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Preparation of five estrone analogs and theoretical analysis of its interaction with aromatase enzyme

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ABSTRACT

Several aromatase inhibitors have been prepared for treatment of breast cancer; nevertheless, their interaction with enzyme surface is not very clear. Therefore, the objective of this investigation was to synthesize and analyze the theoretical activity of five estrone derivatives (compounds **2**-**7**) on aromatase (4kq8 protein) in a theoretical method using some aromatase antagonist (anastrozole, letrozole and exemestane) as controls. The data found showed that both anastrozole and compound **6** could interact with same aminoacid residues such as Ile_{133}, Phe_{134}, Phe_{221}, Ala_{306}, Asp_{309}, Thr_{310}, Val_{310}, Val_{373}, Met_{374}, Leu_{477} and Ser_{478} that are involved in the 4kq8 protein surface. It is noteworthy that several of these aminoacid residues may be involved in the interaction between 4kq8 protein with compounds **2**-**5** and **7**, these differences could induce significantly changes in the biological activity of aromatase through of interaction with **6** compared with the compounds **2**-**5** and **7**. These results indicate that compound **6** could be a good candidate as an aromatase inhibitor which translates as a possible drug for breast cancer.

Keywords: *Estrone derivatives, breast cancer, aromatase, docking.*

1. INTRODUCTION

Cancer breast is main cause of death in female the worldwide, which could be conditioned by several clinical parameters such as genetic, lifestyle, radiation, weigh, alcohol and others [1]. In addition, some reports have been shown that estrogen levels may predispose to develop breast cancer in women [2-4]; it is noteworthy, that some medicaments are used to breast cancer such as estrogen-receptor inhibitors (tamoxifen and fulvestrant) [5, 6] or aromatase inhibitors (anastrozole, letrozol and exametane) [7]; nevertheless, several drugs can produce some adverse effects [8, 9]. Therefore, a series of drugs have prepared for treatment of breast cancer; for example, the synthesis of piperidine-2,6-dione derivative by the reaction of a phenylpiperidine-2,6-dione analog with sulfuric acid/nitric acid with biological activity against aromatase enzyme [10]. Other report showed the preparation of some aromatase inhibitors (imidazol-1-yl derivatives) from bromomethyl and imidazole using an *in vitro* model [11]. In addition, a steroid derivative (DTXSID70473247) was prepared from androstenedione via Clemmenson reaction and their biological activity on aromatase was evaluated using placental microsomes [12]. Also, a study shown the preparation of pyridyl-tetralones derivatives through an aldol condensation of 1-tetralones with 4-pyridinecarboxaldehyde as human placental aromatase inhibitors [13]. Other report indicates the preparation and analyze of pharmacological activity of some imidazolyl-coumarins analogs as human placental aromatase inhibitors [14]. These reports suggest that some drugs can block the biological effect of aromatase; nevertheless, their interaction with enzyme surface is very confusing. Therefore, the aim of this study was carried out the synthesis of several estrone derivatives to evaluate their interaction with the aromatase protein (4kq8) using a docking model.

2. EXPERIMENTAL SECTION

Chemical synthesis.

Both 2-nitroestrone and estrone-indole were prepared using previously methods reported [15, 16]. Additionally, other reagents involved in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point of compounds was assessed using an Electrothermal (900 model). Infrared spectrum (IR) was evaluated using potassium bromide with a Perkin Elmer Lambda 40 apparatus. ^{1}H and ^{13}C NMR spectrum was analyzed on a Varian VXR300/5 FT NMR apparatus at 300 and 75.4 MHz (megahertz) in $CDCl_3$ (deuterated chloroform) using TMS as an internal standard. EIMS spectrum was obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis was determined using a Perkin Elmer Ser. II CHNS/02400 apparatus.

Preparation of 2-ntro-steroid*-indol-4-ol *derivative

Method A:

In a round bottom flask (10 ml), 2-nitroestrone (200 mg, 0.63 mmol), phenylhydrazine hydrochloride (100 mg; 0.69 mmol), and 8 ml of acetic acid:ethanol (3:5) were stirring to reflux for 4 h. The solvent of the mixture obtained was removed under reduced pressure and purified through a crystallization using the methanol:water (4:1) system.

(8aS)-8a-methyl-5-nitro-1,2,6b,7,8,8a,9,14,14a,14b-decahydro-naphtho[2',1':4,5]indeno[1,2-b]indol-4-ol (3)

yielding 54 % of **3**; m.p. 118-120 ^{o}C; IR (V_{max}, cm^{-1}) 3430, 3400, and 1380: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.30-1.54 (m, 9H), 1.60 (s, 3H), 1.66-2.86 (m, 9H), 3.10-3.14 (m, 2H), 6.66 (m, 1H), 7.08-7.42 (m, 4H), 7.86 (m, 1H), 9.00 (broad, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 19.22, 26.74, 27.56, 29.82, 31.12, 35.32, 35.34, 36.78, 44.98, 48.94, 110.82, 114.02, 114.70, 118.22, 119.00, 120.96, 123.58, 125.62, 132.30, 134.32, 134.85, 145.12, 148.48, 153.30 ppm. EI-MS m/z: 388.17 Anal. Calcd. for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21; O, 12.36. Found: C, 74.16; H, 6.18.

Method B:

In a round bottom flask (10 ml), indol-estrone (200 mg, 0.51 mmol), anhydride acetic (1ml) and nitric acid (1 ml), were stirring to room temperature for 12 h. crystallization using the methanol:hexane:water (4:2:1) system to give a nitro-steroid-indol derivative (44% yield); ^{1}H NMR and 13C NMR spectra were determined and were compared with method A product..

Preparation of N-((2-hydroxynaphthalen-1-yl)((2-(((8aS)-8a-methyl-5-nitro-1,2,6b,7,8,8a,9,14,14a,14b-decahydronaphtho [2',1':4,5]indeno[1,2-b]indol-4-yl)amino)ethyl)amino)methyl) acetamide (4).

