Electronic supplementary Information

Development of Novel Ionic Liquids-APIs based on Ampicillin

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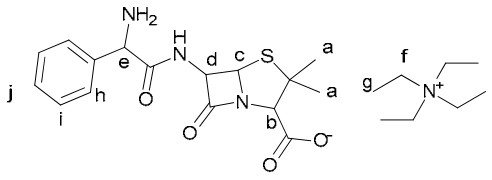
General remarks: Commercially available reagents were purchased from Aldrich, BDH – laboratory reagents and Solchemar and were used as received. The solvents were from Valente & Ribeiro and distilled before used. The basic anion-exchange resin Amberlite IRA-400-OH (ion-exchange capacity 1.4 eq.mL^{-1}) was purchased from Supelco. ^{1}H and ^{13}C NMR spectra in $(CD_3)_2SO$ or CD_3OD (from Euriso-Top) were recorded on a Bruker AMX400 spectrometer at room temperature unless specified otherwise. Chemical shifts are reported downfield in parts per million (ppm). IR spectra were measured on a Perkin Elmer 683. Optical rotations were recorded on a Perkin Elmer 241MC. The water content of the liquid $[P_{6,6,6,14}][Amp]$ was determined by Karl Fischer titration in a 831 KF coulometer Metrohom. Melting temperature (Tm) was determined by melting point apparatus (Stuart Scientific). DSC analysis is carried out using a TA Instruments Q-seriesTM Q200 DSC with a refrigerated cooling system. The sample is continuously purged with 50ml/mim nitrogen. About 5 to 10mg of ampicillin IL is crimped in an aluminum standard sample pan with lid.

Preparation of tetraethylammonium 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [TEA][Amp]:

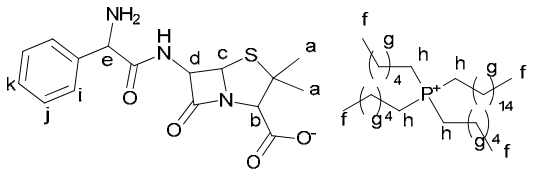
Tetraethylammonium bromide (0.321g; 1.53 mmol) was dissolved in methanol and passed through ion-exchange column Amberlite IRA-400-OH (5 eq., flow rate 0.133mL/mL/min= 8 BV/hr). Then, tetraethylammonium hydroxide solution was added slowly to ampicillin (0.549 g; 1.57 mmol) dissolved in 1M ammonium solution (50mg.mL^{-1}). The reaction mixture was stirred at room temperature for 1 h. After solvent evaporation, the residue was dissolved in 20mL of methanol/acetonitrile (1:9) and left refrigerated overnight (4 ºC) to induce crystallization of excess of the ampicillin. Then ampicillin crystals were filtered from the solution, the solution was evaporated and dried *in vacuo* for 24h. The desired product was obtained as a yellow solid (0.556g; 76.0%). mp 79ºC; $[\alpha]_D^{27}$= 48.7±2.5 (c= 2 mg.mL^{-1} in methanol); ^{1}H-NMR (400.13 MHz, CD_3OD) δ = 7.48 (2H, d, J = 7.4Hz, h), 7.36 (t, 1H, *J* = 7.3Hz, j), 7.30 (m, 2H, i), 5.00 (d, 1H, *J*= 6.0Hz, c), 4.64 (s, 1H, b), 4.33 (d, 1H, *J*= 6.0Hz, d), 3.42, (s, 1H, e) 3.28 (q, 8H, *J* = 7.3 Hz, f), 1.45 (s, 3H, a), 1.28 (tt, 12H, *J* = 1.9 Hz, *J* = 7.3 Hz g), 1.22 (s, 3H, a) ppm; ^{13}C-NMR (100.62 MHz, CD_3OD) δ = 175.58, 174.83, 140.88, 130.06, 129.88, 129.22, 128.58, 77.13, 66.66, 60.19, 60.00, 59.54, 53.27, 53.24, 53.21, 27.79, 27.44, 7.63 ppm; IR (KBr): υ = 3390, 2978, 2929, 1674, 1598, 1488, 1456, 1394, 1304, 1253, 1185, 1174, 1130, 1069, 1029, 1002, 968, 920, 871, 787, 701, 636 cm^{-1}; (EI^{+}) m/z calcd for $C_8H_{20}N^{+}$: 130.1590, found 130.1590; (EI^{-}) m/z calcd for $C_{16}H_{18}N_3O_4S^{-}$: 348.1024, found 348.1013.



