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Solvent-free synthesis of novel vanillidene derivatives of Meldrum′s acid: biological evaluation, DNA and BSA binding study

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Contents

1. General

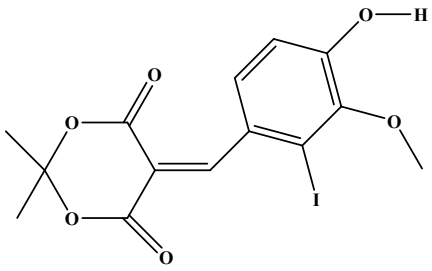
1.1. General methods

Experimental procedures for synthesis 5-(arylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-diones

To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then vanillic aldehyde (10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$: EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the desired product with good purity grade (without recrystallization).

2. Substrate synthesis

5-(4'-hydroxy-2'-iodo-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3a**



$C_{14}H_{13}O_6I$; 404.15 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then iodovanillin (2.78 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the desired product with

good purity grade (without recrystallization). The title compound was obtained in 95% yield. Mp=227-228°C

IR (KBr): 3283, 1739, 1703, 1566, 1496, 1418, 1398, 1292 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.73 (s, 6H), 3.86 (s, 3H), 8.01 (d, 1H, *J* = 1.8 Hz), 8.22 (s, 1H), 8.35 (d, 1H, *J* = 1.8Hz), 10.65 (br. s, 1H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 27.1, 56.4, 84.5, 104.3, 111.7, 117.8, 125.1, 139.1, 146.3, 152.4, 155.8, 160.4, 163.3.

ESI-MS (70 eV): *m/z* (%) = 427 [M^+ + Na] (100%), 404 [M]$^+$ (4.0%); 302 (48.6%), 277 (13.3%),

Anal. Calcd. $C_{14}H_{13}O_6I$ (%): C 41.61, H 3.24; Found: C 41.49, H 3.31.

3a

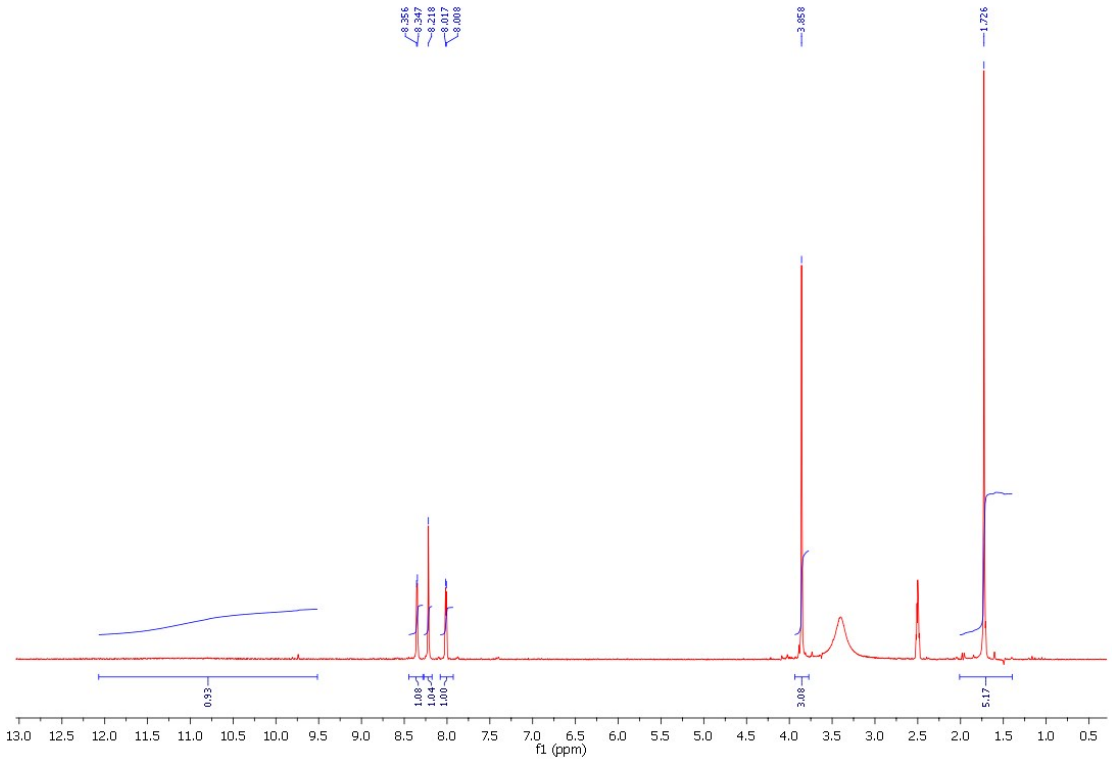


Figure S1 ^{1}H NMR spectrum of compound 3a

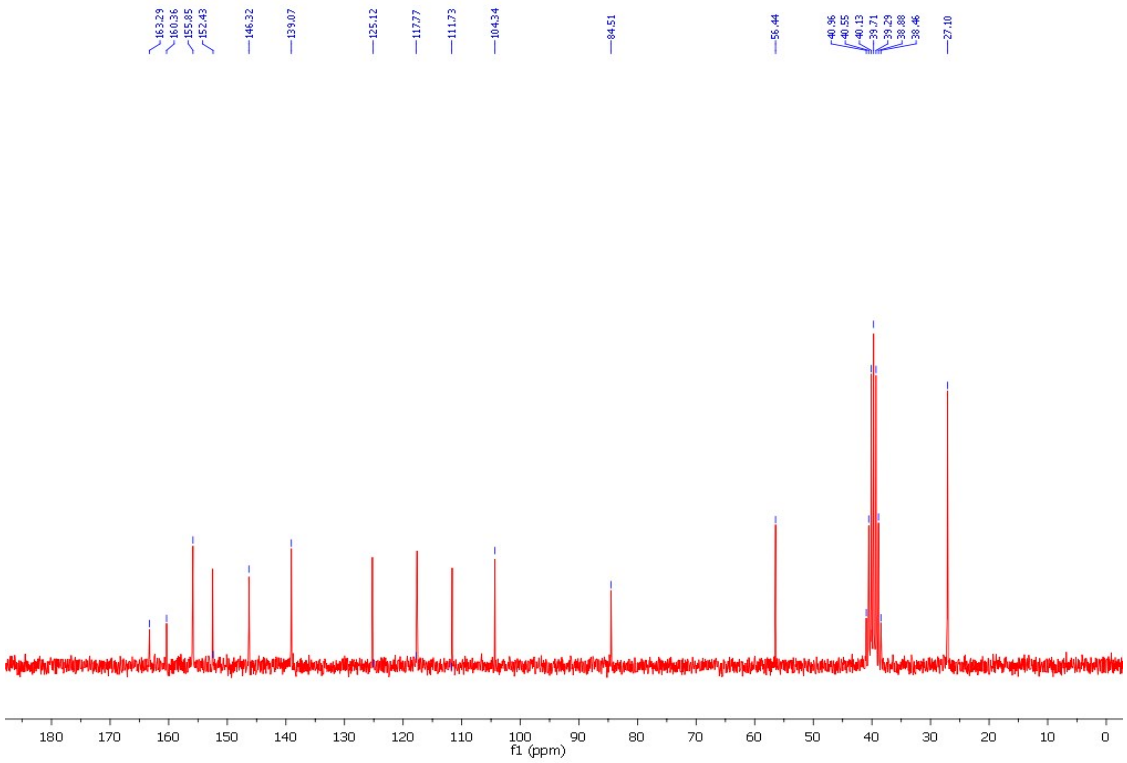
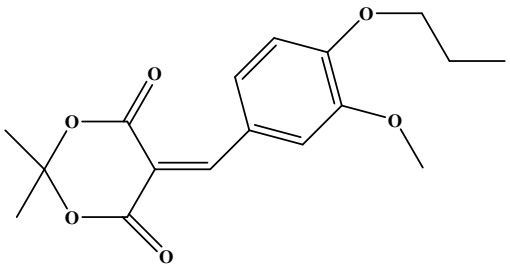


Figure S2 ^{13}C NMR spectrum of compound 3a

5-(3'-methoxy-4'-propoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3b**



$C_{17}H_{20}O_6$; 320.34 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then 3-methoxy-4-propoxybenzaldehyde (1.94 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color,

white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the desired product with good purity grade (without recrystallization). The title compound was obtained in 85% yield. Mp=147°C

IR (KBr): 1749, 1713, 1578, 1560, 1523, 1392, 1274 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07 (t, 3H, *J* = 7.6 Hz), 1.79 (s, 6H), 1.87-1.97 (m, 2H), 3.94 (s, 3H), 4.10 (t, 2H, *J* = 6.8 Hz), 6.94 (d, 1H, *J* = 8.6 Hz), 7.64 (dd, *J* = 8.6, 2.0 Hz, 1H), 8.29 (d, 1H, *J* = 2.2 Hz), 8.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.3, 22, 27.4, 56.2, 70.6, 104, 110.3, 111.3, 116.1, 124.6, 132.6, 148.8, 154.7, 158.2, 160.6, 164.1.

ESI-MS (70 eV): *m/z* (%) = 320 (15.6%) $[M]^+$; 277 (54.6%), 218 (100%), 130 (89.8%)

Anal. Calcd. $C_{17}H_{20}O_6$ (%): C 63.74, H 6.29; Found: C 63.77, H 6.30.

