Electronic Supplementary Material (ESI) for RSC Advances.

Supporting information

Physicochemical and structural properties of lidocaine-based ionic liquid with anti-inflammatory anions

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Experimental procedure:

Infrared (IR) spectra

Infrared spectra of neat ionic liquid samples were measured from 4000 to 650 cm^1 using a Thermo Nicolet Nexus 670 spectrometar. The experiments were performed using a single-reflection ATR accessory equipped with germanium crystal. For solid samples of ibuprofen, lidocaine and salicylic acid, diffused reflection method with KBr pellet was used. The total number of scans was 60, at T=298.15 K with spectral resolution of 2 cm^{-1} in the range of wavenumbers of 650 to 4000 cm^{-1}. All results were analysed using software Omnic version 6.2 and OriginPro 8.

Nuclear magnetic resonance (NMR) spectra

For measuring NMR spectra the Bruker Advance III 400 MHz spectrometer was used. The ^1H and ^{13}C chemical shift was calibrated using tetramethylsilane as an internal standard. All samples were measured in D_2O at T = 298.15 K. The assignation of recorded ^1H NMR spectra was performed using homodecoupling and 2D COSY method. For assignation of ^{13}C NMR spectra selective decoupling technique was applied.

Mass spectra

The mass spectra measuring were conducted by Waters Micromass Quattro II triple quadrupole spectrometer. The ionization process was achieved in ESI+ mode, the interface voltage was set to +2.5 kV to accomplish the highest yield for the ions and to avoid in-source fragmentation. The collision energy was 20 eV and as a drying gas nitrogen was used with flow rate of 15 $l \cdot min^{-1}$. For data treatment the MassLynx software was used.

Thermal characterization

Thermal behaviour of lidocaine salicylate and lidocaine ibuprofenate was investigated using simultaneous TG/DSC thermal analyzer SDT Q600. The thermogravimetric analysis was carried out in an argon atmosphere with flow rate of 50 $cm^3 \cdot min^{-1}$. The heating rate was 20 $^oC \cdot min^{-1}$ up to 350 ^oC. For differential scanning calorimetric (DSC) the differential thermal analyzer DSC Q20 was used. The applied heating rate was 20 $^oC \cdot min^{-1}$ in nitrogen atmosphere. All the samples was firstly cooled to –100 ^oC, than held at that temperature for 20 min and further heated to 300 ^oC.

Density measurements

The densities were measured at atmospheric pressure, with a Rudolph Research Analytical DDM 2911 densimeter in temperature range between 293.15 and 353.15 K. The densimeter was calibrated by measuring the density of air and distilled water in accordance with recommendation. The temperature in densimeter U-tube was controlled by a Peltier unit. Density measurements had viscosity correction and results presented in this Manuscript are mean value of at least three measurements. The standard uncertainty of determining the density is less than $3.0 \cdot 10^{-3}$ $g \cdot cm^{-3}$.

Viscosity measurements

For determination of viscosity the Brookfield Viscometer DV II+Pro was used. The isolated cell was filled with the 16 cm^3 of investigated ionic liquids and temperature were kept constant within ±0.01 K. The adequate spindle type (SC4-18 for lidocaine ibuprofenate, LV-4 for lidocaine salicylate) was immersed in the cell and rotation speed was set to obtain the proper torque (10-90%). The measurements were performed in temperature range from 293.15 to 353.15 K using rotation speed from 0.01 to 1.2 rate per minute (RPM). The presented experimental results represent the mean value of at least three measurements. The relative standard uncertainty of viscosity measurements was less than 2.0%.

Electrical conductivity

The electrical conductivity measurements were performed in Pyrex-cell with platinum electrodes connected on a conductivity meter Jenco 3107 using DC signal. The temperature range was between 293.15 and 353.15 K. The cell constant was determined using NIST recommended standard (0.1M KCl) and its value was 1.0353 cm^{-1}. The obtained results are average value of at least three measurements. The determined relative standard uncertainty for electrical conductivity was 1.5%.

Computational details

The computational simulations were performed using Schrödinger Materials Science Suite 2015-4 package and Yasara Structure. For density functional theory (DFT) calculations, the Jaguar 9.0 program was used. The Hessian analysis was applied to check the validity of optimized structures, and only results with no imaginary wavelengths were considered for further analysis. The dispersion corrected B3LYP-d3 functional was used with basis set 6-31G+ (d,p), along with superposition error (BSSE) developed by the Boys-Bernardi counterpoise method.[10] The determination and analysis of non-covalent interactions (NCI) from optimized structures were conducted using the method of [11].

From the DFT calculations, ion-pair binding energies between cation and anion were predicted. The counter-poise correction was applied to avoid the basis-set superposition error (BSSE) that occurs in determination of binding energies (ΔG_{bin}). The equation used for calculation of ΔG_{bin} was:

$$\Delta G_{bin} = E_{cp}(C-A) - E_{min}(C) - E_{min}(A) + \Delta ZPVE$$

Where E_{cp}(C–A) represent the ion pair counter-poise corrected electronic energy, E_{min}(C) and E_{min}(A) are the electronic energies of the cation and the anion in their most stable geometries. Zero-point vibrational energies ($\Delta ZPVE$) were calculated using scaled B3LYP/6-31G+ (d,p) vibrational frequencies.

For prediction of liphophilicity descriptor, *A*log*P*, firstly the free energy of solvation was calculated using the density based continuum solvation model (SMD).[12] In this model, the solvation free energy change at 298.15 K represents the difference between the solvent and gas electronic energies, required for the corresponding gas-phase calculation. The geometry optimizations were carried out in different solvents,

such as gas phase, water and octanol, with SMD model for the overall solvation effect. The *A*log*P* is calculated using equation:

$$A\log P = \frac{\Delta G_{sol(water)} - \Delta G_{sol(octanol)}}{2.303RT}$$

Where $\Delta G_{sol(water/octanol)}$ is the standard-state solvation free energy change of a given ionic liquid in octanol or in water at 298.15 K. The standard-state solvation free energy represents the free energy of transfer from the gas phase to the condensed phase, under the standard state conditions.

