

Antibacterial activity of Ionic Liquids based on ampicillin against resistant bacteria

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Ricardo Ferraz,^{*ab} Vânia Teixeira,^b Débora Rodrigues,^b Rúben Fernandes,^{bc} Cristina Prudêncio,^{bc} João Paulo Noronha,^a Željko Petrovski^{*a} and Luís C. Branco^{*a}

Antibacterial activities of novel Active Pharmaceutical Ingredient Ionic Liquids (API-ILs) based on ampicillin anion [Amp] have been evaluated. They showed growth inhibition and bactericidal properties on some sensitive bacteria and especially some Gram-negative resistant bacteria when compared to the [Na][Amp] and the initial bromide and chloride salts. For these studies were analysed the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBIC) against sensitive Gram-negative bacteria *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* (clinically isolated), as well as sensitive Gram positive *Staphylococcus Aureus* ATCC 25923, *Staphylococcus epidermidis* and *Enterococcus faecalis* and completed using clinically isolated resistant strains such as *E. coli* TEM CTX M9, *E. coli* CTX M2 and *E. coli* AmpC MOX. From the obtained MIC values of studied API-ILs and standard [Na][Amp] were derived RDIC values (relative decrease of inhibitory concentration). High RDIC values of [C₁₆Pyr][Amp] especially against two resistant Gram-negative strains *E. coli* TEM CTX M9 (RDIC >1000) and *E. coli* CTX M2 (RDIC >100) point clearly to a potential promising role of API-ILs as antimicrobial drugs in particular against resistant bacterial strains.

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Introduction

Ionic liquids (ILs) are usually defined as organic salts with melting points lower than 100 °C (several of them are liquid at room temperature).¹ They became popular due to the large number of possible cation/anion combinations allowing different tunable interactions and potential applications. Some IL properties such as their high thermal and chemical stability, negligible vapor pressure,² high ionic conductivity, lack of inflammability and adjustable solubility have attracted numerous applications across an extensive variety of research areas³ in particular related with organic chemistry, chemical engineering, material science, physical chemistry, analytical chemistry and biotechnology, among others.

One of the most promising applications of ILs seems to be the so-called third generation of ILs (their arrangement with active pharmaceutical ingredients, APIs) or API-ILs.⁴ It is suggested that these compounds can solve problems associated to pharmaceutical industry related with polymorphism and drug solubility.⁴ At the beginning, the uses of ILs in the biosciences

were difficult because of ILs toxicity,⁵ however more recently it was shown lower inherent toxicity and thus a lower impact on human health and the environment from some hydrophobic ILs derived from toxic herbicides.⁵ Presently biocidal properties of large cations, such as benzalkonium and imidazolium species, are also largely used as an advantage, to kill or inhibit bacteria⁶ or yeast⁷ growth. In respect to this area, different publications reported antimicrobial activity studies using microorganisms or cell culture for long alkyl chain quaternary ammonium.⁸ Recently, Cole and co-workers⁹ reported the use of metathesis reaction to produce ILs with long alkyl chain quaternary ammonium and ampicillin anion. Some ILs have been efficiently tested with clinically significant microbial pathogens, including Methicillin-resistant *Staphylococcus aureus* (MRSA).¹⁰

Bacterial resistance to different antibiotics that are commercially available is one of the major public health problems.¹¹ Recent outbreaks of *E. coli* O104 (ref. 12) in Germany as well as the emergence of multi-drug resistant organisms such as Gram-negative Enterobacteriaceae associated to the New Delhi metallo β -lactamase¹³ confirm that this is a remarkable problem for public health, but also at an economic and social point of view. Besides the fact that bacterial resistance increases the mortality and the morbidity some recent publications have reported the financial burden of health care-associated infections (HAIs) in the USA.¹⁴

Innovative therapies involving the use of ILs as a drug delivery platform suggest others attractive opportunities for

^aDepartamento de Química, REQUIMTE-CQFB, Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, 2829-516 Caparica, Portugal. E-mail: ricardoferraz@eu.ipp.pt; z.petrovski@fct.unl.pt; l.branco@fct.unl.pt

^bCiências Químicas e das Biomoléculas, Escola Superior de Tecnologia da Saúde do Porto do Instituto Politécnico do Porto, Rua Valente Perfeito, no 322, 4400-330, Vila Nova de Gaia, Portugal

^cCentro de Farmacologia e Biopatologia Química (U38-FCT) Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal