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Original ResearchArticle

Design and synthesis of two steroid derivatives from 2-nitroestrone and theoretical evaluation of their interaction with BRCA-1

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ABSTRACT

Several compounds have been prepared to treat the breast cancer; however, some of these drugs may produce some side effects. The aim of this study is to synthesize two new steroid derivatives (Compounds **7** or **8**) to evaluate their theoretical interaction with a breast cancer protein (BRCA-1) using a docking model. The preparation of **7** and **8** was carried out using a series of reactions which involves; (i) addition/cyclization; (ii) amination, (iii)etherification and (iv)esterification. Chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. The following stage involved the theoretical evaluation on the interaction of both compounds **7** or **8** with BRCA-1 protein surface using a docking model. The results showed that compound **7** could bound to different type of aminoacid residues of BRCA-1 protein as compared to **8**; this phenomenon, may exert changes in the biological activity of BRCA-1 protein. The resulted data suggest that compound **7** or **8**could be an alternative therapeutic for the treatment of the breast cancer.

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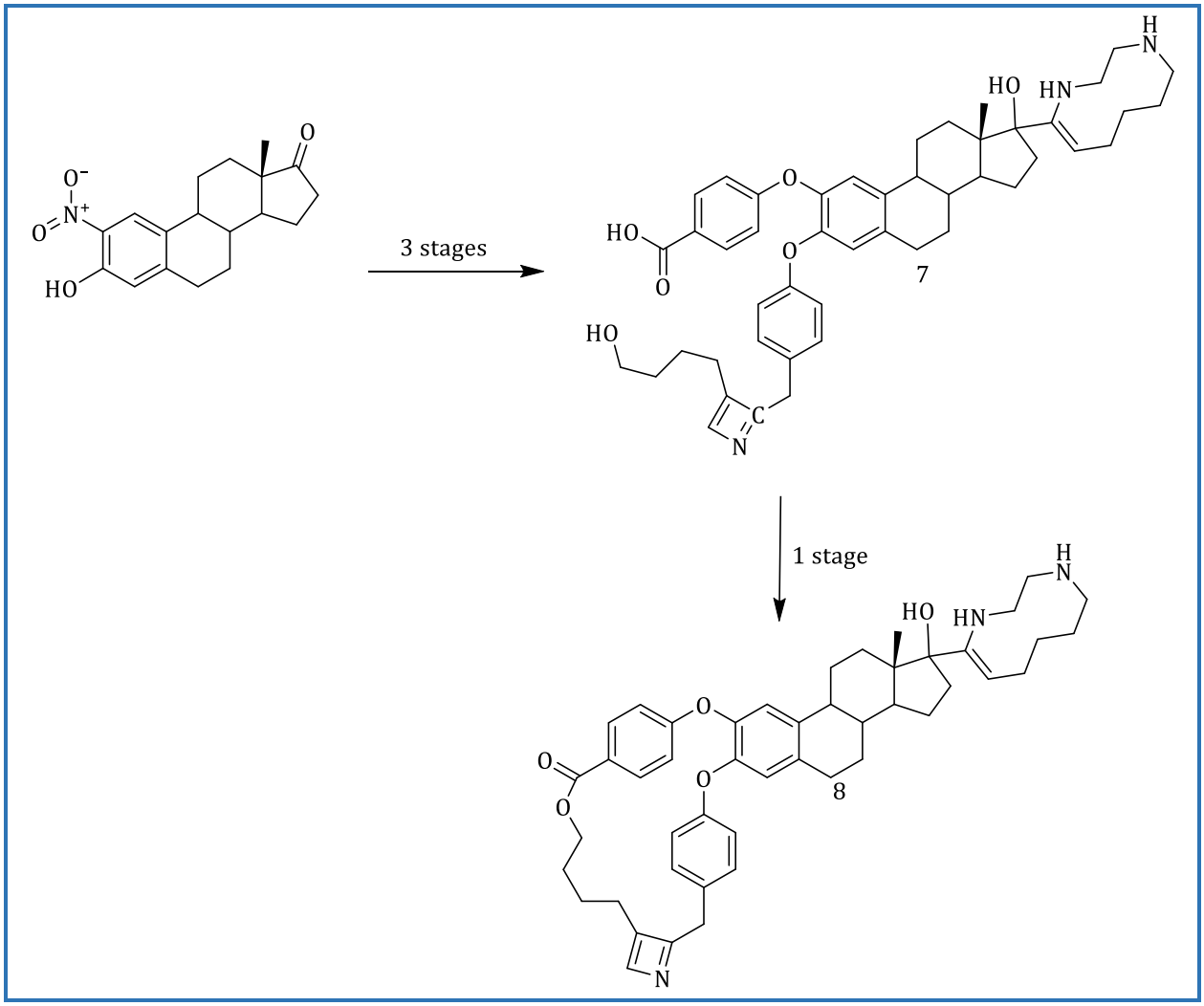
Graphical Abstract



Introduction

Breast cancer is one of the main health problems worldwide [1–4]; It is important to note that some drugs have been used to treat this clinical pathology; however, some of these drugs can produce adverse effects [5–7]. This phenomenon could be due to the different chemical structures of each drug or to the different target cells where they exert their biological activity. In the search for new drugs for cancer treatment, several compounds have been prepared; for example, the preparation of 2-(4-aminophenyl)benzothiazoles with biological activity against breast cancer "*in vitro*" and "*in vivo*" [8]. Also, a series of carboxylic acids analogs was prepared which showed effects against MCF-7 (human breast adenocarcinoma) cells *via* estrogen receptor inhibition [9]. Other study showed the synthesis of a series of acridone derivatives and inhibition of breast cancer resistance protein ABCG2 [10]. In addition, a report showed that ellagic-acid has effects against the

cancer breast in MCF-7 cells *via* estrogen receptor (ERβ) inhibition [11]. Other data indicate the synthesis of 17β-estradiol platinum(II) complexes with biological activity "*in vitro*" on estrogen dependent and independent (ER^+ and ER^-) human breast cancer cells [12]. Also, a report showed that some estradiol and estrone derivatives exert effect against the breast cancer cells (T-47D ER^+) [13]. In addition, a study showed that some carboxamide derivatives can exert effects on a breast cancer protein [BRCA-1) [14]. Also, other data revealed that compound CDDO-methyl ester delays the breast cancer development in BRCA-1 mutated mice [15].

To characterize the observed biological activity of some compounds a variety of theoretical methods have been employed; for example, a study showed the preparation of a series of 3-acyl-5-hydroxybenzofuran derivatives and their theoretical evaluation against breast cancer using a quantum mechanics polarized ligand docking study [16]. The other report had shown the influence of the length and positioning of the antiestrogenic side chain of endoxifen and 4-hydroxytamoxifen on gene activation and growth of estrogen receptor positive cancer cells using a docking model [17]. In addition, theoretical studies suggest that some mangrove derivatives could have biological activity on BRCA-1 [18]. All these results indicate that some drugs exert their effects on BRCA-1; analyzing these data, in this study, two steroid derivatives from 2-nitoestrone were synthesized. In addition, a theoretical study was carried out to characterize its interaction with BRCA-1 (1JM7) protein using a docking model.

