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Preparation of two steroid derivatives and its theoretical interaction with a 17β-hydroxysteroid dehydrogenase type 1

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ABSTRACT

The aim of this study was synthesizing two steroid derivatives to evaluate their theoretical interact with a 17β-hydroxysteroid dehydrogenase type 1. The first stage was achieved by the preparation of a steroid-imino analog (compound **2**) using a reaction of imination and *ii*) etherification. Then, the theoretical interact of two steroid analogs with 17β-hydroxysteroid dehydrogenase type 1 (1IOL) was evaluated using fisetin and methyl paraben as controls in a docking model. The results suggest that steroid derivatives could interact via a different type of aminoacid residues of 1IOL protein surface. However, the compound **2** showed a constant of inhibition lower compared with fisetin, methyl paraben and compound **3**. All these data indicate that steroid derivative could act as 17β-hydroxysteroid dehydrogenase type 1 inhibitor.

Keywords: *17β-hydroxysteroid hydrogenase, fisetin, paraben, docking.*

1. INTRODUCTION

Cancer has increased in recent years around the world in both women and men; this clinical pathology could be conditioned through of changes in the biological activity of some enzymes such as 17β-hydroxysteroid dehydrogenase (17β-HD) [1-3]. For example, a study showed that increasing levels of estradiol can induce the activation of 17β-HD type 1, which results in a higher risk of breast cancer [4]. Other data indicate that 17β-HD type 7 can induce changes in binding immunoglobulin protein (GRP-78) levels in breast cancer cells (MCF-7) [5]. In addition, a report shown that 17β-HD type 5 modulates the biological activity of both inhibitor binding immunoglobulin and tumor-secreted protein phosphoglycerate kinase 1 on MCF-7 cells [6]. Also, there are some studies which display that 17β-HD Type 2 is correlated with androgen-receptor activation in HEC-1A cells [7]. Other study showed that 17β-hydroxysteroid dehydrogenase Type 1 can stimulate breast cancer through dihydrotestosterone inactivation [8]. Here it is important to mention that in the search of some pharmacological therapy, several 17β-HD type 1 inhibitors have been developed; for example, the preparation of 3-(2-bromoethyl)-16β-(m-carbamoylbenzyl)-17β-hydroxy-1,3,5(10)-estratriene as 17β-HD type 1 inhibitor for breast cancer and endometriosis [9]. Other data showed the Pd-Catalyzed microwave-assisted synthesis of phosphonated 13α-estrones as a potential 17β-HSD type 1 inhibitor [10]. In addition, a study showed the addition of chlorine, bromine or iodine onto positions 2 and/or 4 of 17-deoxy-13α-estrone as potent 17β-HSD type 1 inhibitors using human placenta [11]. Other study showed the preparation of (3α,5α,17α)-3-Hydroxy-3-{[4-(3-methoxybenzyl)piperazin-1-yl]methyl}-andros-Androstan-17-ol from dihydrotestosterone as 17β-HSD type 10 inhibitor using an *in vitro* model [12]. All these data suggest that some drugs can be used as 17β-HSD type 1 inhibitors; however, the interaction of some drugs with an enzyme is very confusing, perhaps this phenomenon could be due to; 1) differences in the chemical structure of each drug; or 2) to different methods used in each experiment. Therefore, the aim of this study was to synthesize two steroid derivatives to evaluate its theoretical interaction with 17β-HSD type 1 using a docking model.

2. MATERIALS AND METHODS

General methods.

The estradiol-ethylenediamine derivative was prepared using a previous method reported [13]. In addition, all the reagents used in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were determined using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a Varian VXR300/5 FT NMR spectrometer at 300 and 75.4 MHz (megahertz) in $CDCl_3$ (deuterated chloroform) using TMS (tetramethylsilane) as an internal standard. EIMS (electron impact mass spectroscopy) spectra were determined using a Finnigan

Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were determined from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

Chemical Synthesis.

