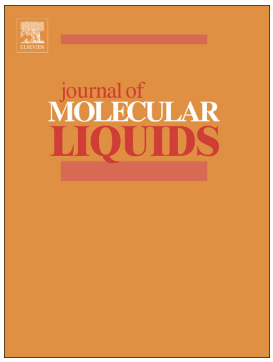


Synthesis and characterization of chiral ionic liquids based on quinine, l-proline and l-valine for enantiomeric recognition

Tânia E. Sintra, Mikhail G. Gantman, Sónia P.M. Ventura, João A.P. Coutinho, Peter Wasserscheid, Peter S. Schulz

PII: S0167-7322(18)36299-8
DOI: https://doi.org/10.1016/j.molliq.2019.03.084
Reference: MOLLIQ 10625

To appear in: *Journal of Molecular Liquids*

Received date: 3 December 2018
Revised date: 5 February 2019

Please cite this article as: T.E. Sintra, M.G. Gantman, S.P.M. Ventura, et al., Synthesis and characterization of chiral ionic liquids based on quinine, l-proline and l-valine for enantiomeric recognition, Journal of Molecular Liquids, https://doi.org/10.1016/j.molliq.2019.03.084

Synthesis and characterization of chiral ionic liquids based on quinine, L-proline and L-valine for enantiomeric recognition

Tânia E. Sintra,[a] Mikhail G. Gantman,[b] Sónia P. M. Ventura,[a] João A. P. Coutinho,[a] Peter Wasserscheid[b] and Peter S. Schulz*[b]

[a] CICECO - Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Campus Universitário de Santiago 3810-193 Aveiro, Portugal

[b] Department of Chemical and Biological Engineering (CBI), Institute of Chemical Reaction Engineering, University of Erlangen-Nuremberg, Egerlandstraße 3, 91058 Erlangen, Germany

*Corresponding author: e-mail address: peter.schulz@fau.de

Abstract: The separation of enantiomers remains a major challenge for the pharmaceutical industry. In this work, eight chiral ionic liquids (CILs) directly derived from the 'chiral pool' were synthesized and characterized in order to develop enantioselective systems, for the chiral resolution. According to their chiral cations, three different groups of CILs were prepared, namely based on quinine, L-proline and L-valine, and their enantiomeric recognition ability evaluated. For that purpose the diastereomeric interactions between a racemic mixture of Mosher's acid sodium salt and each CIL were studied using ^{19}F-NMR spectroscopy. The remarkable chemical shift dispersion induced by some CILs demonstrates their potential application in chiral resolution. Additionally the optical rotation,

thermophysical properties and ecotoxicity against the marine bacteria *Aliivibrio fischeri* of these chiral ionic liquids were addressed.

Keywords: chiral ionic liquids, enantioselectivity, chiral resolution, Mosher's acid, thermophysical properties, ecotoxicity.

1. Introduction

The differences in the pharmacological activities of enantiomers may result in serious problems in the treatment of diseases using racemates.[1] Regulatory authorities therefore require a complete pharmacological and toxicological characterization of each enantiomer separately, even when the drug is commercialized as a racemate.[2,3] Furthermore, the commercialization of the therapeutically active isomer should be prioritized. In order to get single enantiomer drugs, there are three approaches to produce them: chiral pool synthesis (limited by the availability of precursors from natural sources), asymmetric synthesis (requiring specific expensive catalysts) and chiral resolution. Taking into consideration the chiral resolution, crystallization is still one of the most used technique, due to its simplicity of operation and cost‐efficiency.[4] Nevertheless, the direct crystallization of an enantiomer from a racemic solution is only achievable when the enantiomers in their mixtures form separate but pure crystals, which only represent 5 to 10 % of the racemates. On the other hand, enantioselective chromatographic methods have been widely used for resolving racemates. However, large-scale chromatographic processes are expensive and require careful design and optimization.[4] The enantioselective liquid-liquid extraction has been considered as an attractive technology to get isolated enantiomers from racemic mixtures in a continuous mode, being easy to scale-up, to use in continuous operation, and of low cost.[5] The chiral selector plays a key role in this extraction process, and the chiral recognition mechanism follows the "three-point rule" by which chiral recognition requires a minimum of three simultaneous

interactions between the chiral selector and the enantiomers, at least one of these interactions being stereochemically dependent.[6] The most used chiral selectors are cyclodextrin derivatives, tartrate derivatives, crown ethers and metal complexes.[5]

Ionic liquids (ILs) are a class of solvents that, due to their unique properties, have been proposed in the past few years as alternatives to volatile organic compounds for many applications.[7,8] Chiral ionic liquids (CILs) are a subclass of ILs with a chiral moiety at the cation, anion or both. The first CIL reported was the 1-butyl-3-methylimidazolium lactate, by Seddon and co-workers.[9] Afterwards, the synthesis of imidazolium-CILs based on chiral amines (D-α-phenylethylamine) or amino acids (L-alanine, L-leucine, and L-valine) was described by Bao.[10] Since then many examples of CILs were reported and explored for various applications, namely in separation processes where CILs have been used as chiral selectors, background electrolyte additives, chiral ligands and chiral stationary phases in chromatographic and electrophoretic techniques.[11–17] Some of the CILs known for their chiral recognition ability have been used as NMR chiral shift reagents for the discrimination of racemates.[18–24] Recently, chiral imidazolium-based ILs naturally derived from carvone[25] and D-xylose[26] have demonstrated excellent enantioselective discrimination of the racemic Mosher's acid salt. In 2015, aqueous biphasic systems based on CILs and salts were proposed for the enantiomeric separation of amino acids.[27,28] In this work, CIL is not only a constituent of the biphasic system as well as the chiral selector.[27,28] These preliminary results show still limited enantioselectivities.

In this work we prepared eight novel CILs for chiral resolution directly derived from the 'chiral pool'. The diastereomeric interactions between a racemic mixture of Mosher's acid sodium salt and each CIL were studied using ^{19}F-NMR spectroscopy and additionally they were characterized regarding their optical rotation, thermophysical properties and ecotoxicity against the marine bacteria *Aliivibrio fischeri* (*A. fischeri*).

