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## Synthesis of Esters of 6-(2,5-Dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoic Acid as Potential Transdermal Penetration Enhancers

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**Abstract:** Skin penetration enhancers are used to allow formulation of transdermal delivery systems for drugs that are otherwise insufficiently skin-permeable. The series of seven esters of 6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoic acid as potential transdermal penetration enhancers was formed by multistep synthesis. The general synthetic approach of all newly synthesized compounds is presented. Structure confirmation of all generated compounds was accomplished by IR, <sup>1</sup>H, <sup>13</sup>C NMR and HR-MS spectroscopy. All the prepared compounds were analyzed using RP-HPLC method for the lipophilicity measurement and their lipophilicity (log *k*) was determined.

**Keywords:** Transdermal penetration enhancers; 6-Aminohexanoic acid derivatives; Lipophilicity.

### INTRODUCTION

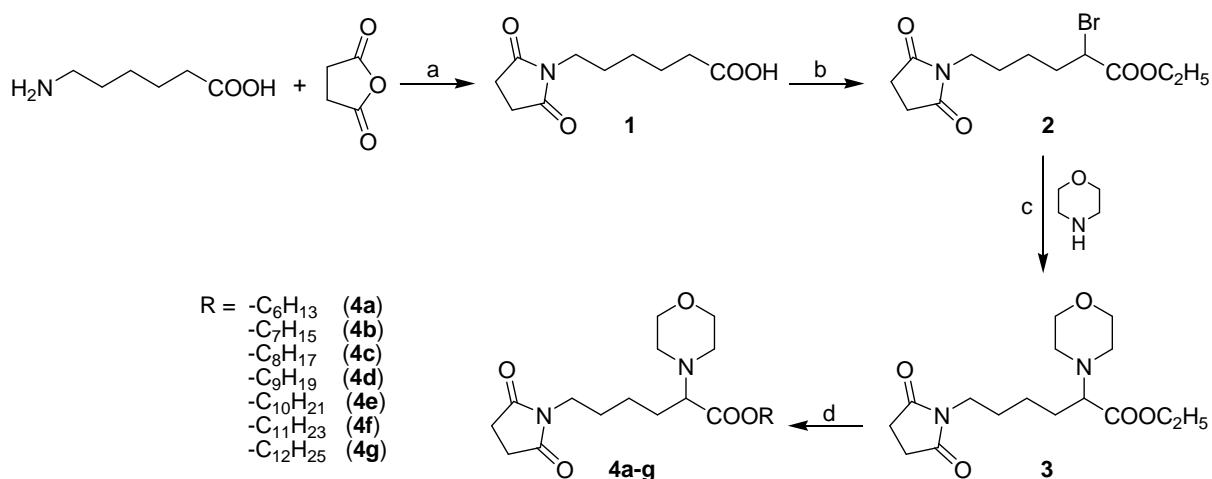
Transdermal penetration enhancers (also called sorption promoters or accelerants) are special pharmaceutical excipients that interact with skin components to increase the penetration of drugs from topical dosage forms to blood circulation. Numerous compounds (with different chemical structures) have been evaluated as penetration enhancers and a number of potential sites and modes of action were identified [1,2]. Some of the important penetration enhancers, as classified by Sinha and Kaur [3], are terpenes and terpenoids, pyrrolidinones, fatty acids and esters, sulfoxides, alcohols and glycerides and miscellaneous enhancers including phospholipids, cyclodextrin complexes, amino acid derivatives, lipid synthesis inhibitors, clofibric acid, dodecyl-*N,N*-dimethylamino acetate and enzymes.

This is a follow-up paper to our previous articles [4-6] dealing with a multistep synthesis of seven alkyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoates with C<sub>6</sub>-C<sub>12</sub> linear alkyl ester chains. Lipophilicity (log *k*) of the compounds was determined using RP-HPLC.

