



Interaction of a nine steroid derivatives with aromatase enzyme surface using a theoretical model

Lauro Figueroa Valverde^{1,†}, Marcela Rosas Nexticapa^{2,*}, María Magdalena Álvarez Ramírez², Virginia Mateu Armand², Maria Lopez Ramos¹, Tomas Lopez Gutierrez¹, Silvia Delgado Moreno¹, and Juliette Mijangos Sanchez¹.

¹Pharmacochemistry Laboratory at the Faculty of Biological Chemistry Sciences of the Autonomous University of Campeche, Av. Agustín Melgar s / n, Col Buenavista c.p. 24039 Campeche Cam., Mexico.

²Faculty of Nutrition, Universidad Veracruzana. Medicos y odontologos s / n, c.p. 91010, Xalapa, Veracruz. Mexico.

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Abstract

Some aromatase enzyme inhibitors drugs have been used to treat cancer; however, their interaction with aromatase is not clear. The aim of this study was to evaluate the possible interaction of nine steroid derivatives with aromatase enzyme surface using 3eqm protein, exemetane and formestene as theoretical tools in Docking Server program. The results showed differences in the aminoacid residues involved in the interaction of steroid derivatives (1-9) with 3eqm protein surface compared with exemetane and formestene. Besides, the inhibition constant for steroid derivatives 1, 2 and 5 was lower compared to exemetane and formestene drugs. In conclusion, the steroid derivatives 1, 2 and 5 could act as aromatase enzyme inhibitors and this phenomenon could be translated as good compounds to treat breast cancer.

Keywords: Steroids, Derivatives, Cancer, Exemetane, Formestene.

[†] E-mail: lauro_1999@yahoo.com; lfiguero@uacam.mx

^{*}E-mail: rosasnm@yahoo.com



1. Introduction

From several years the breast cancer is one of the main public health problems worldwide [1-3]. Some drugs to try breast cancer such as Abemaciclib [4], anastrozole [5], exemestane [6], formestene [7] and others. However, some drugs can produce secondary effects such as neutropenia and diarrhea [8], osteonecrosis [9], cutaneous vasculitis [10], and thrombocytopenia [11]. In search of new therapeutic alternatives, some aromatase inhibitors have been prepared to treat breast cancer; for example, the synthesis and biological evaluation of (±)-Abyssinone II for chemoprevention of breast cancer [12]. Another data indicate that compound 4-(1-Propanoyl-2,3-dihydro-1H-indol-5-yl)-isoquinoline can act as aromatase inhibitor using V79 MZh cells expressing human CYP11B1 and CYP11B2 [13]. Besides, a study showed that some 3-deoxy steroids derivatives can inhibit the biological activity of aromatase using an enzymatic model [14]. Another study indicates that 5α-Androst-3-en-17-one exerts anti-aromatase activity in a human placental microsomal model [15]. All these data indicate that several compounds can be used as aromatase inhibitor; however, their interaction with aromatase surface is not clear. Analyzing these data the aim of this study was to evaluate the interaction of nine steroid derivatives with aromatase surface using 3eqm protein, exemestane, formestene as theoretical tools in a Docking Server program.

2. Material and Methods

Some steroid derivatives (Figure 1) were used to evaluate their possible interaction with 3eqm protein the chemical names:

2.1 Chemical names

1 = 17-Iodo-androst-16-ene [16].

5 = 5-oxo-A-nor3,5-secocholestan-3-oic acid [17].

6 = 4-aza-3-oxo-cholest-5-en [17].

9 = Bromo-vinyl aldehyde-steroid [18].

11 = 16-dehydropregnenolone acetate [19].

15 = Acetic acid 17-bromo-16-formyl-10,13-dimethyl-2,3,4,7,8, 9,10,11,12,13,14,15-

dodecahydro-1H-cyclopenta[a]phenanthren-3-yl ester [20]

17 = 17-Chloro-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthrene-16-carbaldehyde [21].

18 = (1S,2S,11S,14S)-7-methoxy-14-methyl-16-azahexacyclo- [12.11.0.0^{2,11}.0^{5,10}.0^{15,24}.0^{17,22}]pentacosa-5(10),6,8,15(24),16,18,20,22-octa-ene. [21].

26 = 2-Bromo-3-hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-cyclopenta[a]phenanthren-17-one [22].

2.2 Protein-Ligand

Theoretical interaction of steroid derivatives with 3eqm (PDB DOI: <https://doi.org/10.2210/pdb3EQM/pdb>) protein surface using Docking Server program [23].

