INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student : **AFSANA YASHMEEN**

Roll Number : **11612202**

Programme of Study : **Ph.D.**

Thesis Title:

Design, Synthesis and Study of Photophysical/Biophysical Properties of Small Molecular Scaffold Peptides and Fluorescent β-Lactams

Name of Thesis Supervisor(s) : **Prof. Subhendu Sekhar Bag**

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SHORT ABSTRACT

This Thesis has a total of five chapters out of which the **Chapter 1** is a literature review about the β-hairpin and β-sheet peptidomimetics. This review chapter contains a critical survey of conformationally constrained small molecular scaffold as inducer of particular secondary structure in a peptide, such as β-hairpin and β-sheet peptidomimetics. **Chapter 2** includes uracil-di-aza-amino acid **($U^{r}AA$)** as a new family of molecular scaffold with ability to induce β-hairpin structure with H-bonded β-sheet conformation in a short peptide which is demostrated in two designed fluorescent pentapeptides. We established the dual mechanism of exciplex emission in **ExcipFRET**-peptide **2.61** containing donor-acceptor triazolyl unnatural fluorescent amino acids $^{TMnap}Ala^{Do}$ and $^{TPy}Ala^{Do}$ at *N*- and *C*- terminus respectively, forming a FRET pair. On the other hand fluorescent pentapeptide **Excim**-peptide **2.64** with triazolyl fluorescent unnatural amino acid $^{TPy}Ala^{Do}$ at both the termini showed excimer emission in its β-sheet conformation. Both the peptides maintainning their predefined photophysics were found to interact with a model biomolecule BSA with fluorescence swith-on response. The exploration of sequence specific DNA binding event of $U^{r}AA$ scaffold and study of interaction with other protein biomolecules is the future prospect of this work. **Chapter 3** includes the synthesis of *ortho,meta*-aromatic amino acid scaffold ($^{o,m\text{-}Ar}TAA$). Its incorporation into trichromophoric fluorescent pentapeptide and study of photophysics established a sequential FRET process. Our designed *ortho-meta*-triazolo aromatic amino acid scaffold ($^{o,m\text{-}Ar}TAA$) was found to induce turn induced β-sheet structure of a short peptide. The fluorescent peptide in the turn induced β-sheet conformation was found to

exhibit relay FRET process from scaffold to **TPy** to **TPer.** This is a newly designed fluorescent peptide that might find wider application in chemical biology. The peptide **3.79** was also used for studying interaction with BSA protein. Sensing of other specific proteins and DNA with this probe is future focus of this work. **Chapter 4** describes the synthesis of triazolo aliphatic amino acids with different spacer length, incorporation into fluorescent pentapeptide containing triazolyl methoxynaphthalene (^{TMnap}**Ala**^{Do}) and triazolyl pyrene (^{TPy}**Ala**^{Do}) amino acids at the two termini and their conformational analysis. The study on the spacer length dependent FRET event in these designed peptides is the main concern of this chapter. With increase in chain length of the molecular scaffold the extent of flexibility increases that allowed to enhance the extent of FRET. Distance dependent FRET in a peptide is a new concept and would have potential application in designing fluorescent peptide probe for studying protein-peptide probe in future.

Chapter 5 includes the synthesis of fluorescent triazolyl β-lactams and fluorimetric sensing of chemical cleavage of β-lactam ring. The cleavage of the β-lactam ring of two selected out of twelve synthesised fluorescent triazolylpenicilines, (^{TMNap}**β-Lac**^{Do} and ^{TPy}**β-Lac**^{Do}) with aminomethylpyrene (**AMePy**) as fluoroscent nucleophile was found to be signaled via the generation of FRET/exciplex and excimer emission respectively. We have synthesized a newly designed triazolyl donor-acceptor chromophore decorated fluorescent penicilines, which marked a novel class of unnatural fluorescent β-lactams. We established the dual path to exciplex and excimer emission respectively, after clevage of two decorated β-lactams. This is the first report of design of a fluorescent β-lactam with a predicted photophysical properties after ring cleavage. . The investigation on the change in photophysical proterty upon chemical clevage of β- lactam ring can be treated as a model to study the kinetics of β-lactam succeptibility toward chemical/enzymatic cleavage and monitoring the β-lactamase activity via fluorescence in future.