Experimental

Materials and methods

The compounds 2-nitro-estrone was prepared using the previously reported method [19]. Additionally, all the reagents used in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point for the compounds was evaluated using an electrothermal (900 model). Infrared spectra (IR) were determined using KBr pellets on a PerkinElmer 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 MHz 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 PerkinElmer Ser. II CHNS/02400 elemental analyzer.

Preparation of steroid propargylic alcohol

A solution of 2-nitroestrone (0.50 mmol), 6-chloro-1-hexyne (70 µL; 0.58 mmol), sodium hydroxide (20 mg, 0.5 mmol) and 5 mL methanol/ dimethyl sulfoxyde (3:1) was stirred for 10 h at room temperature. The obtained mixture was dried under reduced pressure and, then, purified by crystallization using the methanol/water (4:1) system.

*17-(6-chloro-hex-1-ynyl)-13 methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (**2**)*

Yield 54%, mp 182-184 °C,IR (KBr) (ν_{max}/ cm^{-1}): 3400, 2260, 1270 and 802.^{1}H NMR (500 MHz, $CDCl_3$): δ0.90 (s, 3H), 1.22-1.70 (m, 5H), 1.74 (m, 2H), 1.76-1.86 (m, 3H), 1.92 (m, 2H), 2.10-2.12 (m, 2H), 2.20 (m, 2H), 2.32-2.92 (m, 5H), 3.56 (m, 2H), 6.64 (m, 1H), 7.66 (broad, 2H), 7.82 (m, 1H). ^{1}C NMR (100 MHz, $CDCl_3$): δ12.3, 19.2, 23.7, 26.3, 26.8, 27.7, 29.8, 31.4, 34.9, 36.5, 37.8, 44.9, 45.2, 48.1, 52.8, 80.1, 81.8, 83.4, 114, 123.5, 132.3, 132.9, 145, 148.5. EI-MS m/z: 431.18 Anal. Calcd for $C_{24}H_{30}ClNO_4$: C, 66.73; H, 7.00; Cl, 8.21, N, 3.24; O, 14.82; Found: C, 66.68; H, 8.16.

Synthesis of steroid propargylic alcohol amino

A solution of compound **2** (0.50 mmol), ethylenediamine (59 µL, 75 mmol), triethylamine (60 µL, 43 mmol) and 3 mL of methanol was stirred for 12 h at room temperature. The mixture was dried under reduced pressure and purified by crystallization using the methanol/hexane/water (4:2:1) system.

*17-[6-(2-amino-ethylamino)-hex-1-ynyl]-13 methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (**3**)*

Yield 44%, mp 196-198 °C,IR (KBr) (ν_{max}/ cm^{-1}): 3402, 3382, 2258 and 1270.^{1}H NMR (500 MHz, $CDCl_3$):δ 0.90 (s, 3H), 1.22-1.38 (m, 3H), 1.44-1.50 (m, 4H), 1.52-2.40 (m, 11H), 2.64-2.72 (m, 4H), 2.76 (m, 2H), 2.77-2.92 (m, 3H), 5.0 (broad, 5H), 6.64-7.82 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$):δ12.3, 19.0, 23.6, 25.9, 26.8, 27.7,28.3, 29.8, 34.9, 36.5, 37.8, 41.4, 44.9, 48.1, 49.9, 52.4, 52.8, 80.1, 81.7, 83.4, 114.0, 123.5, 132.3, 132.9, 145.0, 148.5. EI-MS m/z: 455.27 Anal. Calcd for $C_{26}H_{37}N_3O_4$: C, 68.54; H, 8.19; N, 9.22; O, 14.05; Found: C, 68.44; H, 8.12.

Preparation of a steroid octahydro-[1,4]diazecine derivative

A solution of compound **3** (0.50 mmol), copper(II) chloride anhydrous (94 mg, 0.70 mmol), and 3 mL of methanol was stirred for 24 h at room temperature. The obtained mixture was dried under reduced pressure and purified by crystallization using the methanol/water (4:1) system.

*13-methyl-2-nitro-17-(1,2,3,4,7,8,9,10-octahydro-[1,4]diazecin-5-yl)-7,8,9,11,12,13,14, 15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (**4**)*

Yield 65%, mp 212-214 °C,IR (KBr) (ν_{max}/ cm^{-1}): 3400, 3340 and 1270: ^{1}H NMR (500 MHz, $CDCl_3$):*δ* 0.76 (s, 3H), 1.14-1.38 (m, 3H), 1.44 (m, 2H), 1.68-1.92 (m, 6H), 1.98 (m, 2H), 2.00-2.36 (m, 3H), 2.42-2.70 (m, 6H), 2.76-2.90 (m, 3H), 3.14 (m, 2H), 5.20 (d, 1H, *J* = 0.78 Hz), 5.29 (broad, 4H), 6.64-7.82 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):*δ* 21.0, 24.7, 25.9, 27.3, 27.7, 28.9, 29.8, 30.8, 30.9, 35.9, 38.1, 41.5, 44.9, 46.6, 46.9, 48.8, 53.1, 89.8, 101.8, 114.0, 123.5, 132.3, 132.9, 145.0, 148.5, 153.1. EI-MS m/z: 455.27 Anal. Calcd for $C_{26}H_{37}N_3O_4$: C, 68.54; H, 8.19; N, 9.22; O, 14.05; Found: C, 68.46; H, 8.10.

Preparation of a steroid ether derivative

A solution of compound **4** (0.50 mmol), 1-nitro-4-prop-2-ynyl-benzene (80 mg, 0.5 mmol), potassium carbonate anhydrous (50 mg, 0.36 mmol) and 3 mL of dimethyl sulfoxide was stirred for 24 h at room temperature. The mixture was dried under reduced pressure and purified by crystallization using the methanol/hexane/water (4:2:1) system.

*{4-[17-hydroxy-13 methyl-2-nitro-17-(1,2,3,4,7,8,9,10-octahydro-[1,4]diazecin-5-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yloxy]-phenyl}-acetonitrile (**5**)*

Yield 46%, mp 156-158 °C,IR (KBr) (ν_{max}/ cm^{-1}):3402, 3340, 2280, 1272 and 1248: ^{1}H NMR (500 MHz, $CDCl_3$):*δ*0.76 (s, 3H), 1.14-1.38 (m, 3H), 1.44 (m, 2H), 1.68-1.92 (m, 6H), 1.98 (m, 2H), 2.00-2.36 (m, 3H), 2.42 (m, 2H), 2.60 (m, 1H), 2.64-2.69 (m, 3H), 2.76-2.90 (m, 3H), 3.14 (m, 2H), 3.64 (m, 2H), 3.82 (broad, 3H), 5.20 (d, 1H, *J* = 0.78 Hz), 6.74 (m, 1H), 7.12-7.40 (m, 4H), 7.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):*δ* 21.0, 23.4, 24.7, 25.9, 27.3, 27.7, 28.9, 29.7, 30.8, 30.9, 35.9, 38.1, 41.5, 44.9, 46.6, 46.9, 48.8, 53.1, 89.8, 101.8, 112.6, 117.4, 119.8, 122.4, 125.6, 129.7, 133.9, 138.5, 147.8, 149.9, 153.1, 157.9. EI-MS m/z: 570.32 Anal. Calcd for $C_{34}H_{42}N_4O_4$: C, 71.55; H, 7.42; N, 9.82; O, 11.21; Found: C, 71.48; H, 7.36.

