Supplementary Information

Highly water soluble room temperature superionic liquids of APIs

Gonçalo V. S. M. Carrera,a,† Miguel M. Santos,a,† Alexandra Costa,a Luis Paulo N. Rebelo,a Isabel M. Marrucho,b,c M. Nunes da Ponte,a Luis C. Brancoa,*

Reagents and Solvents

The commercial reagents were used as supplied: Ampicillin trihydrated was supplied by Medicamenta S. A. R. L., 6-Aminopenicillanic acid with a purity of 96% from Aldrich, racemic Ibuprofen purchased from Alfa-Aesar with a purity of 99%, racemic Naproxen sodium salt with a purity of 99% purchased from Sigma Aldrich, Norfloxacin ≥ 96 % was supplied by Fluka, Ciprofloxacin – provided by Bayer with a (purity ≥ 99.8%), 1,1,3,3 tetramethylguanidine (TMG) 99% and 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN) 98% were supplied by Sigma-Aldrich and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), ≥ 99%, was provided by Fluka. Solvents were also used as supplied: Dichloromethane supplied by Sigma-Aldrich p.a. grade, Methanol provided by Sigma-Aldrich HPLC grade, Ethanol HPLC grade supplied by Carlo Erba and Deionized water processed by Diwer Technologies water max w2 equipment.

Characterization

1H and 13C NMR spectra recorded on a Bruker AMX400 spectrometer. Chemical shifts are reported downfield in parts per million from a tetramethylsilane reference. IR spectra were recorded on a Perkin Elmer FTIR Spectrometer, Spectrum 1000 and Spectrometer FTIR Bruker Tensor 27. The samples were prepared in KBr or NaCl matrices. DSC experiments were carried out using a TA Instruments Q-series TM Q200 DSC equipped with a refrigerated cooling system. The sample is continuously purged with 50 mL/min of N2. Between 2 and 10 mg of sample were placed in an aluminum TA Tzero Pan and Hermetic Lid. Elemental analysis were performed by Laboratório de Análises at REQUIMTE, Departamento de Química Faculdade de Ciências e Tecnologia (Monte de Caparica) using a Thermo Finnigan-CE Instruments equipment, model Elemental Analyser 1112 series.
Experimental procedures

With the exception of the API-ILs from naproxen, all ionic liquids and molten salts based on superbases were prepared according to the following general procedure:

A solution of organic superbase was added dropwise to the API in equimolar quantities dissolved or dispersed in the same solvent. The solution was further diluted 50% with the same solvent. Upon stirring at room temperature for a period of time the solvent was removed in a rotary evaporator and the product was obtained pure after drying under high vacuum.

Bis(dimethylamino)methaniminium(6R)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [TMGH][APA]

(+)-6-Aminopenicellanic acid (557 mg, 2.580 mmol) reacted with tetramethylguanidine (300 mg) in dichloromethane (1 mL each) for 90 minutes. The product is an orange paste obtained in 99% yield (897 mg, 2.544 mmol). \( T_g = 6.6 \degree C; \) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.53 (d, J = 4.1 Hz, 1H), 4.43 (d, J = 4.1 Hz, 1H), 4.19 (s, 1H), 2.97 (s, 12H), 1.64 (s, 3H), 1.59 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 178.0, 172.5, 162.1, 73.3, 69.4, 64.0, 61.9, 39.9, 32.2, 27.5 ppm; FTIR (KBr): 3405, 2969, 2933, 1763, 1650, 1609, 1570, 1410, 1395, 1320, 1066, 693 cm\(^{-1}\); anal. calcd for C\(_{13}\)H\(_{25}\)N\(_5\)O\(_3\)S\(_2\)O: C, 44.23; H, 7.82; N, 19.84; found: C, 43.70; H, 7.20; N, 19.68.

