Prodrug ionic liquids: functionalizing neutral active pharmaceutical ingredients to take advantage of the ionic liquid form

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Table of Contents

1. Materials and Methods

Chemicals. All chemicals unless otherwise stated were purchased from Sigma-Aldrich Chemical Company (Saint Louis, MO) in reagent grade ≥98% and used without further purification. Deionized water used in the buffer preparation and synthesis was obtained with a specific resistivity of 17.25 MΩ·cm at 25 °C from a commercial deionizer by Culligan (Northbrook, IL).

Nuclear Magnetic Resonance Spectroscopy (NMR). ^{1}H and ^{13}C NMR spectra were collected utilizing a Bruker (Madison, WI) spectrometer 500 MHz Bruker Avance Spectrometer Bruker/Magnex UltraShield 500 MHz magnet operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C spectra, respectively.

Thermogravimetrical Analysis (TGA). TGA experiments were performed on a TA Instruments (New Castle, DE) model 2950 Thermogravimetric Analyzer under a stream of nitrogen. Samples between 5 and 10 mg were placed on a platinum pan and were heated from 25 °C to 800 °C with a constant heating rate of 5 °C/min and with a 30 min isotherm at 75 °C to remove any remaining volatiles. Decomposition temperatures ($T_{5\%onset}$) were reported as the onset temperature with respect to the initial 5 wt% mass loss.

Differential Scanning Calorimetry (DSC). Thermal transitions were measured on a Mettler Toledo Star DSC unit (samples **2**, **3**, **4**, **5**, **7**, **8**) (Leicester, UK) or a Mettler Toledo DSC1 Star unit (sample **6**) under a stream of nitrogen. Samples (5-10 mg) were placed in closed aluminum pan perforated with a pin-hole. A typical cycle consisted of initially heating the samples from 25 to 110 °C at a heating rate of 5 °C/min, a 5 min isotherm, cooling at a rate of 5 °C/min to -70 °C, and a final 5 min isotherm at -70 °C. Sample **6** (~7.5 mg) was heated between 25-70 °C with a heating rate of 5 °C/min followed by a 15 min isotherm and then cooled with a cooling rate of 5 °C/min to -50 °C followed by a 15 min isotherm at -50 °C. The cycle was repeated twice to ensure consistency of the observed thermal transitions.

Single Crystal X-ray Diffraction. Data were collected on a Bruker diffractometer with an Apex II CCD area detector equipped with a low-temperature device, using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were measured at 173 K (-100 °C) using a strategy of omega scans of 0.5° per frame. Data collection, integration, and absorption corrections were performed using the APEX2[1] software suite from Bruker and SADABS.[2] Structure solution and refinement were conducted using the SHELXTL[3] software package from Bruker. Packing diagrams for the structures were made using Mercury from the Cambridge Crystallographic Data Center.[4] The two structures were solved by direct methods. Non-hydrogen atoms in all structures were located from the difference map and refined anisotropically through least squares refinement against F^2. Hydrogen atoms were placed in calculated positions and allowed to ride on the carrier atom. Hydrogen atoms on methyl groups were refined using a riding rotating model. The X-ray crystallographic information file can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: data_request@ccdc.cam.ac.uk). CCDC 908447 and 908448 contain the supplementary crystallographic data for the structures described in this paper.

2. Buffer Preparation

The solutions of SIF and SGF (without the added enzymes) were prepared in accordance with the United States Pharmacopeia (USP) guidelines, while the PBS solution was prepared from the commercially available tablets sold by Sigma-Aldrich (Saint Louis, MO).

Preparation of phosphate buffer saline (pH = 7.4). Phosphate buffer saline solution was prepared by dissolving 1 tablet (commercially available and sold by Sigma-Aldrich Chemical Company (Saint Loius, MO)) in 200 mL deionized water.

Preparation of simulated intestinal fluid (pH = 6.8) without added pancreatin.[5] In a 100 mL volumetric flask, 0.6805 g KH_2PO_4, and 0.0896 g NaOH were weighed accurately and and diluted to volume with deionized water to get 100 mL solution.

Preparation of simulated gastric fluid (pH = 1.2) without added pepsin.[6] In a 100 mL volumetric flask, 0.200 g NaCl, and 0.7 mL concentrated HCl (to adjust to pH = 1.2) were dissolved and diluted to volume with deionized water to get 100 mL solution.