Molecular dynamics (MD) simulations were performed using a modified AMBER force field. The parameters for MD simulations of lidocaine, ibuprofen and salicylate were obtained from geometrically optimized structures. The simulations for pure ionic liquids (number of ion pairs was 264) were performed in the simulation box with periodic boundary conditions. The cut-off radius was set to 10 Å. The NPT ensemble was used, and the temperature (298.15 K) and pressure ($1 \cdot 10^5$ Pa) was controlled by Nose-Hoover thermostat. For the computation of long-range electrostatic interactions, the Ewald method was used with no truncation in investigated systems. The simulation time was 30 ns, while equilibrium phase last 10 ns which were excluded from further analysis. The trajectories are integrated via the Verlet leapfrog algorithm combined with the quaternion method for rotations with a time step of 2 fs and later analyzed.

The total structure-function *S*(q) of the ionic liquids were calculated from equation:

$$S(q) = \frac{\rho_o \sum_i^n \sum_j^n x_i x_j f_i(q) f_j(q) \int_0^\infty 4\pi r^2 (g_{ij}(r) - 1) \frac{\sin qr}{qr} dr}{\left[\sum_i^n x_i f_i(q)\right]^2}$$

where, $g_{ij}(r)$ is the radial pair distribution function for atoms of type *i* and *j*; x_i is the fraction of atom type *i*; $f_i(q)$ is the x-ray atomic form factor for the i^{th} type atom; and ρ_o is the number density. The possible finite trunctation of *g*(*r*) at large values of *r* was avoided by applying Lorche window function.

The obtained total structure factor *S*(*q*) can be separated into ionic contribution:

$$S(q) = S_{c-c}(q) + S_{a-c}(q) + S_{c-a}(q) + S_{a-a}(q)$$

where *a* and *c* are an anionic and cationic contribution, respectively.

Table S1. Provenance and purity of the chemicals.

Chemical name	Provenance	CAS Number	Purification method	Mass fraction purity
Lidocaine	TCI	137-58-6	-	$\omega \geq 0.99$
Ibuprofen	TCI	15687-27-1	-	$\omega \geq 0.98$
Salicylic acid	Sigma Aldrich	69-72-7	-	$\omega \geq 0.99$
Methanol	Sigma Aldrich	67-56-1	-	$\omega \geq 0.998$

[a]P_2O_5= phosphorus pentoxide

Table S2. Phase transitions of investigated ILs.

Ionic liquid	T_{onset} (°C)	$T_{5\%onset}$ (°C)	T_g (°C)	T_m (°C)
Lidocaine ibuprofenate	215.48	171.32	-30.30	/
		165.19 [7] 174.00 [13] 181.00 [8]	-27.00 [13] -27.37 [7]	
Lidocaine salicylate	208.56	151.20	-13.10	189.99
		158.47 [9]	-19.78 [9]	

Table S3. The fitting parameters obtained for viscosity using the VFT equation.

Parameters	Lidocaine ibuprofenate	Lidocaine salicylate
A / (mPa·s)	49.20	920.1
B / (K)	112.1	364.0
T_g / (K)	274.6	265.2
R^2	0.999	0.998

Table S4. Values of viscosity, shear stress, shear rate and revolution per minute of the spindle for lidocaine ibuprofenate at T= 298.15 K at p = 0.1mPa.

RPM	η / (mPa·s)	Shear stress / ($N \cdot m^{-2}$)	Shear rate / (s^{-1})
0.07	5570.24	0.51	0.09
0.1	5606.87	0.74	0.13
0.2	5890.83	1.56	0.26
0.3	5742.38	2.27	0.40

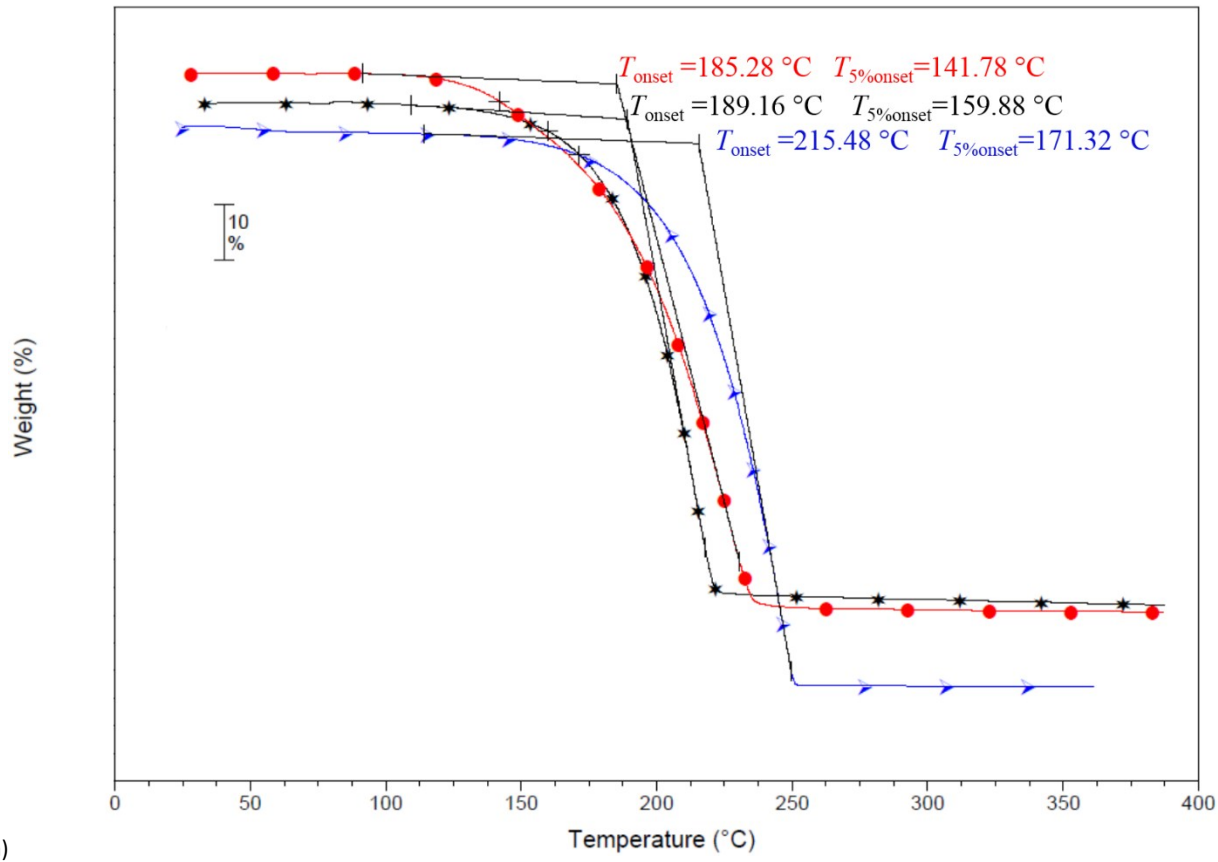
0.4	5748.27	3.03	0.53
0.5	5731.78	3.78	0.66

