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FERROCENE ESTER AND AMIDE DERIVATIVES OF DESMURAMYL PEPTIDE: SYNTHESIS AND ANALYSIS OF INTRAMOLECULAR INTERCATIONS AND INTERACTIONS WITH NOD2 RECEPTOR

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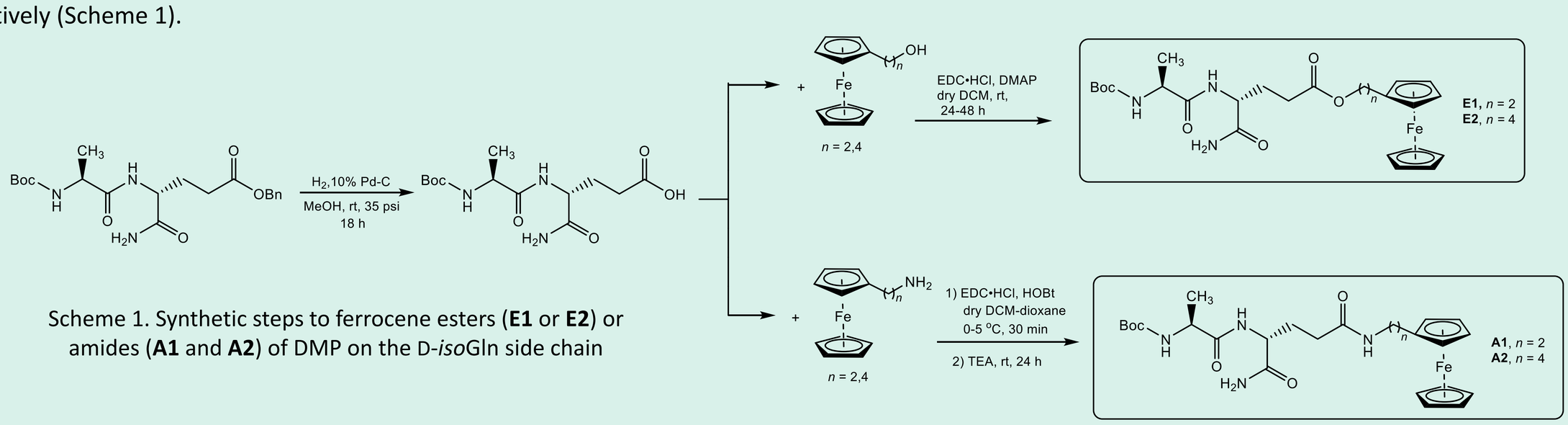
INTRODUCTION

Desmuramyl peptide (L-Ala-D-*iso*Gln, DMP) is a pharmacophore of muramyl dipeptide (Mur*N*Ac-L-Ala-D-*iso*Gln, MDP), a peptidoglycan fragment which stimulates immune response. MDP activates NOD2 and through cascade events stimulates the production of cytokines.[1]

SYNTHESIS OF FERROCENE ESTERS OR AMIDES OF DMP

In this work we described synthesis and structural characterization of ferrocene ester (**E1** and **E2**) and amide (**A1** and **A2**) derivatives of DMP with ferrocene subunit connected *via* linkers of different lenghts (ethyl or butyl) on the side chain of D-*iso*Gln. The lipophilic ferrocene alcohols or ferrocene amines are introduced on the D-*iso*Gln side chain of Boc-protected DMP using modified Steglich esterification procedure (EDC/DMAP) or EDC/HOBt amidation procedure, respectively (Scheme 1).



Scheme 1. Synthetic steps to ferrocene esters (**E1** or **E2**) or amides (**A1** and **A2**) of DMP on the D-*iso*Gln side chain

IR CONFORMATIONAL ANALYSIS

The IR frequencies of the backbone N−H and C=O groups depend on their participation in hydrogen bonds (HBs) and are red shifted and enhanced when an N−H···O=C HB is formed. [2] The red-shifted stretching frequencies of NH (~ 3350 cm^{-1}) indicate their involvement in HBs. Judging from the ratio of free (> 3400 cm^{-1}) and associated NH groups, only a smaller fraction of NH groups in **E1** is involved in HBs. The almost unchanged ratio of free and associated NH bands upon dilution indicates the intramolecular nature of HBs. In addition, an even more pronounced predominance of non-bonded NH groups was observed in **E2**, **A1** and **A2**.