In a round bottom flask (10 ml), compound **3** (0.50 mmol), 2-hydroxy-1-naphthaldehyde (90 mg, 0.52 mmol), ethylenediamine (60 mg, 0.75 mmol) and 4 ml of acetonitrile:ethanol (3:1) were stirred to reflux temperature for 48 h. The solvent of the mixture obtained was removed under reduced pressure and purified through a crystallization using the methanol:water (4:1) system.

yielding 54 % of **4**, m.p. 76-78 ^{o}C; IR (V_{max}, cm^{-1}) 3432, 3398, 1648 and 1380: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.30-1.54 (m, 2H), 1.60 (s, 3H), 1.66-1.86 (m, 2H), 1.98 (s, 3H), 2.00-2.06 (m, 4H), 2.50-2.56 (m, 2H), 2.86-3.14 (m, 5H), 3.52 (m, 2H), 6.52 (m, 1H), 6.80 (m, 1H), 7.08-7.22 (m, 2H), 7.24 (m, 1H), 7.26 (m, 1H), 7.32 (m, 1H), 7.42 (m, 1H), 7.58-7.80 (m, 4H), 7.88 (broad, 5H), 8.22 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 23.56, 24.40, 26.74, 27.56, 28.94, 31.13, 35.31, 36.42, 36.78, 45.00, 47.10, 47.32, 48.70, 60.68, 111.64, 113.16, 114.60, 117.50, 117.54, 118.60, 119.30, 119.78, 124.15, 124.24, 125.10, 128.60, 126.88, 128.94, 129.34, 131.44, 136.38, 140.02, 140.75, 140.96, 147.36, 151.02, 152.44, 170.12 ppm. EI-MS m/z: 643.31 Anal. Calcd. for $C_{39}H_{41}N_5O_4$: C, 72.76; H, 6.42; N, 10.88; O, 9.94. Found: C, 72.68; H, 6.36.

N-{37-methyl-4-oxa-16,19,35-triazanonacyclo[20.18.0.$0^{3,20}$.$0^{5,14}$.$0^{8,13}$.$0^{25,40}$.$0^{26,37}$.$0^{28,36}$.0^{29}…1(22),2,5(14),6,8(13),9,11,20,28(36), 29(34),30,32-dodecaen-15-yl}acetamide (5)

In a round bottom flask (10 ml), compound **4** (0.50 mmol), potassium carbonate (50 mg, 0.36 mmol) and 4 ml of dimethyl sulfoxide were stirred to reflux temperature for 48 h. The solvent of the mixture obtained was removed under reduced pressure and purified through a crystallization using the methanol:hexane:water (4:1:1) system.

yielding 66 % of **5**, m.p. 60-62 ^{o}C; IR (V_{max}, cm^{-1}) 3430, 1650 and 1112: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.30-1.54 (m, 2H), 1.60 (s, 3H), 1.66-1.86 (m, 2H), 1.96 (s, 3H), 2.00-2.86 (m, 6H), 3.06 (m, 2H), 3.08-3.12 (m, 3H), 3.60 (m, 2H), 4.40 (m, 1H), 6.30-6.36 (m, 2H), 6.96 (m, 1H), 7.00 (broad, 4H), 7.08-7.26 (m, 3H), 7.34 (m, 1H), 7.44 (m, 1H), 7.66-8.06 (m, 4H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C:23.56, 24.40, 26.74, 27.56, 28.94, 31.13, 35.31, 36.42, 36.78, 44.90, 45.40, 47.32, 48.18, 70.14, 107.63, 111.64, 117.51, 118.60, 119.00, 119.28, 119.78, 121.44, 123.36, 123.73, 124.35, 125.10, 125.78, 128.18, 129.12, 129.22, 129.38, 129.88, 130.14, 137.68, 140.72, 140.75, 147.26, 152.42, 170.12 ppm. EI-MS m/z: 596.31 Anal. Calcd. for $C_{39}H_{40}N_4O_2$: C, 78.49; H, 6.76; N, 9.39; O, 5.36. Found: C, 78.00; H, 6.70.

6-(N-{37-methyl-4-oxa-16,19,35-triazanonacyclo[20.18.0.$0^{3,20}$.$0^{5,14}$.$0^{8,13}$.$0^{25,40}$.$0^{26,37}$.$0^{28,36}$.0^{29}…1(22),2,5(14),6,8(13),9,11,20, 28(36),29(34),30,32-dodecaen-15-yl}acetamido)hex-5-ynoic acid (6)

In a round bottom flask (10 ml), compound **5** (0.50 mmol), 5-hexynoic acid (61 µl, 0.54 mmol), Copper(II) chloride anhydrous (70 mg, 0.52 mmol) in 5 ml of methanol were stirred to room temperature for 48 h. The solvent of the mixture obtained was removed under reduced pressure and purified through a crystallization using the methanol:bencene:water (4:1:1) system.

yielding 45 % of **6**, m.p. 128.130 ^{o}C; IR (V_{max}, cm^{-1}) 3432, 1702, 1650 and 1112: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.30-1.54 (s, 3H), 1.58 (s, 3H), 1.66-1.86 (m, 2H), 1.88 (m, 2H), 2.00-2.06 (m, 4H), 2.22 (s, 3H), 2.32 (m, 2H), 2.47 (m, 2H), 2.48 (m,4H), 2.60-3.12 (m, 5H), 3.22-3.70 (m, 4H), 4.40 (m, 1H), 6.32-6.38 (m, 2H), 6.90 (broad, 4H), 694 (m, 1H), 7.08-7.25 (m, 3H), 7.34 (m, 1H), 7.44 (m, 1H), 7.64-8.06 (m, 4H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 15.82, 20.86, 22.04, 24.38, 26.74, 27.56, 28.94, 31.13, 32.60, 35.30, 36.42, 36.78, 43.16, 45.42, 47.32, 47.93, 61.00, 76.74, 87.41, 107.60, 111.64, 117.51, 118.60, 119.00, 119.28, 119.78, 121.22, 123.14, 123.74, 124.32, 125.13, 125.82, 127.13, 129.14, 129.34, 129.60, 130.16, 130.35, 137.68, 140.72, 140.78, 149.42, 152.42, 170.10, 178.40 ppm. EI-MS m/z: 706.35 Anal. Calcd. for $C_{45}H_{46}N_4O_4$: C, 76.46; H, 6.56; N, 7.93; O, 9.05. Found: C, 76.40; H, 6.50.

