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In silico design, synthesis and toxicological evaluation of 1,3-thiazolidine-2,4-dione derivatives as PPARγ agonists

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Thiazolidinediones (TZD) are ligands for PPARγ used for the treatment of type 2 diabetes mellitus (DM2), though, drugs from this group have been shown to produce hepatic toxicity. The aim of this work is to design a new set of molecules based on the substitution of TZD with electro donating and electro withdrawing heteroatoms, which might activate the PPARγ while minimizing the adverse effects. 130 derivatives were designed. The derivatives contained the polar head of TZD and an aromatic body which served simultaneously as the body and the tail. The physicochemical properties of the derivatives were evaluated using the Molinspiration software and Osiris Property Explorer. Additionally, docking studies were carried out using Autodock 4.0. Two ligands were selected in order to synthesize them through a Knoevenagel condensation, in a solvent free reaction. The products were identified using spectroscopic techniques. Acute oral toxicity was performed as per OECD 425 guideline using healthy female albino Wistar rats. It was found that the compounds are in accordance with Lipinki's rule of 5, and none of them are toxic according to the predictions. In the docking results, the interaction of the ligands was more likely when the derivatives were substituted with electro withdrawing heteroatoms since these enhanced the formation of hydrogen bonding between the head of compound and the ligand binding domain (LBD), leading to the selection of the best two compounds to be synthetized, which will be further mentioned as C40 and C81. C40 consists of the polar head and salycilaldehyde, while C81 consists of the polar head and chlorofluorobenzaldehyde. The proposed methodology was optimal for obtaining the desired products. The compounds were obtained with a yield of 98% and 67%, respectively. According to the toxicity study, it was found that C40 had a LD50 above 2000 mg/kg, while C81 had a LD50 between 700 and 1400 mg/kg.

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