

Synthesis, Characterization and Antiproliferative Activity on Cancer Cell Lines of New Ionic Liquids from Ampicillin

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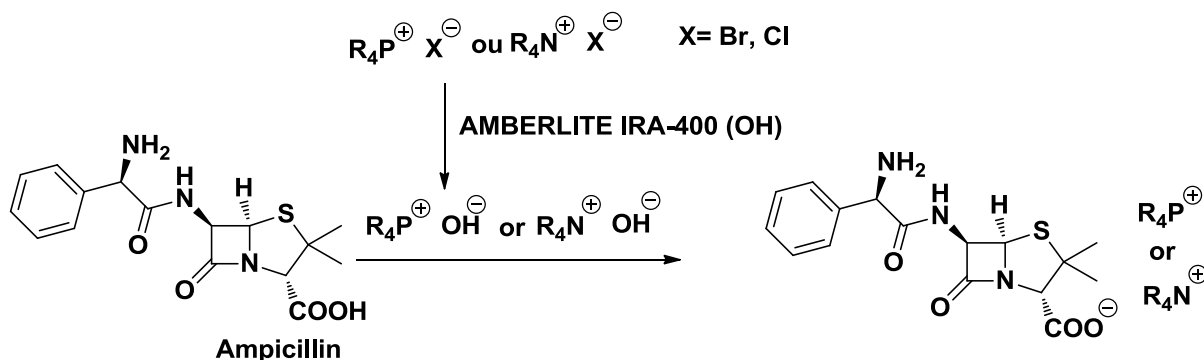
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Ionic Liquids (ILs) are ionic compounds that possess melting temperature below 100°C and they have been a topic of great interest since the mid-1990s due to their unique properties. The range of IL uses has been broadened, due to a significant increase in the variety of physical, chemical and biological ILs properties. They are now used as Active Pharmaceutical Ingredients (APIs) and recent interests are focused on their application as innovative solutions in new medical treatment and delivery options.¹

In this work, our principal objective was the synthesis and investigation of physicochemical and medical properties of ionic liquids (ILs) and organic salts from ampicillin. This approach is of huge interest in pharmaceutical industry as cation and anion composition of ILs and organic salts can greatly alter their desired properties, namely the melting temperature and even synergistic effects can be obtained.^{2,3} For the synthesis of these compounds we used a recently developed method proposed by Ohno *et al.*⁴ for the preparation of quaternary ammonium and phosphonium hydroxides, that were neutralized by ampicillin. After purification we obtained pure ILs and salts in good yields.

These ILs shows good antimicrobial and antifungal activities. As it is well known that some ionic liquids containing phosphonium and ammonium cation also shows anti-cancer activity^{1,5} we also decided to study these compounds against some cancer cell lines.



Scheme 1. Synthesis of ampicillin salts and ILs.

1. Ferraz, R., Branco, L. C., Prudêncio, C., Noronha, J. P., Petrovski, Z, ChemMedChem 2011 in press (DOI:10.1002/cmdc.201100082).
2. Stoimenovski, J., MacFarlane, D. R., Bica, K., Rogers, R. D., *Pharm. J Res.*, **2010**, 27, (4), 521-526.
3. Rogers, R. D., Seddon, K. R. *Science*, **2003**, 302, (5646), 792-793.

4. Fukumoto, K. , Yoshizawa, M., Ohno, H., *J. Am. Chem. Soc.*, **2005**, *127*, (8), 2398-2399.
5. Kumar, V., Malhotra, S. V., *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4643-4646.