2methyl-1-{37-methyl-4-oxa-16,19,35-triazanonacyclo[20.18.0.$0^{3,20}$.$0^{5,14}$.$0^{8,13}$.$0^{25,40}$.$0^{26,37}$.$0^{28,36}$.0^{29}…1(22),2,5(14),6,8(13),9,11,20, 28(36),29(34),30-32-dodecaen-15-yl}1,3,6-triazacyclododec-2-en-11-yn-7-one (7)

In a round bottom flask (10 ml), compound **6** (0.5 mmol), ethylenediamine (60 mg, 0.75 mmol), boric acid (40 mg, 0.61 mmol) and 4 ml of methanol were stirred to room temperature for 48 h. The solvent of the mixture obtained was removed under reduced pressure and purified through a crystallization using the methanol:water (4:1) system.

yielding 56 % of **7**, m.p. 167-169; IR (V_{max}, cm^{-1}) 3432, 3330, 1650 and 1114: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.30-1.54 (s, 3H), 1.57 (m, 1H), 1.58 (m, 2H), 1.60 (s, 3H), 1.66-1.86 (m, 2H), 1.90 (m, 2H), 1.98 (s, 3H), 2.00-2.06 (m, 4H), 2.08 (m, 2H), 2.60-2.86 (m, 2H), 2.90 (m, 2H), 2.94 (m,1H), 3.08-3.12 (m, 3H), 3.22 (m, 2H), 3.58-3.92 (m, 4H), 5.56 (broad, 3H), 6.30-6.34 (m, 2H), 6.88 (m, 1H), 7.08-7.25 (m, 3H), 7.34 (m, 1H), 7.40 (broad, 1H), 7.44 (m, 1H), 7.82-8.04 (m, 4H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 19.12, 19.90, 24.38, 25.14, 26.77, 27.56, 28.94, 31.13, 35.34, 35.75, 36.42, 36.78, 38.90, 45.20, 45.42, 47.32, 49.50, 57.17, 66.92, 75.78, 81.52, 107.60, 111.60, 117.51, 118.62, 119.00, 119.28, 119.78, 122.00, 123.92, 124.35, 124.50, 125.10, 126.54, 127.55, 128.00, 128.62, 129.40, 129.88, 130.14, 137.68, 140.72, 141.46, 148.22, 150.90, 152.42, 167.60 ppm. EI-MS m/z: 730.39 Anal. Calcd. for $C_{47}H_{50}N_6O_2$: C, 77.23; H, 6.89; N, 11.50; O, 4.38. Found: C, 77.18; H, 6.80.

Electronic parameters evaluation (HOMO and LUMO).

The molecular orbitals HOMO and LUMO for all compounds were theoretically evaluated with SPARTAN'06 software package (Wavefunc-tion Inc. Irvine, CA, 2000), using Hartree-fock method at 321-G level [17].

Theoretical evaluation of the interaction between compounds 3 or 7 with aromatase.

Theoretical analysis of interaction of compounds 2-7 on aromatase protein (4kq8) was carried out using a docking program (DockingServer) [18]. In addition, anastrazol, letrozole, exametane were used as controls.

3. RESULTS SECTION

Several compounds have prepared as aromatase inhibitors [10-14]; nevertheless, their interaction with enzyme surface is very confusing; therefore, several studies are needed to evaluate this phenomenon. The objective of this study was to synthesize and evaluate their interaction with the aromatase enzyme using a docking model. [18].

First stage

Synthesis of a steroid-indeno-indol-4-ol-acetamide derivative

There are some studies which showed the preparation of several indole analogs using some reagents such as rhodium [19], palladium [20], phosphine [21], Cu(II) [22], Cobalt(III) [23] and others; However, the handling of some of these reagents requires special conditions and they are also very expensive. In this study, a steroid-indeno-indol-4-ol (**3**) derivative was prepared (Figure 1) by the reaction of 2-nitroestrone with phenylhydrazine in acid medium (Method A) or via nitration of compound **2** (steroid-indole derivative) with nitric acid/anhydride acetic to form **3**. It is noteworthy that Method A showed a higher yield compared with Method B. ^{1}H NMR spectra for **3** shown some bands at 0.64 ppm for methyl group which bound to steroid nucleus; at 1.60 ppm for methyl group; at 1.30-1.54, 1.66-6.66 and 7.85 ppm for steroid nucleus; at 7.09-7.43 ppm for indol ring; at 8.96 for hydroxyl group. ^{13}C NMR spectrum for **3** showed some signals at 19.26 ppm for methyl group; at 26.77-48.98, 114.05, 123.56, 132.33-134.33 and 145.09-148.48 ppm for steroid nucleus; at 110.84, 114.72-120.96, 125.60, 134.85 and 153.34 ppm for indol ring. Finally, the mass spectrum from **3** showed a molecular ion (m/z) at 388.17.

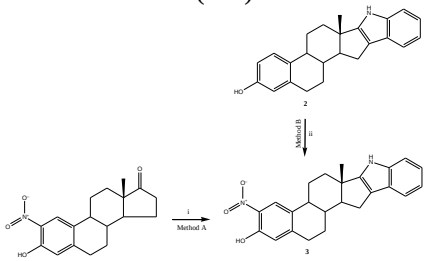

Figure 1. Preparation of a 5-nitro-indol-steroid-acetamide derivative (**3**). Reaction of 2-nitroestrone (**1**) with phenylhydrazine (Method A) to form **3**; also **3** was prepared (Method B) from an indol-estrone derivative (**2**). i = acetic acid; ii = nitric acid/anhydride acetic; iii = ethanol/rt

Synthesis of naphthalen-nitro-steroid-indol-acetamide complex (4)

