# 6th EUROPEAN CHEMICAL BIOLOGY SYMPOSIUM

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# ABSTRACTS BOOK

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# Synthesis of new fluorescent dehydroamino acids for protein labelling

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Site-selective chemical modification has merged as a potential tool for protein functionalization in order to install new functionalities such as fluorescent probes, cytotoxic payloads, etc [1]. When modification is through a reaction with electrophiles, cysteine [2] and lysine [3] sidechains are often targeted, due to their high nucleophilicity. Chemo- and regioselective labelling of certain amino acids in a variety of proteins has been achieved in recent years.

α,β-Dehydroamino acids are well-known electrophiles occasionally used for protein modification, leading to a range of natural and unnatural post-translational modifications (PTM) such as lanthionines and lysinoalanines. However, the low reactivity of these functionalities, which require the concurrence of enzymes for natural PTM, or the use of large electrophile excess for chemical modification, has limited their use and scope.

In this work, the design, synthesis and evaluation for protein labelling of new fluorescent dehydroalanine derivatives, which are soluble in water, is presented. The superior reactivity and chemoselectivity of these reagents as Michael acceptors observed with both small-molecule nucleophiles and proteins, is described.


*Acknowledgements: MINECO (projects CTQ2015-70524-R and RYC-2013-14706).*

***References:***

[1] Boutureira, O.; Bernardes, G.J.L. *Chem. Rev.*, **2015**, *115*, 2174-2195.
[2] Vinogradova, E. V; Zhang, C.; Spokoyny, A. M.; Penlute, B. L.; Buchwald, S.L., *Nature*,, **2015**, *526*, 687-691.
[3] Matos, M. J.; Oliveira, B. L.; Martínez-Sáenz, N.; Guerreiro, A.; Cal, P. M. S. D.; Bertoldo, J.; Maneiro, M.; Elizabeth, P.; Howard, J.; Deery, M. J.; Chalker, J.M.; Corzana, F.; Jiménez-Osés, G.; Bernardes, G.J.L., *J. Am. Chem. Soc.*, **2018**, *140*, 4004-4017.

# SYNTHESIS OF NEW FLUORESCENT DEHYDROAMINO ACIDS FOR PROTEIN LABELLING

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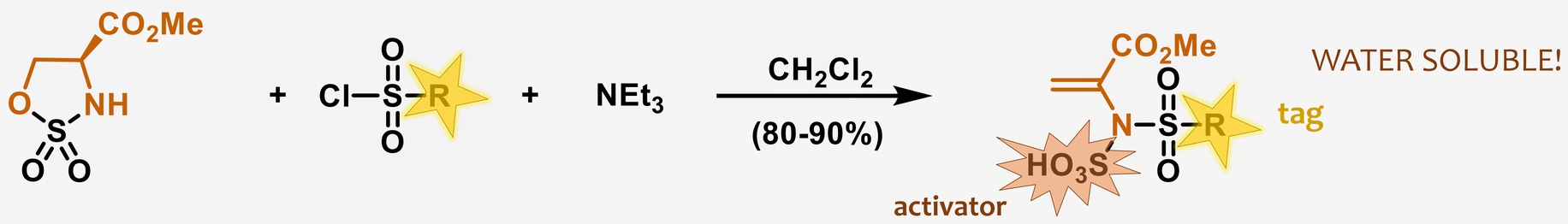
## INTRODUCTION

Site-selective chemical modification has emerged as a potential tool for **protein functionalization** in order to install new functionalities such as fluorescent probes, cytotoxic payloads, etc.[1] Usually, cysteine [2] and lysine [3] sidechains are often targeted with electrophiles due to their high nucleophilicity.

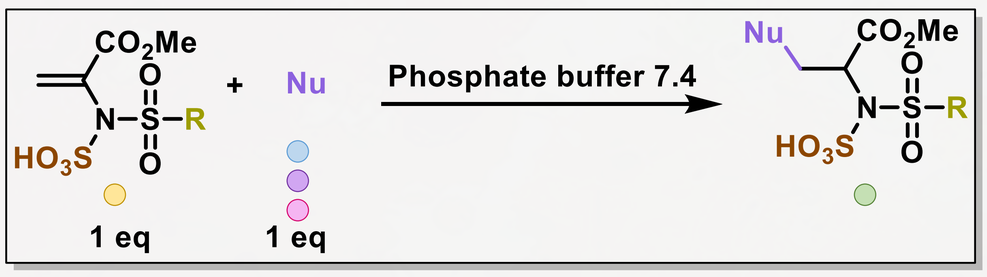
**α,β-Dehydroamino acids** are well-known electrophiles occasionally used for protein modification, leading to a range of natural and unnatural post-translational modifications (PTM) such as lanthionines and lysinoalanines. However, the low reactivity of these functionalities require the concurrence of enzymes for natural PTM or the use of large electrophile excess for chemical modification, which has limited their use and scope.

## OBJECTIVES

**Design, synthesis and evaluation** of **new water soluble fluorescent dehydroalanine derivatives** for protein labelling.