3. Synthesis of Prodrug Ionic Liquid Precursors and Prodrug Ionic Liquids

4-Acetamidophenyl 2-chloroacetate (1).[7] Acetominophen (15.117 g, 50 mmol) and pyridine (7.910 g, 50 mmol) were suspended in anhydrous acetone (200 mL) and chilled to 0 °C under an atmosphere of dry nitrogen. Chloroacetyl chloride (11.290 g, 50 mmol) was added dropwise (due to the violent nature of the reaction) and the resulting solution was warmed to RT and then stirred for an additional 2 h at room temperature. Water (300 mL) was added and the mixture was heated until a clear solution was obtained. The product precipitated upon cooling and was collected *via* filtration, washed with water, and dried under reduced pressure (0.01 mbar, 50 °C) to yield colorless needles. Yield: 72%. ^{1}H NMR (dmso-d_6): 10.04 (s, 1H); 7.62 (d, 2H); 7.10 (d, 2H); 4.68 (s, 2H); 2.04 (s, 3H). ^{13}C NMR (dmso-d_6): 168.33; 166.55; 145.30; 137.35; 121.61; 119.94; 41.29; 23.92. T_m = 206 °C (dec), $T_{5\%onset}$= 199 °C.

1-(2-(4-acetamidophenoxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride (2). 4-Acetamidophenyl 2-chloroacetate (1.138 g, 5 mmol) and *N*-methylimidazole (0.492 g, 6 mmol) were suspended in 50 mL of anhydrous ethyl acetate and refluxed for 48 h. After cooling to room temperature the white precipitate was filtered, washed with ethyl acetate followed by diethyl ether and dried under reduced pressure to give 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride as a white powder. Yield: 79%. ^{1}H NMR (dmso-d_6):10.54 (s, 1H); 9.38 (s, 1H); 7.91 (s, 1H); 7.81 (s, 1H); 7.72 (d, 2H); 7.12 (d, 2H); 5.62 (s, 2H); 3.94 (s, 3H); 2.07 (s, 3H). ^{13}C NMR (dmso-d_6): 168.45; 166.06; 144.90; 137.86; 137.66; 123.76; 123.46; 121.42; 119.88; 49.71; 36.00; 23.89. T_m = 206 °C (dec), $T_{5\%onset}$= 200 °C.

1-(2-(4-acetamidophenoxy)-2-oxoethyl)-1-methylpyrrolidinium chloride (3). 4-Acetamidophenyl 2-chloroacetate (1.138 g, 5 mmol) and *N*-methylpyrrolidine (0.511 g, 6 mmol) were suspended in 50 mL of anhydrous ethyl acetate and refluxed for 48 h. After cooling to room temperature the white precipitate was filtered, washed with ethyl acetate and diethyl ether and dried under reduced pressure to give 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-1-methylpyrrolidinium chloride as white powder. Yield: 97%. ^{1}H NMR (dmso-d_6):10.54 (s, 1H); 7.73 (d, 2H); 7.18 (d, 2H); 4.95 (s, 2H); 3.77 (m, 4H); 3.28 (s, 3H); 2.14 (m, 4H); 2.07 (s, 3H). ^{13}C NMR (dmso-d_6): 168.96; 164.97; 144.87; 138.87; 122.02; 120.32; 65.54; 62.09; 49.79; 24.36; 21.83. DEPT135 (dmso-d_6): 122.03 (pos); 120.32 (pos); 65.53 (neg); 62.07 (neg); 49.77 (pos); 24.36 (pos); 21.82 (neg). T_m = 186 °C (dec), $T_{5\%onset}$= 197 °C.

1-(2-(4-acetamidophenoxy)-2-oxoethyl)pyridinium chloride (4). 4-Acetamidophenyl 2-chloroacetate (1.138 g, 5 mmol) and pyridine (0.475 g, 6 mmol) were suspended in 50 mL

of anhydrous ethyl acetate and refluxed for 48 h. After cooling to room temperature the white precipitate was filtered, washed with ethyl acetate and diethyl ether and dried under reduced pressure to give 1-(2-(4-acetamidophenoxy)-2-oxoethyl)pyridinium chloride as a white powder. Yield: 97%. ^{1}H NMR (dmso-d_6): 10.57 (s, 1H); 9.32 (d, 2H); 8.75 (t, 1H); 8.29 (t, 2H); 7.71 (d, 2H); 7.19 (d, 2H); 6.09 (s, 2H); 2.06 (s, 3H). ^{13}C NMR (dmso-d_6): 168.75; 166.04; 147.35; 146.83; 145.60; 138.07; 128.25; 121.90; 120.29; 41.68; 24.27. T_m = 199 °C (dec), $T_{5\%onset}$= 198 °C.

(2-(4-acetamidophenoxy)-2-oxoethyl)tributylphosphonium chloride (5). 4-Acetamidophenyl 2-chloroacetate (1.138 g, 5 mmol) and tributylphosphine (0.475 g, 6 mmol) were suspended in 50 mL of anhydrous ethyl acetate and refluxed for 48 h. After cooling to room temperature the white precipitate was filtered, washed with ethyl acetate and diethyl ether and dried under reduced pressure to give (2-(4-acetamidophenoxy)-2-oxoethyl)tributylphosphonium chloride. The crude product was crystallized twice from acetonitrile to give (2-(4-acetamidophenoxy)-2-oxoethyl)tributylphosphonium chloride as white powder. Yield: 65%. ^{1}H NMR (dmso-d_6): 10.49 (s, 1H); 7.70 (d, 2H); 7.13 (d, 2H); 4.18 (d, 2H); 2.38 (m, 6H); 1.54 (m, 6H); 1.40 (m, 6H); 0.91 (t, 9H). ^{13}C NMR (dmso-d_6): 168.44; 164.60 (d); 144.81; 137.79; 121.43; 119.90; 23.87; 23.29 (d); 22.64 (d); 18.24 (d); 13.22. ^{31}P NMR (dmso-d_6): 34.84. T_m = 199 °C (dec), $T_{5\%onset}$= 197 °C.

General procedure for the synthesis of docusates 6-9. The corresponding chloride (1 mmol) and silver docusate (1 mmol) were suspended in 50 mL of anhydrous methanol and stirred in the dark at room temperature for 15 min. The suspension was filtered over Celite and the filtrate was evaporated <40 °C. Remaining volatile material was removed under reduced pressure (0.01 mbar, 40 °C) to yield the corresponding docusate product.

1-(2-(4-acetamidophenoxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium docusate (6). Yellow oil. Yield: quantitative. ^{1}H NMR (dmso-d_6): 10.11 (s, 1H); 9.20 (s, 1H); 7.87 (s, 1H); 7.82 (s, 1H); 7.70 (d, 2H); 7.20 (d, 2H); 5.56 (s, 2H); 3.98 (s, 3H); 3.94 (m, 4H); 3.69 (dd, 1H); 2.90 (m, 2H); 2.10 (s, 3H); 1.28 (m, 18H); 0.88 (m, 12H). ^{13}C NMR (dmso-d_6): 171.39; 168.73; 168.69; 166.36; 145.31; 138.20; 137.85; 124.13; 123.87; 121.84; 120.24; 66.55; 66.48; 66.45; 66.42; 61.82; 50.03; 38.53; 38.48; 38.45; 34.47; 30.09; 29.96; 29.91; 28.69; 24.27; 23.54; 23.52; 23.36; 23.34; 22.77; 22.74; 14.26; 14.23; 11.16; 11.13; 11.09. T_g= -33 °C; $T_{5\%onset}$= 217 °C.

1-(2-(4-acetamidophenoxy)-2-oxoethyl)-1-methylpyrrolidinium docusate (7). Yellow oil. Yield: quantitative. ^{1}H NMR (dmso-d_6): 10.1 (s,1H); 7.67 (d, 2H); 7.18 (d, 2H); 4.82 (s, 2H); 3.88 (m, 4H); 3.72 (m, 4H); 3.65 (dd, 1H); 3.25 (s, 3H); 2.89 (m, 2H); 2.14 (m, 4H); 2.05 (s, 3H); 1.50 (m, 2H); 1.26 (m, 16H); 0.82 (m, 12H). ^{13}C NMR (dmso-d_6): 170.99; 168.36; 164.44; 144.47; 137.68; 121.63; 119.81; 66.25; 66.18; 66.07; 65.16; 61.61; 61.48; 49.42; 38.17; 38.13; 38.10; 34.08; 29.73; 29.62; 29.56; 28.33; 23.89; 23.17; 23.16; 22.99; 22.40; 22.38; 21.42; 13.87; 13.85; 10.77; 10.74; 10.70. T_g= -21 °C; $T_{5\%onset}$= 233 °C.

