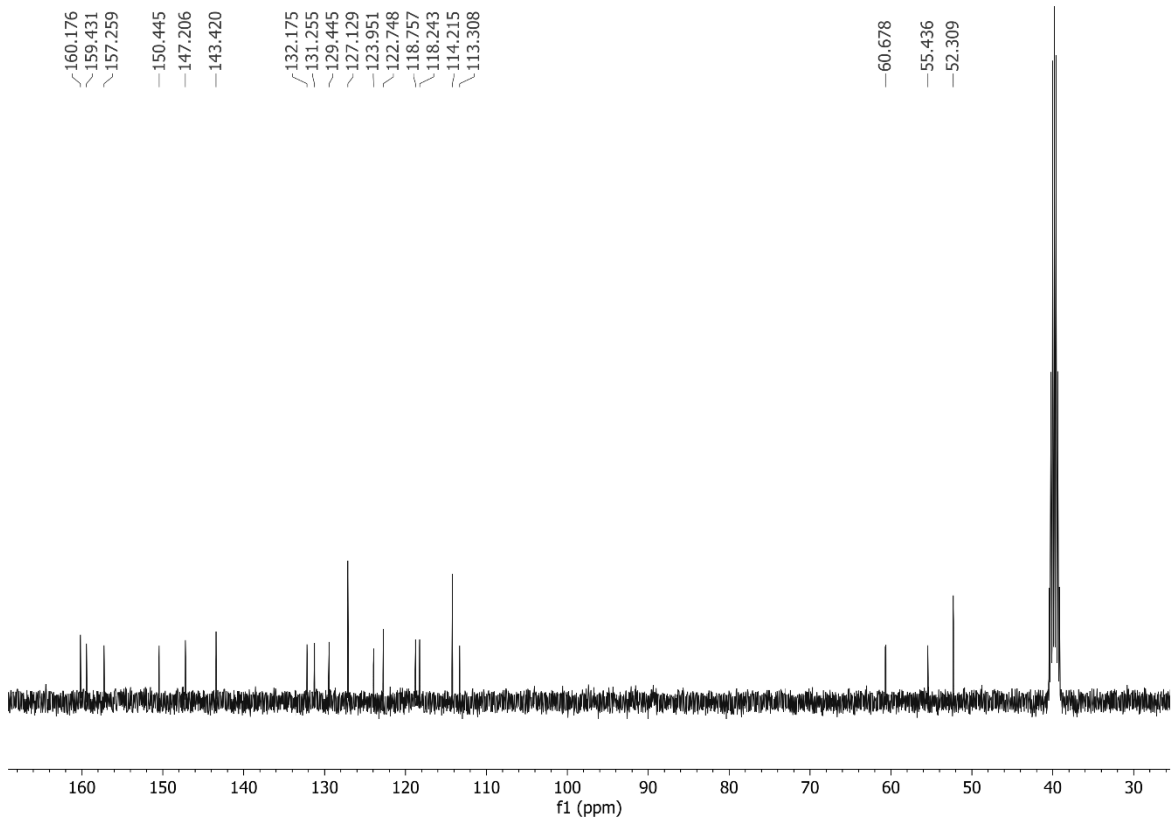

Figure S37. ^{1}H-NMR of compound 14a.

