Medium optimization and subsequent fermentative regulation for the scaled-up production of anti-tuberculosis drug leads ilamycin-E1/E2

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Abstract

Tuberculosis (TB) and its emerged drug resistance exert huge threats on the global health, therefore development of novel anti-TB antibiotics is very essential. Ilamycin-E1/E2 is a pair of cycloheptapeptide enantiomers obtained from a marine-derived Streptomyces atratus SCSIO ZH16-ΔilaR mutant, and become promising anti-TB lead compounds due to their significant anti-TB activities, but their low titer hampered the further clinical development. In this work, the statistical Plackett-Burman design (PBD) model was applied to screen out bacterial peptone as the only significant but negative factor affecting the ilamycin-E1/E2 production. Subsequent single factor optimization revealed that replacement of bacterial peptone with malt extract eliminated the accumulation of porphyrin-type competitive byproduct, and the titer of ilamycin-E1/E2 in shaking flasks was improved from original 13.6±0.8 to 142.7±5.7 mg/L for about 10.5 folds. Furthermore, a pH coordinated feeding strategy was first adopted in scaled-up production of ilamycin-E1/E2. The obtained titer of ilamycin-E1/E2 in 30L was 169.8±2.5 mg/L, while in 300L fermentor was only 131.5±7.5 mg/L due to the unsynchronization of feeding response and pH change. Therefore, the continuous pulse feeding strategy was further applied in 300L fermentor and finally achieved 415.7±29.2 mg/L ilamycin-E1/E2, which represented about 30.5 folds improvement at last. Our work provided the solid basis to achieve sufficient ilamycin-E1/E2 lead compounds and support their potential anti-TB drug development.

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