2. Experimental section

2.1. Materials. Eight CILs based on chiral selector were synthesized, namely [C_1Qui]I, 1-methyl quininium iodide; [C_1Qui][C_1SO_4], 1-methyl quininium methylsulfate; [C_1Qui][NTf_2], 1-methyl quininium bis(trifluoromethylsulfonyl)imide; [$C_1C_1C_1$Pro]I, *N*,*N*-dimethyl-L-proline methyl ester iodide; [$C_1C_1C_1$Pro][C_1SO_4], *N*,*N*-dimethyl-L-proline methyl ester methylsulfate; [$C_2C_2C_2$Pro]Br, *N*,*N*-diethyl-L-proline ethyl ester bromide; [C_1,C_1,C_1Val]I *N*,*N*,*N*-trimethyl-L-valinolium iodide and [C_1,C_1,C_1Val][C_1SO_4], *N*,*N*,*N*-trimethyl-L-valinolium methylsulfate. Quinine (98 wt % of purity), iodomethane (99 wt % of purity), dimethyl sulfate (99 wt % of purity), bis(trifluoromethane)sulfonimide lithium salt (99 wt % of purity), dichloromethane anhydrous (99.8 wt % of purity), ethanol (99.8 wt % of purity), acetone (HPLC grade), potassium carbonate (99 wt % of purity), L-proline (99 wt % of purity), bromoethane (98 wt % of purity), acetonitrile (99.8 wt % of purity), chloroform (99 wt % of purity), L-valine (98 wt % of purity), tetrahydrofuran anhydrous (99.9 wt % of purity), sodium borohydride (99 wt % of purity), sulfuric acid (99.9 wt% of purity), methanol (99 wt % of purity), ethyl acetate (99.8 wt % of purity), potassium hydroxide (90 wt % of purity), formic acid (98 wt % of purity), formaldehyde (37 wt % in water solution), hydrochloric acid (37 wt % in water solution) and Mosher's acid (97 wt % of purity) were acquired from Sigma-Aldrich®.

2.2. Synthesis and Characterization of CILs. Considering the chiral cation, three different groups of CILs were prepared: (I) quinine-, (II) L-proline- and (III) L-valine-based CILs (Scheme 1, 2 and 3). The water content of the CILs was determined by coulometric Karl Fischer titration and was verified to be less than 0.1wt% in all samples. The chemical structures and acronym of all CILs synthesized are depicted in Figure 1. The structure of all compounds synthesized was confirmed by ^{1}H and ^{13}C NMR spectroscopy, and when

appropriate, by the 2D ^{1}H-^{13}C HSQC and ^{1}H-^{1}H Cosy NMR sequences, showing a high purity level of all the ionic structures after their synthesis, as reported in the Supporting Information (Figures S1-S19).

2.2.1. Quinine-based CILs

1-Methyl quininium iodide, $[C_1Qui]I$, was prepared by the dropwise addition of 1.4 mL of iodomethane (22.3 mmol), in a dichloromethane solution, to a solution of quinine (6.9 g, 21.3 mmol) in dichloromethane, at 0 °C and under inert atmosphere. The reaction mixture was stirred overnight at room temperature, under inert atmosphere. The obtained solid was filtrated, washed with acetone, and recrystallized in ethanol. Finally, the residual solvent was removed under reduced pressure and the obtained compound was dried under vacuum (10^{-2} mbar, 313 K) for at least 48 h, affording $[C_1Qui]I$ as a pale yellow solid (6.7 g, 68% yield). 1-Methyl quininium methylsulfate, $[C_1Qui][C_1SO_4]$, was obtained in a very similar manner as $[C_1Qui]I$, using the dimethyl sulfate as the alkylating agent. $[C_1Qui][C_1SO_4]$ was obtained as a white solid (66% yield). 1-Methyl quininium bis(trifluoromethylsulfonyl)imide, $[C_1Qui][NTf_2]$, was prepared by adding an aqueous solution of 8.0 g (17.7 mmol) $[C_1Qui][C_1SO_4]$ to an aqueous solution of 5.3 g (18.6 mmol) $Li[NTf_2]$ leading to the precipitation of $[C_1Qui][NTf_2]$. The final IL was washed three times with 40 mL water. Finally, the residual water was removed under vacuum for at least 48 h, affording $[C_1Qui][NTf_2]$ as a white solid (8.7 g, 79% yield).

2.2.2. L-Proline-based CILs

In order to prepare *N*,*N*-dimethyl-L-proline methyl ester iodide, $[C_1C_1C_1Pro]I$, potassium carbonate (14.4 g, 104.2 mmol) was added into the mixture of L-proline (12.0 g, 104.2 mmol) and acetonitrile (150 ml). After stirring the mixture for 1h at room temperature, 20 mL of iodomethane (321.0 mmol) was added dropwise at 0 °C, under inert atmosphere. The reaction mixture was stirred overnight at room temperature, under inert atmosphere. Then, the solid

was filtered off, and the resulting liquid was concentrated under reduced pressure. The light yellow solid crude was washed with chloroform, filtered, and the liquid phase concentrated under reduced pressure, obtaining a viscous yellow oil. The obtained oil was solubilized and crystallized in ethanol. Finally, the residual solvent was removed under vacuum for at least 48 h, affording $[C_1C_1C_1Pro]I$ as a white solid (4.4 g, 15% yield). To prepare *N*,*N*-dimethyl-L-proline methyl ester methylsulfate, $[C_1C_1C_1Pro][C_1SO_4]$, potassium carbonate (4.8 g, 34.7 mmol) was added to the mixture of L-proline (4.0 g, 34.7 mmol) and acetonitrile (70 ml). After stirring the mixture for 1h at room temperature, 10 mL of dimethyl sulfate (106.0 mmol) were added dropwise at 0 °C, under inert atmosphere. The reaction mixture was stirred overnight at room temperature, under inert atmosphere. Then, the solid was filtered off, and the resulting liquid was concentrated under reduced pressure. Then, the obtained pale yellow liquid was washed with ethyl acetate (3 x 10 mL). Finally, the residual ethyl acetate was removed under reduced pressure, followed by high vacuum for at least 48 h, affording $[C_1C_1C_1Pro][C_1SO_4]$ as pale yellow liquid (7.2 g, 76% yield). In order to obtain *N*,*N*-diethyl-L-proline ethyl ester bromide, $[C_2C_2C_2Pro]Br$, potassium carbonate (4.8 g, 34.7 mmol) was added into the mixture of L-proline (4.0 g, 34.7 mmol) and acetonitrile (70 ml). After stirring the mixture for 1h at room temperature, 8 mL of bromoethane (107.7 mmol) was added dropwise at 0°C, under inert atmosphere. The reaction mixture was stirred at 70 °C for 2 days in an inert atmosphere. After filtering, the resulting liquid was concentrated under reduced pressure. Then, the obtained pale yellow solid was washed with ethyl acetate (3 x 10 mL). Finally, the residual ethyl acetate was removed under reduced pressure, followed by high vacuum for at least 48 h, affording $[C_2C_2C_2Pro]Br$ as a white solid (3.3 g, 34% yield).

