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BOOK OF ABSTRACTS

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Quantum Crystallography Meeting Medicines: Insights to Design New Solid Forms of Rilpivirine

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Producing solid-state modifications to obtain new solid forms is a robust method for the improvement the physicochemical properties of active pharmaceutical ingredients. Deeply understanding the particularities of the target molecule is the key to rationally planning which modification will enhance those properties. The most useful method to understand the nature and energy of intermolecular interactions in crystal packing is an experimental X-ray study, with subsequent topological analysis of the resulting electron density distribution in terms of the Bader's quantum theory "*Atoms in molecules*" (AIM). Herein, we discuss an experimental electron density study of the monoclinic $P2_1/c$ solid-form of Rilpivirine, that is a diarylpyrimidine derivative antiretroviral drug, belonging to a group of second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) used to treat HIV and that possesses a high internal conformational flexibility. This flexibility, combined with the plasticity of its interacting binding site, confers a high high activity as well as reduces the likelihood of resistance compared to other NNRTIs [1]. Furthermore, its cyanovinyl group positions itself in a hydrophobic tunnel of the HIV reverse transcriptase (HIV-RT), an interaction that is conserved despite the enzyme's rearrangements, making Rilpivirine a potent drug against both wild-type and drug-resistant HIV-1 [2]. The x-ray diffraction data were collected until a resolution of 0.78 Å, with λ = 1.54184 Å. The Hirshfeld Atom Refinement (HAR), a method that enables the acquisition of good refinement parameters and information for topological analysis even at conventional resolution, was used to obtain an aspherically model of the electron distribution in the crystal. The HAR procedure was undertaken at a R2SCAN/x2c-TZVPP level of theory with anisotropic refinement of H-atoms positions, using the NoSpherA2 modulus of Olex2 [3]. To recover the physical meaning of the charge density model in the wavefunction generated by HAR, we perform the X-ray constrained wavefunction (XCW) technique through the quantum crystallographic software Tonto, resulting in the X-ray Wavefunction Refinement (XWR). Overall, the topological analysis of the molecular wavefunction shows that there is a good agreement between the electron density concentration at the BCP in agreement with the observed bond lengths, in which longer (weaker) bonds present lower electron density values (N-H), while shorter (stronger) bonds present a higher electron density (C≡N).These results show that quantum crystallography could be a a tool to understand the nature of the intermolecular interactions in crystal packing providing allowing tto evaluate the corresponding energy values providing insights that could contribute to design new solid forms of pharmaceuticals with improved properties.

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