Preparation of a steroid-cyanomethyl-phenoxy-hydroxy-benzoic acid derivative

A solution of compound **5** (0.50 mmol), 4-hydroxybenzoic acid (70 mg, 0.50 mmol), potassium carbonate anhydrous (50 mg, 0.36 mmol) and 3 mL of dimethyl sulfoxyde was stirred for 24 h at room temperature. The obtained mixture was dried under reduced pressure and purified by crystallization using the methanol/water (4:1) system.

*4-[3-(4-Cyanomethyl-phenoxy)-17-hydroxy-13-methyl-17-(1,2,3,4,7,8,9,10-octahydro-[1,4] diazecin-5-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenan- thren-2-yloxy]-benzoic acid (**6**)*

Yield 38%, mp 168-170 °C,IR (KBr) (ν_{max}/ cm^{-1}):3402, 3342, 2280, 1712 and 1248: ^{1}H NMR (500 MHz, $CDCl_3$):*δ* 0.76 (s, 3H), 1.14-1.38 (m, 3H), 1.44 (m, 2H), 1.68-1.92 (m, 6H), 1.98 (m, 2H), 2.00-

2.36 (m, 3H), 2.42 (m, 2H), 2.44-2.60 (m, 2H), 2.64-2.69 (m, 3H), 2.76-2.80 (m, 2H), 3.14 (m, 2H), 3.64 (m, 2H), 5.20 (d, 1H, *J* = 0.78 Hz), 5.56 (broad, 4H), 6.26-6.70 (m, 2H), 6.96-8.06 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$):*δ* 21.0, 23.4, 24.7, 25.9, 27.3, 27.7, 28.9, 29.6, 30.8, 30.9, 35.9, 38.1, 41.5, 45.4, 46.6, 46.9, 48.8, 53.1, 89.8, 101.9, 111.6, 113.2, 113.8, 115.4, 117.4, 122.4, 122.4, 122.9, 123.9, 126.9, 128.0, 129.6, 129.8, 130.3, 131.4, 136.0, 153.1, 160.8, 160.9, 168.40. EI-MS m/z: 661.35 Anal. Calcd for $C_{41}H_{47}N_3O_5$: C, 74.41; H, 7.16; N, 6.35; O, 12.09; Found: C, 71.36; H, 7.08.

Preparation of a 17-hydroxy-steroid-diazecin-benzoic acid derivative

A solution of compound **6** (0.50 mmol), 5-hexyn-1-ol (60 µL, 0.54 mmol), copper(II) chloride anhydrous (94 mg, 0.70 mmol) and 3 mL of dimethyl sulfoxyde was stirred for 24 h at room temperature. The obtained mixture was dried under reduced pressure and purified by crystallization using the methanol/hexane/water (4:2:1) system.

*4-(((13S)-17-hydroxy-3-(4-((4-(4-hydroxybutyl)azet-2-yl)methyl)phenoxy)-13 methyl-17-((Z)-1,2,3,4,7,8,9,10-octahydro-1,4-diazecin-5-yl)-7,8,9,11,12,13,14,15,16,17-decahy- dro-6H-cyclopenta[a]phenanthren-2-yl)oxy)benzoic acid (**7**)*

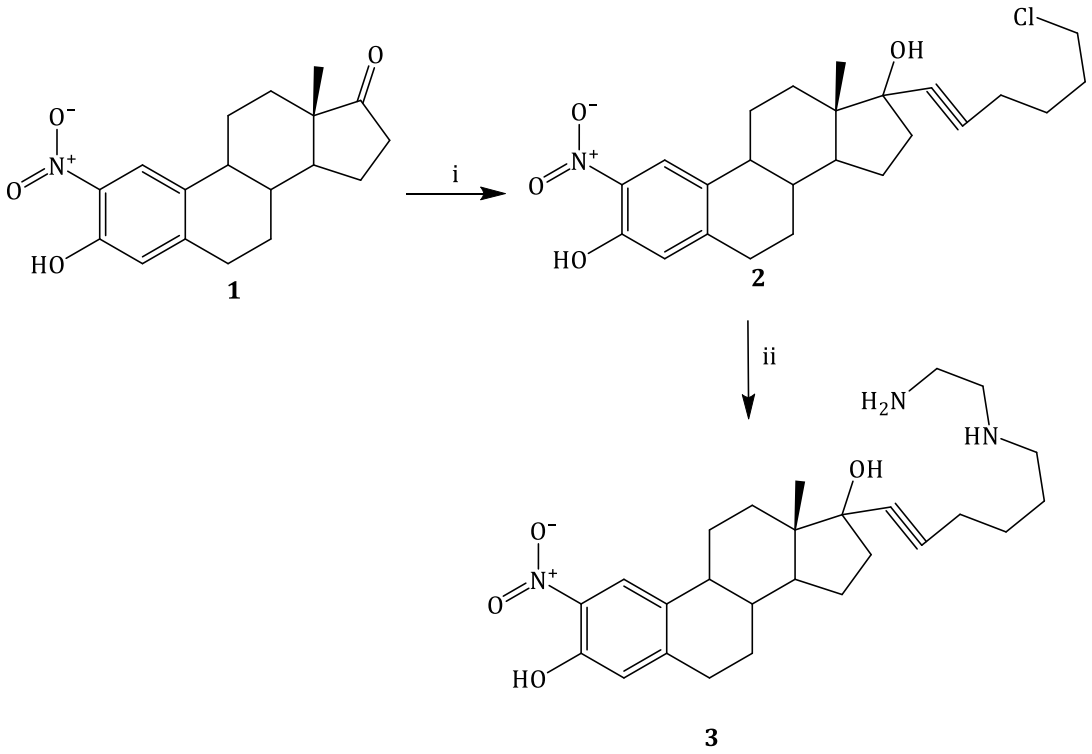
Yield 58%, mp 204-206 °C,IR (KBr) (ν_{max}/ cm^{-1}):3400, 3340, 3320, 1712 and 1248.^{1}H NMR (500 MHz, $CDCl_3$):*δ*0.76 (s, 3H), 1.14-1.38 (m, 3H), 1.44 (m, 2H), 1.54 (m, 2H), 1.65 (m, 2H), 1.68-1.90 (m, 6H), 1.98 (m, 2H), 2.00-2.36 (m, 3H), 2.42 (m, 2H), 2.44-2.60 (m, 2H), 2.64-2.69 (m, 3H), 2.70 (m, 2H), 2.76-2.80 (m,2H), 3.14 (m, 2H), 3.64 (m, 2H), 3.70 (m, 2H), 4.96 (d, 1H, *J* = 1.30 Hz), 5.20 (d, 1H, *J* = 0.78 Hz), 5.66 (broad, 5H), 6.26-6.70 (m, 2H), 6.92-8.06 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$):*δ* 21.0, 21.2, 24.6, 25.9, 27.3, 27.7, 29.0, 29.6, 30.8, 30.9, 31.3, 32.6, 35.9, 38.1, 41.5, 45.4, 45.5, 46.6, 46.9, 48.8, 53.1, 62.2, 89.8, 101.9, 111.3, 111.6, 113.2, 113.8, 115.3, 124.2, 126.1, 126.5, 129.5, 129.8, 130.3, 131.4, 136.0, 153.1, 153.6, 160.8, 161.2, 165.8, 168.4. EI-MS m/z: 759.42 Anal. Calcd for $C_{47}H_{57}N_3O_6$: C, 74.28; H, 7.56; N, 5.53; O, 12.63; Found: C, 74.20; H, 7.48.

