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Shooting three inflammatory targets with a single bullet: Novel multi-targeting anti-inflammatory glitazones

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Abstract:

In search for effective multi-targeting drug ligands (MTDLs) to address low-grade inflammatory changes of metabolic disorders, we rationally designed some novel glitazones-like compounds. This was achieved by incorporating prominent pharmacophoric motifs from previously reported COX-2, 15-LOX and PPARγ ligands. Challenging our design with pre-synthetic docking experiments on PPARγ showed encouraging results. In vitro tests have identified 4 compounds as simultaneous partial PPARγ agonist, potent COX-2 antagonist (nanomolar IC50 values) and moderate 15-LOX inhibitor (micromolar IC50 values). We envisioned such outcome as a prototypical balanced modulation of the 3 inflammatory targets. In vitro glucose uptake assay defined six compounds as insulin-sensitive and the other two as insulin-independent glucose uptake enhancers. Also, they were able to induce PPARγ nuclear translocation in immunohistochemical analysis. Their anti-inflammatory potential has been translated to effective inhibition of monocyte to macrophage differentiation, suppression of LPS-induced inflammatory cytokine production in macrophages, as well as significant in vivo anti-inflammatory activity. Ligand co-crystallized PPARγ X-ray of one of MTDLs has identified new clues that could serve as structural basis for its partial agonism. Docking of the most active compounds into COX-2 and 15-LOX active sites, pinpointed favorable binding patterns, similar to those of the co-crystallized ligands. Finally, in silico assessment of pharmacokinetics, physicochemical properties, drug-likeness and ligand efficiency indices was performed. Hence, we anticipate that the prominent biological profile of such series will rationalize relevant anti-inflammatory drug development endeavors. © 2019 Elsevier Masson SAS

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