Relative standard uncertainties: $u_r(\eta) = 0.02$, $u_r(p) = 0.015$;

Standard uncertainties: $u(T) = 0.015$ K.

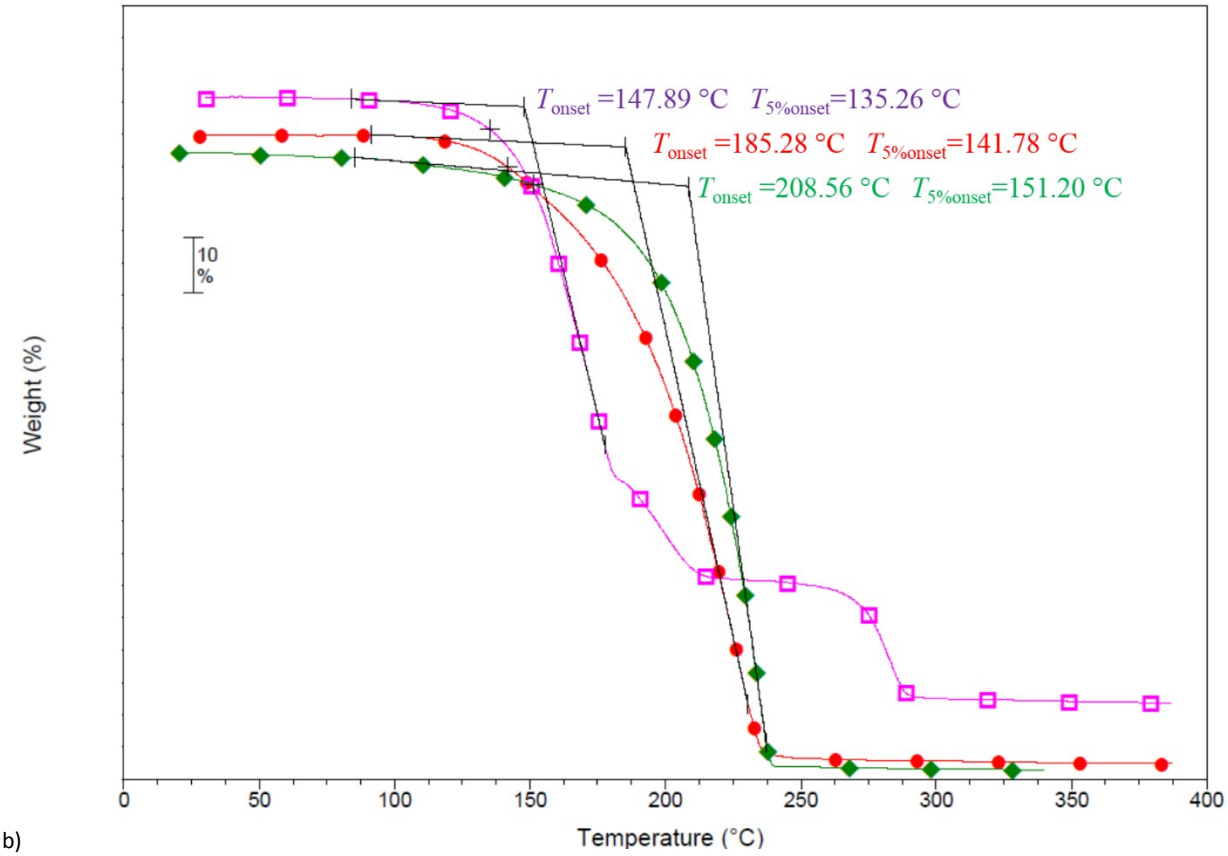
Table S5. The fitting parameters obtained for conductivity using the VFT equation.

Parameters	Lidocaine ibuprofenate	Lidocaine salicylate
A' / (mS·cm^{-1})	176.9	0.876
B' / (K)	1573	133.0
T_g / (K)	180.9	312.0
R^2	0.999	0.994

