Supporting Information
for
Poly(ethylene glycol)s as grinding additives in the mechanochemical preparation of highly functionalized 3,5-disubstituted hydantoins

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Experimental procedures, characterization of new compounds and copies of ¹H and ¹³C NMR spectra
General remarks and experimental procedures

All reagents were commercially available and used without any further purification. L-α-amino esters were used, except when otherwise specified. NMR spectra were recorded at room temperature with the appropriate deuterated solvent (CDCl₃ or DMSO-d₆). Chemical shifts (δ) of ¹H NMR and ¹³C NMR spectra are reported in ppm relative to residual solvent signals (CHCl₃ in CDCl₃: δ = 7.27 ppm for ¹H and CDCl₃: δ = 77.04 ppm for ¹³C NMR; DMSO in d₆-DMSO: δ = 2.54 ppm for ¹H and d₆-DMSO: δ = 40.45 ppm for ¹³C NMR); values for the coupling constants J are given in Hz. ¹H NMR spectra were registered at 300 MHz and 400 MHz. ¹³C NMR spectra were registered at 75 MHz and 100 MHz. HRMS measurements were performed on a TOF mass analyser. LC–MS analyses were performed with HPLC, column Onyx C18, (25 x 4.6 mm), flow 3 mL/min linear gradient CH₃CN in water 0–100% (+ 0.1% HCO₂H) in 2.5 min. Optical rotation measurements were performed at λ = 589 nm (Na lamp), the compounds were solubilized in CHCl₃. The ball-milling experiments were performed in a planetary mill, 12 mL steel jar (50 stainless steel balls, 5 mm Ø). The synthesis of compounds 2a–c, 3a, 4, 5a and 6 (Table 3) was performed according to previously reported procedures [1]. Their identity was assessed by comparison with the spectral data previously published [1]. The optical power was also measured: 2a [α]₀° = 4.11 (c = 1.02, CHCl₃); 2b [α]₀° - 3.33 (c = 1.02, CHCl₃); 2c [α]₀° + 4.66 (c = 1.05, CHCl₃); 3a [α]₀° - 4.60 (c = 1.00, CHCl₃); 4 [α]₀° - 7.33 (c = 1.01, CHCl₃); 5a [α]₀° - 3.36 (c = 1.01, CHCl₃); 6 [α]₀° + 8.48 (c = 1.05, CHCl₃).
General procedure for the synthesis of 3,5-disubstituted hydantoins (Table 3).

**Conditions A, dry grinding.** (Step 1) The α-amino methyl ester hydrochloride (1.0 equiv.) and 1,1'-carbonylimidazole (CDI) (1.3 equiv.) were ground in a 12 mL stainless steel milling jar in a planetary ball-mill at 450 rpm for 40 minutes. (Step 2) The amine (1.6 equiv) and K$_2$CO$_3$ (3.6 equiv) were added and the mixture was ground at 450 rpm for two hours. Distilled water was added to the crude and the desired compound was either precipitated and filtered over sintered glass, or extracted with ethyl acetate. The organic layer was washed with a 10% aq. citric acid solution (× 3) and brine (× 1), dried over MgSO$_4$ and concentrated in vacuo. Only for compounds 3b and 5b a purification by flash chromatography was performed on the crude sample, respectively.

**Conditions B (with MeO-PEG-OMe, compounds 2a,b, 3a, 4, 4b and 6) and C (with HO-PEG-3400-OH, compounds 2a,b, 4, 4b and 6), wet grinding** (Table 3). In the case of PEG-assisted grinding the reaction was performed by a modification of conditions A: the suitable PEG polymer (450 mg/mmol substrate) was added in Step 2. The compound was recovered by extraction with ethyl acetate after addition of distilled water to the reaction mixture. The organic layer was washed with a 10% aq. citric acid and brine, dried over MgSO$_4$ and concentrated in vacuo. When necessary, the compound was purified by flash chromatography.

