

## MS32-P7 New cocrystals of Flurbiprofen and Proline: structural effect of enantiomorphism.

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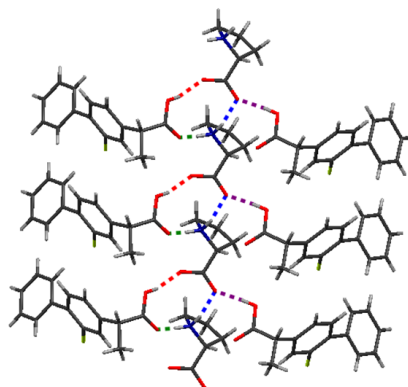
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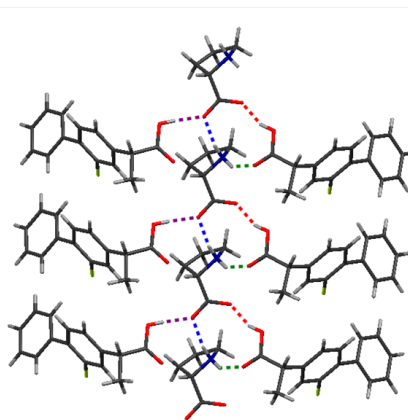
Flurbiprofen (FBP) is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic and analgesic activities and a very low water solubility (8 mg/l).<sup>1</sup> The most common strategy to alter physical and chemical properties of Active Pharmaceutical Ingredients (APIs) is the search for multicomponent crystal forms, mainly salts and cocrystals. Because of their ionic character salts result in the increase of solubility of APIs but also in more stable products easy to recrystallize. When the intervenient molecules do not present adequate properties for salification a more recent approach to modify properties has been adopted: the growth of cocrystals. There are several definitions of pharmaceutical cocrystal, but in general it can be described as a combination of an API and a Generally Recognized As Safe (GRAS) chemical in a stoichiometric ratio, bound by non-covalent interactions. Zwitterionic compounds favor formation of H-bonds and, therefore, cocrystals. The nature of aminoacids (ionic or zwitterionic depending on pH) makes them good candidates to obtain both API salts and cocrystals. Proline (P) shows one of the largest zwitterionic pH ranges (1.80-10.63)<sup>2</sup> so it was chosen for the synthesis of new FBP cocrystals using Liquid Assisted Grinding. FBP has a strong tendency to form racemic compounds by direct interaction of (R)- and (S)-molecules, involving H-bonding in a carboxylic acid dimer.<sup>3</sup> When P is introduced the structure evolves into a trimer composed by a P molecule "sandwiched" between an (R)- and an (S)-FBP. This work registers differences in supramolecular arrangements obtained using D-proline (I) and L-proline (II) as cofomer. In both cases the trimers form chains where P molecules interact by N-H...O<sup>carboxylate</sup> bonds. D-proline forms two O-H...O<sup>carboxylate</sup> interactions, one with S-FBP using the same O atom involved in the P-P interactions and a second with R-FBP involving the other O<sup>carboxylate</sup>. P amino group also participates in a N-H...O=C<sup>carboxylate</sup> bond with the next R-FBP molecule, assisting in the chain formation. If the conformer is L-proline the interactions with (R)- and (S)- molecules are reversed.

Acknowledgements: FCT (RECI/QEQ-QIN70189/2012, SFRH/BPD/78854/2011, UID/QUI/00100/2013).

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R I S



R II S

Figure 1. Supramolecular arrangements of racemic flurbiprofen with D-proline (I) and L-proline (II).

Keywords: cocrystals, flurbiprofen, enantiomorphism