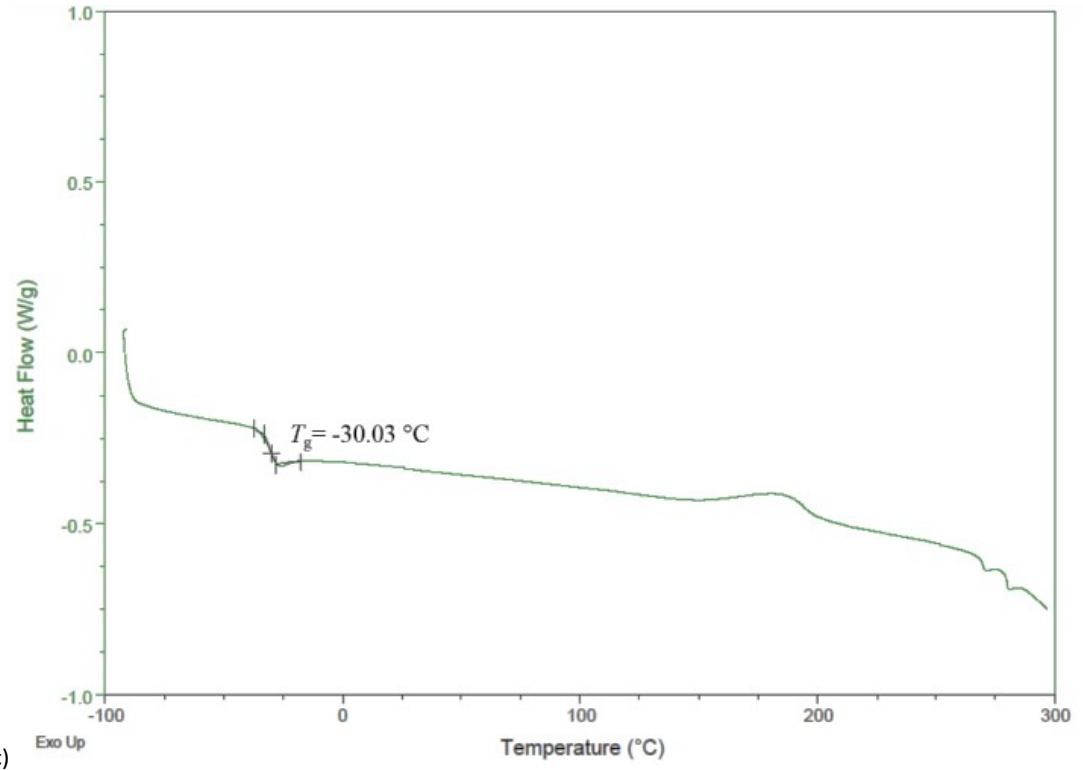

T_{onset} =185.28 °C $T_{5\%onset}$=141.78 °C
T_{onset} =189.16 °C $T_{5\%onset}$=159.88 °C
T_{onset} =215.48 °C $T_{5\%onset}$=171.32 °C
10
%
Weight (%)
0
50
100
150
200
250
300
350
400
Temperature (°C)

a)

b)


T_{onset} =147.89 °C $T_{5\%onset}$=135.26 °C