There are some studies which indicate the preparation of several acetamide analogs using some reagents such as triazole derived [24], proline [25], 4-(4-morpholinyl)benzenamine [26], hydroxy-benzotriazole [27]. However, in this investigation the compound **4** was prepared (Figure 2 and 3) using the multi-component system (compound **3**, acetonitrile, 2-Hydroxy-naphthalene-1-carbaldehyde and ethylene- diamine), it should be noted that no special reagent was required for the preparation of **4**. The results of ^{1}H NMR spectrum of **4** shown some bands at 1.30-1.54, 1.66-1.86, 2.00-2.06, 2.85-3.14, 6.52 and 8.22 ppm for steroid moiety; at 1.60 ppm for methyl group bound to steroid nucleus; at 1.98 ppm for methyl bound to amide group; at 2.04, 2.50-2.57 and 3.54 ppm for methylene groups bound to both amino groups; at 6.80 ppm for amide group; at 7.08-7.22, 7.28 and 7.42 ppm for indol ring; at 7.24, 7.32 and 7.58-7.80 ppm for naphthalene group; at 7.88 ppm for both hydroxyl and amino groups. The ^{13}C NMR spectra showed chemical shifts at 23.56 ppm for methyl group bound to amide; at 24.38 ppm for methyl group bound to steroid nucleus; at 26.74-45.00, 47.32, 114.60, 124.24, 131.44-140.02 and 147.36 ppm to steroid moiety; at 47.10-48.70 ppm for methylene bound to both amino groups; at 60.68 ppm for methylene group bound to both amide and amino groups; at 111.64, 117.50, 118.60-119.78, 125.10, 140.75 and 152.44 ppm for indole ring; at 113.16, 117.54, 124.15, 126.88-129.34, 140.96 and 151.02 ppm for naphthalene group; at 170.12 ppm for amide group. In addition, **4** showed a molecular ion (m/z) at 643.31.

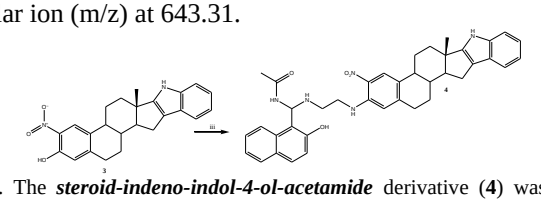

Figure 2. The ***steroid-indeno-indol-4-ol-acetamide*** derivative (**4**) was prepared using the multicomponent system (compound **3**, 2-hydroxy-1-naphthaldehyde, ethylenediamine, acetonitrile). iii = acetonitrile:ethanol.

Preparation of a triazanonacyclo-dodecaen-acetamide derivative via etherification (5)

Several ether derivatives have been synthesized through displacement of nitro groups using some reagents such as methoxy groups [28], fluoride ion [29], nitropropane or nitrocyclohexanone [30], sodium phenoxide [31], nitrobenzamide in DMSO [32]. Therefore, the formation of ether group (compound **5**) was carried out by an internal reaction with dimethyl sulfoxide under mild conditions (Figure 3) using previously reports for preparation of ether groups [33].

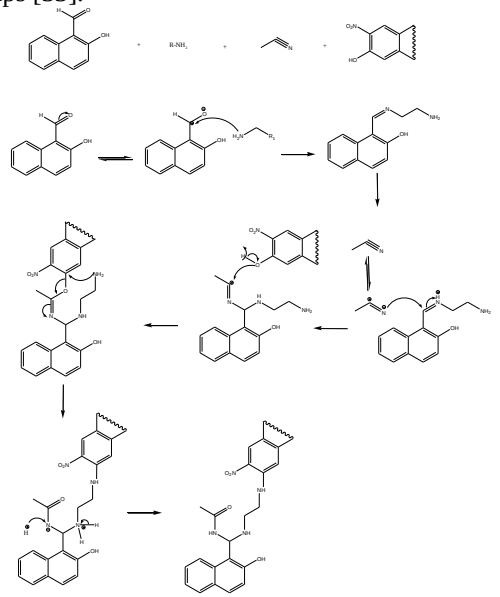

Figure 3. Reaction mechanism for the formation of 5-nitro-indol-steroid-acetamide derivative (compound **4**).

^{1}H NMR spectra for **5** showed several signals at 1.30-1.54, 1.66-1.86, 2.00-2.86, 3.08-3.12 and 6.30-6.36 ppm for steroid moiety; at 1.60 ppm for methyl group bound to steroid nucleus; at 1.96 ppm for methyl bound to amide group; at 3.06, 3.60 and 4.40 ppm for methylene groups bound to both amino groups; at 7.00 ppm for amino and amide groups; at 7.08-7.26 and 7.44 ppm for indole ring; at 6.96, 7.34 and 7.66-8.06 ppm for naphthalene group. ^{13}C NMR spectrum for **5** showed several signals at 23.56 ppm for methyl group bound to amide; at 24.40 ppm for methyl group bound to steroid nucleus; at 26.74-36.78, 45.40-47.32, 107.63, 119.00, 129.38 and 130.14-140.72 ppm for steroid moiety; at 44.90 and 48.18-70.14 ppm for methylene groups bound to both amide and amino groups; at 111.64-118.60, 119.28-119.78, 125.19, 140.75 and 152.42 ppm for indol ring; at 121.44, 124.35, 125.78-129.22, 129.88 and 147.26 ppm for naphthalene group; at 170.12 ppm for amide group. Finally, the mass spectrum from **5** showed a molecular ion (m/z) at 596.31.

Addition of an amide derivative (5) to alkyne group to form 6.

There are some reports on addition of amide to alkyne groups using several reagents such as platinum [34], ruthenium [35], nickel [36], Rhodium/Copper [37] palladium(II) [38] and others. In this study, a triazanonacyclo-acetamido-hex-5-ynoic acid derivative (**6**) was prepared (Figure 3) via reaction of **5** with 5-hexynoic acid in presence of Copper(II). ^{1}H NMR spectra for **6** showed several signals at .130-1.54, 1.66-1.86, 2.00-2.06, 2.60-3.12 and 6.32-6.38 ppm for steroid moiety; at 1.58 ppm for methyl bound to steroid nucleus; at 2.22 for methyl bound to amide group; at 1.88 and 2.32-2.47 ppm for methylene groups bound to both carboxyl and alkyne groups; at 3.22-4.40 ppm for methylene groups bound to both amino and amide groups; at 6.90 ppm for both amino and carboxyl groups; at 6.94, 7.34 and 7.64-8.06 for naphthalene ring; at 7.08-7.25 and 7.44 ppm for indole ring. ^{13}C NMR spectra for **6** showed several signals at 15.82-20.86 and 32.60 ppm for methylene groups bound to both alkyne and carboxyl groups; at 24.38 ppm for methyl group bound to amide group; at 22.04 ppm for methyl group bound to steroid nucleus; at 26.74-31.13, 35.30-36-78, 45.42-47.32, 107.60, 119.00, 129.34, 130.16 and 137.68-140.72 ppm for steroid moiety; at 43.26, 47.93 and 76.74 ppm for methylene groups bound to both amide and amino groups; at 61.00 and 87.41 ppm for alkyne group; at 111.64-118.60, 119.28-119.78, 125.13, 140.78 and 150.42 ppm for indole ring; at 121.22-124.32, 125.82-129.14, 129.60 and 130.35-149.42 ppm for naphthalene group; at 170.10 ppm for amide group; at 178.40 ppm for carboxyl group. In addition, **6** showed a molecular ion (m/z) at 706.35.

