Development and Biological evaluation of API-ILs based on anti-bacterial and anti-fungal drugs

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In recent years Ionic Liquids (ILs) are being applied in life sciences. ILs are being produce with active pharmaceutical drugs (API) as they can reduce polymorphism and drug solubility problems [1] Also ILs are being applied as a drug delivery device in innovative therapies What is appealing in ILs is the ILs building up platform, the counter-ion can be carefully chosen in order to avoid undesirable side effects or to give innovative therapies in which two active ions are paired.

This work shows ILs based on ampicillin (an anti-bacterial agent) and ILs based on Amphotericin B. Also we show studies that indicate that ILs based on Ampicillin could reverse resistance in some bacteria.

The ILs produced in this work were synthetized by the neutralization method described in Ferraz et. al. [2] Ampicillin anion was combined with the following organic cations 1-ethyl-3-methylimidazolium, [EMIM]; 1-hydroxy-ethyl-3-methylimidazolium, [C_2OHMIM]; choline, [cholin]; tetraethylammonium, [TEA]; cetylpyridinium, [C_{16}pyr] and trihexyltetradecylphosphonium, [$P_{6,6,6,14}$]. Amphotericin B was combined with [C_{16}pyr], [cholin] and 1-metohyethyl-3-methylimidazolium, [C_3OMIM]. The ILs-APIs based on ampicillin[2] were tested against sensitive Gram-negative bacteria *Escherichia coli* ATCC 25922 and *Klebsiella pneumonia* (clinical isolated), as well as on Gram positive *Staphylococcus Aureus* ATCC 25923, *Staphylococcus epidermidis* and *Enterococcus faecalis*. The arising resistance developed by bacteria to antibiotics is a serious public health threat and needs new and urgent measures. We study the bacterial activity of these compounds against a panel of resistant bacteria (clinical isolated strains): *E. coli* CTX M9, *E. coli* TEM CTX M9, *E. coli* TEM1, *E. coli* CTX M2, *E. coli AmpC Mox2*.

In this work we demonstrate that is possible to produce ILs from anti-bacterial and anti-fungal compounds. We show here that the new ILs can reverse the bacteria resistance. With the careful choice of the organic cation, it is possible to create important biological and physic-chemical properties. This work also shows that the ion-pair is fundamental in ampicillin mechanism of action.

[1] R. Ferraz, L. C. Branco, C. Prudencio, J. P. Noronha and Z. Petrovski, *Chemmedchem* **2011**, *6*, 975-985.
[2] R. Ferraz, L. C. Branco, I. M. Marrucho, J. M. M. Araujo, L. P. N. Rebelo, M. N. da Ponte, C. Prudencio, J. P. Noronha and Z. Petrovski, *Medchemcomm* **2012**, *3*, 494-497.