Preparation of azeta-steroid-dibenzenacyclotridecaphan-8-one derivative

A solution of compound **7** (0.50 mmol), dicyclohexylcarbodiimide (150 mg, 0.72 mmol)and 3 mL of methanol was stirred for 48 h at room temperature. The obtained mixture was dried under reduced pressure and purified by crystallization using the methanol/benzene/water (4:1:1) system.

*(5^{13}S)-5^{17}-hydroxy-5^{13}-methyl-5^{17}-((Z)-1,2,3,4,7,8,9,10-octahydro-1,4-diazecin-5-yl)-5^7,5^8,5^9,5^{11}, 5^{12},5^{13},5^{14},5^{15},5^{16},5^{17}-decahydro-5^6H-4,6,9-trioxa-1(2,3)-azeta-5(3,2)-cyclo- penta[a]phenanthrena-3,7(1,4)-dibenzenacyclotridecaphan-8-one (**8**)*

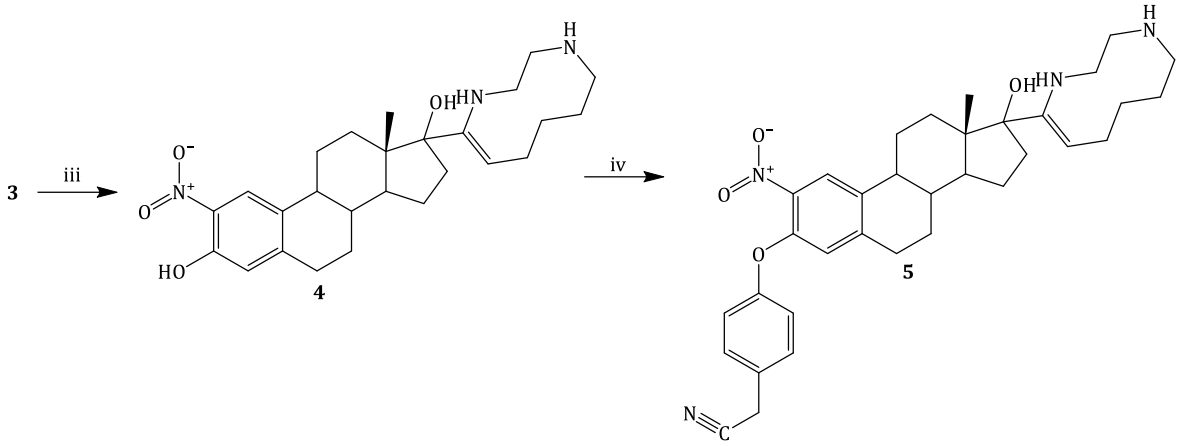
Yielding 54%, mp 308-310 °C,IR (KBr) (ν_{max}/ cm^{-1}):3400, 3342, 3322, 724 and 1248.^{1}H NMR (500 MHz, $CDCl_3$):δ0.76 (s, 3H), 1.14 (m, 1H), 1.22 (m, 2H), 1.38-1.39 (m, 2H), 1.44 (m, 2H), 1.54 (m, 2H), 1.66-1.90 (m, 6H), 1.98 (m, 2H), 2.00-2.14 (m, 2H), 2.26 (m, 2H), 2.34 (m, 1H), 2.42 (m, 2H), 2.44 (m, 1H), 2.60-2.70 (m, 4H), 2.76-2.80 (m, 2H), 3.14 (m, 2H), 3.22 (m, 2H), 3.80 (broad, 3H), 4.30-4.32 (m, 2H), 4.98 (d, 1H, *J* = 1.82 Hz), 5.20 (d, 1H, *J* = 0.78 Hz), 6.26-6.70 (m, 2H), 6.84-8.14 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$):δ 20.6, 21.0, 24.7, 25.9, 27.3, 27.7, 27.9, 29.0, 29.6, 30.1, 30.8, 30.9, 35.9, 35.9, 38.1, 41.5, 45.4, 46.6, 46.9, 48.8, 53.1, 67.4, 89.8, 101.9, 103.0, 111.6, 113.2, 113.8, 115.6, 116.2, 119.0, 119.2, 122.3, 130.8, 131.4, 134.0, 135.2, 135.3, 136.0, 137.0, 137.5, 139.7, 153.1, 154.2, 161.0, 162.4, 162.6, 163.5, 164.4.EI-MS m/z: 861.43 Anal. Calcd for $C_{54}H_{59}N_3O_7$: C, 75.24; H, 6.90; N, 4.87; O, 12.99; Found: C, 75.18; H, 6.82.



Scheme1. Preparation of a steroid-ether derivative **5**. Reaction of 2-nitroestrone **1** with 6-chloro-1-hexyne to form the 17-(6-chloro-hex-1-ynyl)-2-nitro-steroid derivative **2**. Then ethylenediamine (ii) was bound to **2** to synthesis of steroid-propargylic-alcohol-amino **3**

*Physicochemical properties of compound **8***

The theoretical electronic properties, such as HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital) energy, orbital coefficients distribution, molecular dipole moment and HBD (hydrogen bond donor groups) and HBA (Hydrogen Bond Acceptor groups) and TPSA (Topological Polar Surface Area) were evaluated using SPARTAN'06. In addition,



Scheme2. Synthesis of a steroid-ether derivative **5**. Reaction of steroid-propargylic-alcohol-amino **3** with ethylenediamine (iii) to form a steroid-octahydro-[1,4]diazecine derivative **4**. Then **4** was reacted with CopperII chloride to synthesis of **5**. iv = potassium carbonate/dimethyl sulfoxide

logP (logKowin), molecular refractivity (M_R), volume reactivity (V_R) were determined using both chemsketch and avogadro programs [20–22].

*Interaction of both compound **7** or **8** with BRCA-1 protein*

The distance of interaction between **7** to **8** with aminoacid residues of BRCA-1 protein surface were determined using SeeSAR 8.0 program [23].

Thermodynamic parameters

Some studies showed that some thermodynamic parameters can be evidences for confirming the interaction drug-protein [24]; Therefore, in this study a theoretical evaluation was carried out on some thermodynamic parameters involved between the interaction of both compounds **7** and **8** with BRCA-1 protein (1JM7) [25].

