SCREENING OF NOVEL PPAR\(\gamma\) LIGANDS BY BIOPHYSICAL AND CELULAR APPROACHES

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The metabolic syndrome affects at least 25% of the global population, and is characterized by development of conditions like type II diabetes, obesity and hypertension. Currently, most of the efforts to fight against this syndrome relies on controlling nuclear receptors, especially PPAR\(\gamma\). PPARs regulate transcription of genes related to the lipid metabolism, inflammation control and insulin production. However, most of the available drugs, which use these receptors as targets, present side effects. Therefore, researchers are searching for new molecules that can selectively bind to these receptors, modulating them to minimize the side effects. Our objective here is to find some new ligands that can act as PPAR\(\gamma\) agonists. With this purpose, recombinant protein was expressed and purified; structural stability of protein incubated with different ligands was analyzed by CD, DSF and fluorescence quenching of ANS. Also, the proteins were submitted to co-crystallization experiments and these ligands were tested in transactivation and in adipocyte differentiation assays. By our CD, DSF and fluorescence quenching results, we find some ligands that stabilized PPAR\(\gamma\) secondary and tertiary structure. Additionally, these stabilizing ligands showed lower activation levels in transactivation assays. Crystallographic data are being processed in an attempt to solve the structure of PPAR\(\gamma\) with the ligands. Here, we find new promising ligands that follow the rational search of PPAR\(\gamma\) selective modulators, stabilizing the receptor structure, causing a small activation of the receptor and with lower action in adipocyte differentiation.

Key Word: PPAR\(\gamma\), Stabilization, Potency (Agonism).
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