[TEA][Amp]

Preparation of trihexyltetradecylphosphonium 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [$P_{6,6,6,14}$][Amp]:

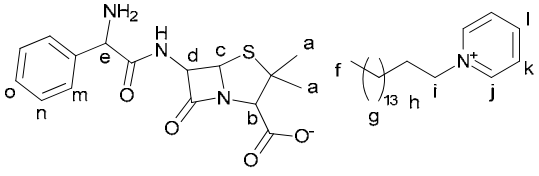
Trihexyltetradecyl phosphonium chloride (1.006g; 1.94mmol) was dissolved in methanol and passed through ion-exchange column Amberlite IRA-400-OH (5 eq., flow rate 0.133mL/mL/min= 8 BV/hr). Then, trihexyltetradecylphosphonium hydroxide solution was added slowly to ampicillin (0.761; 2.18mmol) dissolved in 1M ammonium solution (50mg.mL^{-1}). The mixture was stirred at room temperature for 1 h. After solvent evaporation, the residue was dissolved in 20mL of methanol/acetonitrile (1:9) and left refrigerated overnight (4 ºC) to induce crystallization of ampicillin excess. Then, ampicillin crystals were filtered from the solution which it was evaporated and dried *in vacuo* for 24h. The desired product was obtained as a yellow viscous liquid (1.331g; 80.0%). $[\alpha]_D^{27}$= 22.3±1.5 (c= 2 mg.mL^{-1} in methanol; Water content = 14.7 ppm (determined by Karl Fisher titration) ^{1}H-NMR (400.13 MHz, CD_3OD) δ = 7.48-7.27 (m, 5H, i, j,k), 5.01 (d, 1H, *J*= 6.0 Hz, c), 4.59 (s, 1H, b), 4.31 (d, 1H, *J*= 6.0 Hz, d), 3.44 (s, 1H, e), 2.19 (m, 8H, h), 1.65-1.22 (m, 54H, g and a) 0.94 (m, 12H, f) ppm; ^{13}C-NMR (100.62 MHz, CD_3OD) δ = 175.60, 174.90, 141.97, 129.76, 128.91, 128.35, 77.15, 66.59, 60.34, 60.16, 59.52, 33.12, 32.20, 31.85, 31.70, 31.63, 31.48, 30.85, 30.83, 30.81, 30.71, 30.53, 30.46, 29.92, 27.80, 27.46, 23.79, 23.51, 22.39, 22.35 22.30, 19.50, 19.44, 19.03, 18.97, 14.51, 14.38 ppm; IR (KBr): ν = 3301, 3186, 3060, 2956, 2952, 2855, 1671, 1601, 1485, 1317, 1299, 1268, 1215, 1130, 1111, 1028 cm^{-1}. (EI$^+$) m/z calcd for $C_{32}H_{68}P^+$: 483.5053, found 483.5056; (EI$^-$) m/z calc'd for $C_{16}H_{18}N_3O_4S^-$: 348.1024, found 348.1013.



[$P_{6,6,6,14}$][Amp]

Preparation of 1-hexadecylpyridin-1-ium 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [C_{16}Pyr][Amp]:

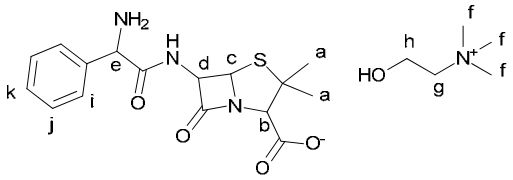
Cetylpyridinium chloride (0.694g; 2.04mmol), was dissolved in methanol and passed through ion-exchange column Amberlite IRA-400-OH (5 eq., flow rate 0.133mL/mL/min= 8 BV/hr). Then, cetylpyridinium hydroxide solution was added slowly to ampicillin (0.714g; 2.12mmol) dissolved in 1M ammonium solution (50mg.mL^{-1}). The mixture was stirred at room temperature for 1 h. After solvent evaporation the residue was dissolved in 20mL of methanol/acetonitrile (1:9) and left refrigerated overnight (4 ºC) to induce crystallization of ampicillin excess. Then, ampicillin crystals were filtered from the solution which it was evaporated and dried *in vacuo* for 24h. The desired product was obatined as a yellow solid (1.018g; 76.4%). mp 86ºC; $[\alpha]_D^{27}$= 51.7±0.9 (c= 2 mg.mL^{-1} in methanol); ^{1}H-NMR (400.13 MHz, CD_3OD) δ = 8.98 (d, 2H, *J* = 5.5Hz, j), 8.58 (t, 1H, *J* = 7.8Hz, l), 8.10 (t, 2H, *J* = 6.70Hz, k) 7.47 (d, 2H, *J* =7.3Hz, m), 7.35 (t, 2H, *J* = 7.4Hz, n), 7.28 (d, 1H, *J*= 7.3Hz, o), 5.0 (d, 1H, *J* =6.0 Hz, c), 4.62 (m, 3H, b and i), 4.33 (d, 1H, *J* = 6.0, d), 3.43 (1H, s, e), 2.01 (m, 2H, h), 1.65-1.11 (m, 32H, a and g), 0.90 (t, 3H, *J*=6.7 Hz, f) ppm; ^{13}C-NMR (100.62MHz, CD_3OD) δ = 175.52, 174.80 , 170.23, 146.87, 145.93, 129.88, 129.78, 129.76, 129.72, 129.56, 129.02, 128.59, 77.15, 66.65, 63.15, 62.40, 61.41, 60,18, 59.55, 33.09, 32.52, 30.80, 30.78, 30.74, 30.65, 30.53, 30.49, 30.15, 27.78, 27.45, 27.73, 23.76, 14.48 ppm;; IR (KBr): ν = 3419, 3061, 2923, 2852, 1688, 1593, 1483, 1456, 1385, 1176, 1130, 1029, 964, 778, 686 cm^{-1}; (EI$^+$) m/z calc'd for $C_{21}H_{38}N^+$: 304.2999, found 304,2999; (EI$^-$) m/z calc'd for $C_{16}H_{18}N_3O_4S^-$: 348,1024, found 348.1013.