Results and discussion

In this study, two steroid derivatives were synthesized from 2-nitrostrone to evaluate their interaction with breast cancer protein (BRCA-1) using a docking model. The first stage involved the synthesis of two steroid derivatives using some strategies as follow:

Preparation of steroid-propargylic-alcohol

There are studies which indicate the synthesis of several propargylic-alcohols using some reagents such as $Ti(O\text{-}i\text{-}Pr)_4$-BINOL complex [26], chiral diamine-coordinated tin(II) triflate [27], $P(PhCH_2NCH_2CH2)_3N$ [28] and others; it is important to note that some of these reagents arevery

expensive and require special conditions. Analyzing these data and the other report which showed the preparation of a propargylic-alcohols in the presence of sodium hydroxide [29], in this work, the estrone was reacted with 5-hexyn-1-ol in basic medium (Scheme1). The ^{1}H NMR spectrum of the compound **2** showed several signals at 0.90 ppm for methyl group bound to steroid nucleus; at 1.22-1.70, 1.76-1.86, 21.0-2.12, 2.82-2.92, 6.64 and 7.64 ppm for steroid moiety; at 1.74, 1.92, 2.20 amd 3.56 ppm for methylene groups bound to cyanide group; at 7.66 ppm for both hydroxyl groups. The ^{13}C NMR spectra display chemical shifts at 12.32 ppm for methyl group bound to nucleus steroid; at 19.2, 26.3, 31.4 and 45.2 ppm for methylene groups bound to cyanide group; at 23.7, 28.8-29.8-34.9, 44.9, 48.1-80.1 and 114-148.5 ppm for steroid moiety; at 81-82-83.4 ppm for alkyne group. Finally, the mass spectrum from **2** showed a molecular ion (m/z) 431.18.

Synthesis of steroid-propargylic-alcohol-amino

There are several methods reported for the preparation of amino derivatives using some chemical tools such as ω-transaminase [30], 1-ethyl-3(3-dimethylamino-propyl)carbodiimide [31], $Pd/CaCO_3$ [32], boric acid [33], p-xitrobenzyl-phosphonic acid [34] and others. In this study, the compound **2** reacted with ethylenediamine in the presence of boric acid (Scheme1) to form a steroid-propargylic-alcohol-amino (**3**). The ^{1}H NMR spectrum of the compound **3** display several signals at 0.90 ppm for methyl group; at 1.22-1.38, 1.52-2.40, 2.77-2.92 and 6.64-7.82 ppm for steroid moiety; at 1.44-1.50, 2.64 and 2.76 ppm for methylene groups bound to both amino and cyanide groups; at 2.64-2.72 ppm for methylene groups bound to both amino groups; at 5.00 ppm for both hydroxyl and amino groups. The ^{13}C NMR spectra showed some chemical shifts at 12.3 ppm for methyl group; at 19, 25.8, 28.3 and 49.9-52.4 ppm for methylene groups bound to both amino and cyanide groups; at 23.6, 26.8-27.7, 29.8-37.8, 44.9-48.1, 52.8-80.1 and 114ppm for steroid moiety; at 41.4 ppm for methylene groups bound to both amino groups. In addition, the mass spectrum from **3** showed a molecular ion (m/z) 455.27.

Preparation of a steroid-octahydro-[1,4]diazecine derivative

There are reports which indicate the synthesis of several diazecine derivatives using some reagents such as formaldehyde [35], Zn/AcOH [36], phthaloyl chloride [37], quinaldine/AcOH [38] and others. In this investigation, a steroid-octahydro-[1,4]diazecine derivative (**4**) was prepared by an internal reaction of **3** using CopperII chloride anhydrous as catalyst (Scheme2). The^{1}H NMR spectrum of the compound **4** showed several signals at 0.76 ppm for methyl group; at 1.14-1.38, 1.60-1.92, 2.00-2.36, 2.76-2.90 and 6.64-7.82 ppm for steroid moiety; at 1.44, 1.98, 2.42, 2.64-2.70, 3.14 and 5.20 ppm for octahydro-[1,4]diazecine ring; at 5.29 ppm for both amino and hydroxyl

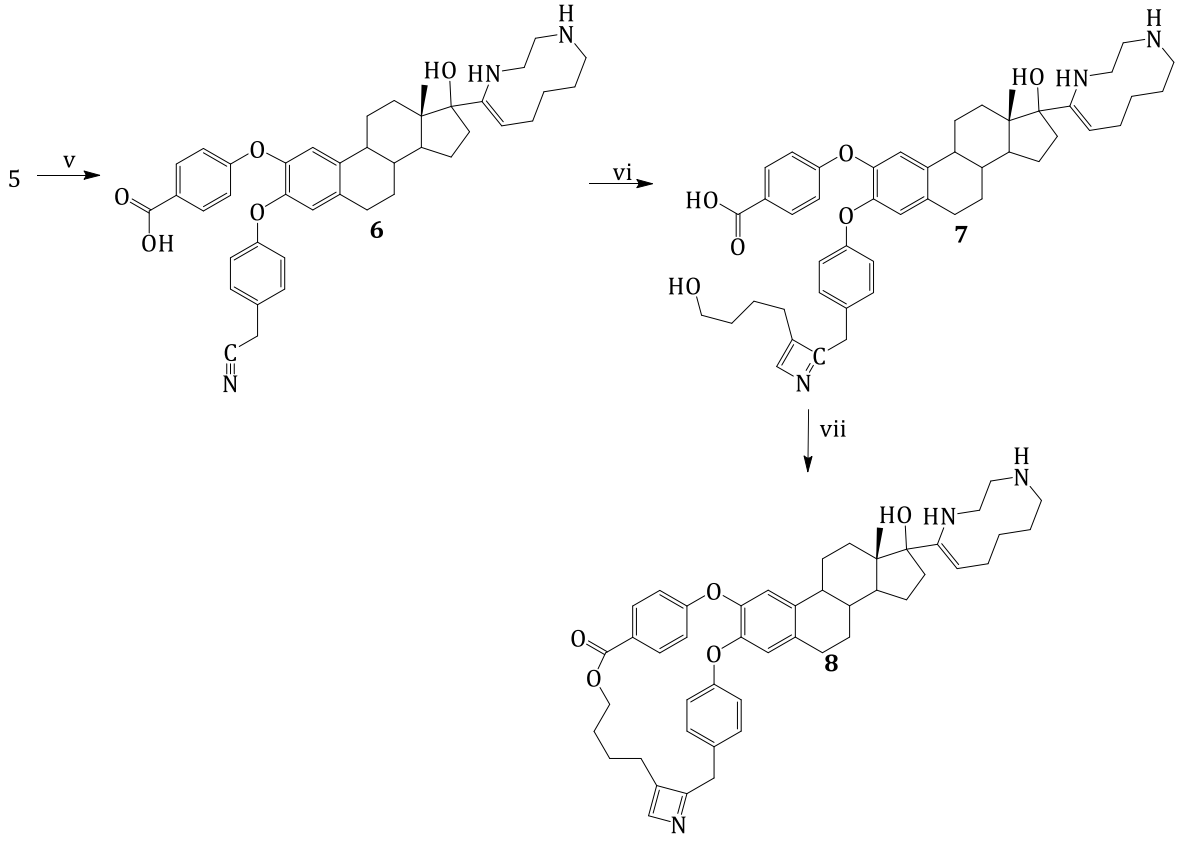
groups. The ^{13}C NMR spectra display several chemical shifts at 21 ppm for methyl group; at 24.7, 25.9, 27.7, 29.8, 30.9-38.1, 44.9-46.6, 53.1-89.8 and 114-148.5 ppm for steroid moiety; at 27.3, 28.9, 30.8, 41.5, 46.9-48.8, 101.8 and 153.1 ppm for octahydro-[1,4]diazecine ring. Finally, the mass spectrum from **4** showed a molecular ion (m/z) 455.27.

