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Synthesis of New Drug-Like Piperazine-2,5-diones by the Ugi/Tandem Process Catalyzed by TMSOTf and Their Molecular Docking

A. M. Jassem[a],*, A. M. Dhumad[a], and F. A. K. Almashal[a]

[a] *Department of Chemistry, College of Education for Pure Sciences, Basrah University, Basrah, 61004 Iraq*
**e-mail: ahmed.majedd@uobasrah.edu.iq*

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Abstract—A new four-components post-Ugi transformation process has been studied. It provides an efficient access to biologically active piperazine-2,5-dione derivatives in high yield. The framework of piperazine-2,5-dione derivatives has been constructed by a tandem-decarboxylation of α-keto carboxylic acids promoted by a green catalyst trimethylsilyl trifluoromethane sulfonate (TMSOTf). Molecular docking study of piperazine-2,5-dione derivatives has been performed with various anticancer target proteins: human androgen receptor (AR) (PDB ID: 1E3G), human steroidogenic cytochrome P450 17A1 (PDB ID: 4NKV), epidermal growth factor receptor 2 HER2 (PDB ID: 3PP0), and estrogen receptor alpha (ERα) (PDB ID: 1A52), and has indicated their possible efficient interactions via hydrogen bonds.

Keywords: post-Ugi transformation, TMSOTf, molecular docking study, piperazine-2,5-dione derivatives

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INTRODUCTION

Piperazine-2,5-dione structures have been incorporated in various molecules of biologically active compounds and drugs, including a vascular disrupting agent (plinabulin **1**) [1], anti-microtubule agent (phenylahistin **2**) [2], potent antitumor products tryprostatin B **3** [3], and alkaloid **4** (*Aspergillus oryzae*) [4] (Fig. 1).

A number of synthetic methods for piperazine-2,5-diones has been reported, nevertheless, there is a considerable demand in new approaches to their synthesis

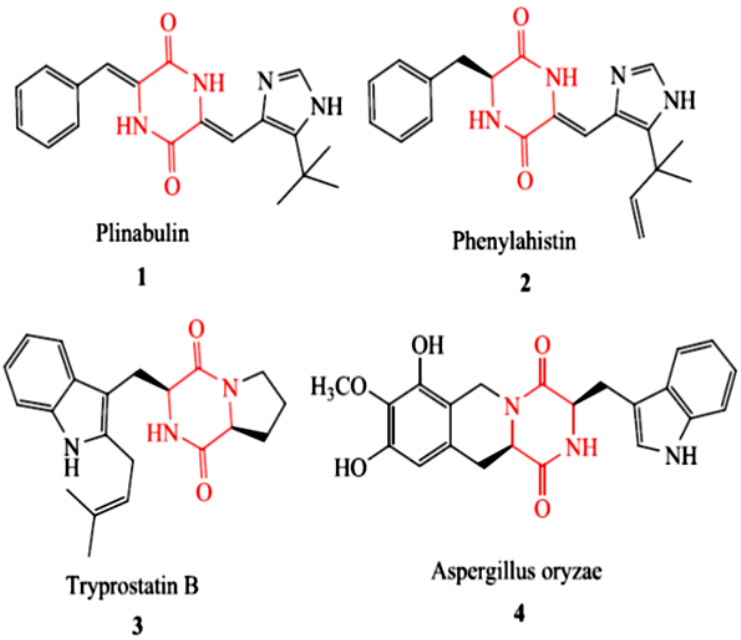

Fig. 1. Some pharmacologically active piperazine-2,5-dione derivatives.