2.2.3. L-Valine-based CILs

L-Valinol, L-2-amino-3-methyl-1-butanol, was obtained by reduction of L-valine, as described in literature.[29] L-Valine (31.0 g, 264.6 mmol) was added to a stirred suspension of

sodium borohydride (25.0 g, 661.5 mmol) in tetrahydrofuran (250 mL). The flask was immersed in an ice-water bath, and a solution of concentrated sulfuric acid (17.5 mL, 330.8 mmol) in ether was added dropwise at such a rate as to maintain the reaction mixture below 20 °C (addition time approximately 3h). The reaction mixture was stirred at room temperature overnight, and then 50 mL of methanol were added carefully to destroy the BH_3 in excess. The mixture was concentrated to c.a. 100 mL and 5 N of potassium hydroxide (250 mL) was added. After removing the tetrahydrofuran and methanol under reduced pressure, the mixture was heated at reflux for 3 h (110 °C). The turbid aqueous mixture was cooled and filtered. The filtrate was diluted with additional water (50 mL). The dichloromethane extraction (4 x 250 mL) followed by evaporation of the solvent left a yellow liquid, which was distilled to yield 15.5 g (57%) of a colourless solid. The *N,N*-dimethylvalinol was synthesized by reductive alkylation of primary amine of L-valinol using the well-known Eschweiler-Clark reaction.[30,31] For that, 30 mL of formic acid (795.0 mmol) were slowly added to an aqueous solution of L-valinol (15.5 g, 150.3 mmol) at 0 °C. The formaldehyde solution (35 mL of 37% wt in a water solution, 470.1 mmol) was added to the resulting solution. The flask was connected to a reflux condenser and heated to 95 °C. A vigorous evolution of CO_2 begins after 2-3 minutes, at which time the flask was removed from the oil bath until the gas evolution notably subsides (15 – 20 min) and then heated at 100 °C overnight. After the solution has been cooled, 70 mL of 4 N hydrochloric acid was added and the solution evaporated to dryness under reduced pressure. The pale yellow liquid was dissolved in 30 mL of water, and the organic base was liberated by the addition of 70 mL of 9 N of potassium hydroxide. The upper organic phase was separated, and the aqueous phase (lower phase) was extracted with dichloromethane (3 x 50 mL). The organic base and the dichloromethane extracts were combined, followed by evaporation of the solvent that left a pale yellow liquid, which was distilled to yield 12.8 g (65%) of a colourless liquid. *N,N,N*-

Trimethyl-L-valinolium iodide, $[C_1C_1C_1Val]I$,[31] was prepared by the dropwise addition of 3.0 mL of iodomethane (48.0 mmol), in a dichloromethane solution, to a solution of *N*,*N*-dimethylvalinol (6.0 g, 45.7 mmol) in dichloromethane, at 0 °C and under inert atmosphere. The reaction mixture was stirred overnight at room temperature, under inert atmosphere. The obtained solid was filtered and the residual solvent removed under high vacuum for at least 48 h, affording $[C_1C_1C_1Val]I$ as white solid (11.3 g, 90% yield). *N*,*N*,*N*-Trimethyl-L-valinolium methylsulfate, $[C_1C_1C_1Val][C_1SO_4]$, was prepared by dropwise addition of 4.0 mL of dimethyl sulfate (43.2 mmol), in a dichloromethane solution, to a solution of *N*,*N*-dimethylvalinol (5.4 g, 41.1 mmol) in dichloromethane, at 0 °C and under inert atmosphere. The reaction mixture was stirred overnight at room temperature, under inert atmosphere. Dichloromethane was removed under reduced pressure and the obtained colorless liquid was dried under high vacuum for at least 48 h, affording $[C_1C_1C_1Val][C_1SO_4]$ as colorless liquid (9.3 g, 88% yield).

2.3. Thermogravimetric Analysis. The onset temperature of decomposition was determined by TGA. TGA was conducted on a Setsys Evolution 1750 (SETARAM) instrument. The sample was heated in an alumina crucible, under nitrogen flow, over a temperature range of 300−1000 K, and with a heating rate of 5 $K \cdot min^{-1}$.

2.4. Differential Scanning Calorimetry. The melting temperatures were measured using a differential scanning calorimetry (DSC), Hitachi DSC7000X model, working at atmosphere pressure. The equipment was previously calibrated with several standards with weight fraction purities higher than 99%. Each sample (5 mg) was submitted to three cycles of cooling and heating at 2 $K \cdot min^{-1}$. The thermal transitions temperatures were taken as the peak temperature. The temperature uncertainty calculated through the average of the standard deviation of several consecutive measurements was better than ± 0.1 K.

2.5. Optical rotation. The optical rotation of the synthesized CILs was carried out at 589 nm using a polarimeter JASCO P-2000 and a cylindrical glass cell CG3-100 3.5 x 100 mm (1mL), at 298 K.

2.6. Microtox Assay. To evaluate the ecotoxicity of the CILs synthesized, the Standard Microtox liquid-phase assay was applied. Microtox is a bioluminescence inhibition method based on the bacterium *A. fischeri* (strain NRRL B-11177) luminescence after its exposure to each sample solution at 288.15 K. In this work, the standard 81.9% test protocol was followed.[32] The microorganism was exposed to a range of diluted aqueous solutions of each compound (from 0 to 81.9 wt %), where 100% corresponds to a previously prepared stock solution, with a known concentration. After 5, 15, and 30 min of exposure to each aqueous solution, the bioluminescence emission of *A. fischeri* was measured and compared with the bioluminescence emission of a blank control sample. Thus, the corresponding 5, 15, and 30 min EC_{50} values (EC_{50} being the estimated concentration yielding a 50% of inhibition effect), plus the corresponding 95% confidence intervals, were estimated for each compound tested by nonlinear regression, using the least-squares method to fit the data to the logistic equation.

2.7. Chiral discrimination ability. After the successful synthesis of the target CILs, the chiral discrimination ability was evaluated by studying the diastereomeric interaction between each CIL and the racemic Mosher's acid sodium salt. For that, each CIL was dissolved in 0.5 mL CD_2Cl_2 to obtain a 0.5 M solution and stirred with 0.2 mL of a saturated aqueous solution of racemic Mosher's acid sodium salt (2.0 M). After stirring, the mixture was allowed to equilibrate overnight at room temperature, aiming at the complete separation of the coexisting phases. At this point, the lower organic rich-phase was carefully separated and analyzed using ^{19}F NMR spectroscopy. Duplicate measurements were carried out. The differentiation of the diastereomers was easily visible via the different shift of the signal of

the CF_3 group in Mosher's acid carboxylate. Racemic Mosher's acid sodium salt was synthesized by stirring racemic Mosher's acid (1.0 g, 4.3 mmol) with an equimolar amount of NaOH (170.8 mg, 4.3 mmol) in 50 ml H_2O for 1 h and subsequent evaporation of the solvent.

3. Results and Discussion

In this work, a series of CILs naturally derived from chiral compounds, namely quinine, L-proline and L-valine, were prepared and characterized. Their acronym and chemical structure are depicted in Figure 1. All CILs were obtained with high purity levels and yield, cf. the Experimental Section.

