Supporting Information for

Antileishmanial Anthracene Endoperoxides: Efficacy in vitro, Mechanisms and Structure-Activity Relationships

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NMR Spectroscopic Data

General. ^{1}H NMR and ^{13}C NMR spectra were measured using a Bruker NEO 400, Bruker MAS 400, or Bruker NEO 500 (Rheinstetten, Germany) NMR spectrometer. Chemical shifts and multiplicities were derived from corresponding ^{13}C APT or HSQC measurements.

9,10-Bis-(1-O-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-anthracene (BisGluAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.80 (2s, 6H; 6-OAc), 2.01 (2s, 6H; 4-OAc), 2.08 (2s, 6H; 3-OAc), 2.23 (2s, 6H; 2-OAc), 3.52 (2ddd, *J* = 9.9, 5.5, 2.7 Hz, 2H; 5-H), 3.89 (2dd, *J* = 12.1, 2.7 Hz, 2H; 6a-H), 4.23 (2dd, *J* = 12.1, 5.6 Hz, 2H;6b-H), 5.21 (2d, *J* = 8.1 Hz, 2H; 1-H), 5.24 (2dd, *J* = 9.9, 9.4 Hz, 2H; 4-H), 5.33 (2dd, *J* = 9.7, 9.4 Hz, 2H; 3-H), 5.64 (2dd, *J* = 9.7, 8.1 Hz, 2H; 2-H), 7.47–7.50 (m, 4H; 2-ANTH, 3-ANTH, 6-ANTH, 7-ANTH), 8.38–8.41 ppm (m, 4H; 1-ANTH, 4-ANTH, 5-ANTH, 8-ANTH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5 (2q; OAc-6), 20.6 (2q; OAc-4), 20.7 (2q; OAc-3), 20.9 (2q; OAc-2), 61.8 (2t; C-6), 68.7 (2d; C-4), 71.9 (2d; C-5), 72.2 (2d; C-2), 73.1 (2d; C-3), 102.8 (2d; C-1), 122.7 (4d; ANTC-1, ANTC-4, ANTC-5, ANTC-8), 125.3 (4s; ANTC-11, ANTC-12, ANTC-13, ANTC-14), 125.7 (4d; ANTC-2, ANTC-3, ANTC-6, ANTC-7), 144.9 (2s; ANTC-9, ANTC-10), 169.4 (2s; OAc-2), 169.5 (2s; OAc-4), 170.4 (2s; OAc-6), 170.5 ppm (2s; OAc-3).

9,10-Bis-(1-O-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-9,10-dihydro-9,10-epidioxidoanthracene (BisGluACEP). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.03 (s, 6H; 2-OAc), 2.05 (s, 6H; 3-OAc), 2.06 (s, 6H; 4-OAc), 2.13 (s, 6H; 6-OAc), 3.86 (ddd, *J* = 10.0, 5.7, 2.3 Hz, 2H; 5-H), 4.25 (dd, *J* = 12.3, 2.2 Hz, 2H; 6a-H), 4.31 (dd, *J* = 12.3, 5.7 Hz, 2H; 6b-H), 5.21 (dd, *J* = 10.0, 9.2 Hz, 2H; 4-H), 5.34 (dd, *J* = 9.6, 9.2 Hz, 2H; 3-H), 5.38 (dd, *J* = 9.6, 7.6 Hz, 2H; 2-H), 5.47 (d, *J* = 7.6 Hz, 2H; 1-H), 7.28 (dd, *J* = 8.5, 7.2 Hz, 2H; 2-ANTH, 7-ANTH), 7.33 (dd, *J* = 8.5, 7.6 Hz, 2H; 3-ANTH, 6-ANTH), 7.59 (d, *J* = 7.6 Hz, 2H; 4-ANTH, 5-ANTH), 7.86 ppm (d, *J* = 7.2 Hz, 2H; 1-ANTH, 8-ANTH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 (q; OAc-3), 20.7 (q; OAc-4), 20.9 (q; OAc-2), 20.9 (q; OAc-6), 62.3 (t; C-6), 68.5 (d; C-4), 71.1 (d; C-2), 72.4 (d; C-5), 72.6 (d; C-3), 96.6 (d; C-1), 102.7 (s; ANTC-9, ANTC-10), 120.2 (d; ANTC-4, ANTC-5), 121.3 (d; ANTC-1, ANTC-8), 127.9 (d; ANTC-2, ANTC-7), 128.3 (d; ANTC-3, ANTC-6), 136.7 (s; ANTC-11, ANTC-12), 138.4 (s; ANTC-13, ANTC-14), 169.5 (s; OAc-2), 169.6 (s; OAc-4), 170.2 (s; OAc-3), 170.6 ppm (s; OAc-6).

9-(1-O-2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-anthracene (MonoGluAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.77 (s, 3H; 6-OAc), 2.00 (s, 3H; 4-OAc), 2.08 (s, 3H; 3-OAc), 2.23 (s, 3H; 2-OAc), 3.49 (ddd, *J* = 10.0, 5.7, 2.6 Hz, 1H; 5-H), 3.83 (dd, *J* = 12.1, 2.6 Hz, 1H; 6a-H), 4.22 (dd, *J* = 12.1, 5.7 Hz, 1H; 6b-H), 5.23 (d, *J* = 8.1 Hz, 1H; 1-H), 5.24 (dd, *J* = 10.0, 9.3 Hz, 1H; 4-H), 5.32 (dd, *J* = 9.7, 9.3 Hz, 1H; 3-H), 5.65 (dd, *J* = 9.7, 8.1 Hz, 1H; 2-H), 7.44–7.48 (m, 4H; 2-ANTH, 3-ANTH, 6-ANTH, 7-ANTH), 7.95–7.99 (m, 2H; 4-ANTH, 5-ANTH), 8.28 (s, 1H; 10-ANTH), 8.38–8.42 ppm (m, 2H; 1-ANTH, 8-ANTH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4 (q; OAc-6), 20.7 (q; OAc-4), 20.8 (q; OAc-3), 21.0 (q; OAc-2), 61.9 (t; C-6), 68.8 (d; C-4), 71.9 (d; C-5), 72.3 (d; C-2), 73.2 (d; C-3), 102.7 (d; C-1), 122.8 (2d; ANTC-1, ANTC-8), 124.0 (d; ANTC-10), 125.0 (2s; ANTC-11, ANTC-12), 125.5 (2d; ANTC-2, ANTC-7), 125.6 (2d; ANTC-3, ANTC-6), 128.1 (2d; ANTC-4, ANTC-5), 132.2 (2s; ANTC-13, ANTC-14), 147.5 (s; ANTC-9), 169.4 (s; OAc-2), 169.5 (s; OAc-4), 170.4 (s; OAc-6), 170.5 ppm (s; OAc-3).