3b

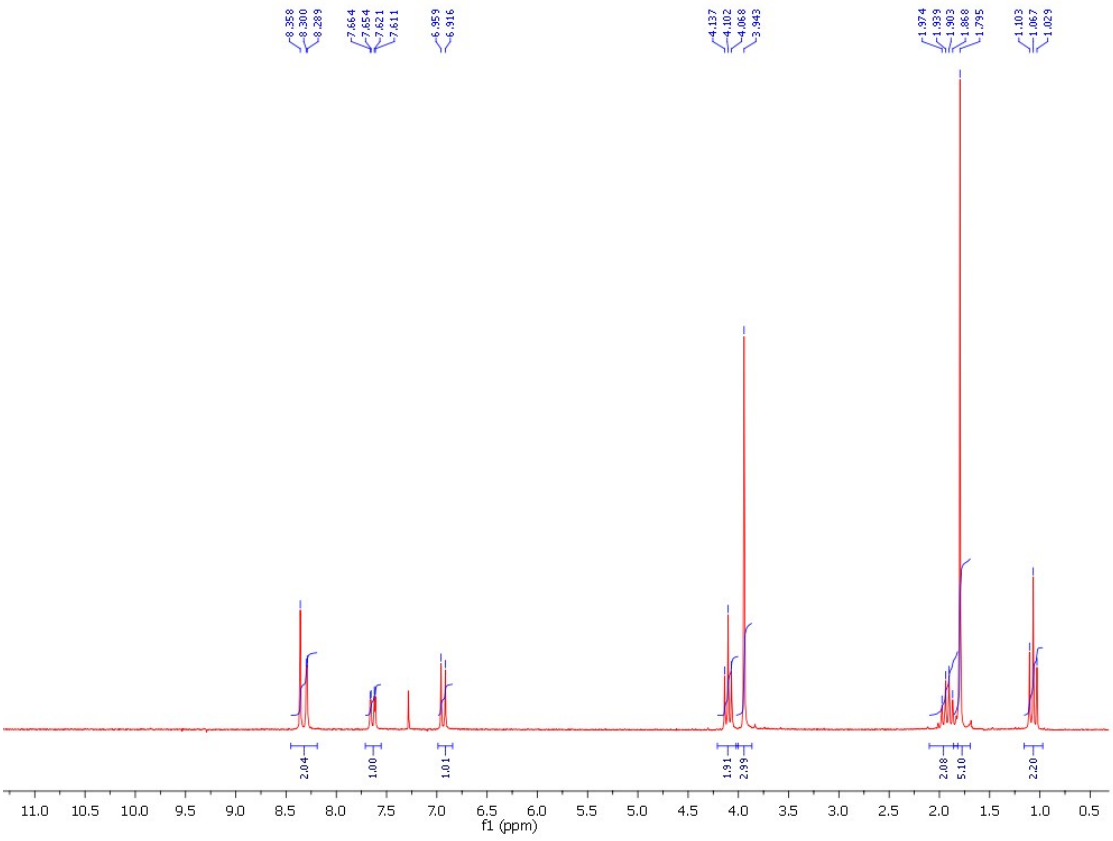


Figure S3 ^{1}H NMR spectrum of compound 3b

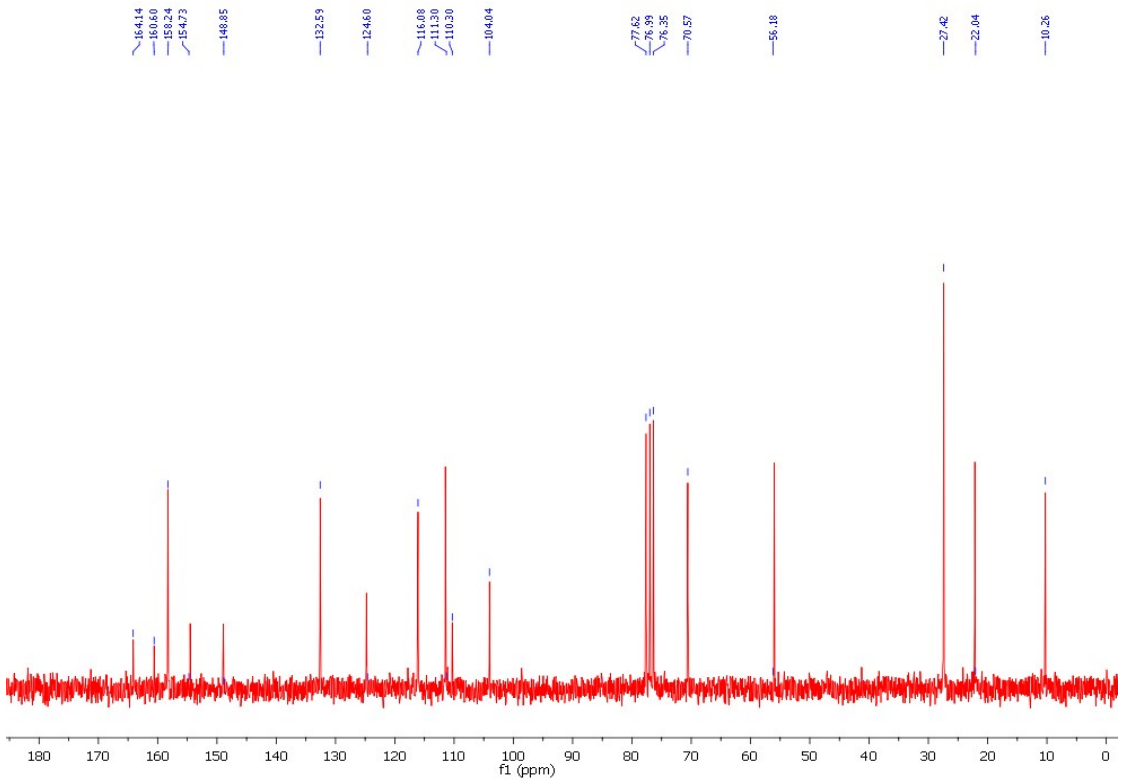
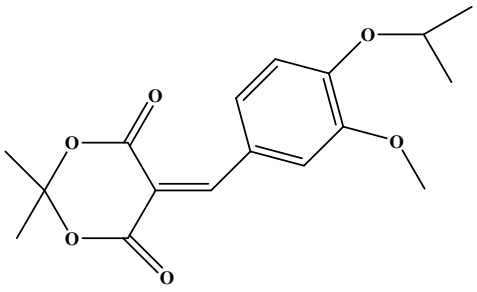


Figure S4 ^{13}C NMR spectrum of compound 3b

5-(4'-isopropoxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3c**



$C_{17}H_{20}O_6$; 320.34 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then 4-isopropoxy-3-methoxybenzaldehyde (1.94 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the

color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the desired product with good purity grade (without recrystallization). The title compound was obtained in 90% yield. Mp=151-152°C

IR (KBr): 1745, 1712, 1548, 1521, 1428, 1397, 1273 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (d, 6H, *J*= 6.2 Hz), 1.79 (s, 6H), 3.93 (s, 3H), 4.68-4.80 (m, 1H), 6.94 (d, 1H, *J* = 8.6 Hz), 7.64 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.29 (d, 1H, *J* = 2.0 Hz), 8.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 27.4, 55.9, 71.6, 104, 110.3, 112.7, 116.1, 124.6, 132.3, 149.4, 153.4, 158.2, 160.6, 164.1.

ESI-MS (70 eV): *m/z* (%) = 320 (15.7%) $[M]^+$; 277 (26.3%), 218 (100%), 150 (43.5%)

Anal. Calcd. $C_{17}H_{20}O_6$ (%): C 63.74, H 6.29; Found: C 63.80, H 6.36.