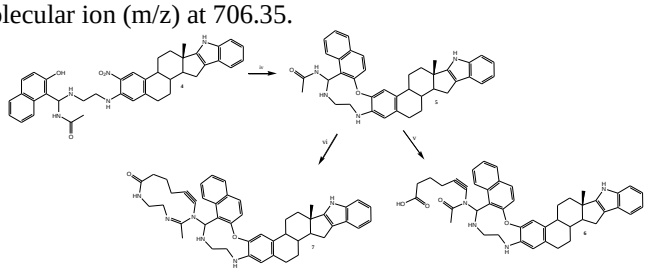

Figure 3. Steroid-triazanonacyclo-7-one (7). Reaction of a (5-nitro-indol-steroid-acetamide derivative (4) with dimethylsulfoxide (iv) to form a steroid-triazanonacyclo-acetamide (5). Then 5 was reacted with 5-hexynoic acid (v) to formation of the steroid-triazanonacyclo-dodecaen-15-yl}acetamido)hex-5-ynoic acid complex (6). Finally, 6 was reacted with ethylenediamine in presence boric acid (vi).

Preparation of a triazacyclododec-2-en-11-yn-7-one derivative

Several triazacyclododecen analogs have been synthesized using some reagents such as Copper(II) [39], Nickel [40], Iron(III) [41], *n*-butyllithium [42]. In this investigation, **6** reacted with ethylenediamine using boric acid as catalyst (Figure 3) to form the triazacyclododec-2-en-11-yn-7-one (**7**). It is important to mention that the use of this reagent does not require special conditions. [43]. ^{1}H NMR spectra for **7** display some signals at 1.30-1.54, 1.66-1.86, 2.00-2.06, 2.60-2.86, 3.08-3.12 and 6.30-6.34 ppm for steroid moiety; at 1.60 ppm for methyl bound to steroid nucleus; at 1.98 ppm for methyl bound to amide group; at 1.58, 1.90, 2.08 and 3.58-3.92 ppm for methylene groups involved in 1,3,6-triaza-cyclododec-2-en-11-yn-7-one system; at 2.90-2.94 and 3.22 ppm for methylene groups bound to both amino groups; at 5.56 ppm for amino groups; at 7.08-7.25 and 7.44 ppm for indol ring; at 6.88, 7.34 and 7.82-8.04 ppm for naphthalene ring. ^{13}C NMR spectrum showed several signals for **7** at 19.12, 25.14, 35.75, 38.90, 45.42-47.32 and 57.17 and 75.788 ppm for methylene groups involved in 1,3,6-triaza-cyclododec-2-en-11-yn-7-one system; at 19.90 ppm for methyl bound to imino group; at 24.38 ppm for methyl bound to steroid nucleus; at 26.77-25.34, 36.42-36.78, 107.60, 119.00, 129.40, 130.14-137.68 and 141.46 ppm for steroid moiety; at 45.20-49.50 and 75.78 ppm for methylene groups bound to both amino groups; at 69.92 and 81.52 ppm for alkyne group; at 111.60-118.62, 119.28-119.78, 125.10, 140.72 and 152.42 ppm for indol ring; at 122.00-124.50, 126.54-128.62 and 148.22 ppm for naphthalene ring; at 150.90 ppm for imino group; at 167.60 ppm for amide group. Additionally, the mass spectrum from **7** display a molecular ion (m/z) at 730.39.

Second stage

Physicochemical parameters of compounds 3-7.

It is noteworthy that some physicochemical factors, such as logP and π have be used to evaluate the degree of lipophilicity of a molecule [44, 45]. It is important to mention, these parameters were determined for compounds **2-7**. The results (Table 1 and 2) indicate that logKow and π were higher for compound **7** compared to **2-6**, which translates to more lipophilicity degree (Table 1). However, it is noteworthy that this phenomenon could be conditioned by other parameters chemical such as molar volume (V_m) and refractivity molar (R_m) which have been relationship with biological activity of some drugs [48]; these physicochemical factors are tools which can used to identify different chemical characteristics that depend of substituents of a specific molecule.To evaluate both V_m and R_m descriptors for compounds **2-7** a previously method reported was used [49]; the results showed that V_m and R_m were higher for both **6** and **7** compared with the compounds **2-5** (Table 3). These data suggest that the steric hindrance and the different conformations involved in compounds **6** or **7** could be determining factors in the biological activity exerted by these steroid derivatives in some biological model.

Table 1. Physicochemical parameters involved in the chemical structure of compounds **2-4**.

