ABSTRACT OF Ph.D. THESIS

Design and Synthesis of Pyrazines, Imidazolones, Chromones and their Anticancer and Transacetylaspe Activities

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The work presented in **Chapter I: Section A** describes the design and synthesis of furopyrazine scaffold as potential conformationally restricted dipeptidomimetics.

In the past few decades, intensive peptide research experienced a significant development consequently leading to the availability of various peptide-based drugs in the market. However, these drugs suffer from some limitations and their use is limited due to their less bioavailability, immunogenicity and low stability. These shortcomings necessitated the development of new peptide or peptidomimetic based drugs. The biological activity of proteins is generally exerted by small regions of their folded surface, which are mainly the secondary structures. Mimicking these secondary structures of the protein such as α-helices, β-helices, β-turn, γ-turns and loops is an attractive approach in drug development. β-turns has been intensively studied among all the non-peptidic molecules mimicking secondary structures of proteins and found that some of them exhibit both high selectivity and enhanced potency.

In this context, we have designed and synthesized functionalized furopyrazines as restricted dipeptide mimic. We created a small library (12 final compounds) of alkyl 2-amido-3-alkyl-6-phenylfuro[3,2-b]pyrazine-7-carboxylates via multistep synthetic routes involving conventional and microwave-assisted synthesis. The structures of all the compounds were unambiguously established on the basis of spectral data (\(^1\)H NMR, \(^13\)C NMR spectra and HRMS) analysis. In all, thirty one compounds (including final compounds and the intermediates compounds) synthesized in present work are novel and are reported for the first time. The computational analysis and X-ray crystallographic study of one of the synthesized compound was used to evaluate the dipeptide mimicking potential of the scaffold.

The work presented in **Chapter I: Section B** describes the synthesis of C-3 aroylated 3,5-dichloro-2-(1H)-pyrazinones using NHC as catalyst.

In the last two decades, 2(1H)-pyrazinones have emerged as useful starting materials for the synthesis of various biologically interesting compounds. Wide range of pharmacologically active groups can easily be introduced to the 2(1H)-pyrazinone scaffold with an ability to
address a diverse set of biological targets. Similar nucleuses to pyrazinones like 3-aroylquinoxalin-2(1H)-ones have been described as late sodium channel inhibitors and 3-benzoyl-2-piperazinyl-quinoxalines have been reported as potential antitumor agents.

A versatile synthesis of the 2(1H)-pyrazinone scaffold is developed, and also four points of molecule diversity in pyrazinone ring was observed. In the present work, we report the C-3 aroylation of 3,5-dichloro-2-(1H)-pyrazinones with various aldehydes using NHC as catalyst. Several different NHC catalysts were screened for the C-3 aroylation of pyrazinone, and N,N-dimethylimidazolium iodide was found to give appreciable results with sodium hydride in DMSO as a solvent. Using the optimized protocol, we have synthesized a small library of twenty-three analogues of 3-aroyl substituted 5-chloro-2-(1H)-pyrazinones in moderate to high yields. All the compounds synthesized are novel and we report for the first time. The structures of all the compounds were unambiguously established on the basis of spectral data (1H NMR, 13C NMR spectra and HRMS) analysis.

The work presented in Chapter II describes the silver (I) catalyzed synthesis of tetrasubstituted 2-imidazolones.

The study of silver catalysis, providing novel methodologies for C-C and C-X (X = heteroatom) bond formation with the interesting mechanic pathways is significantly increasing with years. Silver (I) complexes are used as either co-catalysts or Lewis acids. Due to their low catalytic efficiency, silver catalyst has emerged as important synthetic methods for a variety of organic transformations viz. cycloadditions, cycloisomerizations, allylations, aldol reactions and even C—H bond activation of terminal alkynes. In that context, our group recently reported Ag(I) catalysed synthesis of 2-iminoimidazolines via guanylation of secondary propargylamines, having strong structural resemblance with the 2-imidazolones possessing various biological activities which include anti-tumor, antioxidant, antibacterial and anti-viral properties.

In the present work, we report the synthesis of tetrasubstituted 2-imidazolones from secondary propargylamines and isocyanates via cycloisomerisation of propargylurea using Ag(I) as catalyst. We started our synthesis with the investigation of condensation between methyl propargylamine and various substituted isocyanates. Different silver catalysts were screened for the synthesis of substituted 2-imidazolones. However, the best results were obtained with the AgOTf as catalyst in acetonitrile at 80 °C. A small library of twenty-two
novel analogs of 2-imidazolones has been synthesized and is reported for the first time. The structures of all the compounds were unambiguously established on the basis of spectral data ($^1$H NMR, $^{13}$C NMR spectra and HRMS) analysis.

The work presented in **Chapter III** describes the synthesis of novel chromones and their evaluation for anticancer and transacetylase activities.

Chromones are heterocyclic compounds having a benzopyran-4-one as their major skeletal structure and are found to exhibit various biological activities, among them anti-microbial, anti-viral, anti-cancer, enzyme inhibition, anti-inflammatory, anti-oxidant, antiplatelet and many more activities. A vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure.

Realizing chromone scaffolds as potent biological nucleuses, we have synthesized 3-alkyl substituted chromones. First, acylation of substituted phenols was achieved with different aliphatic carboxylic acids using ZnCl$_2$, followed by the cyclization of acylated using BF$_3$.$\text{Et}_2$O and MeSO$_2$Cl in DMF as solvent, resulting in our desired, 3-alkyl substituted chromones in moderate to good yields. Further, 3-alkyl-7-hydroxy/7,8-dihydroxy substituted chromones were acylated by using acetic anhydride and DMAP as catalyst in THF as solvent. A small library of fourteen compounds of 3-alkyl substituted chromones and their corresponding acetylated derivatives have been synthesized, and the structures of all the compounds were unambiguously established on the basis of spectral data ($^1$H NMR, $^{13}$C NMR spectra and HRMS) analysis.

The potency of these 3-alkyl substituted chromones was evaluated for the CRTAase catalysed modulation of activity of enzyme proteins, such as inhibition of cystolic glutathione-S-transferase (GST) and inhibition of platelet aggregation. Structure-activity relationship study indicated a gradual decline in CRTAase activity with the increase in size of the alkyl group, however, no significant ADP induced platelet aggregation inhibition, and NOS activation was observed.

In addition, the synthesized compounds were evaluated for anticancer activity against three cancer cell lines namely ovarian adenocarcinoma (SK-OV-3), breast carcinoma (MCF-7), and Human T-cell lymphoblast-like (CCRF-CEM) cell lines. The best compound inhibited the cell proliferation of MCF-7 and SK-OV3 cancer cell lines by 50-60 % at a concentration of 50 µM.