3c

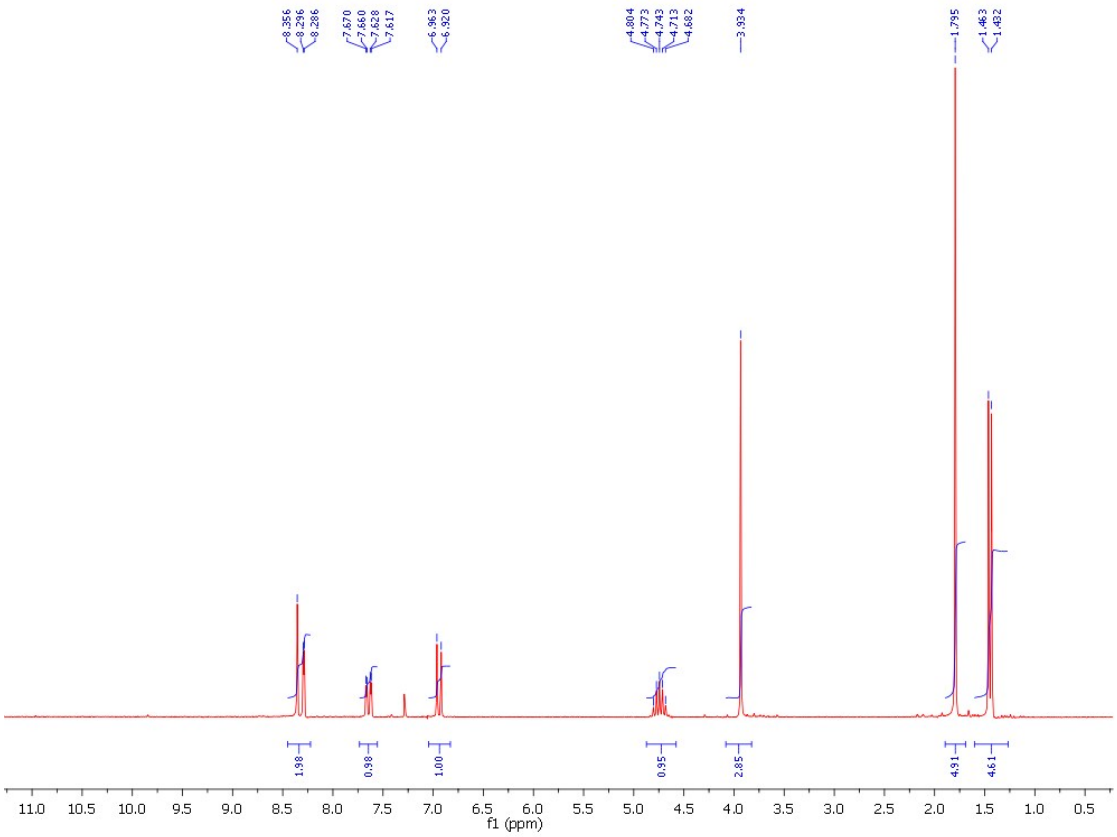


Figure S5 ^{1}H NMR spectrum of compound 3c

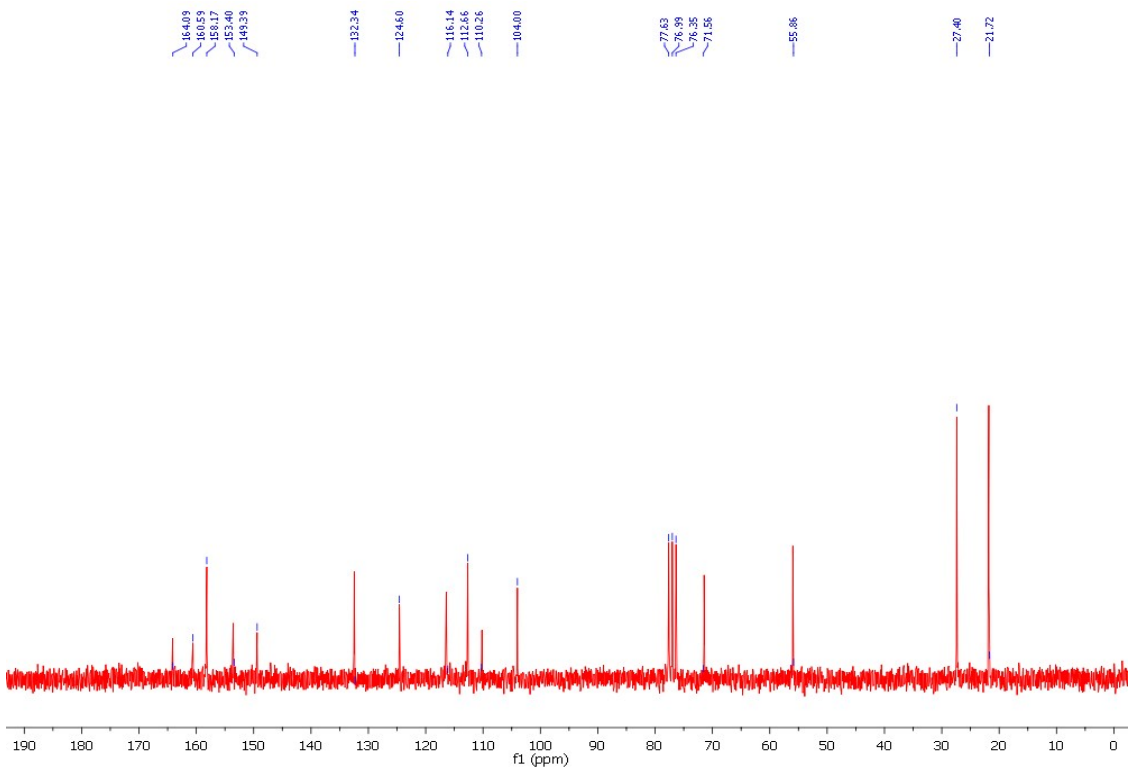
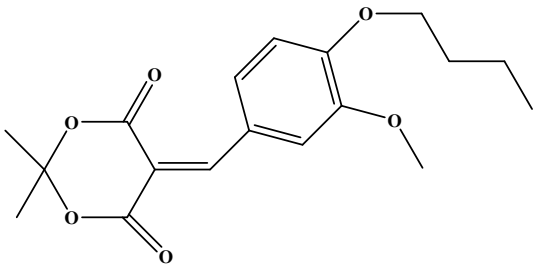


Figure S6 ^{13}C NMR spectrum of compound 3c

5-(4'-butoxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3d**



$C_{18}H_{22}O_6$; 334.36 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then 4-butoxy-3-methoxybenzaldehyde (2.08 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid

washed with small portions of cold ethanol and then dried at room temperature to afford the desired product with good purity grade (without recrystallization). The title compound was obtained in 88% yield. Mp=140°C

IR (KBr): 1748, 1713, 1577, 1559, 1523, 1392, 1278 cm^{-1}.

^{1}HNMR (200 MHz, $CDCl_3$): δ = 0.99 (t, 3H, *J* = 7.4 Hz), 1.43-1.61 (m, 2H), 1.79 (s, 6H), 1.79-1.95 (m, 2H), 3.94 (s, 3H), 4.14 (t, 2H, *J* = 6.8 Hz), 6.94 (d, 1H, *J* = 8.4 Hz), 7.64 (dd, *J* = 8.6, 2.0 Hz, 1H), 8.29 (d, 1H, *J* = 2.0 Hz), 8.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 19.1, 27.4, 30.8, 56, 68.9, 104.1, 110.3, 111.4, 116.1, 124.8, 132.6, 148.9, 154.6, 158.3, 160.6, 164.2.

ESI-MS (70 eV): *m/z* (%) = 334 (8.4%) $[M]^+$; 277 (25.4%), 232 (26.1%), 151 (100%)

Anal. Calcd. $C_{18}H_{22}O_6$ (%): C 64.66, H 6.63; Found: C 64.57, H 6.60.