The adoption by the industry of renewable natural sources as starting materials has become a topic of increasing importance. Due to its recognized application as chiral selector,[33–38] quinine, a natural alkaloid, was selected to incorporate three CILs here studied. The synthesis of $[C_1Qui]I$ was already described in literature;[39] however to the best of our knowledge, $[C_1Qui][C_1SO_4]$ and $[C_1Qui][NTf_2]$ have not been reported hitherto. Natural amino acids and their derivatives provide the most abundant renewable natural chiral pool, and can form an efficient, practical, and facile precursor for the preparation of chiral compounds. Since amino acids have both a carboxylic acid residue and an amino group in a single molecule, they can be used as either anions or cations. In the present work, three L-proline- and two L-valine-based CILs were prepared and characterized. L-Proline is a representative amino acid with the chiral centre in the pyrrole ring, so the CILs derived from L-proline cannot be racemized easily.[21] While the synthesis of $[C_1C_1C_1Pro]I$ and $[C_2C_2C_2Pro]Br$ reported in literature comprises two steps, esterification and *N*-alkylation,[21] the here proposed synthetic route is simpler, being a one-pot synthesis. The here reported L-valine-based ILs were readily obtained from this branched-chain amino acid in a three step synthesis: reduction of L-valine, Eschweiler-Clark reaction, followed by *N*-alkylation.[40] Zhao et al.[41] have already reported

the preparation of $[C_1C_1C_1Val]I$ by using a similar procedure. To the best of our knowledge, the synthesis of $[C_1C_1C_1Pro][C_1SO_4]$ and $[C_1C_1C_1Val][C_1SO_4]$ have not been reported hitherto.

For all the obtained CILs their optical rotation, melting and decomposition temperatures, and ecotoxicity were estimated. The specific rotations, $[\alpha]_D^{25}$, of the CILs and respective chiral precursor are indicated in Table S1. While L-proline-based CILs present optical rotations with lower magnitude than L-proline, quinine and L-valine based CILs show higher optical activity when compared with respective precursors.

Decomposition and melting temperatures of the CILs were measured by TGA and DSC, respectively, and are presented in Table 1. From the TGA profiles depicted in the Supporting Information (Figure S20), as well as from the Td values, it is possible to conclude that all CILs studied present a high thermal stability, at least up to 445 K. Nevertheless, $[C_1C_1C_1Val]I$ decomposes immediately after its melting temperature is reached.

Table 1. Temperature of fusion (T_{fus}) and temperature of decomposition (T_d) of the obtained CILs.

CIL	T_{fus} / K	T_d / K
$[C_1Qui]I$	497.55	510.23
$[C_1Qui][C_1SO_4]$	464.25	514.08
$[C_1Qui][NTf_2]$	404.31	525.48
$[C_1C_1C_1Pro]I$	377.00	491.09
$[C_1C_1C_1Pro][C_1SO_4]$	230.38	548.19
$[C_2C_2C_2Pro]Br$[a]	376.00	451.07
$[C_1C_1C_1Val]I$[b]	495.25	503.99
$[C_1C_1C_1Val][C_1SO_4]$	321.76	485.65
Quinine	448.15[c]	
L-Proline	501.15[c]	
L-Valine	568.15[c]	

[a] Solid-solid transition temperature = 349.89 K. [b] Solid-solid transition temperature = 379.19 K. [c] ChemSpider database (http://www.chemspider.com; at October 11th, 2017).

The ecotoxicological impact of the CILs studied was evaluated using the standard Microtox acute assay. Althougth ILs have been considered as an innovative approach to sustainable chemistry, their solubility in water allows their easy access to the aquatic compartment, which makes them potentially hazardous compounds to aquatic organisms.[42] The standard assay using the luminescent marine bacteria *A. fischeri*, the Microtox® bioassay, is today one of the most widespread toxicological bioassays due to its quick response, simplicity and cost-effective implementation. Indeed, this assay has been widely used to evaluate the toxicity of various ionic liquid families.[43–47] Thus, EC_{50} values ($mg \cdot L^{-1}$), the estimated concentration yielding a 50% of luminescence inhibition of the bacteria *A. fischeri*, were determined for each CIL after 5, 15, and 30 min of exposure to the marine bacteria, and reported in the Supporting Information, Table S2. In general, the exposure time had little or no impact on the ecotoxicity of the studied compounds. In order to contemplate the entire toxic effect, only the EC_{50} values obtained after 30 min of exposure were considered for further discussion. With the exception of quinine-based CILs which belongs to the category "acute 3" ($10 < EC_{50} < 100$ $mg \cdot L^{-1}$), the remaining CILs can be classified as non-hazardous substances ($EC_{50} > 100$ $mg \cdot L^{-1}$), according to the European Legislation for the aquatic ecosystems.[48] According to Passino's classification,[49] the CILs here investigated can be categorized as: "moderately toxic" (quinine-based CILs, with $10 < EC_{50} < 100$ $mg \cdot L^{-1}$), "practically harmless" ($[C_1C_1C_1Pro][C_1SO_4]$, with $100 < EC_{50} < 1000$ $mg \cdot L^{-1}$) and "harmless" (L-valine-based CILs, $[C_1C_1C_1Pro]I$ and $[C_2C_2C_2Pro]Br$, with $EC_{50} > 1000$ $mg \cdot L^{-1}$). Figure 2 shows the EC_{50} data of the CILs in mM, being possible to rank their ecotoxicity according to the following tendency (30 min of exposure): $[C_1C_1C_1Val]I < [C_1C_1C_1Pro]I < [C_1C_1C_1Val][C_1SO_4] < [C_2C_2C_2Pro]Br < [C_1C_1C_1Pro][C_1SO_4] < [C_1Qui]I < [C_1Qui][C_1SO_4] < [C_1Qui][NTf_2]$. Considering the anion impact, the results obtained suggest that the replacement of an iodide by a methylsulfate anion increases the toxicity of the CILs against *A.*

fischeri. Additionally, their toxicity increases with the chiral cation nature, following the trend: $[C_1C_1C_1Val]^+$ < $[C_1C_1C_1Pro]^+$ < $[C_1Qui]^+$. This trend may be related with the enhancement of the ILs hydrophobic/lipophilic character, defined in several works by the octanol-water partition coefficients (K_{ow}),[50,51] which is in accordance with the log K_{ow} of their precursors (-0.01, 0.05 and 2.51 for L-valinol, L-proline methyl ester and quinine, respectively).[52]

After their synthesis and characterization, the enantiomeric recognition ability of CILs was evaluated. For that, the diastereomeric interactions between a racemic mixture of Mosher's acid sodium salt and each CILs were studied using ^{19}F-NMR spectroscopy. The split of the signal related to the CF_3-group of the racemic Mosher's acid sodium salt indicates the chiral discrimination properties of CILs. The chemical shift difference of the CF_3 signals of racemic Mosher's acid sodium salt in presence of CILs are summarized in Table 2. As presented in Figure 3, quinine- and L-valine-based CILs and $[C_1C_1C_1Pro]I$ show good splitting of the CF_3 signal of racemic Mosher's acid sodium salt, while in the case of $[C_1C_1C_1Pro][C_1SO_4]$ and $[C_2C_2C_2Pro]Br$ no splitting was observed. Considering the quinine-based CILs, the split of the signal related to the CF_3-group of the racemic Mosher's acid sodium salt increases with the anion nature, following the trend: I^- < $[C_1SO_4]^-$ < $[NTf_2]^-$. This trend may be related with the enhancement of the counter anion hydrophobic/lipophilic character, which is in agreement with previous data.[24] The same trend was observed for the L-valine-based CILs. The remarkable chemical shift dispersion induced by some of the CILs demonstrates their potential application in chiral resolution.