(S)-3-[4'-(4-Methyl-1H-pyrazol-1-yl)-phenylmethyl]-5-benzyl-2,4-imidazolidinedione (3b, Table 3, entry 5). The reaction scale was 1 mmol (conditions A). The compound was obtained by precipitation in water and purified by flash chromatography (linear gradient of AcOEt in Et$_2$O: 0–10%). White solid (108
mg, 30% isolated yield); $[\alpha]_D^{20} \text{ - 66.6 (c = 1.04, CHCl}_3$); $^1H$ NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm): 7.68 (s, 1H, ImH), 7.58 (s, 1H, ImH), 7.54 (d, $J = 6.2$ Hz, 2H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.32-7.23 (m, 3H, ArH), 7.20-7.12 (m, 2H), 5.38 (s, 1H, NH), 4.60 (m, 2H, NCH$_2$), 4.28 (dd, $J = 8.4$ and $J = 3.7$ Hz, 1H, NCH), 3.27 (dd, $J = 8.6$ and $J = 3.7$ Hz, 1H CH$_2$/H$_a$), 2.86 (dd, 1H $J = 8.6$ and $J = 5.4$ Hz, 1H CH$_2$/H$_b$), 2.16 (s, 3H CH$_3$); $^{13}$C NMR (CDCl$_3$ 75 MHz) $\delta$ (ppm): 172.8, 156.7, 142.1, 139.9, 135.1, 129.7, 129.4, 129.1, 127.6, 125.4, 118.9, 118.5, 58.5, 41.7, 37.9, 29.8, 9.1; ESI-(+) m/z: 402.1 [M + CH$_3$CN + H]$^+$, 361.2 [M + H]$^+$, 268.4 [M – PhCH$_3$]$^+$, 228.4, 184.4, 151.9, 130.3, 100.6 [M – CH$_2$PhPyr-CH$_2$Ph]$^+$. HRMS ESI-(+): calcd for C$_{21}$H$_{21}$N$_4$O$_2$ [M + H]$^+$ 361.1665, found 361.1665.

(S)-3-(Furan-2-ylmethyl)-5-benzyl-2,4-imidazolidinedione (3c, Table 3, entry 6). The reaction scale was 1.0 mmol (conditions A). The compound was obtained by precipitation in water. White solid (190.0 mg, 70% isolated yield); $[\alpha]_D^{20} \text{ - 3.4 (c = 1.03, CHCl}_3$); $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ (ppm): 8.31 (s, 1H, FuH), 7.48 (s, 1H, FuH), 7.26-7.19 (m, 3H, ArH), 7.15-7.10 (m, 2H, ArH) 6.29 (dd, $J = 3.1$ and $J = 1.9$ Hz, 1H, FuH), 5.83 (d, $J = 3.2$ Hz, 1H, NH), 4.45 (t, $J = 5.0$ Hz, 1H, NCH), 4.35 (q, $J = 9.4$ Hz, 2H, NCH$_2$), 2.97-2.95 (m, 2H, CH$_2$); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ (ppm): 173.1, 155.9, 149.5, 142.6, 135.4, 129.9, 128.3, 126.9, 110.6, 107.6, 57.3, 36.5, 34.5; ESI-(+) m/z: 271.2 [M + H]$^+$, 203.0 [M - Fu]$^+$, 186.3, 102.0 [M – CHFu- CPH]$^+$. HRMS ESI-(+): calcd for C$_{15}$H$_{15}$N$_2$O$_3$ [M + H]$^+$ 271.1087, found 271.1083.

(S)-3-[4’-(4-Methyl-1H-pyrazol-1-yl)-phenylmethyl]-5-((carboxybenzylamino)butyl)-2,4-imidazolidinedione (5b, Table 3, entry 9). The reaction scale was 0.7557 mmol. The crude was precipitated by AcOEt (conditions A) or purified by column chromatography (37% $^1H$ NMR yield, conditions C, linear
gradient of EtOH in Et₂O: 0-10%). White solid (223.0 mg, 62% isolated yield for Conditions A); [α]D 20° - 5.4 (c = 1.00, CHCl₃); ¹H NMR (DMSO-d₆, 300 MHz) δ (ppm): 8.36 (s, 1H, PyrH), 8.21 (s, 1H, PyrH), 7.74 (d, J = 8.4 Hz, 2H, ArH), 7.53 (s, 1H), 7.41-7.18 (m, 8H, ArH + NH), 4.99 (s, 2H, CH₂O), 4.53 (s, 2H, NCH₂), 4.12 (t, J = 6.6 Hz, 1H, NCH), 2.96 (m, 2H, NCH₂), 2.09 (s, 3H CH₃), 1.80-1.18 (m, 6H, (CH₂)₃); ¹³C NMR (DMSO-d₆, 75 MHz) δ (ppm): 174.2, 156.6, 156.1, 141.6, 139.0, 137.3, 134.2, 128.5, 128.3, 127.7, 126.0, 117.9, 117.7, 65.1, 56.3, 30.9, 28.9, 21.5, 8.71; ESI-(+) m/z: 476.0 [M + H]+. HRMS ESI-(+): calcd for C₂₆H₃₀N₅O₄ [M + H]+ 476.2298, found 476.2294.