2.3 Thermodynamic parameters

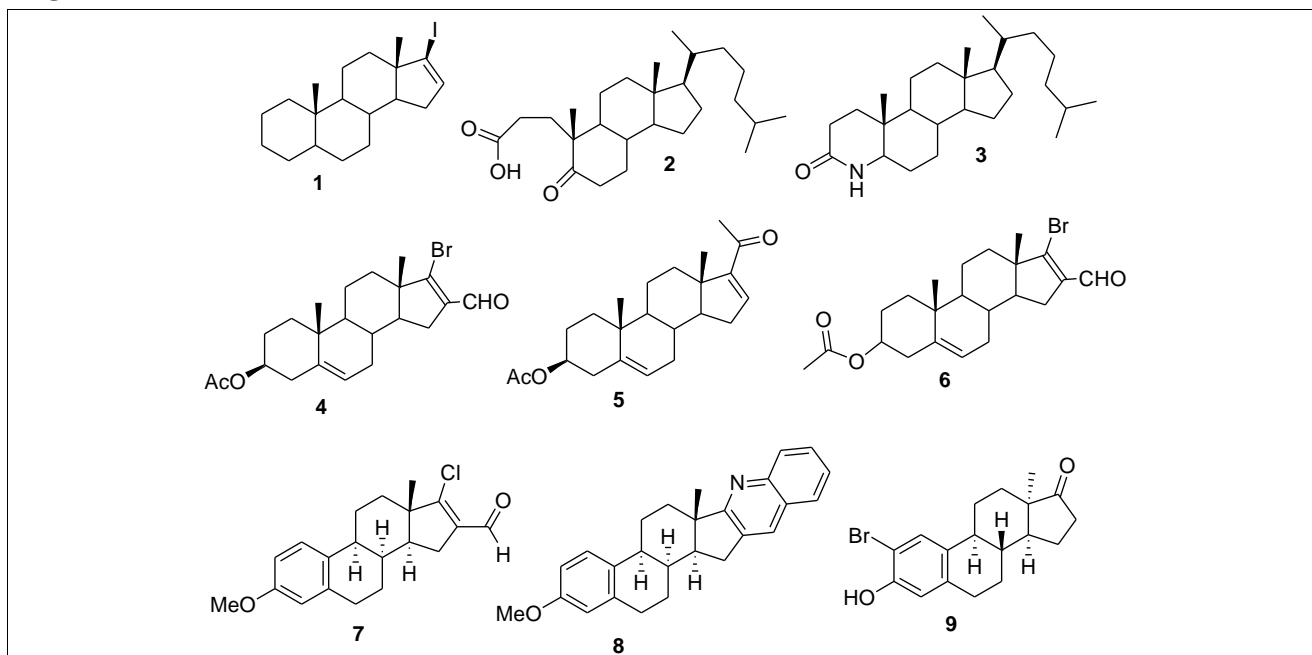
The energy levels were determined using DockingServer program [23].

3. Results and Discussion

In the literature there are reports which indicate that some drugs act as aromatase inhibitors in cancer cells [13-15]; however, their interaction with aromatase surface is not clear. The aim of this research was to evaluate the theoretical interaction of nine steroid derivatives with aromatase enzyme using 3eqm protein surface, exemestane and formestene as theoretical tools in DockingServer program. The results (Table 1 and Figure 2) showed that exemestane and formestene interacts with different amino acid residues involved in the 3eqm protein surface compared with steroid derivatives (1 to 9); this phenomenon suggest that possible interaction is due to different functional groups involved in the chemical structure of each steroid derivatives (Table 1 and Figure 2).

