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Hydrogen bonding networks of nalidixic acid–copper(II) complexes†

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The usage of quinolone antibiotics has been threatened by antimicrobial resistance, and therefore it is of utmost importance to revitalize these drugs with approaches that may lead to improved properties and increased efficiency. Herein, the formation of hydrogen bonding networks of nalidixic acid–Cu(II) complexes is presented as a possible pathway to achieve that goal.

The increasing interest in copper complexes has been motivated by their potential applications for medical/pharmaceutical purposes,¹ as they have been revealing promising activity as antimicrobial,² antiviral,³ anti-inflammatory⁴ and even anticancer agents.⁵ Copper can readily exist in Cu(I) and Cu(II) oxidation states, and this property endows this trace metal with the ability to participate as a catalytic cofactor in several vital biological processes, from bacteria to humans.^{6,7}

Modifying biologically active structures used in medical therapeutics to improve their efficiency and bioavailability is becoming an increasingly recurring approach. Metallopharmaceuticals have been evidenced as an outstanding alternative, increasing considerably the activity of the drugs, and often displaying different mechanisms of action and improving their bioavailability.⁸ Moulton and Ma, for instance, have already proved that the use of discrete coordination complexes in drug delivery is a good approach to alter the lipophilicity and solubility of pharmaceutically active species.^{9,10} Lately, the antimicrobial approach of these drugs has attracted special interest considering that intracellular metals strongly influence the activity of antibiotics.⁸

Quinolones are a family of widely prescribed antibiotics with a broad spectrum of activity and act by inhibiting

supercoiling of bacterial DNA by binding to bacterial topoisomerase II (DNA gyrase) and topoisomerase IV in Gram-positive species.¹¹ This effect seems to be induced by a metal-dependent mechanism, mediated by the increase of enzyme–DNA cleavage complexes, stressing the importance of the interaction of this drug with a transition metal ion present in the cytoplasm, such as copper(II), to induce DNA cleavage.^{12,13} In fact, studies of quinolone–copper complexes have shown changes in the physicochemical properties of pharmaceuticals, such as the decrease of antibiotics' hardness¹⁴ and improved lipophilicity, allowing modification in the potency and even in the specificity of the drug.^{2,10}

Nalidixic acid (NALD) was the first quinolone antibiotic used to treat urinary tract infections caused mostly by Gram-negative bacteria. This quinolone was taken off the pharmaceutical market due to its low solubility and was substituted with improved similar active pharmaceutical ingredients.^{15,16} However, the increasing occurrence of acquired bacterial resistance, observed in different bacterial species treated with quinolones, has been threatening the usage of this drug class,¹⁷ and therefore, improving this drug's activity by changing its mechanism of action and physicochemical properties can be a good alternative to work around the problem.

The chelation of nalidixic acid to copper has shown to be a promising alternative to improve the efficiency of the drug.^{16,18} For instance, biological studies on a reported copper complex with nalidixic acid and 1,10-phenanthroline (Phen), [Cu(Phen)(NALD)(H₂O)][NO₃]₃·3H₂O, have shown that it interacts with DNA and other nucleic acids such as rRNA and mRNA,¹⁹ without the need to bind to enzymes.^{20,21} This interaction is influenced by different DNA–drug interactions including the formation of hydrogen bonds.^{12,16,18} Hydrogen bonding has manifold possibilities of donor and acceptor group-interactions between the drug and the DNA helix, and depending on the drug's characteristics, the interaction might be completely different.^{22,23} In metallopharmaceuticals, for instance, the presence of

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- 28 J. McKinnon, M. Spackman and A. Mitchell, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2005, **60**, 627–668.
- 29 M. Servati-Gargari, S. K. Seth, R. L. LaDuca, O. Z. Yesilel, A. Pochodylo, A. Bauzá, B. C. Jana, T. Arslan, A. Frontera and G. Mahmoudi, *Inorg. Chim. Acta*, 2015, **438**, 220–231.
- 30 J. Dalal, N. Sinha, H. Yadav and B. Kumar, *RSC Adv.*, 2015, **5**, 57735–57748.
- 31 R. Soman, S. Sujatha, S. De, V. C. Rojisha, P. Parameswaran, B. Varghese and C. Arunkumar, *Eur. J. Inorg. Chem.*, 2014, **2014**, 2653–2662.