2,3,4,6,7,8,9,10-Octahydropyrimido[1,2-a]azepinium(6R)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [DBUH][APA]

(+)-6-Aminopenicellanic acid (282 mg, 1.302 mmol) reacted with DBU (200 mg) in dichloromethane (1 mL each) for 90 minutes. The product is an orange paste obtained in 92% yield (483 mg, 1.19 mmol). \( T_g = 83.8 \degree C; \) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.56 (d, J = 4.1 Hz, 1H), 4.44 (d, J = 4.1 Hz, 1H), 4.25 (s, 1H), 3.51 – 3.36 (m, 6H), 2.89 – 2.80 (m, 2H), 1.99 (quint, J = 5.8 Hz, 2H), 1.79 – 1.69 (m, 4H), 1.69 – 1.58 (m, 8H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 177.8, 173.1, 166.1, 73.1, 69.5, 64.0, 62.0, 54.3, 48.7, 38.1, 32.5, 32.1, 29.1, 27.6, 27.0, 24.2, 19.7 ppm; FTIR (KBr): 3419, 3134, 2934, 1769, 1649, 1601, 1392, 1324, 1208, 1128, 1107, 984, 519 cm\(^{-1}\); anal. calcd for C\(_{17}\)H\(_{28}\)N\(_4\)O\(_3\)S\(_2\)O: C, 50.47; H, 7.97; found: C, 50.53; H, 7.70; N, 13.40.

3,4,5,6,7,8-hexahydro-2H-pyrrolo[1,2-a]pyrimidin-5-ium(25,5R,6R)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [DBNH][APA]

(+)-6-Aminopenicellanic acid (564 mg, 2.608 mmol) reacted with DBN (324 mg) in dichloromethane (2 mL each) for 90 minutes. The product is an orange paste obtained in quantitative yield (885 mg, 2.608 mmol). \( T_g = 78.7 \degree C; \) \(^1\)H NMR (400 MHz, CD\(_3\)OD): \( \delta \) 5.47 (d, J = 4.1 Hz, 1H), 4.48 (d, J = 4.1 Hz, 1H), 4.15 (s,
bis(dimethylamino)methaniminium(2⁵S,6⁵R,8⁵R)-6-((R)-2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [TMGH][AMP]

Ampicillin trihydrated (173 mg, 0.430 mmol) reacted with tetramethylguanidine (50 mg) in dichloromethane (1 mL each) for 90 minutes. The product is a white paste obtained in 95% yield (205 mg, 0.410 mmol), T_g = 114.6 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.98 (d, J = 8.9 Hz, 1H), 7.45 – 7.30 (m, 5H), 5.62 – 5.55 (m, 2H), 4.58 (s, 1H), 4.32 (s, 1H), 3.01 (s, 12H), 1.68 (s, 3H), 1.63 (s, 3H) ppm; ^13C NMR (100 MHz, CDCl_3): δ 173.8, 172.8, 172.9, 165.0, 140.4, 129.0, 127.0, 73.9, 67.3, 64.8, 59.6, 57.6, 39.7, 32.1, 27.4 ppm; FTIR (KBr): 3418, 2980, 1768, 1680, 1653, 1597, 1406, 129.1, 128.3, 127.3, 74.1, 67.7, 64.9, 60.0, 58.0, 54.4, 48.8, 38.2, 32.3, 29.8, 29.2, 27.6, 27.1, 24.2, 19.8 ppm; anal. calcd for C_{21}H_{32}N_{6}O_{4}S: C, 50.38; H, 7.25; N, 16.79; found: C, 50.50; H, 7.18; N, 16.47.

2,3,4,6,7,8,9,10-Octahydropyrimido[1,2-a]azepinium(2⁵S,6⁵R,8⁵R)-6-((R)-2-amino-2-phenyl-acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [DBUH][AMP]

