Electronic Supplementary Information associated with the paper

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

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1. General

1.1. General methods

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

To a mortar 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 followed by TLC (eluent CHCl₃ : 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

\[
\text{C}_{14}\text{H}_{13}\text{O}_{5}\text{I}; 404.15 \text{ g/mol}
\]

According to general procedure 1.1 To a mortar 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 followed by TLC (eluent CHCl₃: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.

¹H NMR (200 MHz, DMSO-d₆): 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).

¹³C NMR (50 MHz, DMSO-d₆): 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%),


3a

Figure S1 ¹H 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

$\text{C}_{17}\text{H}_{20}\text{O}_6$; 320.34 g/mol

According to general procedure 1.1 To a mortar 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 followed by TLC (eluent CHCl₃: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.

**¹H NMR (200 MHz, CDCl₃):** 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).

**¹³C NMR (50 MHz, CDCl₃):** 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. C₁₇H₂₀O₆ (%):** 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’-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, 3c

\[
\text{C}_{17}\text{H}_{20}\text{O}_6; \ 320.34 \text{ g/mol}
\]

According to general procedure 1.1 To a mortar 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 followed by TLC (eluent CHCl₃: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.

**¹H NMR (200 MHz, CDCl₃):** 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).

**¹³C NMR (50 MHz, CDCl₃):** 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. C₁₇H₂₀O₆ (%): C 63.74, H 6.29; Found: C 63.80, H 6.36.

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

\[ \text{C}_{18}\text{H}_{22}\text{O}_6; 334.36 \text{ g/mol} \]

According to general procedure 1.1 To a mortar 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 followed by TLC (eluent CHCl₃: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$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta = 0.99$ (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$_3$): $\delta = 13.7$, 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](image-url)
(E)-5-(4’-(but-2’-enyloxy)-3’-methoxybenzylidenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, 3e

\[
\text{C}_{18}\text{H}_{20}\text{O}_6; 332.35 \text{ g/mol}
\]

According to general procedure 1.1 To a mortar 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.

**¹H NMR (200 MHz, CDCl₃):** 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).

**¹³C NMR (50 MHz, CDCl₃):** 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. C₁₈H₂₀O₆ (%): C 65.05, H 6.07; Found: C 64.98, H 6.02.

3e

Figure S9 ¹H 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

\[
\text{C}_{16}\text{H}_{16}\text{O}_7; 320.29 \text{ g/mol}
\]

According to general procedure 1.1 To a mortar 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 followed 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.

**¹H NMR (200 MHz, CDCl₃):** \( \delta = 1.80 \) (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).

**¹³C NMR (50 MHz, CDCl₃):** \( \delta = 20.6, 27.5, 56, 104.5, 114.2, 116.9, 122.9, 129.1, 130.3, 144.4, 144.6, 151.1, 157.1, 159.9, 163.3, 168.2. \)

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

Anal. Calcd. C₁₆H₁₆O₇ (%): C 60.00, H 5.04; Found: C 59.95, H 5.01.

3f

![Figure S11 ¹H NMR spectrum of compound 3f](image)
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 mortar 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 followed by TLC (eluent CHCl₃: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\(_3\)): \(\delta = 1.29\) (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\(_3\)): \(\delta = 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): \(m/\text{z}\) (%) = 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’-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, **3h**

\[
\begin{array}{c}
\text{C}_{17}\text{H}_{19}\text{BrO}_6; 399.23 \text{ g/mol}
\end{array}
\]

According to general procedure 1.1 To a mortar 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$_3$): $\delta = 1.80$ (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$_3$): $\delta = 27.5$, 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](image)
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 mortar 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.

**¹H NMR (200 MHz, CDCl₃):** 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).

**¹³C NMR (50 MHz, CDCl₃):** 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. C₁₈H₂₁BrO₆ (%): C 52.31, H 5.12; Found: C 52.28, H 5.15.

3i

![Figure S17 ¹H NMR spectrum of compound 3i](image-url)
According to general procedure 1.1 To a mortar 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 followed by TLC (eluent CHCl₃: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$_3$): $\delta$ = 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$_3$): $\delta$ = 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