Preparation of 7-hydroxy-6-{[(2-{[(2-hydroxynaphthalen-1-yl)methylidene]amino}ethyl) amino]methyl}-11a-methyl-2H,3H,3aH,3bH,4H,5H,9bH,10H,11H-cyclopenta[a]phenanthren-1-one (2)

In a round bottom flask (10 ml), compound **1** (200 mg, 0.58 mmol), 2-hydroxy-1-naphthaldehyde (100 mg, 0.58 mmol), boric acid (50 mg 0.80 mmol) and 5 ml of methanol were stirred to reflux for 12 h. The solution obtained was reduced pressure and purified through a crystallization using the methanol:bencene (4:1) system; yielding 44% of product; m.p. 88-90 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 3360, 3322 and 1712: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.20-2.60 (m, 15H), 3.04 (m, 2H), 3.72 (m, 2H), 3.80 (m, 2H), 6.54 (m, 1H), 6.80 (m, 1H), 6.90 (m, 1H), 7.56 (m, 1H), 7.58 (broad, 3H), 7.66-8.70 (m, 5H) ppm. 13.82, 21.63, 26.02, 27.40, 27.69, 31.72, 35.91, 37.52, 44.53, 46.00, 47.8, 50.62, 50.84, 53.40, 106.32, 112.54, 121.10, 122.73, 123.75, 124.54, 126.27, 127.30, 127.90, 129.12, 131.26, 133.95, 136.52, 136.88, 148.96, 159.80, 163.52, 220.52 ppm. EI-MS m/z: 496.27. Anal. Calcd. for $C_{32}H_{36}N_2O_3$: C, 77.39; H, 7.31; N, 5.64; O, 9.66. Found: C, 77.30; H, 7.24.

Synthesis of 4-[(6-{[(2-{[(2-hydroxynaphthalen-1-yl)methylidene]amino}ethyl)amino]methyl}-11a-methyl-1-oxo-2H,3H,3aH,3bH,4H,5H,9bH,10H,11H-cyclopenta[a] phenanthren-7-yl)oxy] benzonitrile (3)

In a round bottom flask (10 ml), compound **2** (200 mg, 0.40 mmol), potassium carbonate (55 mg, 0.40 mmol) and 10 ml of dimethyl sulfoxide were stirred to reflux for 12 h. The solution obtained was reduced pressure and purified through a crystallization using the methanol:water (4:1) system; yielding 44% of product; m.p. 112-114 ^{o}C; IR (V_{max}, cm^{-1}) 3402, 3360, 3322, 2240 and 1710: 0.90 (s, 3H), 1.20-2.60 (m, 15H), 3.04 (m, 2H), 3.60 (m, 2H), 3.64 (m, 2H), 3.80 (m, 2H), 6.48-6.70 (m, 2H), 6.80 (m, 1H), 6.82 (m, 2H), 7.18 (m, 2H), 7.58-8.44 (m, 5H), 8.70 (d, 1H, J = 1.50 Hz) 8.80 (broad, 2H) ppm. 13.82, 21.62, 23.42, 26.02, 27.41, 27.70, 31.72, 35.92, 37.53, 45.20, 46.00, 47.82, 50.62, 50.82, 53.40, 106.30, 111.92, 117.42, 121.10, 121.80, 122.48, 122.74, 123.26, 123.80, 126.24, 126.34, 127.31, 129.12, 129.30, 129.84, 129.84, 130.86, 133.92, 136.52, 141.40, 152.02, 154.82, 159.80, 163.50, 220.54 ppm. EI-MS m/z: 611.31. Anal. Calcd. for $C_{40}H_{41}N_3O_3$: C, 78.53; H, 6.76; N, 6.87; O, 7.85. Found: C, 78.48; H, 6.70.

Physicochemical properties.

Several electronic parameters such as HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital), molar refractivity, molar volume, polarizability, parachor, index of refraction, surface tension and density were evaluated using ACDLab [15] and SPARTAN´06 program [16].

Pharmacophore evaluation.

The 3D pharmacophore model for the compounds 2, 3 and 4 was determinate using LigandScout 4.08 software [17]

Theoretical evaluation of the interaction between both compounds 2 and 3 with 17β-hydroxysteroid dehydrogenase type 1 (3HB4).

The interaction of compound 4 with 1IOL [18] protein was carried out using the Docking Server software [19]; additionally, two 17β-HD types 1 inhibitors such as fisetin and methyl paraben [20, 21] were used as controls.

3. RESULTS

Some data indicate that several drugs can exert biological activity against the 17β-HD type 1; however, their interaction with this enzyme is very confusing. Therefore, in this investigation, two steroid derivatives were prepared to characterize their interaction with 17β-HD type 1; the first stage was achieved by the synthesis of two steroid derivatives as follows:

Preparation of a steroid-imino-derivative (2.)

There are several reports to synthesis of imino-derivatives using some reagents such as iron or cobalt [22], $ClCH_2COCl/Et_3N$ [23], Iodide [24], $KSCN/Br_2$ [25], HOAc [26] and others. In this study, the estradiol-ethylenediamine reacted with 2-hydroxy-1-naphthaldehyde to form a hydroxynaphthalen-steroid derivative (2).

