In Silico Study on N-Ferrocenylmethyl-N-Phenylpropionohydrazide and N-Ferrocenylmethyl-N-Pheylbenzohydrazide as Anticancer Drugs for Breast and Prostate Cancer

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Keywords: free binding energy; binding constant; AutoDock; molecular docking; antitumor activity.

Abstract. Molecular docking calculations were used to evaluate the antitumor activities of N-ferrocenylmethyl-N-phenylpropionohydrazide (FP) and N-ferrocenylmethyl-N-pheylbenzohydrazide (FH) against the enzymes of breast cancer 17-beta-hydroxysteroid dehydrogenase type 1 (17 β -HSD1) and human steroidogenic cytochrome P450 17A1 prostate cancer mutant A105L (CYP17A1). The molecular docking study was performed using the open source AutoDock 4.2 software. The obtained results showed that both FP and FH bind with 17 β -HSD1 and CYP17A1 via hydrogen bonds, binding free energy values for the adducts FH-17 β -HSD1 and FH-CYP17A1 were respectively equal to -27.67 and -27.55 KJmol⁻¹, while for the adducts FP-17 β -HSD1 and FP-CYP17A1 they were respectively equal to -29.13 and 29.18 KJmol⁻¹. The negative values and the magnitude of the obtained binding free energy indicated respectively the spontaneity and the electrostatic interaction of both ligands FP and FH with 17 β -HSD1 and CYP17A1 receptors as the dominant mode. Finally the ligand FP binds more strongly to the receptor CYP17A1 and forms two respective hydrogen bonds with Arg96 and His373; this finding clearly indicate that FP is best qualified as potential drug candidature for breast and prostate cancer.

Introduction

Prostate cancer and breast cancer have become the second and the third most common cause of cancer death among men and women respectively. Although these type of cancers caused by different anatomical and physiological tissues, both these tissues share the common feature of requiring sex steroid-dependent development. The American Cancer Society estimated one man in six will be diagnosed with prostate cancer during his lifetime. A little over 1.8 million men in the United States are survivors of prostate cancer, about 200,000 new cases of breast cancer are diagnosed every year and about 50,000 women die annually from the breast cancer [1,2].

Current treatment for cancer is purposed to cure symptom and to improve quality of life. Treatment for prostate cancer commonly uses androgen replacement therapy. Unfortunately, many side effect showed important numbers in male, for example impotency, loss of libido, and gynecomastia [3]. Therefore, looking for new drug target of prostate cancer therapy is still more than need.

The enzyme 17 β -HSD1 is known to catalyse the last step in the synthesis of the hormone Oestradiol. This hormone stimulates breast cancer and other oestrogen-related diseases. Therefore the inhibition of the enzyme 17 β -HSD1 represents a possible drug target for breast cancer treatment and can be considered as a requirement for breast cancer therapy [4].

The enzyme CYP17A1 catalysis causes either steroid precursors of glucocorticoids like cortisol that regulate immune response or androgens like testosterone that guide the development and maintenance of men characteristics or are converted to estrogens in women [5]. In later life, however, androgens drive the development of prostate cancer. The inhibition of the enzyme CYP17A1 also represents a possible drug target for prostate cancer treatment and can be considered as a requirement for prostate cancer therapy [6].

In this paper docking studies have been performed to study the antitumor activities and to understand the binding efficiency of two ferrocene derivatives named N-ferrocenylmethyl-N-phenylpropionohydrazide (FP) and N-ferrocenylmethyl-N-phenylbenzohydrazide (FH) study using the open source AutoDock Vina software.

Materials and Methods

All the computational calculations were carried out using AutoDock Vina 4.2 program [7] and were performed by the PC windows 10 with Intel Core i5 microprocessor, 4 GB memory and 32 Bit operating system.

The chemical structures of the ligands N-ferrocenylmethyl-N-phenylpropionohydrazide and N-ferrocenylmethyl-N-phenylbenzohydrazide were optimized using Gaussian 09 program package [8].