9-(1-O-2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-9,10-dihydro-9,10-epidioxidoanthracene (MonoGluAcEP). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* = 1.97 (s, 3H; 2-OAc), 2.02 (s, 3H; 3-OAc), 2.03 (s, 3H; 4-OAc), 2.11 (s, 3H; 6-OAc), 3.88 (ddd, *J* = 10.1, 6.0, 2.4 Hz, 1H; 5-H), 4.22 (dd, *J* = 12.3, 2.4 Hz, 1H; 6_a-H), 4.30 (dd, *J* = 12.3, 6.0 Hz, 1H; 6_b-H), 5.18 (dd, *J* = 10.1, 9.3 Hz, 1H; 4-H), 5.32 (dd, *J* = 9.7, 9.3 Hz, 1H; 3-H), 5.34 (dd, *J* = 9.7, 7.7 Hz, 1H; 2-H), 5.50 (d, *J* = 7.7 Hz, 1H; 1-H), 5.99 (s, 1H; 10-ANTH), 7.31−7.36 (m, 4H; 2-ANTH, 3-ANTH, 6-ANTH, 7-ANTH), 7.42−7.46 (m, 2H; 4-ANTH, 5-ANTH), 7.58−7.59 (m, 1H; 1-ANTH), 7.89−7.92 ppm (m, 1H; 8-ANTH); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* = 20.8 (q; OAc-3),

20.8 (q; OAc-4), 20.9 (q; OAc-2), 21.0 (q; OAc-6), 62.6 (t; C-6), 68.8 (d; C-4), 71.5 (d; C-2), 72.6 (d; C-3), 72.9 (d; C-5), 80.4 (d; ANTC-10), 96.9 (d; C-1), 103.5 (s; ANTC-9), 120.5 (d; ANTC-1), 121.6 (d; ANTC-8), 123.5 (d; ANTC-5), 123.6 (d; ANTC-4), 128.2 (d; ANTC-7), 128.3 (d; ANTC-3), 128.4 (d; ANTC-2), 128.6 (d; ANTC-6), 137.6 (s; ANTC-11), 138.3 (s; ANTC-12), 138.6 (s; ANTC-13), 139.7 (s; ANTC-14), 169.7 (s; OAc-2), 169.9 (s; OAc-4), 170.2 (s; OAc-3), 170.7 ppm (s; OAc-6).

9,10-Bis-(3-pyridyl)-2-*tert*butylanthracene (mPyBuAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9H, *t*Bu), 7.38−7.41 (m, 2H, 6-ANTH, 7-ANTH), 7.41 (d, *J* = 8.9 Hz, 1H, 3-ANTH), 7.51 (s, 1H, 1-ANTH), 7.54−7.61 (m, 5H, 4-ANTH, 5-ANTH, 8-ANTH, 5-HPy, 5'-HPy), 7.60−7.65 (m, 2H, 4-HPy, 4'-HPy), 8.77 (br, m, 2H, 2-HPy), 8.86 ppm (br, m, 2H, 6-HPy, 6'-HPy). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.69 (q, *t*Bu), 35.04 (s, *t*Bu), 120.5 (d, ANTC-1), 123.4 (d, PyC-5, PyC-5'), 125.45 (d, ANTC-6), 125.6 (d, ANTC-4), 126.1 (d, ANTC-7), 126.3 (d, ANTC-5), 126.4 (d, ANTC-3), 128.4 (s, ANTC-9), 128.5 (s, ANTC-11), 128.7 (s, ANTC-10), 129.8 (s, ANTC-12), 130.1 (s, ANTC-9), 130.2 (s, ANTC-10), 132.0 (s, ANTC-13), 132.1 (s, ANTC-14), 133.1 (s, PyC-3, PyC-3'), 133.3 (s, ANTC-2), 134.4 (d, PyC-4), 134.8 (d, PyC-4'), 138.8 (d, ANTC-8), 148.2 (d, PyC-6, PyC-6'), 151.6 ppm (d, PyC-2, PyC-2').

9,10-Bis-(3-pyridyl)-2-*tert*butyl-9,10-dihydro-9,10-epidioxidoanthracene (mPyBuAcEP). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, *t*Bu), 7.08 (d, *J* = 8.2 Hz, 1H, 3-ANTH), 7.13 (m, 2H, 6-ANTH, 7-ANTH), 7.14 (s, 1H, 1-ANTH), 7.26 (m, 2H, H-ANT5, H-ANT8), 7.27 (d, *J* = 8.2 Hz, 1H, 4-ANTH), 7.60−7.63 (m, 2H, 4-HPy, 4'-HPy), 8.05−8.10 (m, 2H, 5-HPy, 5'-HPy), 8.85 (br, m, 2H, 2-HPy, 2'-HPy), 9.01−9.03 ppm (m, 2H, 6-HPy, 6'-HPy). ^{13}C NMR (100 MHz, $CDCl_3$): δ =31.2 (q, *t*Bu), 34.9 (s, *t*Bu), 82.9 (s, ANTC-9), 83.3 (s, ANTC-10), 120.3 (d, ANTC-1, ANTC-8), 123.0 (d, PyC-5, PyC-5', ANTC-3, ANTC-5), 123.2 (d, ANTC-4), 124.9 (d, ANTC-6, ANTC-7), 128.0 (d, PyC-4, PyC-4'), 128.1 (s, ANTC-2),136.4 (s, ANTC-11, ANTC-14), 138.7 (s, ANTC-12, ANTC-13), 139.7 (s, PyC-3, PyC-3'), 148.9 (d, PyC-6, PyC-6'), 151.6 ppm (d, PyC-2, PyC-2').

9,10-Bis-(2-pyridyl)-2-(nonyl-2-oxo)-anthracene (oPy2C8Ac). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.3 Hz, 3H, AlkylH-9), 1.29 (m, 8H, 5-AlkylH−8-AlkylH), 1.59 (m, 2H, 4-AlkylH), 2.30 (t, *J* = 7.4 Hz, 2H, 3-AlkylH), 5.14 (s, 2H, 1-AlkylH), 7.32 (s, 1H, 1-ANTH), 7.33−7.40 (m, 2H, 6-ANTH, 7-ANTH), 7.50−7.59 (m, 8H, 3-ANTH, 4-ANTH, 3-HPy, 3'-HPy, 4-HPy, 4'-HPy, 5-HPy, 5'-HPy), 7.99−8.01 (m, 2H, 5-ANTH, 8-ANTH), 8.98−9.01 ppm (6-HPy, 6'-HPy). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (q, AlkylC-9), 22.5 (t, AlkylC-8), 24.7 (t, AlkylC-7), 28.9 (t, AlkylC-6), 29.0 (t, AlkylC-5), 31.6 (t, AlkylC-4), 34.0 (t, AlkylC-3), 66.2 (t, AlkylC-1), 122.7 (d, ANTC-1, ANTC-8), 125.1 (d, PyC-4, PyC-4'), 125.5 (d, ANTC-4), 125.8 (d, PyC-3, PyC-3'), 126.2 (d, PyC-5, PyC-5'), 126.8 (d, ANTC-6, ANTC-7), 126.9 (d, ANTC-3, ANTC-5), 127.0 (s, ANTC-2), 127.1 (s, ANTC-11), 129.3 (s, ANTC-12, ANTC-13), 129.9 (s, ANTC-14), 133.2 (s, ANTC-9, ANTC-10), 149.8 (s, PyC-3, PyC-3'), 157.9 (d, PyC-6, PyC-6'), 178.7 ppm (s, AlkylC-2).

9,10-Bis-(2-pyridyl)-2-(nonyl-2-oxo)- 9,10-dihydro-9,10-epidioxidoanthracene (oPy2C8AcEP). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3H, 9-AlkylH), 1.25 (m, 8H, 5-AlkylH−8-alkylH), 1.56−1.58 (m, 2H, 4-AlkylH), 2.25 (t, *J* = 7.3 Hz, 2H, 3-AlkylH), 5.00 (s, 2H, 1-AlkylH), 7.18−7.21 (m, 7 H, 1-ANTH, 3-ANTH, 4-ANTH, 5-ANTH, 6-ANTH, 7-ANTH, 8-ANTH), 7.48−7.50 (m, 2H, 3-PyH, 3'-PyH), 7.82−7.83 (m, 2H, 4-PyH, 4'-PyH), 7.94−7.95 (m, 2H, 5-PyH, 5'-PyH), 8.88−8.89 ppm (m, 2H, 6-PyH, 6'-PyH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (q, AlkylC-9), 22.9 (t, AlkylC-8), 25.2 (t, AlkylC-7), 29.2 (t, AlkylC-6), 29.4 (t, AlkylC-5), 31.9 (t, AlkylC-4), 34.6 (t, AlkylC-3), 66.0 (t, AlkylC-1), 84.4 (s, ANTC-9, ANTC-10), 122.7 (d, ANTC-5, ANTC-8), 123.4 (d, ANTC-1), 123.6 (d, ANTC-3, ANTC-4), 123.8 (d, ANTC-6, ANTC-7), 127.5 (d, PyC-3, PyC-3'), 127.8 (d, PyC-4, PyC-4'), 127.9 (d, PyC-5, PyC-5'), 135.8 (s, ANTC-11), 137.7 (s, ANTC-14), 137.8 (s, ANTC-12), 140.2 (ANTC-13), 154.4 (d, PyC-6, PyC-6'), 173.8 ppm (s, AlkylC-2).

