Phenolic *N*-acyl hydrazone derivatives: *In silico* assessment of potential antibacterial activity against selected G^+ and G^- strains

Jovica Branković[1*], Zorica D. Petrović[1], and Vladimir P. Petrović[1]

[1] University of Kragujevac, Faculty of Science, Department of Chemistry, R. Domanovića 12, 34000 Kragujevac, Serbia; e-mail: jovica.brankovic@pmf.kg.ac.rs

* *Corresponding author*

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Abstract: In this work, a series of phenolic *N*-acyl hydrazones was investigated *in silico* against six selected *E. coli* and *S. aureus* bacterial proteins. Generally, the obtained molecular docking results revealed significantly higher binding affinities of analogs **a–n** towards selected enzymes in comparison to standard compounds. In the case of *E. coli* proteins **1hnj**, **1c14**, and **6ntw**, the lowest binding energies were calculated for derivatives **l** (-8.5 kcal/mol), **d** (-9.0 kcal/mol), and **k** (-8.2 kcal/mol), respectively. On the other hand, the highest binding affinity towards the *S. aureus* **3u2d**, **1mwu**, and **1jij** enzymes was expressed by derivatives **a**, **d**, and **j**, with binding energies of -8.3, -8.4, and -9.4 kcal/mol, respectively. The obtained *in silico* results indicate the potential inhibitory activity of selected phenolic *N*-acyl hydrazone derivatives against *E. coli* and *S. aureus* bacterial proteins and represent a valuable ground base for future *in vitro* experiments.

Keywords: phenolics, hydrazone, antibacterial activity, molecular docking

1. Introduction

Bacterial drug resistance represents a serious public concern. The emergence of drug-resistant bacteria was considerably affected by inadequate use of antibiotics, improper hygiene, and inadequate prevention and control of bacterial infections in health care [1]. Particularly, *E. coli* and *S. aureus* bacterial strains are recognized for their ability to develop multidrug resistance to antibiotics [2], [3]. Such an outcome triggered the necessity for novel antibacterial agents expressing diverse modes of action [4]. In the endeavor to discover efficient antibacterial agents, fruitful research exposed diverse hydrazone hybrids exerting activity against various bacterial strains [5], [6]. Moreover, the presence of multiple hydrogen-bond donor and acceptor sites enables the hydrazone core to interact with amino acid residues, thus expressing the inhibitory activity on many enzymes [7]. These virtues of hydrazone-type compounds prompted us to evaluate *in silico* inhibitory activity of a series of phenolic *N*-acyl hydrazones against selected *E. coli* and *S. aureus* proteins as multiple targets, particularly those involved in the DNA, protein, and fatty acid biosynthesis, bacterial cell wall, and drug resistance.

2. Results and Discussion

Fourteen hydrazone derivatives **a–n** derived from 2,3-dihidroxybenzoic acid and 2,3,4-trihidroxybenzoic acid bearing different ring B substitution (Figure 1) were subjected to molecular docking with *S. aureus* GyrB ATPase (PDB: **3u2d**), methicillin acyl-Penicillin binding protein 2a (PDB: **1mwu**), and tyrosyl-tRNA synthetase (PDB: **1jij**), and *E. coli* beta-ketoacyl-acyl carrier protein synthase III (PDB: **1hnj**), enoyl reductase (PDB: **1c14**), and L,D-transpeptidase YcbB (PDB: **6ntw**). Molecular docking was performed using AutodockVina software. The grid box was set to embrace the active sites, which were initially confirmed by employing CASTp software.