1-(2-(4-acetamidophenoxy)-2-oxoethyl)pyridinium docusate (8). Yellow glass. Yield: quantitative. ^{1}H NMR (dmso-d_6): 10.08 (s, 1H); 9.15 (d, 2H); 8.74 (t, 1H); 8.28 (t, 2H); 7.65 (d, 2H); 7.18 (d, 2H); 5.93 (s, 2H); 3.88 (m, 4H); 3.66 (dd, 1H); 2.86 (m 2H); 2.04 (s, 3H); 1.26 (m, 18H); 0.82 (m, 12H). ^{13}C NMR (dmso-d_6): 171.03; 168.38; 168.35; 165.59; 147.02; 146.46; 144.94; 137.59; 127.93; 127.45; 121.47; 119.86; 66.22; 66.16; 66.12; 66.06; 61.46; 60.41; 38.17; 38.13; 38.10; 34.11; 29.73; 29.61; 29.56; 28.33; 23.91; 23.20; 23.17; 22.99; 22.41; 22.38; 13.90; 13.88; 10.81; 10.77; 10.73. T_g= 25 °C; $T_{5\%onset}$= 238 °C

(2-(4-acetamidophenoxy)-2-oxoethyl)tributylphosphonium docusate (9). Yellow oil. Yield: quantitative. ^{1}H NMR (dmso-d_6): 10.07 (s, 1H); 7.64 (s, 2H); 7.14 (s, 2H); 4.07 (d, 2H); 3.88 (s, 4H); 3.62 (s, 1H); 2.84 (m, 2H); 2.36 (s, 6H); 2.04 (s, 3H); 1.49 (m, 14H); 1.23 (m, 16H); 0.89 (m, 21H). ^{13}C NMR (dmso-d_6): 168.40; 166.10; 144.90; 137.90; 137.70; 123.80; 123.50; 121.40; 119.90; 49.70; 36.00; 23.90. T_g= -17 °C; $T_{5\%onset}$= 227 °C.

4. X-ray Crystallographic Structures of 3 and 5

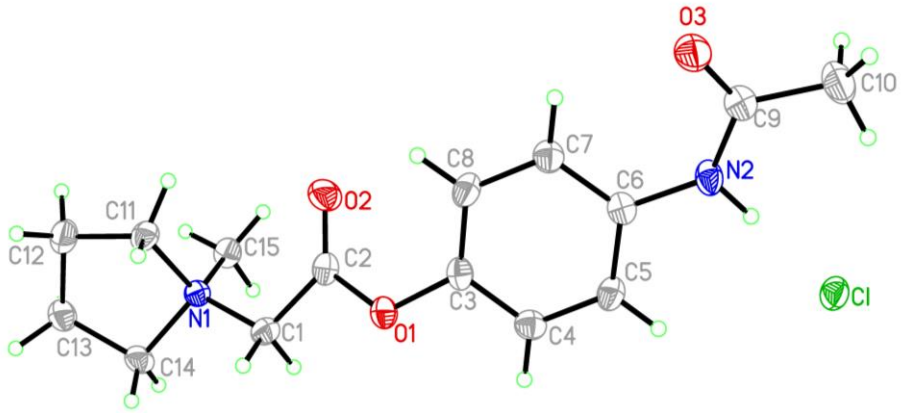


Fig. S1 Thermal ellipsoid plot of 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-1-methylpyrrolidinium chloride (**3**) (50% probability ellipsoids).