T_{onset} =185.28 °C $T_{5\%onset}$=141.78 °C
T_{onset} =208.56 °C $T_{5\%onset}$=151.20 °C
10 %
Weight (%)
0
50
100
150
200
250
300
350
400
Temperature (°C)

c)



d)

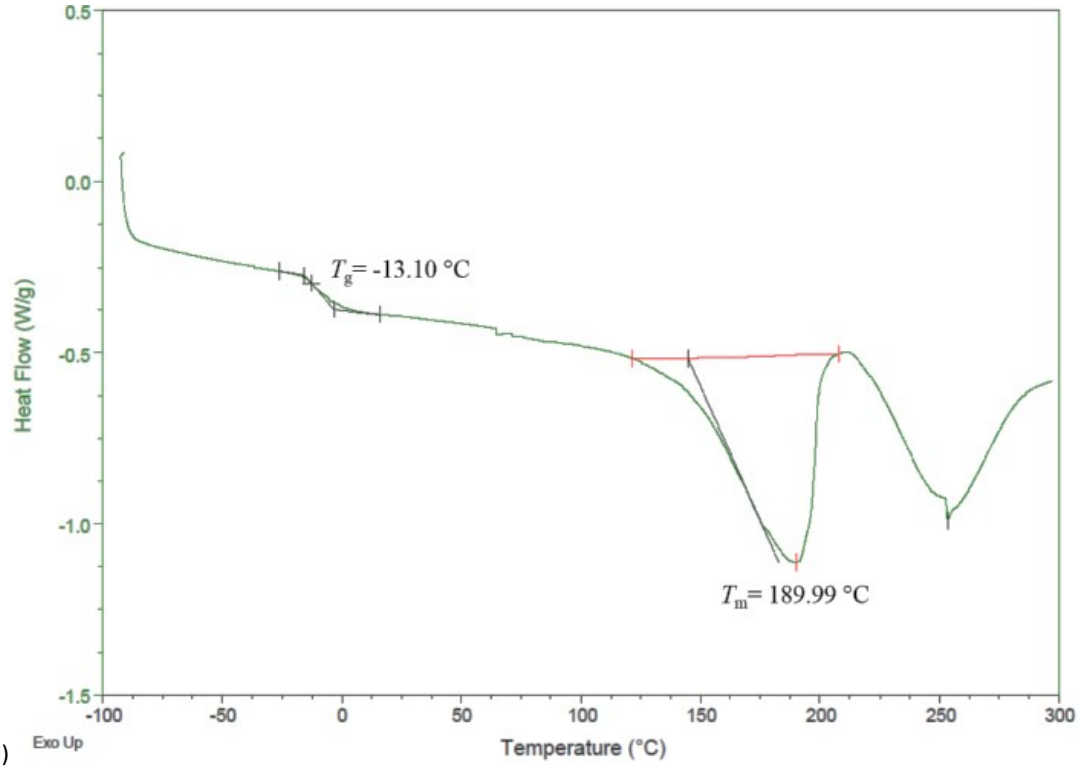
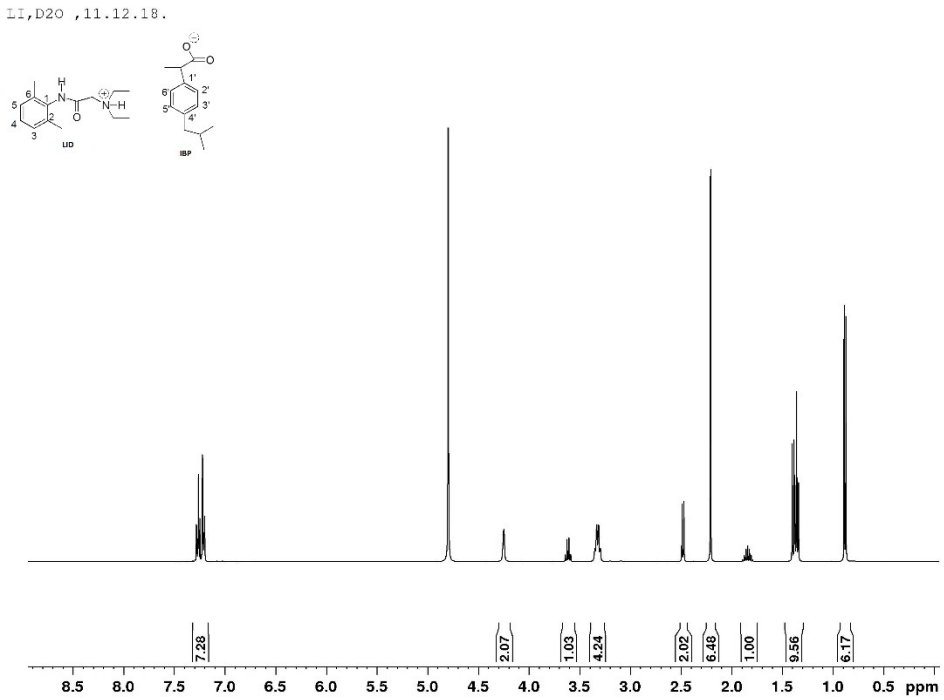
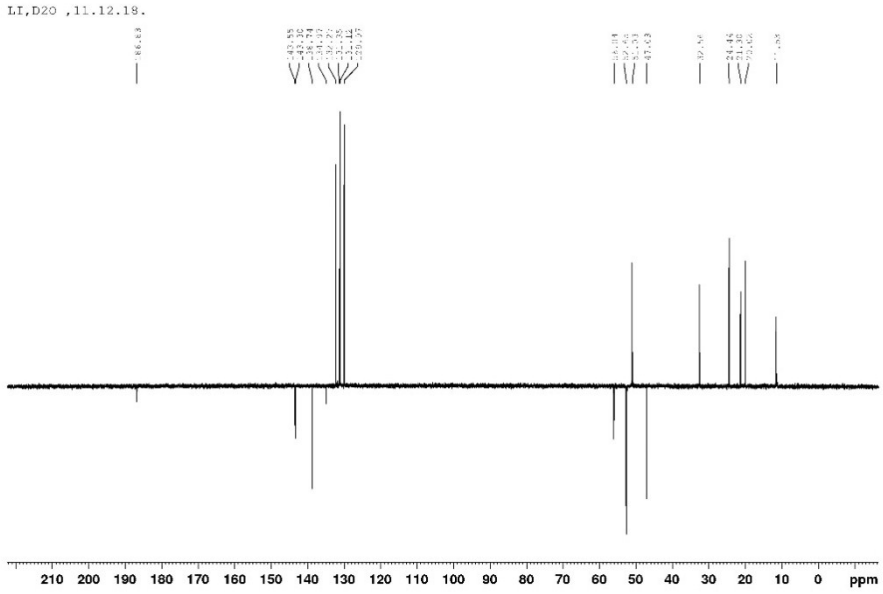


