1. Experimental

**Materials.** Ibuprofen sodium, ephedrine, phosphate buffered saline (PBS), ethanol (95%), and HPLC grade acetic acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). Lidocaine hydrochloride and lidocaine were supplied by Spectrum Chemical Mfg. Corp. (Garden, CA, USA). Bupivacaine hydrochloride was supplied by MP Biomedicals, LLC (Santa Ana, CA, USA), and 4-tert-butylbenzoic acid was from Alfa Aesar (Ward Hill, MA, USA). HPLC grade acetonitrile (CH$_3$CN) and methanol were purchased from Fisher Scientific (Pittsburgh, PA, USA). Deuterated DMSO (DMSO-$d_6$) was purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). All the above mentioned chemicals were used as received without further purification.

The Franz diffusion cell system was purchased from PermeGear, Inc. (Hellertown, PA, USA). The model silicone membrane, with a thickness of 0.01 inch, was supplied by Specialty Manufacturing Inc. (Saginaw, MI, USA). Deionized (DI) water was obtained from a commercial deionizer (Culligan, Northbrook, IL, USA) with a specific resistivity of 16.82 MΩ·cm at 25 °C.
Re-distilled water for membrane transport experiments and liquid chromatography–mass spectrometry (LC-MS) was with a specific resistivity of 18.00 MΩ·cm at 25 °C.

Synthesis of ibuprofen free acid, [P4444][Ibu], [Lid][Ibu], [Lid]m[Ibu]n, and [Eph][Ibu]

Ibuprofen free acid: 15 mmol [Na][Ibu] was dissolved in 20 mL DI water. HCl solution (2 M, 7.5 mL, containing 15 mmol HCl), was added dropwise to the [Na][Ibu] solution. The mixture was stirred at room temperature for 2 h. The produced ibuprofen was not soluble in water and precipitated from the solution. The precipitate was separated by filtration, washed with DI water twice (100 mL x 2), and dried in an oven (Precision Econotherm Laboratory Oven, Natick, MA) at 65 °C for 72 h. (1H NMR (500 MHz, DMSO-d6): 12.26 (s, 1H); 7.18 (d, 2H); 7.12 (d, 2H); 3.64 (q, 1H); 2.41 (d, 2H); 1.82 (m, 1H); 1.36 (d, 3H); 0.87 (d, 6H); Tm = 74.1 °C.)

[P4444][Ibu] and [Lid][Ibu]: Procedures for synthesizing [P4444][Ibu] (ca. 4 g) and [Lid][Ibu] (ca. 4 g) followed our previous work. Both [P4444][Ibu] and [Lid][Ibu] are liquids at room temperature. Spectroscopic characterization (NMR and FT-IR) indicated that these two compounds are pure.

[Lid]m[Ibu]n: Lidocaine ibuprofen with other lidocaine to ibuprofen mole ratios ([Lid]m[Ibu]n, each in ca. 4 g) were prepared by grinding the corresponding amounts of lidocaine and ibuprofen together in a hot mortar (100 °C) until free-flowing clear liquids were obtained (ca. 5 min). After cooling to room temperature, the mixtures solidified or remained liquid depending on the lidocaine to ibuprofen mole ratio (Fig. S14).

[Eph][Ibu]: [Eph][Ibu] (5 mmol) was prepared by grinding equal mole amounts of ephedrine (5 mmol) and ibuprofen (5 mmol) in a hot mortar (100 °C) until a free-flowing clear liquid was obtained (ca. 5 min). After cooling to room temperature, [Eph][Ibu] solidified. (1H NMR (500 MHz, DMSO-d6): δ (ppm) = 7.33 (m, 4H), 7.20 (m, 3H), 7.05 (d, 2H), 4.84 (d, 1H), 3.48 (q, 1H), 2.90 (m, 1H), 2.40 (t, 5H), 1.80 (m, 1H), 1.30 (d, 3H), 0.85 (d, 6H), 0.80 (d, 3H); IR (neat): ν = 3028, 2929, 2694, 2493, 1557, 1449, 1376, 1346, 1277, 1123, 1056, 994, 745, 697 cm⁻¹; Tm = 110 °C.)