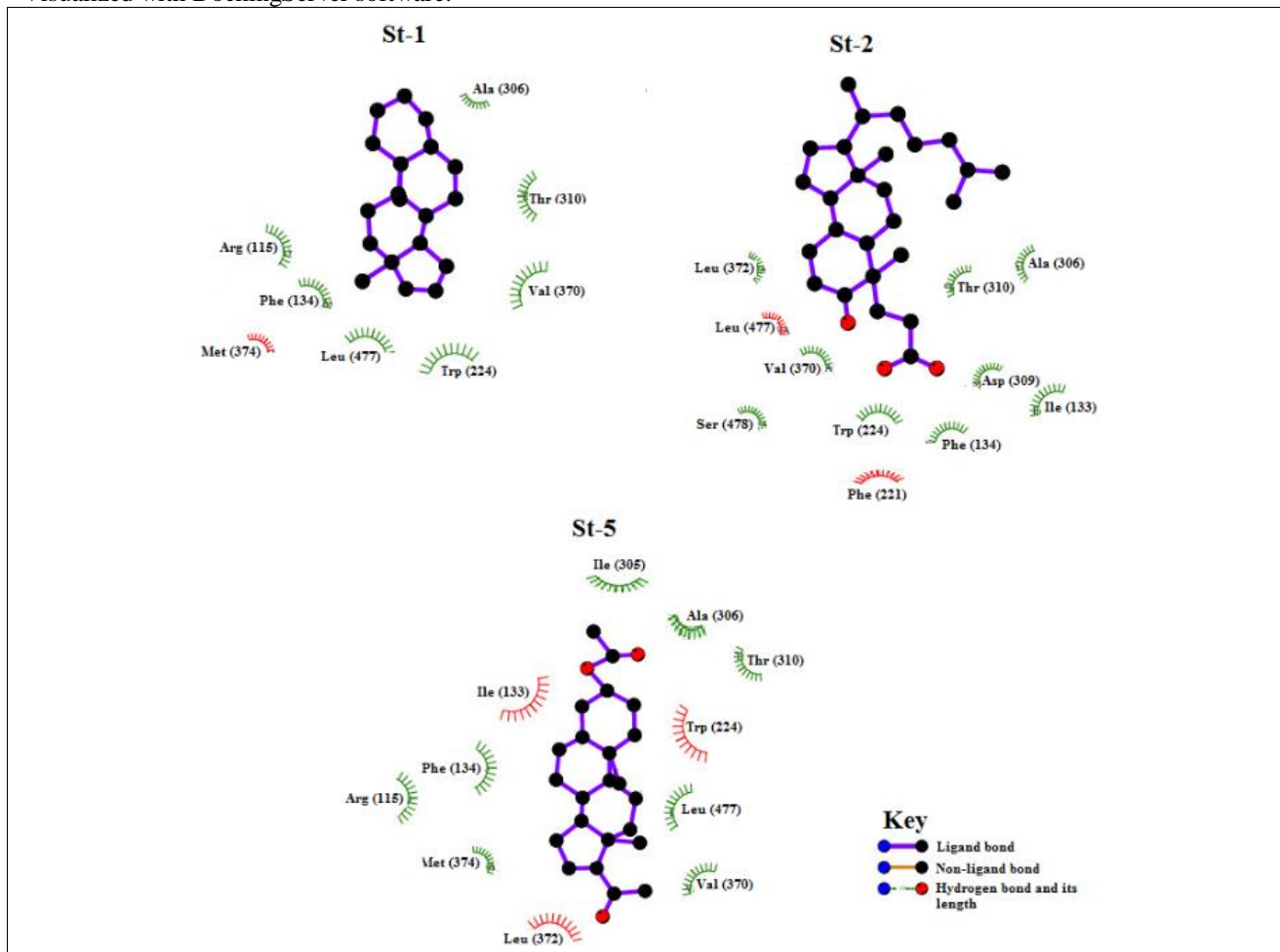


Figure 1. Chemical structure of steroid derivatives.



Source: Authors.

Figure 2. Aminoacid residues involved in the interaction of steroid derivatives (1, 2 and 5) with 3eqm protein surface. Visualized with DockingServer software.



Source: Authors.



Table 1. Theoretical interaction of exemetane, formestene and steroid derivatives (1-9) with 3qem protein surface.

