Exploring beta blocking as a possible mechanism of anticancer action of 2-thiohydantoins

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Abstract: This study is a continuation of our previous work in which we examined the anticancer potential of a series of zingerone 2-thiohydantoin derivatives. Using molecular docking, we explored whether beta blocking is a possible mechanism of their anticancer action. Active and inactive derivatives were docked into the structure of the beta-2 adrenergic receptor and their preferred binding sites, binding affinities and interactions were compared and discussed. The results show a discernible difference in which the active and inactive derivatives interact with the receptor and indicate that beta blocking could be a possible mechanism of their anticancer action.

Keywords: 2-thiohydantoin, beta-2 adrenergic receptor, molecular docking

1. Introduction

Hydantoins are a large family of cyclic ureide compounds, known for their uses in medicine and various branches of industry [1]. They are highly regarded in medicinal chemistry and considered a valuable scaffold in drug discovery. Recent developments in hydantoin chemistry and SAR design strategies have yielded vast libraries of hydantoin compounds aimed at utilization in targeted therapy for various diseases, cancer most notably [2]. Overexpression of certain proteins in various cancer types can make them suitable for a specific, target-based therapy approach. Beta-2 adrenergic receptor was shown to be a promising anticancer target, as its expression has been linked to the development and progression of various types of cancer [3].

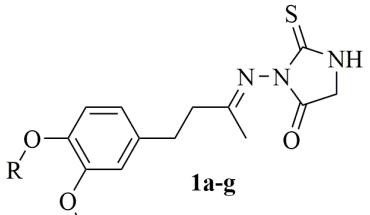

Figure 1. Structure of the zingerone 2-thiohydantoin derivatives.

In our previous work, we reported the synthesis and anticancer activity of a series of zingerone 2-thiohydantoin derivatives (Figure 1) [4]. Following these results, the aim of this study is a molecular docking investigation of the binding affinity of these compounds towards the beta-2 adrenergic receptor, in order to elucidate whether beta blocking is a possible mechanism of their anticancer action.

2. Methodology

Structures of the ligands were optimized using Gaussian09 software [5], using the B3LYP functional and 6-311++G** basis set. AutoDock Vina was used for molecular docking calculations [6]. Docking was done on the whole protein, and not on separate parts, such as the active binding site, because there is no experimental data on the binding sites of the examined molecules. The spacing of the grid box was set to 1.0 Å and grid box dimensions were 60x56x100 Å, exhaustiveness was set to 100 and the number of generated docking poses was 9. The native ligand, norpeinephrine and the known beta-blockers, propranolol and salbutamol, were docked in the binding pocket of the receptor, in a grid box with dimensions 22x22x22 Å. The crystal structure of the beta-2 adrenergic receptor deposited under the PDB ID: 3NY8 was obtained from the Protein Data Bank [7]. The selected receptor structure has a resolution of 2.84 Å, which is considered adequate for reliable docking results. The receptor structure was prepared for docking by removing co-crystallized water molecules and other ligands. BIOVIA Discovery Studio was used for visualization and examination of ligand-receptor interactions [8].

3. Results and Discussion

In order to determine whether the beta-2 adrenergic receptor is a potential target for the anticancer action of these compounds, the most active compound **1e** was docked into the structure of the protein, along with an inactive derivative **1a**, for comparison. The active compound **1e** binds within the binding pocket of the receptor (Figure 2, green), between the structures of the seven transmembrane helices, while the inactive **1a** binds outside of the binding pocket, on the surface of the receptor (Figure 2, blue).

Calculated binding free energies of the investigated compounds are given in Table 1. When comparing the binding affinities of the investigated compounds, the active compound **1e** has a low binding free energy of -9.9 kcal mol^{-1}, lower than that of the native ligand, norepinephrine, while the inactive **1a** has a less negative binding free energy value of -8.5 kcal mol^{-1}. Moreover, the binding free energy of **1e** was lower than that of known beta blockers, propranolol and salbutamol (-8.0 and -8.1 kcal mol^{-1}).

