

Abstract

The Ameliorating Effect of Phenylsulfonamide Derivatives on Scopolamine-Induced Memory Impairment in Mice via Inhibition of mPGES-1 [†]

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Abstract: Our previous research showed that a novel series of phenylsulfonyl hydrazide derivatives reduced LPS-induced PGE₂ levels in RAW 264.7 macrophage cells via an inhibition of mPGES-1 enzyme. As a continuous work, new phenylsulfonamide derivatives (**5a–5k**) as methylene analogues of phenylsulfonyl hydrazide derivatives, including **MPO-0063**, were synthesized and biologically evaluated in vitro. Among synthetic compounds, **5a** (**MPO-0112**) showed decreased inhibitory activity against PGE₂ production (IC₅₀: 0.34 μ M) compared to **MPO-0063** (IC₅₀: 0.04 μ M) but inhibited the mPGES-1 enzyme (IC₅₀: 7.37 μ M) similar to **MPO-0063** (IC₅₀: 0.10 μ M) together with excellent selectivity over COX-enzymes (COX-1 and 2). According to recent studies on the close correlation between up-regulation of mPGES-1 and Alzheimer's disease, we investigated whether **5a** could ameliorate scopolamine-induced memory impairment using the passive avoidance test. The memory impairment-ameliorating effect of **5a** (1.0 mg/kg, p.o.) was found to be effective, comparable to that of donepezil (5 mg/kg, p.o.) as a positive control. On the other hand, **5a** exhibited little or weak AChE and BuChE inhibitory activity, which implies that **5a** could ameliorate scopolamine-induced memory impairment by inhibiting mPGES-1 enzyme instead of cholinesterase enzymes. In addition, **MPO-0112** exhibited a favorable in vitro CYP profile, which is suggestive of no potential drug–drug interactions. Therefore, these overall results suggest that **5a** as a selective mPGES-1 inhibitor may be a novel therapeutic agent for diseases associated with cognitive deficits, such as Alzheimer's disease.

Keywords: mPGES-1; phenylsulfonamide derivatives; Memory Impairment

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