

Abstract

# Inhibition of LPS-Induced PGE<sub>2</sub> Production by Arylsulfonamide Derivatives via the Selective Inhibition of mPGES-1 Enzyme <sup>†</sup>

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<sup>†</sup> Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 7 August 2019

**Abstract:** Microsomal prostaglandin E synthase-1 (mPGES-1) is responsible for the massive prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) formation during inflammation. Increasing evidence reveals mPGES-1 inhibitors as a safe alternative to nonsteroidal anti-inflammatory drugs. Recently, we reported that a novel series of phenylsulfonyl hydrazide derivatives could reduce LPS-induced PGE<sub>2</sub> levels in RAW 264.7 macrophage cells via an inhibition of the mPGES-1 enzyme. However, a few of the phenylsulfonyl hydrazide derivatives showed poor metabolic stability in liver microsomes. In order to identify new mPGES-1 inhibitors with improved metabolic stability, therefore, a series of arylsulfonamide derivatives has been synthesized and biologically evaluated against PGE<sub>2</sub> production and the mPGES-1 enzyme. Among them, MPO-0186 inhibits the production of PGE<sub>2</sub> (IC<sub>50</sub> = 0.20 μM) in A549 cells via inhibition of mPGES-1 (IC<sub>50</sub> = 0.49 μM in a cell-free assay) together with high selectivity over both COX-1 and COX-2. A molecular docking study theoretically suggests that MPO-0186 could inhibit PGE<sub>2</sub> production by blocking the PGH<sub>2</sub> binding site of the mPGES-1 enzyme. Furthermore, MPO-0186 demonstrated good metabolic stability in human liver microsomes and no significant inhibition observed in clinically relevant CYP isoforms.

**Keywords:** mPGES-1; inflammation; arylsulfonamides



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