The ^{1}H NMR spectra for **2** (Figure 1) showed several signals at 0.90 ppm for methyl bound to steroid nucleus; at 1.20-2.60, 6.54 and 6.90 ppm for steroid moiety: at 3.72 ppm for methylene bound to both amino group and ring A of steroid nucleus; at 6.80 and 7.56-8.70 ppm for phenyl groups; at 3.04, 3.80 ppm for methylene groups bound to both amino groups; at 7.58 ppm for both amino and hydroxyl groups. ^{13}C NMR spectra for **2** showed several signals at 13.82 ppm for methyl bound o steroid nucleus; at 21.63-37.52, 46.00-50.62, 112.54, 124.54, 127.90, 131.26, 136.88-148.96 ppm for steroid moiety; at 44.53 ppm for methylene bound to both ring A and amino group; at 50.84-53.40 ppm for methylene groups bound to both amino groups; at 106.32, 121.10-123.75, 126.27-127.30, 129.12, 133.95-136.52 and 159.80 ppm for phenyl groups; at 163.52 ppm for imino group; at 220.52 ppm for ketone group. In addition, compound **2** showed a molecular ion (m/z) at 496.27.

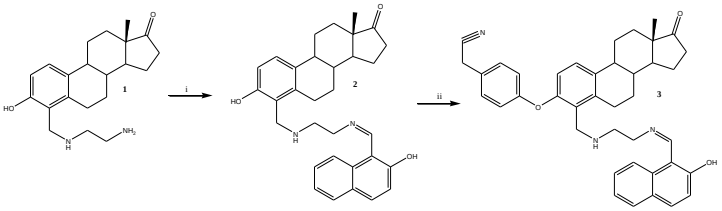

Figure 1. Synthesis of two steroid-derivatives (**2** or **3**). Reaction of estradiol-ethylenediamine (**1**) with 2-hydroxy-1-naphthaldehyde to form a hydroxynaphthalen-steroid derivative (**2**). Then, 2 reacted with (4-Nitro-phenyl)-acetonitrile to synthesis of *a* steroid-naphthalen-methylene-ethylenediamine derivative (**3**).

Preparation of a steroid-naphthalen-methylene-ethylenediamine derivative (3).

Some methods have been reported for preparation of ether derivatives using some reagents such as methoxy groups [27],

fluoride ion [28], nitroparaffin [29], sodium phenoxide [30], nitrobenzamide in DMSO [31] and others. In this regard, compound **2** was reacted with (4-Nitro-phenyl)-acetonitrile (Figure 1) to form an ether-steroid derivative (**3**) using previously reports for preparation of ether groups [32]. The ^{1}H NMR spectra for **3** showed several signals at 0.90 ppm for methyl bound to steroid nucleus; at 1.20-2.60 and 6.48-6.70 ppm for steroid moiety: at 3.04, 3.80 ppm for methylene groups bound to both amino groups; at 3.60 ppm for methylene bound to both amino group and ring A of steroid nucleus; at 3.64 ppm for methylene bound to both phenyl and alkyne groups; at 6.82-8.44 ppm for phenyl groups; at 8.80 ppm for both amino and hydroxyl groups. ^{13}C NMR spectra for **3** showed several signals at 13.82 ppm for methyl bound o steroid nucleus; at 21.62, 26.02-37.53, 46.00-50.62, 111.92, 126.34, 129.30-130.86 and 141.40-151.02 ppm for steroid moiety; at 23.42 ppm for methylene bound to both phenyl and alkyne groups; at 45.20 for methylene bound to both ring A and amino group; at 50.82-53.40 ppm for methylene groups bound to both amino groups; at 106.30, 121.10-126.64, 127.31-129.12, 133.92-136.52 and 154.82-159.80 ppm for phenyl groups; at 117.40 ppm for nitrile; at 163.50 ppm for imino group; at 220.54 ppm for ketone group. Finally, the compound **3** showed a molecular ion (m/z) at 611.31.

Electronic parameters relationship to compounds 2 and 3.

Molecular orbitals HOMO and LUMO for 2 and 3 were evaluated using SPARTAN´06 program, with Hartee-Fock metod at 321-G level [16]. The results showed that both HOMO an LUMO were higher for compound **3** compared with **2** (Figure 2).

