



Using dicationic ionic liquids to upgrade the cytotoxicity and solubility of poorly water-soluble drugs

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ABSTRACT

New dicationic ionic liquids (DcILs) based on carboxylic acid-derived, *N*-acetyl amino acid-derived or bromide anions, and ammonium cations were synthesized and characterized. DcILs were employed as co-solvents to improve the solubility of ibuprofen and ketoprofen belonging to BCS class II. These DcILs demonstrated to be less cytotoxic towards fibroblasts L929 cells and contributed to an augment in the solubility of both drugs when compared with monocationic ionic liquids (McILs). The cytotoxic profile of some of these ILs was established, and when the linker between two ammonium cations was an ether group or a short alkyl chain an IC₅₀ higher than 200 mM for fibroblasts L929 cells was achieved.

The anion structure showed to be a key factor in the solubility of both drugs, being the family of carboxylic acid-derived, the one that presented the most significant effect, followed by *N*-acetyl amino acid-derived and finally bromide. The two dimensional ¹H¹H- NOESY NMR spectra showed the interaction between the IL and the two oral drugs, responsible for the improvement of their solubility. The lipophilicity (logP) of ibuprofen and ketoprofen reduced in the presence of these new DcILs.

1. Introduction

Oral drug delivery (ODD) is the most widely accepted route of administration by patients, compared to other routes of administration, such as parenteral, due to the ease of administration, painless and requires less patient care and supervision costs (Homayun et al., 2019). Although, ODD also has disadvantages, such as low solubility and permeability, and elevated degradation of some drug molecules (DM) (Alqahtani et al., 2021). In order to try to address these disadvantages, oral delivery based on ionic liquids (ILs) has become appealing as an alternative for more efficient ODD (Homayun et al., 2019). ILs have demonstrated the ability to improve specific drug transport to the target site of action (Wu et al., 2021).

The ability of ILs to solvate drugs by improving their solubility is defined by the ionic interactions between ILs and drugs (Moshikur et al., 2021). Solvation power of an IL is extremely reliant on the properties of its constituent cations and anions, thus the choice of a suitable counterion is of utmost importance for the rate at which an IL can solubilize the DM. Both cation and anion have a meaningful impact on the IL's physicochemical properties, ability to dissolve drugs and toxicity. Usually, toxicity issues related with the use of some IL cations and anions were re-

ported (Pedro et al., 2020). However, toxicity has been shown to vary depending on the cation/anion combination of the IL (Petkovic et al., 2010). Effectiveness of the dissolution process of a drug in the presence of IL relies on the capacity of IL to interact with the DM to form IL-drug interactions that are more stable than drug-drug and IL-IL interactions (Petkovic et al., 2010).

Dicationic ionic liquids (DcILs) are a class of novel ILs containing of two cationic moieties associated with a spacer and two anionic moieties. DcILs are more advantageous than traditional monocationic ionic liquids (McILs) as they exhibit greater thermal and chemical stability, outstanding structural tunability and higher heat capacity (Sidat et al., 2019). Due to their characteristics and tunability, DcILs are suitable for a wide range of applications, such as high-temperature organic synthesis, chromatographic stationary phases, stable quasi-solid-state dye-sensitized solar cell, separation process, and new high-temperature lubricant (Yang Xuzhao and Yun, 2023). The physicochemical properties of DcILs can also be tuned by modifying the length and type of spacer connecting the cation heads, as well as the type of cations (Zafer et al., 2009).

The introduction of a new cationic moiety in the ammonium cation to prepare a DcIL, can further, reduce the toxicity of the IL due to an

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enhancement of its polarity. DcILs have a smaller environmental effect than their monocationic counterpart, which indicates an improvement on biocompatibility (Guglielmero et al., 2018). As mentioned earlier, the toxicity of an IL is determined by the characteristics of its cations/anions. The head groups and the chain length of the cationic structure have been shown to greatly influence the toxicity of the IL (Montalbán et al., 2018). Whereas, increasing the length of central chain makes dicationic compounds more toxic, just as increasing the length of the alkyl side chain in monocationic compounds makes them more toxic (Flieger and Flieger, 2020). Long alkyl side or linkage chains, the increase in the number of $-\text{CH}_2\text{CH}_2\text{OH}$ groups and multiple covalent bonds are structural characteristics able to substantially enhance toxicity of dicationic compounds (Anderson et al., 2005). However, the knowledge on DcILs cytotoxicity is still scarce.

Pérez et al. (Pérez et al., 2020) assessed the cytotoxicity of ten pyridinium-based ILs, five dicationic ionic liquids ($[\text{C}_2(\text{Pyr})_2]\text{Br}_2$, $[\text{C}_4(\text{Pyr})_2]\text{Br}_2$, $[\text{C}_6(\text{Pyr})_2]\text{Br}_2$, $[\text{C}_8(\text{Pyr})_2]\text{Br}_2$ and $[\text{C}_{12}(\text{Pyr})_2]\text{Br}_2$) and the five homologous McILs in four cell lines (HeLa, MCF-7 and EA.hy926 human cell lines and BGM which is a green monkey cell line). Overall, dicationic ionic liquids have been shown to be less cytotoxic than their McILs counterparts, which means that dicationic ionic liquids can be specifically synthesized as an alternative to McILs, for biological and pharmaceutical applications where they still have limited used.

Our group has previously synthesized McILs based on cholinium cation and *N*-acetyl amino acids (Jesus et al., 2019) and alkyl sulfonates (Jesus et al., 2021) as anions to improve the solubility of paracetamol and sodium diclofenac. Further, we have also synthesized new dianionic ILs based on ammonium cation and phosphonate (D.A.S. Agostinho et al., 2021) and dicarboxylic acids (D.A.S. Agostinho et al., 2021) as anion, which enhanced the solubility of oral drugs (ODs) BCS II as ibuprofen (IBU) and piroxicam (PXM). In this work, a new class of DcILs based on the ammonium cation and carboxylic and *N*-acetyl amino acids as anion were synthesized. Thirteen new DcILs and three McILs (for comparative purposes) were synthesized and are represented in Fig. 1. These new ILs were examined as co-solvents to improve the solubility of ketoprofen (KETO) and IBU, Fig. 2. Furthermore, their cytotoxicity was evaluated using L929 cells.

