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Synthesis of Esters of Substituted 6-Aminohexanoic 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 substituted 6-aminohexanoic 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 ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

INTRODUCTION

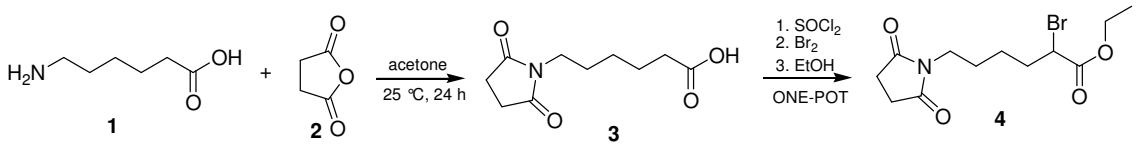
Transdermal penetration enhancers (also called sorption promoters or accelerants) are special pharmaceutical excipients that interact with skin components to increase penetration of drugs from the topical dosage forms to blood circulation. Numerous compounds have been evaluated as penetration enhancers and many potential sites and modes of action have been identified for them [1]. Some of the important penetration enhancers as classified Sinha and Kaur [2] 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 paper describes a multistep synthesis of seven alkyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoates with C_6–C_{12} linear alkyl ester chains.

RESULTS AND DISCUSSION

6-Aminohexanoic acid (**1**) and succinic anhydride (**2**) as starting materials for multistep synthesis were used, and by their reaction 6-(2,5-dioxopyrrolidin-1-yl)hexanoic acid (**3**) was obtained. Under optimised Schwenk and Papa procedure [3, 4] acid **3** in one-pot synthesis gave ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**4**).
As the critical step of synthesis has been found out the C–N nucleophilic coupling of pyrrolidin-2-one and ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**4**). This C–N bond-forming reaction of α-bromocarboxylic compound **4** and 5-membered ω-lactam ring was carried out under catalysis by powdered copper(I) oxide and ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (**5**) was obtained.

The series of seven targeted alkyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoates (**6a-g**) was formed by conventional base-catalyzed transesterification [5] of the key intermediate **5** in the excess of corresponding primary unbranched alcohol.

Scheme



Compound	R
6a	C_6H_{13}
6b	C_7H_{15}
6c	C_8H_{17}
6d	C_9H_{19}
6e	$C_{10}H_{21}$
6f	$C_{11}H_{23}$
6g	$C_{12}H_{25}$

EXPERIMENTAL

6-(2,5-Dioxopyrrolidin-1-yl)hexanoic acid (**3**). To a suspension of 6-aminohexanoic acid (**1**) (34.4 g, 262.0 mmol) in acetone (140 mL) was added dropwise a solution of succinic anhydride (**2**) (45.0 g, 450.0 mmol) in acetone (230 mL). The reaction mixture was stirred at room temperature for 24 hours after which it was filtered and the pure white powder product was washed with acetone. Yield: 82%. M.p. 100–102 °C. ^{1}H NMR (500 MHz, DMSO), δ: 12.05 (s, 1H, OH), 3.02 (t, 2H, J = 7.0 Hz, N–CH_2), 2.90 (s, 4H, O=CH_2–CH_2=O), 2.41 (t, 2H, J = 6.0 Hz, OOC–CH_2), 2.32–2.15 (m, 4H, CH_2), 1.52–1.24 (m, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO), δ: 174.25, 173.66, 38.27, 33.52, 28.72, 28.62, 25.83, 24.11. IR (cm^{-1}) 3315, 2929, 1688, 1560, 1414, 1250, 1183.

Ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**4**). To the organic acid **3** (45.8 g, 214.8 mmol), held at 30 °C, thionyl chloride (29.4 g, 247.0 mmol, 17.9 mL) was added slowly dropwise and the mixture was stirred at 60-80 °C until the gas evolution essentially stopped. At 80 °C Br_2 (36.1 g, 225.5 mmol, 11.6 mL) was added dropwise at approximately the rate that the Br_2 was consumed. Stirring continued for several hours until the evolution of HBr nearly stopped. Absolute ethanol (27 mL) was added slowly to the crude acid chloride at 20–30 °C. After stirring overnight, the mixture was evaporated until dry under vacuum and the residue was dissolved in diethyl ether (50 mL). The solution was washed with dilute $NaHSO_3$ and water, the organic layer was dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under rotary evaporation. The crude product (yield: 94.2%) was purified by vacuum distillation using a Vigreux column (b.p. 160–165 °C/ 0.35 mbar) to yield 55.9 g (81%) colourless oil, R_F 0.44 (propan-2-ol 100%), ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.16 (q, 2H, J = 7.0 Hz, O–CH_2), 4.11 (t, 1H, J = 7.3 Hz, Br–CH), 3.44 (t, 2H, J = 7.2 Hz, N–CH_2), 2.64 (s, 4H, O=CH_2–CH_2=O), 1.99 (q, 2H, J = 7.3 Hz, CH–CH_2), 1.54 (qi, 2H, J = 7.0 Hz, CH_2), 1.43–1.15(m, 2H, CH_2), 1.23 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 176.94, 169.43, 61.84, 45.63, 38.23, 34.17, 28.08, 26.77, 24.43, 13.82. IR (cm^{-1}) 2939, 1730, 1692, 1436, 1399, 1143, 818.

Ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (**5**). Pyrrolidin-2-one (4.0 g, 46.9 mmol) was added slowly to a suspension of NaH (51.5 mmol, 60% dispersion in mineral oil) in dry DMF (100 mL). The mixture was stirred for a few minutes until the evolution of hydrogen gas stopped. Compound **3** (10.0 g, 31.2 mmol) and Cu_2O (1.1 g, 7.8 mmol) were then added, and the mixture was refluxed under argon for 9 hours. The cooled mixture was poured onto ice, filtered and extracted with chloroform. The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under rotary evaporation. The crude product was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether 3:1) provided a light yellow oil, yield 6.7 g (66%). R_F 0.45 (propan-2-ol 100%). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.66 (dd, 1H, J^1 = 5.0 Hz, J^2 = 10.6 Hz, CH), 4.16 (q, 2H, J = 7.1 Hz, O–CH_2), 3.50 (t, 2H, J = 7.2 Hz, N–CH_2), 3.54–3.29 (m, 2H, CH_2pyrr.), 2.70 (s, 4H, O=CH_2–CH_2=O), 2.42 (t, 2H, J = 8.0 Hz, CH_2pyrr.), 2.17–1.95 (m, 2H, CH_2pyrr. and 1H from CH_2–CH), 1.78–1.56 (m, 2H, CH_2 and 1H from CH_2–CH), 1.34–1.28 (m, 2H, CH_2), 1.26 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.13, 175.78, 170.76, 61.12, 53.51, 43.53, 38.26, 30.73, 28.08, 27.03, 23.35, 18.21, 14.07. IR (cm^{-1}) 2927, 1767, 1687, 1401, 1284, 1187, 1153, 1027.

General procedure for preparation alkyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoates (6a-g). The mixture of ethyl ester **5** (7.7 mmol), appropriate primary alcohol (38.5 mmol) and metallic sodium (3.85 mmol) was stirred at 90 °C in an 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 $MgSO_4$, 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-(2-oxopyrrolidin-1-yl)hexanoate (6a). Light yellow oil, yield 62 %, R_F 0.27 (ethylacetate/petroleum ether 5:1). ^{1}H NMR (200 MHz, *CDCl₃*) δ: 4.70 (dd, J = 10.61, 4.79 Hz, 1H, CH), 4.06 (t, J = 6.61 Hz, 2H, $COOCH_2$), 3.52–3.24 (m, 2H, CH_2pyrr.), 3.46 (t, J = 6.98 Hz, 2H, NCH_2), 2.68 (s, 4H, $COCH_2$), 2.40 (t, J = 7.95 Hz, 2H, CH_2pyrr.), 2.15–1.85 (m, 4H, CH_2pyrr., $CHCH_2$), 1.77–1.51 (m, 4H, CH_2), 1.35–1.18 (m, 8H, CH_2), 0.86 (t, J = 6.15 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, *CDCl₃*) δ: 184.46, 177.23, 170.82, 65.33, 53.55, 43.56, 38.28, 31.34, 30.75, 28.50, 28.39, 28.10, 27.05, 25.43, 22.42, 20.63, 18.21, 13.89. IR (cm^{-1}) 3300, 2980, 1848, 1736, 1688, 1592, 1448, 1336, 1272, 1192, 1096, 920, 712, 632.

Heptyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (6b). Light yellow oil, yield 59 %, R_F 0.28 (ethylacetate/petroleum ether 5:1). ^{1}H NMR (200 MHz, *CDCl₃*) δ: 4.67 (dd, J = 10.70, 4.97 Hz, 1H, CH), 4.03 (t, J = 6.59 Hz, 2H, $COOCH_2$), 3.44 (t, J = 7.22 Hz, 2H, NCH_2), 3.36 (dq, J = 15.40, 9.27 Hz, 2H, CH_2pyrr.), 2.65 (s, 4H, $COCH_2$), 2.37 (t, J = 7.84 Hz, 2H, CH_2pyrr.), 2.08–1.82 (m, 4H, CH_2pyrr., $CHCH_2$), 1.75–1.45 (m, 4H, CH_2), 1.30–1.19 (m, 10H, CH_2), 0.83 (t, J = 6.60 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, *CDCl₃*) δ: 177.13, 175.66, 170.78, 65.25, 53.46, 43.47, 38.22, 31.53, 30.69, 28.69, 28.38, 28.05, 27.00, 25.68, 23.31, 22.41, 18.16, 13.90. IR (cm^{-1}) 3380, 3020, 1768, 1736, 1672, 1640, 1432, 1352, 1192, 1160, 1032, 808, 632.

Octyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (6c). Light yellow oil, yield 62 %, R_F 0.25 (ethylacetate/petroleum ether 5:1). ^{1}H NMR (200 MHz, *CDCl₃*) δ: 4.71 (dd, J = 10.74, 4.92 Hz, 1H, CH), 4.06 (t, J = 6.67 Hz, 2H, $COOCH_2$), 3.47 (t, J = 7.23 Hz, 2H, NCH_2), 3.39 (dq, J = 15.34, 7,7 Hz, 2H, CH_2pyrr.), 2.69 (s, 4H, $COCH_2$), 2.41 (t, J = 7.90 Hz, 2H, CH_2pyrr.), 2.11–1.86 (m, 4H, CH_2pyrr., $CHCH_2$), 1.76–1.48 (m, 4H, CH_2), 1.33–1.20 (m, 12H, CH_2), 0.86 (t, J = 6.40 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, *CDCl₃*) δ: 177.13, 175.68, 170.87, 65.33, 54.45, 53.59, 43.57, 38.33, 31.70, 30.77, 29.08,

28.50, 28.19, 28.13, 27.10, 25.82, 23.42, 22.56, 18.27, 13.99. IR (cm^{-1}) 3380, 1688, 1592, 1512, 1432, 1320, 1160, 1096, 984, 824, 632.

Nonyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (6d). Light yellow oil, yield 55 %, R_F 0.25 (ethylacetate/petroleum ether 5:1). ^{1}H NMR (200 MHz, *CDCl$_3$*) δ: 4.71 (dd, *J* = 10.78, 4.92 Hz, 1H, CH), 4.07 (t, *J* = 6.72 Hz, 2H, $COOCH_2$), 3.48 (t, *J* = 7.24 Hz, 2H, NCH_2), 3.39 (dq, *J* = 15.34, 7,7 Hz, 2H, CH_2pyrr.), 2.69 (s, 4H, $COCH_2$), 2.41 (t, *J* = 8.11 Hz, 2H, CH_2pyrr.), 2.12–1.86 (m, 4H, CH_2pyrr., $CHCH_2$), 1.79–1.52 (m, 4H, CH_2), 1.33–1.21 (m, 14H, CH_2), 0.86 (t, *J* = 6.40 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, *CDCl$_3$*) δ: 177.21, 175.75, 170.89, 65.36, 53.54, 43.54, 38.33, 31.79, 30.79, 29.41, 29.17, 28.48, 28.14, 27.11, 25.82, 23.42, 22.61, 18.26, 14.06. IR (cm^{-1}) 3380, 3020, 1816, 1736, 1672, 1592, 1528, 1432, 1352, 1288, 1192, 1160, 1032, 856, 824, 728, 632.

Decyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (6e). Light yellow oil, yield 58 %, R_F 0.23 (ethylacetate/petroleum ether 5:1). ^{1}H NMR (200 MHz, *CDCl$_3$*) δ: 4.69 (dd, *J* = 10.71, 4.94 Hz, 1H, CH), 4.05 (t, *J* = 6.59 Hz, 2H, $COOCH_2$), 3.45 (t, *J* = 7.22 Hz, 2H, NCH_2), 3.37 (dq, *J* = 15.39, 9.27 Hz, 2H, CH_2pyrr.), 2.67 (s, 4H, $COCH_2$), 2.38 (t, *J* = 7.98 Hz, 2H, CH_2pyrr.), 2.09–1.84 (m, 4H, CH_2pyrr., $CHCH_2$), 1.77–1.50 (m, 4H, CH_2), 1.31–1.15 (m, 16H, CH_2), 0.84 (t, *J* = 6.40 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, *CDCl$_3$*) δ: 177.09, 175.65, 170.85, 65.31, 53.58, 43.56, 38.31, 31.80, 30.75, 29.43, 29.20, 29.11, 28.49, 28.12, 27.08, 25.80, 23.40, 22.58, 18.26, 13.99. IR (cm^{-1}) 3380, 2980, 1752, 1688, 1592, 1432, 1272, 1160, 1080, 840, 728.

Undecyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (6f). Light yellow oil, yield 54 %, R_F 0.24 (ethylacetate/petroleum ether 7:1). ^{1}H NMR (200 MHz, *CDCl$_3$*) δ: 4.70 (dd, *J* = 10.70, 4.96 Hz, 1H, CH), 4.06 (t, *J* = 6.57 Hz, 2H, $COOCH_2$), 3.53–3.24 (m, 2H, CH_2pyrr.), 3.47 (t, *J* = 7.22 Hz, 2H, NCH_2), 2.68 (s, 4H, $COCH_2$), 2.40 (t, *J* = 7.90 Hz, 2H, CH_2pyrr.), 2.11–1.78 (m, 4H, CH_2pyrr., $CHCH_2$), 1.74–1.52(m, 4H, CH_2),1.33–1.17 (m, 18H), 0.86 (t, *J* = 6.45 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, *CDCl$_3$*) δ: 177.05, 175.60, 170.89, 65.33, 53.67, 43.62, 38.36, 31.86, 30.78, 29.53, 29.45, 29.25, 29.15, 28.56, 28.25, 28.15, 27.13, 25.85, 23.45, 22.61, 18.31, 13.99. IR (cm^{-1}) 3379, 3020, 1736, 1672, 1592, 1528, 1432, 1352, 1288, 1192, 1160, 1032, 824, 632.

Dodecyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (6g). Light yellow oil, yield 56 %, R_F 0.24 (ethylacetate/petroleum ether 7:1). ^{1}H NMR (200 MHz, *CDCl$_3$*) δ: 4.71 (dd, *J* = 10.77, 4.84 Hz, 1H, CH), 4.06 (t, *J* = 6.72 Hz, 2H, $COOCH_2$), 3.53–3.24 (m, 2H, CH_2pyrr.), 3.47 (t, *J* = 7.25 Hz, 2H, NCH_2), 2.69 (s, 4H, $COCH_2$), 2.40 (t, *J* = 7.97 Hz, 2H, CH_2pyrr.), 2.11–1.86 (m, 4H, CH_2pyrr., $CHCH_2$), 1.78–1.50 (m, 4H, CH_2), 1.40–1.15 (m, 20H), 0.86 (t, *J* = 6.35 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, *CDCl$_3$*) δ: 177.08, 175.64, 170.87, 65.34, 53.65, 43.62, 38.35, 35.35, 31.87, 30.78, 29.58, 29.53, 29.46, 29.28, 29.15, 28.55, 28.23, 28.15, 27.12, 25.85, 23.44, 22.62, 18.31, 14.01. IR (cm^{-1}) 3380, 2940, 1752, 1672, 1624, 1592, 1432, 1272, 1192, 1160, 1016, 952, 904, 824, 744, 648.

CONCLUSION

In this work series of seven alkyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoates with C_6–C_{12} linear alkyl ester chain as potential transdermal penetration enhancers were prepared. Biological activities of these newly synthesized compounds are under further investigation.

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