Table S1: List of abbreviations and IUPAC names of all AcEPs and analogues (Ac).

Abbreviation	IUPAC Name
Ac	anthracene
AcEP	9,10-dihydro-9,10-epidioxidoanthracene
1062MeAcEP	9,10-Bis(1-methylpyridinium-4-yl)-9,10-dihydro-9,10-epidioxidoanthracene trifluoro-methanesulfonate
BisGluAc	9,10-Bis-(1-O-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-anthracene
BisGluAcEP	9,10-Bis-(1-O-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-9,10-dihydro-9,10-epidioxidoanthracene
DPAc	9,10-diphenylanthracene
DPAcEP	9,10-diphenyl-9,9-dihydro-9,10-epidioxidoanthracene
MB359EP	2-*tert*-Butyl-1,4-bis-(1-O-2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,4-dihydro-1,4-epidioxidonaphthalene
MonoGluAc	9-(1-O-2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-anthracene
MonoGluAcEP	9-(1-O-2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-9,10-dihydro-9,10-epidioxidoanthracene
mPyAc	9,10-bis-(3-pyridyl)-anthracene
mPyAcEP	9,10-bis-(3-pyridyl)-9,10-dihydro-9,10-epidioxidoanthracene
mPyBuAc	9,10-Bis-(3-pyridyl)-2-*tert*butylanthracene
mPyBuAcEP	9,10-Bis-(3-pyridyl)-2-*tert*butyl-9,10-dihydro-9,10-epidioxidoanthracene
oOMeAc	9,10-bis(2-methoxyphenyl)-anthracene
oOMeAcEP	9,10-bis(2-methoxyphenyl)-9,10-dihydro-9,10-epidioxidoanthracene
oPyAc	9,10-bis-(2-pyridyl)-anthracene
oPyAcEP	9,10-bis-(2-pyridyl)-9,10-dihydro-9,10-epidioxidoanthracene
oPy2C8Ac	9,10-Bis-(2-pyridyl)-2-(nonyl-2-oxo)-anthracene
oPy2C8AcEP	9,10-Bis-(2-pyridyl)-2-(nonyl-2-oxo)-9,10-dihydro-9,10-epidioxidoanthracene
pPyBuAc	9,10-bis-(4-pyridyl)-anthracene
pPyBuAcEP	9,10-bis-(2-pyridyl)-9,10-dihydro-9,10-epidioxidoanthracene

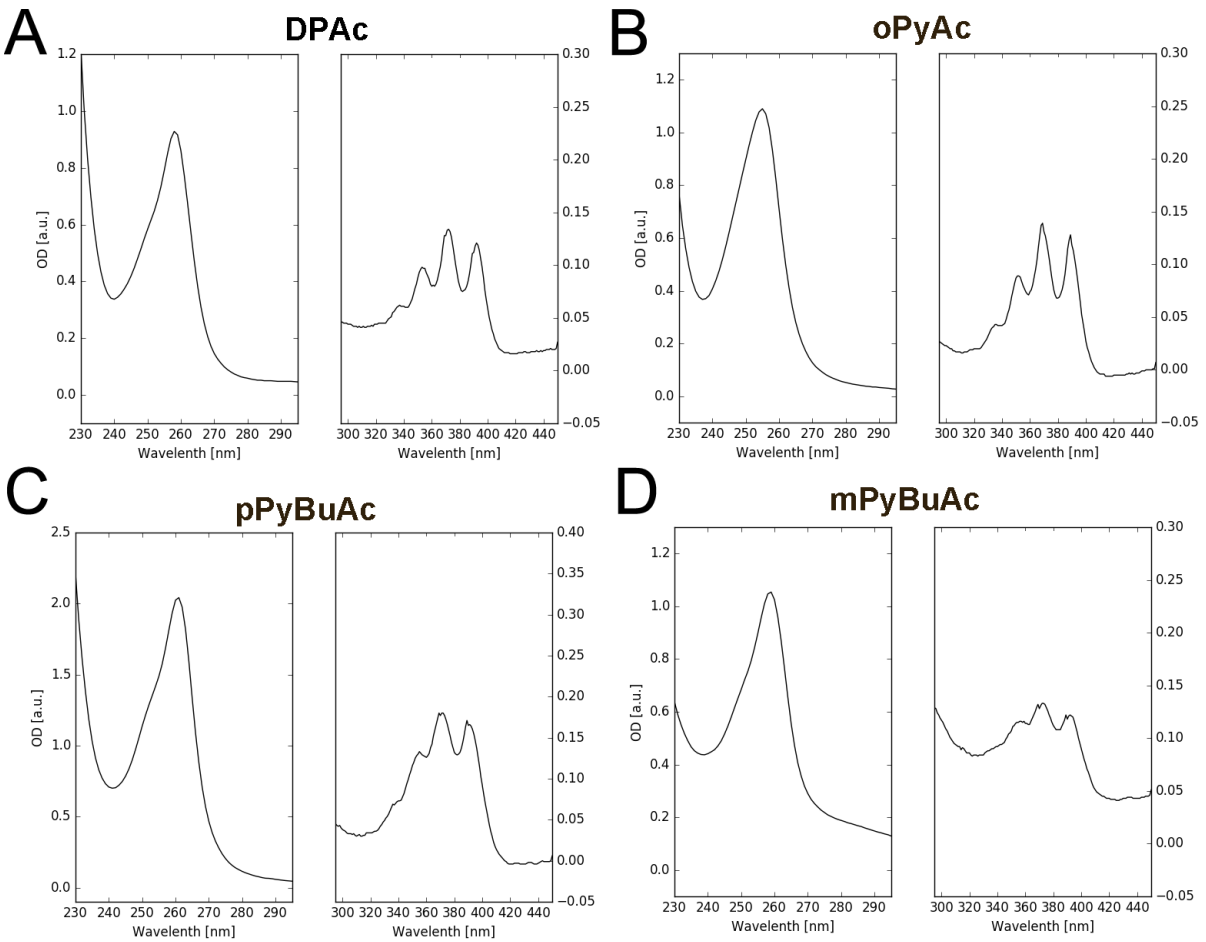


Figure S1: UV spectra of non-endoperoxidic Ac analogs (40 μM). (A) DPAc, (B) oPyAc, (C) pPyBuAc and (D) mPyBuAc.