## RESULTS AND DISCUSSION

The starting material ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**2**) was prepared by multistep synthesis from 6-aminohexanoic acid. This amino acid was condensed with succinic anhydride to obtain succinimide intermediate **1**, which was then transformed by means of one-pot synthesis under the optimized Schwenk and Papa procedure conditions [7,8] to  $\alpha$ -bromocarboxylate **2**. The synthesis route is shown in Scheme 1 and was reported recently [4,5]. The problems associated with the generation of  $\alpha$ -bromocarboxyl compounds were reported by Brychtova et al. [5]. Ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (**3**) was obtained by reaction of  $\alpha$ -bromocarboxylate **2** and morpholine. The problems associated with this C-N coupling reaction were reported by Brychtova et al. [6]. The series of seven targeted alkyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoates (**4a-g**) was formed by conventional base-catalyzed transesterification [9] of the key intermediate **3** in the excess of corresponding primary unbranched alcohol.

**Scheme 1.** Synthesis of target esters **4a-4g**: (a) acetone, 25 °C, 24h; (b) one pot synthesis: SOCl<sub>2</sub>, Br<sub>2</sub>, EtOH; (c) toluene, reflux, 5h; (d) Na, R-OH.



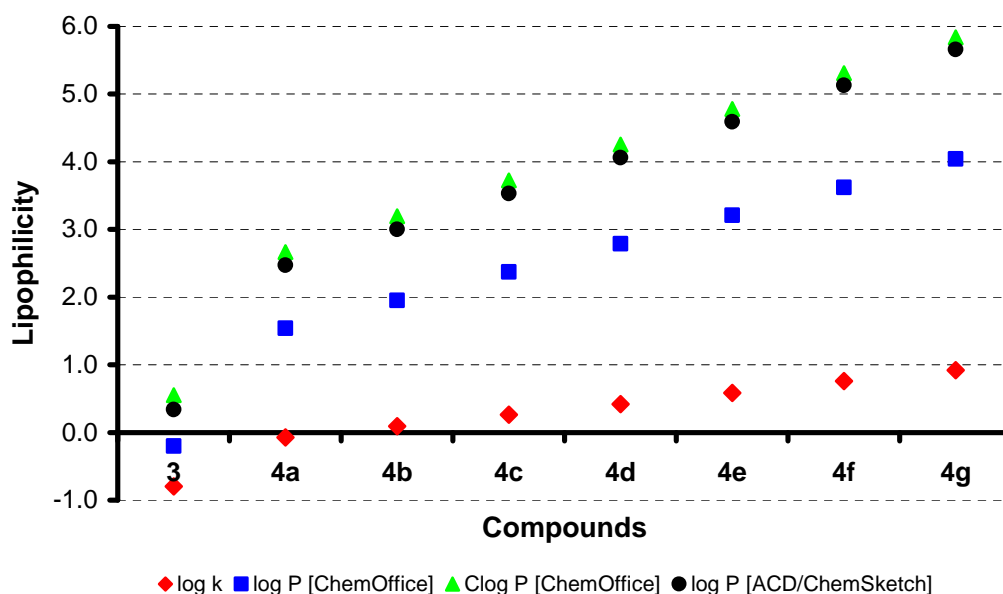
Hydrophobicities (log *P*/Clog *P* values) of the studied compounds **3**, **4a-4g** were calculated using two commercially available programmes (ChemOffice Ultra and ACD/ChemSketch) and measured by means of RP-HPLC determination of capacity factors *k* with subsequent calculation of log *k*. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using end-capped non-polar C<sub>18</sub> stationary RP column. The results are shown in Table 1 and illustrated in Figure 1.

**Table 1.** Comparison of calculated lipophilicities (log *P*/Clog *P*) with determined log *k* values.

Comp.	log <i>k</i>	log <i>P</i> /Clog <i>P</i> ChemOffice	log <i>P</i> ACD/ChemSketch
<b>3</b>	-0.7951	-0.20 / 0.550	0.34 ± 0.54
<b>4a</b>	-0.0736	1.54 / 2.666	2.47 ± 0.54
<b>4b</b>	0.0934	1.95 / 3.195	3.00 ± 0.54
<b>4c</b>	0.2613	2.37 / 3.724	3.53 ± 0.54
<b>4d</b>	0.4177	2.79 / 4.253	4.06 ± 0.54
<b>4e</b>	0.5834	3.21 / 4.782	4.59 ± 0.54
<b>4f</b>	0.7588	3.62 / 5.311	5.13 ± 0.54
<b>4g</b>	0.9221	4.04 / 5.840	5.66 ± 0.54

As expected, ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (**3**) showed the lowest lipophilicity, whereas dodecyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (**4g**) possessed the highest lipophilicity. It can be assumed, that the calculated log *P*/Clog *P* data and the determined log *k* values correspond to the expected lipophilicity increasing within the series of the evaluated compounds (ethyl <<< hexyl < heptyl < nonyl < decyl < undecyl < dodecyl derivatives). As expected, the dependence of log *k* on the length of the unbranched alkyl chain is linear ( $r = 0.9994$ ,  $n = 8$ ). Log *k* data specify lipophilicity within this series of the discussed compounds.

