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Design and synthesis of two azete-phenylene-dibenzoic acid derivatives and theoretical evaluation of their interaction with BRCA-1 protein

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ABSTRACT

Several compounds have been prepared to the treatment of breast cancer; however, some of these drugs may produce some adverse effects. The objective of this investigation carried out the synthesis of two azete-phenylene-dibenzoic acid derivatives (compounds **4** or **5**) and analyze its theoretical interaction with the BRCA-1 protein surface. The preparation of 4 and **5** was carried out using a series of reactions which involves; *i*) addition (2 + 2); *ii*) etherification and *iii*) formation of allylamino groups. Chemical structure of azete derivatives was carried out using elemental analysis and nuclear magnetic resonance spectra. The following stage involved the theoretical evaluation of the interaction of both compounds **7** or **8** with BRCA-1 protein surface using a docking model. The results showed that compound **4** could bound to the different type of aminoacid residues of BRCA-1 protein compared with **5**. All these data indicate that both compounds could be an alternative therapy for treatment of breast cancer via BRCA-1 protein inhibition.

Keywords: *BRCA-1 protein, breast cancer, azete-phenylene-dibenzoic acid derivatives, protein inhibition.*

1. INTRODUCTION

Breast cancer is one of the main health problems worldwide [1-4]. Some drugs have used for the treatment of 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 of 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 were prepared which showed effects against MCF-7 cells (human breast adenocarcinoma) via estrogen receptor inhibition [9]. Another report has shown the synthesis of a series of acridone derivatives and inhibition of breast cancer via interaction with ABCG2 protein [10]. Additionally, a study indicates that ellagic-acid has effects against cancer breast in MCF-7 cells via estrogen receptor inhibition [11]. Other data have shown the synthesis of a 17β-estradiol derivative with biological activity on breast cancer cells via estrogen receptor activation. [12]. Also, a report showed that some estradiol and estrone derivatives exert effects against breast cancer cells [13]. In addition, a study indicated that some carboxamide derivatives can exert effects on a breast cancer protein (BRCA-1) [14]. Other study showed that a methyl-ester analog can produce breast cancer via BRCA1 activation [15].

It is noteworthy that a variety of theoretical methods have been used to characterize the biological activity of some compounds against breast cancer; for example, a theoretical study suggests that some mangrove derivatives could have biological activity on BRCA-1 [16]. Also, a study showed the preparation of a series of 3-acyl-5-hydroxybenzofuran derivatives and their theoretical evaluation on breast cancer using a quantum mechanics polarized ligand docking study [17]. Another report indicates that endoxifen and 4-hydroxy tamoxifen have antiestrogenic activity against cancer cells using a docking model [18]. All these results indicate that some drugs exert their effects on cancer breast; analyzing these data, in this study two azete-phenylene-dibenzoic acid derivatives were synthesized. In addition, a theoretical study was carried out to characterize its interaction with BRCA1 protein (1N5O) using a docking model.

2. EXPERIMENTAL SECTION

Chemical synthesis. All the reagents used in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point for azete derivatives was carried out on an Electrothermal (900 model). Infrared spectra (IR) was analyzed using KBr pellets on a Perkin Elmer Lambda 40 spectrometer.^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectrum was determinate 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 analyzed using a

Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were carried out using a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

Preparation of a dinitrobenzoyl-azete-dione derivative

A solution of 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphtalene-5,8-dione (87 mg, 0.50 mmol), 2-(4-nitrophenyl)acetonitrile (162 mg; 1.00 mmol), CopperII chloride anhydrous (135 mg; 1.00 mmol) and 5 ml methanol was stirring at room temperature for 48 h. The solvent of mixture obtained was removed under reduced pressure and purified by crystallization using the methanol:water (4:1) system.

(2aR,3R,3aS,7aR,8R,8aS)-2,5-bis(4-nitrobenzyl)-2a,3,3a,4a,6a,7a,8,8a-octahydro-3,8-methanonaphtho[2,3-b:7,6-b']bis(azete)-4,7-dione (2)

yielding 54 % of product, m.p. 84-86 ^{o}C; IR (V_{max}, cm^{-1}) 3320, 1722 and 1485: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.62-2.86 (m, 3H), 2.96-2.98 (m, 2H), 3.56 (m, 2H), 3.68 (m, 1H), 3.70 (m, 2H), 4.50-5.20 (m, 2H), 5.50-5.60 (m, 2H), 7.26-7.94 (m, 8H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 27.66,42.80, 4.68, 44.82, 48.50, 50.80, 51.22, 52.09, 52.25, 52.55, 68.26, 123.92, 124.15, 129.02, 129.60, 140.22, 140.28, 146.64, 172.92, 178.16, 192.42, 199.00 ppm. EI-MS m/z: 498.15 Anal. Calcd. for $C_{27}H_{22}N_4O_6$: C, 65.05; H, 4.45; N, 11.24; O, 19.26 Found: C, 65.00; H, 4.38.

