Invited Lecture
Inter-Disciplinary Explorations in Chemistry (I-DEC 2018)

Talk Exploring the physicochemical and biological attributes of thioamidated peptides

Jayanta Chatterjee*
Molecular Biophysics Unit
Indian Institute of Science
(E-mail:jaynata@iisc.ac.in)

Abstract:
Designing bioactive peptides containing thioamide functionality to modulate their pharmacological properties has been thwarted so far because of various synthetic challenges. The fast, efficient, and inexpensive synthesis and incorporation of a wide range of thionated amino acids into a growing peptide chain on a solid support using standard SPPS will be presented. The utility of the protocol will be demonstrated in the synthesis of dithionated linear and monothionated cyclic peptides, which has been a daunting task. I will further elucidate that substituting a single atom, O to S (amide to thioamide) in a peptide bond results in global restriction of conformational flexibility in peptide macrocycles with minimal perturbation of the parent conformation. The van der Waals interaction between C=S and the surrounding atoms is the major driving force in inducing the conformational restriction, resulting in well-defined structures of these cyclic peptides with static 3-D presentation of the pharmacophores. Utilizing this property of thioamides, we report the development of a superactive antagonist of pro-angiogenic avb3, avb5 and a5b1 integrins responsible for cancer cell proliferation and survival. Using simple thio-scanning and spatial screening of a non-efficacious and conformationally flexible cyclic peptide, we could achieve more than 10^5 folds enhancement in its efficacy *in cellulo* by a single O to S substitution. The developed peptide shows better efficacy in inhibiting the pro-angiogenic integrins than the drug candidate Cilengitide with a significantly enhanced serum half-life of 36 h as compared to Cilengitide (12 h). Long shelf-life, absence of non-specific toxicity and resistance to degradation of the thioamidated macrocyclic peptides in human serum suggest the promise of thioamides in markedly improving the affinity, efficacy and pharmacology of peptide macrocycles. I will also show the enormous potential of thioamide in improving the oral bioavailability of cyclic peptides that has been a rather difficult and complex parameter to handle.

References and Notes:

1. Verma, H.; Khatri, B.; Chakraborti, S.; Chatterjee, J. *Chem. Sci.* **2018**, *9*, 2443-2451.

Invited Lecture
Inter-Disciplinary Explorations in Chemistry (I-DEC 2018)

Bio-Sketch of Speaker

Dr. Jayanta Chatterjee
Assistant Professor

Molecular Biophysics Unit
Indian Institute of Science
Address: CV Raman Road, Bangalore 560012
Contact Number: +91-8022932053
e-Mail: jaynata@iisc.ac.in

Jayanta completed his studies in chemistry with organic chemistry specialization from University of Pune in 2004, after which he moved to the laboratory of Prof. Horst Kessler in TU Munich, Germany working for his PhD while learning about "*peptides*". After that he moved to Japan for a short stint and then came back to Germany for his postdoctoral training in the laboratory of Dr. Maja Köhn at EMBL-Heidelberg. This training resulted in his long-term interest on "*peptides as chemical tools*" to perturb biological systems. The research in our laboratory: Peptide Engineering Lab at the Molecular Biophysics Unit is primarily devoted towards the development of simple chemical modifications to improve the pharmacological properties of peptides: low intestinal permeability, low metabolic stability and rapid systemic clearance. Our model systems are macrocyclic peptides and synthetic mini-proteins, which have shown great potential as therapeutics. Thus, we utilise our expertise in peptide synthesis, Nuclear Magnetic Resonance (NMR) based structure elucidation and bio-assay development to generate cell-surface receptor antagonists, chemical tools to perturb intracellular protein-protein interactions and next-generation antimicrobials.