

Abstract

# Tracing Potential Covalent Inhibitors of an E3 Ubiquitin Ligase Through Target-Focused Modelling <sup>†</sup>

Imane Bjiij <sup>1,2</sup>, Pritika Ramharack <sup>1</sup>, Shama Khan <sup>3</sup>, Driss Cherqaoui <sup>2</sup> and Mahmoud Soliman <sup>1,\*</sup>

<sup>1</sup> Molecular Bio-Computation & Drug Design Lab, School of Health Sciences, University of KwaZulu-Natal, Westville, Durban 4000, South Africa

<sup>2</sup> Département de Chimie, Faculté des Sciences Semlalia, Université Cadi Ayyad, Av. My Abdellah, BP2390 Marrakech, Morocco

<sup>3</sup> Department of Clinical Microbiology and Infectious Diseases, School of Pathology, University of the Witwatersrand, Johannesburg 2193, South Africa

\* Correspondence: soliman@ukzn.ac.za

<sup>†</sup> Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 14 November 2019

The Nedd4-1 E3 Ubiquitin ligase has been implicated in multiple disease conditions due its overexpression. Although the Nedd4-1 E3 Ubiquitin ligase is an enzyme that may be targeted either covalently, or non-covalently, there are few studies that demonstrate effective inhibitors of the enzyme. In this work, we aimed to identify covalent inhibitors of Nedd4-1. This task however, proved to be challenging due to the limited available electrophilic moieties in virtual libraries. We therefore opted to divide an existing covalent Nedd4-1 inhibitor in two parts: A non-covalent binding part and a pre-selected  $\alpha$ ,  $\beta$ -unsaturated ester that forms the covalent linkage with the protein. A non-covalent pharmacophore model was built based on the active site binding investigations followed by validating the covalent conjugation. Thirty compounds were selected and covalently docked into the catalytic site of the Nedd4-1. Multiple filtrations were effected before selecting 5 hits that were later analysed by molecular dynamic simulations to check their stability and explore their binding landscape in complex with the protein. All in all, two inhibitors with optimum overall stability and more stabilising interactions were kept for eventual biological evaluation. Our improved pharmacophore model approach serves as a robust method that will illuminate the screening for novel covalent inhibitor in drug discovery.



© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).