Analysis of the amino acid environment within the binding sites of the investigated compounds revealed that the binding of **1e** within the binding pocket (Figure 3, left) involved one conventional hydrogen bond, two non-classical, carbon-hydrogen bonds, a π/sulfur interaction and various hydrophobic (π/π, π/alkyl and alkyl/alkyl) interactions. By comparison, the binding of **1a** outside of the binding pocket consists of only weaker hydrophobic π/π and π/alkyl interactions and the hydantoin moiety does not seem to be involved in any interactions with the receptor (Figure 3, right). These results could offer

a possible explanation for the difference in the anticancer activities of the investigated compounds, as they show a discernible difference in the binding modes, interactions and affinities of the active and inactive compounds.

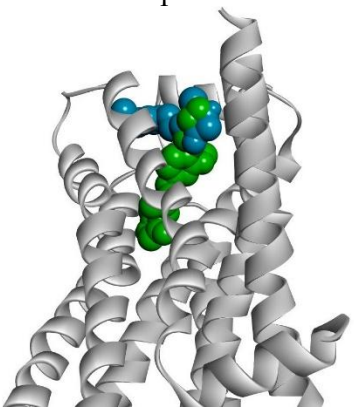

Figure 2. Binding sites of the active compound **1e** (green) and inactive compound **1a** (blue).

Table 1. Binding free energies (ΔG / kcal mol^{-1}) and binding sites of investigated compounds for the beta-2 adrenergic receptor.

Ligand	Binding pocket	Out of binding pocket
1e	-9.9	
1a		-8.5
norepinephrine	-7.3	
propranolol	-8.0	
salbutamol	-8.1	

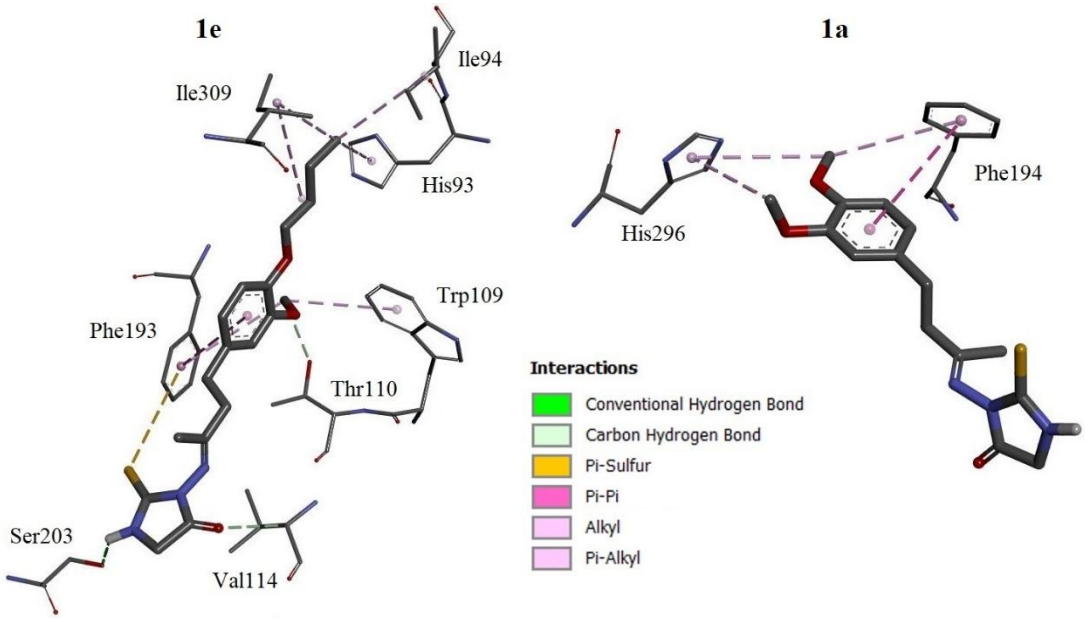

Figure 3. Amino acid environments within the binding sites of **1e** (left) and **1a** (right).

4. Conclusions

Employing SAR design strategies and investigating and developing novel compounds for targeted therapy is crucial for further advancements in drug design. This study suggests that the blocking of the beta-2 adrenergic receptor is a possible mechanism of anticancer action of 2-thiohydantoin derivatives. Further experimental validation is needed in order to evaluate the merit of the molecular docking predictions. These results, in combination with future experimental validation, could contribute to the developmental framework for novel thiohydantoin based anticancer beta blockers.

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