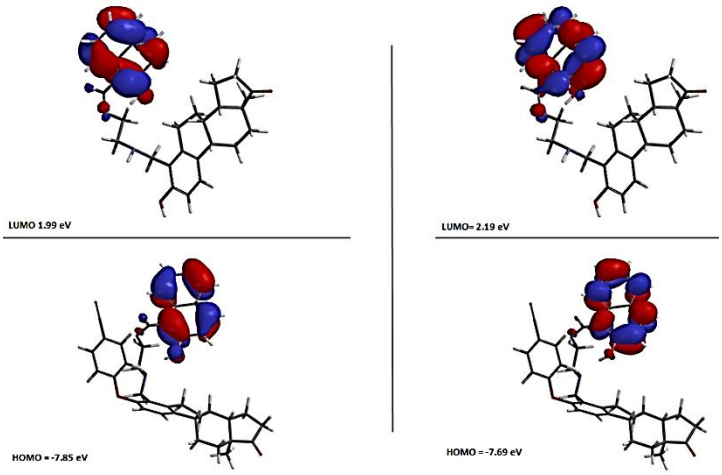

Figure 2. In the scheme are showed both HOMO and LUMO for compounds 2 (left) and 3 (right). Visualized with SPARTAN´06 program.

Table 1. Physicochemical parameters of compounds **2, 3** and **4**. The values were calculated using both ACDLabs and Spartan softwars.

Parameter	Compound 2	Compound 3
Molar Refractivity (cm^3)	143.70	175.91
Molar Volume (cm^3)	381.70	47.30
Polarizability (cm^3)	56.98	69.73
Parachor (cm^3)	1024.90	1261.10
Index of refraction	1.67	1.66
Surface Tension (dyne/cm)	51.90	51.20
Density g/cm^3	1.30	1.26

In addition, other physicochemical parameters showed in the table 1 were evaluated the results indicate that molar refractivity and molar volume were higher for compound 3 compared with 2. These data suggest that steric hindrance, conformational preferences and internal rotation of 3 could influence the interaction with some biomolecules.

Pharmacophore Modeling.

There are some studies that indicate that the pharmacophore is the three-dimensional orientation adopted by the functional groups of a molecule to be able to interact with some proteins [33].

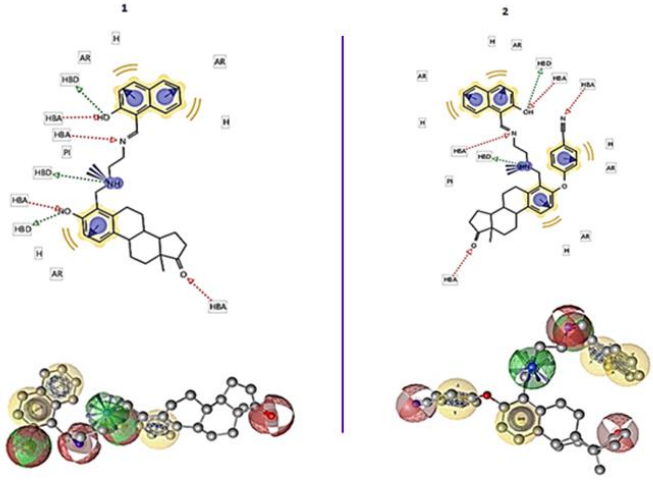

Figure 3. Scheme represents a pharmacophore from both compounds **2** and **3** using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, green).

This pharmacophore model can furnish a new insight to design novel molecules that can enhance or inhibit the function of the target and will be useful in drug discovery strategies. Therefore, in this study, LigandScout software [17] was used to develop a pharmacophore model of compounds **2** and **3**. The results showed in Figure 3 indicated that there is a different type of functional groups involved in the compounds **2** and **3** that can interact via hydrophobic contacts or as hydrogen bond acceptors or as hydrogen bond donor with some biomolecules .

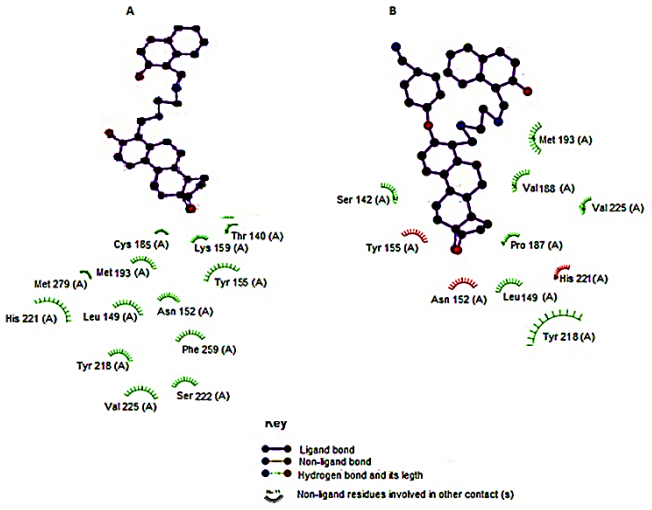

Figure 3. Theoretical analysis showed the binding sites for compounds 2 (A) and 3 (B) with some amino acid residues involved in 17β-HD type 1 (1IOL). The visualization was carried out using the DockingServer software.

