



Glucosylated Thiamphenicol: A new veterinary antimicrobial prodrug resistant to bacterial enzymatic inactivation – *In vitro* and *In vivo* evaluation using *Galleria mellonella* larval model infected *Salmonella enterica*

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Rok wydania

2026

Czasopismo

Carbohydrate Research

Numer woluminu

565

Strony

109935/1-109935/9

DOI

10.1016/j.carres.2026.109935

Kolekcja

Naukowa

Język

Angielski

Typ publikacji

Artykuł

Streszczenie

Thiamphenicol (TAM) is an amphenicol antibiotic widely used in veterinary medicine, whose efficacy is increasingly compromised by enzymatic inactivation mediated by chloramphenicol acetyltransferases (CATs). These enzymes acetylate the 3-hydroxyl group of phenicols, abolishing ribosomal binding and antibacterial activity. Here, we report the synthesis and evaluation of thiamphenicol-3-O- β -d-glucopyranoside (TAMG) as a glucosidic prodrug designed to mask the CAT-susceptible site. TAMG was obtained via Schmidt glucosylation followed by Zemplén deprotection and fully characterized by NMR and HPLC-MS. In contrast to TAM, TAMG showed complete resistance to CAT-mediated acetylation *in vitro*, consistent with steric shielding of the 3-OH group. Electrochemical stress testing revealed enhanced redox robustness of the glucosylated derivative. *In vivo* evaluation using a *Galleria mellonella* infection model demonstrated that TAMG was non-toxic up to 100mg/kg and provided complete protection against *Salmonella enterica* infection across the tested dose range in the *Galleria mellonella* model, without the need for exogenous β -glucosidase activation. These findings highlight 3-O-glucosylation as a practical strategy to overcome CAT-driven resistance in veterinary phenicol therapy.

Słowa kluczowe

Thiamphenicol, 3-O- β -d-glucopyranoside, Glucosylation, Prodrug, Chloramphenicol acetyltransferase, Electrochemistry-MS, *Galleria mellonella*, Veterinary antibiotic, *Salmonella enterica*

Adres publiczny

<http://dx.doi.org/10.1016/j.carres.2026.109935>

Plik został wygenerowany dnia 2026-08-25 16:48:03

Adres w repozytorium <https://old.chem.uni.wroc.pl/pl/repozytorium/ghdJ-YI>.