Jawsamycin is a potent and selective GPI biosynthesis inhibitor that targets PIG-A and shows antifungal properties *in vivo*

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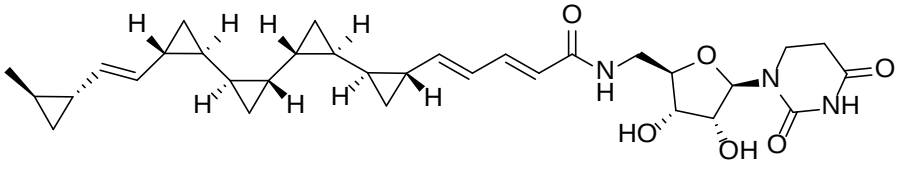
A reporter gene-based screen focusing on antifungal compounds that modulate glycosylphosphatidylinositol (GPI) anchoring of proteins identified the oligocyclopropyl-containing natural product Jawsamycin (FR-900848) as a potent hit. Target identification by genetic methods supported inhibition at the level of UDP-glycosyltransferase, the first step in the GPI biosynthesis[1, 2]. Identification of resistance-conferring point mutations highlighted the catalytic subunit SPT14/PIG-A to be the primary target of Jawsamycin. Jawsamycin showed potent and cidal inhibition of pathogenic fungi of the Mucorales order with good selectivity over the human enzyme. The therapeutic potential of PIG-A inhibition was tested in a murine mucormycosis model. Jawsamycin is the first-in-class chemical probe targeting PIG-A, has shown encouraging *in vitro* and *in vivo* activities providing an exciting starting point for chemical improvement of its derivatives for treatment of devastating invasive fungal infections.



Jawsamycin (FR-900848)

1) McLellan, C.A. et al. Inhibiting GPI anchor biosynthesis in fungi stresses the endoplasmic reticulum and enhances immunogenicity. ACS chemical biology 7, 1520-1528 (2012)
2) Mutz, M. & Roemer, T. The GPI anchor pathway: a promising antifungal target? Future Med Chem 8, 1387-1391 (2016)