2	$-CH_3$ [aliphatic carbon]	0.5473
	$-CH_2-$ [aliphatic carbon]	2.4555
	-CH [aliphatic carbon]	1.0842
	Aromatic Carbon	4.1160
	-OH [hydroxy, aromatic attach]	**-0.4802**
	Aromatic Nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.2676
	Fused aliphatic ring unit correction	-1.3684
	Equation Constant	0.2290
	π	2.8948
	Log Kow	6.3248
3	$-CH_3$ [aliphatic carbon]	0.5473
	-CH2- [aliphatic carbon]	2.4555
	-CH [aliphatic carbon]	1.0842
	Aromatic Carbon	4.1160
	-OH [hydroxy, aromatic attach]	-0.4802
	$-NO_2$ [nitro, aromatic attach]	-0.1823
	Aromatic Nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.2676
	Ring reaction -> -NO2 with -OH/amino/azo	0.5777
	Fused aliphatic ring unit correction	-1.3684
	Equation Constant	0.2290
	π	0.3954
	Log Kow	6.7202
4	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	3.4377
	-CH [aliphatic carbon]	1.4456
	-NH- [aliphatic attach]	-2.9924
	Aromatic Carbon	7.0560
	-OH [hydroxy, aromatic attach]	-0.4802
	-N [aliphatic N, one aromatic attach]	-0.9170
	$-NO_2$ [nitro, aromatic attach]	-0.1823
	-C(=O)N [aliphatic attach]	-0.5236
	Aromatic Nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.2676
	Ring reaction -> -NO2 with -OH/amino/azo	0.5777
	Fused aliphatic ring unit correction	-1.3684
	Equation Constant	0.2290
	π	0.3979
	LogKow	7.1181

Electronic parameters evaluation of both highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO)

There are some reports which suggest that both HOMO) and LUMO are two factors involved in biological activity of some drugs [48]. Therefore, in this investigation both HOMO and LUMO were evaluated (Table 3) using Spartan software [49]. The results showed in table 3 indicated that HOMO values were higher for **6** compared with the compounds **2-5** and **7**; these data indicate that **6** exert strong electro donating ability compared with **2-5** and **7**. In addition, these results suggest that **6** could induce changes in some biological system compared to **2-5** in a similar way with other types of molecules [48].

It is noteworthy that there are some studies suggest that other physicochemical factors are involved in the activity of several drugs, such as hydrogen bond donor groups. (HBD) and hydrogen bond acceptor groups (HBA) which may exert also changes on some biological system [50]. In this regard, these physicochemical descriptors have been evaluated using some pharmacophore models [51, 52];

Table 2. Physicochemical factors from compounds **5-7**.

5	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	3.4377
	-CH [aliphatic carbon]	1.4456
	-NH- [aliphatic attach]	-2.9924
	Aromatic Carbon	7.0560
	-N [aliphatic N, one aromatic attach]	-0.9170
	-O- [aliphatic O, two aromatic attach]	0.2923
	-C(=O)N [aliphatic attach]	-0.5236
	Aromatic Nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.2676
	Fused aliphatic ring unit correction	-1.3684
	Equation Constant	0.2290
	π	
	Log Kow	7.4952
6	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	4.9110
	-CH [aliphatic carbon]	1.4456
	#C [acetylenic carbon]	0.2668
	-NH- [aliphatic attach]	-1.4962
	-N< [aliphatic attach]	-1.8323
	Aromatic Carbon	7.0560
	-N [aliphatic N, one aromatic attach]	-0.9170
	-O- [aliphatic O, two aromatic attach]	0.2923
	-COOH [acid, aliphatic attach]	-0.6895
	-C(=O)N [aliphatic attach]	-0.5236
	Aromatic Nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.2676
	Fused aliphatic ring unit correction	-1.3684
	Equation Constant	0.2290
	π	0.3771
	Log Kow	8.2097
7	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	5.8932
	-CH [aliphatic carbon]	*1*.4456
	C [aliphatic carbon - No H, not tert]	0.9723
	#C [acetylenic carbon]	0.2668
	-NH- [aliphatic attach]	-2.9924
	-N< [aliphatic attach]	-1.8323
	Aromatic Carbon	7.0560
	-N [aliphatic N, one aromatic attach]	-0.9170
	-O- [aliphatic O, two aromatic attach]	0.2923
	-C(=O)N [aliphatic attach]	-0.5236
	Aromatic Nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.2676
	-N=C [aliphatic attach]	-0.0010
	Fused aliphatic ring unit correction	-1.3684
	-C-N=C-N-C- [cyclic] structure correction	-0.6000
	Equation Constant	0.2290
	π	0.5468
	LogKow	8.7565

Here, it is important to mention some studies suggest that both HBD and HBA can condition some pharmacokinetic process of drugs in the human body []; analyzing this hypothesis, the theoretical data found in is study suggest that compounds **2** to **7** could have the ability of penetrate some barrier biological of human body. However, it is noteworthy that the rule does not predict if a compound could be pharmacologically active; therefore, other type of studies must be carried out to determine the interaction between some compounds with several biological targets such as proteins or enzymes.

It is important to mention that pharmacophores are generally used to evaluate some chemical characteristics that are related with the biological activity of several molecules. Analyzing these data, in this investigation a theoretical study was carried out using a pharmacophore model [53]. The theoretical results (Figure 4-6) showed several hydrogen bond donor groups; such as -OH for the compound **2**; -NH- for **3-7**. Other theoretical data showed several hydrogen bond acceptor groups such as $-NO_2$ for **2**; -OH for both **3** and **4**; -NHCO- for **5** and **6**; =N- for **7**. In addition, other theoretical results (table 3) showed both HBA (< 10) and for HBD (< 5) values for compounds **2** to **7**.

Table 3. Physicochemical parameters of compounds **2-7**.

	Compounds					
Parameter	**2**	**3**	**4**	**5**	**6**	**7**
V_m (cm^3)	277.80	289.70	485.50	448.60	520.60	543.60
R_m (cm^3)	105.56	112.10	189.79	179.20	206.88	215.30
Polarizability	69.08	61.237	68.91	86.41	95.10	53.824
Dipole moment (debyte)	7.73	8.97	9.74	4.32	7.59	10.47
PSA (Å^2)	62.818	61.237	91.391	50.091	64.544	53.834
Energy (au)	1247.82	1247.77	2058.06	1855.10	2333.02	2269.74
HOMO (eV)	-5.97	-6.19	-4.46	-4.50	-3.32	-4.75
LUMO (eV)	1.10	0.95	0.69	1.14	0.64	1.30
Gap energy, eV (HOMO-LUMO)	-7.07	-7.14	-5.15	-5.64	-3.96	-6.05
HBD	2	2	4	2	3	3
HBA	5	5	9	6	8	8

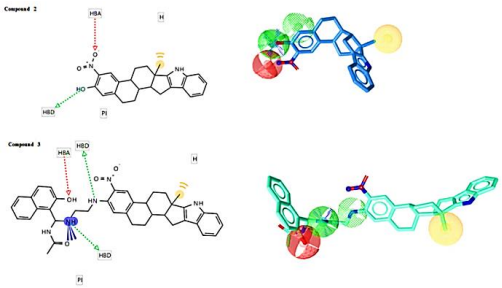

Figure 4. Scheme represents a pharmacophore model from both compounds **2** and **3** using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red), hydrogen bond donor (HBD, green) and a positive ionizable (PI).