2. Materials and methods

2.1. Materials

N-Methyldiethanolamine ($\geq 98.0\%$), 1,6-dibromohexane (98.0%), 1-bromohexane (99.0%), 1,4-dibromohexane (99%), 1,10-dibromohexane (98.0%), 1-octanol (99.0%), Amberlite™ IRN-78, 4-isobutyl- α -methylphenylacetic acid (IBU) (99.0%), ketoprofen (98%) were purchased from Alfa Aesar. Bis(2-bromoethyl) ether (98%) was acquired from TCI. Acetic acid (99%), butyric acid (99%) and *N*-acetyl glycine (99%) were supplied by Aldrich. Ethyl acetate and acetonitrile were purchased from Carlo Erba Reagents and hexane from Laborspirit. Deuterium oxide (99.9%) and dimethyl sulfoxide- d_6 (99.8%) were produced by Eurisotop.

N-Acetyl alanine and *N*-acetyl phenylalanine were synthesized as described in literature (Jesus et al., 2019).

2.2. General procedure for the synthesis of $[\text{N}_{1,6,2\text{OH},2\text{OH}}]\text{Br}$

Methyldiethanolamine (100 mmol) was mixed with the alkylating agent 1-bromohexane (2 equiv.), and *n*-hexane in a pressure reaction vessel, keeping at 80–90 °C for a day. IL was washed with ethyl acetate to eliminate the excess alkylating agent. Subsequently, IL was dried in the vacuum, and their purity validated by ^1H NMR. This IL was achieved 95% yield.

2.3. General procedure for the synthesis of $[(\text{N}_{1,2\text{OH},2\text{OH}})_2\text{C}_2\text{OC}_2]\text{Br}_2$, $[(\text{N}_{1,2\text{OH},2\text{OH}})_2\text{C}_4]\text{Br}_2$, $[(\text{N}_{1,2\text{OH},2\text{OH}})_2\text{C}_6]\text{Br}_2$ and $[(\text{N}_{1,2\text{OH},2\text{OH}})_2\text{C}_{10}]\text{Br}_2$

Methyldiethanolamine (2 equiv.) and the alkylating agent, 1,4-dibromobutane or 1,6-dibromohexane or 1,10-dibromodecane or bis(2-bromoethyl) ether (1 equiv.) were mixed in acetonitrile in a pressure reaction vessel. The mixture was maintained during one day at 90 °C. The dicationic ionic liquids were washed with ethyl acetate and dried in vacuum at 50 °C for 1–2 days.

2.4. General procedure for the metathesis reaction

An aqueous solution of quaternary or bisquaternary ammonium salt was slowly passed through an anion exchange column Amberlite™ IRN-78. Then, the corresponding hydroxide solution was gradually added to a solution of carboxylic acid or *N*-acetyl amino acid in the ratio 1.0 equiv. or 2.0 equiv. in the case of McILs or DcILs, respectively. The remaining procedure can be found in the work previously published by our group (D.A.S. Agostinho et al., 2021). The amount of water present in the ILs was determined by coulometric Karl-Fischer titrations, obtaining final water values of less than 1000–1500 ppm. Additionally, AgNO_3 test was applied to prove the absence of halogen in the synthesized ILs. The purity of the McILs and DcILs synthesized were characterized by ^1H and ^{13}C NMR.

2.5. Differential scanning calorimetry (DSC)

Roughly 5–10 mg of each IL was added into a hermetic aluminum TA Tzero pan. The DSC cell was incessantly purged with nitrogen gas at 50 mL/min. Operating conditions that IL is subjected to in DSC analysis depend largely on its melting point. The technique was repeated 3 times: a) cooling ramp to -90 °C at 10 °C/min; b) heating ramp at 10 °C/min to a temperature of 30 °C above its expected melting point. Glass transition (T_g) and melting (T_m) temperatures (peak) were determined.

2.6. General procedure for the determination of the solubility limit of ibuprofen and ketoprofen

In our previous work developed by Daniela A. S. Agostinho (D.A.S. Agostinho et al., 2021) the general procedure for the determination of the limit solubility of ibuprofen can be found. In the case of Ketoprofen the procedure for determining the solubility limit is similar to the one used for piroxicam, also referred to in the same article mentioned above, changing only the wavelength at which the absorbance maximum is measured for Ketoprofen. The pH was measured during the assay and the value remained unchanged. Triplicates were prepared for each sample and maximum absorbance was measured, by UV-Vis VWR® spectrophotometer, model UV-6300 PC, at 222 nm and 262 nm to IBU and KETO, respectively. The solubility of the drugs in the presence of each IL was determined based on a calibration curve that was prepared for each drug, in water, at 25 °C, see Figure S1

7. Absorbance values were kept under 1. The statistical analysis was achieved by Graphpad Prism 7.

2.7. General procedure for the determination of partition coefficient and log P

The K_{ow} and log P values of IBU and KETO in the presence of ILs were calculated using the shake-flask method described in literature (Baka et al., 2008) and also in our previous works (Jesus et al., 2019; Jesus et al., 2021; D.A.S. Agostinho et al., 2021; D.A.S. Agostinho et al., 2021). The calibration curve that allows the calculation of the drug concentration in the water-rich phase is shown in Figure S18, to calculate the drug concentration in the octanol-rich phase the amount of drug present in the water-rich phase is subtracted from the amount of drug initially dissolved. K_{ow} and log P values were determined

