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Synthesis of Azole Conjugates with Triterpenes of Lupane Series

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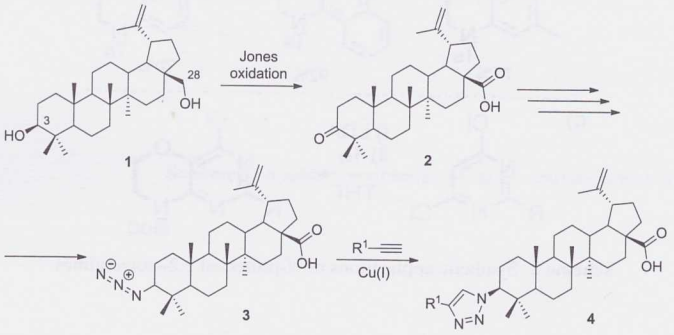
Introduction

Betulin is a naturally occurring triterpene found in the outer layer of birch bark. Since this tree species is very commonly found in Latvia and betulin is easy to isolate, our research group has taken interest in the synthesis and biological properties of its derivatives. In addition, betulin itself has shown anti-HIV-activity and certain cytotoxicity[1]. On the other hand, azole heterocycles are a well-established pharmacophores, thanks to their non-covalent binding with various receptors and enzymes.

Results and Discussions

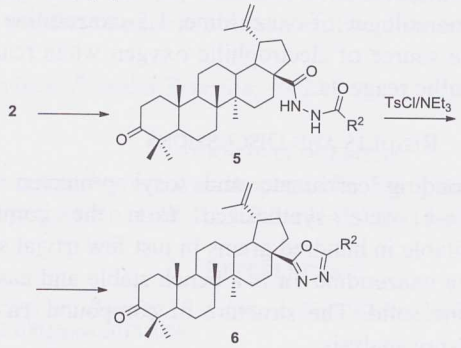
Herein, we report an approach towards the synthesis of azole conjugates with betulin, namely, in positions C-3 and C-28.

The key reaction of 1,2,3-triazole ring introduction in position C-3 was chosen to be Cu(I) catalysed 1,3-dipolar cycloaddition on 3-azidobetulinic acid carried out with different terminal alkynes. Betulin (**1**) was used as a starting material and was extracted from birch bark. The process started with Jones oxidation [2] yielding up to 86 % of betulonic acid (**2**) and was continued by its reductive amination [3] yielding 82 % of 3-aminobetulinic acid as a diastereomeric mixture. Due to its poor solubility, no further purification was performed and 3-azidobetulinic acid (**3**) was synthesized as a precursor of the final product in the subsequent diazotransfer reaction (Scheme 1).



Scheme 1. General route for the preparation of betulinic acid 1,2,3-triazole conjugates.

The key intermediates of the second synthetic strategy were betulonic acid hydrazide derivatives. Reaction between betulonic acid and aromatic carboxylic acid hydrazides gave mixed hydrazides. The treatment of **5** with TsCl in basic conditions resulted in the corresponding 1,3,4-oxadiazole **6** (Scheme 2) [4].



Scheme 2. Synthetic procedure for the preparation of betulonic acid hydrazide derivatives and further cyclization yielding betulonic acid 1,2,3-oxadiazole conjugates.

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