Ampicillin trihydrated (528 mg, 1.304 mmol) reacted with DBU (208 mg) in dichloromethane (4 mL each) for 90 minutes. The product is a white paste obtained in 91% yield (659 mg, 1.187 mmol), T_g = 105.1 °C, ^1H NMR (400 MHz, CDCl_3): δ 7.97 (d, J = 9.5 Hz, 1H), 7.44 – 7.29 (m, 5H), 5.61 – 5.55 (m, 2H), 5.62 – 5.55 (m, 2H), 4.58 (s, 1H), 4.35 (s, 1H), 3.50 – 3.39 (m, 6H), 2.91 – 2.83 (m, 2H), 2.01 (quint, J = 5.8 Hz, 2H), 1.82 – 1.74 (m, 4H), 1.68 (s, 3H), 1.64 (s, 3H) ppm; ^13C NMR (100 MHz, CDCl_3): δ 174.0, 173.0, 172.9, 166.3, 140.6, 129.1, 128.3, 127.3, 74.1, 67.7, 64.9, 60.0, 58.0, 54.4, 48.8, 38.2, 32.3, 29.8, 29.2, 27.6, 27.1, 24.2, 19.8 ppm; FTIR (KBr): 3424, 2968, 2933, 1770, 1649, 1603, 1386, 1324, 1269, 1208, 1107, 984, 700 cm\(^{-1}\); anal. calcd for C_{25}H_{35}N_{5}O_{4}S_{2}: C, 54.75; H, 7.39; N, 12.77; found: C, 54.92; H, 6.93; N, 13.05.

3,4,5,6,7,8-hexahydro-2H-pyrrolo[1,2-a]pyrimidin-5-ium(2⁵S,6⁵R,8⁵R)-6-((R)-2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [DBNH][AMP]

Ampicillin trihydrated (600 mg, 1.487 mmol) reacted with DBN (185 mg) dichloromethane (4 mL each) for 90 minutes. The product is a yellow paste obtained in quantitative yield (783 mg, 1.486 mmol), T_g = 115.3 °C; ^1H NMR (400 MHz, CD_3OD): δ 7.46 – 7.26 (m, 5H), 5.51 (d, J = 3.9 Hz, 1H), 5.44 (d, J = 3.9 Hz, 1H), 4.61 (s, 1H), 4.15 (s, 1H), 3.68 (t, J = 7.2 Hz, 2H), 3.44 (t, J = 5.6 Hz, 2H), 3.39 (t, J = 5.6 Hz, 2H), 2.86
(t, J = 8.0 Hz, 2H), 2.15 (quint, J = 7.5 Hz, 2H), 2.03 (quint, J = 5.6 Hz, 2H), 1.60 (s, 3H), 1.52 (s, 3H) ppm; 
$^{13}$C NMR (100 MHz, CD$_3$OD): δ 175.1, 175.0, 174.8, 165.9, 141.4, 129.7, 129.1, 128.2, 75.0, 68.2, 65.6, 59.6, 58.9, 54.7, 43.5, 39.3, 31.5, 31.2, 28.0, 19.7, 19.6 ppm; FTIR (KBr): 3424, 2967, 2931, 2888, 1770, 1680, 1602, 1395, 1309, 1128, 1069, 701 cm$^{-1}$; anal. calcd for C$_{23}$H$_{31}$N$_{5}$O$_{4}$S.2.3H$_2$O: C, 53.64; H, 6.97; N, 13.60; S, 6.23; found C, 53.85; H, 7.38; N, 13.59; S, 5.73.

bis(dimethylamino)methaniminium 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylate, [TMGH][CIP]
Ciprofloxacin (200 mg, 0.604 mmol) reacted with tetramethylguanidine (70 mg) in 1:1 methanol/water (2 mL each) for 3 hours. The product is a white solid obtained in quantitative yield (269 mg, 0.603 mmol). mp > 200 °C; $^1$H NMR (400 MHz, CD$_3$OD): δ 8.43 (s, 1H), 7.90 (d, J = 13.8 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 3.58 (m, J = 3.6 Hz, 1H), 3.26 (t, J = 4.7 Hz, 4H). 3.04 (t, J = 4.7 Hz, 4H), 2.98 (s, 12H), 1.35 – 1.28 (m, 3H), 1.17 – 1.11 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CD$_3$OD): δ 176.3, 172.9, 163.3, 154.6 (d, J = 247.1 Hz), 147.0, 146.2 (d, J = 10.9 Hz), 140.1, 123.3 (d, J = 6.9 Hz), 119.4, 112.9 (d, J = 23.0 Hz), 106.5 (d, J = 2.8 Hz), 51.8 (d, J = 4.2 Hz), 46.4, 39.9, 35.5, 8.5 ppm; FTIR (KBr): 3422, 2969, 1629, 1575, 1479, 1403, 1384, 1293, 1257, 1038, 941, 825, 732, 622 cm$^{-1}$; anal. calcd for C$_{22}$H$_{31}$FN$_{6}$O$_{3}$: C, 55.59; H, 7.25; N, 17.68; found: C, 55.69; H, 7.22; N, 17.88.

