Lipophilic Efficiency as an Important Metric in the Design of SARS coronavirus 3C-like proteinase (3CL-pro) Inhibitors: Guidepost towards Lead Selection and Optimization in the Treatment of COVID-19

George Oche Ambrose1[a,1], Joseph Enya [b], Tamonokorite AbelJack-Soala [a], Bukola Temitope Fabunmi [c], Ajayi Kolawole Temidayo [d], Bankole Olukayode Olusola [a,e]

[a] *Dept. of Biochemistry, Faculty of Life Sciences, University of Ilorin, Ilorin, Nigeria*

[b] *Dept. of Anatomy, Basic Medical Sciences, University of Ilorin, Ilorin, Nigeria*

[c] *Biological Sciences Department, Achievers University Owo, Ondo, Nigeria*

[d] *Dept. of Microbiology, Faculty of Life Sciences, University of Ilorin, Ilorin, Nigeria*

[e] *Biochemistry Unit, Dept. of Science Laboratory Technology, Federal Polytechnic Ilaro, Ogun State, Nigeria*

Abstract

Pfizer researchers reported in 2018 that lipophilic efficiency (LipE) is an important metric that is increasingly being applied to medicinal chemistry drug discovery programs. In this perspective, drug discovery examples have been strictly applied when adopting LipE to guide medicinal chemistry lead optimization toward candidate drugs with exceptional efficacy and safety *in vivo* potential, especially when guided by optimization based on physicochemical properties. In general, most medicinal chemists only consider potency and try to increase it during hits and lead optimization or when studying the structure-activity relationship. It should be noted that lipophilicity should be considered in conjunction with potency variations to ensure both the safety (drug-likeness) and the efficacy of the candidate drug. Therefore, the aim of this study is to identify successful potential leads against 3CL-pro and optimize them for maximum potency and safety in COVID-19 treatment with a design strategy approach. 3CL-pro inhibitors with lipophilic efficacy and related bioactivity data were obtained from the Chembl database and analyzed based on relationship between LipE and logP (lipophilic). The 2D physicochemical descriptors of the compounds were calculated. Quantitative Structural-Activity Relationships (QSAR) model was built and bioactivities of novel compounds were predicted while molecular mechanism was inferred by docking assay. Based on analysis, 80 novel compounds were found, 6 of the novel compounds (36, 37, 46, 47, 77 and 79) revealed an increase in both LipE and potency with logP decrease, which makes them better alternatives to existing 3CL-pro inhibitors in the treatment of COVID-19.

Keywords: COVID-19; Lipophilic; QSAR model; 3CL-pro inhibitors; drug

1. Introduction

From a global public health and socioeconomic perspective, there is an urgent expectation to come-up with a rapid intervention that includes effective vaccines and antiviral drugs to stop the spread of the current pandemic virus [1] designated as coronavirus disease 2019 (COVID-19), broadcasted by the

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[1]Corresponding author. *Email addresses:* ocheab1@gmail.com (G.A. Oche)

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