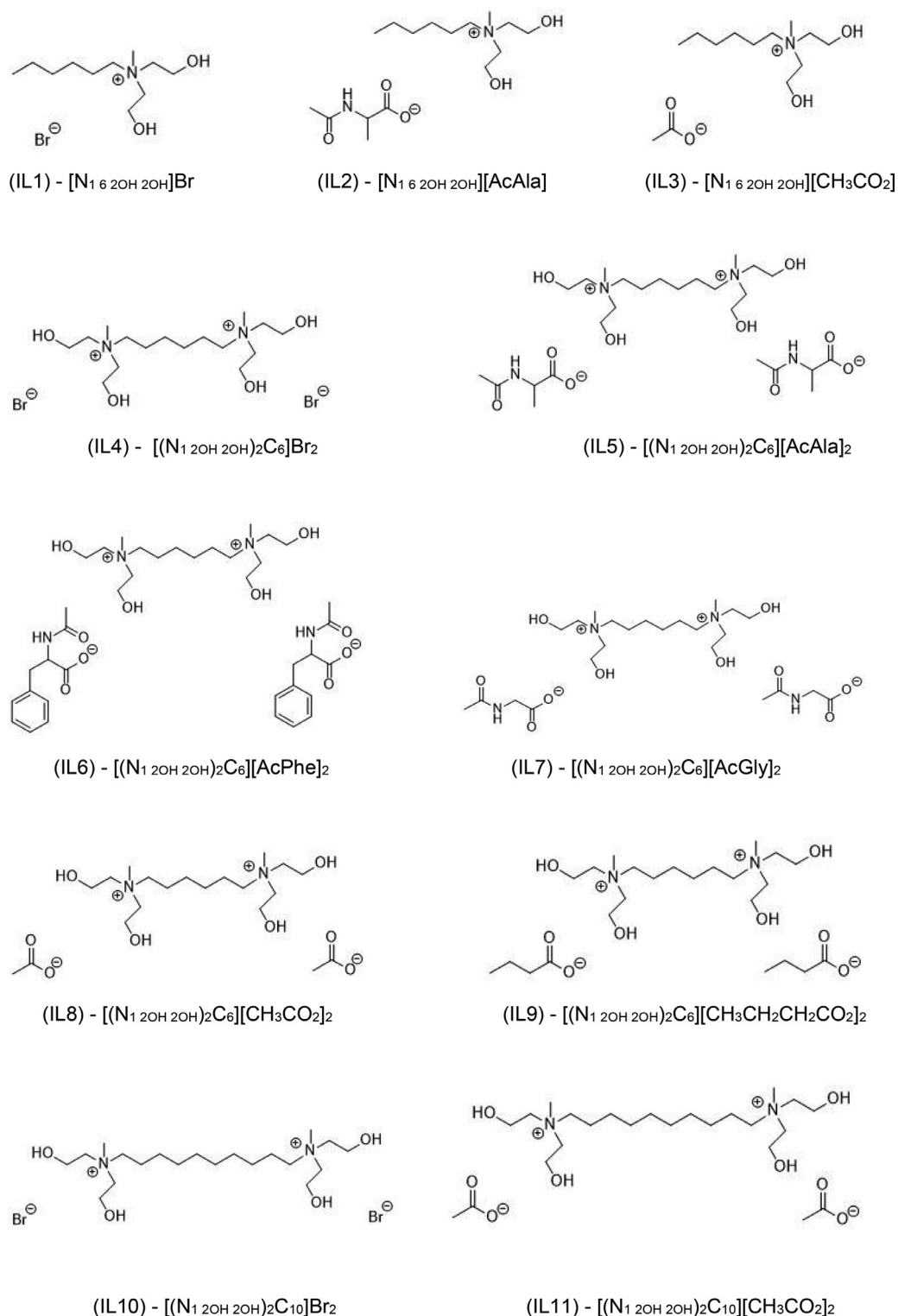


Fig. 1. Chemical structure of monocationic and dicationic ionic liquids.

using equations present in our previous works (Jesus et al., 2019; D.A.S. Agostinho et al., 2021).

2.8. Cytotoxicity evaluation

Cytotoxicity was evaluated in Fibroblasts L929 cells. The procedure regarding cell culture, viability assays and statistical analysis can be found in our previous works (D.A.S. Agostinho et al., 2021;

D.A.S. Agostinho et al., 2021). In the cell viability assays, the IL concentrations tested ranged from 25 to 750 mM.

3. Results and discussion

3.1. ILs synthesis

Following the experimental procedure described previously, 13 DcILs and 3 McILs were synthesized in good yields (95–99%) and high

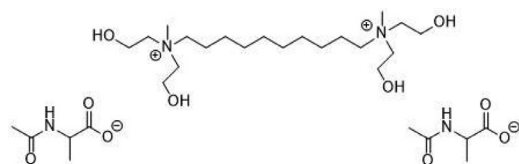
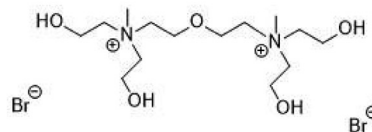
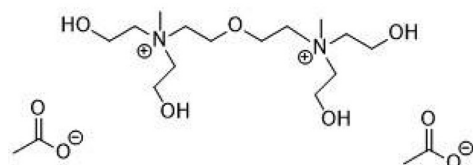
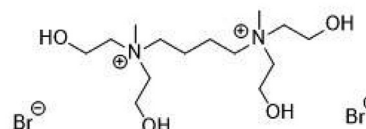
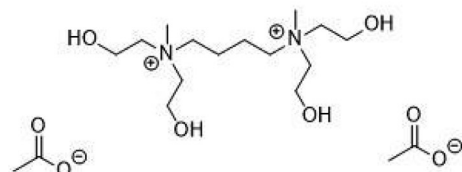
(IL12) - $[(N_{1,2OH,2OH})_2C_{10}][AcAla]_2$ (IL13) - $[(N_{1,2OH,2OH})_2C_2OC_2]Br_2$ (IL14) - $[(N_{1,2OH,2OH})_2C_2OC_2][CH_3CO_2]_2$ (IL15) - $[(N_{1,2OH,2OH})_2C_4]Br_2$ (IL16) - $[(N_{1,2OH,2OH})_2C_4][CH_3CO_2]_2$

Fig. 1. Continued

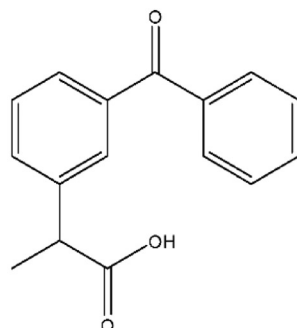
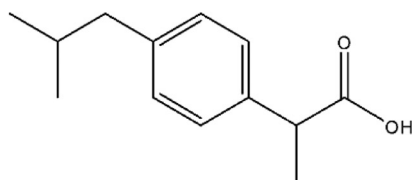


Fig. 2. Chemical structure of IBU (left) and KETO (right).

