Evaluating the ADMET properties of Isosteric Substiution in Schiff Base Derivatives

Kostić D. Marina[1*], Obradović M. Jasmina[1], Dragojević S. Jovana[2], Divac M. Vera[2]

[1] University of Kragujevac, Institute for Information Technologies Kragujevac, Department of Science, Jovana Cvijića bb, Kragujevac, Serbia; e-mail: marinak@uni.kg.ac.rs, jasmina.obradovic@uni.kg.ac.rs
[2] University of Kragujevac, Faculty of Science, Department of Chemistry, Radoja Domanovića 12, Kragujevac, Serbia; email: jovana.marjanovic@pmf.kg.ac.rs, vera.divac@pmf.kg.ac.rs

* *Corresponding author*

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Abstract: Three Schiff base analogues (**1–3**) derived from Nilofabicin by incorporating *ortho*-substituted aldehydes (OH, NH_2, SH) were evaluated via *in silico* ADMET profiling. Compound **1** with OH substituent demonstrated the most favorable pharmacokinetic properties, including high gastrointestinal absorption, acceptable lipophilicity, and compliance with multiple drug-likeness rules. While compound **2** with NH_2 group also showed promising characteristics, compound **3** (SH substituent) exhibited drawbacks such as low solubility and absorption. These results highlight the impact of isosteric substitutions on drug-likeness and oral bioavailability.

Keywords: Isosteric effect, Schiff base, Nilofabicin, ADMET

1. Introduction

Nilofabicin (also known as CG-400549) is a novel antibiotic candidate that belongs to the class of FabI inhibitors [1,2]. FabI (enoyl-acyl carrier protein reductase) is an essential enzyme involved in bacterial fatty acid biosynthesis—a validated antibacterial target. Nilofabicin has shown potent activity against Gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Pharmacologically, nilofabicin features a Schiff base (imine) functional group, which is important for its binding to the FabI active site. However, the presence of this imine also raises concerns about metabolic stability, prompting interest in isosteric modifications to improve its ADMET properties. From the other side, Schiff bases are a class of compounds characterized by a functional imine group (–CH=N–), typically formed by the condensation of a primary amine with an aldehyde or ketone. They hold significant biological importance due to their diverse pharmacological activities [3]. Schiff bases exhibit a wide range of biological activities, including antimicrobial, antiviral, antitumor, anti-inflammatory, and antioxidant properties. Their imine linkage plays a critical role in interacting with biological targets, such as enzymes and DNA, often enhancing binding affinity and selectivity.

Taking all the above into account, we performed an in silico investigation of Schiff base analogues derived from Nilofabicin, combining its amino fragment with three *ortho*-substituted aromatic aldehyde motifs (–OH, –NH_2, and –SH) to explore how isosteric modifications influence predicted pharmacokinetic and safety profiles.

2. Methodlogy

ADMET properties of the selected compounds were predicted using *in silico* tools, including SwissADME and pkCSM [4], to evaluate pharmacokinetic behavior and potential toxicity.

3. Results and Discussion

The molecular structures of the investigated Schiff base analogues **1-3** (Figure 1), designed through the combination of Nilofabicin's amino moiety with ortho-substituted aldehydes, are shown below to illustrate the variations introduced by each isosteric modification, OH substitution in the case of compound **1**, NH_2 in **2** and SH in compound **3**.

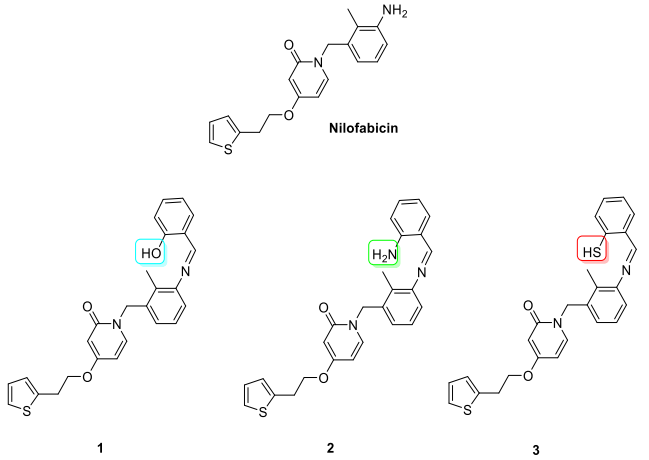

Figure 1. The structures of Nilofabicin and derived isosteric Schiff base derivatives

ADMET analysis was performed *in silico* to evaluate key pharmacokinetic and safety-related properties of the designed Schiff base analogues, with the most relevant results summarized in the Table 1 below.

