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DESIGN AND SYNTHESIS OF NOVEL DESMURAMYL PEPTIDE GLYCOCONJUGATES

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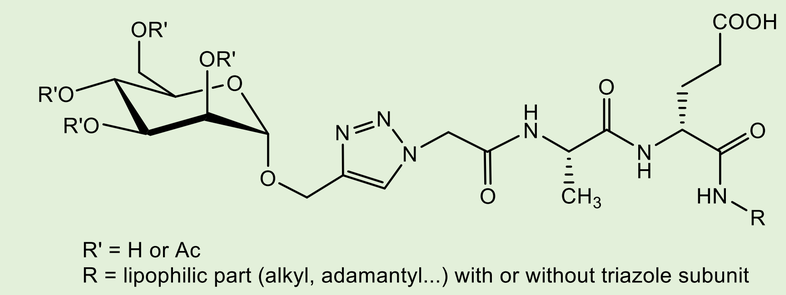
INTRODUCTION

Muramyl dipeptide (MDP, Mur*N*Ac-L-Ala-D-*iso*Gln) is the minimal structural motif of peptidoglycan with adjuvant properties. Since the muramyl group isn't essential for inducing this response, various structurally simplified desmuramyl peptide analogues (DMP, L-Ala-D-*iso*Gln) lacking the hydrophilic *N*-acetylmuramyl moiety were, so far, designed and synthesized by our group.[1,2] Successful structural modifications of DMP were carried out by introducing a mannose subunit to the amino-group of L-Ala via a glycolyl linker and/or incorporation of various lipophilic subunits through an amide bond to the α- or γ-position of D-*iso*Gln.

[1] V. Petrović Peroković, Ž. Car, J. Draženović, R. Stojković, L. Milković, M. Antica, Đ. Škalamera, S. Tomić, R. Ribić, *Molecules* **2021**, 26, 6352.
[2] V. Petrović Peroković, Ž. Car, M. Bušljeta, D. Mihelec, M. Paurević, S. Ivanković, R. Stojković, R. Ribić, *Int. J. Mol. Sci.* **2022**, 23, 8628-8648.

SYNTHESIS

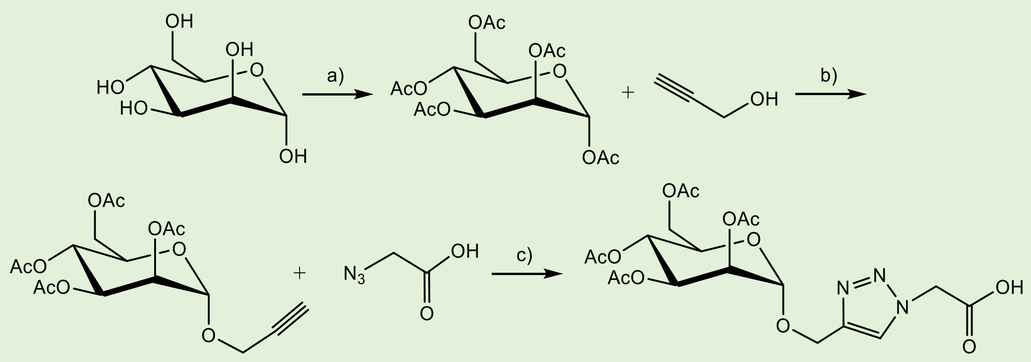
In the continuation of our research, new DMP derivatives were designed in which the mannose subunit is attached via triazole linkers to the peptide part (Fig. 1). In the synthesis of novel DMP derivatives two steps are crucial: a) preparation of a mannose-triazole precursor (Scheme 1) and b) preparation of an appropriately protected DMP precursor for binding lipophilic substituents by an amide bond (Scheme 2). In addition to the classical solution-phase peptide synthesis, a new approach under microwave conditions is currently being investigated in the preparation of DMP.



R' = H or Ac
R = lipophilic part (alkyl, adamantyl...) with or without triazole subunit

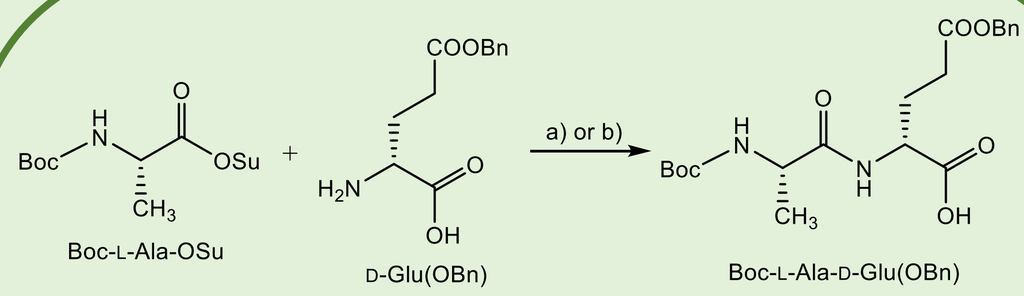
Figure 1. General structure of novel desmuramyl peptide mannoconjugates

SYNTHESIS OF MANNOSE-TRIAZOLE PRECURSOR



Scheme 1. Reagents and conditions: a) Ac_2O, I_2, rt, 45 min, Ar, 95%; b) $BF_3 \times OEt_2$, dry DCM, 0 °C to rt 30 min, 24 h, Ar 80%; c) $CuSO_4 \times 5\ H_2O$, Na-ascorbate, dioxane/H_2O = 4:3, 35 °C, 24 h, Ar, 63%.