3d

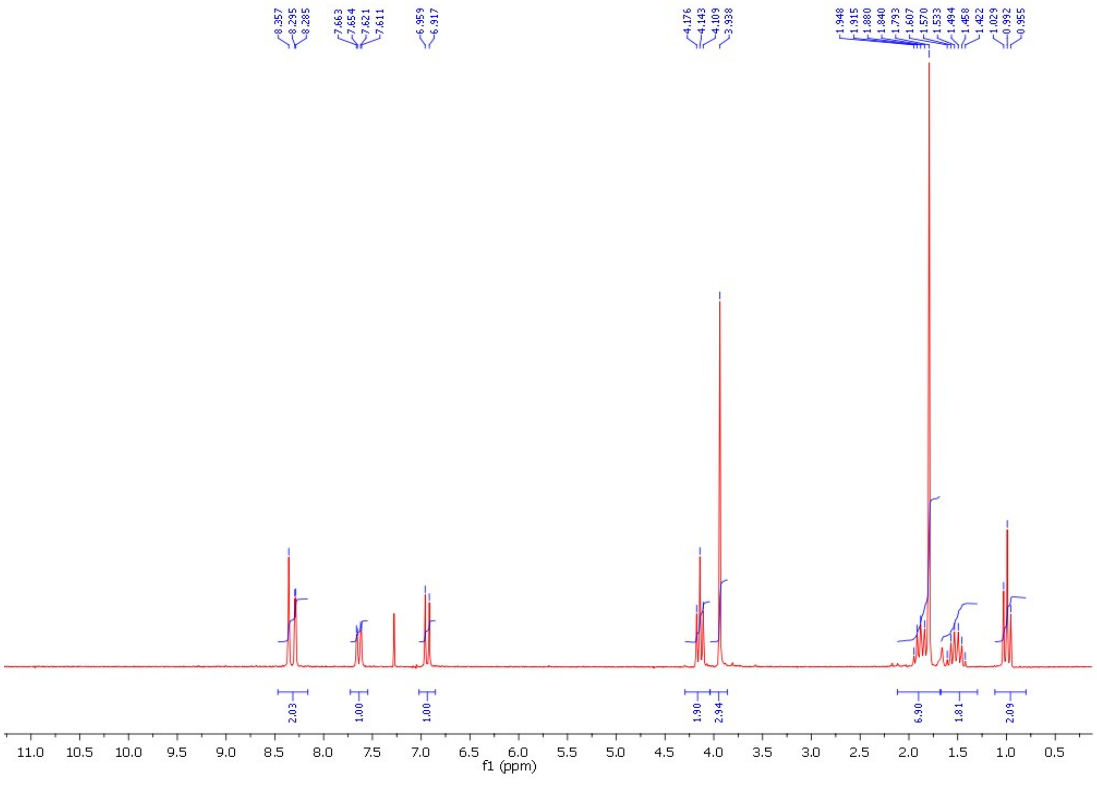


Figure S7 ^{1}H NMR spectrum of compound 3d

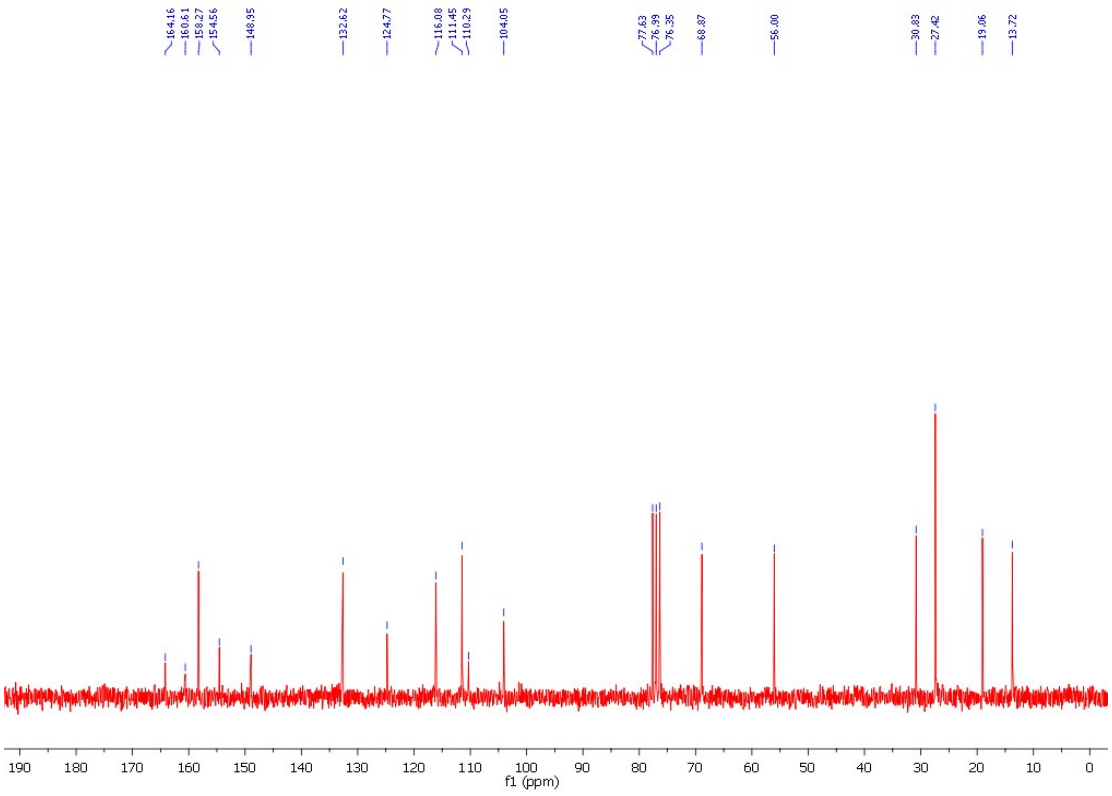
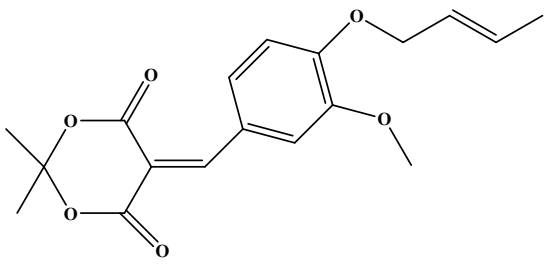


Figure S8 ^{13}C NMR spectrum of compound 3d

(*E*)-5-(4'-(but-2'-enyloxy)-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3e**



$C_{18}H_{20}O_6$; 332.35 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then (*E*)-4-(but-2-enyloxy)-3-methoxybenzaldehyde (2.06g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to

afford the desired product with good purity grade (without recrystallization). The title compound was obtained in 96% yield. Mp=155-157°C

IR (KBr):1742, 1705, 1546, 1519, 1395, 1286, 1268 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.75-1.79 (m, 9H), 3.94 (s, 3H), 4.65 (d, 1H, *J* = 6.0 Hz), 4.79 (d, 1H, *J* = 5.0 Hz), 5.77-5.97 (m, 2H), 6.95 (d, 1H, *J* = 8.6 Hz), 7.63 (dd, *J* = 8.6, 2.0 Hz, 1H), 8.29 (d, 1H, *J* = 2.0 Hz), 8.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.8, 27.4, 55.9, 69.7, 104, 110.4, 111.8, 115.9, 124.8, 124.9, 131.9, 132.4, 148.9, 154, 158.2, 164.1.

ESI-MS (70 eV): *m/z* (%) = 332 (45.4%) $[M]^+$; 277 (69.1%), 230 (45%), 175 (100%)

Anal. Calcd. $C_{18}H_{20}O_6$ (%): C 65.05, H 6.07; Found: C 64.98, H 6.02.

3e

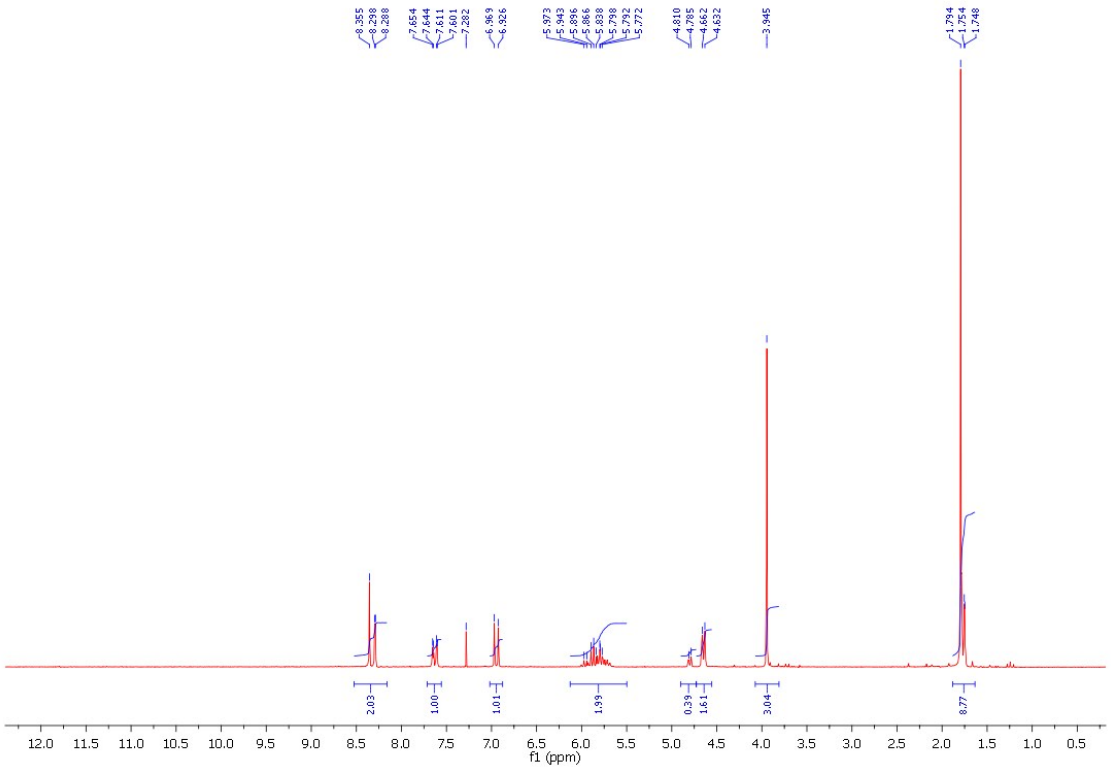


Figure S9 ^{1}H NMR spectrum of compound 3e

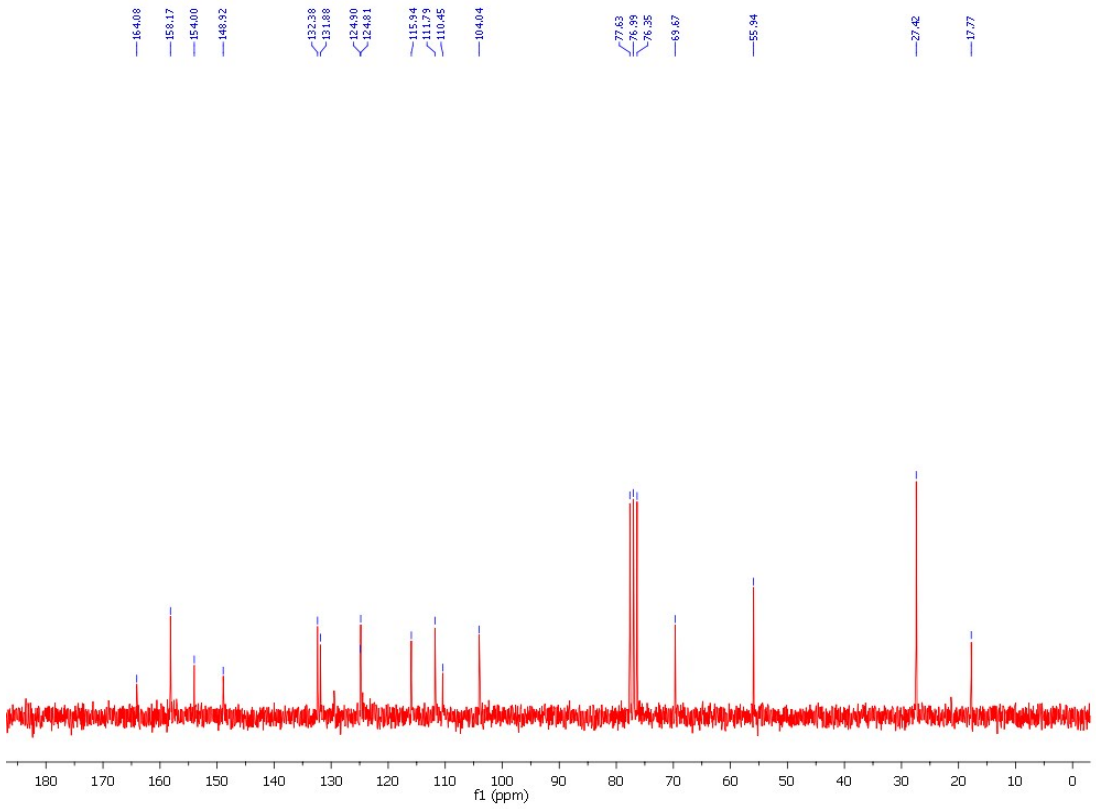
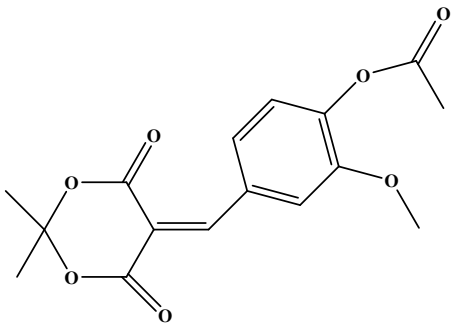


Figure S10 ^{13}C NMR spectrum of compound 3e

5-(4'-acetoxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3f**



$C_{16}H_{16}O_7$; 320.29 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then 4-acetoxy-3-methoxybenzaldehyde (1.94 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the

desired product with good purity grade (without recrystallization). The title compound was obtained in 97% yield. Mp=170°C

IR (KBr): 1764, 1732, 1615, 1582, 1513, 1396, 1373, 1282 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 6H), 2.35 (s, 3H), 3.91 (s, 3H), 7.15 (d, 1H, *J* = 8.2 Hz), 7.57 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.22 (s, 1H), 8.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.6, 27.5, 56, 104.5, 114.2, 116.9, 122.9, 129.1, 130.3, 144.4, 144.6, 151.1, 157.1, 159.9, 163.3, 168.2.