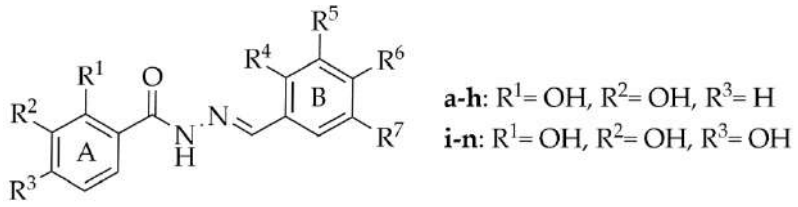


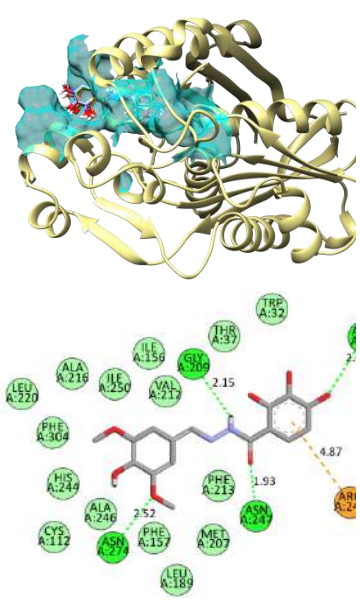
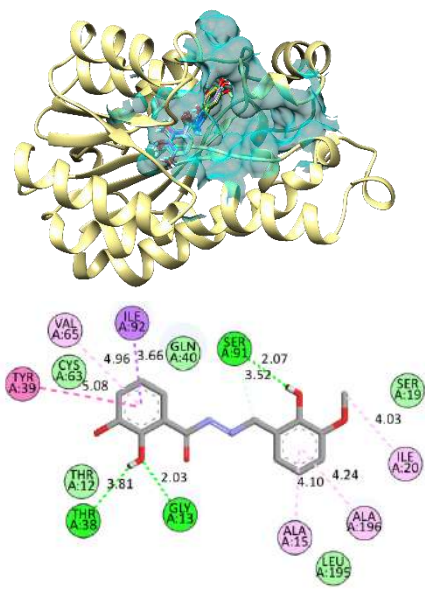
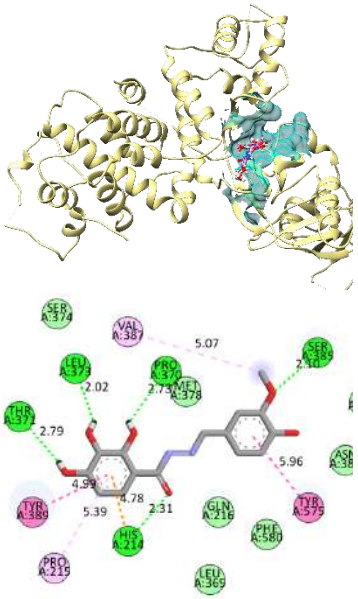
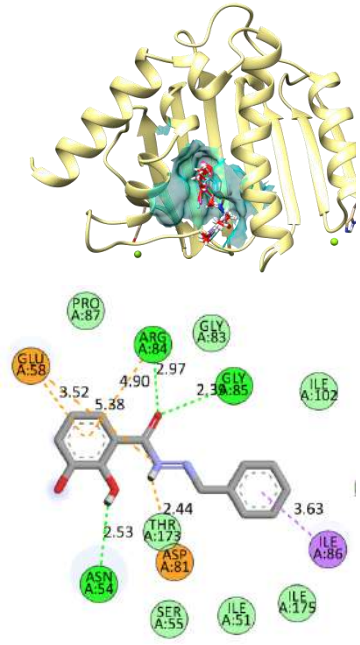
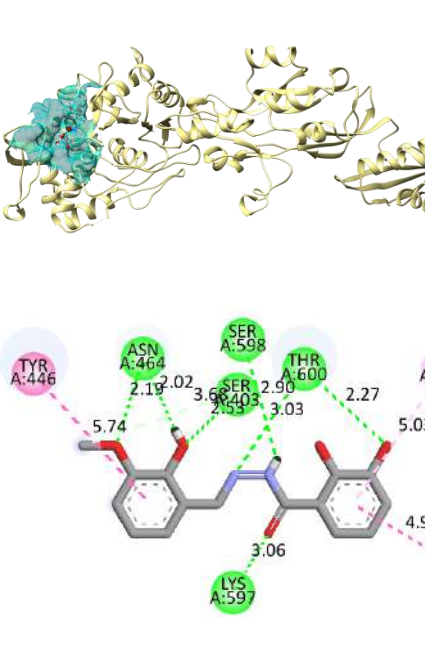
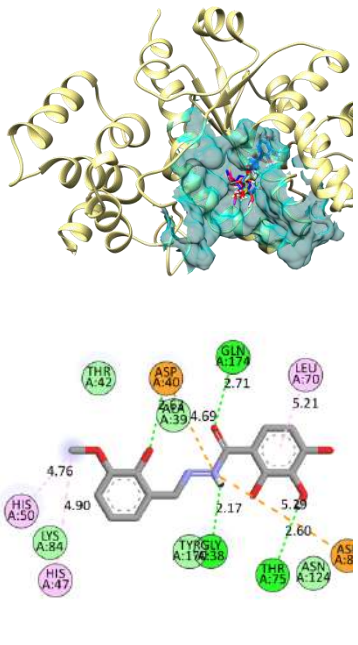
Figure 1. The skeleton of the investigated hydrazone derivatives **a–n.**