Interaction of both compounds 2 and 3 with 17β-HD type 1 (1IOL).

There are reports to evaluate the interaction of several drugs with some biomolecules using theoretical models [34-37]. In this study the interaction of both compounds 2 and 3 with 1IOL enzyme [18] was evaluated using the fisetin and methyl paraben as controls in a Docking model [19]. The theoretical data (Table 2) showed that compound **2** interact with different type of amino acid residues involved in 1IOL surface compared with compound **3,** fisetin and methyl paraben. This phenomenon could involve other type intramolecular interactions due to changes in the energy levels.

Table 2. Aminoacid residues involved in the interaction of fisestin and compounds **2** and **3** with 17β-HD type 1 (3HB4).

----------Compounds----------			
Methyl Paraben	**Fisetin**	**2**	**3**
Leu_{96}	Ser_{142}	Thr_{140}	Ser_{142}
Tyr_{218}	Leu_{149}	Leu_{149}	Leu_{149}
His_{221}	Asn_{152}	Asn_{152}	Asn_{152}
Ser_{222}	Cys_{185}	Tyr_{155}	Tyr_{155}
Val_{225}	Pro_{187}	Lys_{159}	Pro_{187}
Phe_{226}	Val_{188}	Cys_{185}	Val_{188}
Met_{279}	Thr_{190}	Met_{193}	Met_{193}
Glu_{282}	Met_{193}	Tyr_{218}	Tyr_{218}
Val_{283}	Tyr_{218}	His_{221}	His_{221}
	Ser_{222}	Ser_{222}	Val_{225}
		Val_{225}	
		Phe_{259}	
		Met_{279}	

Thermodynamic parameters.

Some studies showed that several thermodynamic parameters may be involved in the interaction drug-protein [38]. Analyzing these data, in this study a theoretical ass was carried out to evaluate several thermodynamic factors involved in the interaction of fisetin, methyl paraben and the compounds **2** and **3** with the 1IOL protein such as 1) free energy of binding which determinate the energy value that require a molecule to interact with a protein in a water environment. 2) Electrostatic energy that is the product of electrical charge and electrostatic potential, which are involved in the ligand-protein system; 3) total intermolecular energy and 4) Van der Waals (vdW) + hydrogen bond (Hbond) + desolvation energy (Desolv. Energy; which have an influence on the movement of water molecules into or out of the ligand-protein system) using a theoretical model [19]. Theoretical data (Table 3) indicates that there are differences in the thermodynamic parameters of compound **2** compared with fisetin, methyl paraben and compound **3**.

Additionally, the inhibition constant (Ki) for compound **2** was lower than Ki for fisetin, methyl paraben and compound **3** (Table 3). This phenomenon suggests that these differences could be translated as a higher inhibition of biological activity of 17β-hydroxysteroid dehydrogenase type 1 **(**1IOL**)** in the presence of compound **2** in comparison with fisetin, methyl paraben and compound **3**.

Table 3. Termodynamic parameters involved in the interaction of fisetin and compounds **2** and **3** with 17β-HD type 1 (3HB4).

Compound	Est. Free Energy of Binding (Kcal/mol)	Est. Inhibition Constant, Ki (μM)	VdW + Hbond +desol Energy (Kcal/mol)	Electrostatic Energy (Kcal/mol)	Total intermolec. Energy (Kcal/mol)	Interact. Surface
Methyl Paraben	-3.55	2.50	-4.25	-0.18	-4.43	461.65
Fisetin	-5.75	60.51	-6.21	-0.10	-6.32	678.67
2	-7.96	1.45	-10.08	-0.19	-10.27	1159.68
3	-9.43	122.14	-11.03	-0.00	-11.03	1255.97

4. CONCLUSIONS

In this study, a facile synthesis of two steroid-derivatives is reported. In addition, theoretical interact suggest that of compound **2** could act as 17β-hydroxysteroid dehydrogenase type 1 inhibitor; this phenomenon could be translated as a good candidate for the treatment of cancer.

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6. ACKNOWLEDGEMENTS

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