Table 1
DSC data for the five ILs.

Ionic Liquid	T_m (°C)	T_g (°C)	T_c (°C)
IL3	48.13	-64.50	-18.31
IL5	108.23	—	—
IL16	148.41	-49.39	—
IL8	89.13	-35.84	—
IL11	83.19	-37.61	—

purity (99%). The 1H and ^{13}C NMR spectra of McILs and DcILs synthesized are presented in Figures S1-S16.

3.2. Differential scanning calorimetry (DSC)

Some of the new ionic liquids synthesized were waxy and DSC was used to determine T_m (melting temperature), T_g (glass transition) and T_c (cold crystallization).

The monocationic ionic liquid IL3 is the one with the smaller melting point temperature (see Table 1). Moreover, differently from what happened with the other DcILs exhibited a cold crystallization peak under

heating before the normal melting peak. The DcILs IL5 and IL16 present a melting temperature higher than 100 °C, but this is not relevant for this application (An Introduction to Ionic Liquids). Apart from IL5 all the compounds present glass transition temperatures. As an example, the DSC spectrum for IL8 is presented in Fig. 3.

3.3. Solubility assays

In this work the solubility of IBU and KETO was determined in aqueous media at 37 °C to mimic the body temperature. For ibuprofen the solubility was 60.4 mg/L and for ketoprofen 187.6 mg/L, which is in agreement with literature data (D.A.S. Agostinho et al., 2021).

The effect of a slight quantity of IL as co-solvent, to facilitate solubility of IBU and KETO was evaluated in aqueous solutions. In Fig. 4(A) for ibuprofen, with 0.3 mol% of IL, the solubility decreases when the linker between the two ammoniums increases from C_4 to C_{10} and increases when the linker is an ether group for the same acetate anion.

For KETO (Fig. 4(B)), the increase in alkyl linker don't have a tendency in solubility and when the linker in an ether group, the solubility decreases, for acetate anion.

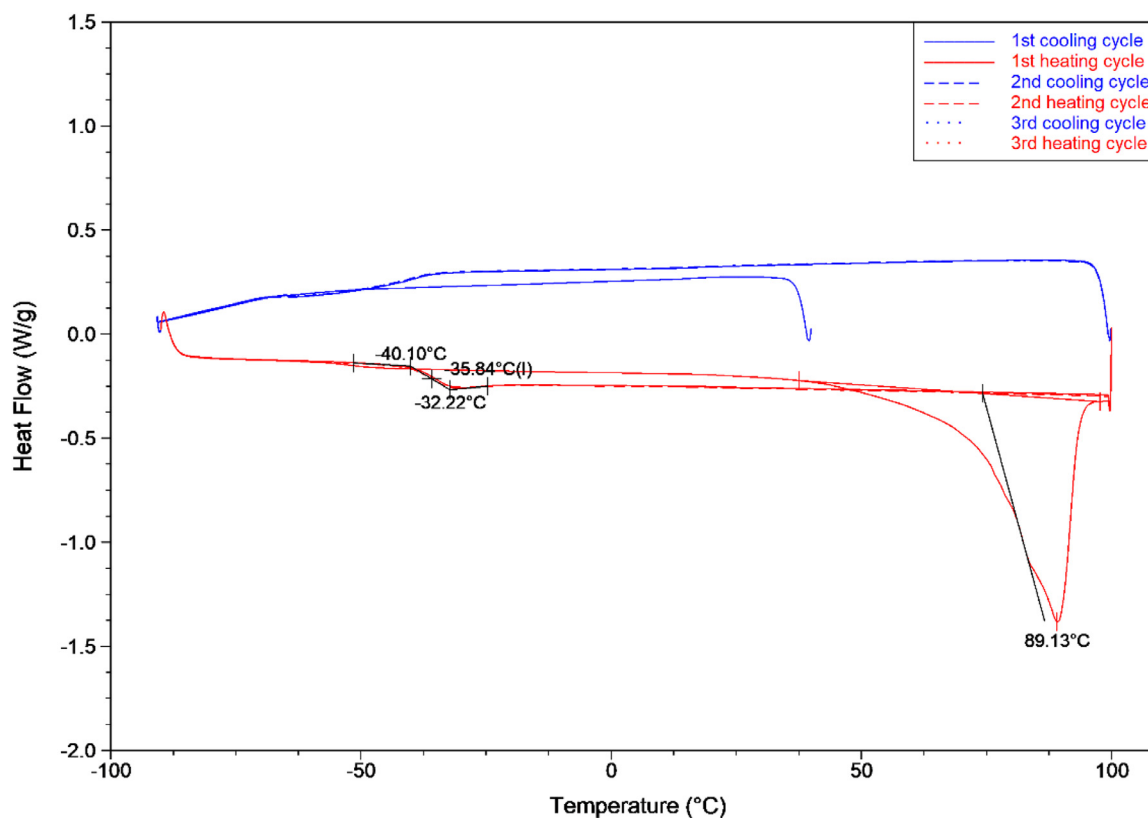


Fig. 3. DSC thermogram of IL8, $N_2=50$ mL/min, ramp 10 °C/min.