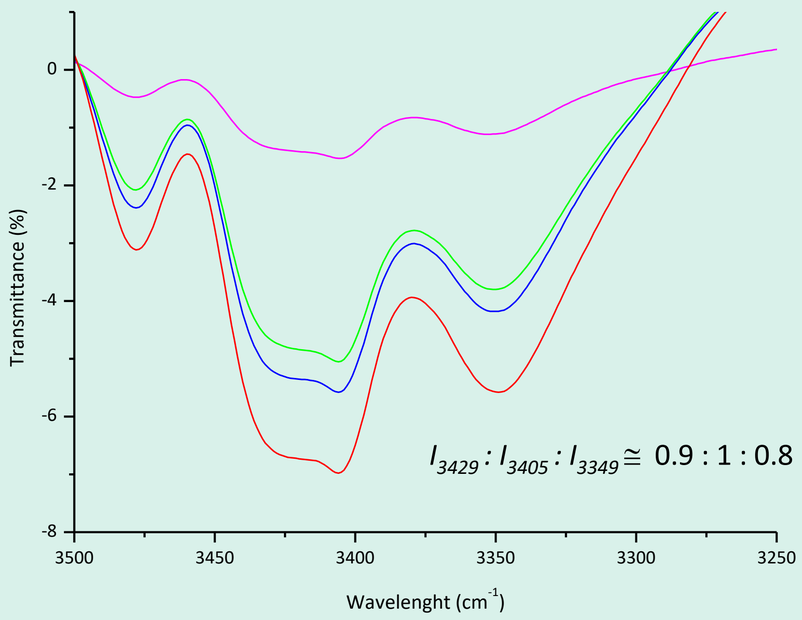


Fig. 1. The NH stretching vibrations in IR spectra of **E1** in CH_2Cl_2 [(—) $c = 5\times10^{-2}$ M, (- - -) $c = 2.5\times10^{-2}$ M, (· · ·) $c = 1.25\times10^{-2}$ M, (- · -) $c = 6.13\times10^{-3}$, and the ratio of the free and associated NH bands.

INTERACTIONS WITH NOD2 RECEPTOR

The potential of the compounds for NOD2 receptor activation was explored by docking study. In general, docking scores are better for ester and amide derivatives **E1** and **A1** (Fig. 2) with shorter C2 spacer between the DMP and ferrocene part then in case of compounds **E2** and **A2**. Dock score is -7.7 Kcal/mol for **E1** and -7.8 Kcal/mol for **A1** and overall eight (**E1**) or seven (**A1**) H-bonds are being formed, respectively. Characteristic H-bonds are formed between C=O of Ala, C=O and NH_2 from α-$CONH_2$ with corresponding amino acid residues of NOD2 receptor. Ferrocene is placed in the hydrophobic pocket formed by the aromatic amino acids Phe831, Trp887 and Trp911

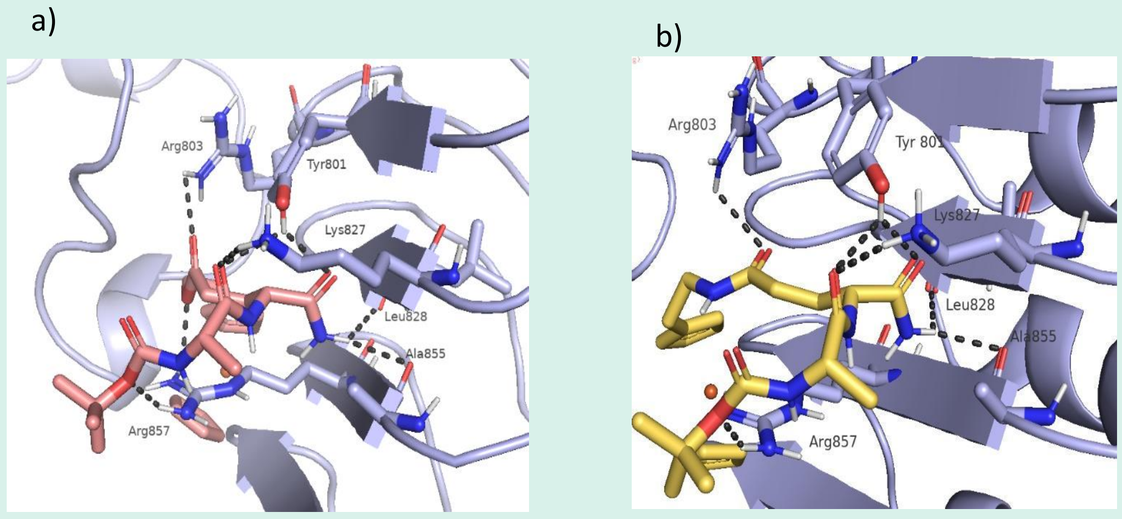


Fig. 2. Structures of complex between compound a) E1 and b) A1 and NOD2

CONCLUSIONS

- Ferrocene esters **E1** and **E2** and amides **A1** and **A2** of DMP are succesfully prepared in good overall yields using modified Steglich esterification method (EDC/DMAP) and EDC/HOBt amidation, respectively.
- The peptides studied are involved in intramolecular hydrogen bonds to a lesser extent.
- The conformation of the studied derivatives does not differ significantly regarding the length of the linker and the type of chemical bond by which ferrocene is bound. The explored compounds are a part of a broader structure-activity relationship study to which these results contribute.

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