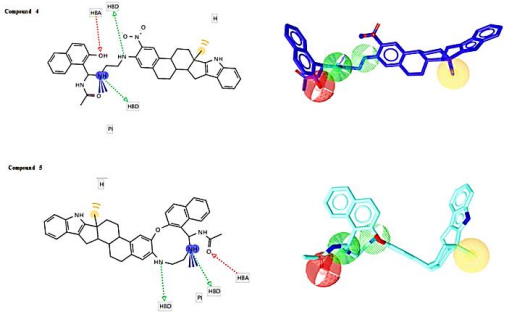

Figure 5. Pharmacophore from both compounds **4** and **5** using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red), hydrogen bond donor (HBD, green) and a positive ionizable (PI).

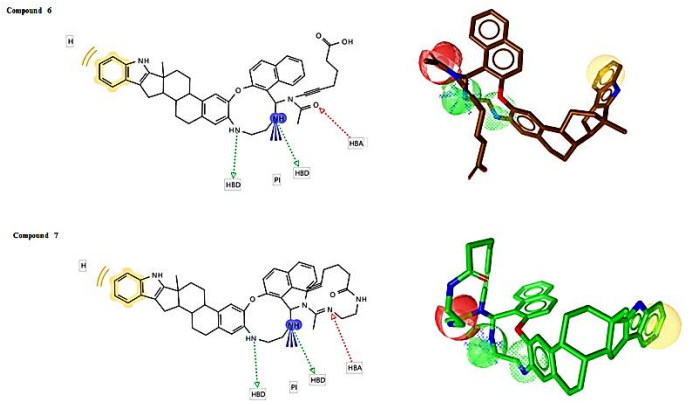

Figure 6. Scheme represents a pharmacophore from both compounds **6** and **7** using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red), hydrogen bond donor (HBD, green) and a positive ionizable (PI).

Evaluation of interaction of compounds 3-7 with aromatase protein (4kq8).

There are some studies that indicate that several substances can interact with some macromolecules which can be translated as the physiological regulation of some enzymes [54]; it is noteworthy that several drugs can exert changes biological activity of specific enzyme. In order, to evaluate this phenomenon some theoretical models have been used to predict the interaction of some drugs with enzymes [55]. Therefore, in this investigation was carried out a theoretical analysis of interaction of compounds **3-7** with aromatase protein (4kq8) [56] using a Docking model [57]. The results shown in figures 7-9 and table 4 indicate the interaction of compounds **2**-7 several with amino acid residues involved in enzyme surface (4kq8).

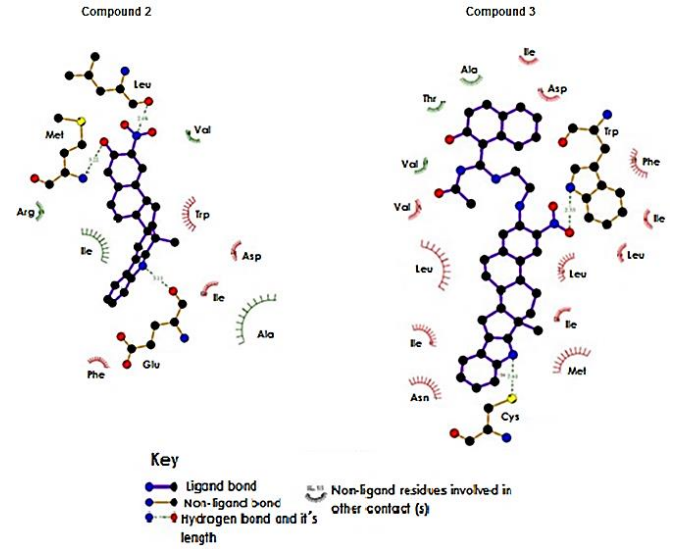

Figure 7. The scheme shows the binding of compounds **2** and **3** with some aminoacid residues of the aromatase enzyme (4kq8). The visualization was carried out with Dockingserver software.

However, to determine whether compounds **2-7** could act as aromatase inhibitors; also, theoretical interaction of enzyme with some aromatase antagonists, such as anastrozole, letrozole and exemestane was evaluated. The results (Figures 7-9 and Table 4) showed that anastrozole could interact with several aminoacid residues such as Ile_{133}, Phe_{134}, Phe_{221}, Ala_{306}, Asp_{309}, Thr_{310}, Val_{310}, Val_{373}, Met_{374}, Leu_{477} and Ser_{478} which are involved in the aromatase (4kq8 protein) surface. It is noteworthy that also **6** could bind to these types of aminoacid residues; however, only some of these aminoacid residues may participate in the interaction between 4kq8 protein with compounds **2-5** and **7**; this phenomenon could involve other type intramolecular interactions due to changes in the energy levels.

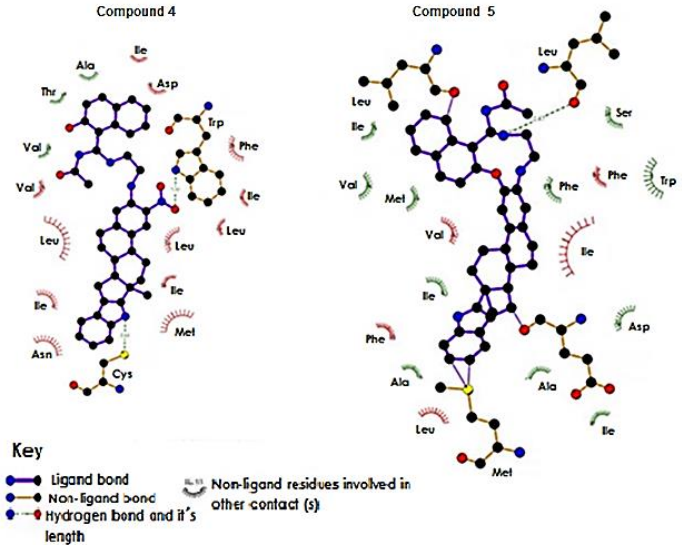

Figure 8. The scheme shows the binding sites of compounds **4** and **5** with some amino acid residues of aromatase enzyme (4kq8). The visualization was carried out with Dockingserver software.