Membrane transport procedure. Diffusion experiments were conducted following a literature protocol using a Franz-type diffusion cell, which consists of two chambers, the donor and the receiver compartment, with a diffusion area of 1.77 cm². The diffusion cell was maintained under stirring at constant temperature of 37 °C by a circulating water bath. Degassed
PBS buffer (pH = 7.4, 12.0 mL) was used as the receiver solution. The receiver chamber has a side arm through which samples can be taken out at different time intervals. The silicone membrane was cut to the appropriate size and allowed to soak overnight in ethanol. The membrane was taken out, dried in air and then mounted between the donor and receiver chambers, which were sealed together using Parafilm.

The assembled Franz cell was placed in the diffusion system (Fig. S1) and allowed to equilibrate for 30 min before use. Samples with specific concentrations were either introduced in the donor compartment (EtOH solutions) or applied directly onto the membrane on the donor side (neat sample), and Parafilm was used to seal the donor chamber to reduce the evaporation of EtOH and water absorption. Samples (0.5 mL) were taken out through the sampling arm of the receiver compartment at specific time intervals and immediately replaced by an equal volume of degassed PBS at the appropriate temperature. (If bubbles accidentally formed during the experiment, they could be removed by carefully tilting the Franz cell to allow the air bubbles to escape via the sampling arm.) Samples were sealed and stored at room temperature until analysis was performed.

Fig. S1 Picture of the diffusion system with six-station vertical cell stirrers.

**Characterization**

**NMR:** $^1$H NMR spectra were obtained using a Bruker Avance 500 MHz NMR spectrometer (Karlsruhe, Germany). Studies in DMSO-$d_6$ were conducted at 25 °C, while NMRs of neat [Lid]$_m$[Ibu]$_n$ were taken at 70 °C by loading the samples in capillaries using DMSO-$d_6$ as the
external lock. Solutions of [Lid]$_m$[Ibu]$_n$/EtOH solutions were examined at 25 °C by loading the solutions in capillaries using DMSO-$d_6$ as the external lock.

$^{15}$N NMR data and $^{15}$N 2D Heteronuclear Multiple-Bond Quantum Coherence (HMBC) data were collected utilizing a Bruker spectrometer 600 MHz Bruker Avance Spectrometer Bruker/Magnex UltraShield 600 MHz magnet. Chemical shifts are reported in $\delta$ (ppm).

**Fourier Transform Infrared Spectroscopy (FT-IR):** Infrared spectra were recorded using neat samples on a Perkin-Elmer (Dublin, Ireland) Spectrum 100 FT-IR spectrometer featuring an attenuated total reflection (ATR) sampler equipped with a diamond crystal with 24 scans at 2 cm$^{-1}$ resolution. Spectra were obtained in the range of 400–4000 cm$^{-1}$.

**Differential scanning calorimetry (DSC):** Thermal transitions (melting point and glass transitions) of lidocaine free base, ibuprofen free acid, and [Lid]$_m$[Ibu]$_n$ were determined on a Mettler Toledo Star$^e$ DSC1 (Columbus, OH, USA) unit under nitrogen. Samples between 5–10 mg were placed in aluminium pans and were heated from 25 °C to 100 °C with a heating rate of 5 °C min$^{-1}$ and cooled to −50 °C min$^{-1}$ with an intracooler with a cooling rate of 5 °C min$^{-1}$. Three cycles were measured for each sample.

**Density and viscosity:** Density data was collected using an Anton Paar DMA 5000 density meter. The density of the compounds was determined using the ‘oscillating U-tube principle’. The viscosity measurements were performed using a falling ball technique on an Anton Paar AMVn viscosity meter.

**Conductivity:** Conductivity measurements were carried out on a locally designed dip cell probe containing two platinum wires covered in glass. The cell constant was determined using a solution of 0.01 M KCl solution at 25 °C. The conductivities were obtained by measuring the complex impedance between 0.1 Hz and 1 MHz on a Solartron (Farnborough, UK) 1296 dielectric interface. A Eurotherm 2204e temperature controller, interfaced to the Solartron and a cartridge heater set in a brass block with a cavity for the cell, was used to control the temperature. A K-type thermocouple was set in the block adjacent to the cell.