Structure optimisation

The geometry of both ligands structures N-ferrocenylmethyl-N-phenylpropionohydrazide and N-ferrocenylmethyl-N-phenylbenzohydrazide were first optimized by molecular mechanics (MM), then they were fully re-optimised by the DFT/ B3LYP method with the 6-311 G++ (d,p) base using Gaussian 09 program package [8]. The optimized 3D structure of both ligands are presented in the Fig. 1.

Figure 1. ORTEP representation of FP and FH, displacement ellipsoids are drawn at the 30% probability level; colour codes are Gray75 carbon, white hydrogen, Blue nitrogen, Red oxygen, and Green iron

Selection of Protein

The X-ray crystal structure of the enzyme of breast cancer 17-beta-hydroxysteroid dehydrogenase type 1 (17 β -HSD1) and human steroidogenic cytochrome P450 17A1 prostate cancer mutant A105L (CYP17A1) (PDB ID :3HB5 and 4NKV) were obtained from Protein Data Bank [9]. The measurement details and the 3D structures of both enzymes are shown in the Table 1 and Fig. 2.

The binding free energy of the docked structure of both ligands FP and FH with the receptors 17 β -HSD1 and CYP17A1 are summarized in Table 2.

Table 2. Binding free energy and binding constant values obtained for FP-17 β -HSD1 and FP-CYP17A1 and FH-17 β -HSD1 and FH-CYP17A1 adducts by molecular docking approach

	FH		FP	
	17 β -HSD1	CYP17A1	17 β -HSD1	CYP17A1
-ΔG (KJ.mol⁻¹)	27.67	27.55	29.13	29.18
K(M⁻¹)	7.22×10^{-4}	6.87×10^{-4}	13.05×10^{-4}	13.27×10^{-4}

Molecular docking study of FP-17 β -HSD1 and FH-17 β -HSD1 interaction

The results indicate that the ligand FP interact with the receptor 17 β -HSD1 by its oxygen atom via a hydrogen bond to the hydrogen atom of the NH group of the residue Val188, Fig. 3a. These interactions are zoomed out for better visual examination in Fig. 3b and are presented as a secondary structure surface view in Fig. 5a. The hydrogen bonds between the ligand FP and the receptor 17 β -HSD1 are presented as small green spheres in Fig. 6a. Moreover, the ligand FH is attached to the receptor 17 β -HSD1 by the hydrogen of its amino group to the OG function of the residue Arg247, Fig. 4a. The interactions are also zoomed out for better visual examination in Fig. 4b and are presented as a secondary structure surface view in a same manner as for the ligand FP, Fig. 5b. The hydrogen bonds between the ligand FH and the receptor 17 β -HSD1 are presented as small green spheres, Fig. 6b.

Figure 3. The interaction between the ligand FP and the receptor 17 β -HSD1, (a) secondary structure view, (b) zoomed view

Figure 4. The interaction between the ligand FH and the receptor 17β-HSD1, (a) secondary structure view, (b) zoomed view

Figure 5. The interaction between the ligand FP(a)/FH(b) and the receptor 17β-HSD1, the secondary structure surface view

Figure 6. Hydrogen bonding between FP (a)/FH(b) ligands and 17 β -HSD1 receptor's residue (The H-bond interaction is represented by small green spheres)

The bond's lengths and energy values of the hydrogen bonds illustrated in Figs. 3, 4 and 6 are tabulated in Table 3. It can be seen that the ligand FP binds more strongly to the residue Val188 of the enzyme 17 β -HSD1. As this enzyme represents a drug target for breast cancer treatment, we can assume that the ligand FP is better qualified as potential drug candidature for breast cancer than the ligand FH. This assumption is based on the higher binding free energy values of the interaction of FP with both receptors (Table 2) and also on the higher energy values of hydrogen bonds formed between FP and both receptors (Table 3 and 4).