Synthesis of a dioxo-azete-dibenzoic acid (3)

A solution of **2** (250 mg; 0.50 mmol), 4-hydroxybenzoic acid (140 mg; 1.02 mmol), boric acid (62 mg; 1.00 mmol) and 5 ml methanol was stirring to room temperature for 48 h. The solvent of mixture obtained was removed under reduced pressure and purified by crystallization using the methanol:water (4:1) system.

4,4'-(((((2aR,3R,3aS,7aR,8R,8aS)-4,7-dioxo-2a,3,3a,4,4a,6a,7,7a,8,8a-decahydro-3,8-methanonaphtho[2,3-b:7,6-b']bis(azete)-2,5-diyl)bis(methylene))bis(4,1-phenylene))bis(oxy))dibenzoic acid (3)

yielding 48 % of product, m.p. 180-182 ^{o}C; IR (V_{max}, cm^{-1}) 3322, 1720, 1485 and 1148: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.62-2.86 (m, 3H), 2.96-2.98 (m, 2H), 3.56 (m, 2H), 3.68 (m, 1H), 3.70 (m, 2H), 4.50-5.20 (m, 2H), 5.50-5.60 (m, 2H), 6.82-8.04 (m, 16H), 10.82 (broad, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 27.70, 42.80, 44.68, 44.82, 48.51, 50.80, 51.22, 52.06, 52.25, 52.55, 68.28, 114.72, 115.04, 117.22, 124.22, 126.50, 126.54, 129.72, 130.38, 133.90, 156.70, 158.25, 168.40, 172.92, 178.12, 192.42, 199.00 ppm. EI-MS m/z: 680.21. Anal. Calcd. for $C_{41}H_{32}N_2O_8$: C, 72.34; H, 4.74; N, 4.12; O, 18.80 Found: C, 72.26; H, 4.68.

Preparation of a 3-hydroxy-4-methoxyphenyl-allyl-azete-dibenzoic acid derivative (4)

A solution of **3** (340 mg; 0.50 mmol), eugenol (164 mg; 1.00 mmol), boric acid (62 mg; 1.00 mmol) and 5 ml methanol was stirring to room temperature for 48 h. The solvent of mixture obtained was removed under reduced pressure and purified by crystallization using the methanol:hexane:water (4:2:1) system.

4,4'-(((((2aS,3R,3aS,7aR,8R,8aS)-1,6-bis((E)-3-(3-hydroxy-4-methoxyphenyl)allyl)-4,7-dioxotetradecahydro-3,8-methano-naphtho[2,3-b:7,6-b']bis(azete)-2,5-diyl)bis(methyl-ene))bis(4,1-phenylene))bis(oxy))dibenzoic acid (4)

yielding 38 % of product, m.p. 220-222 ^{o}C; IR (V_{max}, cm^{-1}) 1722, 1710, 1182 and 1146: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.54-1.86 (m, 2H), 2.36 (m, 1H), 2.38-2.48 (m, 1H), 2.60 (m, 1H), 2.68 (m, 1H), 2.80 (m, 1H), 2.96 (m, 1H), 3.00 (m, 1H), 3.06-3.18 (m, 2H), 3.34 (m, 1H), 3.36 (m, 1H), 3.37-3.48 (m, 2H), 3.76 (m, 1H), 4.10-4.30 (m, 2H), 5.14 (m, 1H), 6.30 (d, 1H, J = 6.44 Hz), 6.42 (d, 1H, J = 6.44 Hz), 6.72 (m, 2H), 6.78-7.00 (m, 8H), 7.20-8.05 (m, 18H), 10.90 (broad, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 31.22, 39.90, 42.12, 42.80, 49.55, 51.00, 53.98, 55.25, 55.72, 56.02, 56.04, 56.10, 56.82, 66.42, 73.11, 111.94, 113.00, 117.25, 120.70, 124.25, 125.85, 126.10, 126.12, 127.02, 127.32, 127.87, 128.23, 128.92, 129.14, 130.76, 133.15, 133.42, 135.89, 147.70, 149.88, 155.17, 158.25, 168.40, 198.44, 206.12 ppm. ppm. EI-MS m/z: 1008.38 Anal. Calcd. for $C_{61}H_{56}N_2O_{12}$: C, 72.60; H, 5.59; N, 2.78; O, 19.03 Found: C, 72.52; H, 5.50.

