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-1 beta-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. (C) 2019 Elsevier B.V. All rights reserved.

Keywords

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