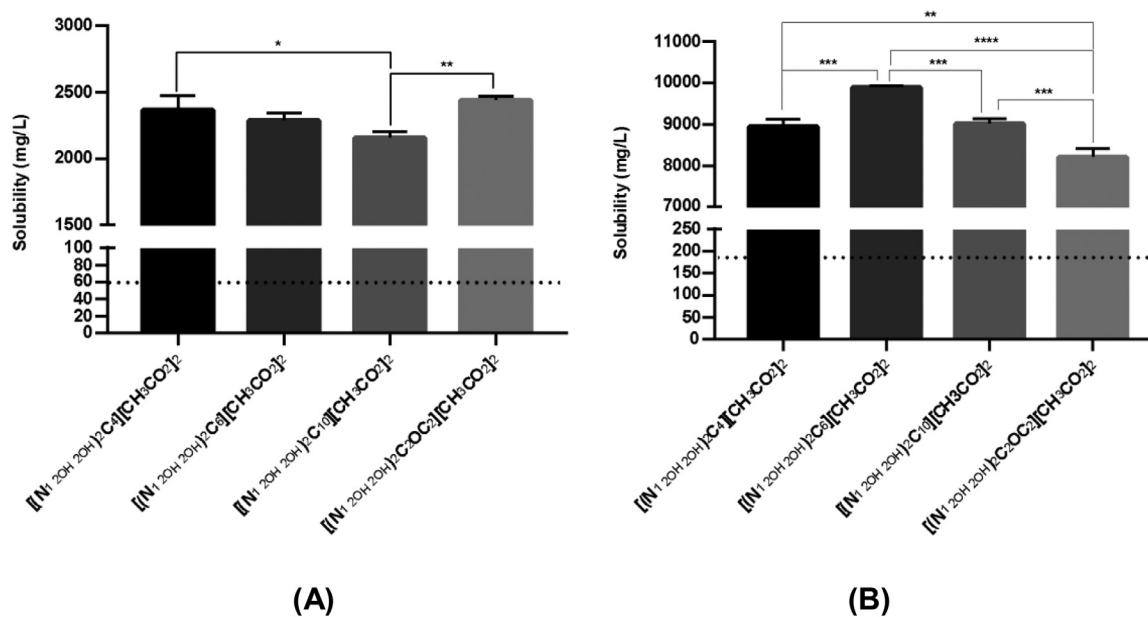


Fig. 4. Solubility of ibuprofen (A) and ketoprofen (B) in aqueous solutions with 0.3 mol% of DcILs. The results were expressed as the mean \pm SD of the three independent experiments. Statistically significant differences are represented in asterisks: * $p = 0.0250$, ** $p = 0.0040$, *** $p = 0.0008$ and **** $p < 0.0001$.

In the case of IBU, using an aqueous solution with 0.2 mol% of IL, the effect of anion in the solubility of the drug is significant, as it can be seen in Fig. 5(A). When the anion is derived from a *N*-acetyl amino acid the increment is only 8-fold, but when the anion is a carboxylate, the increment is 30-fold.

As it was observed for ibuprofen, the anion structure had a significant impact on the solubility of ketoprofen (see Fig. 5(B)). For a common

cation, when a bromide anion is used the increment is only 1.4-fold, while for an acetyl amino acid-derived anion the increment increases to 8-fold for acetyl phenylalanine and reaches 12-fold for acetyl alanine and acetyl glycine. Moreover, when the anion was a carboxylate, the increment was 35-fold.

As it can be seen in Fig. 6, dicationic ionic liquids with *N*-acetyl alaninate and acetate as anion had a larger effect in the

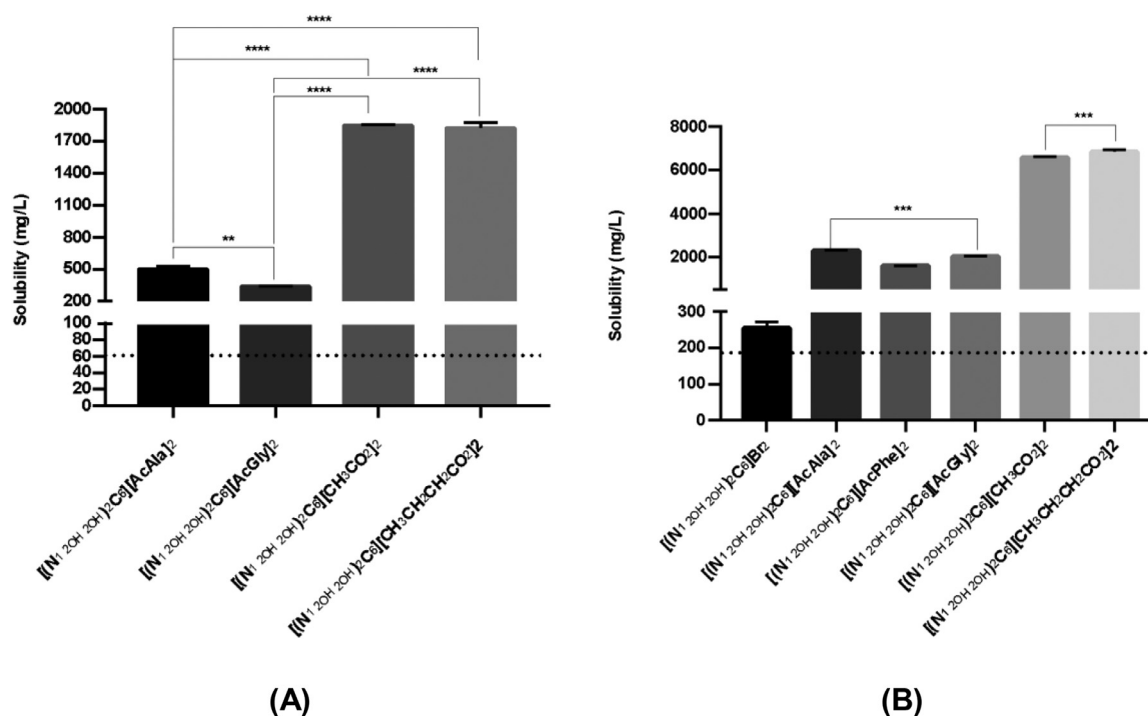


Fig. 5. Solubility of ibuprofen (A) and ketoprofen (B) in aqueous solutions with 0.2 mol% of DcILs. The results were expressed as the mean \pm SD of the three independent experiments. Statistically significant differences are represented in asterisks: ** $p = 0.0040$, *** $p = 0.0008$ and **** $p < 0.0001$.

