Infrared Spectroscopic Studies of Novel Hydroxybisphosphonates and Molecular Modelling of their Interaction with Hydroxyapatite

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Bisphosphonates (BPs) are a class of drugs widely used in the treatment of several metabolic bone disorders associated with increased bone resorption, including osteoporosis, Paget's disease and metastic bone disease [1]. Although BPs can directly inhibit the cellular activity of osteoclasts, their ability to adsorb to bone mineral is also an important factor in determining their potency and duration of action [2]. In this study, we performed a molecular modelling analysis, by molecular mechanics, of the molecular structures of hydroxy(1H-indazol-3-yl)methylenediphosphonic acid (BP1; Figure 1a) and hydroxy(1-methyl-1H-indazol-3-yl)methylenediphosphonic acid (BP2; Figure 1b) and examined their interactions with hydroxyapatite (HA) by energy-minimising 50 different orientations for judiciously selected low energy conformers of each ligand at 10 Å from the mineral surface. We also calculated the vibrational spectra for each BP with semiempirical methods and compared then with FTIR spectra obtained experimentaly. The calculated interaction energies of the studied BPs with HA suggests that BP2 interacts stronger with hydroxyapatite than BP1. These results are in agreement with *in vitro* and *in vivo* studies of the ^{153}Sm-BPs complexes. Complex ^{153}Sm-BP2 showed, *in vitro*, higher HA binding than complex ^{153}Sm-BP1. *In vivo* studies showed different farmacokinetics parameters with complex ^{153}Sm-BP2 presenting initial higher levels of bone uptake than complex ^{153}Sm-BP1, which concentration is increasing during the 24 h period studied [3].

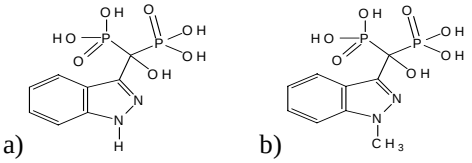

Figure 1 – a) hydroxy(1H-indazol-3-yl)methylenediphosphonic acid – BP1;
b) hydroxy(1-methyl-1H-indazol-3-yl)methylenediphosphonic acid– BP2.

Acknowledgments: This project is funded by Fundação para a Ciência e a Tecnologia (Project POCI/QUI/55508/2004)

References

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