Table 2. Chemical shift difference of the CF_3 signals of racemic Mosher's acid sodium salt in the presence of each CIL under study.

CIL	$\Delta\delta^{R/S} \pm \sigma$ / Hz
$[C_1Qui]I$	21.0 ± 1.6
$[C_1Qui][C_1SO_4]$	34.5 ± 1.8
$[C_1Qui][NTf_2]$	54.8 ± 0.6
$[C_1C_1C_1Pro]I$	7.8 ± 1.2
$[C_1C_1C_1Pro][C_1SO_4]$	NS
$[C_2C_2C_2Pro]Br$	NS
$[C_1C_1C_1Val]I$	8.4 ± 0.5
$[C_1C_1C_1Val][C_1SO_4]$	10.3 ± 0.2

NS - no splitting observed for the CF_3 signal.

4. Conclusion

Herein eight CILs were efficiently synthesized from naturally occurring enantiopure compounds (L-valine, L-proline and quinine) and characterized regarding their optical rotation, thermophysical properties and ecotoxicity against the marine bacteria *A. fischeri*. All CILs synthesized exhibit a high thermal stability, at least up to 445 K. Furthermore, with the exception of quinine-based CILs, they present low ecotoxicity being in general considered as "practically harmless" or even "harmless" for the bacteria analyzed. Among all the CILs investigated, quinine-based compounds were particularly promising for the future use in enantiomeric separations, as outstanding shift differences were observed in case of Mosher's acid carboxylate as a racemic probe.

Acknowledgements

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, POCI-01-0145-FEDER-007679 (FCT Ref. UID /CTM /50011/2013), financed by national funds through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement. The authors acknowledge the FCT funding through the projects "Multi-purpose strategies for broadband agro-forest and fisheries by-products valorization: a step forward for a truly integrated biorefinery (POCI-01-0145-FEDER 016403) and "ChiResus-Chiral resolution of drugs in centrifugal partition chromatography

using enantioselective aqueous biphasic systems (POCI-01-0145-FEDER-030750). T.E. Sintra acknowledges COST Action CM1206 (EXIL – Exchange on Ionic Liquids) for the STSM grant (COST-STSM-CM1206-34926). S.P.M. Ventura acknowledges FCT/MEC for a contract under *Investigador* FCT 2015 contract number IF/00402/2015.

REFERENCES

1. Ariens, E. J. Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology. *Eur. J. Clin. Pharmacol.* **1984**, *26*, 663–668.
2. U.S. Food and Drug Administration. FDA'S Policy Statement for the Development of New Stereoisomeric Drugs. *Chirality* **1992**, *4*, 338–340.
3. European Medicines Agency - Quality - Investigation of chiral active substances http://www.ema.europa.eu/ema/index.jsp;curl=pages/medicines/pips/EMEA-001743-PIP01-14/pages/about_us/general/index.jsp?curl=pages/regulation/general/general_content_000706.jsp&mid=WC0b01ac0580028bfd (accessed Aug 30, 2017).
4. Lorenz, H.; Seidel-Morgenstern, A. Processes To Separate Enantiomers. *Angew. Chemie Int. Ed.* **2014**, *53*, 1218–1250.
5. Schuur, B.; Verkuijl, B. J. V.; Minnaard, A. J.; de Vries, J. G.; Heeres, H. J.; Feringa, B. L. Chiral Separation by Enantioselective Liquid–liquid Extraction. *Org. Biomol. Chem.* **2011**, *9*, 36–51.
6. Pirkle, W. H.; Pochapsky, T. C. Considerations of Chiral Recognition Relevant to the Liquid Chromatography Separation of Enantiomers. *Chem. Rev.* **1989**, *89*, 347–362.
7. Rogers, R. D. CHEMISTRY: Ionic Liquids--Solvents of the Future? *Science.* **2003**, *302*, 792–793.
8. Tröger-Müller, S.; Brandt, J.; Antonietti, M.; Liedel, C. Green Imidazolium Ionics-From Truly Sustainable Reagents to Highly Functional Ionic Liquids. *Chem. - A Eur. J.* **2017**, *23*, 11810–11817.
9. Earle, M. J.; McCormac, P. B.; Seddon, K. R. Diels–Alder Reactions in Ionic Liquids. *Green Chem.* **1999**, *1*, 23–25.

10. Bao, W.; Wang, Z.; Li, Y. Synthesis of Chiral Ionic Liquids from Natural Amino Acids. *J. Org. Chem.* **2002**, *68*, 591–593.
11. Bica, K.; Gaertner, P. Applications of Chiral Ionic Liquids. *European J. Org. Chem.* **2008**, *2008*, 3235–3250.
12. Payagala, T.; Armstrong, D. W. Chiral Ionic Liquids: A Compendium of Syntheses and Applications (2005-2012). *Chirality* **2012**, *24*, 17–53.
13. Liu, Q.; Wu, K.; Tang, F.; Yao, L.; Yang, F.; Nie, Z.; Yao, S. Amino Acid Ionic Liquids as Chiral Ligands in Ligand-Exchange Chiral Separations. *Chem. - A Eur. J.* **2009**, *15*, 9889–9896.
14. Ríos-Lombardía, N.; Busto, E.; Gotor-Fernández, V.; Gotor, V.; Porcar, R.; García-Verdugo, E.; Luis, S. V.; Alfonso, I.; García-Granda, S.; Menéndez-Velázquez, A. From Salts to Ionic Liquids by Systematic Structural Modifications: A Rational Approach Towards the Efficient Modular Synthesis of Enantiopure Imidazolium Salts. *Chem. - A Eur. J.* **2010**, *16*, 836–847.
15. Foreiter, M. B.; Gunaratne, H. Q. N.; Nockemann, P.; Seddon, K. R.; Srinivasan, G. Novel Chiral Ionic Liquids: Physicochemical Properties and Investigation of the Internal Rotameric Behaviour in the Neat System. *Phys. Chem. Chem. Phys.* **2014**, *16*, 1208–1226.
16. Kimaru, I. W.; Morris, L.; Vassiliou, J.; Savage, N. Synthesis and Evaluation of L-Phenylalanine Ester-Based Chiral Ionic Liquids for GC Stationary Phase Ability. *J. Mol. Liq.* **2017**, *237*, 193–200.
17. Singh, A.; Chopra, H. K. Synthesis, Characterization and Applications of Some Novel DMAP-Based Chiral Ionic Liquids. *J. Mol. Liq.* **2018**, *266*, 106–111.
18. Wasserscheid, P.; Bösmann, A.; Bolm, C. Synthesis and Properties of Ionic Liquids Derived from the 'Chiral Pool.' *Chem. Commun.* **2002**, *112*, 200–201.
19. Clavier, H.; Boulanger, L.; Audic, N.; Toupet, L.; Mauduit, M.; Guillemin, J.-C. Design and Synthesis of Imidazolinium Salts Derived from (l)-Valine. Investigation of Their Potential in Chiral Molecular Recognition. *Chem. Commun.* **2004**, *0*, 1224–1225.
20. Levillain, J.; Dubant, G.; Abrunhosa, I.; Gulea, M.; Gaumont, A.-C. Synthesis and Properties of Thiazoline Based Ionic Liquids Derived from the Chiral Pool. *Chem. Commun.* **2003**, *0*, 2914–2915.
21. Gao, H.-S.; Hu, Z.-G.; Wang, J.-J.; Qiu, Z.-F.; Fan, F.-Q. Synthesis and Properties of Novel Chiral Ionic Liquids from L-Proline. *Aust. J. Chem.* **2008**, *61*, 521–525.