ESI-MS (70 eV): *m/z* (%) = 320 (10.9%) $[M]^+$; 277 (52%), 175 (32.5%), 107 (100%)

Anal. Calcd. $C_{16}H_{16}O_7$ (%): C 60.00, H 5.04; Found: C 59.95, H 5.01.

3f

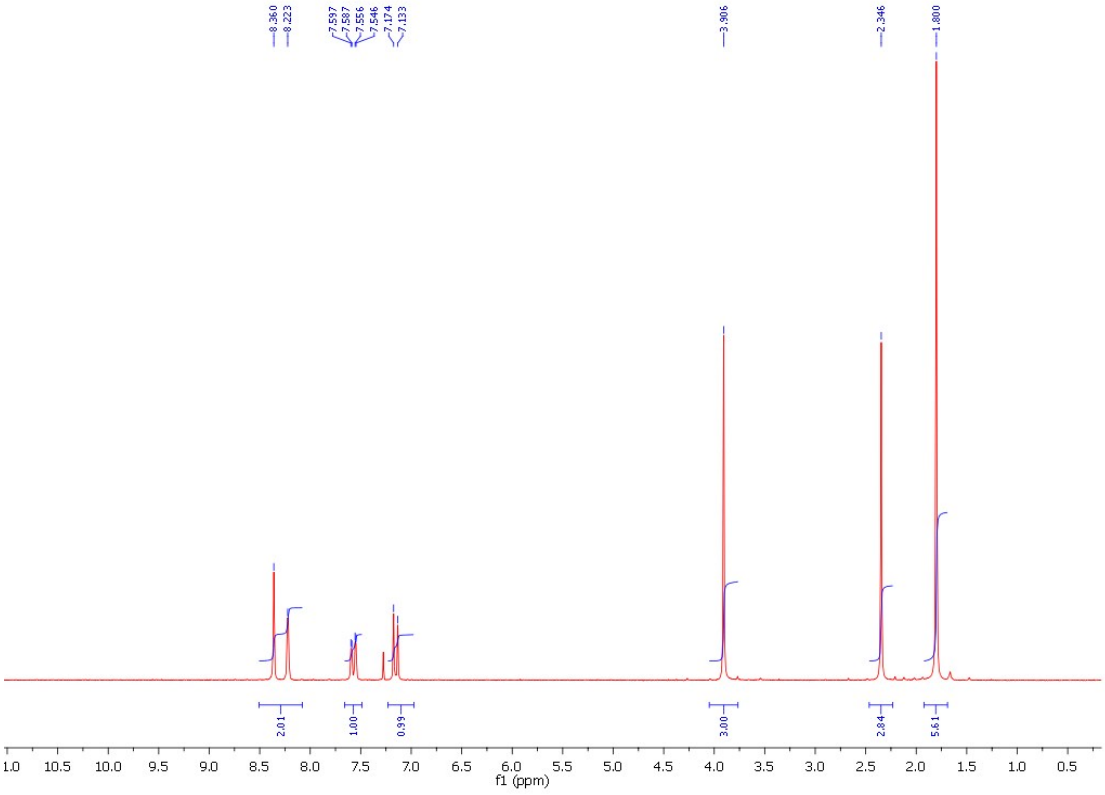


Figure S11 ^{1}H NMR spectrum of compound 3f

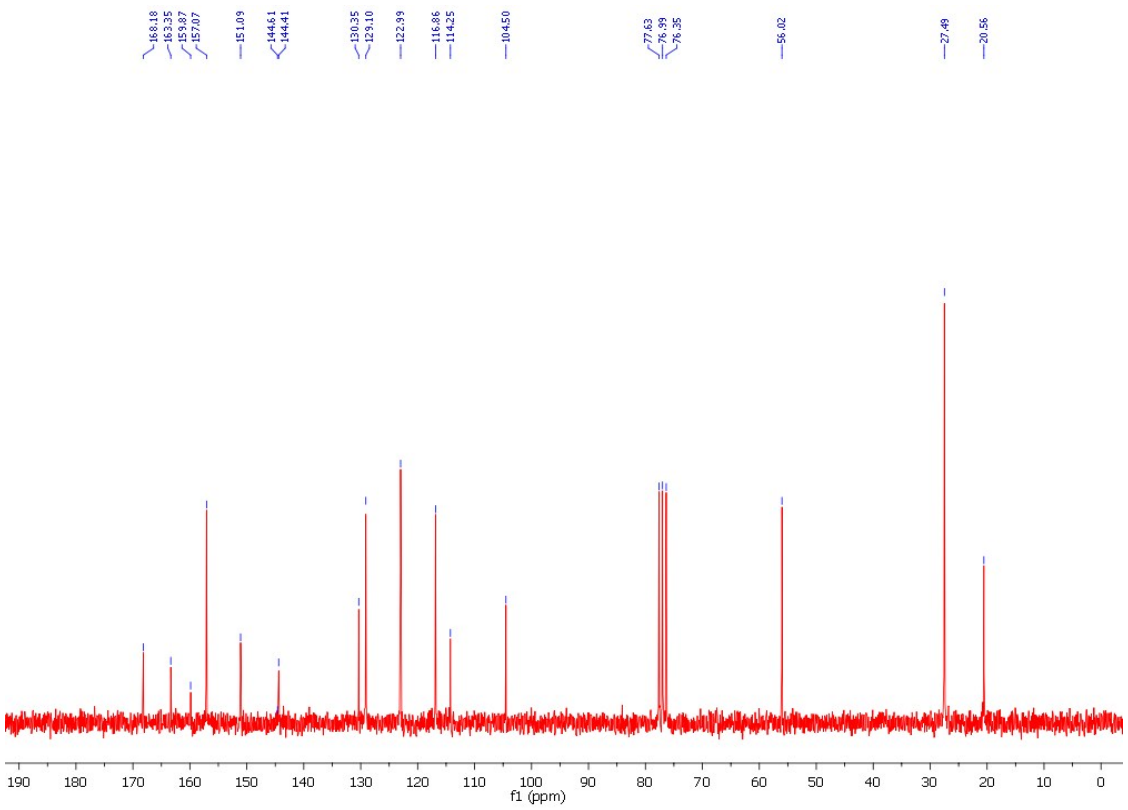
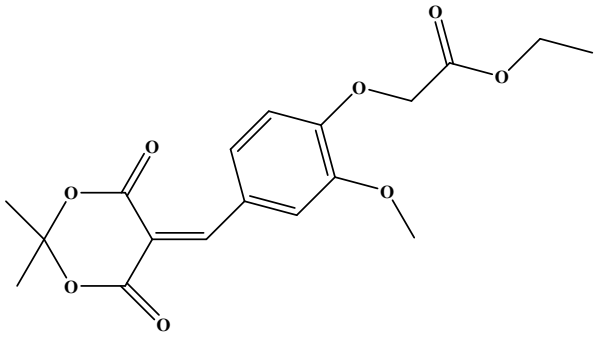


Figure S12 ^{13}C NMR spectrum of compound 3f

Ethyl 2-(4-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidenyl)methyl)-2-methoxyphenoxy)acetate, **3g**



$C_{18}H_{20}O_8$; 364.35 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then ethyl 2-(4-formyl-2-methoxyphenoxy)acetate (2.38 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the

desired product with good purity grade (without recrystallization). The title compound was obtained in 95% yield. Mp=104-105°C

IR (KBr): 1774, 1748, 1728, 1703, 1577, 1556, 1508, 1384, 1274 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, 3H, *J* = 7.0 Hz), 1.79 (s, 6H), 3.96 (s, 3H), 4.28 (q, 2H, *J* = 7.2 Hz), 4.80 (s, 2H), 6.82 (d, 1H, *J* = 8.6 Hz), 7.61 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.29 (d, 1H, *J* = 2.0 Hz), 8.35 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 27.4, 56, 61.6, 65.8, 104.2, 111.5, 112.2, 116.5, 126, 131.5, 148.9, 152.6, 157.8, 160.4, 163.9, 167.8.

ESI-MS (70 eV): *m/z* (%) = 364 (5.2%) $[M]^+$; 291 (2%), 262 (30.4%), 79 (100%)

Anal. Calcd. $C_{18}H_{20}O_8$ (%): C 59.34, H 5.53; Found: C 59.30, H 5.46.

3g

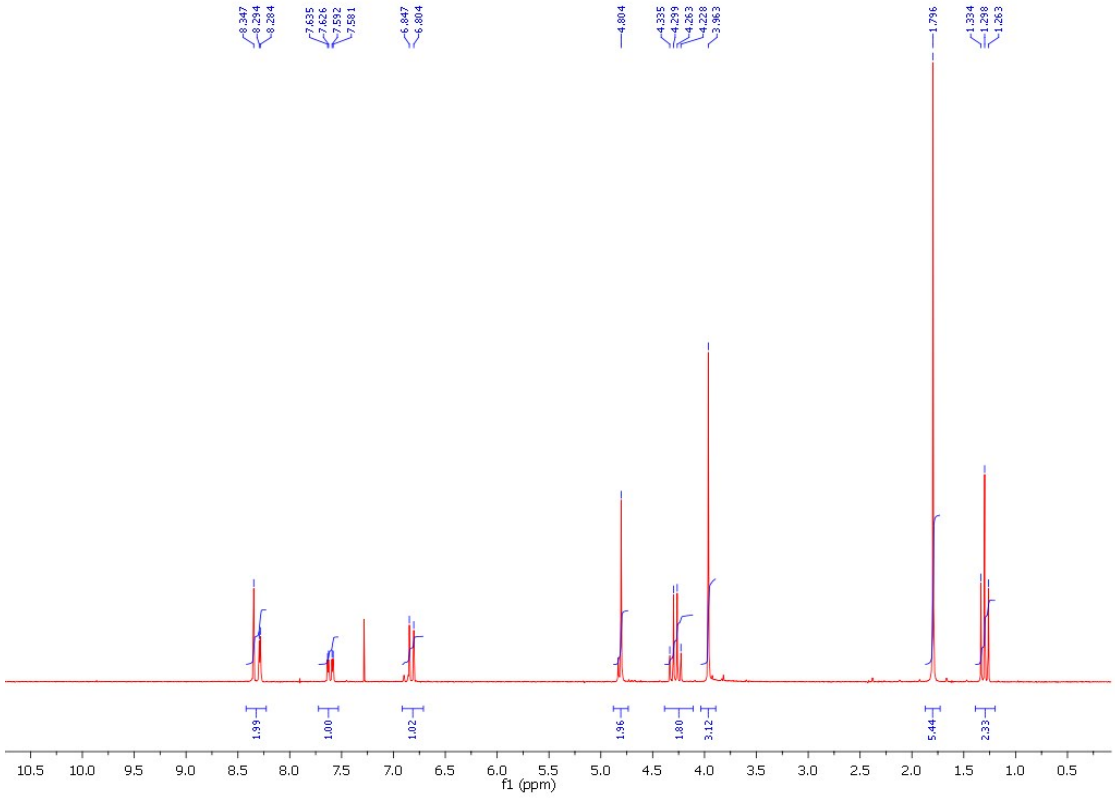


Figure S13 ^{1}H NMR spectrum of compound 3g

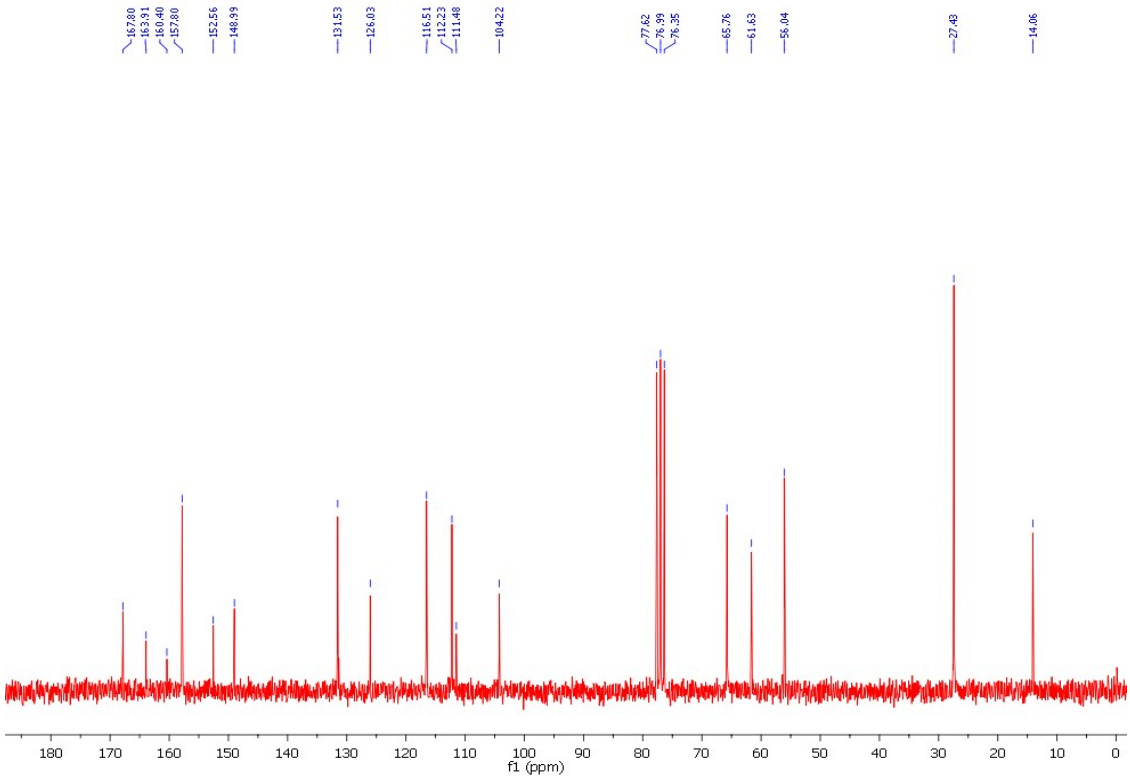
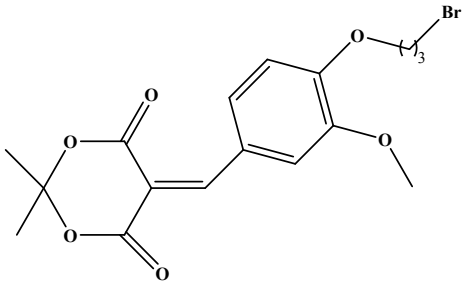


Figure S14 ^{13}C NMR spectrum of compound 3g

5-(4'-bromopropoxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3h**



$C_{17}H_{19}BrO_6$; 399.23 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then 4-(3-bromopropoxy)-3-methoxybenzaldehyde (2.73 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the desired product with good purity grade (without recrystallization). The title compound was obtained in 91% yield. Mp=135°C

IR (KBr): 1748, 1711, 1580, 1563, 1522, 1390, 1273 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 6H), 2.36-2.47 (m, 2H), 3.64 (t, 2H, *J* = 6.4 Hz), 3.94 (s, 3H), 4.28 (t, 2H, *J* = 6.0 Hz), 6.98 (d, 1H, *J* = 8.4 Hz), 7.64 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.29 (d, 1H, *J* = 2.2 Hz), 8.36 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.5, 29.5, 31.9, 56, 66.5, 104.1, 111.1, 111.8, 116.2, 125.3, 132.3, 149, 153.9, 158.1, 160.6, 164.1.

ESI-MS (70 eV): *m/z* (%) = 399 (18.3%) $[M]^+$; 319 (29.7%), 297 (100%) 276 (40.1%)

Anal. Calcd. $C_{17}H_{19}BrO_6$ (%): C 51.14, H 4.80; Found: C 51.18, H 4.84.