2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepinium 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylate, [DBUH][CIP]
Ciprofloxacin (800 mg, 2.414 mmol) reacted with DBU (368 mg) in 1:1 methanol/water (4 mL each) for 2 hours. The product is a white solid obtained in quantitative yield (1165 mg, 2.410 mmol). mp > 200 °C; $^1$H NMR (400 MHz, CD$_3$OD): δ 8.45 (s, 1H), 7.91 (d, J = 13.5 Hz, 1H), 7.48 (d, J = 7.3 Hz, 1H), 3.63-3.57 (m, 3H), 3.54 (t, J = 5.8 Hz, 2H), 3.39-3.33 (t, J = 5.8 Hz, 2H), 3.29 – 3.24 (m, 4H), 3.07 – 3.01 (m, 4H), 2.72 – 2.67 (m, 2H), 2.03 (quint, J = 4 Hz, 2H), 1.83 – 1.63 (m, 6H), 1.36 – 1.28 (m, 2H), 1.17 – 1.11 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CD$_3$OD): δ 176.3, 172.9, 167.5, 154.6 (d, J = 247.1 Hz), 147.0, 146.2 (d, J = 11.0 Hz), 140.1, 123.4 (d, J = 6.1 Hz), 112.9 (d, J = 23.1 Hz), 106.5 (d, J = 2.7 Hz), 55.3, 51.9 (d, J = 4.4 Hz), 46.5, 39.4, 35.5, 33.7, 30.0, 27.5, 25.0, 20.5, 8.5 ppm; FTIR (KBr): 3424, 2965, 1648, 1631, 1583, 1478, 1383, 1293, 1257, 998, 825, 733, 623 cm$^{-1}$; anal. calcd for C$_{26}$H$_{34}$FN$_{5}$O$_{3}$: C, 54.44; H, 7.73; N, 12.21; found: C, 54.97; H, 7.68; N, 12.58.

3,4,5,6,7,8-hexahydro-2H-pyrrolo[1,2-a]pyrimidin-5-ium 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate, [DBNH][CIP]
Ciprofloxacin (600 mg, 1.811 mmol) reacted with DBN (225 mg) in a 1:1 mixture of methanol/water (3 mL each) for 2 hours. The product is a white solid obtained in 99 % yield (822 mg, 1.793 mmol). mp 160
°C dec.; T<sub>g</sub> = 66.4 °C; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.46 (s, 1H), 7.91 (d, J = 13.7 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 3.68 (t, J = 7.2 Hz, 2H), 3.59 (hept, J = 3.5 Hz, 1H), 3.45 (t, J = 5.7 Hz, 2H), 3.41 (t, J = 5.7 Hz, 2H), 3.29 – 3.24 (m, 4H), 3.07 – 3.01 (m, 4H), 2.89 (t, J = 7.9 Hz, 2H), 2.15 (quint, J = 7.6 Hz, 2H), 2.04 (quint, J = 5.8 Hz, 2H), 1.86 – 1.28 (m, 2H), 1.18 – 1.11 (m, 2H) ppm; <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD): δ 176.3 (d, J = 2.2 Hz), 172.9, 165.8, 154.6 (d, J = 2.2 Hz), 147.0, 146.2 (d, J = 10.7 Hz), 140.1, 123.4 (d, J = 7.1 Hz), 119.6, 112.9 (d, J = 23.1 Hz), 106.5 (d, J = 2.8 Hz), 54.5, 51.9 (d, J = 4.5 Hz), 46.5, 43.5, 39.6, 35.5, 31.2, 19.8, 19.6 (t, J = 10.7 Hz), 8.5 ppm; FTIR (KBr): 3425, 3134, 2954, 1680, 1626, 1586, 1490, 1382, 1297, 1254, 936, 835, 735, 624 cm<sup>-1</sup>.