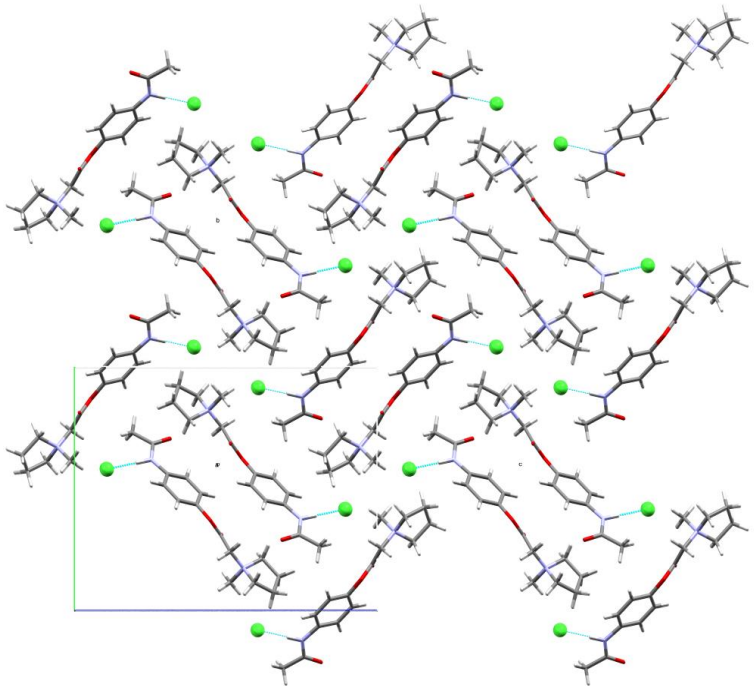


Fig. S2 Packing diagram of **3** viewed down the *a* axis.

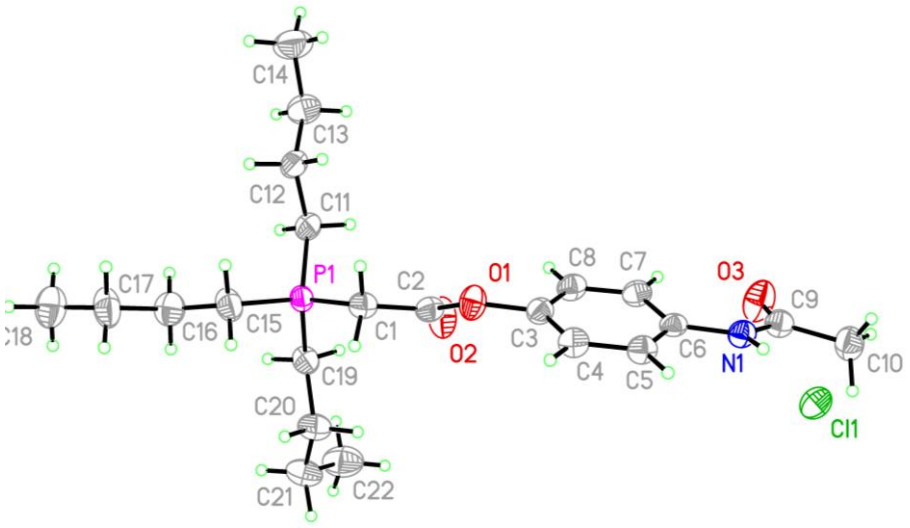


Fig. S3 Thermal ellipsoid plot of (2-(4-acetamidophenoxy)-2-oxoethyl)tributylphosphonium chloride **5** (50% probability ellipsoids).

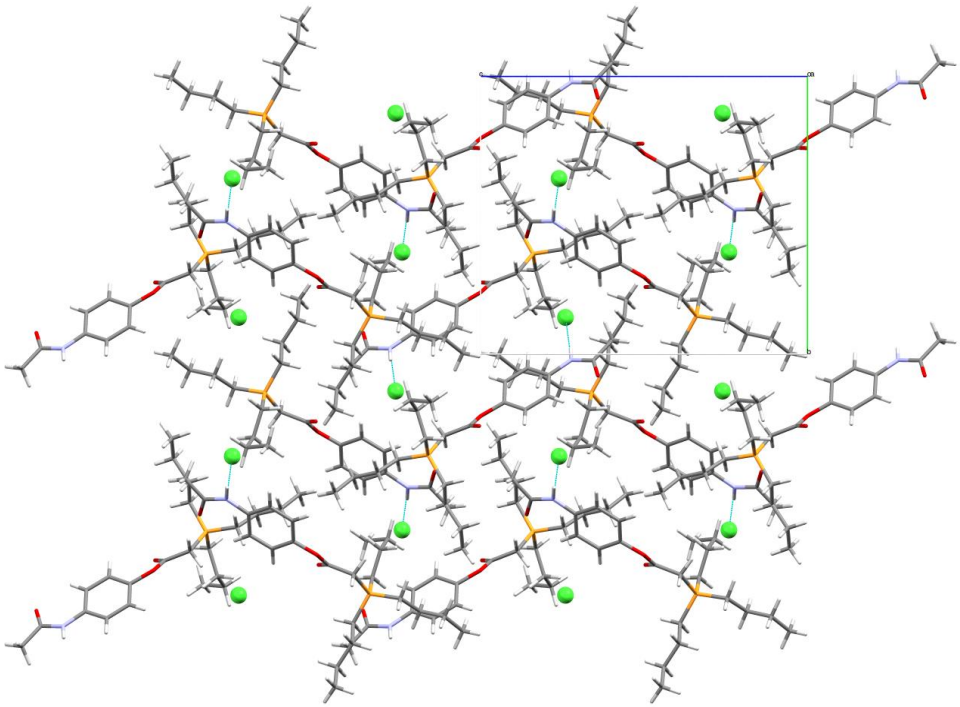
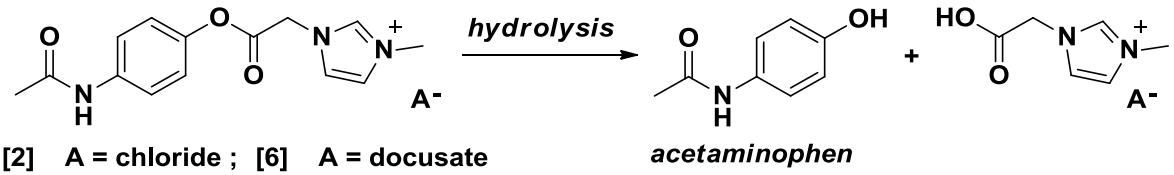


