Journal of Molecular Structure 1290 (2023) 135926

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Histamine derived Schiff bases and corresponding spinaceamines - synthesis, characterization and biological evaluation

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ARTICLE INFO

Keywords:
histamine
Schiff base
spinaceamine
DNA interaction
biological activity
molecular docking

ABSTRACT

The synthesis of eight new histamine-based Schiff bases and cyclic derivatives spinaceamines was accomplished by the reaction of corresponding aldehydes and histamine as amine-counterpart in absolute ethanol. Bearing in mind that the presence of the imino group/or spinaceamine core in the organic molecular scaffold could bring prominent pharmaceutical properties, all synthesised compounds have been screened for their antimicrobial activities against a range of different bacterial and fungal strains and antioxidant activity, as well as for interactions with bovine serum albumin (BSA) and DNA molecules. According to the observed MIC values, the best activity for both, fungal and bacterial species, was displayed by the compound **3c** bearing histamine and quinoline moieties in the structure, especially for *Staphylococcus aureus*. Results obtained in the fluorescence quenching experiments have confirmed ability of tested compounds for DNA and BSA binding, while docking simulations revealed the site I of sub-domain IIA of BSA as a location of binding sites of tested compounds, as well as the minor grove and intercalation interactions with quite similar possibilities to be considered as compounds DNA-binding modes. Further, the molecular docking studies also gave insight into binding modes to the targeted enzymes (CYP51, cytochrome P450 and TyRS) related to the antifungal and antibacterial potential of tested compounds. Two compounds were selected, Schiff base **3c** and spinaceamine **4d**, to assess the stability of compounds under the physiological conditions (UV-vis spectroscopic study) and *in silico* ADME properties (SwissADME software), where both compounds have shown the stability after 72 hours in selected medium, and a potential as a drug based on their ADME properties.

1. Introduction

Schiff bases, discovered in 1984 by Hugo Schiff, represent imine functionality-bearing condensation products of reaction between amines and aldehydes/ketones [1]. The pharmaceutical potential of Schiff bases is well established, since many members of this big class of compounds exhibit different biological activities, such as antifungal [2], anti-inflammatory [3] antibacterial [4], antioxidant [5], antitumor [6], cardiovascular [7] etc. The reaction between carbonyl group and amine functionality underlays many biological processes, such as enzyme catalysis, visual process and collagen cross-linking [8]. While it was found that the presence of imino group in these molecules is beneficial for their biological activities [9,10], the proper combination of the aldehyde and amine structural backbone moieties can also contribute to the pharmacological features.

Schiff bases have also found immense application in many other fields, such as material science, where they can be used for solar shells [11], optical switching [12], but also as catalysts, pigments, polymer stabilizers [13], etc. Of particular importance is the fact that, due to the presence of imine group in the structure, Schiff bases have attracted attention in the medicinal chemistry as valuable pharmacophores for the design and synthesis of different transition metal complexes with promising biomedical application in the anticancer, antiviral, antimicrobial sphere [14,15]. Beside the versatile chelating properties and pronounced biological activities, the benefits of the use of Schiff bases as ligands for the construction of metallo-drugs are also reflected in their flexibility and possibility for the fine tuning of desired features - the structure of Schiff bases can be easily modified to provide the presence

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https://doi.org/10.1016/j.molstruc.2023.135926
Received 15 March 2023; Received in revised form 24 May 2023; Accepted 31 May 2023
Available online 3 June 2023