Norfloxacin (142 mg, 0.430 mmol) reacted with tetramethylguanidine (50 mg, 0.430 mmol) in methanol (1 mL each) for 3 hours. The product is a white solid, obtained in 95% yield (178 mg, 0.409 mmol). mp > 200 °C; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.37 (s, 1H), 7.94 (d, J = 14.0 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 4.35 (quart, J = 7.0 Hz, 2H), 3.28 – 3.20 (m, 4H), 3.07 – 3.00 (m, 4H), 1.48 (t, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ 175.5 (d, J = 2.0 Hz), 166.4, 163.6, 152.7 (d, J = 248.4 Hz), 147.5, 145.6 (d, J = 10.3 Hz), 137.0, 119.7 (d, J = 7.3 Hz), 111.2 (d, J = 22.8 Hz), 110.4, 105.3 (d, J = 3.2 Hz), 50.9 (d, J = 3.7 Hz), 48.6, 45.5, 39.2, 14.3 ppm; FTIR (KBr): 3423, 3200, 2975, 2942, 1629, 1575, 1493, 1382, 1269, 1185, 927, 831, 627 cm<sup>-1</sup>; anal. calcd for C<sub>21</sub>H<sub>31</sub>FN<sub>6</sub>O<sub>3</sub>.1.5H<sub>2</sub>O: C, 54.65; H, 7.43; N, 18.21; found: C, 54.55; H, 7.12; N, 17.89.

Norfloxacin (214 mg, 0.650 mmol) reacted with DBU (100 mg) in methanol (1 mL each) for 2 hours. The product is a yellow solid obtained in 89% yield (273 mg, 0.580 mmol). mp 160 °C; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.39 (s, 1H), 7.94 (d, J = 13.7 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 4.35 (quart, J = 7.1 Hz, 2H), 3.62 – 3.56 (m, 2H), 3.53 (t, J = 5.8 Hz, 2H), 3.36 (t, J = 5.8 Hz, 2H), 3.28 – 3.21 (m, 4H), 1.82 – 1.64 (m, 6H), 1.49 (t, J = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ 174.1, 167.3, 163.8, 152.2 (d, J = 247.4 Hz), 146.1, 144.8 (d, J = 10.2 Hz), 136.6, 121.2 (d, J = 6.4 Hz), 116.0, 111.3 (d, J = 22.4 Hz), 105.0 (d, J = 2.9 Hz), 52.7, 51.0 (d, J = 4.0 Hz), 47.7, 45.5, 39.2, 32.4, 28.6, 26.7, 24.3, 20.0, 14.3 ppm; FTIR (KBr): 3423, 3266, 3134, 2985, 2939, 1650, 1630, 1584, 1493, 1388, 1256, 1184, 1106, 931, 827, 738, 626 cm<sup>-1</sup>; anal. calcd for C<sub>25</sub>H<sub>34</sub>FN<sub>5</sub>O<sub>3</sub>.1.5H<sub>2</sub>O: C, 59.48; H, 7.35; N, 13.87; found: C, 59.44; H, 7.38; N, 13.98.
Norfloxacin (600 mg, 1.885 mmol) reacted with DBN (234 mg) in 1:1 methanol/water (2 mL each) for 2 hours. The product is a yellow paste obtained in quantitative yield (830 mg, 1.884 mmol). T_g = -0.4 °C; \(^1\)H NMR (400 MHz, CD\(_3\)OD): \(\delta\) 8.39 (s, 1H), 7.95 (d, \(J = 13.7\) Hz, 1H), 7.02 (d, \(J = 7.1\) Hz, 1H), 4.36 (quart, \(J = 7.1\) Hz, 2H), 3.68 (t, \(J = 7.1\) Hz, 2H), 3.47 – 3.37 (m, 4H), 3.28 – 3.22 (m, 4H), 3.06 – 3.00 (m, 4H), 2.88 (t, \(J = 7.9\) Hz, 2H), 2.15 (quint, \(J = 7.6\) Hz, 2H), 2.03 (quint, \(J = 5.6\) Hz, 2H), 1.49 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD): \(\delta\) 176.1 (d, \(J = 2.5\) Hz), 172.9, 165.8, 154.4 (d, \(J = 246.8\) Hz), 147.3, 146.5 (d, \(J = 10.7\) Hz), 138.2, 124.0 (d, \(J = 7.0\) Hz), 119.8, 113.1 (d, \(J = 22.8\) Hz), 105.8 (d, \(J = 2.8\) Hz), 54.6, 51.9 (d, \(J = 4.3\) Hz), 49.6, 46.5, 43.5, 39.4, 31.2, 30.9 (t, \(J = 7.0\) Hz), 19.8, 19.6 (d, \(J = 10.5\) Hz), 14.7 ppm; FTIR (KBr): 3418, 3229, 3131, 2960, 2884, 1680, 1626, 1584, 1491, 1387, 1256, 1183, 1129, 1037, 931, 825, 738, 625 cm\(^{-1}\); anal. calcd for C\(_{23}\)H\(_{30}\)FN\(_5\)O\(_3\): C, 50.41; H, 7.65; N, 12.78; found: C, 50.56; H, 7.66; N, 12.49.