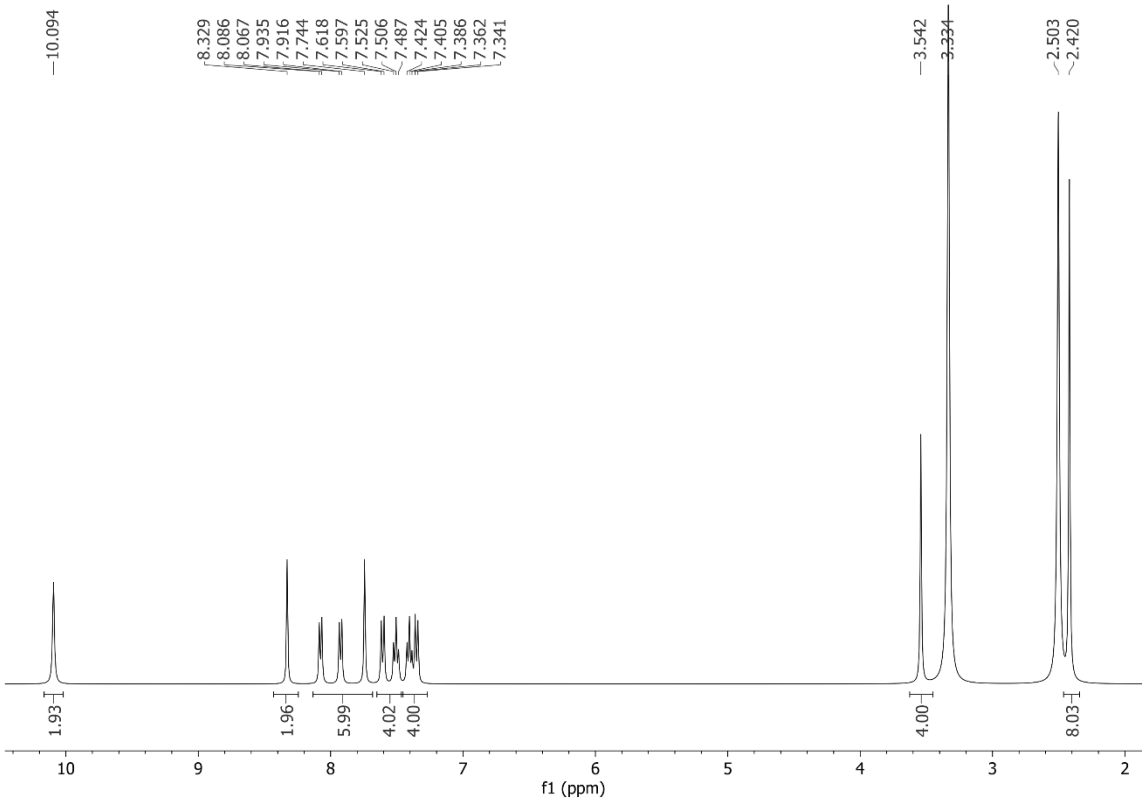

Figure S38. ^{13}C-NMR of compound 14a.

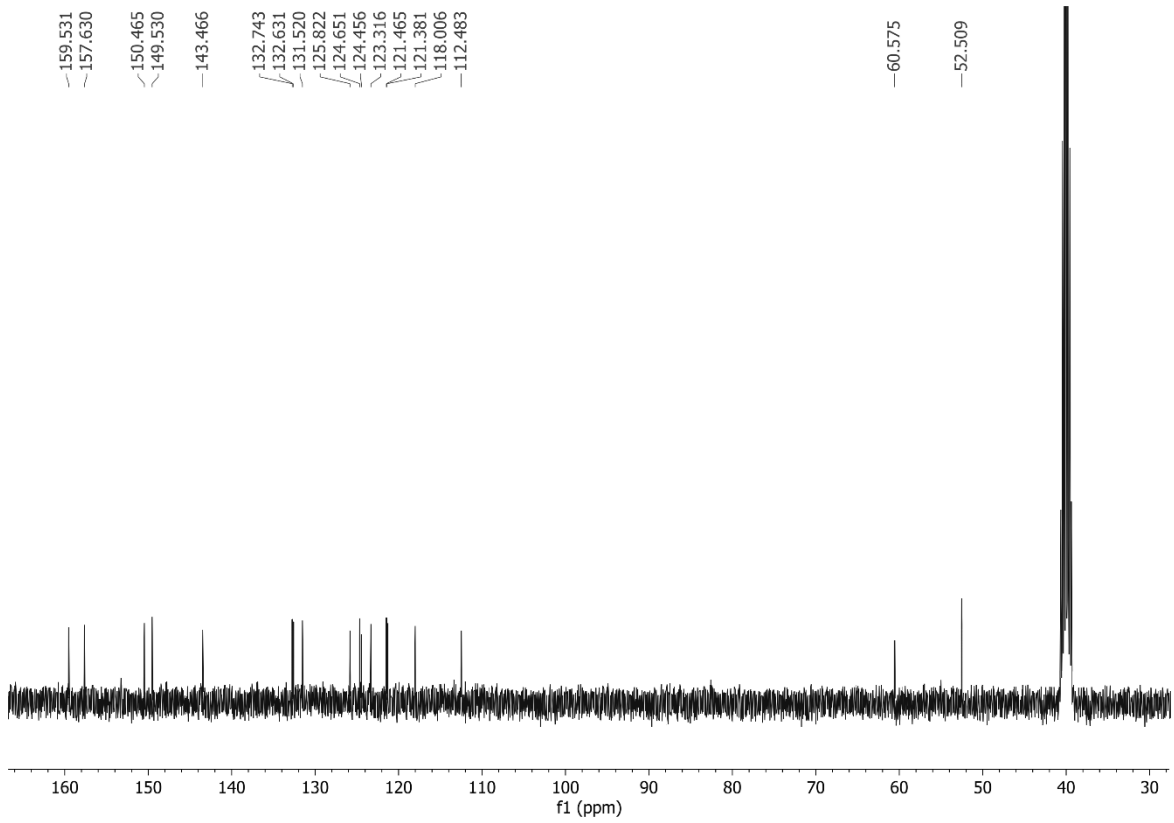

Figure S39. ^{1}H-NMR of compound 14b.