Figure S1. a) TG curves for starting components —● lidocaine, and —▼ibuprofen, and synthesized —► lidocaine ibuprofenate; b) TG curves for starting components —●lidocaine, and —□ salicylic acid, and synthesized —◆ lidocaine salicylate; c) DSC curve of lidocaine ibuprofenate and d) DSC curve of lidocaine salicylate.

a)


LI,D2O ,11.12.18.
LID
IBP
7.28
2.07
1.03
4.24
2.02
6.48
1.00
9.56
6.17
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

b)


LI,D2O ,11.12.18.
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

c)

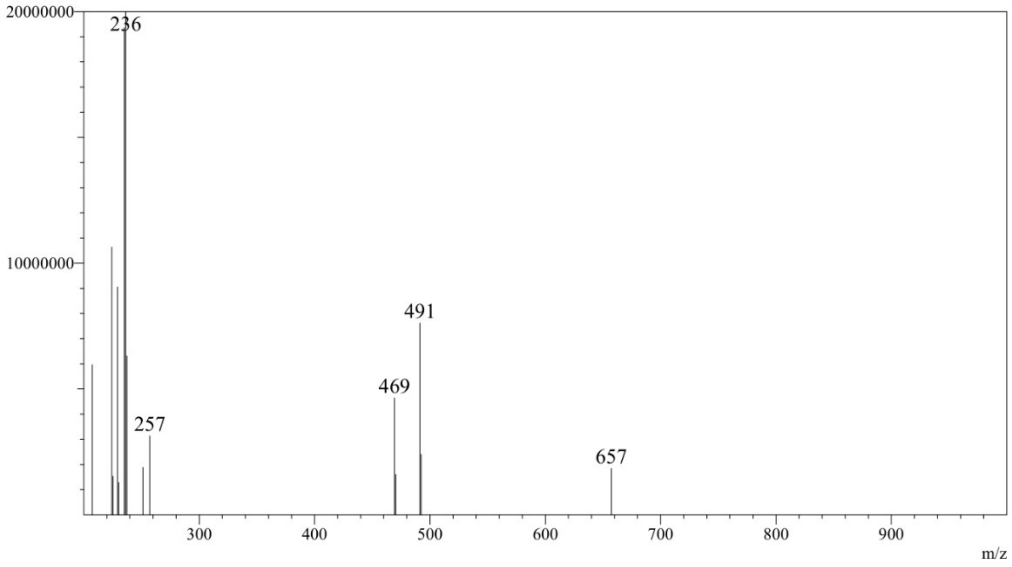


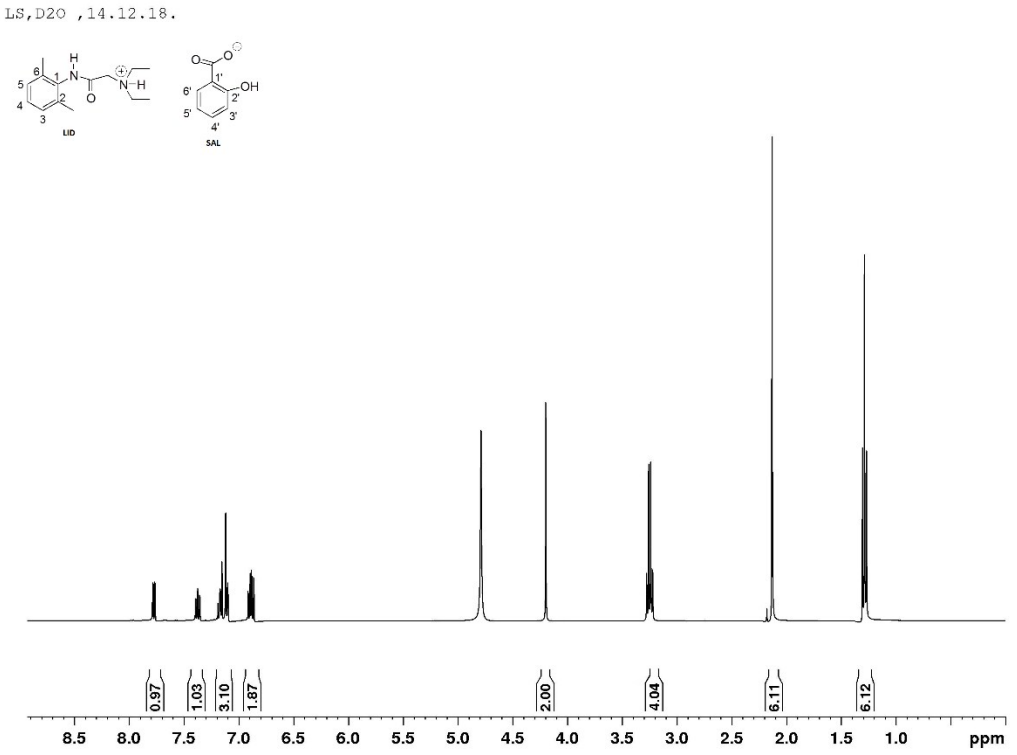
Figure S2. a) ^{1}H, b) ^{13}C NMR, and c) MS spectra for synthesized lidocaine ibuprofenate.

^{1}H NMR (D_2O): 0.88 (d, 6 H, $J_{(CH3)2CH}$ = 6.7 Hz, $(CH_3)_2CH$, **IBP**);1.36 (t, 6 H, J_{CH3CH2} = 7.3 Hz, $2CH_2CH_3$, **LID**); 1.72 (d, 3 H, J_{CHCH3} = 7.2 Hz, $CHCH_3$, **IBP**);1.84 (m, 1 H, $CHCH_3$, **IBP**);2.21 (s, 6 H,$2CH_3$, **LID**);2.48 (d, 2 H, J_{CH2CH} = 7.2 Hz,$(CH_3)_2CHCH_2$, **IBP**);3.32 (q, 4 H, J_{CH3CH2} = 7.3 Hz, $2CH_2CH_3$, **LID**);3.61 (q, 1 H, J_{CHCH3} = 7.2 Hz, $CHCH_3$, **IBP**);4.24 (s, 2 H, CH_2CO, **LID**);7.19-7.29 (m, 7 H, Ar-H, **LID**, **IBP**).

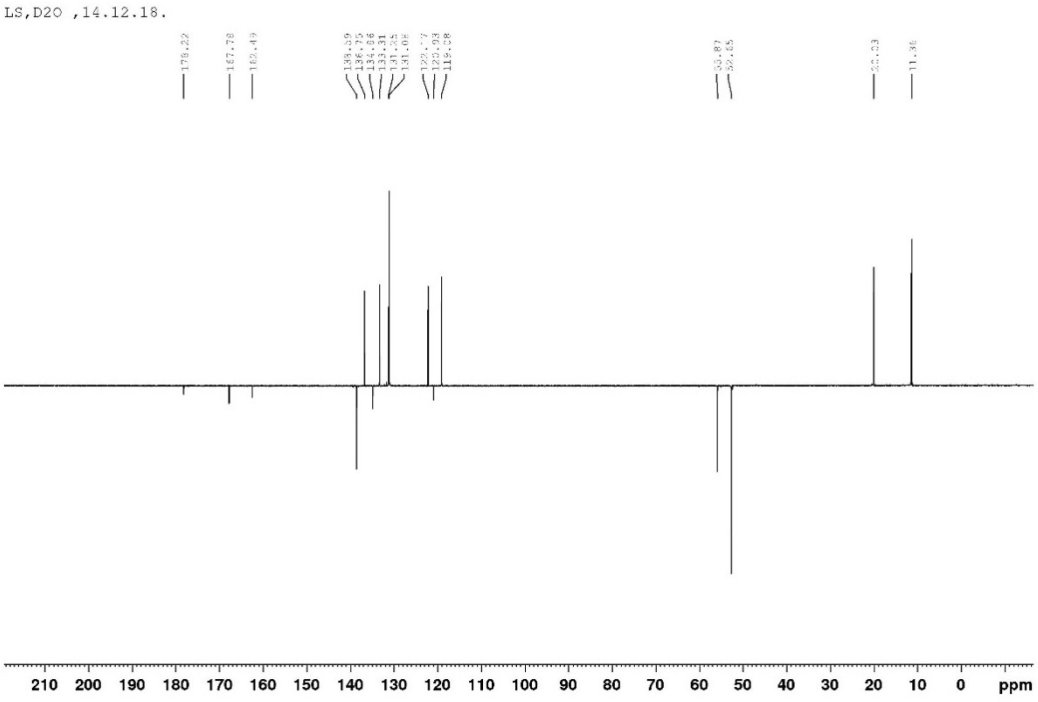
^{13}C NMR(D_2O):11.53 (CH_2CH_3, **LID**);20.02 (CH_3, **LID**);21.30 ($CHCH_3$, **IBP**);24.44($(CH_3)_2CH$, **IBP**);32.56 ($(CH_3)_2CH$, **IBP**);47.03($(CH_3)_2CHCH_2$, **IBP**);51.03($CHCH_3$, **IBP**);52.65(CH_2CH_3, **LID**); 56.04(CH_2CO, **LID**); 129.97 (C-2′,C-6′, **IBP**); 131.12(C-3,C-5, **LID**);131.35 (C-4, **LID**);132.27(C-3′,C-5′, **IBP**); 134.97(C-1, **LID**);138.74(C-2, C-6, **LID**);143.30(C-4′, **IBP**);143.55(C-1′, **IBP**);168.85(CH_2CO, **LID**); 186.83 (C=O, **IBP**).