Synthesis of a steroid-ether derivative

Some other reports showed the preparation of several ether derivatives via displacement of nitro group using methoxide as dipolar aprotic solvent [39, 40]. In this study, compound **5** was synthesized by the reaction of **4** with 4-nitrobenzoyl azide in the presence of dimethyl sulfoxide at mild conditions (Scheme 2). The ^{1}H NMR spectrum of the compound **5** showed several signals at 0.76 ppm for methyl group; at 1.14-1.38, 1.68-1.92, 2.00-2.36, 2.60, 2.76-2.90, 6.74 and 7.92 ppm for steroid moiety; at 1.44, 1.98, 2.42, 264-2.69, 3.14 and 5.20 ppm for octahydro-[1,4]diazecine ring; at 3.64 ppm for methylene group bound to both phenyl and cyanide groups; at 3.82 ppm for both amino and hydroxyl groups; at 7.12-7.40 for phenyl groups. The ^{13}C NMR spectra display several chemical shifts at 21 ppm for methyl group; at 23.4 ppm for carbon bound to both phenyl and cyanide groups; at 24.7-25.9, 27.7, 29.7, 30.9-38.1, 44.9-46.6, 53.1-89.8, 112.6, 119.8 and 133.9-149.9ppm for steroid moiety; at 27.3, 28.9, 30.8, 41.5, 46.9-48.8, 101.8 and 153.1 ppm for octahydro-[1,4]diazecine ring; at 117.4 for cyanide group; at 12.4-129.7 and 157.9 ppm for phenyl groups. Additionally, the mass spectrum from **5** showed a molecular ion (m/z) 570.32.

Preparation of a steroid-cyanomethyl-phenoxy-hydroxy-benzoic acid derivative

A second etherification was carried out via displazament of nitro group involved in the compound **5** with 4-hydroxybenzoic acid to form the compound **6** (Scheme 3). The ^{1}H NMR spectrum of **6** showed several signals at 0.76 ppm for methyl group; at 1.14-1.38, 2.00-2.36, 2.44-2.60, 2.76-2.80 and 6.26-6.70 ppm for steroid moiety; at 5.56 ppm for carboxyl, amino and hydroxyl groups; at 1.98, 2.42, 2.64-2.69, 3.14 and 5.20 ppm for octahydro-[1,4]diazecine ring; at 3.64 ppm for carbon bound to both phenyl and cyanide groups; at 6.96-8.06 ppm for phenyl groups. The ^{13}C NMR spectra display several chemical shifts at 21 ppm for methyl group; at 23.4 ppm for carbon bound to both cyanide and phenyl groups; at 24.7-25.9, 27.7, 29.6, 30.9-38.1, 45.4-46.6, 53.1-89.8, 111.6-113.2, 126.9-129.8 and 129.8-136ppm for steroid moiety; at 27.3, 28.9, 30.8, 41.5, 46.9-48.8, 101.9 and 153.1 ppm for octahydro-[1,4]diazecine ring; at 115.3-115.4, 122.4-129.6, and 160.8-160.9ppm for phenyl groups; at 117.4 for cyanide group; at 168.4 ppm for carboxyl group. Finally, the mass spectrum from **6** showed a molecular ion (m/z) 661.35.



Scheme3. Synthesis of an azeta-steroid-dibenzenacyclotridecaphan-8-one derivative **8**. Reaction of steroid-ether derivative **5** with 4-hydroxybenzoic acid (v) to form a steroid-benzoic acid derivative **6**. Then, **6** was reacted with 5-hexyn-1-ol (vi) to synthesis of 17-hydroxy-steroid-diazecin-benzoic acid **7**. Finally, the compound **8** was prepared via internal esterification reaction with dicyclohexylcarbodiimide (vi)

Preparation of a steroid-azete derivative

Azete derivatives constitute a biologically important class of compounds; diverse azete compounds have been synthesized using several reagents such as for $Rh_2(OAc)_4$ [41], *N*-nitrenes [42], 2,3-dibromopropylamine [43], 1-aminoacetylenes [44] and others; it is important to note that some agents are dangerous and require special conditions. Therefore, in this study the compound **6** reacted with 5-hexyn-3-ol in the presence of CopperII to form an azete derivatives (**7**) via the addition 2 + 2 (Scheme 3). The ^{1}H NMR spectrum of the compound **7** showed several signals at 0.76 ppm for methyl group; at 1.14-1.38, 1.68-1.90, 2.44-2.60, 2.76-2.80 and 6.26-6.70 ppm for steroid moiety; at 5.66 ppm for both amino and hydroxyl groups; at 1.44, 1.98, 2.00-2.36, 2.42, 2.64-2.69, 3.14 and 5.20 ppm for octahydro-[1,4]diazecine ring; at 1.54, 1.65, 2.70 and 3.64 ppm for methylene groups bound to both hydroxyl and cyanide groups; at 3.70 ppm for carbon bound to both phenyl and cyanide groups; at 4.96 for azete ring; at 6.92-8.06 ppm for phenyl groups. The ^{13}C

NMR spectra display several chemical shifts at 21 ppm for methyl group; at 21.2, 31.3-32.6 and 62.2 ppm for methylene groups bound to both hydroxyl and azete ring; at 24.6-25.9, 27.7, 29.6, 30.9, 35.9-38.1, 45.4, 46.6, 53.1, 89.8, 111.6-113.2 and 129.8-136ppm for steroid moiety; at 27.3, 29, 30.8, 41.5, 46.9-48.8, 101.9 and 153.1 ppm for octahydro-[1,4]diazecine ring; at 45.5 ppm for carbon bound to both phenyl group and azete ring; at 11.3, 153.6 and 165.8 ppm for azete ring; at 113.8-129.5 and 160.8-161.2 for phenyl groups; at 168.4 ppm for carboxyl group. In addition, the mass spectrum from **7** showed a molecular ion (m/z) 759.42.

Synthesis of a steroid-ester derivative

There are diverse reagents to produce esters derivatives, nevertheless; most of the conventional methods have found only a limited use for this purpose [45–47]. In this study, a previously reported method for esterification of steroids was used [48]; in this sense, the compound **7** reacted with 4-hydroxybenzoic acid in the presence of dicyclohexylcarbodiimide to form **8** (Scheme 3). The ^{1}H NMR spectrum of the compound **8** showed several signals at 0.76 ppm for methyl group; at 1.14, 1.38-1.39, 1.66-1.90, 2.00-2.14, 2.34, 2.44, 2.76-2.80 and 6.26-6.70 ppm for steroid moiety; at 1.44, 1.98, 2.42, 2.60-2.70, 3.14 and 5.20 ppm for octahydro-[1,4]diazecine ring; at 1.22, 1.54, 2.26 and 4.30-4.32 ppm for methylene bound to both ester and azete ring; at 3.22 ppm for carbon bound to both phenyl group and azete ring; at 4.98 ppm for azete ring; at 6.88-8.14 ppm for phenyl groups. The ^{13}C NMR spectra display several chemical shifts at 21.02 ppm for methyl group; at 20.6, 27.9, 30.1and 67.4 ppm for methylene groups bound to both ester group and azete ring; at 24.7-25.9, 27.7, 29.6, 30.9-35.9, 38.1, 40.4-46.6, 53.1, 89.8, 111.6-113.2, 131.4-134 and 136-137ppm for steroid moiety; at 27.3, 29, 30.8, 41.5, 46.9-48.8, 101.9 and 153.1 ppm for octahydro-[1,4]diazecine ring; at 35.9 ppm for carbon bound to both phenyl group and azete ring; at 115.6-130.8, 135.2-135.3, 137.5 and 154.2-162.4ppm for phenyl groups; at 103.0, 139.7 and 163.5 ppm for azete ring; at 164.4 ppm for ester group. Additionally, the mass spectrum from **8** showed a molecular ion (m/z) 861.43.

