**SUPPORTING INFORMATION**

**Poly(ethylene) glycols and mechanochemistry for the preparation of bioactive 3,5-disubstituted hydantoins.**

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**General Remarks and Experimental Procedures**

Table S1. Screening of mechanochemical parameters to prepare 2 by Method A.

Table S2. Synthesis of hydantoins. Comparison between mechanochemical (BM) and solution methods.

Chiral HPLC Analyses for compound 4 (Methods A and B, with and without MeO-PEG-2000-OMe) (Table 4)

$^1$H NMR, $^{13}$C NMR and IR spectra of compounds 2, 4-19, 21, 24 (Table 2), and 25-26 (Scheme 2).

**General Remarks and Experimental Procedures**

All reagents were commercially available. All the starting α-amino esters were in the L-form. 5-Phenyl hydantoin was prepared as previously described.$^1$ NMR spectra were recorded at room temperature with the appropriate deuterated solvent (CDCl$_3$ or $d_6$-DMSO). Chemical shifts (δ) of $^1$H NMR and $^{13}$C NMR spectra are reported in ppm relative to residual solvent signals (CHCl$_3$ in CDCl$_3$: δ = 7.26 ppm for $^1$H and CDCl$_3$: δ = 77.04 ppm for $^{13}$C NMR); $J$ values are given in Hz. $^1$H and $^{13}$C NMR spectra were registered at 300 MHz or 400 MHz, the samples were prepared by dissolving 15 mg of hydantoin in 0.7 mL of deuterated solvent. $^1$H and $^{13}$C NMR were recorded using 32 and 4096 scans respectively. The identity of analytically pure final products was assessed by comparison of their $^1$H NMR data previously described in the literature and by their fragmentation in LC/MS. HRMS measurements were performed on a TOF mass analyser. Analytical high performance liquid chromatography (HPLC) was performed with a UV-detector at 214 nm using a CHROMOLITH RP18 column (50 x 4.6 mm), flow 5 mL/min, linear gradient CH$_3$CN in water 0-100% (+ 0.1% TFA) in 3 min. LC-MS analyses were performed by HPLC, column Onyx C$_{18}$, (25 x 4.6 mm), flow 3 mL/min linear gradient CH$_3$CN in water 0-100% (+ 0.1% HCO$_2$H) in 2.5 min. Melting points were measured on a Büchi Melting Point 510 apparatus and are uncorrected. Infrared spectra were recorded on a Nexus™ E.S.P. (Thermo Nicolet, USA) FT-IR spectrometer equipped with high pressure diamond cell. The ball-milling experiments were performed in a MM200 vibrational ball mill (Retsch GmbH, Haan, Germany) using 5 mL stainless steel jar (2 stainless steel balls, 5 mm Ø), a PM100 planetary mill (Retsch GmbH, Haan, Germany) using a 12 mL stainless steel jar (25 or 50 stainless steel balls, 5 mm Ø) or a Pulverisette 7 Premium (Fritsch GmbH, Idar-Oberstein, Germany) using a 20 mL stainless steel jar (40 stainless steel
balls, 5 mm Ø). All compounds displayed identical spectral data compared to literature. Enantiomeric excess (e.e.) and ratio (e.r.) were measured using a Beckman Coulter System Gold 126 Solvent Module HPLC machine and Beckman Coulter System Gold 168 Detector. Column: direct phase CHIRACEL OD-RH (0.46 x 25 cm) for compound 4, using n-hexanes and 2-propanol as solvents (ratio 90:10 v/v, Flow: 1 mL/min, λ = 214 nm).

Table S1. Screening of mechanochemical parameters to prepare 2 by Method A.

