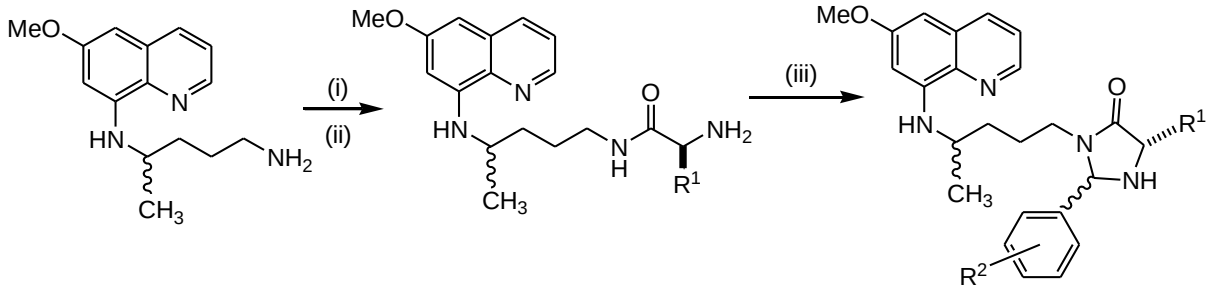
Steroselective Synthesis of Imidazolidin-4-ones from α-Amino Amides of the Antimalarial Primaquine and Substituted Benzaldehydes

Ferraz, Ricardo[a,b]; **Gomes, José R. B.**[a]; **Passo,Joana** [a]; **Oliveira, Eliandre de**[c]; **Moreira, Rui** [d]; **and Paula Gomes**[a]

[a]*CIQUP - Departamento de Química da Faculdade de Ciências do Porto, Portugal*
[b]*Departamento de Ciências Biomédicas,*
Escola Superior de Tecnologia da Saúde do Porto – Instituto Politécnico do Porto,
Praça Coronel Pacheco, nº15, 4050-453, Porto, Portugal,
rvf@estsp.ipp.pt
[c]*Proteomics Platform, Barcelona Science Park, Spain*
[d]*CECF, Faculdade de Farmácia da Universidade de Lisboa, Portugal*

Imidazolidin-4-ones are commonly employed as skeletal modifications in bioactive oligopeptides, either as proline surrogates or for protection of the N-terminal amino acid against aminopeptidase-catalysed hydrolysis[1]. We have been working on the synthesis of imidazolidin-4-ones of the antimalarial primaquine[2], through acylation of primaquine with an α-amino acid and subsequent reaction of the resulting α-aminoamide with a ketone or aldehyde. Thus, when using racemic primaquine, an optically pure chiral α-amino acid and an aldehyde as starting materials, four imidazolidin-4-one diastereomers are to be expected (Scheme 1). However, we have recently observed that imidazolidin-4-one synthesis was stereoselective when 2-carboxybenzaldehyde (2CBA)* was used, as only two diastereomers were produced[2]. Computational studies have shown that the imine formed prior to ring closure had, for structures derived from 2CBA, a quasi-cyclic rigid structure[2]. This rigid conformation is stabilized by an intramolecular hydrogen bond involving the C=O oxygen atom of the 2-carboxyl substituent in 2CBA and the N-H group of the α-amino amide moiety[2]. These findings led us to postulate that the 2-carbonyl substituent in the benzaldehyde moiety was the key for the stereoselective synthesis of the imidazolidin-4-ones[2].



Scheme 1 – General synthetic route for imidazolidin-4-ones of primaquine: (i) DCCI, HOBt, N□-BocAAOH; (ii) TFA, Na_2CO_3; (iii) substituted benzaldehyde in refluxing methanol, TEA, molecular sieves.

[1] A. Bak, M. Fich, B. D. Larsen, S. Frokjaer and G. J. Friis, *Eur. J. Pharm. Sci.*, 1999, **7**, 317.
[2] P. Gomes, M. J. Araújo, M. Rodrigues, N. Vale, Z. Azevedo, J. Iley, P. Chambel, J. Morais and R. Moreira, *Tetrahedron*, 2004, **60**, 5551.
* the non-IUPAC name "2-carboxybenzaldehyde" was chosen instead of "2-formyl-benzoic acid", so that the aldehyde functionality, which is involved in the reactions under study, could be emphasized.