## MICHAEL ADDITION




### SMALL MOLECULE

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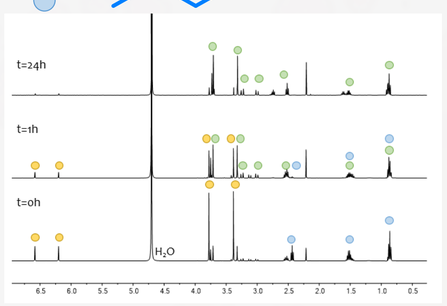


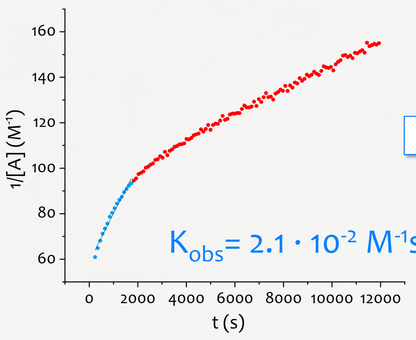


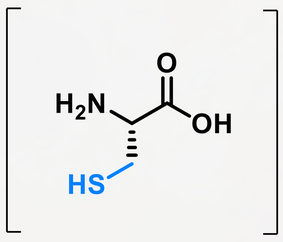


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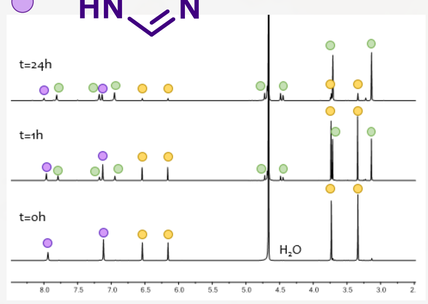
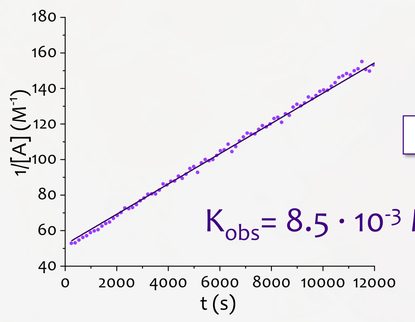
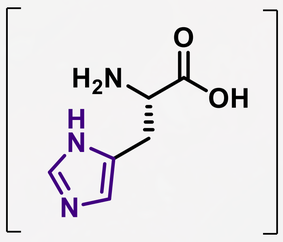
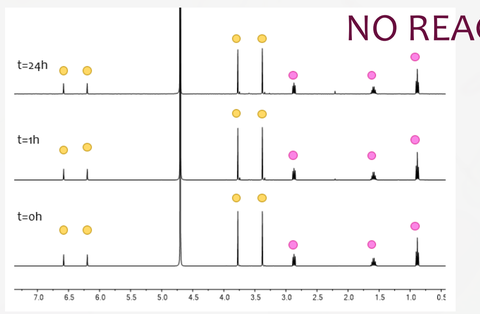


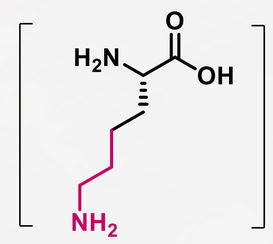




**Nu:** 

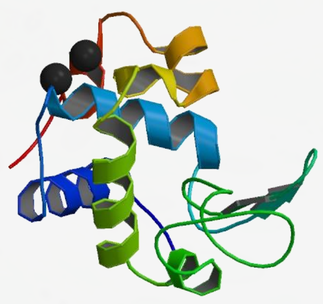

NO REACTION!

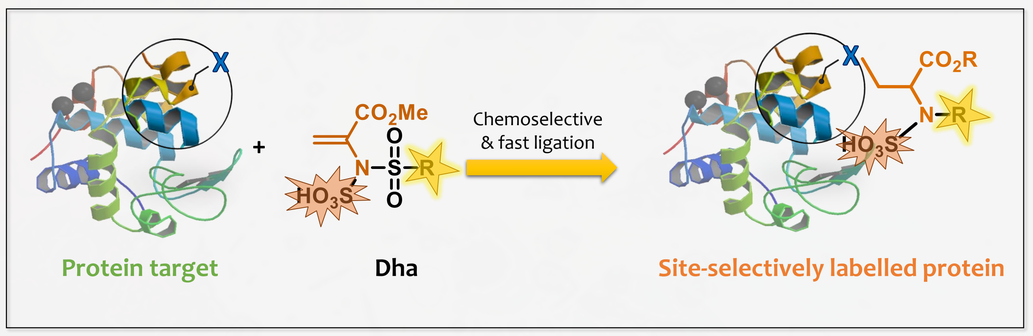



### PROTEINS

**LYSOZYME HEN EGG-WHITE**
(Non Cys, **1 His**, 6 Lys)






**UPLC-MS** [(M+11/11) protein MW is seen]




Site-selectively labelled protein
(1 Dha)

In **1 h, >50% conversion** is observed. Incorporation of 1 Dha unit is dominant.

**Relative reactivity:** Thiol (cysteine) > Imidazole (Histidine) >>> Amine (Lysine)

## ACKNOWLEDGEMENTS

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## REFERENCES

[1] Boutureira, O.; Bernardes, G.J.L. *Chem. Rev.*, **2015**, *115*, 2174-2195.

[2] Vinogradova, E. V; Zhang, C.; Spokoyny, A. M.; Penlute, B. L.; Buchwald, S.L., *Nature,*, **2015**, 526, 687-691.

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