22. Vasiloiu, M.; Cervenka, I.; Gaertner, P.; Weil, M.; Schröder, C.; Bica, K. Amino Alcohol-Derived Chiral Ionic Liquids: Structural Investigations toward Chiral Recognition. *Tetrahedron: Asymmetry* **2015**, *26*, 1069–1082.
23. Ishida, Y.; Miyauchi, H.; Saigo, K. Design and Synthesis of a Novel Imidazolium-Based Ionic Liquid with Planar Chirality. *Chem. Commun.* **2002**, *0*, 2240–2241.
24. Heckel, T.; Winkel, A.; Wilhelm, R. Chiral Ionic Liquids Based on Nicotine for the Chiral Recognition of Carboxylic Acids. *Tetrahedron: Asymmetry* **2013**, *24*, 1127–1133.
25. Santamarta, F.; Vilas, M.; Tojo, E.; Fall, Y. Synthesis and Properties of Novel Chiral Imidazolium-Based Ionic Liquids Derived from Carvone. *RSC Adv.* **2016**, *6*, 31177–31180.
26. Jayachandra, R.; Reddy, S. A Remarkable Chiral Recognition of Racemic Mosher's Acid Salt by Naturally Derived Chiral Ionic Liquids Using 19 F NMR Spectroscopy. *RSC Adv.* **2016**, *6*, 39758–39761.
27. Wu, D.; Zhou, Y.; Cai, P.; Shen, S.; Pan, Y. Specific Cooperative Effect for the Enantiomeric Separation of Amino Acids Using Aqueous Two-Phase Systems with Task-Specific Ionic Liquids. *J. Chromatogr. A* **2015**, *1395*, 65–72.
28. Wu, H.; Yao, S.; Qian, G.; Yao, T.; Song, H. A Resolution Approach of Racemic Phenylalanine with Aqueous Two-Phase Systems of Chiral Tropine Ionic Liquids. *J. Chromatogr. A* **2015**, *1418*, 150–157.
29. Abiko, A.; Masamune, S. An Improved, Convenient Procedure for Reduction of Amino Acids to Aminoalcohols: Use of NaBH4-H2SO4. *Tetrahedron Lett.* **1992**, *33*, 5517–5518.
30. Icke, R.; Wisegarver, B.; Alles, G. B-PHENYLETHYLDIMETHYLAMINE. *Org. Synth.* **1945**, *25*, 89.
31. Brunet, J.-J.; Chauvin, R.; Chiffre, J.; Huguet, S.; Leglaye, P. New Chiral Zwitterionic Iron Hydride Complexes with 'Ephosium' and 'Valphosium' Ligands. *J. Organomet. Chem.* **1998**, *566*, 117–123.
32. AZUR Environmental, MicrotoxOmniTM Software for Windows® 95/98/NT. Carlsbad, CA, U.S.A.,1999.
33. Ianni, F.; Carotti, A.; Marinozzi, M.; Marcelli, G.; Di Michele, A.; Sardella, R.; Lindner, W.; Natalini, B. Diastereo- and Enantioseparation of a Nα-Boc Amino Acid with a Zwitterionic Quinine-Based Stationary Phase: Focus on the Stereorecognition Mechanism. *Anal. Chim. Acta* **2015**, *885*, 174–182.

34. Ianni, F.; Pataj, Z.; Gross, H.; Sardella, R.; Natalini, B.; Lindner, W.; Lämmerhofer, M. Direct Enantioseparation of Underivatized Aliphatic 3-Hydroxyalkanoic Acids with a Quinine-Based Zwitterionic Chiral Stationary Phase. *J. Chromatogr. A* **2014**, *1363*, 101–108.

35. Keunchkarian, S.; Padró, J. M.; Gotta, J.; Nardillo, A. M.; Castells, C. B. Synthesis and Evaluation of a Chiral Stationary Phase Based on Quinine: Enantioresolution of Dinitrophenyl Derivatives of α-Amino Acids. *J. Chromatogr. A* **2011**, *1218*, 3660–3668.

36. Bicker, W.; Chiorescu, I.; Arion, V. B.; Lämmerhofer, M.; Lindner, W. Contributions to Chromatographic Chiral Recognition of Permethrinic Acid Stereoisomers by a Quinine Carbamate Chiral Selector: Evidence from X-Ray Diffraction, DFT Computations, 1H NMR, and Thermodynamic Studies. *Tetrahedron: Asymmetry* **2008**, *19*, 97–110.

37. Lindner, W.; LÄMMERHOFER, M.; Maier, N. Cinchonan Based Chiral Selectors for Separation of Stereoisomers. PCT/EP97/02888, 1997.

38. Julínek, O.; Krupička, M.; Lindner, W.; Urbanová, M. Enantioselective Interaction of Carbamoylated Quinine and (S)-3,5-Dinitrobenzoyl Alanine: Theoretical and Experimental Circular Dichroism Study. *Phys. Chem. Chem. Phys.* **2010**, *12*, 11487–11497.

39. Piette, V.; Lindner, W.; Crommen, J. Enantioseparation of Anionic Analytes by Non-Aqueous Capillary Electrophoresis Using Quinine and Quinidine Derivatives as Chiral Counter-Ions. *J. Chromatogr. A* **2000**, *894*, 63–71.

40. Toda, F.; Tanaka, K. New Chiral Ammonium Salt Hosts Derived from Amino Acids: Very Efficient Optical Resolution of 2,2′-Dihydroxy-1,1′-Binaphthyl by Complexation with These Host Compounds. *Chem. Commun.* **1997**, *24*, 1087–1088.