3h

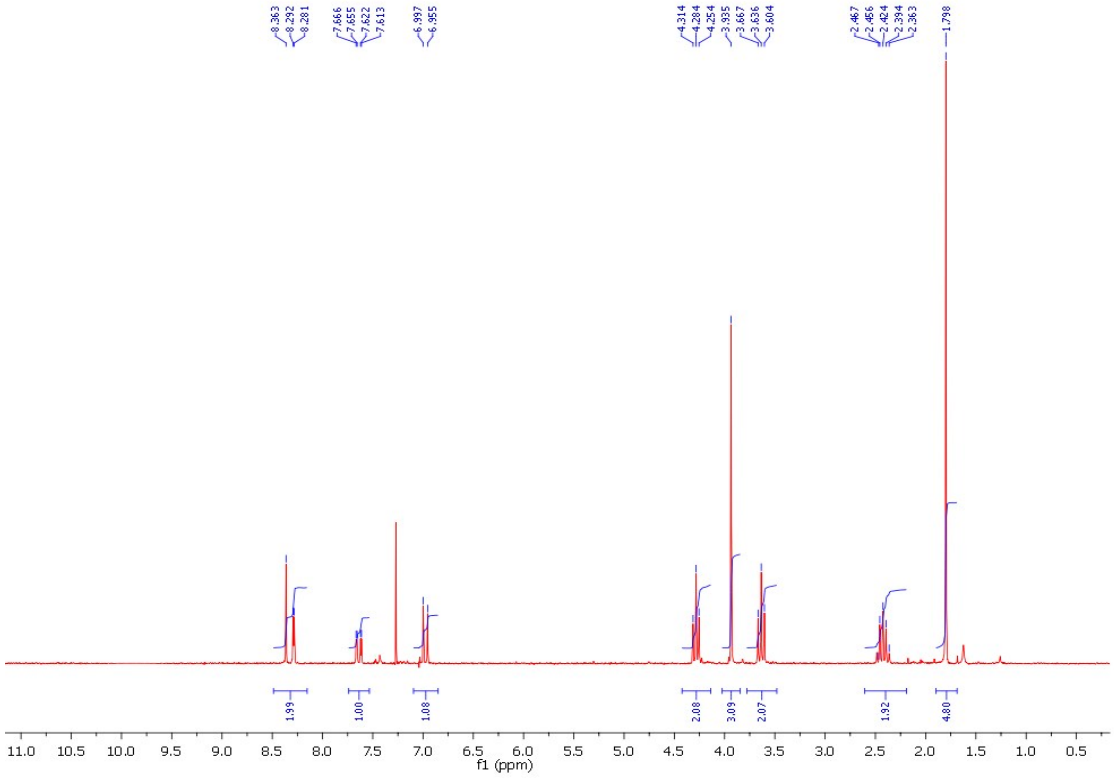


Figure S15 ^{1}H NMR spectrum of compound 3h

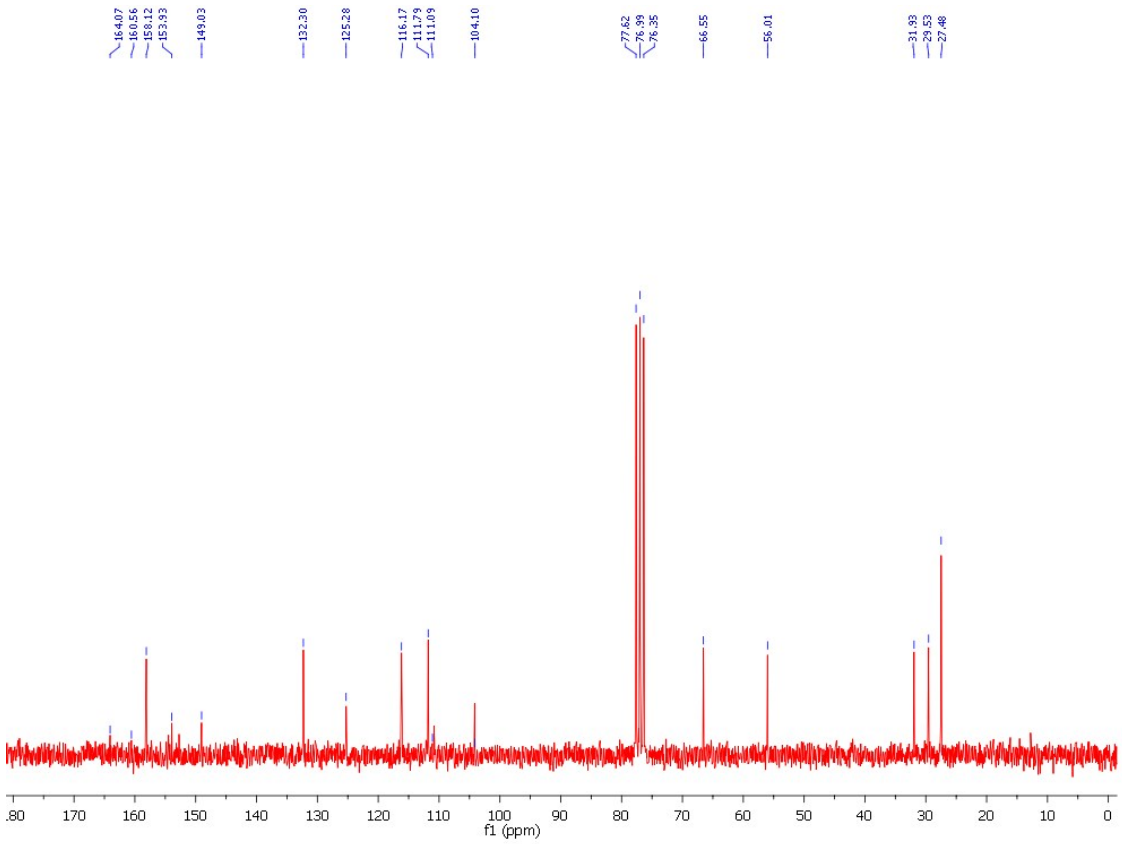
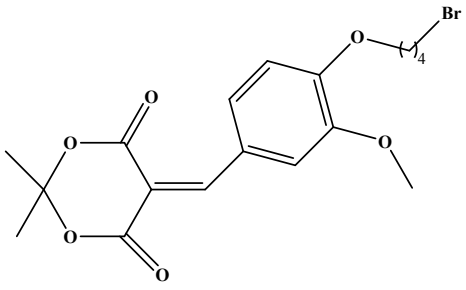


Figure S16 ^{13}C NMR spectrum of compound 3h

5-(4'-bromobutoxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3i**



$C_{18}H_{21}BrO_6$; 413.26 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then 4-(4-bromobutoxy)-3-methoxybenzaldehyde (2.87 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the

desired product with good purity grade (without recrystallization). The title compound was obtained in 91% yield. Mp=118-121°C

IR (KBr): 1748, 1713, 1580, 1563, 1398, 1272 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 6H), 2.06-2.09 (m, 2H), 3.51 (t, 2H, *J* = 6.2 Hz), 3.94 (s, 3H), 4.17 (t, 2H, *J* = 5.8 Hz), 6.93 (d, 1H, *J* = 8.6 Hz), 7.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.28 (d, 1H, *J* = 2.2 Hz), 8.35 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.4, 29.2, 33.1, 55.9, 68.1, 104.1, 110.6, 111.5, 116.1, 125, 132.4, 148.9, 154.1, 158.1, 160.5, 164.1.

ESI-MS (70 eV): *m/z* (%) = 413 (35.4%) $[M]^+$; 313 (86.2%), 311 (100%), 277 (34.1%)

Anal. Calcd. $C_{18}H_{21}BrO_6$ (%): C 52.31, H 5.12; Found: C 52.28, H 5.15.