Figure S2

^{1}H NMR (500 MHz) spectrum

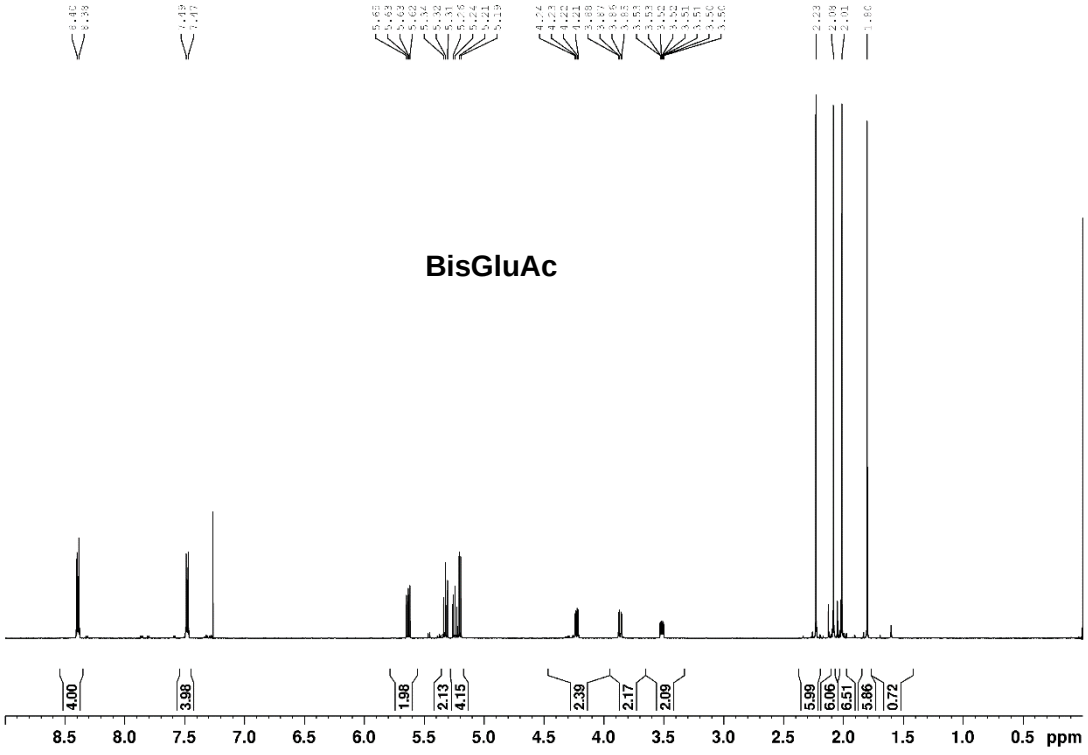


Figure S3

^{13}C NMR (125 MHz) spectrum

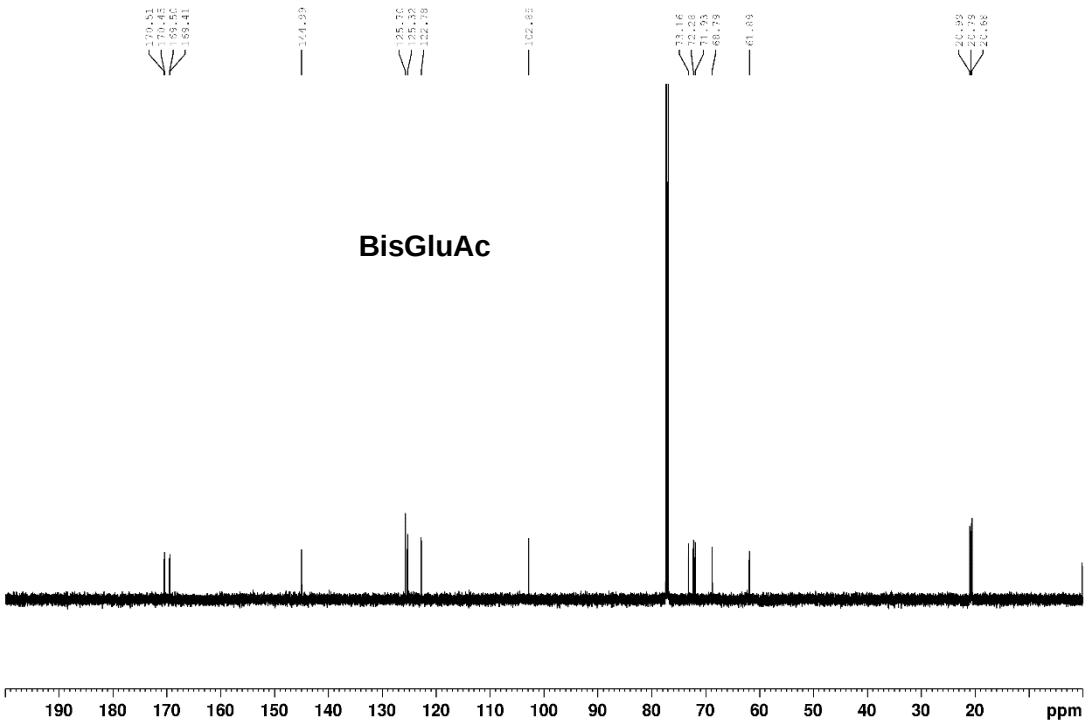


Figure S4

^{1}H NMR (500 MHz) spectrum

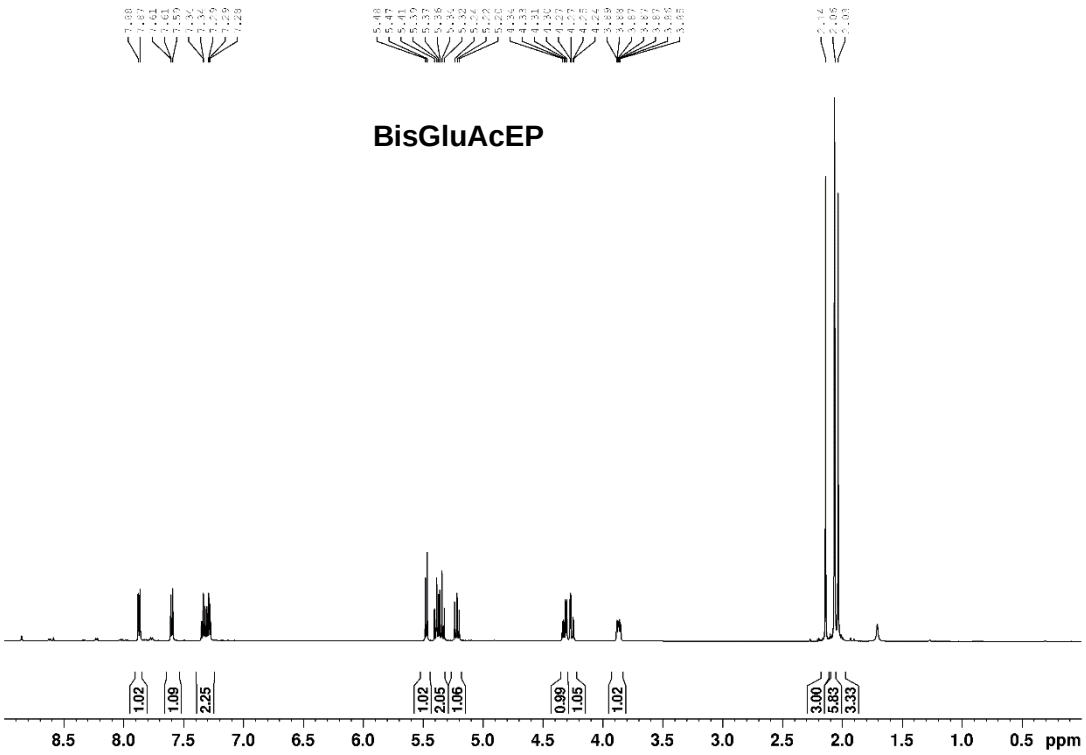


Figure S5

