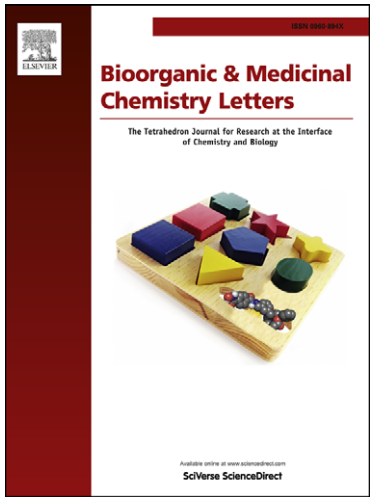

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Fragment-Based Discovery of Novel and Selective mPGES-1 Inhibitors Part 1: Identification of Sulfonamido-1,2,3-Triazole-4,5-Dicarboxlic acid

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Abstract: Microsomal prostaglandin E synthase-1 (mPGES-1) is an inducible prostaglandin E synthase that catalyzes the conversion of prostaglandin PGH_2 to PGE_2 and represents a novel target for therapeutic treatment of inflammatory disorders. It is essential to identify mPGES-1 inhibitor with novel scaffold as new hit or lead compound for the purpose of the next-generation anti-inflammatory drugs. Herein we report the discovery of sulfonamido-1,2,3-triazole-4,5-dicarboxylic derivatives as a novel class of mPGES-1 inhibitors identified through fragment-based virtual screening and in vitro assays on the inhibitory activity of the actual compounds. 1-[2-(*N*-Phenylbenzenesulfonamido)ethyl]-1*H*-1,2,3-triazole-4,5-dicarboxylic acid (**6f**) inhibits human mPGES-1 (IC_{50} of 1.1 μM) with high selectivity (*ca.*1000-fold) over both COX-1 and COX-2 in a cell-free assay. In addition, the activity of compound **6f** was again tested at 10 μM concentration in presence of 0.1% Triton X-100 and found to be reduced to 1/4 of its original activity without this detergent. Compared to the complete loss of activity of nuisance inhibitor with the detergent, therefore, compound **6f** would be regarded as a partial nuisance inhibitor of mPGES-1 with a novel scaffold for the optimal design of more potent mPGES-1 inhibitors.

Prostaglandin E_2 (PGE_2) is a key mediator in inflammation, pain, fever, atherosclerosis and tumorigenesis.[1] The biosynthetic pathway of PGE_2 involves two sequential enzymatic actions from arachidonic acid (AA). AA is released from the membrane and then converted to PGH_2 by cyclooxygenases (COX-1/COX-2),[2] followed by the subsequent isomerization of PGH_2 into PGE_2