Based on the results presented in Table 1, all analogs expressed higher binding affinities towards selected proteins in comparison to standard inhibitors (SI). Here, all investigated compounds were docked within predicted active sites in all cases (Table 2). The most favorable interactions with *S. aureus* **3u2d**, **1mwu**, and **1jij** enzymes were observed for derivatives **a** (R^4, R^5, R^6, R^7=H) **d** (R^4=OH; R^5=OCH_3; R^6, R^7=H), and **j** (R^4=OH; R^5=OCH_3; R^6, R^7=H), whereas for *E.coli* **1hnj**, **1c14**, and **6nwt** analogs **l** (R^4=H; R^5, R^7=OCH_3; R^6=OH), **d**, and **k** (R^4, R^7=H; R^5=OCH_3; R^6=OH) were identified as those with the highest binding affinity, respectively. The insight into the potential bioactive conformations and 2D diagrams for the highest affinity compounds revealed multiple established hydrogen bonds (green); and Van der Waals interactions (light green); alkyl, π-alkyl, π-π, π-amide, and π-sigma interactions (purple); as well as π-anion, π-cation, and salt bridges (orange) (Table 2), with both A and B moieties. Generally, the presence of *o*-vanillin, vanillin, and syringaldehyde moieties on the B side was identified as most favorable for interaction establishment.

Table 1. Calculated binding affinities (kcal/mol) of compounds **a–n** against selected proteins.

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**SI**
3u2d	**-8.3**	-8.3	-8.2	-8.1	-8.2	-7.1	-8.2	-8.2	-8.3	-8.1	-8.1	-7.1	-8.2	-8.1	-7.6
1mwu	-7.8	-8.1	-7.8	**-8.4**	-8.0	-8.0	-8.1	-8.0	-7.8	-8.4	-8.0	-7.8	-8.2	-8.1	-7.8
1jij	-8.7	-9.0	-8.7	-9.2	-8.7	-8.9	-9.0	-8.8	-8.8	**-9.4**	-8.9	-8.8	-9.2	-9.1	-8.4
1hnj	-7.7	-7.6	-7.9	-8.0	-8.3	-8.4	-7.8	-8.1	-7.7	-8.0	-8.3	**-8.5**	-7.9	-8.2	-7.2
1c14	-8.2	-8.5	-8.2	**-9.0**	-8.6	-8.5	-8.6	-8.3	-8.3	-8.7	-7.8	-7.9	-7.7	-7.8	-7.7
6ntw	-7.5	-7.6	-7.7	-7.7	-8.0	-7.8	-7.9	-7.8	-7.7	-7.9	**-8.2**	-7.9	-8.1	-8.1	-6.6

Table 2. Selected *E. coli* and *S. aureus* proteins presented with potential bioactive conformations of compounds **a-n** and 2D interaction diagrams for the highest binding affinity compounds.

PDB: **1hnj**	PDB: **1c14**	PDB: **6ntw**
		
analog **l**	analog **d**	analog **k**
PDB: **3u2d**	PDB: **1mwu**	PDB: **1jij**
		
analog **a**	analog **d**	analog **j**

3. Conclusions

In the present work, molecular docking analysis was performed with selected phenolic-*N*-acyl hydrazones and bacterial proteins of *E. coli* and *S. aureus* strains. The obtained results exposed notably higher binding affinities of compounds **a–n** towards selected proteins in comparison to standard compounds. In the case of *E. coli* **1hnj**, **1c14**, and **6ntw** proteins, derivatives **l** (-8.5 kcal/mol), **d** (-9.0 kcal/mol), and **k** (-8.2 kcal/mol) were identified as those with the highest binding affinities, respectively. For *S. aureus* proteins **3u2d**, **1mwu**, and **1jij**, the lowest binding energy values were calculated for analogs **a**, **d**, and **j** (-8.3, -8.4, and -9.4 kcal/mol, respectively). Insight into the potential bioactive conformations exposed multiple favorable interactions responsible for the enhanced binding affinity towards investigated proteins. The presence of *o*-vanillin, vanillin, and syringaldehyde moieties on the B side of the molecule was identified as most favorable for interaction establishment.

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