Compound	Amino Acid Residues
Exemetane	Arg ₁₁₅ ; Ile ₁₃₃ ; Phe ₁₃₄ ; Trp ₂₂₄ ; Thr ₃₁₀ ; Val ₃₇₀ ; Leu ₄₇₇
Formestene	Ile ₁₃₃ ; Phe ₁₃₄ ; Trp ₂₂₄ ; Ile ₃₀₅ ; Asp ₃₀₉ ; Thr ₃₁₀ ; Val ₃₇₀ ; Leu ₄₇₇
1	Arg ₁₁₅ ; Phe ₁₃₄ ; Trp ₂₂₄ ; Ala ₃₀₆ ; Thr ₃₁₀ ; Val ₃₇₀ ; Met ₃₇₄ ; Leu ₄₇₇
2	Ile ₁₃₃ ; Phe ₁₃₄ ; Phe ₂₂₁ ; Trp ₂₂₄ ; Asp ₃₀₉ ; Thr ₃₁₀ ; Val ₃₇₀ ; Leu ₃₇₂ ; Leu ₄₇₇ ; Ser ₄₇₈
3	Arg ₁₁₅ ; Ile ₁₃₃ ; Phe ₁₃₄ ; Phe ₁₃₄ ; Phe ₂₂₁ ; Trp ₂₂₄ ; Glu ₃₀₂ ; Ile ₃₀₅ ; Ala ₃₀₆ ; Asp ₃₀₉ ; Thr ₃₁₀ ; Val ₃₇₀ ; Leu ₃₇₂ ; Met ₃₇₄ ; Leu ₄₇₇ ; Ser ₄₇₈
4	Ile ₁₃₃ ; Phe ₁₃₄ ; Trp ₂₂₄ ; Ile ₃₀₅ ; Ala ₃₀₆ ; Thr ₃₁₀ ; Val ₃₇₀ ; Leu ₃₇₂ ; Met ₃₇₄ ; Leu ₄₇₇ ; Ser ₄₇₈
5	Arg ₁₁₅ ; Ile ₁₃₃ ; Phe ₁₃₄ ; Trp ₂₂₄ ; Ile ₃₀₅ ; Ala ₃₀₆ ; Thr ₃₁₀ ; Val ₃₇₀ ; Leu ₃₇₂ ; Met ₃₇₄ ; Leu ₄₇₇
6	Arg ₁₁₅ ; Ile ₁₃₃ ; Phe ₁₃₄ ; Phe ₂₂₁ ; Asp ₃₀₉ ; Thr ₃₁₀ ; Val ₃₆₉ ; Val ₃₇₀ ; Met ₃₇₄ ; Leu ₄₇₇ ; Ser ₄₇₈ ; His ₄₈₀
7	Ile ₁₃₃ ; Phe ₁₃₄ ; Phe ₂₂₁ ; Trp ₂₂₄ ; Ile ₃₀₅ ; Ala ₃₀₆ ; Asp ₃₀₉ ; Thr ₃₁₀ ; Val ₃₇₀ ; Met ₃₇₄ ; Leu ₄₇₇ ; Ser ₄₇₈
8	Ile ₁₃₃ ; Phe ₁₃₄ ; Phe ₁₄₈ ; Trp ₂₂₄ ; Glu ₃₀₂ ; Ile ₃₀₅ ; Ala ₃₀₆ ; Thr ₃₁₀ ; Val ₃₇₀ ; Leu ₃₇₂ ; Met ₃₇₄ ; Leu ₄₇₇
9	Arg ₁₁₅ ; Ile ₁₃₃ ; Trp ₂₂₄ ; Ala ₃₀₆ ; Asp ₃₀₉ ; Thr ₃₁₀ ; Leu ₃₇₂ ; Val ₃₇₃ ; Met ₃₇₄ ; Leu ₄₇₇

Source: Authors.

Table 2. Thermodynamic values for exemetane, formestene and steroid derivatives (1-9)

Comp	A	B	C	D	E	F
Exam	-10.1	33.9	-10.1	-0.0	-10.1	515.6
Form	-10.5	17.7	-10.3	-0.2	-10.5	498.6
1	-12.0	1.5	-11.9	-0.0	-12.0	478.1
2	-3.4	2.8	-7.6	0.2	-7.4	584.7
3	-4.2	757.0	-5.6	0.0	-5.6	664.0
4	-1.6	65.0	-2.2	-0.1	-2.4	578.5
5	-2.65	11.4	-3.4	-0.0	-3.5	586.0
6	-1.48	81.9	-2.4	0.1	.2.3	615.6
7	-9.37	135.2	-9.9	0.0	-9.9	549.8
8	-1.13	147.3	-1.4	0.0	-1.4	622.5
9	-9.45	118.7	-9.5	-0.1	-9.7	484.9

Note: **A** = Est: Free Energy of Binding (kcal/mol); **B** = Inhibition Constant, Ki (mM); **C** = vdW + Hbond + desolv Energy (kcal/mol); **D** = Electrostatic Energy (kcal/mol); **E** = Total Intermolec. Energy (kcal/mol); **F** = Interact. Surface; Exam = exemetene; Form = formostene. **Source:** Authors.

4. Thermodynamic parameters

Several studies have reported some thermodynamic processes involved in the formation of the protein-ligand complex using some methods and programs such as Isothermal titration calorimetry [26], quantum mechanics/molecular mechanics [27] termott [28] and DockingServer [23]. In this way, DockingServer program was used to evaluate some thermodynamic factors involved in the

interaction of exemetane, formestene and steroid derivatives with 3eqm protein surface. The results showed differences in the thermodynamic parameters involved in the interaction of steroid derivatives and exemetane, formestene with a 3eqm protein surface. In addition, the inhibition constant (Ki) for steroid derivatives 1, 2 and 5 was lower compared to exemetane and formestene (Table 2). These results suggest that compounds 1, 2 and 5 could produce changes in the biological



activity of aromatase, which could be translated as a good agent for breast cancer treatment.

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