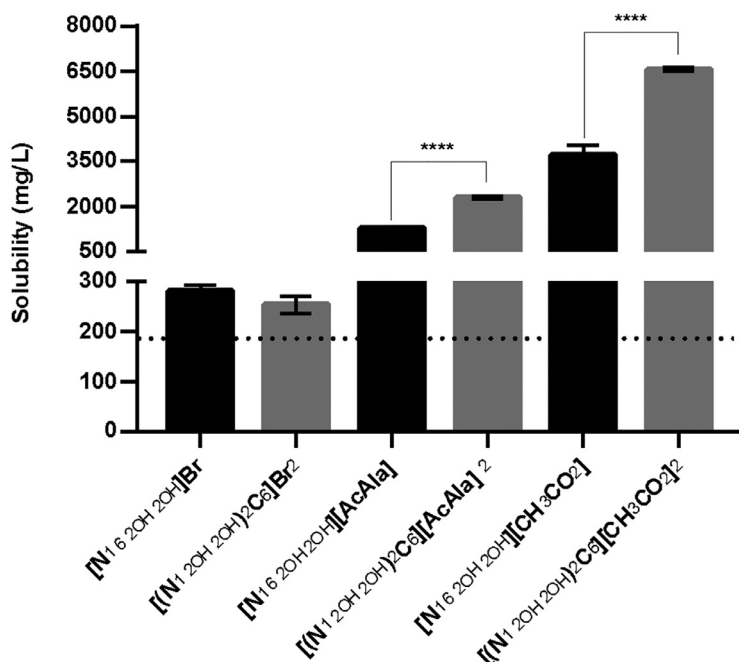


Fig. 6. Solubility of Ketoprofen in aqueous solutions with 0.2 mol% of monocationic and dicationic ILs. The results were expressed as the mean \pm SD of the three independent experiments. Statistically significant differences are represented in asterisks: **** $p < 0.0001$.

solubility of ketoprofen, when compared with the McILs ones for 0.2 mol% IL. The increment in solubility of ketoprofen in the DcIL $[(N_{1,2OH,2OH})_2C_6][CH_3CO_2]_2$ (IL8) was 35-fold, while it was only 20-fold for McIL $[N_{1,6,2OH,2OH}][CH_3CO_2]$ (IL3). When anion is bromide, the values were equivalent, for DcILs and McILs.

With the IL8 (0.05 mol%) and after 5 min at 37 °C, a solubility of 759 mg/L was achieved, corresponding to a highest dose than an adult can take (600 mg). These results showed that this DcIL is a good cosolvent for ibuprofen. A 400 mg dose of IBU typically takes about 45 min for its effect to be noticed by the patient, which can be critical in an acute

pain situation where rapid relief of symptoms is critical (Santos et al., 2019).

3.4. Two dimension $^1H^1H$ -noesy

The intermolecular interaction between ionic liquid and ODs (ketoprofen and ibuprofen) was examined by two-dimensional $^1H^1H$ -nuclear overhauser effect spectroscopy (NOESY). The deuterated solvent used was d_6 -DMSO since we needed to follow the deviation of all peaks,

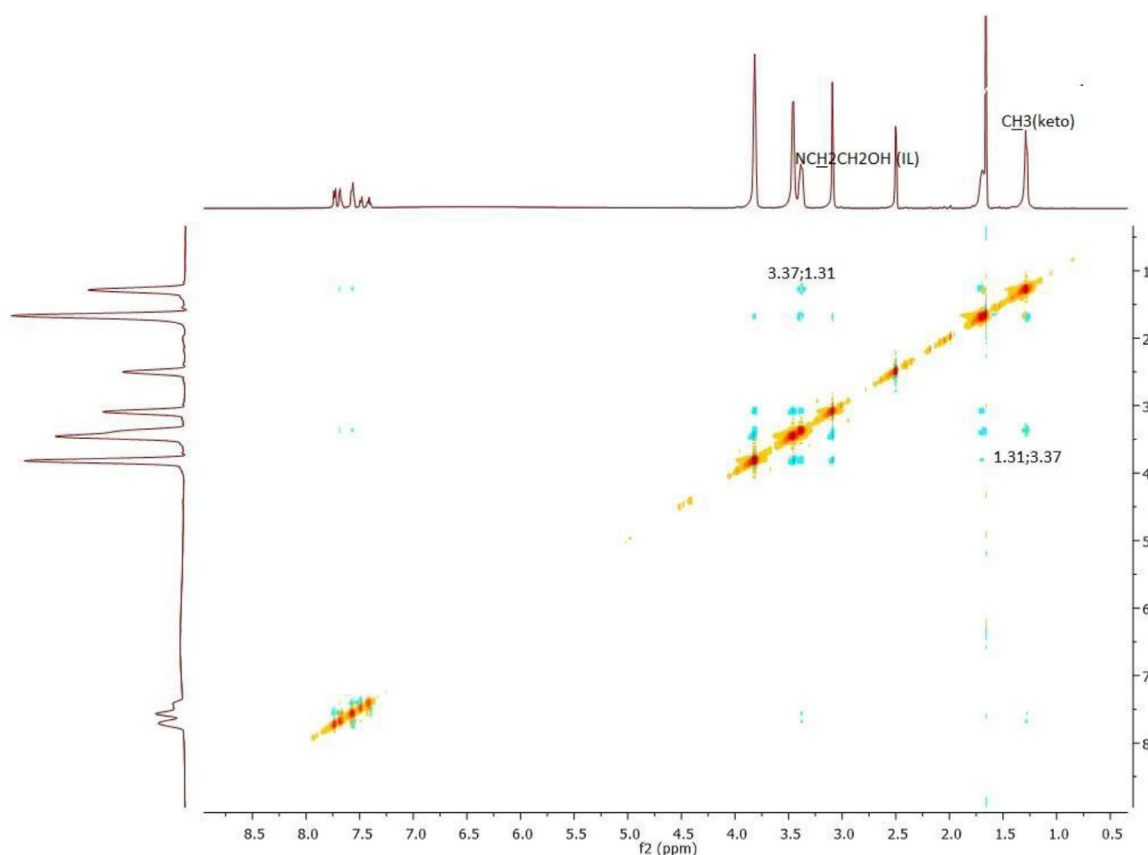


Fig. 7. 2D ^1H - ^1H -NOESY spectrum of ketoprofen with 0.3 mol% of IL8 in dms0-d_6 and representation of the interactions between ketoprofen and IL.

including the ones from the OH groups. The concentration of IL8 used was 0.3 mol%.

The results for ketoprofen show an interaction between the $-\text{CH}_3$ of ketoprofen at δ 1.31 ppm and the methylene group connected to N atom of the cation ($-\text{NCH}_2\text{CH}_2\text{OH}$) at δ 3.37 ppm as can be seen in Fig. 7.

Analogously, the NOESY experiment performed using ibuprofen indicates an interaction between methyl group for anion at δ 1.77 ppm and methyl group for ibuprofen at δ 0.89 ppm, see Figure S21.

