

Amino-acid based amphiphiles as chemical permeation enhancers, for transdermal drug delivery: Synthesis and *In vitro* permeation activity

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Background

Transdermal drug delivery (TDD) is the direct delivery of drugs through the skin so that they can reach systemic circulation. This methodology offers numerous **advantages** over the most conventional routes of administration, such as oral and parenteral drug delivery. In fact, it avoids liver and gastrointestinal first pass effects, it is painless, non-invasive and easy-to-use, presenting this way enhanced patient compliance [1]. Nevertheless, TDD has not yet reached its full potential, and it is still **limited** to a small number of drugs with favorable lipophilic behavior and low molecular mass. The *stratum corneum* (SC), the uppermost layer of the skin, constitutes the biggest barrier to drug penetration, mostly because of its unique lipidic composition and lipid structural organization. To circumvent this difficulty, one of the most studied strategies consists in the use of **chemical permeation enhancers** (CPEs). Particularly, amino acid-based amphiphiles represent an important class of biocompatible, biodegradable and reversible CPEs, showing enhanced activity [2,3].

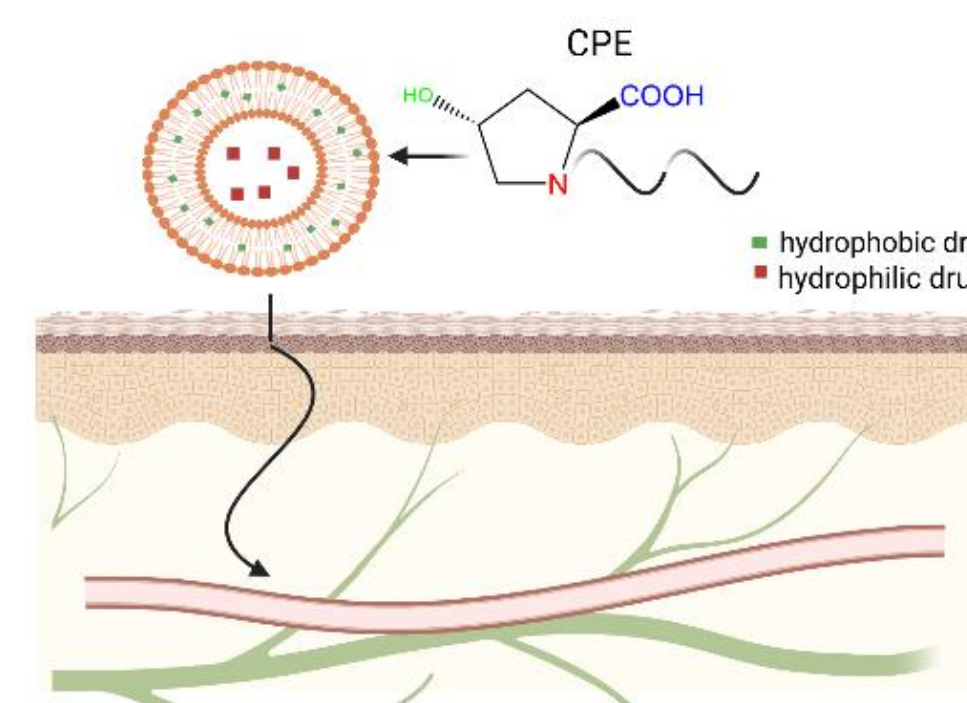


Figure 1. Schematic representation of TDD (made using biorender).