^{13}C NMR (125 MHz) spectrum

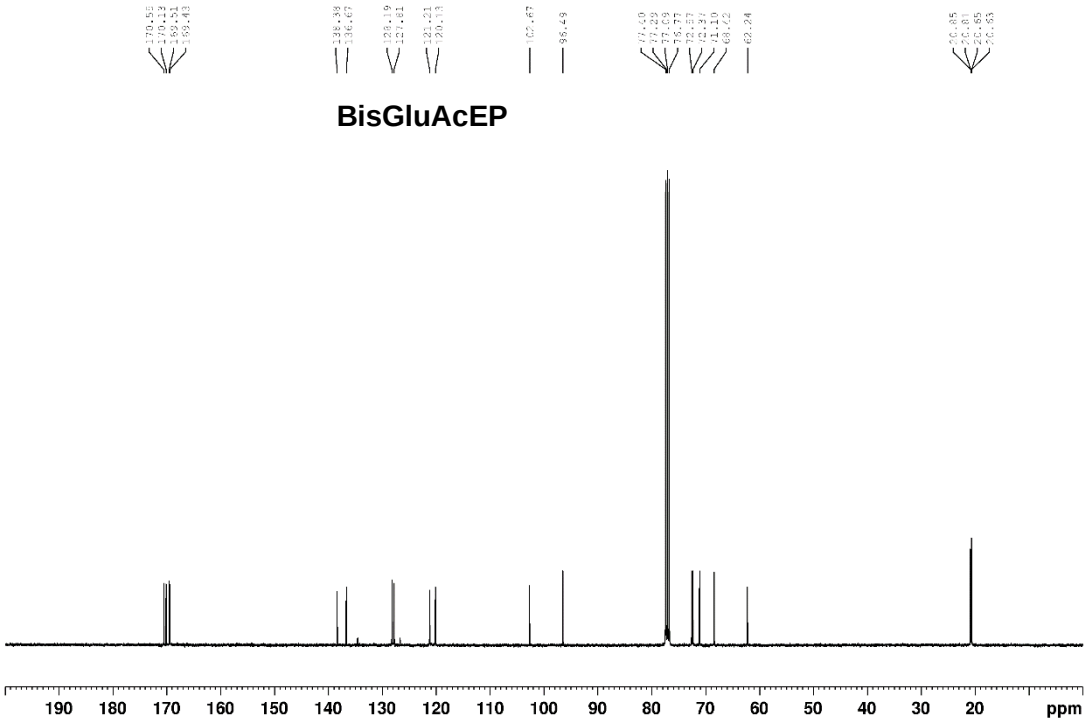


Figure S6

^{1}H NMR (500 MHz) spectrum

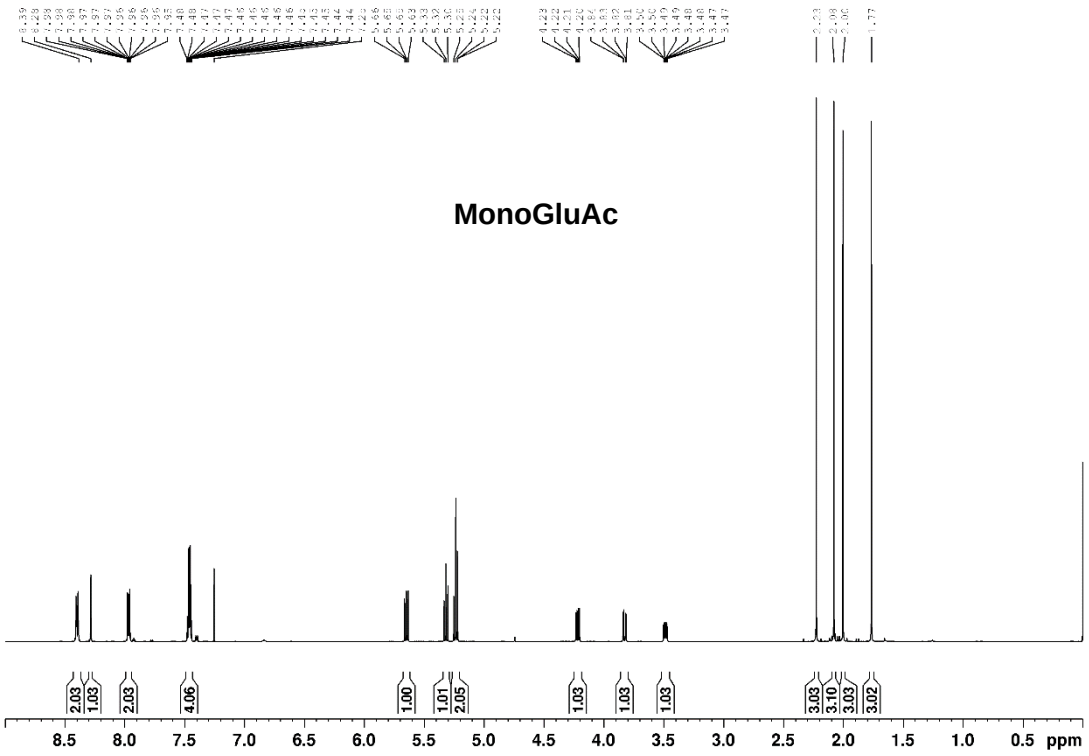


Figure S7

^{13}C NMR (125 MHz) spectrum

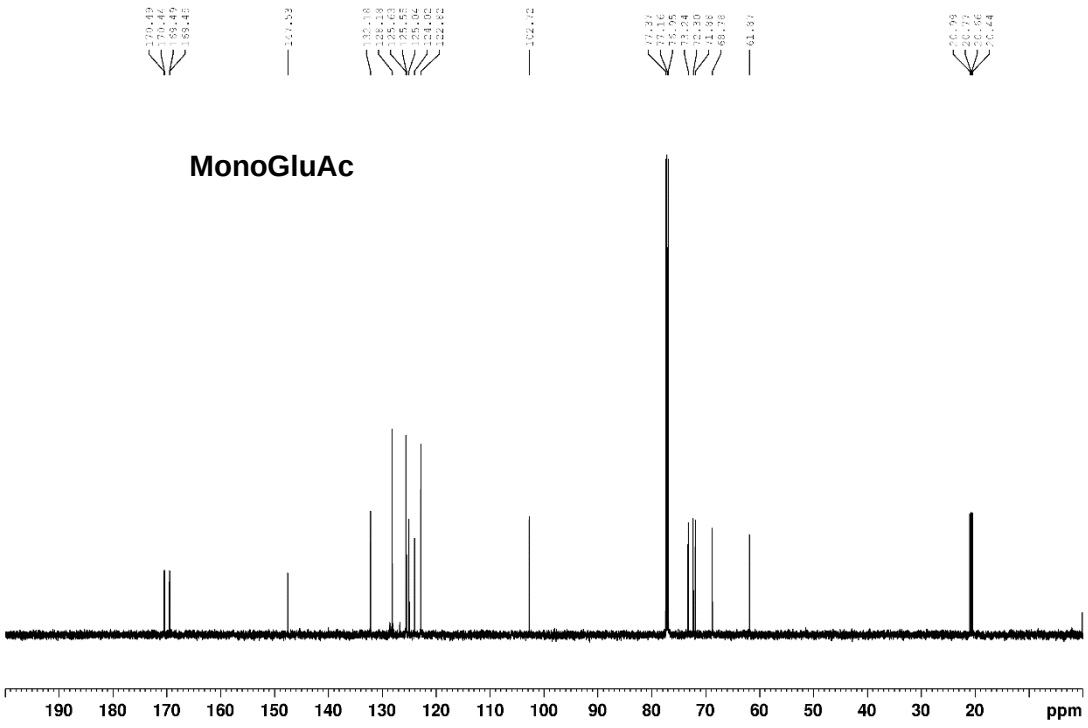


Figure S8