3.5. Octanol-water partition coefficient and log P

The partition coefficient (log P) is important to know how the compounds will behave in certain environments and is widely used in pharmacology to understand how drugs will distribute in the human body. As mentioned above, the ketoprofen and ibuprofen are class II drugs, thus having a low solubility and a high permeability. As these drugs are orally administered, they must be able to permeate the lipid bilayers of the intestinal epithelium. Hence, a certain lipophilicity to pass this bilayer is needed, but also a certain degree of hydrophilicity is required so that the drug can be retained. According to literature, ketoprofen has a log P of 3.12 (Czyrski, 2019) and ibuprofen 3.97 (Czyrski, 2019) and this should ideally be between 0 and 3 (Shokri et al., 2012), so that these are more hydrophilic.

The log P values of both drugs were determined with the ionic liquid IL8 at 0.1 mol% using the shake flask method.

The log P value for ibuprofen in water could not be determined because there was no full separation of the aqueous phase from the octanol phase (emulsion between the two phases), so it was considered the literature value. The log P values determined for ketoprofen and the drugs with the ionic liquid are showed in Table 2.

The log P value of ketoprofen experimentally determined proved to be slightly smaller than the one reported in the literature.

Table 2

Log P values for IBU and KETO in aqueous and IL+water solutions.

Drug/Media	Log P
Ketoprofen/Water	2,70
Ibuprofen/water	3,97 (Czyrski, 2019)
Ketoprofen/aqueous solution with 0,1 mol% IL8	0,39 \pm 0,04
Ibuprofen/aqueous solution with 0,1 mol% IL8	1,28 \pm 0,08

Using the ionic liquid IL8, it was possible to lower the log P value of both drugs thus making them more hydrophilic. Obtaining a log P value in the recommended range $0 < \log P < 3$ was one of our goals.

3.6. Cytotoxicity evaluation

For the cytotoxicity study, we have selected the nine dicationic ILs, $[(\text{N}_{1,2}\text{OH})_2\text{C}_6]\text{Br}_2$ (IL4), $[(\text{N}_{1,2}\text{OH})_2\text{C}_6][\text{AcAla}]_2$ (IL5), $[(\text{N}_{1,2}\text{OH})_2\text{C}_6][\text{AcGly}]_2$ (IL7), $[(\text{N}_{1,2}\text{OH})_2\text{C}_6][\text{CH}_3\text{CO}_2]_2$ (IL8), $[(\text{N}_{1,2}\text{OH})_2\text{C}_{10}][\text{CH}_3\text{CO}_2]_2$ (IL11), $[(\text{N}_{1,2}\text{OH})_2\text{C}_2\text{OC}_2][\text{CH}_3\text{CO}_2]_2$ (IL14), $[(\text{N}_{1,2}\text{OH})_2\text{C}_4][\text{CH}_3\text{CO}_2]_2$ (IL16), $[(\text{N}_{1,2}\text{OH})_2\text{C}_6][\text{AcPhe}]_2$ (IL6), $[(\text{N}_{1,2}\text{OH})_2\text{C}_6][\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2]_2$ (IL9) and two monoanionic $[\text{N}_{1,2}\text{OH}][\text{AcAla}]$ (IL2) and $[\text{N}_{1,2}\text{OH}][\text{CH}_3\text{CO}_2]$ (IL3), for comparison purposes. DcILs were selected taking in account different anions and linkers.

The results of the IL cytotoxicity performed on the L929 cell line are described at Fig. 8 and Table 3.

Observing Table 3, we may conclude that dicationic ionic liquids IL6 and IL9 are considered toxic because of the anion $[\text{AcPhe}]^-$ and $[\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2]^-$. Acetyl phenylalanine is an aromatic ring and the increase in alkyl chain of butyric anion, increases drastically the cytotoxicity of ILs. Butyric acid, due to its alkyl chain was expected to increase the cytotoxicity of the ionic liquid, as has already been reported in the

