# Generation of Peptidomimetic Fluorophores via Amenable Chemistry with Multicomponent Reaction (ACMR) Scaffolds

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**DOCTOR OF PHILOSOPHY IN CHEMISTRY**

By

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## CERTIFICATE

This is to certify that the thesis titled **"Generation of Peptidomimetic Fluorophores via Amenable Chemistry with Multicomponent Reaction (ACMR) Scaffolds"** submitted by Shyam Shankar E. P. to the University of Calicut for the award of the degree of Doctor of Philosophy in Chemistry, is the result of the bonafide research work carried out at the Department of Chemistry, University of Calicut under my guidance and supervision. The contents of the thesis have been checked for plagiarism using the software 'Urkund' and the similarity index falls under permissible limit. I further certify that the topic discussed in this thesis has not been previously formed the basis of the award of any degree, diploma or associateship of any other University or Institute.

August 2019 D. Bahulayan

# DECLARATION

I, Shyam Shankar E. P. hereby declare that the thesis titled **"Generation of Peptidomimetic Fluorophores via Amenable Chemistry with Multicomponent Reaction (ACMR) Scaffolds**" is the report of the original research work carried out by me under the supervision of Dr. D. Bahulayan, Professor, Department of Chemistry, University of Calicut for the award of the degree of Doctor of Philosophy in Chemistry of the University of Calicut and further that this thesis contains no material previously submitted for a degree, diploma, associateship, fellowship or other similar titles of any other University or Society.

University of Calicut
August 2019

Shyam Shankar E. P.

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## CONTENTS

# PREFACE

Fluorescent peptides are an important class of compounds since such moieties have a plethora of applications in medicinal chemistry, drug discovery, diagnosis and therapy. The peptide fluorophores are used in visualizing intracellular processes and have vast applications as fluorescent inhibitors and drug carriers. However, the preparation of such probes requires multistep synthetic protocols, large resources, manpower and expensive machinery leading to the escalation of manufacturing costs. Hence the search for new cost-effective alternatives in terms of the utility of potential new synthetic methodologies is highly demanding. Multicomponent reactions (MCR) and Click-Chemistry are examples of such potential synthetic protocols useful for the step economic and cost-effective synthesis of functional scaffolds. Inspired with these thoughts, two widely accepted bioactive heterocycles such as coumarin and chromene were selected and decorated with suitable functionalities using MCR-Click protocols to obtain peptidomimetic fluorophores. The discussion on the synthesis and the evaluation of the photophysical and biological properties of these new fluorescent inhibitors are the subject matter of this thesis.

The thesis has been divided into five chapters. The first chapter presents an overview of the significance of simple and properly functionalized fluorescent probes for material applications, cellular level bioimaging, and medicinal applications, with a special focus to coumarin and chromene derivatives. Various features and applications of the derivatives of these two moieties have been summarized in this chapter. Moreover, brief descriptions of a few potential synthetic

strategies which can be used for the proper functionalization of the aforesaid molecules are also included in this chapter.

Chapter 2 presents a multicomponent reaction (MCR) assisted step economic protocol for the synthesis of coumarin based deep blue-emitting fluorescent molecule named as “Ugi EML BLUE” suitable for various light emission based applications. The solution state and solid-state fluorescence, pH sensitivity and significant physical properties were evaluated, interpreted and documented. A plausible mechanism for the origin of light emission from this molecule is also presented based on experimental and computational methods.

Chapter 3 is the continuation of chapter 2 and in this chapter, the biological applications of the Intramolecular Charge Transfer (ICT) based blue emitting fluorescent probe Ugi EML BLUE is presented. The binding properties of the Ugi EML BLUE against human CDK2 protein were studied via docking methods. The docking studies showed that Ugi EML BLUE can effectively interact with the ATP binding sites of CDK2. The positive results obtained from the docking studies were extended to the bioimaging as well as antineoplastic applications on HeLa cells. The *in vitro* biological activity studies revealed the remarkable potential of Ugi EML BLUE as a dual functional molecule that can be used not only as a CDK2 targeted fluorescent probe for bioimaging but also as a CDK2 targeted inhibitor for HeLa cells.

Chapter 4 presents a new series of Chromene-Triazole-Coumarin Triads synthesized through the employment of a solvent free mechanochemical multicomponent reaction followed by copper catalyzed (3+2) azide-alkyne cycloaddition (click chemistry). The

molecules were investigated for their fluorescence and CDKs induced anticancer properties. Half numbers of the molecules showed the fluorescence in the solution state through ICT based electronic transitions whereas, the other half showed solid state fluorescence through aggregation induction. Computational studies on binding affinity revealed that all the molecules are in general selective towards CDK2 and CDK4. The studies on *in vitro* biological activity showed that the selected molecules are promising lead structures for undertaking further studies to develop fluorescent inhibitors of CDK2/CDK4 induced tumors. They showed appreciable IC50 values against the human cervical cancer cell line (HeLa).

Chapter 5 presents the conclusions and future aspects of the work presented in this thesis. As discussed in chapters 2 to 4, this study has demonstrated the facile synthetic routes to the efficient fluorescent inhibitors decorated with the appropriate functionalities and their applications in various fields such as light emission devices, bioimaging, and anticancer agents, etc. We hope that further in-depth studies based on this work will make an impact on the development of cost effective cancer therapeutics and efficient fluorescent probes for a broad spectrum of applications.