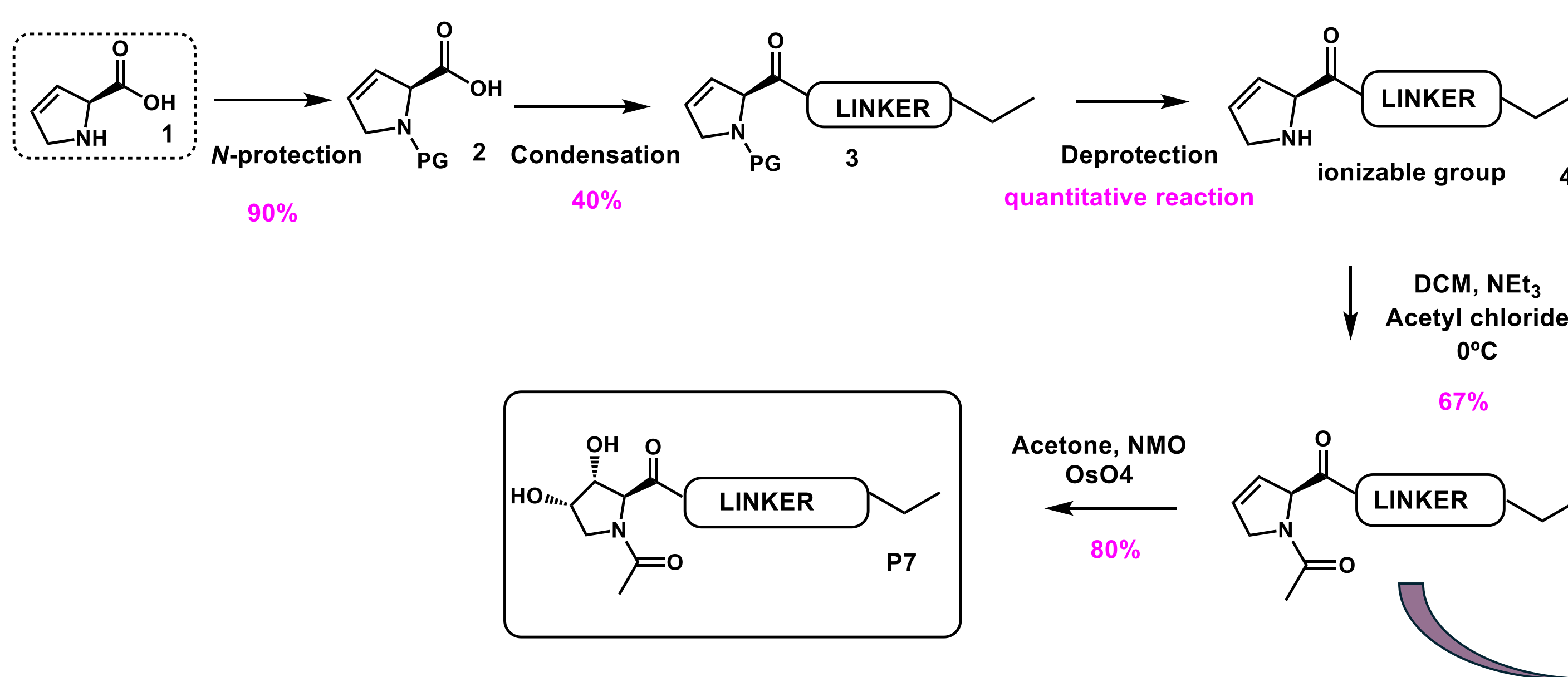
In this regard and to contribute to this field, this work **aims** at:

- Synthesis of amphiphilic proline and proline mimetic-derived surfactants (monomeric and dimeric) and development of DES thereof;
- Permeation enhancement evaluation using Franz diffusion cells;
- Study of the thermodynamic properties of the amphiphiles;
- Cytotoxicity evaluation in fibroblasts and keratinocytes using the MTS assay.