Electronic parameters evaluation (HOMO and LUMO)

The molecular orbitals HOMO and LUMO for the compounds **7** and **8** were theoretically evaluated with SPARTAN'06 software, using Hartree-Fock method at 321-G level [37]. The results showed (Figure 1) that LUMO values were lower for the compound **8** as compared to **7**; in addition, HBD and HBA values were different for two compounds (Table 1), these data indicate that **8** has a different electron-donation ability as compared to **7**.

*Physicochemical parameters of both compounds **7** and **8***

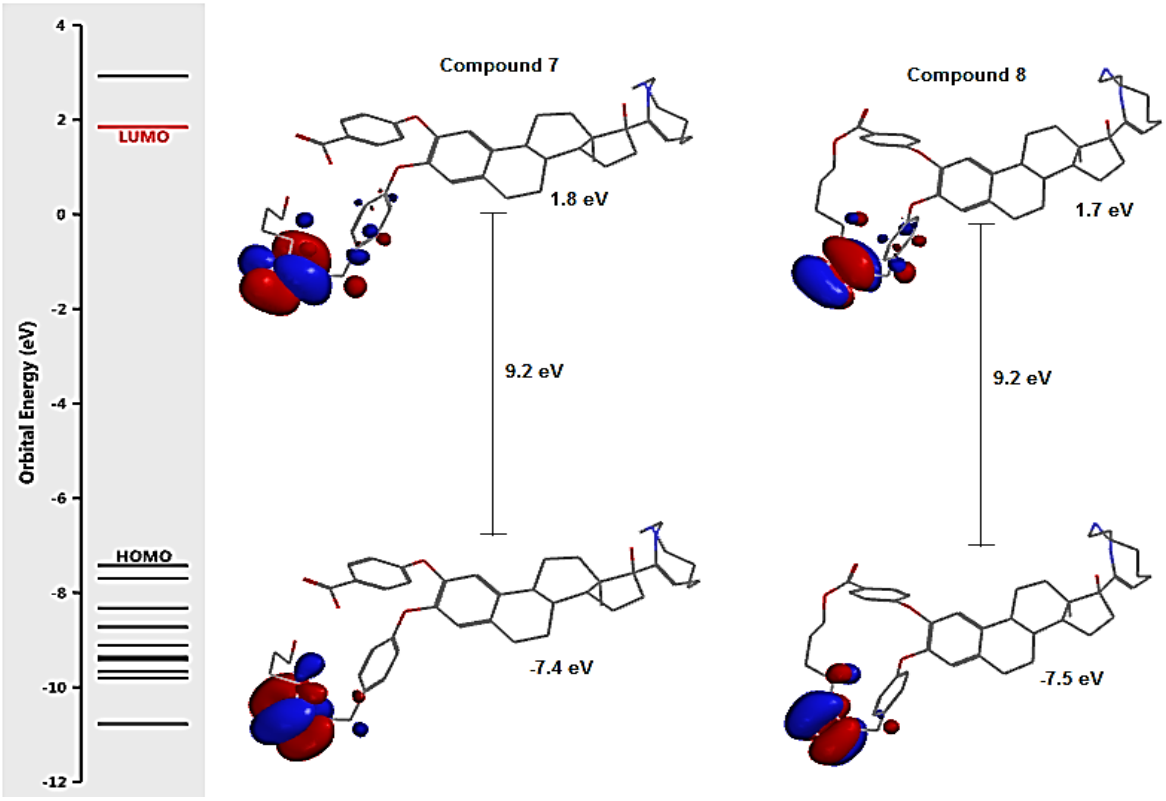


Figure 1. Molecular orbitals (HOMO and LUMO) involved in the compounds **8**. Visualized with SPARTAN'06 software

Some physicochemical parameters have been used as predictors of lipophilicity degree of some compounds such as logP and π [49]; in this sense, a theoretical analysis on lipophilicity degree of compound **7** and **8** was evaluated using the parameters *logP* and π. It is noteworthy that *logP* (logKow) determins the lipophilicity degree; in addition, logKow represents the lipophilic effects of all molecules [49]. The results shown in Table 1 indicated that logKow and π were higher for compound **8 as** compared to **7**.

This phenomenon could be conditioned by other chemicals involved in the chemical structure of **7** or **8** such as molar volume (M_V) and molar refractory (M_R) that are two physicochemical parameters which could produce several changes in some biological models. These physicochemical factors are tools for the correlation of different properties that depend on characteristics of substituents attached to a constant reaction center. To evaluate both M_V and M_R descriptors in this study, a previously reported method was used [50]. The theoretical results showed (Table 2) that M_V and M_R were higher for **8 as** compared to **7**. These data suggest that steric hindrance, conformational preferences, and internal rotation could be factors that influence the

biological activity by compound **8** on some biological model. Analyzing these data and a study which indicates that some physiochemical factors of several drugs such as hydrogen bond donor groups (HBD) hydrogen bond acceptor groups (HBA), and topological polar surface area (TPSA) are used to predict the biological activity of some compounds in different theoretical models [51]; in this study these physicochemical parameters (Table 1) were evaluated using the Spartan 6.0 software.

Table 1. Physicochemical parameters (logP, [logKow], and π) of both compounds **7** and **8**

Compound	Gropus	
Compound 7	-CH_3 (aliphatic carbon)	0.5473
	-CH_2 (aliphatic carbon)	8.3487
	-CH (aliphatic carbon)	1.0842
	C (aliphatic carbon - No H, not tert)	0.9723
	=CH- or =C< (olefinc carbon)	1.5344
	-OH (hydroxy, aliphatic attach)	-2.8172
	-NH (aliphatic attach)	-2.9924
	Aromatic Carbon	5.2920
	-O (aliphatic O, two aromatic attach)	0.5846
	-COOH (acid, aromatic attach)	-0.1186
	-tert Carbon (3 or more carbon attach)	0.5352
	-N=C (aliphatic attach)	-0.0010
	Multi-alcohol correction	0.4064
	Ortho-subst on di-aromatic ether (non-cyl)	-1.6792
	Fused aliphatic ring unit correction	-1.3684
	Equation Constant	0.2290
	π	2.6517
	Log Kow	10.5573
Compound 8	-CH_3 (aliphatic carbon)	0.5473
	-CH_2 (aliphatic carbon)	8.3487
	-CH (aliphatic carbon)	1.4456
	C (aliphatic carbon - No H, not tert)	1.9446
	-OH (hydroxy, aliphatic attach)	-1.4086
	-NH (aliphatic attach)	-2.9924
	Aromatic Carbon	5.2920

-O (aliphatic O, two aromatic attach)	0.5846
-C(=O)O (ester, aromatic attach)	-0.7121
-tert Carbon (3 or more carbon attach)	0.5352
-N=C (aliphatic attach)	-0.0010
Cyclic ester correction	-2.1154
Fused aliphatic ring unit correction	-1.3684
Equation Constant	0.2290
π	2.6517
Log Kow	13.2117