Preparation of a 1,6-dicinnamyl-4,7-dioxo-azete-2,5-diyl-dibenzoic acid (5)

A solution of **3** (340 mg; 0.50 mmol), cinnamaldehyde (132 mg; 1.00 mmol), boric acid (62 mg; 1.00 mmol) and 5 ml methanol was stirring to room temperature for 48 h. The solvent of mixture obtained was removed under reduced pressure and purified by crystallization using the methanol:water (4:1) system.

4,4'-(((((2aS,3R,3aS,7aR,8R,8aS)-1,6-dicinnamyl-4,7-dioxote-tradecahydro-3,8-metha-nonaphtho[2,3-b:7,6-b']bis(azete)-2,5-diyl)bis(methylene))bis(4,1-phenylene))bis(oxy))dibenzoic acid (5)

yielding 45 % of product, m.p. 214-216 ^{o}C; IR (V_{max}, cm^{-1}) 1722, 1712, 1148 and 1178: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.54-1.86 (m, 2H), 2.36 (m, 1H), 2.38-2.48 (m, 1H), 2.60 (m, 1H), 2.68 (m, 1H), 2.80 (m, 1H), 2.96 (m, 1H), 3.00 (m, 1H), 3.06-3.18 (m, 2H), 3.34 (m, 1H), 3.36 (m, 1H), 3.37-3.48 (m, 2H), 3.76 (m, 1H), 4.10-4.30 (m, 2H), 5.14 (m, 1H), 6.30 (d, 1H, J = 6.44 Hz), 6.42 (d, 1H, J = 6.44 Hz), 6.74 (m, 2H), 6.78-7.00 (m, 8H), 7.20-7.40 (m, 12H), 7.56-8.06 (m, 6H), 10.90 (broad, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 31.22, 39.92, 42.12, 42.82, 49.55, 51.00, 53.98, 55.22, 55.72, 56.04, 56.82, 66.42, 73.14, 117.22, 124.25, 125.85, 125.92, 126.10, 126.12, 127.02, 127.30, 127.87, 128.23, 128.60, 128.92, 129.14, 129.16, 133.87, 135.52, 135.79, 155.17, 158.25, 168.40, 198.47, 206.14 ppm. EI-MS m/z: 916.37., Anal. Calcd. for $C_{59}H_{52}N_2O_8$: C, 77.27; H, 5.72; N, 3.05; O, 13.96 Found: C, 72.52; H, 5.50.

Physicochemical properties of compounds 4 and 5

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, logP (logKowin), molecular refractivity (M_R), volume reactivity (V_R) were determined using both ChemSketch and Avogadro programs [19-21].

Interaction of both compound 4 or 5 with BRCA1 protein.

Interaction of compounds **4** or **5** with aminoacid residues of BRCA1 protein surface (1N5O) were determinated using Dockingserver program [22, 23].

Thermodynamic parameters. Theoretical evaluation was carried out on some thermodynamic parameters involved between the interaction of both compounds **7** and **8** with BRCA1 protein (1N5O) [23].