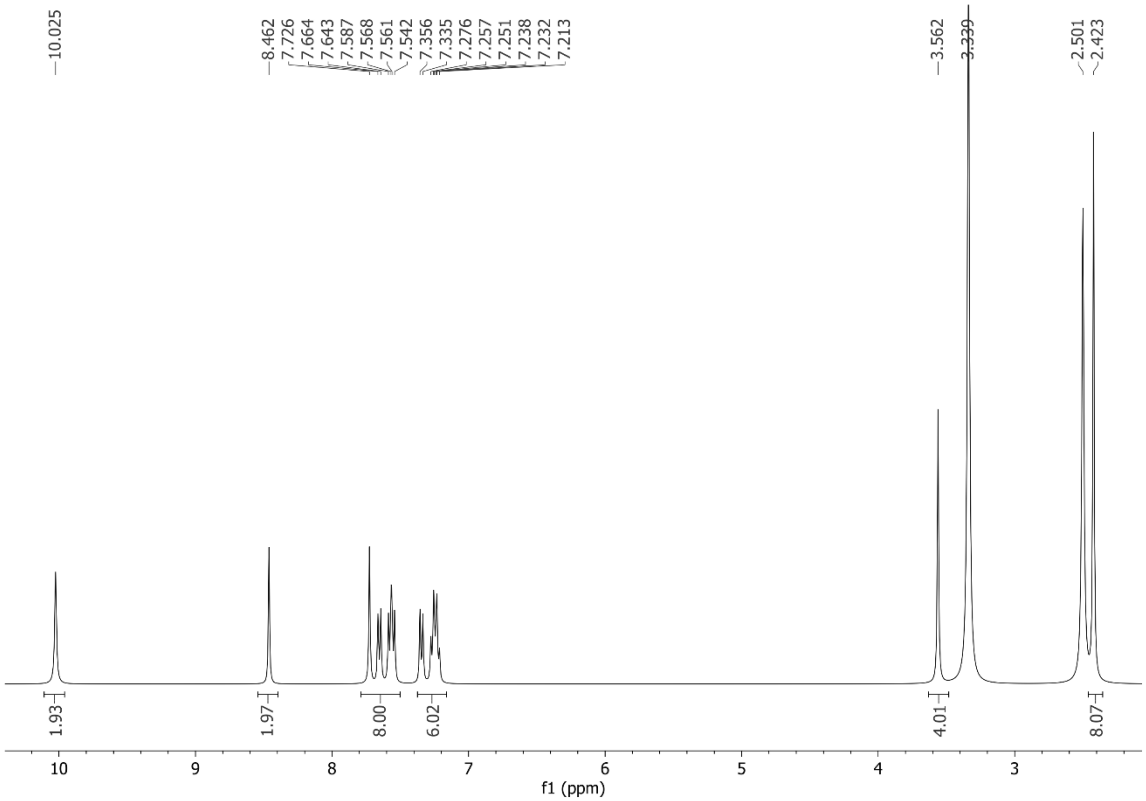

Figure S40. ^{13}C-NMR of compound 14b.