(S)-3-(Furan-2-ylmethyl)-5-((carboxybenzylamino)butyl)-2,4-imidazolidinedione (5c, Table 3, entry 10). The reaction scale was 0.7557 mmol (conditions A). NaCl (250 mg) was added during Step 1 [2]. The crude was precipitated by Et₂O then purified by column chromatography (linear gradient of MeOH in CH₂Cl₂: 0-1%). White solid (107 mg, 37% isolated yield); [α]D 20° -26.5 (c = 1.00, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.36-7.32 (m, 6H), 6.31 (m, 2H), 6.16 (m, 1H), 5.09 (s, 2H), 4.69 (s, 1H), 4.65 (s, 2H), 4.02-3.97 (m, 1H), 3.17 (m, 2H), 1.91-1.86 (m, 1H), 1.52-1.28 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ (ppm): 173.5, 157.0, 156.8, 156.7, 149.0, 142.6, 136.6, 128.7, 128.3, 128.2, 110.6, 108.9, 66.9, 57.1, 40.5, 40.4, 35.0, 31.1, 29.5, 21.5; ESI-(+) m/z 408.2 [M+Na]⁺, 171.0 [(M-ZNH-Fu) + H]⁺; HRMS ESI-(+) calcd for C₂₀H₂₄N₃O₅ [M+H]⁺ 386.1716 found 386.1714.

(S)-3-(1'-Methyl-1H-pyrazol-3'-methyl)5-((carboxybenzylamino)butyl)-2,4-imidazolidinedione (5d, Table 3, entry 11): The reaction scale was 0.7557 mmol (Conditions A). The compound was recovered after liquid-liquid extraction with ethyl acetate and water. White solid (140.0 mg, 47% isolated yield); [α]D 20° - 7.64 (c = 1.02,
CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ (ppm): 7.38-7.30 (m, 5H, ArH), 7.22 (d, $J = 2.2$ Hz, 1H, ImH), 6.16 (d, $J = 2.2$ Hz, 1H), 5.84 (s, 1H, NH), 5.09 (s, 2H, CH$_2$O), 4.84 (m, 1H, NH), 4.67 (s, 2H, NCH$_2$), 4.03 (t, $J = 5.1$ Hz, 1H, NCH), 3.81 (s, 3H, CH$_3$), 3.25-3.11 (m, 2H, NCH$_2$), 1.98-1.82 (m, 1H, CH$_2$/H$_a$), 1.81-1.66 (m, 1H, CH$_2$/H$_b$), 1.56-1.30 (m, 4H, (CH$_2$)$_2$); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ (ppm): 173.7, 157.3, 156.7, 147.2, 136.7, 131.2, 128.7, 128.3, 104.9, 66.9, 57.1, 40.5, 39.9, 36.1, 31.1, 29.6, 21.6; ESI-$(+)$ $m/z$: 422.1 [M+Na]$^+$, 400.2 [M + H]$^+$, 338.4, 292.1 [M − PhCH$_2$O]$^+$; HRMS ESI-$(+)$: calcd for C$_{20}$H$_{26}$N$_5$O$_4$ [M + H]$^+$ 400.1985, found 400.1983.

References


Compound 2b
Compound 2b
Compound 2c
Compound 4b
Compound 4b
Compound 4c

CHCl₃

H₂O

SiO₂
Compound 4d

RG 8
RG 8 after wash
proton10ppmSI CDCl3 /opt/topspin lapp-f1 8

f1 (ppm)

S15
Compound 4d