INTERNATIONAL MASTER IN
SUSTAINABLE
DRUG DISCOVERY

STUDYING THE EFFECT OF GLYCON MODIFICATIONS ON THE ANTITRYPANOSOMAL ACTIVITY: A STORY OF METHYL GROUPS

Moustafa Ali Khallaf

Local Supervisor:

Prof. Serge Van Calenbergh (Ghent University)

Academic Promotor:

Dr. Baptiste Villemagne (University of Lille)

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UNIVERSITEIT GENT

MEDICAL UNIVERSITY OF GDAŃSK

Université de Lille

university of groningen

Summary:

Neglected tropical diseases such as Human African trypanosomiasis and Chagas disease remain a major health burden, and current chemotherapies are limited by toxicity, resistance, and stage-restricted efficacy. Nucleoside analogues are attractive candidates because trypanosomatid parasites lack de novo purine biosynthesis, yet most structure–activity relationship (SAR) work has focused on the nucleobase, leaving the contribution of the ribose—especially its conformation— comparatively underexplored. This dissertation investigates the introduction of a methyl substituent at three different positions of the glycon to bias sugar conformation. In a later stage, the effect of such modifications on the antitrypanosomal activity will be evaluated.

The core objective was to design and synthesize 3- and 4-C-methyl ribofuranose donors and to couple them, together with a 2-C-methyl donor, to selected purine and 7-deazapurine nucleobases to build a focused nucleoside library. The 3-C-methyl donor was obtained from a xylofuranose-derived precursor via introduction of a quaternary C-3 center, while the 4□C□methyl donor was prepared from a 4-hydroxymethyl ribofuranose using a Garegg-type iodination–reduction to achieve formal deoxygenation at C-4; in both cases, protecting groups were tailored for Vorbrüggen glycosylation and a unified deprotection sequence.

Natural purines (adenine, guanine) were included as “baseline” substrates, while tubercidin and 7-deazainosine scaffolds were chosen as privileged antitrypanosomal cores. Key base modifications (such as selected C7 substituents and 6-O-alkyl chains) were introduced at late stages from common intermediates, enabling efficient diversification. Optimisation of the glycosylation step was a central part of the work, establishing conditions that gave high yields and remained effective with less nucleophilic deazapurine bases.

Overall, the thesis establishes practical access to 3-C- and 4-C-methyl ribofuranose donors and shows that they can be combined with carefully chosen nucleobases under optimised conditions to furnish a structurally coherent library of C-methyl-modified nucleosides. This library is now ready for conformational analysis and biological evaluation, enabling the proposed conformational–activity relationship to be tested and providing a platform for future nucleoside analogue discovery against trypanosomatid parasites.