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Fasihi Mohd Aluwi, M.F.[a] , Rullah, K.[b] , Koeberle, A.[c] , Werz, O.[c] , Abdul Razak, N.S.[d] , Wei, L.S.[e] , Salim, F.[f] , Ismail, N.H.[f] , Jantan, I.[g] , Wai, L.K.[d]

Design and synthesis of a novel mPGES-1 lead inhibitor guided by 3D-QSAR CoMFA
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[a] Faculty of Industrial Science & Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak, Gambang, Pahang 26300, Malaysia
[b] Department of Pharmaceutical Chemistry, Kuliyyah of Pharmacy, International Islamic University Malaysia, Bandar Indera Mahkota, Kuantan, Pahang 25200, Malaysia
[c] Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Friedrich-Schiller-University Jena, Jena, 07743, Germany
[d] Drug and Herbal Research Centre, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul AzizKuala Lumpur 50300, Malaysia
[e] Department of Microbiology, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, Serdang, Selangor 43400, Malaysia
[f] Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA, Kampus Puncak Alam, Puncak Alam, Selangor 42300, Malaysia
[g] School of Pharmacy, Taylor University Lakeside Campus, No 1, Jalan Taylor's, Subang Jaya, Selangor Darul Ehsan 47500, Malaysia

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 PGE2 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. © 2019 Elsevier B.V.

Author Keywords
3D-QSAR CoMFA; mPGES-1; PAINS; PGE2

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Correspondence Address
Wai L.K.; Drug and Herbal Research Centre, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul AzizMalaysia; email: david_lam@ukm.edu.my

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