Results

Monomeric proline and proline mimetic amphiphilic derivatives

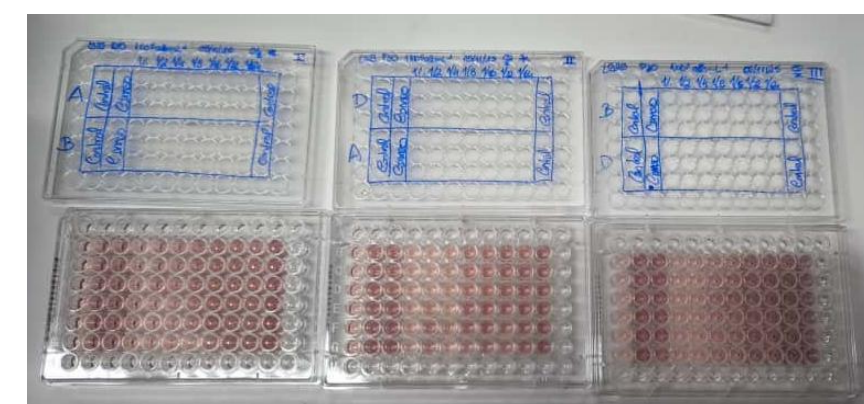
• Synthesis of monomeric derivatives



Scheme 1. Synthesis of P7

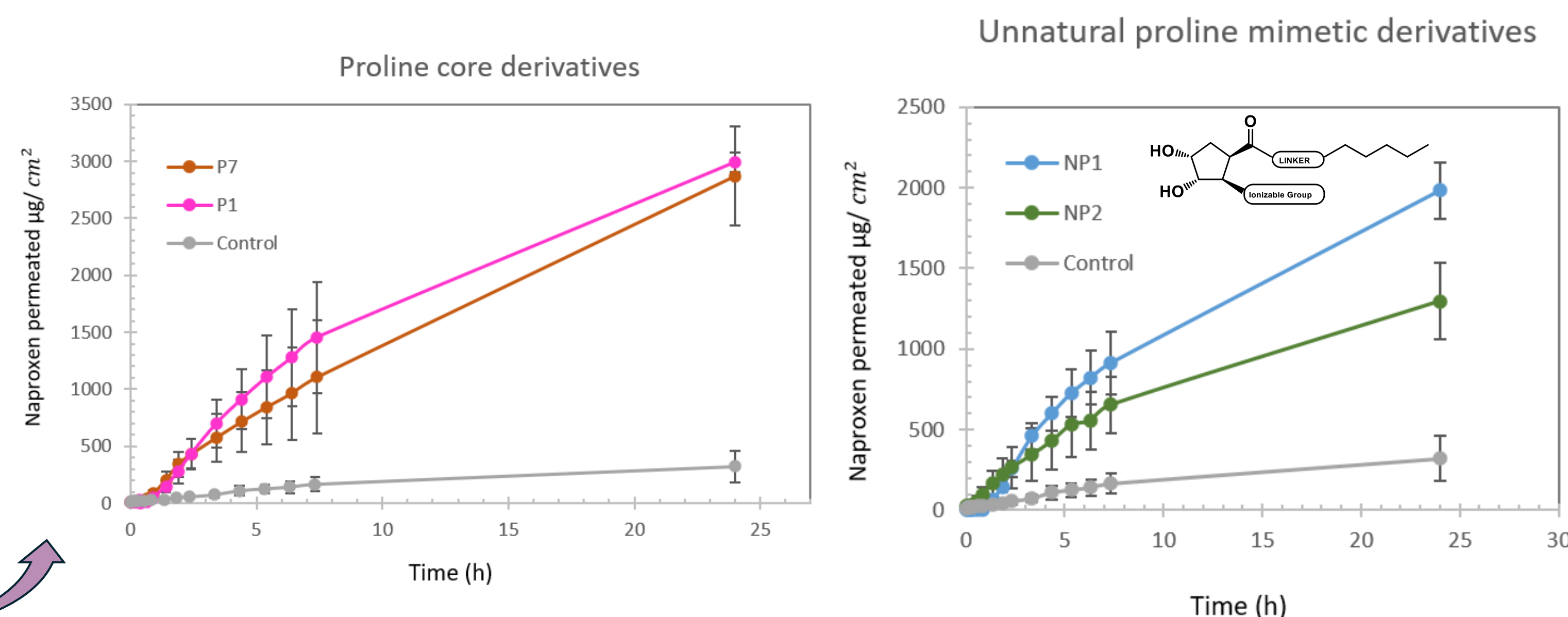
The major difficulties encountered in the represented chemical synthesis (**scheme 1**) included the condensation reaction for obtention of **3** and the amide bond formation reaction for obtention of **5**. These reactions provided lower yields due to the harsh purification of the target crudes.

• Cytotoxicity evaluation (on-going work)



Preliminary cytotoxicity studies conducted in L929 cells with the monomeric derivatives indicate that the compounds are non-toxic. These experiments are still on-going.

• Permeation enhancement potential evaluation with Franz diffusion cells



Graphs 1 and 2. Permeation enhancement profiles of the monomeric amphiphilic compounds.

Table 1. Permeation enhancement parameters obtained for the monomeric family.

