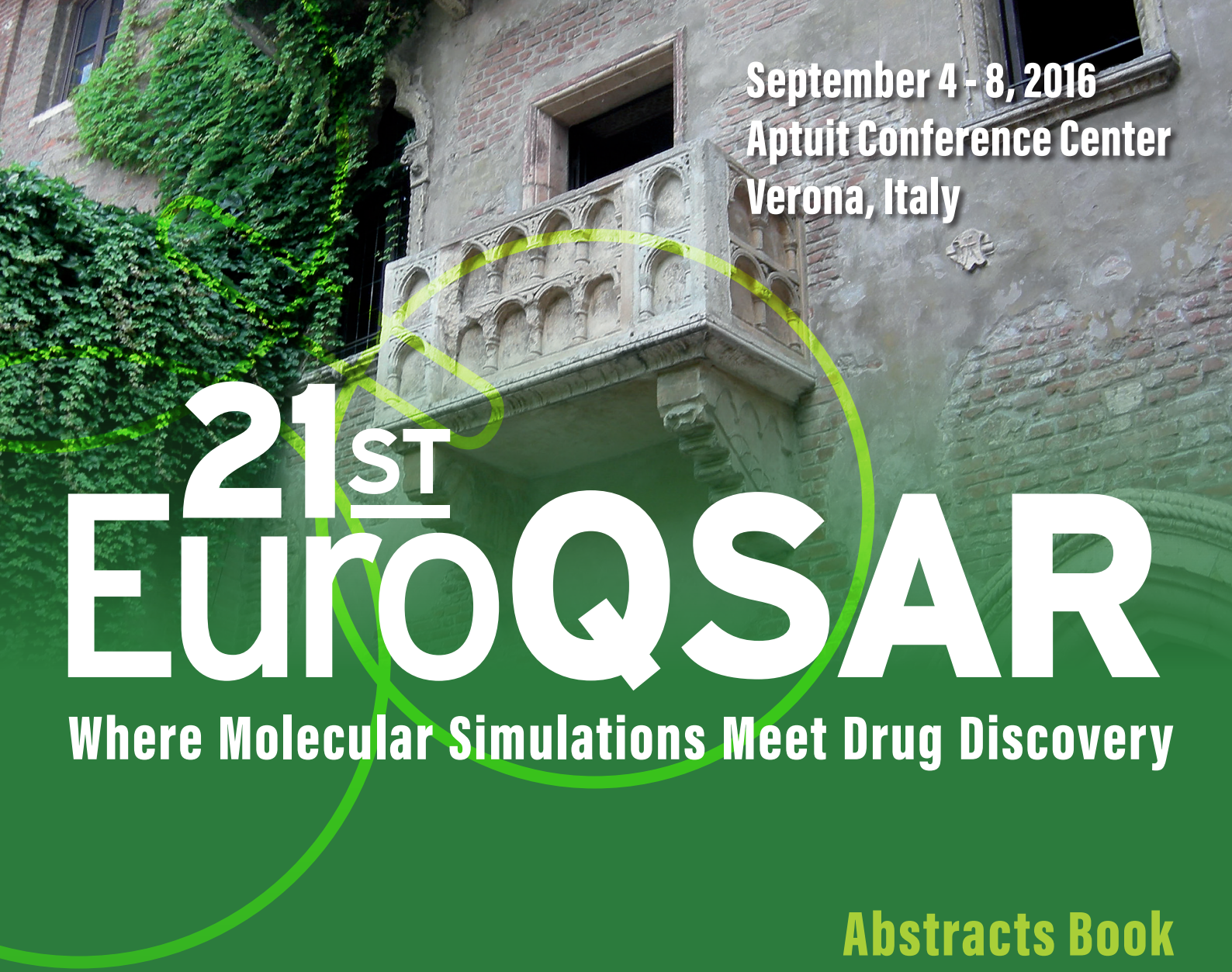

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A DYNAMIC - MULTIPLE RECEPTOR CONFORMATIONS (MD-MRC) APPROACH TO ENHANCE EARLY ENRICHMENT IN VIRTUAL SCREENING. A CASE STUDY ON PPAR-ALPHA

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Computer-aided drug design (CADD) often consider proteins as rigid. This can sometimes impact on the virtual screening results because of a reduced space of likely side chains conformations that can be explored [1,2]. Therefore, Molecular Dynamics (MD) simulations can be used, prior to virtual screening, to add flexibility to proteins, and study them in a dynamical way [3,4]. Furthermore, the use of multiple receptor conformations (MRC), using protein crystals with dfferent ligands, can help to better elucidate the role of the ligand on protein active conformation, and then explore the most common interactions between small molecules and the receptor. Such an approach can help the rational design of new molecules. In this work, we evaluated the contribution of the combined use of MD together with MRC, applied to Peroxisome Proliferator-Activated Receptor alpha (PPARα), to examine common ligand-protein interactions within the complexes and their abundance frequency (**Fig.1**). These findings were then exploited as features for pharmacophore generation (**Fig.2**) and constraints for the docking grid generation to use in a virtual screening. We found that, information derived from short multiple MD simulations, carried out on different protein crystals, can improve virtual screening results for this receptor in terms of early enrichment of active ligands. In the end we adopted a consensus scoring based on docking score and pharmacophore alignment to rank our dataset. Our results, showed an increase in the ability to discriminate active from inactive compounds, referred to the early recognition, when screening is performed using MD-MRC approach.

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