SYNTHESIS OF PROTECTED DIPEPTIDE UNIT



Scheme 2. Reagents and conditions: a) TEA, THF, Ar(g), 0 °C to rt, 24 h, 95%; b) MW assisted synthesis (Table 1).

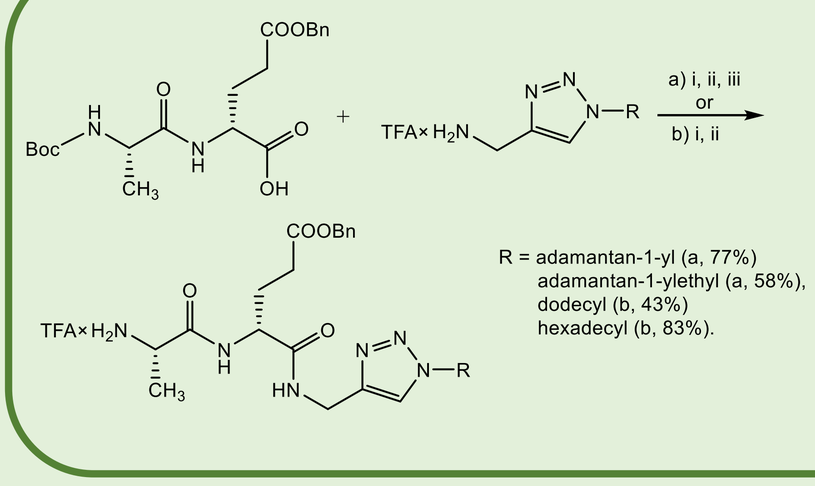
Table 1. Optimized conditions and results for MW assisted synthesis of Boc-L-Ala-D-Glu(OBn)

m (D-Glu(OBn)) / mg	*n* (D-Glu(OBn)) / mmol	*n* (Boc-L-Ala-OSu) / mmol	*V* (TEA) / mL	*V* (THF) / mL	Yield / %
50	0.21	0.21	0.059	1	88
200	0.84	0.84	0.235	4	80
500	2.10	2.10	0.585	10	82

All reactions were performed using CEM Discover SP Microwave Reaction System at the same conditions:

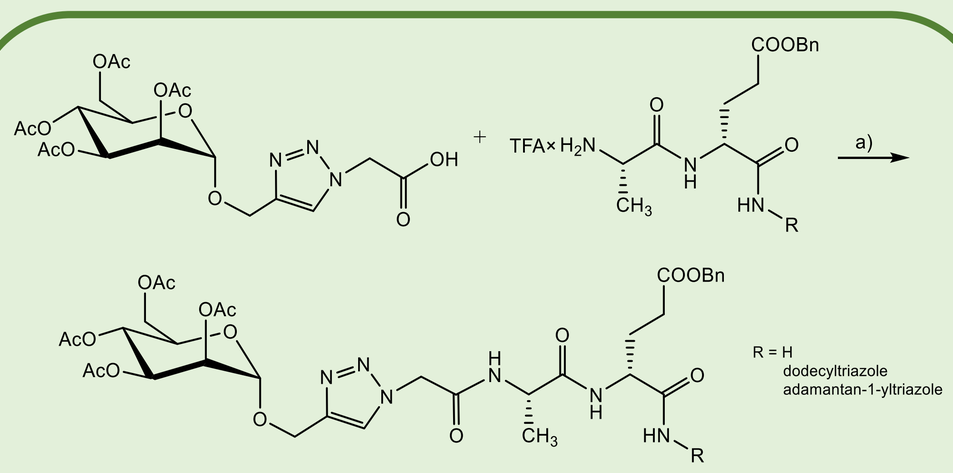
t / min	75
T / °C	50
p / psi	250
power / W	150

SYNTHESIS OF LIPOPHILIC DERIVATIVES OF DMP



Scheme 3. Reagents and conditions: (a) (i): NMM, *n*-buthyl chloroformate, THF, Ar, -10 °C, 2 h, (ii) NaHCO3, rt, 2 h; (iii) TFA, dry DCM, rt, 4h. b) (i) HBTU, TEA, dry THF/DCM (1:1), Ag, rt, 24 h; (ii) TFA, dry DCM, rt, 4h.

SYNTHESIS OF MANNOSYLATED DERIVATIVES OF DMP



Scheme 4. Reagents and preliminary conditions: EDC×HCl, HOBt, TEA, dry DCM, Ar, 0 °C to rt, 24 h.

CONCLUSIONS

- novel mannose-triazole subunit was successfully prepared from propargylated mannose subunit and azidoacetic acid by Cu(I) catalysed click reaction (CuAAC, Scheme 1)
- the protected dipeptide Boc-L-Ala-D-Glu(OBn) was prepared by conventional synthesis (Scheme 2) and microwave-assisted synthesis (Table 1) which significantly shortened the reaction time
- lipophilic derivatives of DMP were prepared using activated ester method (adamantan-1-yl, adamantan-1-ylethyl) or HATU condensation reagent (dodecyl, hexadecyl) for amide bond formation on α-position of DMP (Scheme 3)
- preliminary condensation of mannose-triazole precursor with DMP and lipophilic derivatives of DMP using EDC/HOBt method was successfully carried out, and the optimization of the reaction conditions is in progress
- the immunological activity of fully deprotected DMPP mannoconjugates will be evaluated in future studies.

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