(R,S)-Ibuprofen (50 mg, 0.247 mmol) reacted with tetramethylguanidine (29 mg) in methanol (1 mL each) for 3 hours. The product is a white solid obtained in 98% yield (78 mg, 0.239 mmol). T_g = -11.8 °C, T_m = 115.4 °C; \(^1\)H NMR (400 MHz, CD\(_3\)Cl): \(\delta\) 7.72 (d, \(J = 7.9\) Hz, 2H), 6.98 (d, \(J = 7.9\) Hz, 2H), 3.54 (q, \(J = 7.0\) Hz, 1H), 2.76 (s, 12H), 2.38 (d, \(J = 7.0\) Hz, 2H), 1.80 (hept, \(J = 7.0\) Hz, 1H), 1.42 (d, \(J = 7.0\) Hz, 3H), 0.87 (d, \(J = 7.0\) Hz, 6H) ppm; \(^{13}\)C NMR (100 MHz, CD\(_3\)Cl): \(\delta\) 180.4, 162.5, 142.3, 138.8, 128.7, 127.6, 49.0, 45.2, 39.6, 30.4, 22.5, 19.8 ppm; FTIR (KBr): 3420, 2957, 2928, 2870, 1670, 1608, 1568, 1461, 1411, 1389, 1364, 1067, 883, 680 cm\(^{-1}\); anal. calcd for C\(_{18}\)H\(_{31}\)N\(_2\)O\(_2\): C, 66.51; H, 9.74; N, 12.93; found: C, 66.32; H, 9.86; N, 12.93.

