Design and synthesis of a novel mPGES-1 lead inhibitor guided by 3D-QSAR CoMFA

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ABSTRACT

The search of novel mPGES-1 inhibitors has recently intensified probably due to the superior safety in comparison to existing anti-inflammatory drugs. Although two mPGES-1 inhibitors have entered clinical trials, none has yet reached the market. In this study, we performed modifications guided by 3D-QSAR CoMFA on **2**, which is an unsymmetrical curcumin derivative with low binding affinity towards mPGES-1. To counter the PAINS properties predicted for **2**, the diketone linker was replaced with a pyrazole ring. On the other hand, both prenyl and carboxylate ester groups were introduced to improve the activity. When tested *in vitro*, **11** suppressed PGE_2 biosynthesis in activated macrophages and showed promising human mPGES-1 inhibition in microsomes of interleukin-1β-stimulated A549 cells. Altogether, **11** has been identified as a potential mPGES-1 inhibitor and could be a promising lead for a novel class of mPGES-1 inhibitors.

KEYWORDS

3D-QSAR CoMFA; PGE_2; mPGES-1; PAINS

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