**Liquid chromatography–mass spectrometry (LC-MS):** Concentrations of lidocaine and ibuprofen in the receiver phase were determined with a Bruker HCTultra PTM discovery system (Billerica, MA, USA) connected to an Agilent 1200 capillary LC (Agilent Technologies, Santa Clara, CA, USA), equipped with a house capillary column (ZORBAX SB-C18, 150×0.5 mm, 5 mm). Bupivacaine hydrochloride was used as the internal standard compound for lidocaine, and
4-tert-butylbenzoic acid was used as the ibuprofen internal standard. The mobile phase consisted of H2O (0.04% acetic acid) and acetonitrile (60:40, v/v), and at 6 min, the mobile phase started to gradually change to 100% CH3CN. The mobile phase was pumped at a flow rate of 10 µL min⁻¹. The sample was injected using an autosampler, with injection volume of 2 µL. The MS detection mode was positive during the first 8 min and was changed to negative at 8 min. Calibration curves for lidocaine and ibuprofen were determined using [Lid][Ibu]/solvent (H2O/CH3CN, 60:40) stock solutions with concentrations ranging from 1.0 × 10⁻⁷ M to 5.0 × 10⁻⁶ M. Before injection into the LC-MS system, the membrane transport samples were diluted to the linear concentration ranges using a mixture of H2O/CH3CN (60:40, v/v).

**Electrospray ionization mass spectroscopy (ESI-MS):** The ESI-MS spectra of [Lid]₄[Ibu]₄, [Lid][Ibu], and [Lid]₃[Ibu]₄ were collected using a Bruker HCTultra PTM Discovery System (Billerica, MA, USA) equipped with an ESI resource operating in the negative ionization mode. The samples dissolved in HPLC grade methanol were infused by a syringe pump with a flow rate of 3 µL/min. The capillary voltage was 1.0 kV.
2. Liquid chromatography–mass spectrometry (LC-MS)

**LC chromatogram**

Concentration of bupivacaine hydrochloride (internal standard for lidocaine) in the solutions was determined to be $1 \times 10^{-7}$ M, and that of 4- tert-butylbenzoic acid (internal standard for ibuprofen) was $1 \times 10^{-6}$ M. Typical LC chromatogram is shown in Fig. S2, which indicates that under the current LC-MS conditions, the four compounds, lidocaine (peak 1), bupivacaine (peak 2), 4- tert-butylbenzoic acid (peak 3), and ibuprofen (peak 4) can be efficiently separated.

![Fig. S2 Typical LC chromatogram.](image-url)
Calibration curves

[Lid][Ibu] stock solutions with different concentrations, ranging from $1.0 \times 10^{-7}$ M to $5.0 \times 10^{-6}$ M, were prepared and analyzed by LC-MS. The peak area ratio of the drug to internal standard as a function of their concentration ratio is shown in Fig. S3, left. It was found that when the concentration varied from $1.0 \times 10^{-7}$ M to $1.0 \times 10^{-6}$ M, peak area ratios of lidocaine/bupivacaine are linear to the concentration ratios, and ibuprofen/4-tert-butylbenzoic acid peak area ratios varied linearly with the concentration ratios in the range from $1.0 \times 10^{-7}$ M to $5.0 \times 10^{-6}$ M. Calibration curves for lidocaine and ibuprofen are shown in Fig. S3, right.

Fig. S3 Left: Scattered data points of peak area ratio of drug/internal standard as a function of concentration ratio; Right: Calibration curves of lidocaine and ibuprofen. (Bup –bupivacaine; TBA –4-tert-butylbenzoic acid)
3. LC-MS vs. UV results

Fig. S4 Comparison of concentrations obtained by LC-MS vs. UV in membrane transport of [Lid][Ibu]/EtOH (0.5 M).
4. Permeation of ethanolic solutions (0.5 M) of lidocaine free base, ibuprofen free acid, and [Lid][Ibu] with error bars

![Graph showing permeation of ethanolic solutions](image)

**Fig. S5** Permeation as a percentage of applied dose in mol% vs. time from ethanolic lidocaine free base and ibuprofen free acid donor solutions to PBS with error bars.

