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Molecular Modelling of the Interaction of Novel Hydroxybisphosphonates 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 [1-3]. 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 [4]. In this study, we performed a molecular modelling analysis, by molecular mechanics [5], of the molecular structures of hydroxy(1H-indazol-3-yl)methylene-diphosphonic acid (BP1; Figure 1a) and hydroxy(1-methyl-1H-indazol-3-yl)-methylenediphosphonic acid (BP2; Figure 1b) and examined their interactions with hydroxyapatite by energy-minimising 50 different orientations for judiciously selected low energy conformers of each ligand at 10 Å from the mineral surface. Their interaction energy 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 [6].

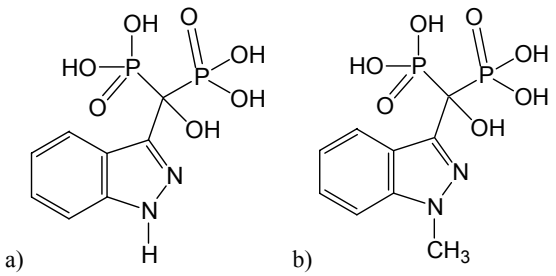

Figure 1 – a) hydroxy(1H-indazol-3-yl)methylenediphosphonic acid – BP1;
b) hydroxy(1-methyl-1H-indazol-3-yl)methylenediphosphonic acid– BP2.

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