Compound	Naproxen (10mg/mL)		
	Jss (µg/cm ² /h)	ER	Q 24h (µg/cm ²)
Control	21±8	-	321±137
NP1	183.±12	8	1982±174
NP2	95±14	4	1296±236
P1	201± 74	9	2994 ±86
P7	134 ± 71	6	2868±436



Double-chained proline derived surfactants

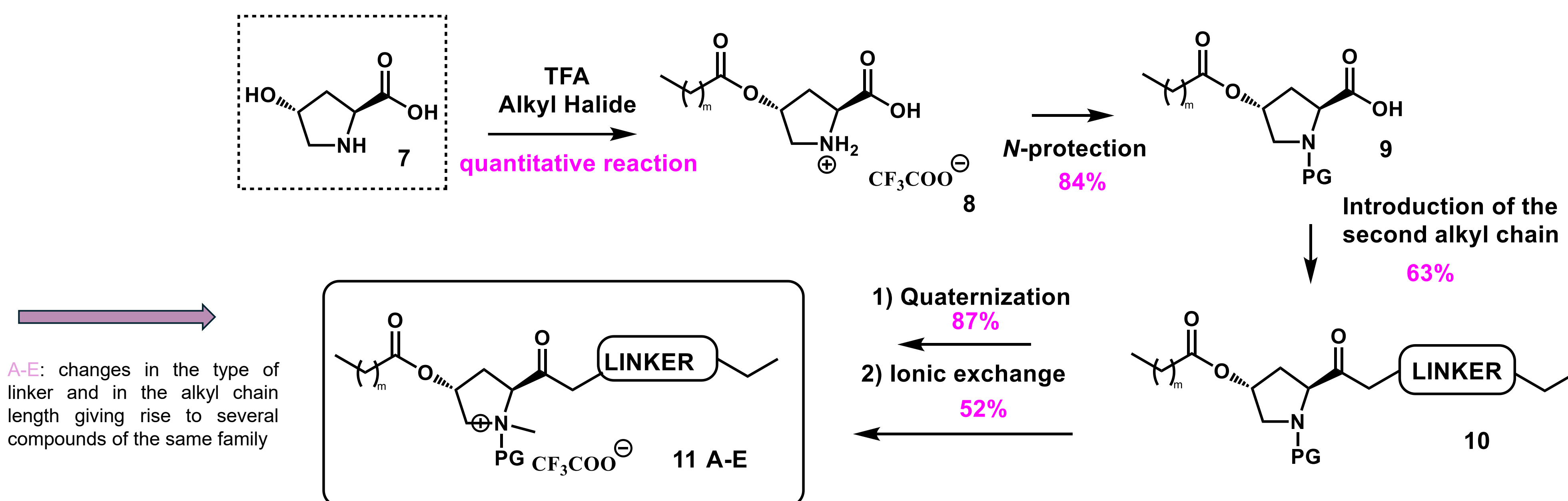
• Thermodynamic studies with DSC and TG.

Table 2. Melting points and degradation temperatures of the double-chained compounds.

Compound 11	T _m / °C	ΔH _f / kJ·mol ⁻¹	T _{deg} / °C
A	61.4	60.6	299
B	70.6	74.9	305
C	66.2	64.9	306
D	61.6	74.0	302
E	62.2	57.6	314

The target structures of the designed dimeric family presented low melting points and high thermal stability.

• Synthesis of double-chained derivatives



Scheme 2. Synthetic route followed for obtention of the dimeric 4-hydroxyproline derivatives.

All the reactions presented good to high yields, after optimization.

Conclusions:

In this work, **several families** of target structures were synthesized to be tested for their potential as chemical permeation enhancers. All the synthetic steps were optimized and the reactions provided high yields. The final compounds were characterized by ¹H-NMR, ¹³C-NMR, DEPT and ESI-MS.

The monomeric derivatives **highly enhanced naproxen's permeation** with ER values between 4-9; preliminary cytotoxicity assessments using the MTS assay indicate that the compounds are non-toxic for L929 cells.

Dimeric derivatives presented melting temperatures bellow 100° C, which is favourable for permeation enhancement, and high thermal stability.

Future prospects include the study of the **aggregation behaviour** and **self-assembly** properties of the amphiphiles as well as the development of **Deep Eutectic Systems** thereof for the transdermal delivery of a wide variety of drugs.

References:

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