[C_{16}Pyr][Amp]

Preparation of (2-Hydroxyethyl)trimethylammonium 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [choline][Amp]:

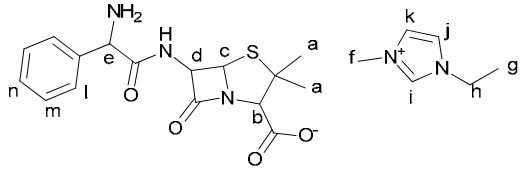
(2-Hydroxyethyl)trimethylammonium chloride (0.546g; 3.91mmol) was dissolved in methanol and passed through ion-exchange column Amberlite IRA-400-OH (5 eq., flow rate 0.133mL/mL/min= 8 BV/hr). Then, choline hydroxide solution was slowly added to ampicillin (1.606g; 4.60mmol) dissolved in 1M ammonium solution (50mg.mL^{-1}). The mixture was stirred at room temperature for 1 h. After solvent evaporation, the residue was dissolved in 20mL of methanol/acetonitrile (1:9) and left refrigerated overnight (4 ºC) to induce crystallization of ampicillin excess. Then, ampicillin crystals were filtered from the solution which it was evaporated and dried *in vacuo* for 24h. The desired product was obtained as a yellow solid (1.252g; 70.7%). mp 58ºC; $[\alpha]_D^{27}$= 52.3±0.8 (c= 2 mg.mL^{-1} in methanol) ^{1}H-NMR (400.13 MHz,(CD_3OD) δ = 7.49-7.27 (m, 5H, i, j, k), 5.00 (d, 1H, *J*=6.0 Hz, c), 4.65 (s, 1H, b), 4.34 (d, 1H, *J*= 6.0Hz, d), 3.98 (m, 2H, h), 3.46 (m, 2H, g), 3.42 (s, 1H, e), 3.19 (s, 9H, f), 1.45 (s, 3H, a), 1.22 (s, 3H, a) ppm; ^{13}C-NMR (100.62 MHz, CD_3OD) δ = 175.59, 174.91, 174.82, 140.95, 129.88, 129.22, 128.56, 77.11, 69.06, 66.67, 60,20, 60.04, 59.53, 57.10, 54.73, 27.78, 27.47 ppm; IR (KBr): ν = 3042, 2826, 1668, 1595, 1490, 1456, 1385, 1285, 1194, 1132, 1086, 1005, 922, 866, 784, 740, 702 cm^{-1}; (EI^+) m/z calc'd for $C_5H_{14}NO^+$: 104,1070, found 104.1070; (EI^-) m/z calc'd for $C_{16}H_{18}N_3O_4S^-$: 348,1024, found 348.1013.



[choline][Amp]

Preparation of 1-ethyl-3-methyl-1*H*-imidazol-3-ium 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate [EMIM][Amp]:

1-Ethyl-3-methyl-1*H*-imidazol-3-ium chloride (0.576; 3.93mmol), was dissolved in methanol and passed through ion-exchange column Amberlite IRA-400-OH (5 eq., flow rate 0.133mL/mL/min= 8 BV/hr). Then the 1-ethyl-3-methylimidazolium hydroxide solution was slowly added to Ampicillin (1.606g; 4.60mmol) dissolved in 1M ammonium solution (50mg.mL^{-1}). The mixture was stirred at room temperature for 1 h. After solvent evaporation, the residue was dissolved in 20mL solution (methanol/acetonitrile 1:9) and left refrigerated overnight (4 ºC) to induce crystallization of excess of ampicillin. Then, ampicillin crystals were filtered from the solution which it was evaporated and dried *in vacuo* for 24h. The desired product was obtained as a yellow solid (1.709g; 94.6%). mp 70-72 ºC) $[\alpha]_D^{27}$= 89.3±5.5 (c= 2 mg.mL^{-1} in methanol); ^{1}H-NMR (400.13 MHz, CD_3OD) δ = 7.63 (d, 1H, *J* = 1.9Hz, k), 7.55 (d, 1H, *J* = 1.9Hz, j),7.48-7.46 (m, 2H, l), 7.36-7.32 (m, 2H, m), 7.27-7.25 (m, 1H, n); 5.01 (d, 1H, *J*=6.0 Hz, c), 4.59 (s, 1H, b), 4.32 (d, 1H, *J*=6.0 Hz, d) 4.24 (q, 2H, *J*= 7.4Hz, h), 3.90 (s, 3H, f), 3.43 (s, 1H, e), 1,52 (t, 3H, *J*= 7.4Hz, g), 1.46 (s, 3H, a), 1.22 (s, 3H, a) ppm; ^{13}C-NMR (100.62, MHz, CD_3OD) δ = 175.57 , 175.15, 174.84, 141.24, 129.83, 129.12, 128.50, 124.96, 123.31, 77.12, 66.67, 60,18, 60.11, 59.54, 46.03, 36.46, 27.78, 27.47, 15.63 ppm; IR (KBr): ν = 3381, 2974, 2925, 2828, 1668, 1591, 1516, 1456, 1393, 1255, 1169, 1130, 1029, 962, 877, 824, 788, 746, 702, 648 cm^{-1}; (EI^+) m/z calc'd for $C_6H_{11}N_2^+$: 111,0917, found 111.0917; (EI^-) m/z calc'd for $C_{16}H_{18}N_3O_4S^-$: 348,1024, found 348.1013.



[EMIM][Amp]

Preparation of 3-(2-hydroxyethyl)-1-methyl-1*H*-imidazol-3-ium 6-(2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate [C_2OHMIM][Amp]:

3-(2-Hydroxyethyl)-1-methyl-1*H*-imidazol-3-ium chloride (0.625; 3.86 mmol), was dissolved in methanol and passed through ion-exchange column Amberlit IRA-400(OH) (5 eq., flow rate 0.133mL/mL/min= 8 BV/hr). Then the hydroxide solution formed was slowly added to Ampicillin (1.624g; 4.65mmol; 1.2eq) dissolved in 1M ammonium solution (50mg.mL^{-1}). The mixture was stirred at room temperature for 1 h. After solvent evaporation, the residue

was dissolved in 20mL of methanol/acetonitrile (1:9) and left refrigerated overnight (4 ºC) to induce crystallization of excess of ampicillin. Then, ampicillin crystals were filtered from the solution which it was evaporated and dried *in vacuo* for 24h. The desired product was obtained as a yellow solid (1.593g ; 86.8%). mp 115-117 ºC; $[\alpha]_D^{26}$= 86.3±4.5 (c= 2 mg.mL^{-1} in methanol); ^{1}H-NMR (400.13 MHz, CD_3OD) δ = 7.61 (d, 1H, *J*= 1.8Hz, k), 7.55 (d, 1H, *J* = 1.8Hz, j), 7.47 (d, 2H, *J* = 7.2Hz, l), 7.35 (t, 2H, *J*= 7.3Hz, m), 7.29 (d, 1H, *J* = 7.2Hz, n), 5.00 (d, 1H, *J*=6.0 Hz, c), 4.63 (s, 1H, b), 4.33 (d, 1H, *J*=6.0 Hz, d), 4.28 (t, 2H, *J*=3.8 Hz, g), 3.92 (s, 3H, f), 3.87(t, 2H, *J*=3.8 Hz), 3.42(s, 1H, e), 1.45(s, 3H, a), 1.22 (s, 3H, a) ppm; ^{13}C-NMR (100.62 MHz, CD_3OD) δ = 175.60, 175.17, 174.85, 141.22, 129.85, 129.14, 128.51, 124.74, 124.03, 77.11, 66.67, 61.06, 60.19, 60.12, 59.53, 53.29, 36.46, 27.78, 27.48 ppm; IR (KBr): ν = 3394, 2969, 288, 2836, 1674, 1545, 1456, 1394, 1299, 1253, 1167, 1131, 1073, 1027, 1071, 871, 784, 752, 702, 652, 622 cm^{-1}; (EI$^+$) m/z calc'd for $C_6H_{11}N_2O^+$: 127,0866, found 127.0866; (EI$^-$) m/z calc'd for $C_{16}H_{18}N_3O_4S^-$: 348,1024, found 348.1013.