^{1}H NMR (500 MHz) spectrum

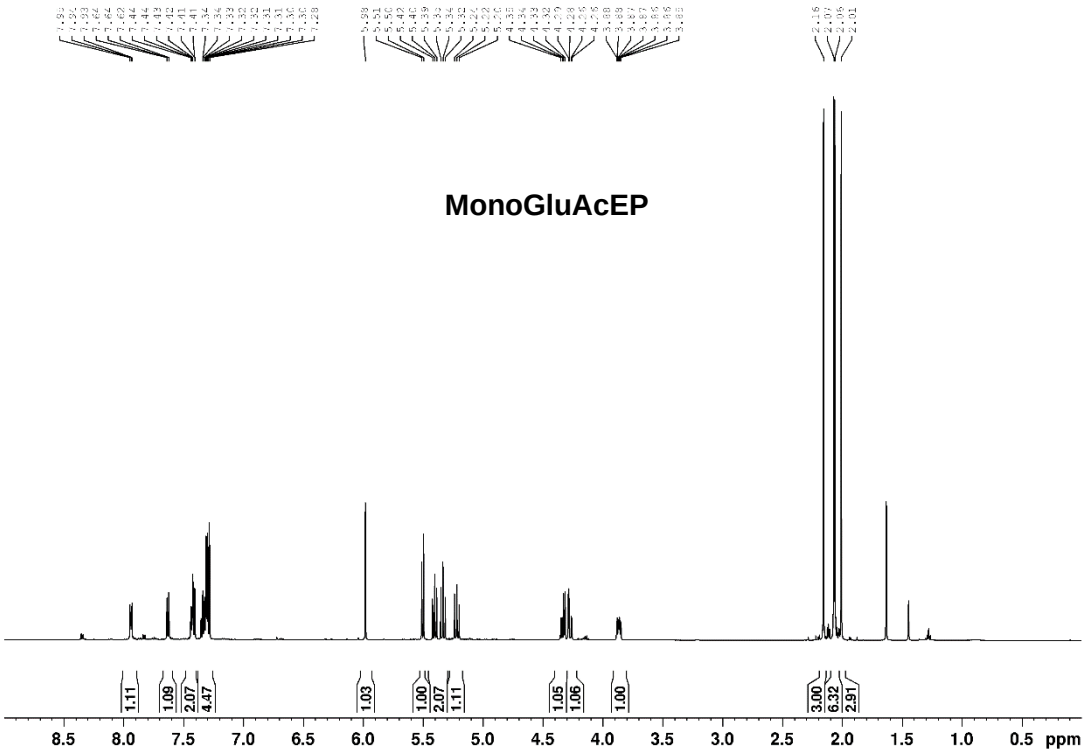


Figure S9

^{13}C NMR (125 MHz) spectrum

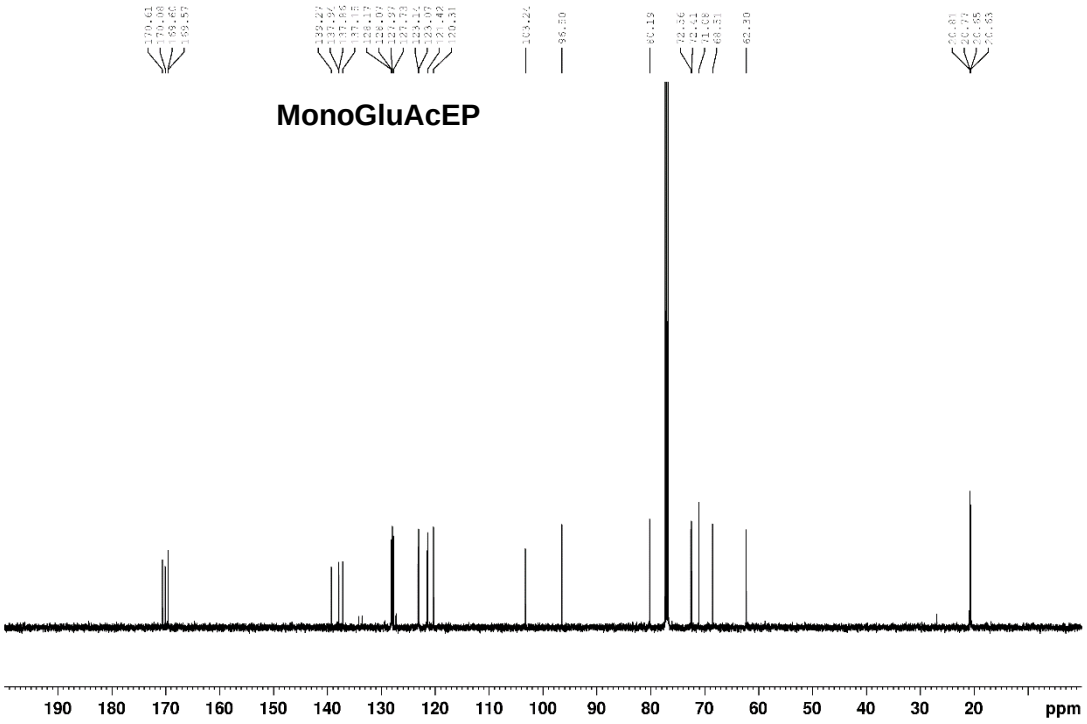


Figure S10

^{1}H NMR (400 MHz) spectrum

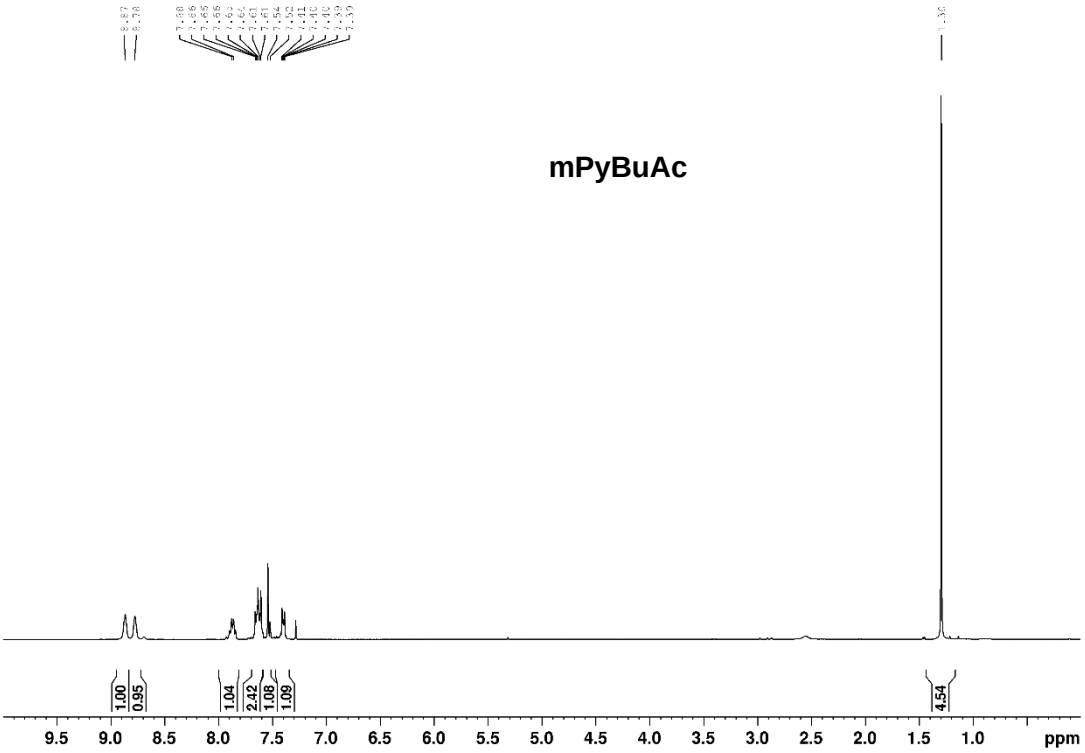


Figure S11

^{13}C NMR (100 MHz) spectrum