<table>
<thead>
<tr>
<th>Ball-Mill</th>
<th>Jar Material</th>
<th>Frequency (Hz) / Rotation speed (rpm)</th>
<th>Time (min.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBM</td>
<td>Stainless steel</td>
<td>450 rpm</td>
<td>120</td>
<td>76</td>
</tr>
<tr>
<td>VBM</td>
<td>Stainless steel</td>
<td>30 Hz</td>
<td>120</td>
<td>75</td>
</tr>
<tr>
<td>VBM</td>
<td>WC</td>
<td>30 Hz</td>
<td>120</td>
<td>74</td>
</tr>
</tbody>
</table>

Table S2. Synthesis of hyantoin. Comparison between mechanochemical (BM) and solution methods.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BM (A or B)(^{a})</td>
</tr>
<tr>
<td>2</td>
<td>84, B</td>
</tr>
<tr>
<td>11</td>
<td>79, A</td>
</tr>
<tr>
<td>12</td>
<td>40, B</td>
</tr>
<tr>
<td>13</td>
<td>75, B</td>
</tr>
<tr>
<td>14</td>
<td>58, B</td>
</tr>
<tr>
<td>16</td>
<td>65, B</td>
</tr>
<tr>
<td>17</td>
<td>25, B</td>
</tr>
<tr>
<td>18</td>
<td>85, A</td>
</tr>
</tbody>
</table>

\(^{a}\) For the same compound, the method giving the better yield was reported. Method A: α-amino ester (1 equiv.), R²NCO (3 equiv.), K₂CO₃ (3 equiv.), 30 Hz, 120 min; Method B: (step 1) α-amino ester (1 equiv.), CDI (1.3 equiv.), 450 rpm, 40 min.; (step 2) R²NH₂ (1.6 equiv.), K₂CO₃ (3.6 equiv.), 450 rpm, 120 min.; \(^{b}\) For some compounds no comparison with solution procedure is possible: compounds 4-6, 9 and 15 are hitherto unknown; compounds 7 and 8 are commercially available (509€/g) but the preparation in solution was never reported in the literature.

REFERENCES

Chiral HPLC analyses of compound 4 prepared with Method B (Table 4):

Reaction performed from H-L-Leu-OMe*HCl, without MeO-PEG-2000-OMe

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.617</td>
<td>9137192</td>
<td>52.366</td>
</tr>
<tr>
<td>2</td>
<td>10.267</td>
<td>311400</td>
<td>47.634</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17448592</td>
<td>100.000</td>
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</table>

Reaction performed from H-D-Leu-OMe*HCl, without MeO-PEG-2000-OMe

<table>
<thead>
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<th>Area Percent</th>
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</thead>
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<tr>
<td>1</td>
<td>8.733</td>
<td>8296740</td>
<td>47.540</td>
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<tr>
<td>2</td>
<td>10.167</td>
<td>9155359</td>
<td>52.460</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17452099</td>
<td>100.000</td>
</tr>
</tbody>
</table>
Reaction performed from H-L-Leu-OMe*HCl, with MeO-PEG-2000-OMe

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.483</td>
<td>1819680</td>
<td>82.362</td>
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<tr>
<td>2</td>
<td>7.750</td>
<td>389687</td>
<td>17.638</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Total</strong></td>
<td><strong>100.000</strong></td>
</tr>
</tbody>
</table>

**Totals** | **2209367** | **100.000**
Chiral HPLC analyses of compound 4 prepared with method A (Table 4):

Reaction performed from H-L-Leu-OMe*HCl, without MeO-PEG-2000-OMe

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.567</td>
<td>11129368</td>
<td>53.248</td>
</tr>
<tr>
<td>2</td>
<td>9.017</td>
<td>9771464</td>
<td>46.752</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Totals</strong></td>
<td><strong>20900832</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>100.000</strong></td>
</tr>
</tbody>
</table>