41. Zhao, J.; Zheng, M.-X.; Lin, Y.-J.; Chen, Y.-C.; Ruan, Y.-P.; Zhang, H. Inclusion Resolution of 1,1'-Bi-2-Naphthol: Crystal Structure and CD Spectroscopy of the Inclusion Complexes. *Acta Physico-Chimica Sin.* **2010**, *26*, 1832–1836.

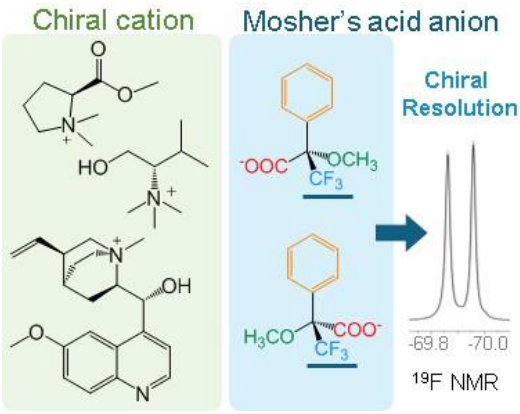
42. Thuy Pham, T. P.; Cho, C.-W.; Yun, Y.-S. Environmental Fate and Toxicity of Ionic Liquids: A Review. *Water Res.* **2010**, *44*, 352–372.

43. Ventura, S. P. M.; Marques, C. S.; Rosatella, A. A.; Afonso, C. A. M.; Gonçalves, F.; Coutinho, J. A. P. Toxicity Assessment of Various Ionic Liquid Families towards Vibrio Fischeri Marine Bacteria. *Ecotoxicol. Environ. Saf.* **2012**, *76*, 162–168.

44. Viboud, S.; Papaiconomou, N.; Cortesi, A.; Chatel, G.; Draye, M.; Fontvieille, D.

Correlating the Structure and Composition of Ionic Liquids with Their Toxicity on Vibrio Fischeri: A Systematic Study. *J. Hazard. Mater.* **2012**, *215*, 40–48.

45. Samorì, C.; Pasteris, A.; Galletti, P.; Tagliavini, E. Acute Toxicity of Oxygenated and Nonoxygenated Imidazolium-Based Ionic Liquids to Daphnia Magna and Vibrio Fischeri. *Environ. Toxicol. Chem.* **2007**, *26*, 2379–2382.
46. Sintra, T. E.; Nasirpour, M.; Siopa, F.; Rosatella, A. A.; Gonçalves, F.; Coutinho, J. A. P.; Afonso, C. A. M.; Ventura, S. P. M. Ecotoxicological Evaluation of Magnetic Ionic Liquids. *Ecotoxicol. Environ. Saf.* **2017**, *143*, 315–321.
47. Taha, M.; Almeida, M. R.; Silva, F. A. e.; Domingues, P.; Ventura, S. P. M.; Coutinho, J. A. P.; Freire, M. G. Novel Biocompatible and Self-Buffering Ionic Liquids for Biopharmaceutical Applications. *Chem. - A Eur. J.* **2015**, *21*, 4781–4788.
48. EU, Environmental Hazards 10 March 2011 http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev01/English/04e_part4.pdf (accessed Oct 13, 2018).
49. Passino, D. R. M.; Smith, S. B. Acute Bioassays and Hazard Evaluation of Representative Contaminants Detected in Great Lakes Fish. *Environ. Toxicol. Chem.* **1987**, *6*, 901–907.
50. Montalbán, M. G.; Hidalgo, J. M.; Collado-González, M.; Díaz Baños, F. G.; Víllora, G. Assessing Chemical Toxicity of Ionic Liquids on Vibrio Fischeri: Correlation with Structure and Composition. *Chemosphere* **2016**, *155*, 405–414.
51. Ropel, L.; Belvèze, L. S.; Aki, S. N. V. K.; Stadtherr, M. A.; Brennecke, J. F. Octanol–water Partition Coefficients of Imidazolium-Based Ionic Liquids. *Green Chem.* **2005**, *7*, 83–90.
52. ChemSpider database http://www.chemspider.com (accessed Oct 13, 2018).



Graphical Abstract

Highlights

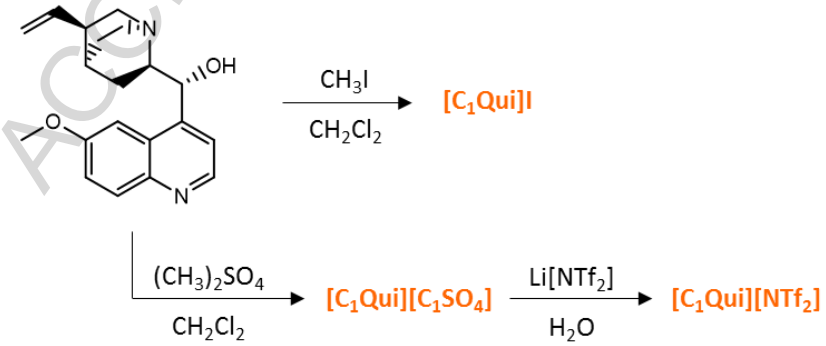
Chiral ionic liquids derived from valine, proline and quinine are successfully prepared.

In general, these chiral compounds exhibit high thermal stability and low ecotoxicity.

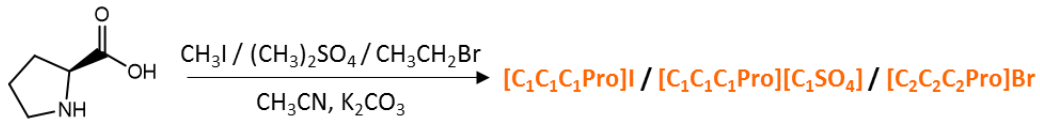
Outstanding shift difference of racemic Mosher's acid carboxylate are observed.

Quinine-based compounds seem to be particularly promising for chiral resolution.

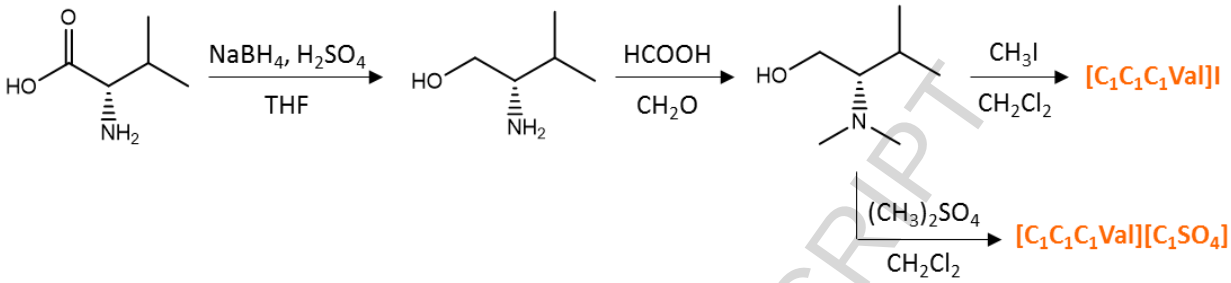
Schemes and Figures



Scheme 1. Synthesis scheme followed to prepare the quinine-based CILs.