**Figure 1.** Comparison of the log *P*/Clog *P* values computed using two the programs with the calculated log *k* values. Compounds **3** and **4a-g** are ordered according to the increase in log *k* values.



## EXPERIMENTAL

### General

All reagents were purchased from Sigma-Aldrich (Schnelldorf, Germany) or Merck (Darmstadt, Germany). Kieselgel 60, 0.040-0.063 mm (Merck) was used for column chromatography. TLC experiments were performed on alumina-backed silica gel 40 F<sub>254</sub> plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and evaluated in iodine vapour. The melting points were determined on a Mikro-Heiztisch System PolyTherm A apparatus (Wagner & Munz, Munich and Hund, Wetzlar, Germany) and are uncorrected. Infrared (IR) spectra were recorded on a Smart MIRacle™ ATR ZnSe for Nicolet™ 6700 FT-IR Spectrometer (Nicolet - Thermo Scientific, U.S.A.). The spectra were obtained by accumulation of 256 scans with 2 cm<sup>-1</sup> resolution in the 4000-600 cm<sup>-1</sup> region. All <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance-500 FT-NMR spectrometer (500 MHz for <sup>1</sup>H and 125 MHz for <sup>13</sup>C, Bruker Comp., Karlsruhe, Germany). Chemical shifts are reported in ppm (δ) to internal Si(CH<sub>3</sub>)<sub>4</sub>, when diffused easily exchangeable signals are omitted. Mass spectra were measured using the LTQ Orbitrap Hybrid Mass Spectrometer (Thermo Electron Corporation, U.S.A.) with direct injection into APCI source (400 °C) in the positive mode.

## Synthesis

*6-(2,5-Dioxopyrrolidin-1-yl)hexanoic acid (1)*. Was described by Brychtova et al. [4,5].

*Ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (2)*. Was described by Brychtova et al. [4,5].

*Ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (3)*. Morpholine (13.4 mmol) was dissolved in toluene (25 mL) and compound **2** (6.7 mmol) was added. The mixture was refluxed under argon for 5 hours. The solvent was evaporated and the rest was suspended in Et<sub>2</sub>O, solid was filtered off, washed with Et<sub>2</sub>O and the filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH. Yield: 80%. A yellow oil. R<sub>F</sub> 0.53 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5). IR (cm<sup>-1</sup>) 2948 (C–H), 2855 (C–H), 1697 (C=O imide), 1400 (C–N), 1150 (C–O ester), 1114 (C–O morph.). <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ: 4.18 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>), 3.74–3.63 (m, 4H, OCH<sub>2</sub> morph.), 3.50 (t, *J*=7.4 Hz, 2H, NCH<sub>2</sub>), 3.10 (t, *J*=7.4 Hz, 1H, CH), 2.71 (s, 4H, OCCH<sub>2</sub>CH<sub>2</sub>CO), 2.66–2.48 (m, 4H, NCH<sub>2</sub> morph.), 1.80–1.52 (m, 4H, CH<sub>2</sub>), 1.45–1.27 (m, 2H, CH<sub>2</sub>), 1.29 (t, *J*=7.1 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>), δ: 177.07, 171.72, 67.54, 67.38, 60.19, 49.95, 38.57, 28.29, 28.13, 27.38, 23.32, 14.48. HR-MS: for C<sub>16</sub>H<sub>27</sub>O<sub>5</sub>N<sub>2</sub> [M+H]<sup>+</sup> calculated 327.1914 m/z, found 327.1915 m/z [6].