Table 2. Structural properties of both compounds **7** and **8**

Parameter	Compound **7**	Compound **8**
Molar refractivity	215.00 ± 0.5 cm^3	212.13 ± 0.5 cm^3
Molar volume	584.90 ± 7.0 cm^3	568.40 ± 7.0 cm^3
Parachor	1573.90 ± 8.0 cm^3	1526.20 ± 8.0 cm^3
Index of refraction	1656.00 ± 0.05	1.669.00 ± 0.05
Surface tension	52.30 ± dyne/cm	5.19 ± 7.0 dyne/cm
Density	1.29.01 g/cm^3	1.30 ± 0.45 g/cm^3
Polarizability	85.23 cm^3	84.09 ± 0.50 cm^3
Dipole moment	7.21 debye	6.70 debye
Topological polar surface area	105.111 $Å^2$	81.138 $Å^2$
E. HOMO	-7.4 eV	-7.5 eV
E. LUMO	1.8 eV	1.7 eV
HBD count	4	2
HBA count	8	7

The results indicate that HBA was < 10 and < 5 HBD and values these data indicate that both compounds **7** and **8** could be well absorbed such happening with another type of compounds [52]. Another result showed that TPSA for **8** was lower as compared to the compound **7**; It is noteworthy, that there are studies which indicate that this physicochemical parameter could condition the ability of drugs to penetrate the blood-brain barrier affinity and exhibit biological activity on intestine nervous central system [52].

Theoretical analysis

To evaluate the interaction of both compounds **7** and **8** with BRCA1 protein (1JM7) [24] a docking model was used [23]. The results showed (Figure 2 and Table 3 and 4) that **8** could interact with different types of amino acid residues of BRCA1 protein as compared to **7**.In addition,the theoretical results suggest that the distance between Asn_{16}, Gln_{19} and Lys_{20} is lower as compared to other aminoacid residues that may bound to compound **7**. Additionally, the Ile_{15}, Met_{18}, Gln_{19}, Ile_{21} and Leu_{22} aminoacid residues may have higher interaction with the compound **8**. Analyzing this hypothesis and other studies indicate that some thermodynamic parameters are evidences for confirming the interaction of drug-protein [54]. In this study a theoretical evaluation was carried out on some thermodynamic parameters such as free energy of binding, electrostatic energy, total intermolecular energy, vdW + on some thermodynamic parameters such as free energy of binding, electrostatic energy, total intermolecular energy, vdW + Hbond + desol energy and inhibition constant. The results showed differences in the intramolecular energy involved in the interaction for compound **7** or **8** with the BRCA1 protein.

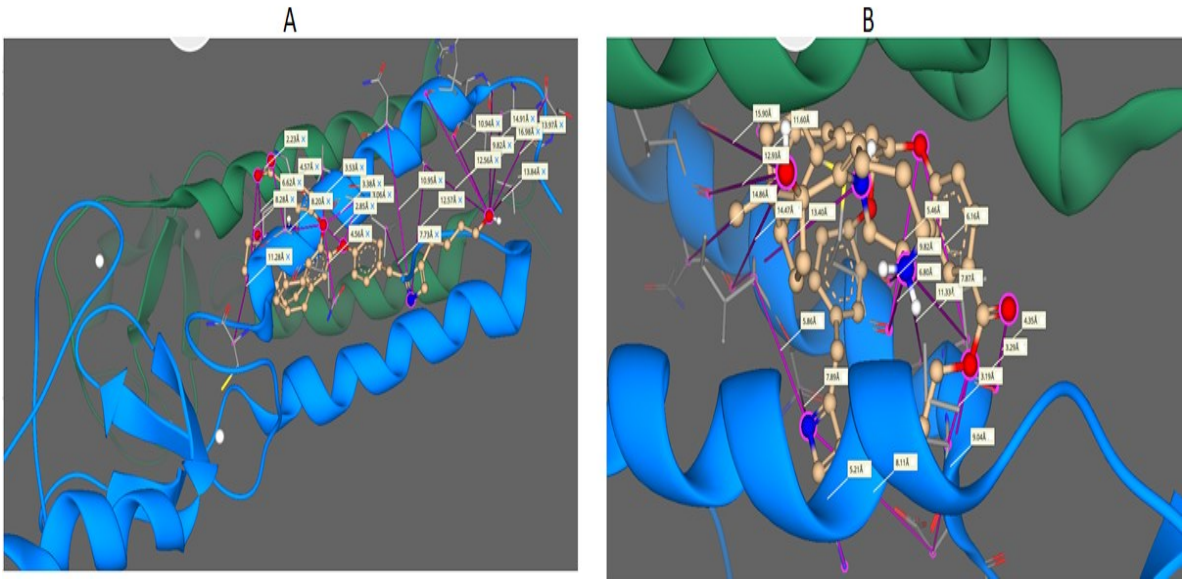


Figure 2. Distance between functional groups of both compounds **7** (A) and **8** (B) and aminoacid residues of BRCA1 protein (1JM7). Visualized with SeeQSAR software

Table 3. Distance between the aminoacid residues of 1JM7 protein and both nitrogen and oxygen atoms of compound **7**

Aminoacid residues	Nitrogen	Oxygen
Leu_3	–	13.84 (hydroxyl)
Ser_4	–	13.97 (hydroxyl)

Leu_6	–	16.98 (hydroxyl)
Arg_7	–	14.91 (hydroxyl)
Val_8	–	9.82 (hydroxyl)
Glu_9	–	10.94 (hydroxyl)
Val_{11}	–	12.56 (hydroxyl)
Ile_{15}	12.57 (azete ring)	–
Asn_{16}	7.73 (azete ring)	3.06 (ether)
Ala_{17}	10.95 (azete ring)	7.53 (ether)
Asn_{18}	–	–
Gln_{19}	–	4.56 (ether)
Lys_{20}	–	4.57, 6.62 (carboxyl)
Ile_{21}	–	8.28 (carboxyl)
Cys_{24}	–	11.28 (hydroxyl)

Table 4. Distance between the aminoacid residues of 1JM7 protein and both nitrogen and oxygen atoms of compound **8**

Aminoacid residues	Nitrogen	Oxygen
Glu_{10}	–	15.90 (hydroxyl)
Val_{11}	–	12.93 (hydroxyl)
Gln_{12}	13.40 (diazecine ring)	14.47 (hydroxyl)
Asn_{13}	–	14.86 (hydroxyl)
Val_{14}	–	11.60 (hydroxyl)
Ile_{15}	5.86 (azete ring)	–
Asn_{16}	7.89 (azete ring)	–
Ala_{17}	9.82 (diazecine ring)	–
Met_{18}	6.80 (diazecine ring)	5.46 (ether)
Gln_{19}	5.21 (azete ring)	–
Lys_{20}	11.38 (diazecine ring)	6.16 (ether)
Ile_{21}	7.87 (diazecine ring)	3.29, 4.35 (ester)
Leu_{22}	–	3.19 (ester)
Glu_{23}	8.11 (azete ring)	9.04 (ester)

Conclusion

The resulted data indicate that both compounds **7** or **8** could interact in a manner different from amino acids residues on the surface of BRCA1 protein which could be the result of different functional groups involved in the chemical structure of the compounds.

Disclosure statement

No potential conflict of interest was reported by the authors.

Orcid

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