3i

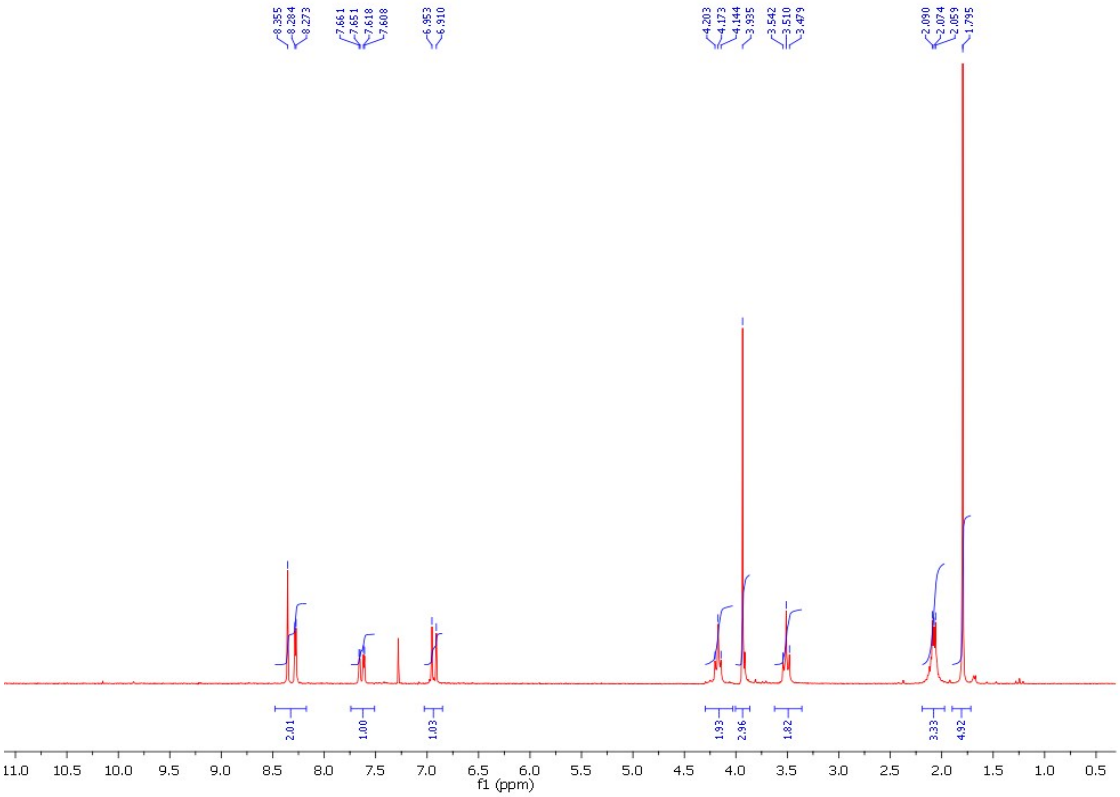


Figure S17 ^{1}H NMR spectrum of compound 3i

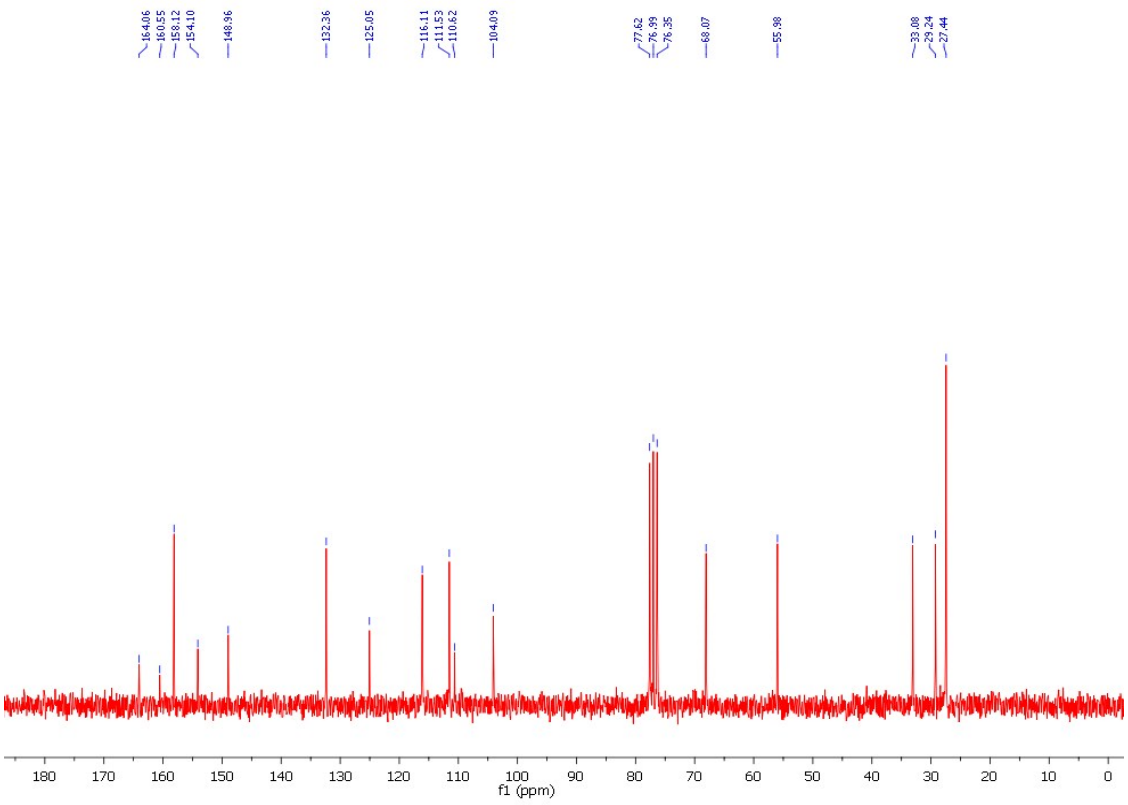
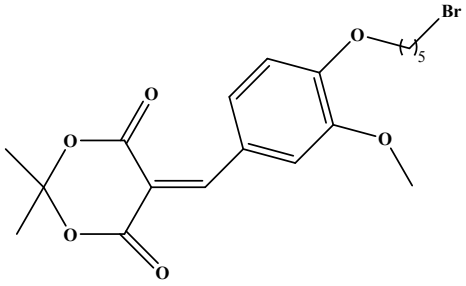


Figure S18 ^{13}C NMR spectrum of compound 3i

5-(4'-bromopentyloxy-3'-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3j**



$C_{19}H_{23}BrO_6$; 427.29 g/mol

According to general procedure 1.1 To a morthar are homogenized Meldrum`s acid (1.58 g, 11 mmol), then 4-(5-bromopentyloxy)-3-methoxybenzaldehyde (3.01 g, 10 mmol) and finally 5 mol% of PTSA (0.086 g, 0.5 mmol) was added at room temperature. Solid mixture very fast changed the color, white in light green. The reaction was folowed by TLC (eluent $CHCl_3$:EtOAc 4:1). The solid washed with small portions of cold ethanol and then dried at room temperature to afford the desired product with good purity grade (without recrystallization). The title compound was obtained in 91% yield. Mp=103-105°C.

IR (KBr): 1748, 1713, 1578, 1561, 1523, 1391, 1273 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.65-1.76 (m, 2H), 1.79 (s, 6H), 1.83-2.03 (m, 4H), 3.45 (t, 2H, *J* = 6.8 Hz), 3.94 (s, 3H), 4.15 (t, 2H, *J* = 6.6 Hz), 6.93 (d, 1H, *J* = 8.6 Hz), 7.64 (dd, *J* = 8.6, 2.0 Hz, 1H), 8.28 (d, 1H, *J* = 2.0 Hz), 8.35 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.6, 27.4, 28, 32.3, 33.3, 55.9, 68.8, 104.1, 110.5, 111.5, 116.1, 124.9, 132.4, 148.9, 154.2, 158.1, 160.6, 164.1.

ESI-MS (70 eV): *m/z* (%) = 427 (37.8%) $[M]^+$; 325 (80%), 261 (100%), 166 (48.2%)

Anal. Calcd. $C_{19}H_{23}BrO_6$ (%): C 53.41, H 5.43; Found: C 53.20, H 5.38.

3j

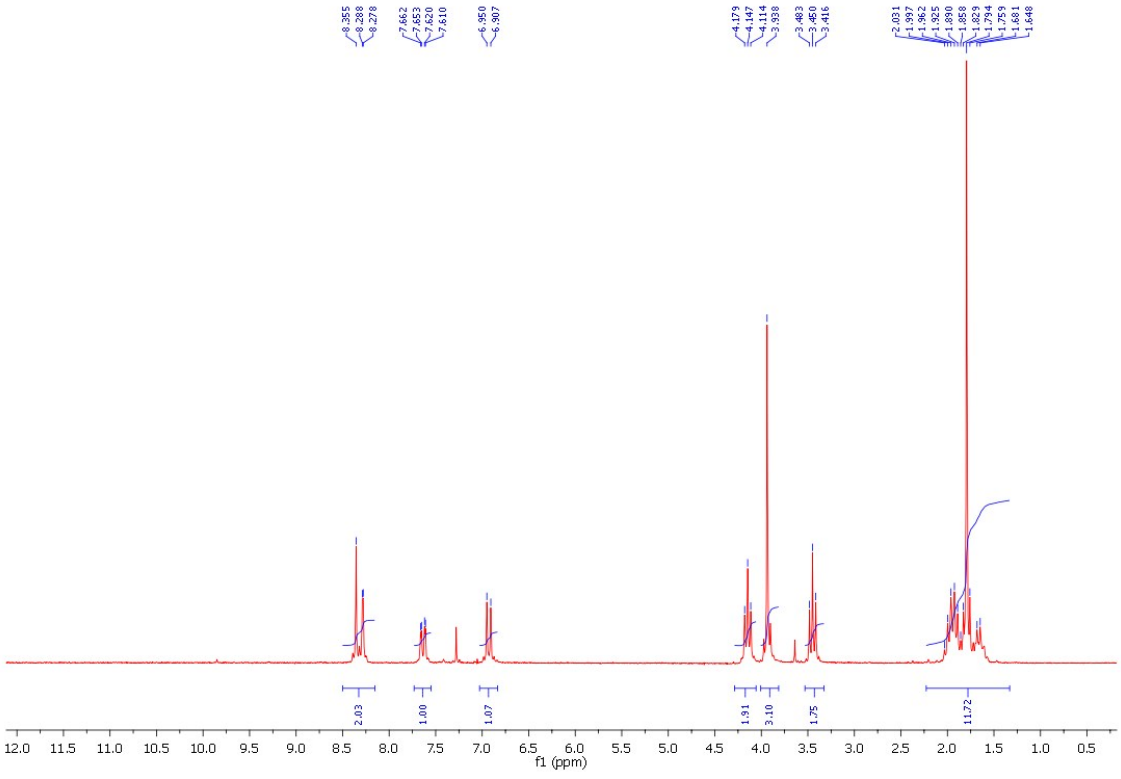


Figure S19 ^{1}H NMR spectrum of compound 3j

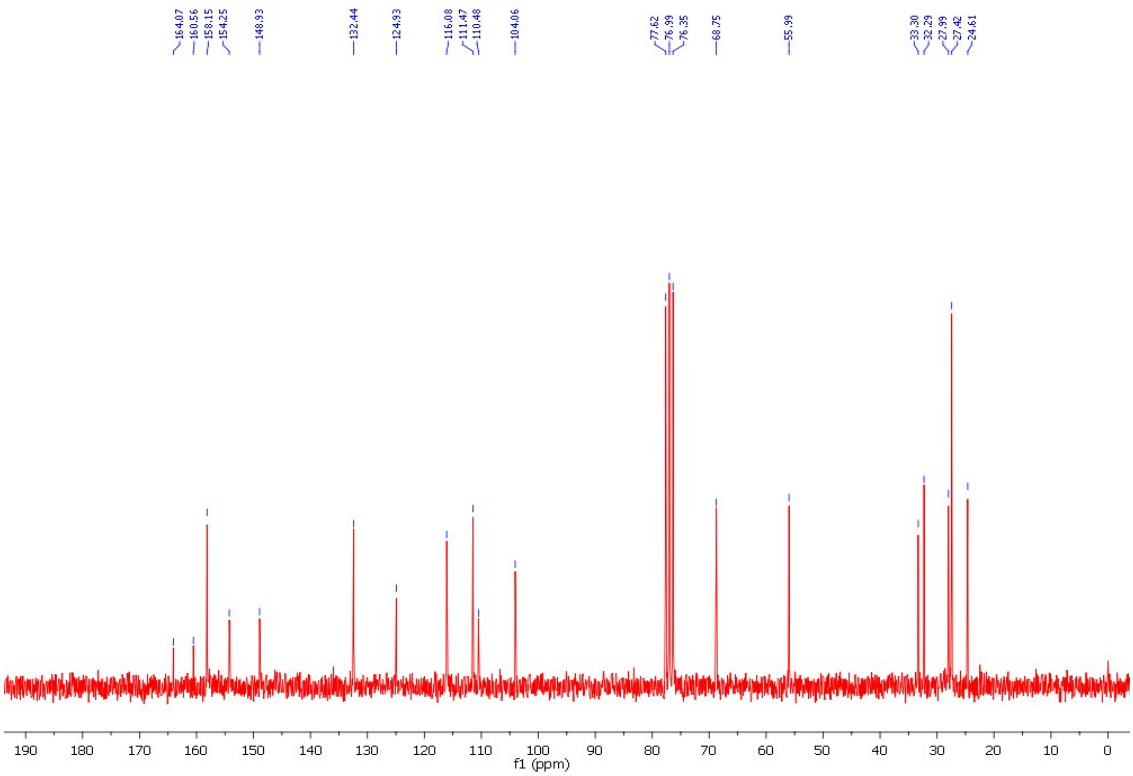


Figure S20 ^{13}C NMR spectrum of compound 3j