![Graph showing permeation of ethanolic solutions](image)

**Fig. S6** Permeation as a percentage of applied dose in mol% vs. time from ethanolic [Lid][Ibu] donor solution to PBS with error bars.
5. Membrane transport of [Lid][Ibu]/EtOH vs. Lid/EtOH + Ibu/EtOH

![Graph comparing permeation of [Lid][Ibu]/EtOH (▲) with Lid/EtOH + Ibu/EtOH (▲).]

**Fig. S7** Comparison of membrane transport of [Lid][Ibu]/EtOH (▲) with that of Lid/EtOH + Ibu/EtOH (▲).
6. Characterization of [P4444][Ibu], [Eph][Ibu], and [Lid][Ibu]

![NMR spectrum comparison](image1)

**Fig. S8** Comparison of $^1$H NMR spectrum of [P4444][Ibu] with that of ibuprofen free acid in DMSO-$d_6$ at 25 °C.

![FT-IR spectra](image2)

**Fig. S9** FT-IR spectra of ibuprofen free acid (red), [P4444][Ibu] (dark grey), and [Na][Ibu] (purple).
Fig. S10 Comparison of $^1$H NMR spectrum of [Eph][Ibu] with that of ibuprofen free acid in DMSO-$d_6$ at 25 °C.

Fig. S11 FT-IR spectra of ibuprofen free acid (red), [Eph][Ibu] (dark yellow), and [Na][Ibu] (purple).
Fig. S12 $^1$H NMR spectra of [Lid][Ibu], lidocaine free base, and ibuprofen free acid in DMSO-$d_6$ at 25 °C.

Fig. S13 FT-IR spectra of neutral lidocaine (black) and ibuprofen (red), and solid salts [Lid][Cl] (dark green), [Na][Ibu] (purple), and [Lid][Ibu] (blue).
7. Pictures of $[\text{Lid}]_m[\text{Ibu}]_n$

Fig. S14 Pictures of $[\text{Lid}]_m[\text{Ibu}]_n$ after cooling to room temperature.
8. Characterization of neat [Lid]\_m[Ibu]\_n

**DSC**

![DSC diagram](image_url)

**Fig. S15** (a): Comparison of DSC curves of lidocaine free base, ibuprofen free acid, and [Lid]\_m[Ibu]\_n (Ratios in the legends are lidocaine to ibuprofen mole ratios); (b): DSC curve of [Lid]\_1[Ibu]\_9 with all three cycles shown.
Fig. S16 $^1$H NMR of neat [Lid]$_m$[Ibu]$_n$ and lidocaine free base at 70 °C using DMSO-$d_6$ as external lock.
### $^{15}$N NMR of neat $[\text{Lid}]_m[\text{Ibu}]_n$

Table S1 $^{15}$N NMR chemical shifts of neat $[\text{Lid}]_m[\text{Ibu}]_n$.

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<th>Mole fraction of ibuprofen</th>
<th>Amine N</th>
<th>Temperature ($^\circ$C)</th>
<th>Chemical shift (ppm)</th>
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Fig. S17 (a): Full FT-IR spectra of lidocaine free base, [Lid][Cl], [Lid]$_n$[Ibu]$_n$, [Na][Ibu], and ibuprofen free acid; (b): spectra of [Lid]$_n$[Ibu]$_n$ with excess ibuprofen.
**Electrospray Ionization Mass Spectroscopy (ESI-MS)**

**Fig. S18** ESI-MS spectra of [Lid]₄[Ibu]₁, [Lid][Ibu], and [Lid]₁[Ibu]₄ under negative mode.
9. $^1$H NMR of [Lid]$_m$[Ibu]$_n$/EtOH

**Fig. S19** $^1$H NMR of [Lid]$_m$[Ibu]$_n$/EtOH, ibuprofen/EtOH, [Na][Ibu]/EtOH, [Lid][Cl]/EtOH, and lidocaine/EtOH solutions at 25 °C using DMSO-$d_6$ as external lock (concentration of the solutions: 0.5 M).

**References**