Taking into consideration results presented in Table 1, it can be concluded that compound **1**, bearing OH substituent offers the most balanced profile in the terms of GI absorption, druglikenes and medicinal chemistry alerts. The in silico ADMET analysis of the compound **1** revealed a favorable pharmacokinetic and drug-likeness profile. With a molecular weight of 444.55 g/mol, one hydrogen bond donor, and four acceptors, the compound fits well within drug-like parameters.

Table 1. ADMET properties of compounds **1-3**

Compound	1	2	3
Physicochemical properties			
Molecular weight	444.55g/mol	443.56g/mol	460.61g/mol
H-bond Donors/Aceptors	1/4	1/3	0/3
TPSA	92.06 Å²	97.85 Å²	110.63 Å²
Rotatable bonds	8	8	8
Lipophilicity			
Consensus LogP	4.81	4.68	5.41
Solubility			
Solubility LogS (ESOL) / Class	-5.47	-5.26	-5.89
Pharmacokinetics			
GI Absorption	High	High	Low
BBB Permeant	No	No	No
PgP substrate	Yes	Yes	Yes
CYP Inhibition	CYP2C19, CYP2C9, CYP3A4	CYP2C19, CYP2C9, CYP3A4	CYP2C19, CYP2C9, CYP3A4
Druglikeness			
Lipinski / Veber / Egan / Muegge	All passed	All pased	Pased Lipinski and Veber
Ghose rule	Violated	Violated	Violated
Bioavailability Score	0.55	0.55	0.55
Medicinal Chemistry			
PAIN/Brenk Alerts	0/1 (imine)	0/2 (aniline, imine)	0/2 (imine, thiol)

Its topological polar surface area (TPSA) of 92.06 Å² suggests a good balance between solubility and membrane permeability, and the consensus LogP value of 4.81 indicates moderate lipophilicity, supporting good oral bioavailability. Although solubility predictions varied—with ESOL classifying the compound as moderately soluble and SILICOS-IT indicating poor solubility—the compound demonstrated high gastrointestinal absorption and is not predicted to cross the blood–brain barrier. It is a substrate of P-glycoprotein and shows inhibitory activity against CYP2C19, CYP2C9, and CYP3A4, which may imply potential drug–drug interactions. The compound complies with major drug-likeness filters, including Lipinski, Veber, Egan, and Muegge, though it violates the Ghose rule due to a high molar refractivity (>130). It showed no PAINS alerts and only one Brenk alert related to the imine group. With a synthetic accessibility score of 3.65, the molecule is considered moderately easy to synthesize. Overall, these properties suggest promising oral drug potential with some considerations for metabolism and solubility. While similar results have been observed in the case of compound **2**, bearing amino group in the structure, the compound **3** with SH substituent may suffer from low absorption, poor solubility, and high lipophilicity, with more red flags for drug development. The –OH acts as both a good H-bond donor and acceptor, enhancing solubility and membrane permeability, while NH_2 group presented in compound **2** is also a good H-bond donor but less polar than –OH. –SH is a weak H-bond donor and contributes little to polarity.

4. Conclusions

Among the Schiff base derivatives investigated, compound **1** bearing a hydroxyl group—presented the most balanced pharmacokinetic and drug-likeness profile, making it the most promising candidate for further development. Its favorable GI absorption, moderate lipophilicity, and minimal medicinal chemistry alerts suggest good oral drug potential. In contrast, compound **3** (SH-substituted) exhibited limitations such as low absorption and solubility, indicating poor drug development potential. These findings underscore the importance of functional group selection in optimizing pharmacological profiles.

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