Biologically Active Usaturated α,β-Ketones Containing a Cycloacetal Fragment

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Abstract. Previously, we synthesized saturated ketones and unsaturated alcohols containing a 1,3-dioxane fragment via chemoselective reduction of unsaturated α,β-unsaturated ketones. Molecular docking of the obtained compounds was performed, and primary screening of the synthesized compounds was conducted using DIP-SLIDE rapid tests. The studies demonstrated that the selectively reduced derivatives exhibited lower bactericidal activity compared to the initial unsaturated α,β-unsaturated ketones.

Keywords: Selective reduction, 1,3-dioxane, Aldol condensation, α,β-unsaturated ketones, Molecular docking

1. Introduction

One promising direction in organic chemistry is the synthesis of biologically active compounds - including those with bactericidal properties - from readily available petrochemical feedstocks. Our results indicate significant potential for further research aimed at developing novel antimicrobial and antifungal agents based on 1,3-dioxanes, whose structural features differ fundamentally from those of known antibacterial drugs.

The application of 1,3-dioxacyclanes in fine organic synthesis has been described for the production of various herbicides [1-2] and plant growth regulators [3], antioxidants [4], corrosion inhibitors and scale inhibitors [5-6], as well as antibacterial agents [7]. Derivatives of 1,3-dioxane exhibit antithrombotic activity [8-9]. Moreover, incorporation of an acetal fragment into a molecule is known to enhance antibacterial activity by increasing compound lipophilicity [10-11].

Molecular docking can improve the reliability and predictive quality of compound screening [3]. This work presents the synthesis of selectively reduced derivatives of unsaturated α,β-unsaturated ketones, computational assessment of their toxicological risks and molecular docking studies, as well as primary microbiological screening of the synthesized compounds using rapid tests.

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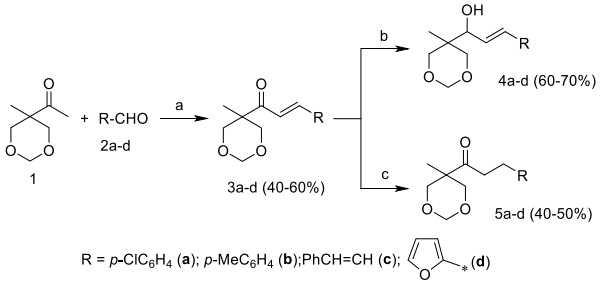
2. Synthesis

We have previously studied the selective reduction of unsaturated α,β-ketones containing a 1,3-dioxane fragment [12]. Condensation of 5-acyl-5-methyl-1,3-dioxane **1** with a series of aldehydes **2a-d** (*p*-chlorobenzaldehyde, *p*-tolualdehyde, cinnamaldehyde and furfural) in the presence of sodium methoxide at room temperature leads to the formation of the corresponding α,β-unsaturated ketones **3a-d** with yields of 40–60% (path «a»). Subsequent chemoselective reduction led to the formation of unsaturated alcohols **4a-d** in the $NaBH_4$-CH_3OH system (path «b») or saturated ketones **5a-d** in the $NaBH_4$-CH_3COOH system (path c) (see Scheme 1).



Scheme 1. Synthesis of unsaturated α,β-ketones and their selective reduction.

3. Activity

Computer Prediction and Study of Biological Activity

To determine the potential biological activity of the obtained compounds, we performed a prediction using the PASS-online program [13], which indicated the possible presence of antibacterial activity (see Table 1).

Table 1. PASS-online Prediction of Some Compounds.

Compounds	Predicted Activity (Pa/Pi)*	
	Antibacterial	Antimycobacterial
3a	0.200/0.118	0.204/0.168
3b	0.256/0.080	0.209/0.162
3c	0.334/0.048	-
5d	0.261/0.077	0.194/0.181

* Pa – probability of activity being present; Pi - probability of activity being absent.

The safety of the obtained compounds was determined by the "OSIRIS Data Warrior" program [14]. The program calculates the probability of toxic risks of the compounds. Table 2 shows the prediction results, indicating the absence of mutagenic and carcinogenic effects, as well as no effect on reproductive functions for the compounds. However, all obtained compounds have a medium degree of risk for irritant effect, and

3c has a high degree of risk. Also, the negative value of "Drug-likeness" for compounds **3b**, **3c**, and **5d** indicates the absence of drugs with a similar structure.

