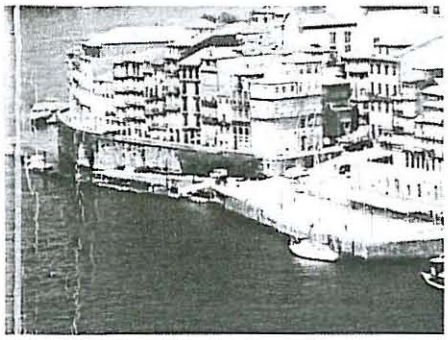

2nd Iberic Meeting on Medicinal Chemistry:

G Protein-Coupled Receptors and Enzymes in Drug Discovery

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Program and Abstracts

Mdm2 as a potential target for mushrooms LMW compounds

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In some human cancer cases, the activity of p53 is inhibited by the overexpressed Mdm2 (E3 ubiquitin-protein ligase Mdm2) oncoprotein.[1] Mdm2 acts as an ubiquitin ligase, resulting in p53 ubiquitination and subsequent p53 proteasomal degradation. The disruption of the Mdm2-p53 interaction using small-molecule inhibitors is recognized as a promising strategy for anticancer drug design.[2] Mushrooms are a vast and yet largely untapped source of powerful new pharmaceutical products. In particular, and most importantly for modern medicine, they represent an unlimited source of compounds with antitumor and immunostimulating properties.[3] In this study, a total of 85 LMW (low molecular weight) compounds present in mushrooms were used in a protein-ligand docking experiment using a Mdm2 protein structure (PDB:1T4E) as receptor protein target.
The 1T4E X-ray structure presents Mdm2 co-crystallized with a known inhibitor, benzodiazepinedione, located in the Mdm2-p53 interaction site with an experimental Ki value of 80 nM.[4] AutoDock Vina, the docking tool used in this study, predicted a Ki value of 79 nM and RMSD (Root Mean Standard Deviation) of 0.033 Å for benzodiazepinedione, when compared to the co-crystallized benzodiazepinedione, thus validating the 1T4E structure for docking subsequent compounds. Virtual screening of the 85 LMW compounds was then performed. Ergosterol (Ki=824 nM) and ergosta-4,6,8(14),22-tetraen-3-one (Ki=824 nM) stand out as the top ranked potential inhibitors for Mdm2. Both compounds were then manually inspected in order to investigate its specific binding mode. The information provided shows several interesting starting points for further development of Mdm2 inhibitors. Furthermore, this study contributes to the valorisation of mushrooms as functional foods.

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