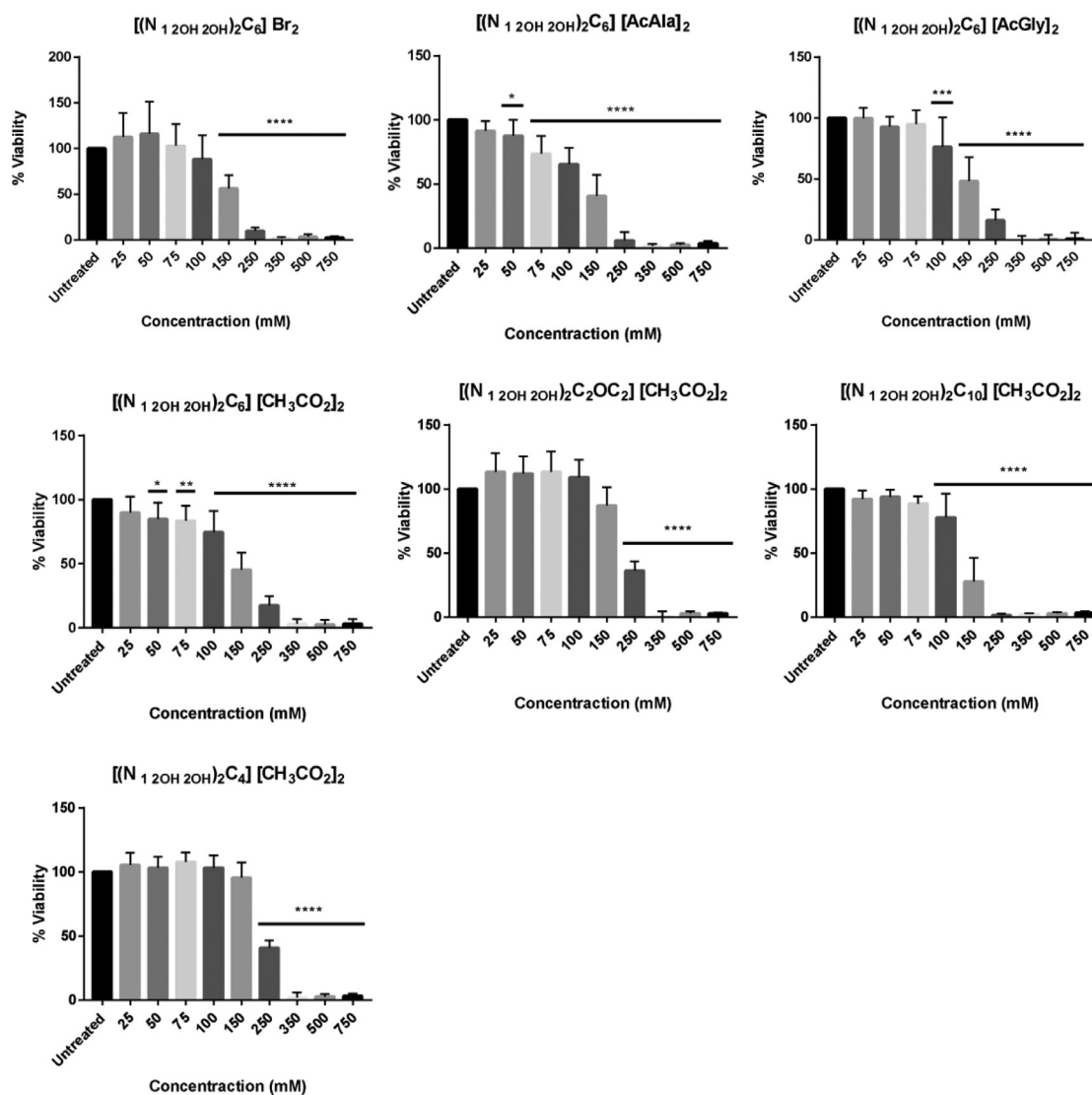


Fig. 8. Cytotoxicity of the ionic liquids in fibroblasts L929 cells to different concentrations of the respective ILs. The results are expressed as the average \pm SD from three independent biological assays. The symbols *, **, *** and **** indicates that the viabilities are statistically significant with $p = 0.0468$ ($0,0138$ for $[(N_{1,2OH,2OH})_2C_6] [CH_3CO_2]_2$), $p = 0.0035$ ($0,0054$ for $[(N_{1,2OH,2OH})_2C_6] [CH_3CO_2]_2$), $p = 0.0005$ e $p = 0.0001$ respectively, when compared to the control.

Table 3
IC₅₀ determination of dicationic and monocationic ILs.

Ionic Liquid	IC ₅₀ (mM)
IL4	126,6 \pm 6,5
IL5	119,8 \pm 11,5
IL7	146,4 \pm 18,4
IL8	138,5 \pm 13,0
IL11	124,6 \pm 9,7
IL14	223,8 \pm 23,3
IL16	238,4 \pm 20,5
IL6	32,4
IL9	7,4
IL2	26,3
IL3	24,2

literature (Ventura et al., 2014). Acetyl phenylalanine due to its aromatic group was also expected to increase cytotoxicity relative to the other acetyl amino acids (Goldenberg et al., 2005).

Both monocationic ionic liquids tested proved to be toxic, because the linear chain (C₆) increases the lipophilicity and consequently toxicity. In DcILs the alkyl chain or ether group are between the two cations, and that cytotoxicity is annulled.

Comparing the McIL IL3 with the DcIL IL8 and the McIL IL2 with the DcIL IL5, we observed that the DcILs are far less toxic than McILs which is in line with what has been reported in the literature (Guglielmero et al., 2018).

When comparing the ionic liquids IL16 (four-carbon linker), IL8 (six-carbon linker), IL11 (ten-carbon linker) and IL14 (linker with an ether group) we could conclude that the ionic liquid with the highest IC₅₀ (least toxic) corresponds to the smallest (four-carbon) linker, followed by the ionic liquid with the ether group, then the one with the six-carbon linker and finally the ten-carbon one. As expected, the increase in the cation linker increases the cytotoxicity of the ionic liquid.

4. Conclusions

This work consisted of the preparation of new DcILs to improve the solubility of poorly water-soluble commercial drugs, namely ketoprofen and ibuprofen. The ionic liquids which resulted in the greatest benefit in terms of both drugs solubility, and which did not show high levels of cytotoxicity were $[(N_{1,2OH,2OH})_2C_6] [CH_3CO_2]_2$ and $[(N_{1,2OH,2OH})_2C_2OC_2] [CH_3CO_2]_2$.

Ketoprofen showed a solubility value of 9901.38 mg/L in the presence of 0.3 mol% of IL [(N₁ 2OH 2OH)₂C₆][CH₃CO₂]₂ (53 times greater than that of the drug alone in water). For ibuprofen, this ionic liquid resulted in a solubility of 2286.86 mg/L at 0.3 mol%, i.e., about 38 times higher than the solubility of the drug in the absence of ionic liquid.

The ionic liquid [(N₁ 2OH 2OH)₂C₂OC₂][CH₃CO₂]₂ at 0.4 mol% promoted an increase of about 50 times the solubility of ketoprofen (9276.25 mg/L) and 46 times for ibuprofen (2788.65 mg/L).

The anions that most favoured the increase in the solubility of the drugs were the carboxylates, followed by acetyl amino acids and finally bromide.

DcILs always presented improved solubility values than McILs, with this result agreeing with that reported in the literature. (Guglielmero et al., 2018)

McILs, as well as DcILs with the butyric acid or acetyl phenylalanine as anion have proved to be toxic.

Using the ionic liquids [(N₁ 2OH 2OH)₂C₆][CH₃CO₂]₂ and [(N₁ 2OH 2OH)₂C₂OC₂][CH₃CO₂]₂ as co-solvent it was possible to considerably increase the solubility of the drugs in water, moving them into class I of the BCS (high solubility and high permeability).

Declarations of Competing Interest

None.

CRedit authorship contribution statement

Ana B.P. Silva: Conceptualization. **Ana R. Jesus:** Conceptualization, Writing – review & editing. **Daniela A.S. Agostinho:** Conceptualization, Writing – original draft. **José M.S.S. Esperança:** Writing – review & editing. **Alexandre Paiva:** Writing – review & editing. **Ana R.C. Duarte:** Writing – review & editing, Supervision. **Patrícia M. Reis:** Writing – original draft, Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jil.2023.100052.

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