Table 2. OSIRIS Data Warrior Prediction for Some Compounds.

Compound	Drug-likeness	Mutagenicity	Carcinogenicity	Reproductive Effect	Irritant Effect
3a	1.881	-	-	-	±
3b	-0.391	-	-	-	±
3c	-3.833	-	-	-	+
5d	-0.201	-	-	-	±

(-)-risk absent; (±) - medium degree of risk; (+) - high degree of risk

Further, to assess the potential bactericidal activity of the obtained compounds, we performed molecular docking. Molecular modeling was carried out using Autodock 4.2.6 software [15]. The construction of 3D models of the compounds and the minimization of their energy using the molecular mechanics method MM2 were performed using ChemBioOffice 10.0 software. Visualization of the ligand-receptor interaction was conducted in Discovery Studio Visualizer v. 17.2.0.16349.

Calculations were performed with proteins of the Gram-positive bacterium *S. aureus*, the Gram-negative bacterium *E. coli*, and the fungus *C. albicans*, obtained from the PDB database [16].

Table 3 presents the calculated values of binding energy and inhibition constants (Ki) for some compounds. According to the calculations, the initial unsaturated α,β-ketones **3a, 3b, 3c** and the reduced ketone **5d** are of the greatest interest. As a result of docking, a good correlation with *in vitro* studies conducted earlier [17] is observed. These studies showed that 5-amyl-5-isopropyl-1,3-dioxane exhibits activity against Gram-positive and Gram-negative bacteria. Relatively high values indicate the possible presence of biological activity.

Table 3. Docking Results: Binding Energy and Inhibition Constants.

Name of Bacteria/Fungus	Protein	Compound	Binding Energy, kcal/mol	Ki Value, nM
S.aureus	6alw	**3a**	-9.00	0.24
		3b	-9.10	0.21
		3c	-8.90	0.29
		5d	-7.20	5.20
	5woo	**3a**	-8.50	0.57
		3b	-8.60	0.48
		3c	-8.90	0.29
		5d	-7.00	7.29
E.Coli	3ude	**3a**	-8.10	1.13
		3b	-8.60	0.48

	1fj4	**3c**	-8.70	0.41
		5d	-7.50	3.13
		3a	-5.40	108.98
		3b	-6.00	39.54
		3c	-7.80	1.88
		5d	-7.50	3.13
C.albicans	7rje	**3a**	-8.70	0.41
		3b	-9.00	0.24
		3c	-8.70	0.41
		5d	-6.90	8.64

Figure 1 shows the location of compound **5d** in the active site of protein 1f4 (*E.coli*). This complex forms a hydrogen bond with THR A:302, which plays an important role in binding with the receptor.

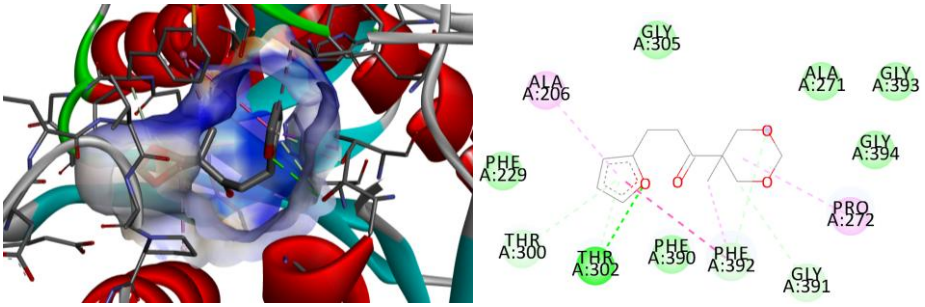


Fig. 1. Location of compound **5d** in the active site of protein 1f4 (*E.coli*).

Figure 2 shows the location of the most active compound **3b** in the active site of protein 6alw (*S.aureus*). The complex does not form hydrogen bonds; however, it is stabilizing π-π stacking interactions with amino acids. This interaction occurs due to the overlap of p-orbitals of aromatic systems containing delocalized π-electrons.