Scheme 2. Synthesis scheme followed to prepare the L-proline-based CILs.



Scheme 3. Synthesis scheme followed to prepare the L-valine-based CILs.

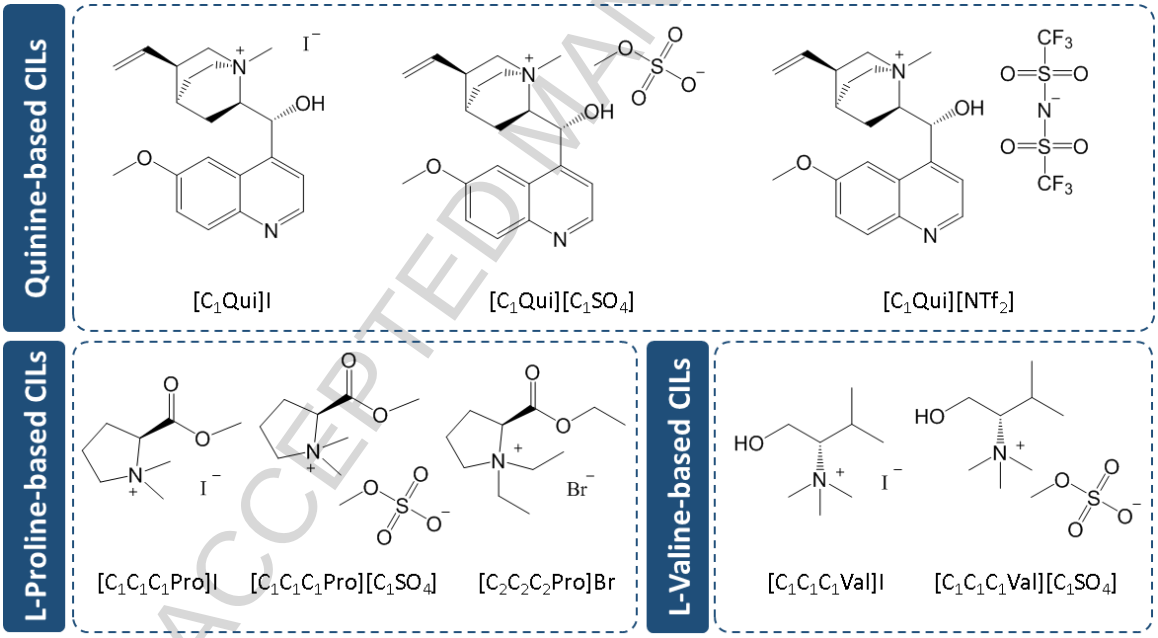


Figure 1. Chemical structures and acronym of all ILs with chiral cation here synthesized.

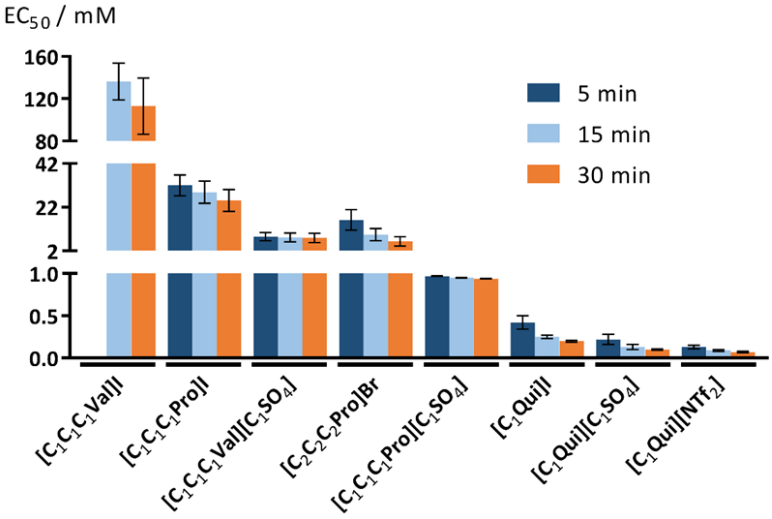


Figure 2. EC50 values (mM) determined after 5, 15, and 30 minutes of *V. fischeri* exposure. The error bars correspond to 95% confidence level limits.

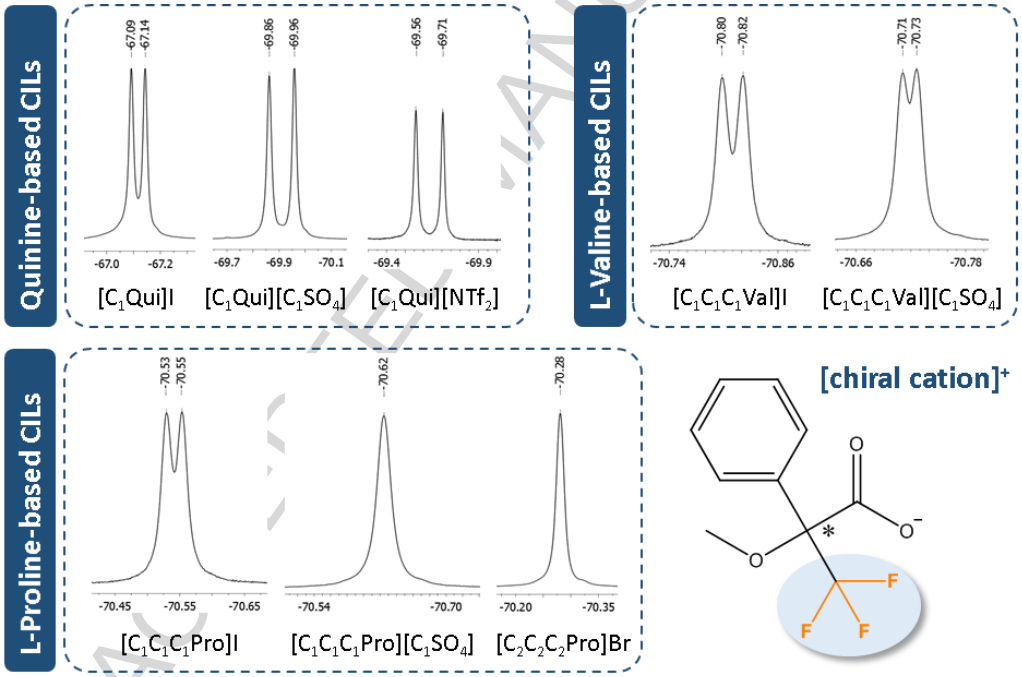


Figure 3. The partial ^{19}F NMR spectra of CILs under study and the racemic Mosher's acid salt complex.