Yield improvement of enediyne yangpumicins in Micromonospora yangpuensis through ribosome engineering and fermentation optimization

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Abstract

Yangpumicins (YPMs), eg. YPM A, F, and G, are newly discovered enediynes from Micromonospora yangpuensis DSM 45577, which could be exploited as promising payloads of antibody-drug conjugates. However, the low yield of YPMs in the wild-type strain (˜1 mg/L) significantly hampers their further drug development. In this study, a combined ribosome engineering and fermentation optimization strategy has been used for yield improvement of YPMs. One gentamycin-resistant M. yangpuensis DSM 45577 strain (MY-G-1) showed higher YPMs production (7.4 ± 1.0 mg/L), while it exhibits delayed sporulation and slender mycelium under scanning electron microscopy. Whole genome re-sequencing of MY-G-1 reveals several deletion and single nucleotide polymorphism mutations, which were confirmed by PCR and DNA sequencing. Further Box–Behnken experiment and regression analysis determined that the optimal medium concentrations of soluble starch, mannitol, and pharmamedia for YPMs production in shaking flasks (10.0 ± 0.8 mg/L). Finally, the total titer of YPM A/F/G in MY-G-1 reached to 15.0 ± 2.5 mg/L in 3-L fermenters, which was about 11-fold higher than the original titer of 1.3 ± 0.3 mg/L in wild-type strain. Our study may be instrumental to develop YPMs into a clinical anticancer drug, and inspire the use of these multifaceted strategies for yield improvement in Micromonospora species.

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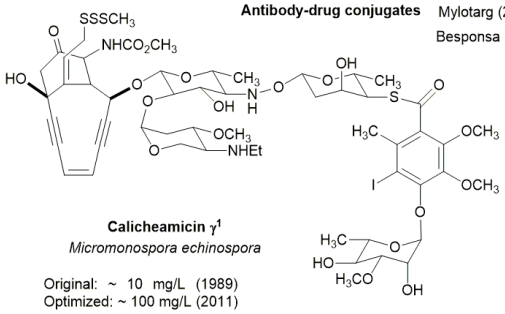
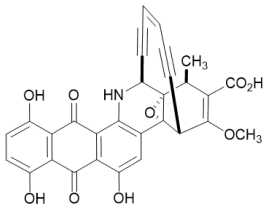
`YPM yield-20210508 Biotechol Bioeng.docx` available at https://authorea.com/users/415500/articles/710022-yield-improvement-of-enediyne-yangpumicins-in-micromonospora-yangpuensis-through-ribosome-engineering-and-fermentation-optimization

Antibody-drug conjugates Mylotarg (2000/2017)
Besponsa (2017)



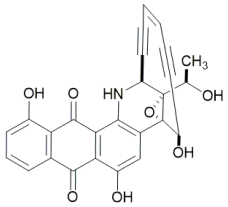
Calicheamicin γ[1]
Micromonospora echinospora

Original: ~ 10 mg/L (1989)
Optimized: ~ 100 mg/L (2011)



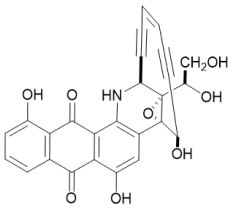
Dynemicin A (DYN A)
Micromonospora chersina sp. nov. M956-I

Original: ~ 0.1 mg/L (1989)
Optimized: 24.7 mg/L (1995)



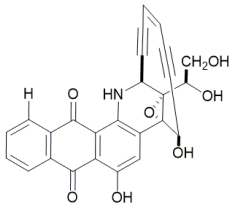
Yangpumicin A (YPM A)
Micromonospora yangpuensis

Original: ~ 0.05 mg/L (2018)
~ 0.8 mg/L (2019)
Optimized: 9.4 ± 0.2 mg/L (this study)



Yangpumicin F (YPM F)
Micromonospora yangpuensis

Original: ~ 0.4 mg/L (2019)
Optimized: 4.6 ± 0.8 mg/L (this study)



Yangpumicin G (YPM G)
Micromonospora yangpuensis

Original: ~ 0.2 mg/L (2019)
Optimized: 1.1 ± 0.4 mg/L (this study)