Table 3. Length and energy values of hydrogen bonds formed between FP/FH ligands and 17 β -HSD1 receptor's residues

Adduct	Bonds	Length (Å)	Energy (Kcal)
FP-17 β -HSD1	Val188:HN–FP:O	1.994	-5.651
FH-17 β -HSD1	Ser11:OG-FH:NH	2.039	-2.758

Molecular docking study of FP- CYP17A1 and FH- CYP17A1 interaction

Docking results of ligands FP and FH with receptor CYP17A1 showed that the ligand FP interact with the receptor CYP17A1 by its oxygen atom via two hydrogen bonds, the first hydrogen bond is formed between the HH12 group of the residue Arg96 and the oxygen atom of the ligand FP, the second is formed between the HE2 group of the residue His373 and the oxygen atom of the ligand FP, Fig. 7a. For better observation these interactions are zoomed out in Fig. 7b and presented as secondary structure surface view in Fig. 9a. Hydrogen bonds between CYP17A1 receptor and FP are also presented as small green spheres, Fig. 10a. Finally the ligand FH forms only one hydrogen bond with the receptor CYP17A1, this bond is between the NH group of the ligand FH and the oxygen atom of the residue Arg440, Fig. 8a. This interaction is also zoomed out for better observation in Fig. 8b and presented as a secondary structure surface view in Fig. 9b. The hydrogen bond is presented as small green spheres, Fig. 10b.

Figure 7. The interaction between the ligand FP and the receptor CYP17A1, (a) secondary structure view, (b) zoomed view

Figure 8. The interaction between the ligand FH and the receptor CYP17A1, (a) secondary structure view, (b) zoomed view

Figure 9. The interaction between the ligand FP(a)/FH(b) and the receptor CYP17A1, the secondary structure surface view

Figure 10. Hydrogen bonding between FP(a)/FH(b) ligands and CYP17A1 receptor residue (The H-bond interaction is represented by small green spheres)

The bond length and energy values of the hydrogen bonds presented in Figs. 7, 8 and 10 are summarized in Table 4. Again it can be seen that the ligand FP binds more strongly to the enzyme CYP17A1 by forming two hydrogen bonds with the residues Arg96 and His373. Based on the fact that the enzyme CYP17A1 is a drug target for prostate cancer treatment, we can assume that the ligand FP is more qualified as potential drug candidature for prostate cancer than the ligand FH.

Table 4. Length and energy values of hydrogen bonds formed between FP/FH ligands and CYP17A1 receptor's residues

Adduct	Bonds	Length (Å)	Energy (Kcal)
FH- CYP17A1	Arg440:O-FH:NH	2.156	-3.233
FP- CYP17A1	Arg96:HH12- FP:O	2.130	-4.542
	His373:HE2-FP:O	2.190	-1.168

Conclusions

In this study, the receptor of breast cancer 17 β -HSD1 and prostate cancer mutant CYP17A1 binding affinity towards the ligands N-ferrocenylmethyl-N-phenylpropionohydrazide and N-ferrocenylmethyl-N-phenylbenzohydrazide were evaluated by molecular docking calculations using AutoDock 4.2 program. The obtained results indicate that both ligands bind to receptors 17 β -HSD1 and CYP17A1 via hydrogen bond interactions with binding constants equal to 13.05×10^{-4} and $13.27 \times 10^{-4} \text{ M}^{-1}$ for the ligand FP, and $7.22 \times 10^{-4} \text{ M}^{-1}$ and 6.87×10^{-4} for the ligand FH respectively which are appropriate values for drugs. Furthermore molecular docking studies further visualize interaction bonds and showed that both docked conformations bind with receptor via hydrogen bonds. Based on the fact that both receptors represent a drug target for breast cancer and prostate cancer treatment, it can be concluded that both studied ligand are qualified as potential drug candidature for breast cancer and prostate cancer.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

The authors are grateful to the Ministry of Higher Education and Scientific Research for financial support project (B00L01UN390120110001). We also acknowledge the support from Laboratory of Valorization and Technology of Saharan Resources (VTRS).

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