(R,S)-Ibuprofen (301 mg, 1.459 mmol) reacted with DBU (220 mg) in methanol (1 mL each) for 6 hours. The product is a colorless paste obtained in 98% yield (512 mg, 1.429 mmol). T_g = -12.0 °C; \(^1\)H NMR (400 MHz, CD\(_3\)Cl): \(\delta\) 7.32 (d, \(J = 8.0\) Hz, 2H), 7.01 (d, \(J = 8.0\) Hz, 2H), 3.60 (q, \(J = 7.1\) Hz, 1H), 3.41 – 3.30 (m, 6H), 2.78 – 2.71 (m, 2H), 2.39 (d, \(J = 7.2\) Hz, 2H), 1.92 (quint, \(J = 6.0\) Hz, 2H), 1.80 (hept, \(J = 6.7\) Hz, 1H), 1.72 – 1.58 (m, 6H), 1.46 (d, \(J = 7.1\) Hz, 3H), 0.87 (d, \(J = 6.7\) Hz, 6H) ppm; \(^{13}\)C NMR (100 MHz, CD\(_3\)Cl): \(\delta\) 180.2, 166.0, 141.4, 139.0, 129.3, 128.7, 127.4, 127.1, 54.1, 48.5, 47.9, 45.0, 37.9, 32.0, 30.2, 29.0, 26.9, 23.9, 22.4, 22.3, 19.5, 19.4 ppm; FTIR (NaCl, Bulk): 3446, 3328, 3093, 2954, 2932, 2868, 1648, 1589, 1456, 1384, 1324, 1207, 857 cm\(^{-1}\); anal. calcd for C\(_{22}\)H\(_{33}\)N\(_2\)O\(_2\): C, 66.37; H, 9.72; N, 7.04; found: C, 66.25; H, 9.47; N, 7.35.
(R,S)-Ibuprofen (500 mg, 2.420 mmol) reacted with DBN (301 mg) in methanol (2 mL each) for 1 hour. The product is a colorless liquid obtained in quantitative yield (800 mg, 2.420 mmol). $T_g = -21.4 \, ^\circ C$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24 (d, J = 7.9 Hz, 2H), 6.95 (d, J = 7.9 Hz, 2H), 3.51 (q, J = 7.1 Hz, 1H), 3.41 (t, J = 7.1 Hz, 2H), 3.32 – 3.24 (m, 4H), 3.19 (t, J = 5.6 Hz, 2H), 2.78 (t, J = 7.9 Hz, 2H), 2.33 (d, J = 7.1 Hz, 2H), 2.04 (quint, J = 7.5 Hz, 2H), 1.84 (quint, J = 5.9 Hz, 2H), 1.74 (hept, J = 6.7 Hz, 1H), 1.38 (d, J = 7.1 Hz, 3H), 0.80 (d, J = 6.7 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 180.8, 164.1, 142.1, 138.5, 128.5, 127.2, 52.8, 48.7, 44.9, 42.3, 37.7, 30.5, 29.4, 22.2, 19.6, 18.7, 18.6 ppm; FTIR (KBr): 3421, 2956, 2927, 2869, 1681, 1388, 1307, 1067, 882, 670 cm$^{-1}$; anal. calcd for C$_{20}$H$_{30}$N$_2$O$_2$.0.5H$_2$O: C, 70.76; H, 9.20; N, 8.25; found: C, 70.63; H, 9.68; N, 7.93.

Naproxen-based ionic liquids were synthesized according to the following general procedure:

Naproxen sodium salt was dissolved in methanol and passed through a cation exchange column of Amberlyst 15 hydrogen (5 eq.). To the obtained solution of naproxen (ca. 50 mL) an equimolar amount of superbase was added as a methanolic solution (5 mL). Upon stirring at room temperature for 1 hour the solvent was removed in a rotary evaporator and the product was obtained pure after drying under high vacuum.

3,4,5,6,7,8,9,10-octahydro-2H-pyrimido[1,2-a]azepin-5-ium 2-(6-methoxynaphthalen-2-yl)-propanoate, [TMGH][NPX]

Naproxen sodium salt (600 mg, 2.379 mmol) and tetramethylguanidine (274 mg) were used. The product is a yellow solid obtained in quantitative yield (820 mg, 2.379 mmol). mp 149 °C; $^1$H NMR (400 MHz, CDCl$_3$): 7.65 (s, 1H), 7.61 – 7.47 (m, 3H), 7.03 – 6.96 (m, 2H), 3.82 (s, 3H), 3.66 (q, J = 7.1 Hz, 1H), 2.56 (s, 12H), 1.48 (d, J = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 180.0, 162.3, 156.9, 140.7, 133.0, 129.1, 129.0, 127.7, 126.1, 125.5, 118.1, 105.5, 55.2, 49.5, 39.3, 19.7 ppm; FTIR (KBr): 3414, 2959, 2935, 1666, 1605, 1568, 1453, 1387, 1262, 1229, 1062, 1028, 925, 857, 819, 747, 688 cm$^{-1}$; anal. calcd for C$_{19}$H$_{27}$N$_3$O$_3$: C, 65.83; H, 8.22; N, 12.07.