Reaction performed from H-L-Leu-OMe*HCl, with MeO-PEG-2000-OMe

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.317</td>
<td>1184789</td>
<td>63.025</td>
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<tr>
<td>2</td>
<td>7.500</td>
<td>695086</td>
<td>36.975</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Totals</strong></td>
<td><strong>1879875</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>100.000</strong></td>
</tr>
</tbody>
</table>
Compound 2
Table 2, entry 1
Compound 2
Table 2, entry 1
Compound 2
Table 2, Entry 1
Compound 4
Table 2, entry 2
Compound 4
Table 2, entry 2

\[
\begin{align*}
&\text{f1 (ppm)} \quad I \\
&13.54 \\
&21.79 \\
&23.18 \\
&25.39 \\
&33.73 \\
&41.03 \\
&55.87 \\
&76.74 \\
&77.16 \\
&77.58 \\
&\text{f1 (ppm)} \quad I \\
&-13.54 \\
&-41.03 \\
&-33.73 \\
&-25.39 \\
&-23.18 \\
&-41.03 \\
&-55.87 \\
&-77.58 \\
&-77.16 \\
\end{align*}
\]
Table 2, Entry 2
Compound 5
Table 2, entry 3
Compound 5
Table 2, entry 3

\[
\begin{align*}
\text{f1 (ppm)} & \\
173.06 & 157.00 & 129.94 & 124.62
\end{align*}
\]
Compound 6
Table 2, entry 4
Compound 6
Table 2, entry 4
Compound 7
Table 2, entry 5
Compound 7
Table 2, entry 5
Compound 8
Table 2, entry 6

$\text{HN} - \text{N} - \text{O}$

$\text{O}$

$\text{HN} - \text{N} - \text{O}$

$\text{H NMR (300 MHz, DMSO)}$

$\delta$ 1.04 (t, $J$ = 7.1 Hz, 1H).
Compound 8
Table 2, entry 6
Compound 8
Table 2, Entry 6
Compound 9
Table 2, entry 7
Compound 9
Table 2, entry 7
Compound 10
Table 2, entry 8
Compound 10
Table 2, entry 8
Compound 11
Table 2, entry 9
Compound 11
Table 2, entry 9
Compound 11
Table 2, Entry 9
Compound 12
Table 2, entry 10
Compound 12
Table 2, entry 10
Compound 12
Table 2, Entry 10
Compound 13
Table 2, entry 11
**Compound 13**

**Table 2, entry 11**
Compound 13
Table 2, Entry 11
Compound 14
Table 2, entry 12
Compound 14
Table 2, entry 12
Compound 15
Table 2, entry 13
Compound 15
Table 2, entry 13
Compound 16  
Table 2, entry 14
Compound 16
Table 2, entry 14
Compound 16
Table 2, Entry 14
Compound 17
Table 2, entry 15
Compound 17
Table 2, entry 15

\[
\begin{array}{cccc}
& 173.00 & 156.10 & 139.25 \\
& 131.01 & 129.01 & 128.80 \\
& 126.99 & 126.99 & 126.99 \\
& 118.28 & 118.28 & 118.28 \\
& 77.58 & 77.16 & 76.74 \\
& 75.74 & 70.34 & 70.34 \\
& 41.15 & 41.15 & & \\
\end{array}
\]
Compound 18
Table 2, entry 16
Compound 18
Table 2, entry 16
Compound 19
Table 2, entry 17

\[
\begin{align*}
&\text{N} \\
&\text{O} \\
&\text{N}
\end{align*}
\]
Compound 19
Table 2, entry 17
Compound 19
Table 2, Entry 17
Compound 21
Table 2, entry 19
Compound 21
Table 2, entry 19

Grease
Compound 21
Table 2, Entry 19
Compound 24
Table 2, entry 22

N
H
N
O
O
CH₂Br₂

2.08 2.47 0.92 3.13 1.00 1.12 1.22 1.01 19.11
Compound 24
Table 2, entry 22
Compound 25
Scheme 2
Compound 25
Scheme 2
Compound 25
Scheme 2
Compound 26
Scheme 2
Compound 26
Scheme 2