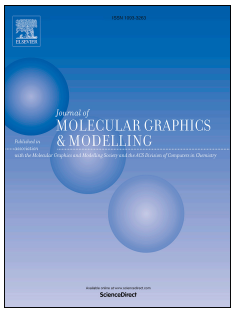
# Journal Pre-proof

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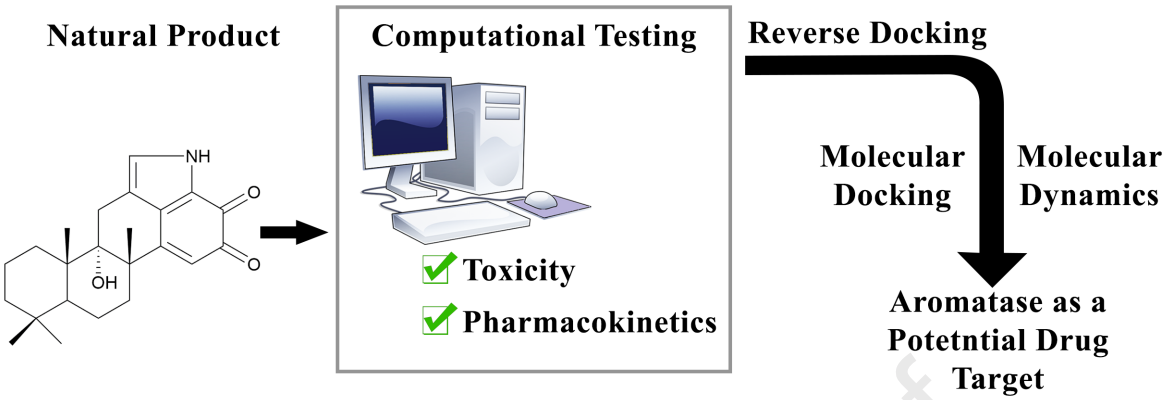

# *In silico* study for prediction of novel bioactivities of the endophytic fungal alkaloid, mycoleptodiscin B for human targets

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**Abstract**

Mycoleptodiscin B is a natural product extracted from the endophytic fungus *Mycoleptodiscus* sp. found in Sri Lanka and Panama with experimentally unexplored activities for human targets. In this study, a computational methodology was applied to determine druggable targets of mycoleptodiscin B. According to the computational toxicity and pharmacokinetics assessment, mycoleptodiscin B was proven to be a suitable drug candidate. Druggable targets for this compound, aromatase, acidic plasma glycoprotein and androgen receptor, were predicted using reverse docking. A two-step validation of those targets was performed using conventional molecular docking and molecular dynamic (MD) simulations, resulting in aromatase being determined as the potential therapeutic target. Based on molecular mechanics/Generalized Born Surface Area (GBSA) free energies and ligand stability inside the active site cavity during its 120 ns MD run, it can be concluded that mycoleptodiscin B is a potent aromatase inhibitor and could be subjected to further *in vitro* and *in vivo* experiments in the drug development pipeline. Consequently, natural product chemists can quickly identify the hidden medicinal properties of their miracle compounds using the computational approach applied in this research.

*Keywords*: Mycoleptodisicin B, Natural products, Drug development, Computational chemistry, Reverse docking, Breast cancer

## 1. Introduction

The structural variability and the diverse range of biological activities shown by natural products have made them superior to the synthetic compounds used in high throughput screening processes in drug development pipelines. Thus, secondary metabolites extracted from plants, flowers, leaves, algae, fungi, bacteria, etc., have shown immense value as lead compounds in drug development [1]. Currently about half of the medications available in the market are of natural product origin or derivatives of them [2].

Annually, a huge number of novel natural products are discovered. However, out of them, identification of pharmaceutically active compounds is expensive and highly time-consuming due to the trial and error process of conducting standard validated assays [1]. Moreover, the microgram quantities of the active compounds isolated are not enough to drive these assays. Even a compound active for an assay may get rejected during the drug development pipeline owing to their poor pharmacokinetics, toxicities and undesirable effects [3]. Therefore, a huge amount of time and money could be saved through a reasonable computational prediction of bioactivities of the novel compounds and their pharmacokinetic and toxicity properties.

Currently, there are well established computational techniques such as virtual screening and pharmacophore modelling which are frequently applied in the traditional drug discovery process to reduce its time and cost [4]. Such tools can be handy for the natural product chemists to discover their medicinal properties. Similarly, we present an integrated computational strategy to explore the human druggable targets of mycoleptodiscin B, which is a recently isolated secondary metabolite of endophytic fungus *Mycoleptodiscus* sp. from Sri Lanka and Panama (**Fig. 1**) [5].