3,4,5,6,7,8,9,10-octahydro-2H-pyrimido[1,2-a]azepin-5-ium 2-(6-methoxynaphthalen-2-yl)-propanoate, [DBUH][NPX]

Naproxen sodium salt (600 mg, 2.379 mmol) and DBU (362 mg) were used. The product is a yellow paste obtained in 96% yield (874 mg, 2.284 mmol). $T_g = 20.1 \, ^\circ C$; $^1$H NMR (400 MHz, CDCl$_3$): 7.71 (s, 1H), 7.65 – 7.52 (m, 3H), 7.06 – 6.99 (m, 2H), 3.84 (s, 3H), 3.71 (q, J = 7.1 Hz, 1H), 3.28 (m, 6H), 2.65 – 2.57 (m, 2H), 2.42 (t, J = 7.1 Hz, 2H), 2.37 (t, J = 7.1 Hz, 2H), 2.25 (q, J = 7.1 Hz, 2H), 2.01 (quint, J = 7.5 Hz, 2H), 1.84 (quint, J = 5.9 Hz, 2H), 1.74 (hept, J = 6.7 Hz, 1H), 1.38 (d, J = 7.1 Hz, 3H), 0.80 (d, J = 6.7 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 180.0, 162.3, 156.9, 140.7, 133.0, 129.1, 129.0, 127.7, 126.1, 125.5, 118.1, 105.5, 55.2, 49.5, 39.3, 19.7 ppm; FTIR (KBr): 3414, 2959, 2935, 1666, 1605, 1568, 1453, 1387, 1262, 1229, 1062, 1028, 925, 857, 819, 747, 688 cm$^{-1}$; anal. calcd for C$_{20}$H$_{30}$N$_2$O$_2$.0.5H$_2$O: C, 70.76; H, 9.20; N, 8.25; found: C, 70.63; H, 9.68; N, 7.93.
1.79 (quint, J = 5.8 Hz, 2H), 1.63 – 1.43 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 180.8, 165.8, 156.9, 140.8, 133.1, 129.2, 129.2, 127.6, 126.3, 125.5, 118.1, 105.6, 55.3, 54.0, 49.3, 48.5, 38.0, 32.0, 29.1, 27.0, 24.1, 19.9, 19.7 ppm; FTIR (KBr): 3420, 3057, 2962, 2867, 1648, 1605, 1566, 1390, 1324, 1229, 1029, 926, 859, 690 cm$^{-1}$; anal. calcd for C$_{23}$H$_{30}$N$_2$O$_3$.CH$_3$OH: C, 69.54; H, 8.27; N, 6.76; found: C, 69.67; H, 8.61; N, 7.20.

**NMR spectra**

$^1$H NMR [TMGH][APA]

$^{13}$C NMR [TMGH][APA]
$^1$H NMR [DBNH][APA]

$^{13}$C NMR [DBNH][APA]
$^1$H NMR [TMGH][AMP]

$^{13}$C NMR [TMGH][AMP]
$^1$H NMR [DBUH][AMP]

$^{13}$C NMR [DBUH][AMP]
$^1$H NMR [TMGH][CIP]

$^{13}$C NMR [TMGH][CIP]
$^1$H NMR [DBUH][CIP]

$^{13}$C NMR [DBUH][CIP]
$^1$H NMR [DBNH][CIP]

$^{13}$C NMR [DBNH][CIP]
$^1$H NMR [TMGH][NOR]

$^{13}$C NMR [TMGH][NOR]
$^1$H NMR [DBUH][NOR]
$^1$H NMR [TMGH][IBU]

$^{13}$C NMR [TMGH][IBU]
$^1$H NMR [DBUH][IBU]

$^{13}$C NMR [DBUH][IBU]
$^1$H NMR [DBNH][IBU]
$^{13}\text{C NMR [DBNH][IBU]}$

$^{1}\text{H NMR [TMGH][NPX]}$
$^{13}$C NMR [DBUH][NPX]

FTIR spectra

[TMGH][APA] vs. 6-aminopenicillanic acid

[DBUH][APA] vs. 6-aminopenicillanic acid
[DBNH][APA] vs. 6-aminopenicillanic acid

[TMGH][AMP] vs. ampicillin
[DBUH][AMP] vs. ampicillin

[DBNH][AMP] vs. ampicillin
[TMGH][CIP] vs. ciprofloxacin

[DBUH][CIP] vs. ciprofloxacin
[DBNH][CIP] vs. ciprofloxacin

[TMGH][NOR] vs. norfloxacin
[DBUH][NOR] vs. norfloxacin
[DBUH][NPX] vs. naproxen

DSC spectra
DSC [DBNH][AMP]