SYNTHESIS OF FUNCTIONALIZED PROBES TO IDENTIFY AND VALIDATE NOVEL THERAPEUTIC AND DIAGNOSTIC TARGETS FOR DRY EYE DISEASE AND IRRITABLE BOWEL SYNDROME

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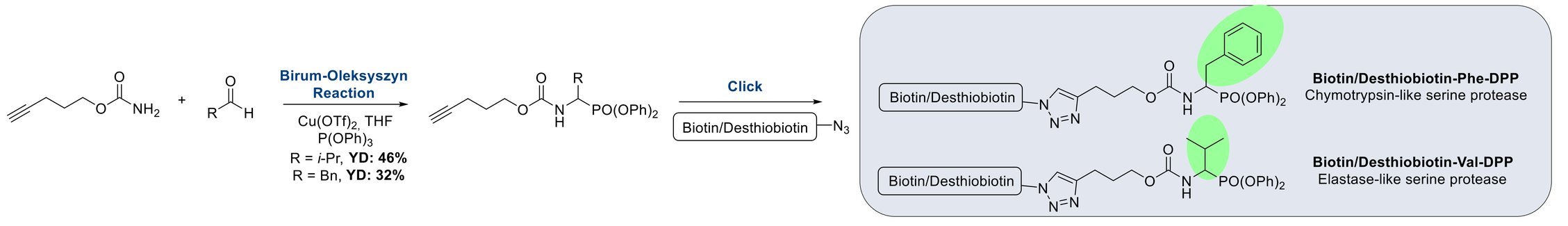
Introduction

Dry Eye Disease (DED) is a chronic, multifactorial disease of the ocular surface accompanied by ocular symptoms, such as ocular surface inflammation and tissue damage [1]. While, Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder, characterized by abdominal pain and accompanied by a change in bowel habit [2]. Visceral hypersensitivity is a major factor underlying abdominal pain in IBS patients [3]. A possible mechanistic similarity between both pathologies has been hypothesized. [4]
Serine proteases belong to the protease family and are involved in several physiological processes, including immune response, cell death and tissue healing. [5] The upregulation of these proteases can increase inflammatory cytokines, degradation of extracellular matrix components, activation of PAR2 or MMP-9, among others. [6,7] We hypothesized that serine proteases play an important role in both DED and IBS.

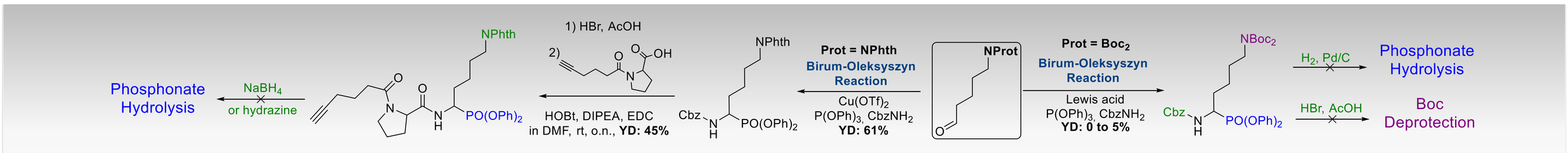
Aim and objective

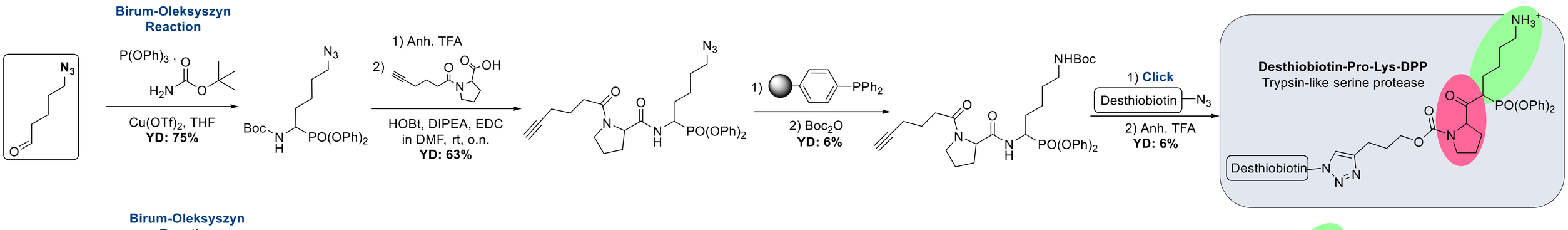
Aminoalkyl diphenyl phosphonate (DPP) has previously been used to generate potent irreversible serine protease inhibitors [8]. In this work, we developed DPP-derived probes for activity profiling of serine proteases involved in DED and IBS in order to understand the mechanism underneath this syndrome.
Based on previous studies of substrate specificity [8,9], a Phe, Val or Lys residue was incorporated at the P1 position to generate Chymotrypsin-, Elastase-, and Trypsin-like protease probe respectively. Recently, protease inhibitors of UAMC library showed to both cause, a significant reduction of both tissue damage and of inflammatory parameters in an eye of a tear-deficient dry eye rat animal model [10] and, a decrease in visceral hypersensitivity in a rat model of post-inflammatory visceral hypersensitivity [11]. Probes of these two hit compounds, UAMC-00050 and UAMC-01162 [10,11], were also synthesized in this work.

Synthesis of DPP-derived probes targeting Chymotrypsin- and Elastase-like Serine protease

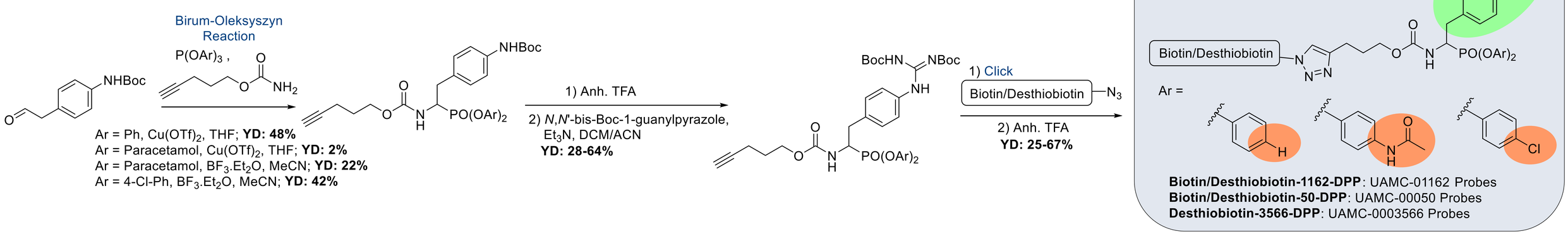


Synthesis of DPP-derived probes targeting Trypsin-like Serine protease





Synthesis of probes of UAMC library hit compounds



Conclusions and Perspectives

- A total of 13 new DPP-based probes have been successfully synthesized, allowing the specific inhibition of the prototypical enzymes targeted: Chymotrypsin-, Elastase-, Trypsin-like serine proteases.
- The DPP-based probes developed in this work will allow the identification of dysregulated peptidases, which will open up the possibility of diagnostic biomarker discovery. Currently, our efforts are focused on the identification of new targets in DED and IBS.

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