ESI-MS (*m/z*): [**LID** + 2]$^{+}$ = 236, [**LID** + Na]$^{+}$ = 257, [**2LID** + H]$^{+}$ = 469, [**2LID** + Na]$^{+}$ = 491

a)


LS,D2O ,14.12.18.
LID
SAL
0.97
1.03
3.10
1.87
2.00
4.04
6.11
6.12
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

b)


LS,D2O ,14.12.18.
178.22
167.78
160.49
139.39
136.75
134.06
133.31
131.65
131.08
122.17
120.94
119.08
55.87
52.65
20.53
11.36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

c)

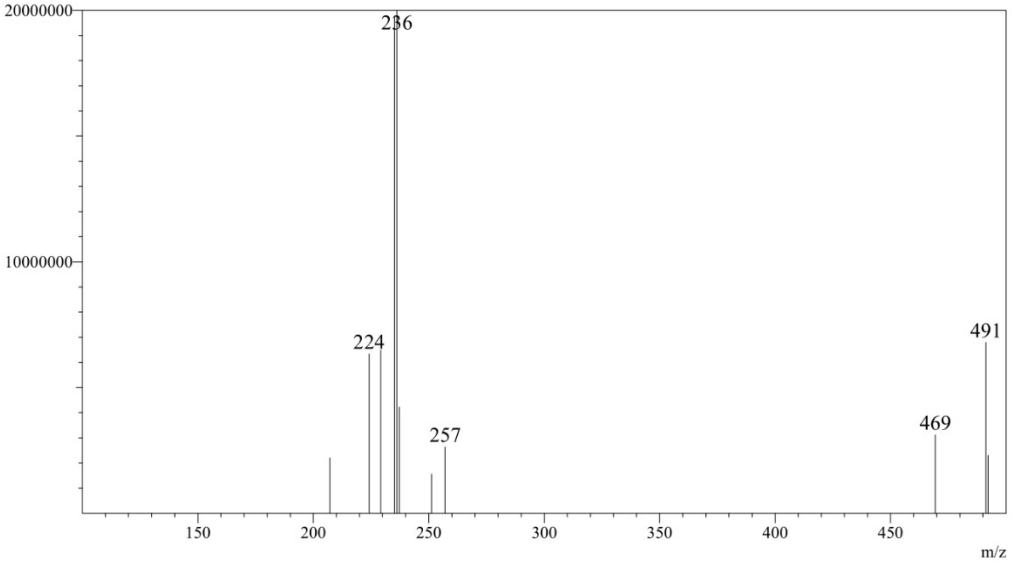


Figure S3. a)^{1}H, b) ^{13}C NMR, and c) MS spectra for synthesized lidocaine salicylate.

^{1}H NMR (D_2O): 1.29 (t, 6 H, J_{CH3CH2} = 7.3 Hz, 2CH_2CH_3, **LID**);2.13 (s, 6 H,2CH_3, **LID**);3.24 (q, 4 H, J_{CH3CH2} = 7.3 Hz, 2CH_2CH_3, **LID**); 4.20 (s, 2 H, CH_2CO, **LID**);6.88(dd, 1 H, $J_{3',4'}$ = 8.1 Hz, $J_{3',5'}$ = 1 Hz, H-3', **SAL**);6.91(td, 1 H, $J_{3',5'}$ = 1.2 Hz, $J_{4',5'}$= 7.5 Hz, $J_{5',6'}$= 7.8 Hz, H-5', **SAL**);7.09-7.19 (m, 3 H, Ar-H, **LID**); 7.37(ddd, 1 H, $J_{4',5'}$= 7.2 Hz, $J_{3',4'}$ = 8.1 Hz, $J_{4',6'}$ = 1.7 Hz, H-4', **SAL**); 7.78 (dd, 1 H, $J_{4',6'}$ = 1.7 Hz, $J_{5',6'}$= 7.8 Hz, H-6', **SAL**).

^{13}C NMR (D_2O): 11.36 (CH_2CH_3, **LID**); 20.03 (CH_3, **LID**); 52.65(CH_2CH_3, **LID**); 55.87 (CH_2CO, **LID**); 119.08(C-3', **SAL**); 120.93(C-1', **SAL**); 122.17(C-5', **SAL**); 131.08(C-3, C-5, **LID**); 131.25(C-4, **LID**); 133.31(C-6', **SAL**); 134.86(C-1, **LID**); 136.75(C-4', **SAL**); 138.74(C-2, C-6, **LID**); 162.49 (C-2', **SAL**); 167.78 (CH_2CO, **LID**); 178.22 (C=O, **SAL**).
ESI-MS (*m/z*): [**LID** + 2]$^{+}$ = 236, [**LID** + Na]$^{+}$ = 257, [**2LID** + H]$^{+}$ = 469, [**2LID** + Na]$^{+}$ = 491