3. RESULTS SECTION

Preparation of an azete derivative

Azete derivatives constitute a biologically important class of compound. Therefore, diverse azete compounds have been synthesized using several reagents such as for $Rh_2(OAc)_4$ [24], N-nitrenes [25], 2,3-dibromopropylamine [26], 1-aminoacetylenes [27] and others; it is noteworthy, that some agents are dangerous and require special conditions. Therefore, in this study 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphtalene-5,8-dione reac- ted with 2-(4-nitrophenyl)acetonitrile in presence of CopperII to form an azete derivatives (**2**) via addition 2 + 2 (Figure 3). ^{1}H NMR spectra of the compound **2** showed several signals at 1.62-2.86, 3.68 and 5.50-5.60 ppm for bicyclo[2.2.1]heptane; at 2.96-2.98 ppm for cyclohexane-1,4-dione ring; at 3.56 and 3.70 ppm for methylene bound to both azete ring and phenyl groups; at 4.50-5.20 ppm for azete ring; at 7.26-7.94 ppm for both phenyl groups. The ^{13}C NMR spectra display chemical shifts at 27.66-42.80, 48.50-50.80 and 52.09 ppm for bicyclo[2.2.1]heptane; at 42.82 ppm for methylene bound to both azete ring and phenyl groups; at 51.22 and 52.55 ppm for cyclohexane-1,4-dione ring; at 68.26, 172.92-178.16 ppm for azete ring; at 123.90-146.64 ppm for both phenyl groups; at 192.42-199.00 ppm for ketone group. In addition, the mass spectrum from **2** showed a molecular ion (m/z) 498.18.

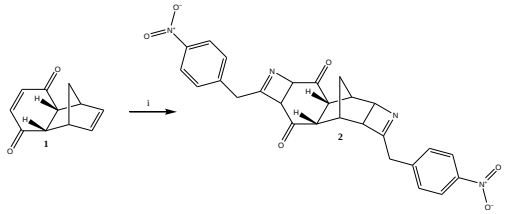

Fig. 1. Preparation of a dinitrobenzoyl-azete-dione derivative (**2**). Reaction of 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphtalene-5,8-dione with 2-(4-nitrophenyl)acetonitrile to form **2**. i = CopperII chloride anhydrous.

Synthesis of an ether derivative

Some reports showed the preparation of several ether derivatives via displacement of the nitro group using methoxide as dipolar aprotic solvent [28, 29]. In this study, compound **3** was synthesized by the reaction of **2** with 4-hydroxybenzoic acid in presence of dimethyl sulfoxide at mild conditions (Figure 2).

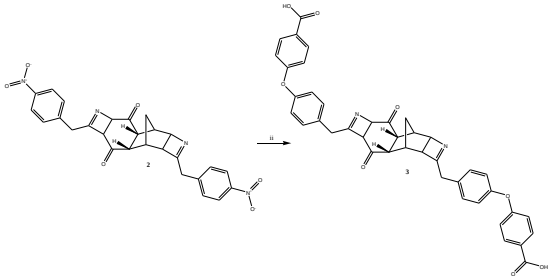

Fig. 2. Synthesisof a dioxo-azete-dibenzoic acid derivative (**3**). Reaction of **2** with 4-hydroxybenzoic acid to form **3.** ii = dimethyl sulfoxide.

^{1}H NMR spectra of **3** showed several signals at 1.62-2.86, 3.68-3.70 and 5.50-5.60 ppm for bicyclo[2.2.1]- heptane; at 2.96-2.98 ppm for cyclohexane-1,4-dione ring; at 3.56 ppm for methylene group bound to both azete ring and phenyl group; at 4.50-5.20 ppm for azete ring; at 6.82-8.04 ppm for phenyl groups; at 10.82 ppm for carboxyl group. ^{13}C NMR spectrum showed several chemical shifts at 27.70-42.80, 48.51-50.80 and 52.06 ppm for bicyclo[2.2.1]heptane; at 44.68-44.82 ppm for methylene linked to both azete ring and phenyl group; at 51.22-52.55 ppm for cyclohexane-1,4-dione ring; at 68.28 and 172.92-178.12 ppm for azete ring; at 114.72-158.25 ppm for phenyl groups; at 168.40 ppm for carboxyl group; at 192.42-199.00 ppm for ketone groups. Finally, the mass spectrum from **3** showed a molecular ion (m/z) 680.21.

Preparation of allylamine derivatives (4 or 5)