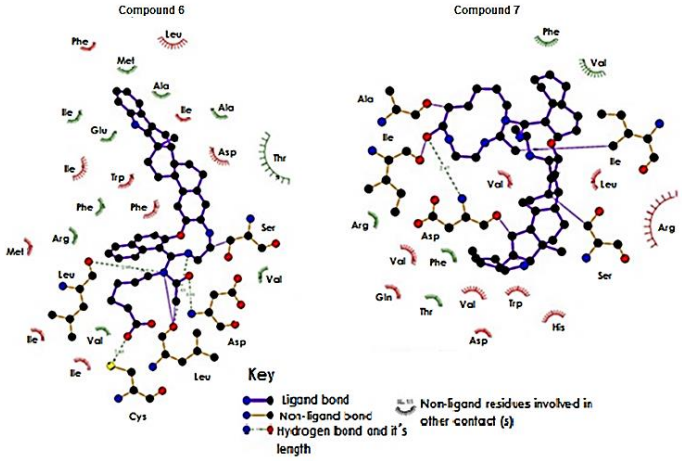

Figure 9. The scheme shows the binding of compounds **6** and **7** with some aminoacid residues of the aromatase enzyme (4kq8). The visualization was carried out with Dockingserver software.

Thermodynamic parameters

There are some reports which indicate that several thermodynamic factors may be involved in the interaction drug-protein [41]; therefore, a theoretical ass was carried out on some thermodynamic parameters involved in the interaction of anastrazol, letrozole, exametane and the compounds **2-7** with the 4kq8 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 [58]; 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) [58] using a theoretical model (dockingserver) [57].

Table 4. Residues aminoacids involved in the interaction between anastrazol, letrozole, exametane and compounds **2-7** with 4kq8 protein.

Arg_{115} Ile_{133} Phe_{134} Phe_{221} Ala_{306} Asp_{309} Thr_{310} Val_{310} Val_{373} Met_{374} Leu_{477} Ser_{478}	Arg_{115} Ile_{133} Phe_{134} Phe_{221} Trp_{224} Ala_{306} Asp_{309} Thr_{310} Val_{370} Leu_{477}	Arg_{115} Ile_{133} Phe_{134} Phe_{221} Trp_{224} Ala_{306} Asp_{309} Thr_{310} Val_{369} Val_{373} Ser_{478}	Arg_{115} Ile_{133} Phe_{148} Trp_{224} Glu_{302} Ile_{305} Ala_{306} Asp_{309} Val_{370} Leu_{372} Met_{374}	Ile_{70} Cys_{74} Ile_{133} Phe_{134} Trp_{224} Leu_{228} Ile_{305} Ala_{306} Asp_{309} Thr_{310} Val_{370} Leu_{372} Val_{373} Met_{374} Ile_{395} Asn_{397} Leu_{477}	Ile_{70} Arg_{115} Ile_{133} Phe_{134} Phe_{148} Phe_{221} Trp_{224} Leu_{228} Asp_{309} Thr_{310} Val_{369} Val_{370} Leu_{372} Val_{373} Met_{374} Leu_{477} Ser_{478} His_{480}	Ile_{132} Ile_{133} Phe_{134} Phe_{148} Leu_{152} Phe_{221} Trp_{224} Glu_{302} Met_{303} Ile_{305} Ala_{306} Asp_{309} Val_{370} Leu_{372} Val_{373} Met_{374} Ile_{398} Ala_{438} Leu_{477} Ser_{478}	Cys_{74} Arg_{115} Ile_{132} Ile_{133} Phe_{134} Phe_{148} Leu_{152} Phe_{221} Trp_{224} Glu_{302} Met_{303} Ile_{305} Ala_{306} Asp_{309} Thr_{310} Val_{370} Asp_{371} Leu_{372} Val_{373} Met_{374} Ile_{395} Ala_{438} Leu_{477} Ser_{478}	Ile_{70} Cys_{74} Met_{127} Ile_{133} Phe_{134} Phe_{148} Trp_{224} Glu_{302} Met_{303} Ile_{305} Ala_{306} Thr_{310} Asp_{371} Leu_{372} Met_{374} Ile_{395} Asn_{397} Cys_{437} Leu_{477}

*Similar residues aminoacids (red); Different residues aminoacids (blue and green).

Table 5. Thermodynamic factors involved in the interaction of anastrazol, letrozole, exametane and compounds **2-7** on aromatase (4kq8).

Compound	Est. Free Energy of Binding (kcal/mol)	vdW + Hbond + desolv. Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Intermol. Energy (kcal/mol)	Interact. Surface
Antrazol	-9.58	-11.41	0.01	-11.41	569.117
Letrozan	-8.67	-9.80	-0.10	-9.90	556.04
Exemestan	-10.61	-10.73	-0.08	-10.81	511.069
2	17.88	17.88	-0.30	17.59	613.343
3	302.49	282.99	-0.25	282.74	907.966
4	296.90	259.15	-0.09	259.07	872.307
5	455.63	455.74	-0.41	455.33	901.322
6	699.38	685.02	-0.32	684.70	996.294
7	926.66	927.57	-1.35	926.22	1018.609

The results showed in the table 5 indicate that all thermodynamic parameters were higher for compound **6** compared with anastrazol, letrozole, exametane and compounds **2-5**; however, these parameters were low in comparison with **7**. This phenomenon indicates that there are differences in the energy levels between the interaction of the compounds studied and the 4kq8 protein, which can be translated as changes in the biological activity of aromatase in the presence of **6** in comparison with the compounds **2-5** and **7**.

4. CONCLUSIONS

Theoretical data indicate that compound **6** could be a good candidate as aromatase inhibitor which translates as a possible drug for breast cancer. Nevrtheless, it is noteworthy that it is necessary to evaluate their activity in some biological model.

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