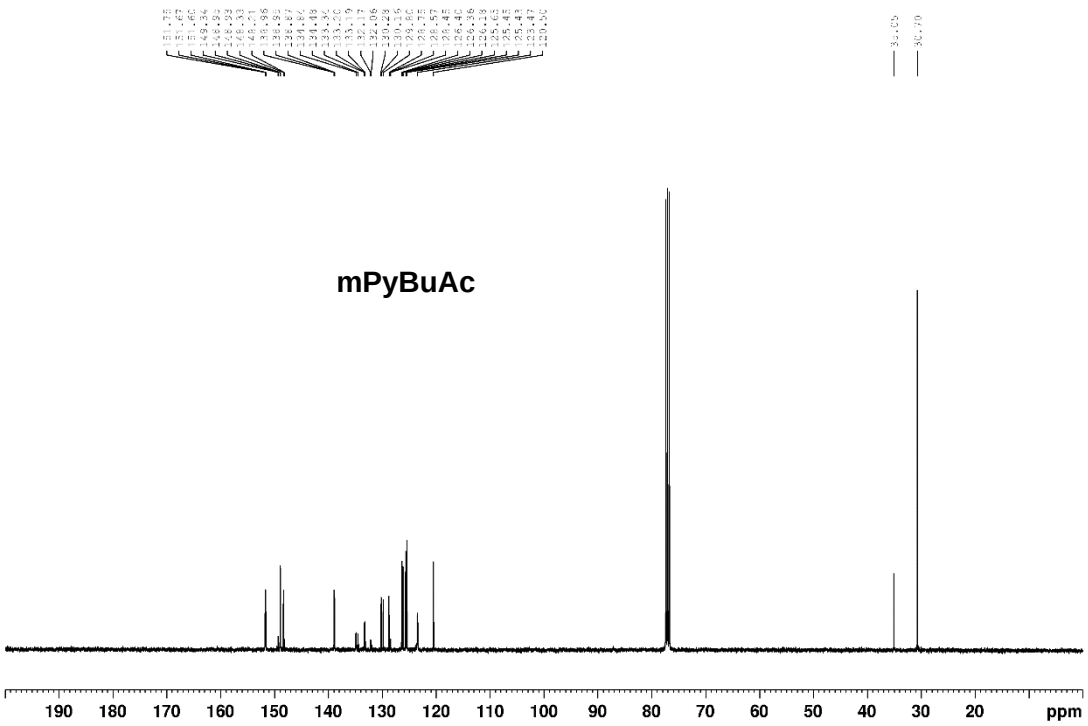


Figure S12

^{1}H NMR (400 MHz) spectrum

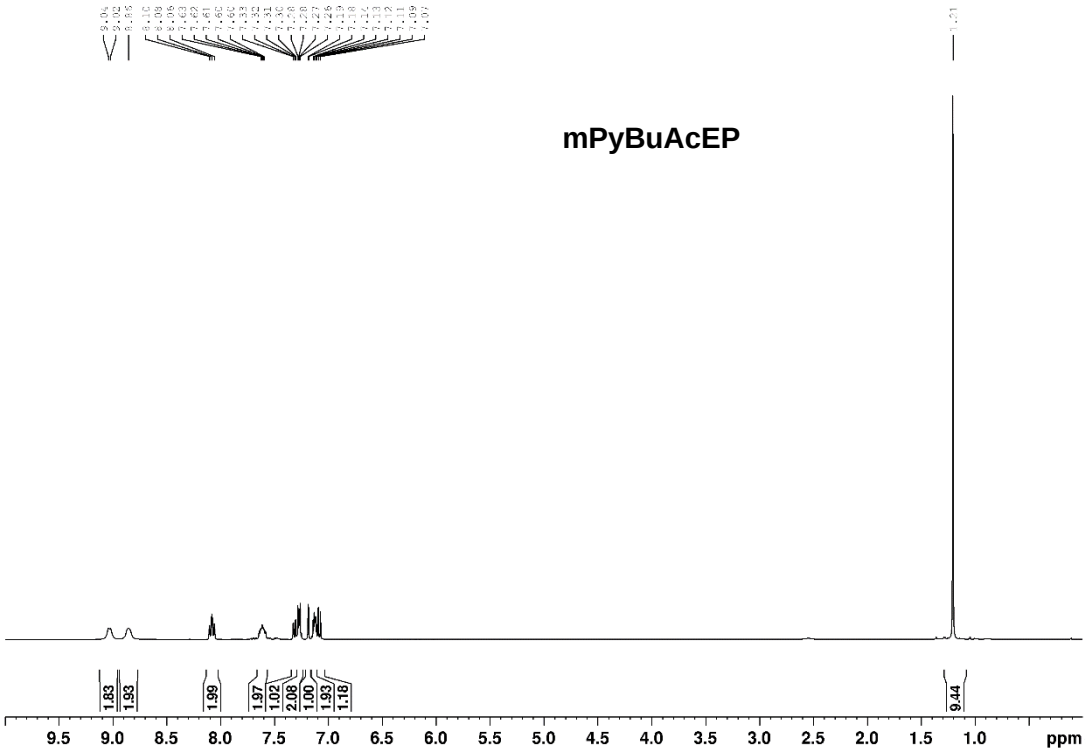


Figure S13

^{13}C NMR (100 MHz) spectrum

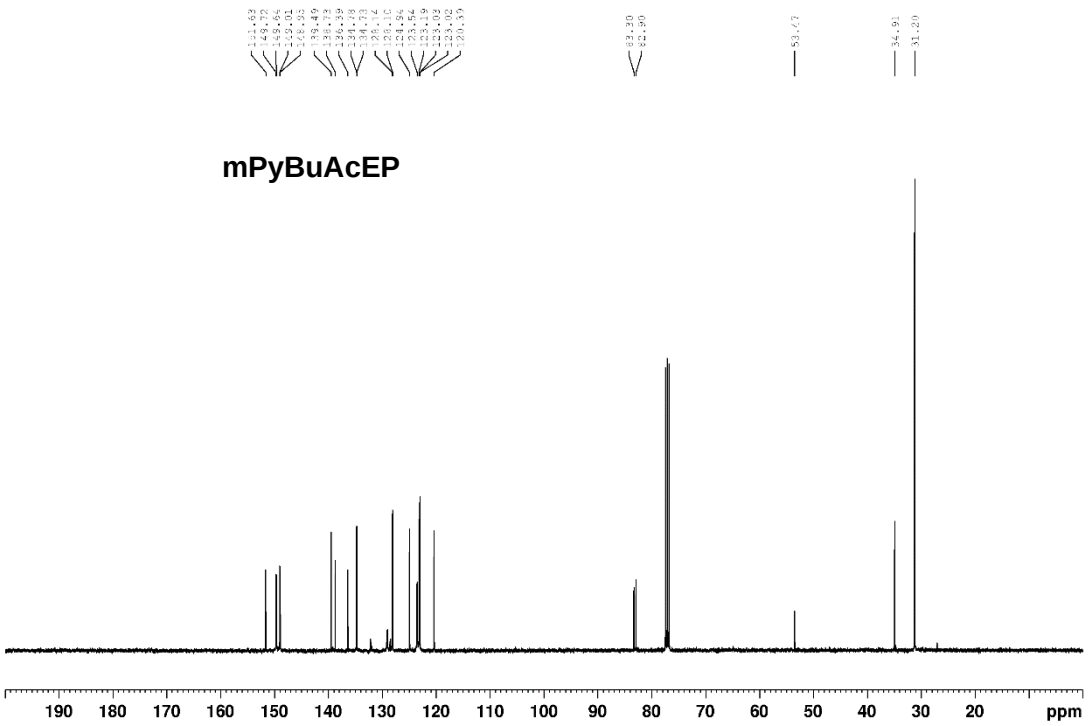


Figure S14

^{1}H NMR (400 MHz) spectrum