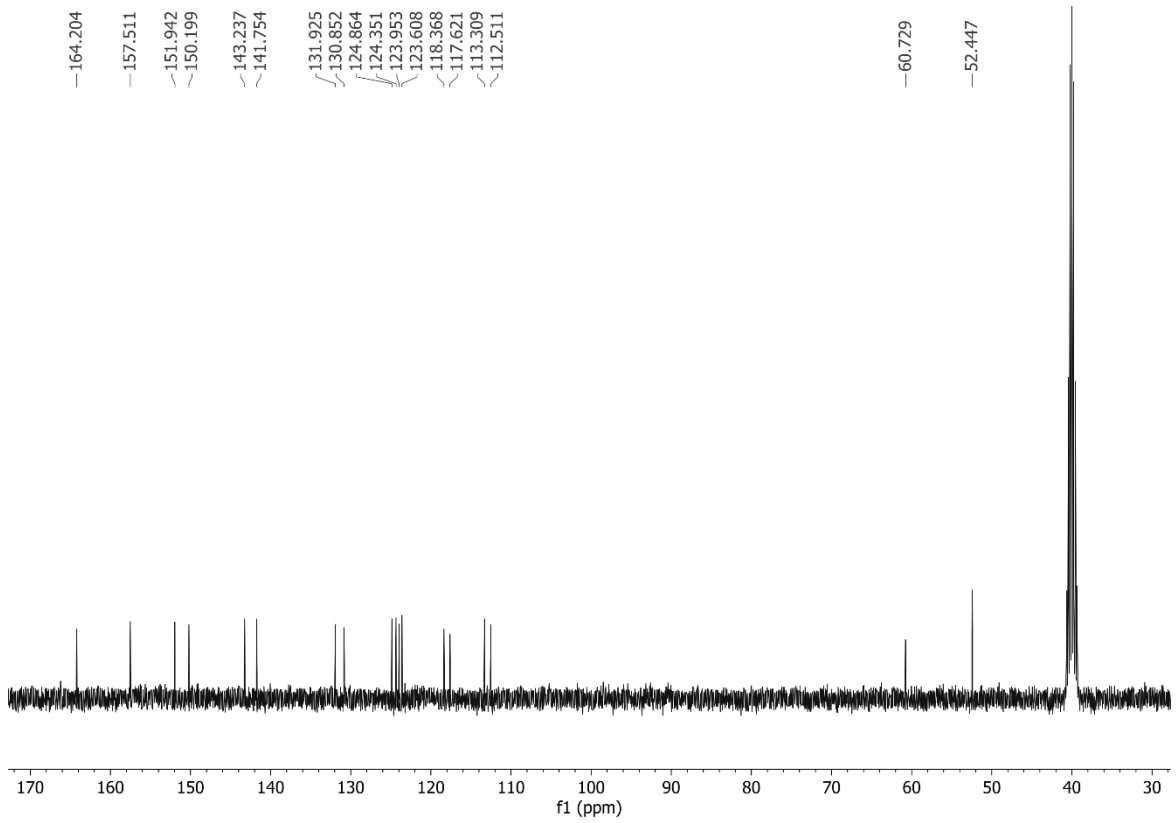

Figure S41. ^{1}H-NMR of compound 14c.

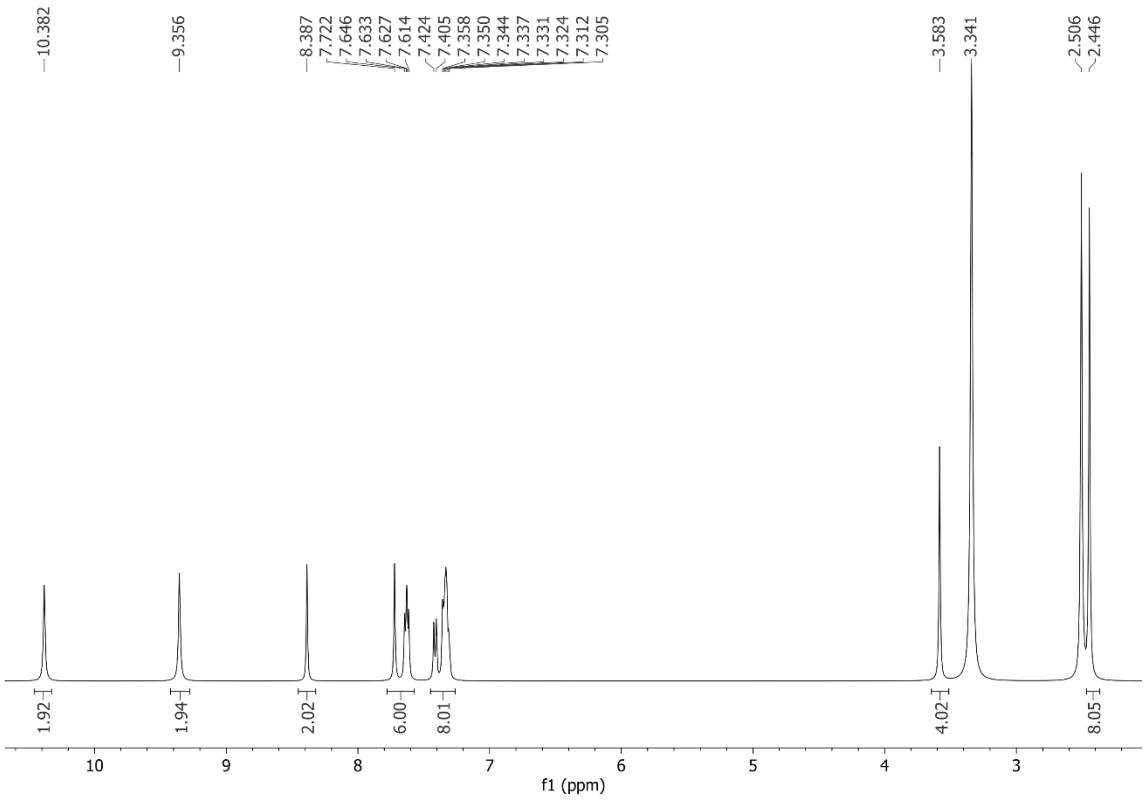

Figure S42. ^{13}C-NMR of compound 14c.