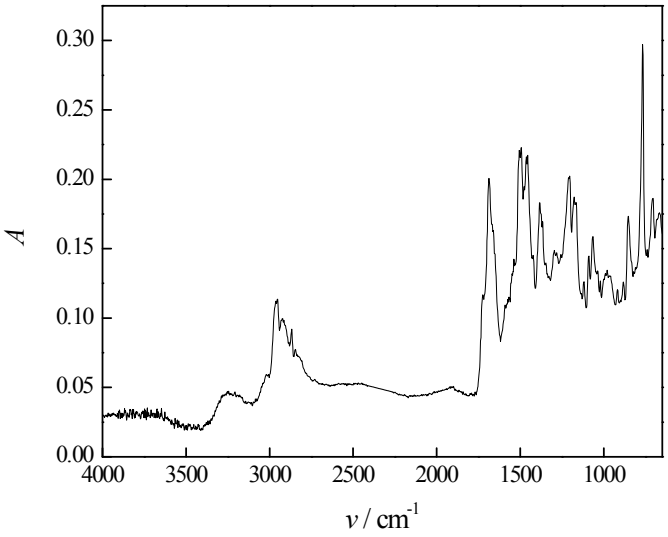


Figure S4. IR spectra of lidocaine ibuprofenate

IR (neat) 3245.59 NH stretch; 2953.17 and 2867.82 C-H stretch; 2354.60 NH stretch; 1687.63 C=O symetric deformation; 1494.55 C-N symetric deformation;1456.01 C-H asymmetric deformation; 1383.74 CH symetric deformation; 1204.14 CH_2 twist; 1119.08 C-O stretch; 1065.50 CH_2 twist; 767.33 aromatic C-H.

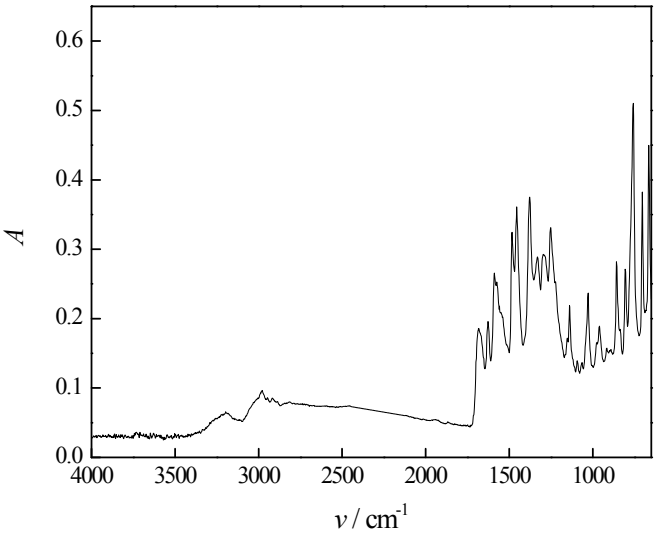
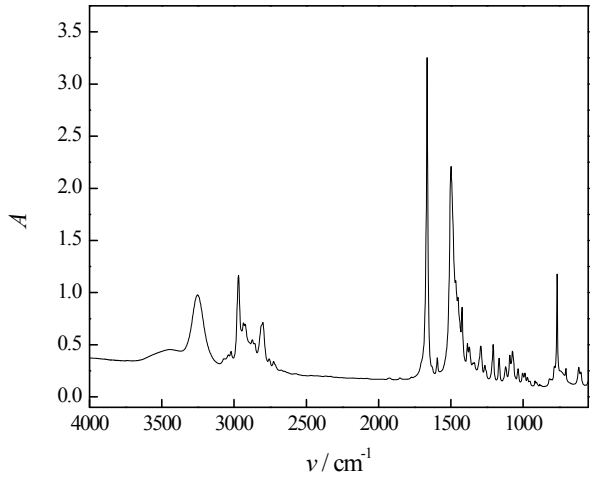
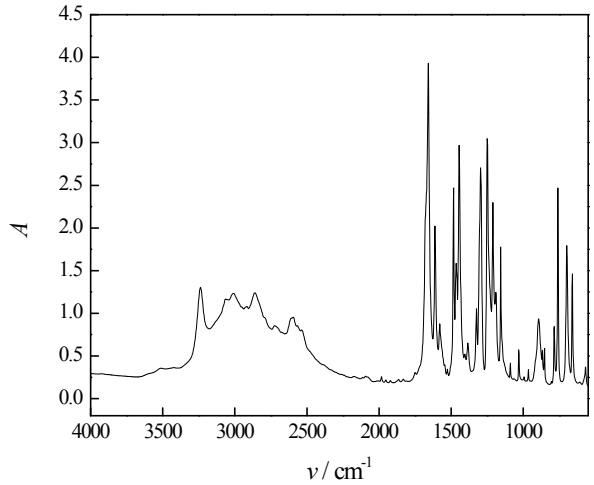


Figure S5. IR spectra of lidocaine salicylate

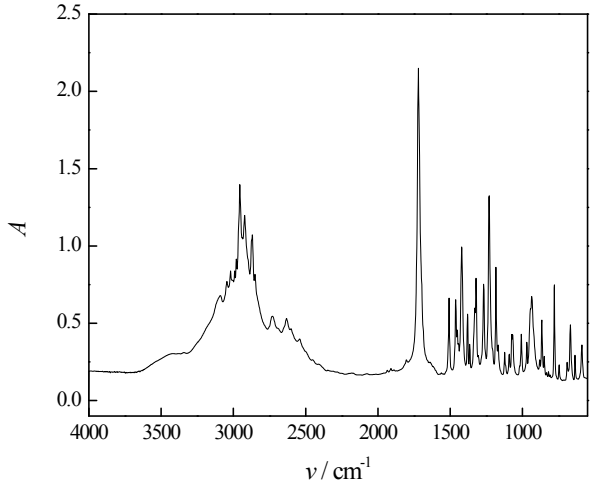
IR (neat) 2978.02 C-H stretch; 1682.91 C=O; 1626.86 C=O symetric deformation; 1589.21 C=C stretch aromatic;1483.69 and 1455.69 CC stretch; 1377.89 C-O stretch; 1296.13 CC stretch; 1252.35 C-O stretch; 1138.98 and 1028.20 CH an in-plane bending mode; 857.69 CH an out-of-plane deformation, 758.30 C-H aromatic.



a)



b)



c)

Figure S6. IR spectra of lidocaine (a), salicylic acid (b), ibuprofene (c)