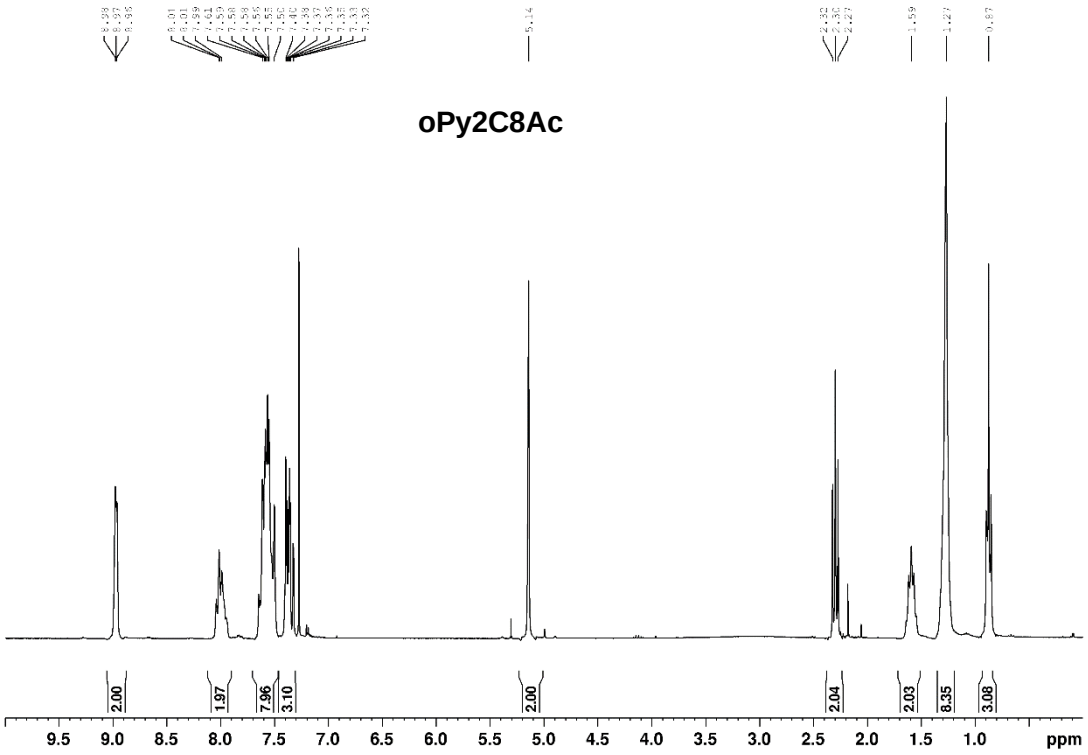


Figure S15

^{13}C NMR (100 MHz) spectrum

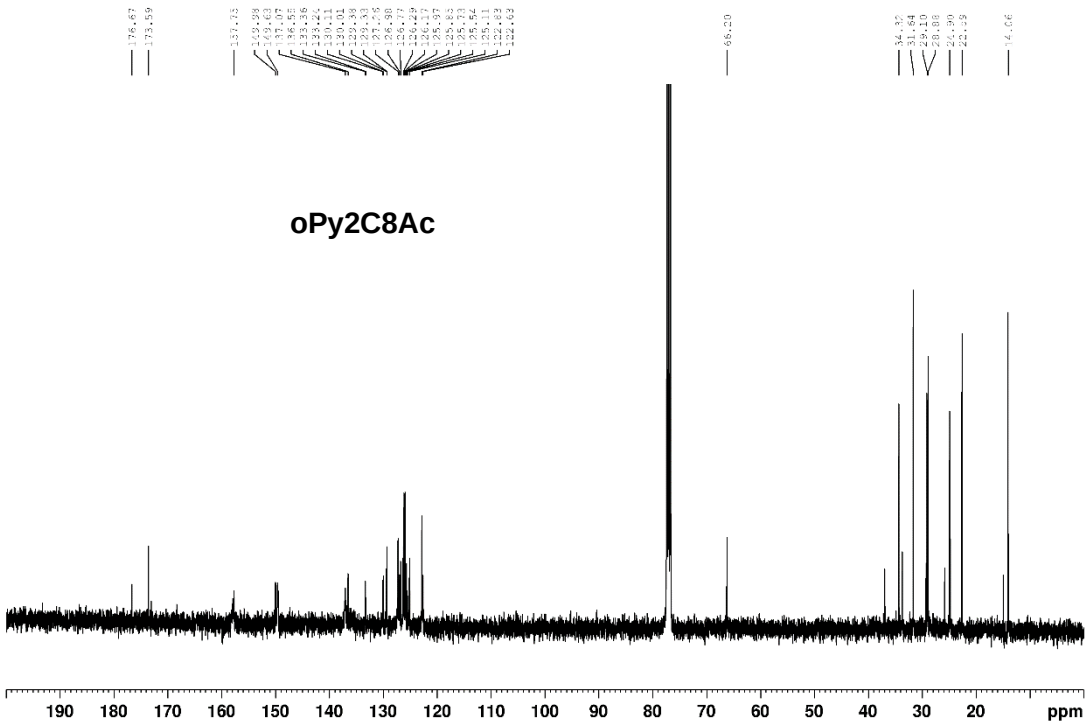


Figure S16

^{1}H NMR (400 MHz) spectrum

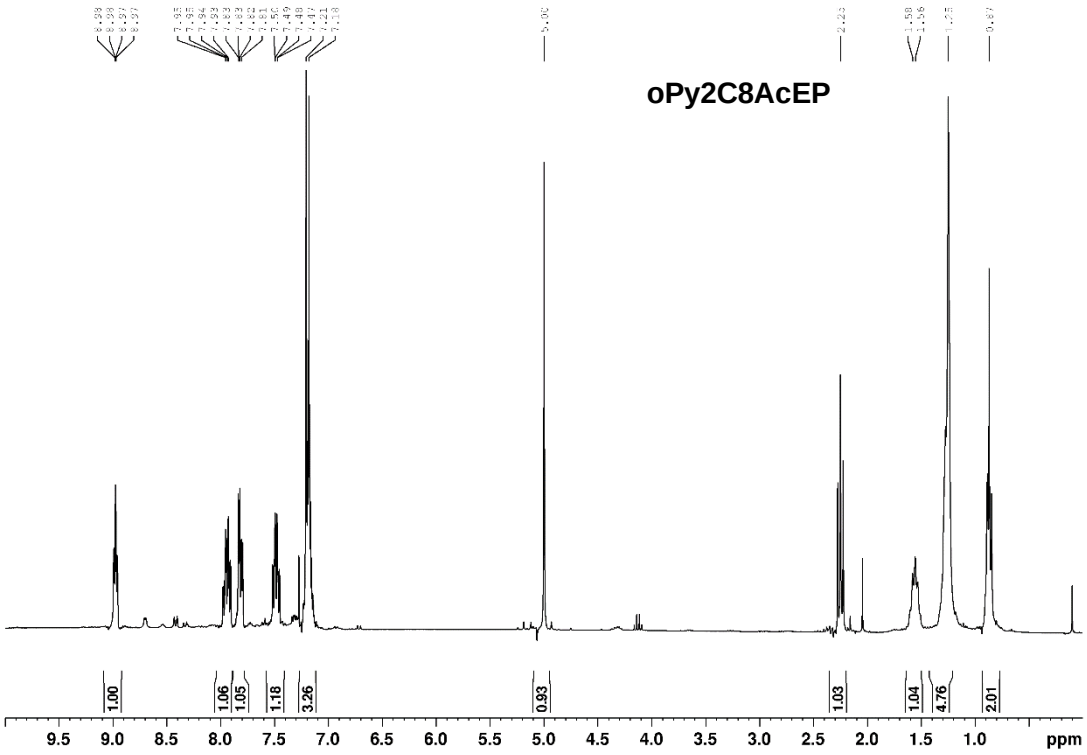


Figure S17

^{13}C NMR (100 MHz) spectrum

