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Development of pseudopeptides and peptidomimetics as eukaryote proteasome inhibitors

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Abstract

Deregulation of the ubiquitin–proteasome system has been implicated in the pathogenesis of many diseases. The regulation of the proteasome activity by specific inhibitors makes this enzyme a promising target for cancer treatment. We present here the design, synthesis and biological evaluation of novel pseudopeptides acting as inhibitors of eukaryote 20S proteasome. D-Amino acids were also introduced into the peptides of interest to reduce proteolysis. ***To cite this article: N. Basse et al., C. R. Chimie 12 2009.***

Résumé

Le protéasome est un complexe multicatalytique jouant un rôle crucial dans le renouvellement intracellulaire des protéines. Il se trouve impliqué dans une grande variété de processus biologiques comme la transcription, la différenciation cellulaire, le cycle cellulaire et la production d'antigènes. La régulation de son activité par des molécules spécifiques est potentiellement d'un grand intérêt pharmacologique. Nous présentons ici la conception, la synthèse et l'évaluation biologique de nouveaux pseudopeptides agissant comme des inhibiteurs du protéasome. Des acides aminés *D* ont aussi été introduits afin de limiter la protéolyse. ***Pour citer cet article : N. Basse et al., C. R. Chimie 12 2009.***

Keywords: Pseudopeptides; Proteasome; Inhibitors

Mots-clés : Pseudopeptides ; Protéasome ; Inhibiteurs

1. Introduction

The proteasome is a multicatalytic protease playing a crucial role in cellular protein turnover in eukaryotic cells. It is involved in the maintenance of the biological

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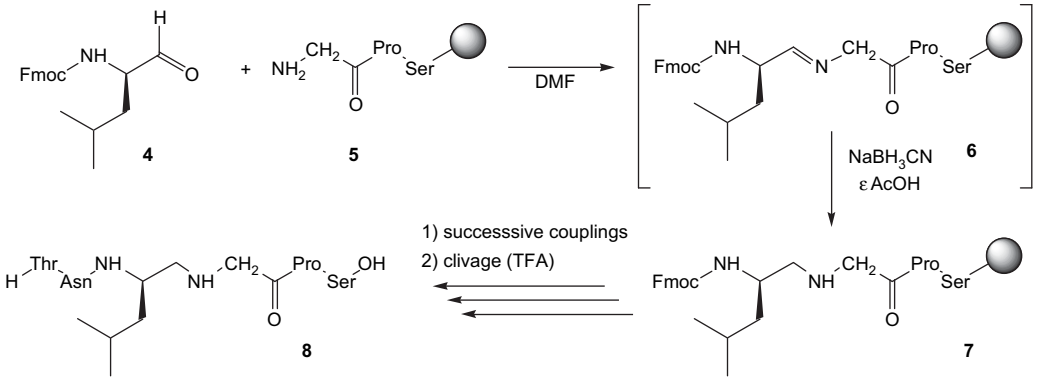
pp89	…YDMYPHFMPTN**LG**PSEEKRVW...
1	PHFMPTN**LG**PSEA
2	PTN**LG**PS
3	TN**LG**PS
8	TNL**ψ[CH$_2$NH]G**PS
15	TNL**ψ[CO-N(NH$_2$)]G**PS

Fig. 1. Chosen sequence from cytomegalovirus protein pp89 and some derived peptides and pseudopeptides. The peptidic bond of pp89, peptides **2** and **3** cleaved by proteasome is indicated in bold type.

homeostasis and degradation of key components of the molecular machinery on which rely important cellular functions such as transcription, cell differentiation, cell-cycle progression, tumor suppression and antigen processing [1]. The regulation of its activity by specific inhibitors makes the proteasome a promising target for cancer treatment as demonstrated by the approval of the peptide boronate bortezomib (or Velcade® or PS-341) by the Food and Drug Administration for the treatment of refractory multiple myeloma [2]. Bortezomib and other proteasome inhibitors are currently undergoing clinical trials for various forms of cancer and cardiovascular diseases. Proteasome inhibitors are also potential drugs to be used in a large variety of diseases such as inflammation, muscular dystrophies, tuberculosis, immunological diseases…. As the peptide boronate bortezomib [3], most proteasome inhibitors are short peptides bearing a reactive group which creates a covalent bond with the catalytic Thr1O$^{\gamma}$ of the three types of proteasome active sites (for reviews see Ref. [4]). It is the case of peptide aldehydes (MG132, MG262) [5], peptide vinyl sulfones [6], and peptide expoxyketones [7] which are covalently bound to the catalytic sites. The natural β-lactones lactacystin (*Streptomyces* sp.) [8], salinosporamide (*Salinospora tropica*) [9] and belactosines A and C (*Streptomyces* sp. UCK14) [10] are non-peptidic molecules that form covalent acyl ester bonds with Thr1O$^{\gamma}$ leading to stable acyl-enzymes [4a]. Bortezomib (injectable preparation) acts quasi-irreversibly with proteasome and important side-effects have been reported [11]. In principle, non-covalent inhibitors should be devoid of the drawbacks associated with the presence of a reactive group as found in covalent inhibitors, i.e., lack of specificity, excessive reactivity, and instability. Nevertheless, non-covalent inhibitors of the proteasome have been investigated less extensively. Ritonavir used in AIDS treatment [12], benzylstatine derivatives [13], lipopeptides [14], the natural tripeptidic TMC-95A [15], and its cyclic [16] and linear [17] analogues have been reported. We used the pseudopeptidic strategy to elaborate new non-covalent inhibitors of 20S proteasome since this was not explored before for proteasome. Pseudopeptides have the advantage of allowing structural modulation of the peptide backbone with possible retention of the side chains required for biological activity. Moreover, the modification of the peptide backbone is expected to enhance resistance to proteolysis in body fluids and cells. This strategy led to several drugs such as antiproteases used in AIDS treatment



Scheme 1.