RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2023, **13**, 27525

Design, synthesis, molecular docking and DFT studies on novel melatonin and isatin based azole derivatives†

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In order to address the pressing demand for newer broad-spectrum antifungal medicines with enhanced activity, computer modelling was utilised to rationally develop newer antifungal azole-based drugs. Based on the drug and active sites of the *Lanosterol* 14 alpha-Demethylases (LAD) of the prominent fungal pathogen *Candida albicans* interaction, Novel triazole-linked melatonin and isatin derivatives **7a–d** and **8a–d** were synthesised using bioisosterism. Besides the experimental synthesis and subsequent characterization, the present study focused on obtaining optimised geometries, frequency calculations, and TD-DFT studies of the synthesised molecules. We also performed molecular docking studies to explore the inhibitory ability of the synthesised compounds against the active sites of the *Lanosterol* 14 alpha-Demethylases (LAD) of the prominent fungal pathogen *Candida albicans*. The binding interactions resulted in positive findings, demonstrating the involvement of the synthesised compounds in the suppression of fungal growth. Comparative analysis of the binding potential of the synthesised molecules and commercially available drug fluconazole revealed a remarkable note: the docking scores for the designed drugs **7b**, **7c**, and **8c** are much greater than those of the fluconazole molecule. The *in silico* study of the designed series of drug molecules serves as an important guideline for further exploration in the quest for potent antifungal agents.

Received 14th August 2023
Accepted 1st September 2023

DOI: 10.1039/d3ra05531k

rsc.li/rsc-advances

Introduction

Heterocycles are an immensely important class of organic compounds, accounting for more than half of all documented organic molecules. They serve as an important core moiety in a wide range of natural products, including haemoglobin, biomolecules, RNA, DNA, proteins, vitamins, and biologically active compounds.[1] Heterocyclic scaffolds are important synthetic precursors for the synthesis of a variety of biologically active compounds. According to recent surveys, an enormous number of molecules are under investigation by researchers, including nitrogen-containing heterocycles such as indoles, pyrimidyl, pyrazolyl, thiazolyl, and pyridyl indoles, for their applications in the field of pharmacological and therapeutic effects.[2–4] Naturally occurring melatonin belongs to the privileged class of indoleamine, which is synthesised and discovered in a variety of species, including bacteria and eukaryotes.[5] Melatonin is a pineal gland hormone produced by serotonin that governs the cycle of sleep and wakefulness, the circadian rhythm, cycles of menstruation, ageing, immunity, and antioxidants in the body, among other things. Melatonin production and release are more intense at night, whereas light exposure suppresses them.[6] Previous research has documented that melatonin has a wide range of physiological effects, including antioxidant,[7,8] cardiovascular,[9,10] anti-inflammatory,[11,12] neuroprotective,[13,14] stroke protective,[15] pain modulatory,[16] antitumor,[17] antibacterial,[18,19] liver injury protective properties,[20] retinal,[21] as well as effects on offspring metabolism,[22] *etc.* 1*H*-indole-2,3-dione, which is commonly referred to as Isatin or indenedione, is a versatile moiety with a broad range of biological activity. Isatin is the precursor for a number of derivatives that possess a broad range of potential biological and pharmaceutical properties[23] such as anticancer properties in various types of cancers,[24–26] antibiotics,[27] anxiogenic,[28] antibacterial,[29] antidiabetic,[30] anticonvulsant,[31] sedative,[32]

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ra05531k