Journal of King Saud University – Science 33 (2021) 101637

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Original article

Repurposing benzimidazole and benzothiazole derivatives as potential inhibitors of SARS-CoV-2: DFT, QSAR, molecular docking, molecular dynamics simulation, and *in-silico* pharmacokinetic and toxicity studies

Ranjan K. Mohapatra [a], Kuldeep Dhama [b], Amr Ahmed El–Arabey [c], Ashish K. Sarangi [d], Ruchi Tiwari [e], Talha Bin Emran [f], Mohammad Azam [g,*], Saud I. Al-Resayes [g], Mukesh K. Raval [h], Veronique Seidel [i,*], Mohnad Abdalla [j,*]

[a] Department of Chemistry, Government College of Engineering, Keonjhar, Odisha 758002, India
[b] Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly 243122, Uttar Pradesh, India
[c] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
[d] Department of Chemistry, School of Applied Sciences, Centurion University of Technology and Management, Odisha, India
[e] Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, Uttar Pradesh Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan (DUVASU), Mathura 281001, India
[f] Department of Pharmacy, BGC Trust University Bangladesh, Chittagong 4381, Bangladesh
[g] Department of Chemistry, College of Science, King Saud University, PO BOX 2455, Riyadh 11451, Saudi Arabia
[h] Department of Chemistry, G. M. University, Sambalpur, Odisha, India
[i] Natural Products Research Laboratory, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom
[j] Key Laboratory of Chemical Biology (Ministry of Education), Department of Pharmaceutics, School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University, 44 Cultural West Road, Shandong Province 250012, PR China

ARTICLE INFO

Article history:
Received 15 August 2021
Revised 28 September 2021
Accepted 29 September 2021
Available online 7 October 2021

Keywords:
DFT
QSAR
SARS-CoV-2 M^{pro}
ACE2
Molecular docking
MD simulation
Pharmacokinetic study

ABSTRACT

Density Functional Theory (DFT) and Quantitative Structure-Activity Relationship (QSAR) studies were performed on four benzimidazoles (compounds 1–4) and two benzothiazoles (compounds 5 and 6), previously synthesized by our group. The compounds were also investigated for their binding affinity and interactions with the SARS-CoV-2 M^{pro} (PDB ID: 6LU7) and the human angiotensin-converting enzyme 2 (ACE2) receptor (PDB ID: 6 M18) using a molecular docking approach. Compounds 1, 2, and 3 were found to bind with equal affinity to both targets. Compound 1 showed the highest predictive docking scores, and was further subjected to molecular dynamics (MD) simulation to explain protein stability, ligand properties, and protein–ligand interactions. All compounds were assessed for their structural, physico-chemical, pharmacokinetic, and toxicological properties. Our results suggest that the investigated compounds are potential new drug leads to target SARS-CoV-2.

1. Introduction

The current COVID-19 pandemic, caused by the highly contagious newly emerged SARS-CoV-2, is a global health threat that affects millions of people worldwide, and impacts negatively on all sectors of society (Mohapatra et al., 2020a; b; Mohapatra and Rahman, 2021). Although the fatality rate for SARS-CoV-2 (~4%) is lower compared to that of SARS-CoV (~10%) and MERS-CoV (~35%), its transmission rate is much higher than that of previously reported coronaviruses (CoVs) (Guo et al., 2020). In many countries, this led to lockdown measures being put into place to minimize human-to-human transmission (Mohapatra et al., 2021b). COVID-19 related deaths have now surpassed those from

* Corresponding authors.
E-mail addresses: mhashim@ksu.edu.sa (M. Azam), veronique.seidel@strath.ac.uk (V. Seidel), mohnadabdalla200@gmail.com (M. Abdalla).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jksus.2021.101637
1018-3647/