

Extended Abstract

# Design, Synthesis, and Pharmacological Evaluation of Novel Quinolone Aryl Sulfonamide Derivatives as Potent GPR55 Antagonists <sup>†</sup>

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**Abstract:** Docking studies of identified GPR55 ligands using a GPR55 inactive state model allow rationalizing key structural features involved in ligand–receptor binding. On this molecular basis, we have designed novel quinolone sulfonamide derivatives with optimized potency and efficacy. These novel molecules compounds are being synthesized and evaluated using a  $\beta$ -arrestin recruitment assay in CHO cells overexpressing human GPR55 and  $\beta$ arr2-GFP.

**Keywords:** GPR55; antagonist; docking; cannabinoids

The orphan Class A G-protein-coupled receptor GPR55 has been proposed as a potential member of the cannabinoid receptor family. This receptor has been implicated in numerous physiopathological conditions, such as metabolic disorders, inflammatory and neuropathic pain, regulation of vascular functions, bone physiology, cancer, and motor coordination.

Diverse studies point towards the phospholipid LPI (lysophosphatidylinositol) as the endogenous ligand for GPR55. In addition, diverse chemical entities, endogenous, phytogenic, and synthetic cannabinoid ligands among them have been shown to modulate this receptor. Nonetheless, pharmacological inconsistencies and the lack of potent and selective GPR55 ligands are delaying the exploitation of such a promising therapeutic target.

In an effort to identify GPR55 ligands, a high-throughput, high-content screening discovered the quinolone aryl sulfonamide ML193 (CID1261822) as an antagonist of this receptor [1]. Using our GPR55 inactive state model [2,3], docking studies of this compound and its analogs helped us to rationalize key structural features involved in ligand–receptor binding. On this molecular basis, we have designed novel quinolone sulfonamide derivatives with optimized potency and efficacy. These novel molecules compounds are being synthesized and evaluated using a  $\beta$ -arrestin recruitment assay in CHO cells overexpressing human GPR55 and  $\beta$ arr2-GFP.

In summary, we pursued a combination of structure–activity relationship development and molecular modeling studies to identify novel potent GPR55 antagonists that may serve as new tools for studying GPR55. [Support: NIH RO1 DA045698].

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