Computational Biology and Chemistry 104 (2023) 107861

Contents lists available at ScienceDirect

Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/cbac

Physicochemical properties, drug likeness, ADMET, DFT studies, and in vitro antioxidant activity of oxindole derivatives

Imad Ahmad [a,1], Haroon Khan [a,*,2], Goncagül Serdaroğlu [b,3]

[a] Department of Pharmacy, Abdul Wali Khan University Mardan, Mardan 23200, Pakistan
[b] Sivas Cumhuriyet University, Math. and Sci. Edu., 58140 Sivas, Turkey

ARTICLE INFO

Keywords:
Oxindole
ADMET
DFT
Drug-likeness
Physicochemical properties
Antioxidant

ABSTRACT

Poor pharmacokinetic and safety profiles create significant hurdles in the drug development process. This work focuses on a detailed understanding of drug discovery interplay among physicochemical, pharmacokinetic, toxicity endpoints, and antioxidant properties of oxindole derivatives. DFT compıutations were also performed at B3LYP/6-311G** level to evaluate the physicochemical properties, global reactivity features, and intramolecular interactions. The BOILED-Egg pharmacokinetic model envisaged gastrointestinal absorption, blood-brain barrier penetration, and no interaction with p-glycoprotein for compounds C1 and C2. The physicochemical evaluation revealed that C1 possesses superior drug-like properties fit for oral absorption. Both derivatives were predicted to have high plasma protein binding, efficient distribution, and inhibiting CYP 450 major isoforms but serve as substrates only for a few of them. Both molecules have mild to moderate clearance rates. Out of ten toxicity parameters, only hepatotoxicity was predicted. DFT results implied that the meta position of the -OH group made the possibility of charge transfer greater than -para positioned -OH, due to the ΔN_{max} (eV) values of molecules C1 and C2 being calculated at 2.596 and 2.477, respectively. Both C1 and C2 exhibited a concentration dependant DPPH and ABTS radical scavenging activity. The chemical structure-physicochemical-pharmacokinetic relationship identified the meta position as the favorite for the electron-withdrawing hydroxyl group. This provides useful insight to medicinal chemists to design 6-chlorooxindole derivatives with an acceptable drug-like and pharmacokinetic property.

1. Introduction

Oxindoles belong to the class of hetero-aromatic organic compounds found in body fluids, mammalian tissues, and various plant species (Cerchiaro and Ferreira, 2006). The first oxindole derivative was extracted as an alkaloid from the bark of a tropical climber *Uncaria tomentosa* (Rudrangi et al., 2011). Its ethnopharmacology revealed numerous olden-era therapies for infections, mild physical inflammations, cancer, arthritis, and gastric ulcer (Laus et al., 1997; Kaur et al., 2016). Scientific nomenclature i.e., IUPAC designates oxindoles as 1, 3-dihydro-2H-indole-2-one (s) with a chemical formula of C8H7NO. Its chemical structure possesses a hexameric benzene ring fused with a pentameric pyrrole and a carbonyl group is attached at its C-2 position (Dreifuss et al., 2010). The efficacy of oxindoles arises from their fully substituted carbon center (Khetmalis et al., 2021). Oxindole derivatives have been identified with numerous pharmacological actions depending upon their structural moiety, i.e. antiangiogenic, antimalarial, antibacterial, antifungal, anticancer, SARS-CoV-2 inhibitors, oxidative stress mitigators, antileishmanial agents, growth hormone secretagogues, antitubercular, antidepressant, Alzheimer's disease therapeutics, aldol reductase inhibitors, antiglycation, alpha-glucosidase inhibitors, glycogen synthase kinase 3β inhibitors, and AMPK activators (Shen et al., 2021; Jang et al., 2022; Lopes et al., 2022; Heravi et al., 2022; Islam et al., 2020; Hublikar et al., 2022; El-Kalyoubi et al., 2022; Hirata et al., 2018; Yousuf et al., 2018; Tokunaga et al., 2001; Suthar et al., 2015; Czeleń and Szefler, 2021; Howard et al., 1992; Khan et al., 2013, 2014; Lozinskaya et al., 2019; Yu et al., 2013).

Amongst computational tools, especially DFT approaches, have been

* Corresponding author.
E-mail addresses: haroonkhan@awkum.edu.pk, hkdr2006@gmail.com (H. Khan).
[1] 0000-0003-2656-1327
[2] 0000-0002-1736-4404
[3] 0000-0001-7649-9168

https://doi.org/10.1016/j.compbiolchem.2023.107861
Received 2 February 2023; Received in revised form 14 March 2023; Accepted 30 March 2023
Available online 31 March 2023