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Synthesis of small molecules targeting paclitaxel-induced MyD88 expression in triple-negative breast cancer cell lines

Khor Poh Yen [a, f], Johnson Stanslas [b], Tianshu Zhang [c, d], Hongyuan Li [c], Xiaohui Wang [c, d], Chan Kok Meng [e], Lam Kok Wai [f]

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Abstract

Acquired paclitaxel (PTX) chemoresistance in triple-negative breast cancer (TNBC) can be inferred from the overexpression of toll-like receptor 4 (TLR4) and myeloid differentiation primary response 88 (MyD88) proteins and the activation of the TLR4/MyD88 cascading signalling pathway. Finding a new inhibitor that can attenuate the activation of this pathway is a novel strategy for reducing PTX chemoresistance. In this study, a series of small molecule compounds were synthesised and tested in combination with PTX against TNBC cells. The trimethoxy-substituted compound significantly decreased MyD88 overexpression and improved PTX activity in MDA-MB-231^{TLR4+} cells but not in HCC^{TLR4-} cells. On the contrary, the trifluoromethyl-substituted compound with PTX synergistically improved the growth inhibition in both TNBC subtypes. The fluorescence titrations indicated that both compounds could bind with MD2 with good and comparable binding affinities. This was further supported by docking analysis, in which both compounds fit perfectly well and form some critical binding interactions with MD2, an essential lipid-binding accessory to TLR4 involved in activating the TLR-4/MyD88-dependent pathway.

Keywords

Triple-negative breast cancer; Small molecule; Paclitaxel; TLR4/MD2; MyD88

Abbreviations

CI, combination index; SI, selectivity index; TNBC, triple-negative breast cancer; MD-2, lymphocyte antigen 96; TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response 88; PTX, Paclitaxel; LPS, lipopolysaccharides; SEM, standard error of the mean