MCR-CLICK SYNTHETIC STRATEGIES FOR THE DEVELOPMENT OF PRIVILEGED SCAFFOLDS BASED FLUORESCENT INHIBITORS AND MULTI-FUNCTIONAL PEPTIDOMIMETICS

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IN
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By

JENCY MOHAN .T

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALICUT
KERALA
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DEPARTMENT OF CHEMISTRY
University of Calicut

Dr. D. Bahulayan
Professor

Calicut University campus,
Malappuram, Kerala,
Tel. (o) 0494 2401144*414
E-mail: bahulayan@yahoo.com

CERTIFICATE

This is to certify that this thesis entitled *"MCR-CLICK synthetic strategies for the development of privileged scaffolds based fluorescent inhibitors and multifunctional peptidomimetics"* submitted by Jency Mohan T. 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.

October 2017 D. Bahulayan

DEPARTMENT OF CHEMISTRY
University of Calicut

Dr. D. Bahulayan
Professor

Calicut University campus,
Malappuram, Kerala,
Tel. (o) 0494 2401144*414
E-mail: bahulayan@yahoo.com

CERTIFICATE

This is to certify that the corrections/suggestions from the adjudicators has been addressed and are incorporated in the appropriate sections of the revised thesis entitled *"MCR-CLICK synthetic strategies for the development of privileged scaffolds based fluorescent inhibitors and multifunctional peptidomimetics"* submitted by Jency Mohan. T to the University of Calicut for the award of the degree of Doctor of Philosophy in Chemistry.

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D. Bahulayan

DECLARATION

I, Jency Mohan T hereby declare that the thesis entitled **"MCR-CLICK SYNTHETIC STRATEGIES FOR THE DEVELOPMENT OF PRIVILEGED SCAFFOLDS BASED FLUORESCENT INHIBITORS AND MULTI-FUNCTIONAL PEPTIDOMIMETICS***"* 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 title of any other University or Society.

University of Calicut
October, 2017

Jency Mohan T

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PREFACE

Privileged structure based design of molecular scaffolds have been widely used as an effective strategy in medicinal chemistry for drug discovery. It involves the introduction of diversity to a single bioactive core with suitable functionalities. Such functionalized scaffolds can provide ligands for diverse receptors and can be able to interact with unrelated and undruggable targets. Numerous heterocycles have been identified and reinvestigated as privileged scaffolds and their synthesis and applications in medicinal chemistry has been well documented. A lion share of such synthesis are based on multistep synthetic protocols with the involvement of large amount of resources, infrastructure and manpower and have a direct impact on the escalated prize of life saving medicines. Hence the investigations to develop an alternative to such costly synthesis is essential. Skilful use of step economic synthesis such as multicomponent coupling reactions (MCR) and close to natural synthetic methodologies such as click chemistry can contribute a lot to achieve this goal. Motivated with these ideas, two privileged heterocycles such as chromene and furan were selected for scaffold modification based on Click-with MCR methodoly to obtain triazole linked peptidomimetics of these scaffolds and that constitutes the topic discussed in this thesis.

The thesis has been divided into five chapters. The first chapter presents an overview of the importance of privileged scaffolds in drug discovery and their biological and material applications with a special emphasis to benzopyarns and furans. Various aspects of these two

privileged structures has been summarized in this chapter, including the applications of new synthetic methodologies for their functionalization and the evaluation of biological properties.

The chapter 2 describes the chemistry and chemical biology of two new series of chromene peptidomimetics with carboxamide and acetamide peptide residues based on Click with MCR synthetic strategy. The fluorescence and anticancer properties of the molecules were evaluated and the molecules showed 2-in-1 properties such as anticancer activity as well as the fluorescence properties suitable for developing bioimaging probes.

Chapter 3 is on the peptidomimetic modifications of another benzopyran (chromene) system such as pyranocoumarin. The pyranocoumarin core scaffold was functionalised with chemical equivalents of α and β-amino acid residues such as α-aminoacylcarboxamide and β-acetamide scaffolds through a triazole linker. The highlight of this chapter is the detailed discussion on the photophysical and biological properties of 24 such new pyranocoumarin derivatives suitable for the development of fluorescent probes or anticancer agents.

Chapter 4 presents the progress of the work from linear peptidomimetics to macrocyclic peptidomimetics by replacing the chromene scaffold with a furan core scaffold using an intra molecular MCR-Click strategy. A discussion on the biological properties of the molecules as well as a brief rationale for the exceptionally high Stokes shifted emission showed by the macrocycles were also presented.

Chapter 5 presents the conclusion and future aspects of the work presented in the thesis. As highlighted in chapters 2-4, this study have made significant advancement in the chemistry, chemical biology and photophysics of large number of chromene and furan peptidomimetics. However further in-depth study based on computational techniques and in vitro and in vivo biological assay is necessary to push this field further ahead to achieve the goal of cost effective and green synthesis of therapeutic agents.

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