*General procedure, compounds 4a-g*. The mixture of ethyl ester **3** (7.7 mmol), appropriate primary alcohol (38.5 mmol) and metallic sodium (3.85 mmol) was stirred at 90 °C in the oil bath until sodium was dissolved completely, then the mixture was heated at 130 °C for 5 to 7 hours and during the reaction ethanol was distilled off as formed. The excess of longer-chain alkyl alcohol was distilled off under reduced pressure and the rest was extracted with acetic acid (0.5 M) and diethylether, organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by column chromatography on silica gel using ethylacetate/petroleum ether (5:1) as the eluent.

*Hexyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (4a)*. A light yellow oil. Yield 53%. R<sub>F</sub> 0.46 (ethylacetate/petroleum ether 5:1). IR (cm<sup>-1</sup>): 2932 (C–H), 2856 (C–H), 1722 (C=O ester), 1697 (C=O imide), 1401 (C–N), 1149 (C–O ester), 1116 (C–O morph.). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), δ: 4.03 (t, *J*=6.6 Hz, 2H, OCH<sub>2</sub>), 3.63–3.57 (m, 4H, OCH<sub>2</sub> morph.), 3.43 (t, *J*=7.4 Hz, 2H, NCH<sub>2</sub>), 3.03 (t, *J*=7.4 Hz, 1H, CH), 2.63 (s, 4H, O=CCH<sub>2</sub>CH<sub>2</sub>C=O), 2.57–2.47 (m, 4H, NCH<sub>2</sub> morph.), 1.69–1.45 (m, 6H, CH<sub>2</sub>), 1.38–1.15 (m, 8H, CH<sub>2</sub>), 0.82 (t, *J*=6.5 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>), δ: 176.98, 171.70, 67.43, 67.25, 64.27, 49.80, 38.40, 31.20, 28.56, 28.17, 28.01, 27.25, 25.49, 23.20, 22.35, 13.81. HR-MS: for C<sub>20</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup> calculated 383.2540 m/z, found 383.2541 m/z.

*Heptyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (4b)*. A light yellow oil. Yield 55%. R<sub>F</sub> 0.47 (ethylacetate/petroleum ether 5:1). IR (cm<sup>-1</sup>): 2930 (C–H), 2855 (C–H), 1722 (C=O ester), 1698 (C=O imide), 1400 (C–N), 1152 (C–O ester), 1116 (C–O morph.). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), δ: 4.10 (t, *J*=6.6 Hz, 2H, OCH<sub>2</sub>), 3.71–3.65 (m, 4H, OCH<sub>2</sub> morph.), 3.50 (t, *J*=7.4 Hz, 2H, NCH<sub>2</sub>), 3.10 (t, *J*=7.4 Hz, 1H, CH), 2.70 (s, 4H, O=CCH<sub>2</sub>CH<sub>2</sub>C=O), 2.64–2.55 (m, 4H, NCH<sub>2</sub> morph.), 1.76–1.52 (m, 6H, CH<sub>2</sub>), 1.42–1.20 (m, 10H, CH<sub>2</sub>), 0.89 (t, *J*=6.5 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>), δ: 177.06, 171.84, 67.58, 67.39, 64.42, 49.94, 38.56, 31.66, 28.81, 28.74, 28.31, 28.13, 27.39, 25.92, 23.34, 22.52, 13.99. HR-MS: for C<sub>21</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup> calculated 397.2697 m/z, found 397.2696 m/z.

*Octyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (4c)*. A light yellow crystalline compound. Yield 68%.  $R_F$  0.47 (ethylacetate/petroleum ether 5:1). Mp. 40.4–41.6 °C. IR ( $\text{cm}^{-1}$ ): 2930 (C–H), 2854 (C–H), 1718 (C=O ester), 1692 (C=O imide), 1402 (C–N), 1149 (C–O ester), 1117 (C–O morph.).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.11 (t,  $J=6.7$  Hz, 2H,  $\text{OCH}_2$ ), 3.71–3.62 (m, 4H,  $\text{OCH}_2$  morph.), 3.50 (t,  $J=7.4$  Hz, 2H,  $\text{NCH}_2$ ), 3.10 (t,  $J=7.4$  Hz, 1H, CH), 2.70 (s, 4H,  $\text{O=CCH}_2\text{CH}_2\text{C=O}$ ), 2.64–2.55 (m, 4H,  $\text{NCH}_2$  morph.), 1.76–1.52 (m, 6H,  $\text{CH}_2$ ), 1.46–1.23 (m, 12H,  $\text{CH}_2$ ), 0.88 (t,  $J=6.5$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 177.10, 171.87, 67.59, 67.41, 64.45, 49.95, 38.58, 31.76, 29.14, 28.75, 28.33, 28.15, 27.41, 25.98, 23.36, 22.61, 14.05. HR-MS: for  $\text{C}_{22}\text{H}_{38}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$  calculated 411.2853 m/z, found 411.2855 m/z.

*Nonyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (4d)*. A light yellow crystalline compound. Yield 51%.  $R_F$  0.48 (ethylacetate/petroleum ether 5:1). Mp. 42.3–43.1 °C. IR ( $\text{cm}^{-1}$ ): 2916 (C–H), 2850 (C–H), 1728 (C=O ester), 1699 (C=O imide), 1400 (C–N), 1158 (C–O ester), 1117 (C–O morph.).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.10 (t,  $J=6.6$  Hz, 2H,  $\text{OCH}_2$ ), 3.71–3.65 (m, 4H,  $\text{OCH}_2$  morph.), 3.50 (t,  $J=7.4$  Hz, 2H,  $\text{NCH}_2$ ), 3.10 (t,  $J=7.4$  Hz, 1H, CH), 2.70 (s, 4H,  $\text{O=CCH}_2\text{CH}_2\text{C=O}$ ), 2.64–2.55 (m, 4H,  $\text{NCH}_2$  morph.), 1.75–1.52 (m, 6H,  $\text{CH}_2$ ), 1.42–1.20 (m, 14H,  $\text{CH}_2$ ), 0.88 (t,  $J=6.4$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 177.10, 171.86, 67.58, 67.40, 64.45, 49.94, 38.58, 31.82, 29.44, 29.19, 28.75, 28.32, 28.14, 27.40, 25.98, 23.35, 22.63, 14.06. HR-MS: for  $\text{C}_{23}\text{H}_{40}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$  calculated 425.3010 m/z, found 425.3011 m/z.

*Decyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (4e)*. A light yellow crystalline compound. Yield 53%.  $R_F$  0.48 (ethylacetate/petroleum ether 5:1). Mp. 45.5–46.1 °C. IR ( $\text{cm}^{-1}$ ): 2924 (C–H), 2854 (C–H), 1699 (C=O imide, C=O ester), 1400 (C–N), 1155 (C–O ester), 1117 (C–O morph.).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.10 (t,  $J=6.7$  Hz, 2H,  $\text{OCH}_2$ ), 3.71–3.65 (m, 4H,  $\text{OCH}_2$  morph.), 3.50 (t,  $J=7.4$  Hz, 2H,  $\text{NCH}_2$ ), 3.10 (t,  $J=7.4$  Hz, 1H, CH), 2.70 (s, 4H,  $\text{O=CCH}_2\text{CH}_2\text{C=O}$ ), 2.64–2.55 (m, 4H,  $\text{NCH}_2$  morph.), 1.76–1.52 (m, 6H,  $\text{CH}_2$ ), 1.42–1.20 (m, 16H,  $\text{CH}_2$ ), 0.88 (t,  $J=6.4$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 177.06, 171.82, 67.54, 67.36, 64.41, 49.91, 38.53, 31.83, 29.46, 29.23, 29.15, 28.71, 28.28, 28.11, 27.37, 25.95, 23.31, 22.61, 14.04. HR-MS: for  $\text{C}_{24}\text{H}_{42}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$  calculated 439.3166 m/z, found 439.3166 m/z.

*Undecyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (4f)*. A light yellow crystalline compound. Yield 52%.  $R_F$  0.49 (ethylacetate/petroleum ether 7:1). Mp. 48.9–49.7 °C. IR ( $\text{cm}^{-1}$ ): 2924 (C–H), 2853 (C–H), 1699 (C=O imide, C=O ester), 1401 (C–N), 1156 (C–O ester), 1117 (C–O morph.).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.10 (t,  $J=6.7$  Hz, 2H,  $\text{OCH}_2$ ), 3.71–3.65 (m, 4H,  $\text{OCH}_2$  morph.), 3.50 (t,  $J=7.4$  Hz, 2H,  $\text{NCH}_2$ ), 3.10 (t,  $J=7.4$  Hz, 1H, CH), 2.70 (s, 4H,  $\text{O=CCH}_2\text{CH}_2\text{C=O}$ ), 2.64–2.55 (m, 4H,  $\text{NCH}_2$  morph.), 1.76–1.52 (m, 6H,  $\text{CH}_2$ ), 1.42–1.17 (m, 18H,  $\text{CH}_2$ ), 0.88 (t,  $J=6.4$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 177.08, 171.84, 67.57, 67.39, 64.43, 49.93, 38.56, 31.87, 29.55, 29.48, 29.29, 29.17, 28.74, 28.31, 28.13, 27.39, 25.97, 23.34, 22.64, 14.06. HR-MS: for  $\text{C}_{25}\text{H}_{44}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$  calculated 453.3323 m/z, found 453.3323 m/z.

*Dodecyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(morpholin-4-yl)hexanoate (4g)*. A light yellow crystalline compound. Yield 53%.  $R_F$  0.49 (ethylacetate/petroleum ether 7:1). Mp. 52.6–53.4 °C. IR ( $\text{cm}^{-1}$ ): 2919 (C–H), 2852 (C–H), 1717 (C=O ester), 1694 (C=O imide), 1401 (C–N), 1155 (C–O ester), 1117 (C–O morph.).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.10 (t,  $J=6.7$  Hz, 2H,  $\text{OCH}_2$ ), 3.71–3.65 (m, 4H,  $\text{OCH}_2$  morph.), 3.50 (t,  $J=7.4$  Hz, 2H,  $\text{NCH}_2$ ), 3.10 (t,  $J=7.4$  Hz, 1H, CH), 2.70 (s, 4H,  $\text{O=CCH}_2\text{CH}_2\text{C=O}$ ), 2.64–2.55 (m, 4H,  $\text{NCH}_2$  morph.),

1.76–1.52 (m, 6H, CH<sub>2</sub>), 1.42–1.17 (m, 20H, CH<sub>2</sub>), 0.88 (t,  $J=6.4$  Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>),  $\delta$ : 177.09, 171.86, 67.58, 67.39, 64.45, 49.94, 38.57, 31.89, 29.60, 29.55, 29.49, 29.31, 29.19, 28.75, 28.31, 28.14, 27.40, 25.98, 23.35, 22.65, 14.07. HR-MS: for C<sub>26</sub>H<sub>46</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup> calculated 467.3479 m/z, found 467.3480 m/z.

### ***Lipophilicity calculations***

Log *P*, *i.e.* the logarithm of the partition coefficient for *n*-octanol/water, was calculated using the programmes CS ChemOffice Ultra ver. 10.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/ChemSketch ver. 12.01 (Advanced Chemistry Development Inc., Toronto, Canada). Clog *P* values (the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions) were generated by means of the CS ChemOffice Ultra ver. 10.0 (CambridgeSoft, Cambridge, MA, U.S.A.) software. The results are shown in Table 1.

### ***Lipophilicity HPLC determination (capacity factor *k* / calculated log *k*)***

The HPLC separation system Agilent 1200 series instrument was used, equipped with a diode array detection (DAD) system, a quaternary model pump, and an automatic injector (Agilent Technologies, Germany). Data acquisition was performed using the ChemStation chromatography software. The chromatographic column Zorbax Eclipse XDB (Agilent Technologies, Germany), C<sub>18</sub> 5  $\mu$ m, 4.6×150 mm, was used. The mixture of MeOH-HPLC grade (85.0%) and H<sub>2</sub>O-HPLC grade (15.0%) was used as a mobile phase. The total flow of the column was 0.4 mL/min, injection 10  $\mu$ L, column temperature 25 °C. The detection wavelength of 204 nm and the bandwidth of 8 nm were chosen. The KI methanolic solution was used for dead time (*t*<sub>D</sub>) determination. Retention times (*t*<sub>R</sub>) were measured in minutes. The capacity factors *k* were calculated using the ChemStation chromatography software according to the formula  $k = (t_R - t_D) / t_D$ , where *t*<sub>R</sub> is the retention time of the solute, whereas *t*<sub>D</sub> denotes the dead time obtained via an unretained analyte. Log *k*, calculated from the capacity factor *k*, is used as a lipophilicity index converted to the log *P* scale [10]. The log *k* values of the individual compounds are shown in Table 1.

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