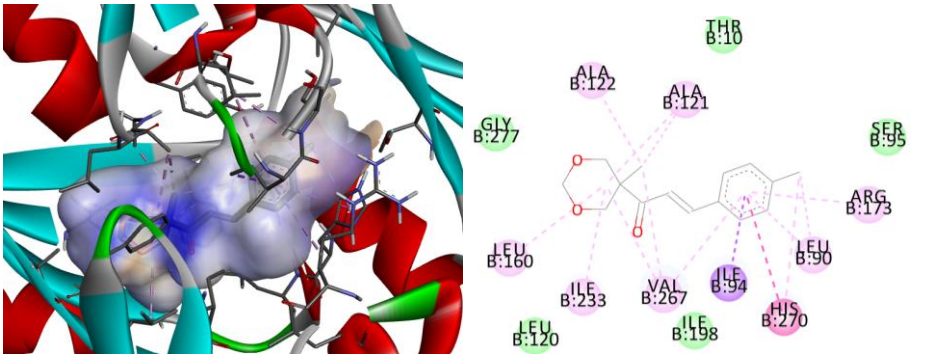


Fig.2. Location of the most active compound **3b** in the active site of protein 6alw (*S.aureus*).

To validate the computational predictions, primary microbiological screening was performed using Dip-Slide plates for total viable count (TVC) determination. TVC is a quantitative measure reflecting the total number of viable microorganisms in a sample, expressed as colony-forming units (CFU) per unit volume or mass. The procedure was conducted as follows [18–20]:

Test substances were dissolved in dimethyl sulfoxide at concentrations of 5×10^{-4} g/mL, 1.25×10^{-4} g/mL, and 3×10^{-5} g/mL and applied to the surface of test slides without contacting the agar coating. Slides were immersed in the test solution for 5–10 seconds to ensure complete contact between the coating and solution, then placed in an incubator at 30–35 °C.

After 48 hours of incubation, bacterial colony growth was observed on the TTC agar surface as straw-colored spots distributed across the entire area. After 96 hours, growth of micromycetes was recorded on rose bengal agar as spherical, shiny, fluffy colonies, along with yeast cultures appearing as flat, dry spots (Table 4).

Table 4. Bacterial and fungal growth depending on the concentration of compounds.

№	Compound	Bacteria					
		Concentration, %					
		$5 \cdot 10^{-4}$ g/mL (0,05%)		$1{,}25 \cdot 10^{-4}$ g/mL (0,0125%)		$3 \cdot 10^{-5}$ g/mL (0,003%)	
		48h	96h	48h	96h	48h	96h
1.	Water	10^7	10^7	10^7	10^7	10^7	10^7
2.	**3a**	ND	ND	ND	ND	ND	ND
3.	**3b**	ND	ND	ND	ND	ND	ND
4.	**3c**	ND	ND	ND	ND	ND	ND
5.	**5d**	ND	ND	ND	ND	ND	ND
		Fungi					
6.	Water	ND	+	ND	+	ND	+
7.	**3a**	ND	ND	ND	ND	ND	ND
8.	**3b**	ND	ND	ND	ND	ND	ND
9.	**3c**	ND	ND	ND	ND	ND	ND
10.	**5d**	ND	ND	ND	ND	ND	ND

ND - no detectable growth; + - visible growth

As shown in Table 4, Gram-negative bacterial colonies appeared on the control samples, whereas the tested compounds (**3a - c** and **5d**) completely inhibited microbial growth at all concentrations tested. Fungal and yeast growth intensity was assessed by comparing sample appearance with manufacturer reference standards.

4. Conclusion

Computer prediction indicated that all synthesized compounds present a moderate irritant risk, except for compound **3c**, which showed a high risk level. Molecular docking

identified the initial unsaturated α,β-unsaturated ketones (**3a**, **3b**, **3c**) and the reduced ketone (**5d**) as the most promising candidates. Primary screening confirmed that these compounds exhibit high activity against Gram-negative bacteria (*E. coli*) and fungi.

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Disclosure of Interests. The authors have no competing interests to declare that are relevant to the content of this article.

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