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Synthesis, Antimicrobial Activity, Anti-HIV Activity, and Molecular Docking of Novel 5-, 6- and 7-Membered Ring (1*H*-Pyrrol-2-yl)aminolactams

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An efficient method has been developed for the synthesis of novel 5-, 6- and 7-membered ring (1*H*-pyrrol-2-yl)aminolactams **5a**–**f**. This method featured Ugi-4-center-3-component reaction (U4 C3 C) followed by a post-transformation reaction. All the newly synthesized (1*H*-pyrrol-2-yl)aminolactams **5a**–**f** have been screened against six microbial species and the results revealed that these lactams exhibited moderate to good activity. These lactams were also tested in an *in vitro* for their antiviral activity against of HIV-1 and HIV-2 replication using MT-4 cells. The testing results showed that compound **5f** is the only compound in the set lactams exhibiting a significant inhibition against HIV-1 replication in cell line with EC_{50} value of 2.74 ± 1.08 μM (CC_{50} of 18.93 ± 4.0 μM), and SI 6. In addition, the compound **5f** was docked with essential proteins of HIV-1 and HIV-2 reverses transcriptase (RT), including HIV-1 and HIV-2 integrases strand proteins (PDB ID: 1EP4, 1FK9, 1HNV, 1VRU, 3DLE, 3DLG, and 3MEC). The docking results revealed that important hydrogen bond interactions and hydrophobic interactions were found between the compound **5f** and the essential amino acids residues of HIV-1 and HIV-2 (RT) proteins.

Introduction

Cyclic amides (lactams) such as pyrrolidin-2-one, piperidin-2-one, and azepan-2-one are found to have broad spectrum biological activities.[1] These lactams have distinguished themselves as pharmaceutically active molecules.[2] The combination of these lactams with five-membered heterocyclic moieties offers versatile building blocks in organic synthetic field with pronounced biological activities. Examples of biological activities of pyrrolidin-2-one cyclic amides include inhibitors such as compound (**A**, Figure 1) which acts as a selective inhibitor of EGFR tyrosine kinase. Compound **A** with free substitution at the C-3 position did not show activity against any kinase, whereas the substitution with a pyrrole moiety at the C-3 position led to enhance the potency against the EGFR kinase.[3] Compound **B** exhibited an efficient seizure protection in the maximal electroshock seizure (MES) and pilocarpine induced status prevention (PISP) tests as epileptic models in comparison with the reference anticonvulsant drugs.[4] In addition, X-ray structure of hymenialdisine (compound **C**)-CDK2 complex revealed some hydrophobic interactions between the substituted pyrrole and the hydrophobic backbone of CDK. These interactions reflect the lipophilic effects of compound **C** against CDK inhibition.[5]

Several methods have been reviewed for the synthesis of 5-, and 6- membered ring lactams fused with various heterocyclic moieties.[6] The majority of these methods are still not satisfactory in viewpoint of using expensive reagents, toxic catalyst, and narrow application scope of starting materials. Thus, facile and efficient methods for the synthesis of these compounds are highly desirable.[7] One method to perform this purpose includes using multicomponent reactions (MCRs). MCRs are a powerful tool to offer an efficient access for constructing complex structural compounds from various starting materials in a one pot.[8] Ugi four-component reaction (U4CC) and its post-transformations are used for the synthesis of novel bioactive compounds, especially drug-like heterocyclic compounds.[9] Common examples of post-Ugi transformation reactions include Ugi/Knoevenagel,[10] Ugi/Heck,[11] Ugi/Pictet-Spengler,[12] Ugi/Diels-Alder,[13] Ugi/aza-Wittig,[14] and Ugi/Aldol.[15]

The replacement of two starting materials in the Ugi reaction (U4CC) with a single bi-functional substance has demonstrated itself as a fruitful methodology towards the synthesis of a variety of drug-like compounds.[16] Particularly, various keto carboxylic acids are employed as a bi-functional substance in the Ugi reaction to offer a facile access into a diversity of different size lactam-type heterocyclic scaffolds.[17] The contribution of hydrazine moiety such as *N*-acyl-, alkoxyacyl-, and *N,N*-dialkylhydrazine in the Ugi reaction was reported in the literature.[18] It was found that the presence of the *N*-acylhydazine linker in the Ugi-products enhanced antibacterial activity.[19] This promoted us to search an efficient strategy for the synthesis of different size lactams based on the use of keto carboxylic acids as a bi-functional component and *N*-acylhydrazine moiety as an amine component.

Herein, we report a new Ugi-(4 C3 C) design employing various keto carboxylic acids **1a**–**f**, a Boc-protected hydrazine **2** as an amine component, and cyclohexylisocyanide **3** followed by a further post-Ugi transformation. Literature revealed that the removal of the Boc group in the obtained Ugi products

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