Fig. S4 Packing diagram of **5** viewed down the *a* axis.

5. Comparison of a 0.1 M PBS solution of chloride 2 vs. a 0.1 M PBS emulsion of docusate 6

Fig. S5 A 0.1 M PBS solution of chloride **2** (left) *vs.* a 0.1 M PBS emulsion of docusate **6** (right)

6. Hydrolysis of compounds 2 and 6.



Scheme S1 Hydrolysis of compounds **2** and **6**.

7. Thermal analysis

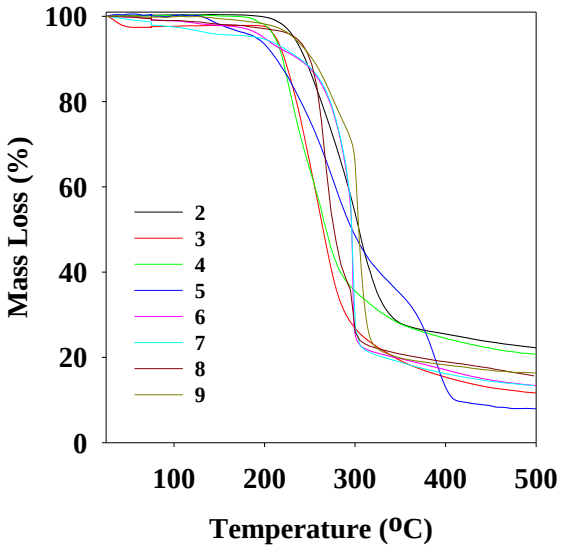


Fig. S6 TGA plots for acetaminophen prodrugs **2-9**

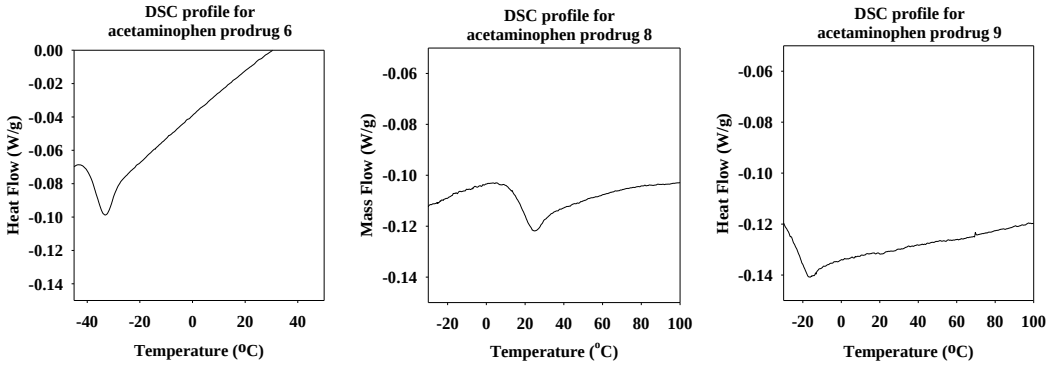


Fig. S7 DSC profiles for acetaminophen prodrugs **6**, **8**, and **9**

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