There are several studies had shown for the synthesis of allylamine analogs using some reagents such as paraformaldehyde [30], rhodium [31], $Pd(OAc_2)$ [32], Iodine [33] and others. In this investigation, two allylamine derivatives were synthetized by the reaction of **3** with cinnamaldehyde or eugenol to form **4** or **5** in presence of boric acid. ^{1}H NMR spectrum for compound **4** showed several signals at 1.55-1.86 and 2.38-2.48 ppm for bicyclo[2.2.1]heptane; at 2.36, 2.62-2.68 and 2.94 ppm for both methylene groups bound to azete rings and phenyl groups; at 2.80 and 3.00 ppm for cyclohexane-1,4-dione ring;; at 3.06-3.18 and 3.37-3.48 ppm for both methylene groups bound to azete rings and alkene groups; at 3.34-3.36, 3.76 and 410-5.14 ppm for both azete rings; at 3.90 for methyl group; at 6.30-6.60 ppm for alkene groups; at 6.78-7.56 and 8.04 ppm for phenyl groups; at 7.90 for both carboxyl groups. The ^{13}C NMR spectra display chemical shifts at 31.22, 41.12 and 55.72 ppm for bicyclo[2.2.1]heptane; at 39.90-39.92-51.00 ppm for both methylene groups bound to azete rings and phenyl groups; at 53.98-56.80 ppm for both azete rings; at 56.02-56.04 for both methylene groups bund to azete rings and alkene groups; at 55.25 and 73.11 ppm for cyclohexane-1,4-dione ring; at 56.10 ppm for methyl group; at 111.94-126.10, 127.32-158.25 ppm for phenyl groups; at 126.12-127.02 ppm for both alkene groups: at 168.40 ppm for both carboxyl groups. In addition, the mass spectrum from **4** showed a molecular ion (m/z) 1008.38.

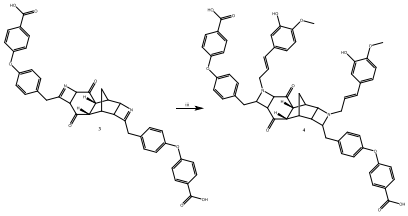

Fig. 3. Preparation of a 3-hydroxy-4-methoxyphenyl-allyl-azete-dibenzoic acid derivative (**4**). Reaction of **3** with eugenol using boric acid as catalyst (iii) to form **4.**

On the other hand, ^{1}H NMR spectrum for compound **5** showed several signals at 1.54-1.86, 2.38-2.48 and 3.36 ppm for bicyclo[2.2.1]heptane; at 2.36, 2.60-2.68 and 2.96 ppm for both methylene groups bound to azete rings and phenyl groups; at 2.80 and 3.00 ppm for cyclohexane-1,4-dione ring; at 3.06-3.18 and 3.37-3.48 ppm for both methylene groups bund to azete rings and alkene groups; at 3,34 and 3.76-5.14 ppm for both azete rings; at 6.30-6.74 ppm for both alkene groups; at 6.78-8.06 ppm for phenyl groups; at 10.90 ppm for both carboxyl groups. ^{13}C NMR spectrum showed several signals at 31.22, 41.12 and 55.72 ppm

for bicyclo[2.2.1]heptane; at 39.92-51.00 ppm for both methylene groups bound to azete rings and phenyl groups; at 53.98-55.22 and 56.82-73.14 ppm for both azete rings; at 56.04 for both methylene groups bound to azete rings and phenyl groups; at 117.22-126.10, 127.30-128.92 and 129.16-158.25 ppm for phenyl groups; at 126.12-127.02 and 129.14 ppm for alkene groups; 168.40 ppm for both carboxyl groups; 198.40-206.10 ppm for ketone groups. finally, the mass spectrum from **5** showed a molecular ion (m/z) 916.37.

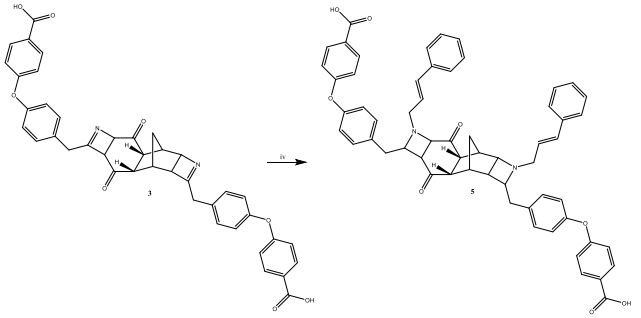

Fig. 4. Preparation of a 1,6-dicinnamyl-4,7-dioxo-azete-2,5-diyl-dibenzoic acid (**5**). Reaction of **3** with cinnamaldehyde in presence of boric acid (iv).

Theoretical evaluation of electronic parameters associated to compounds 4 or 5.

Both molecular orbitals HOMO and LUMO for **4** and **5** were determinate using SPARTAN'06 software, with Hartree-Fock method at 321-G level [34]; the results indicated that both HOMO and LUMO values were higher for **5** compared with **4**.

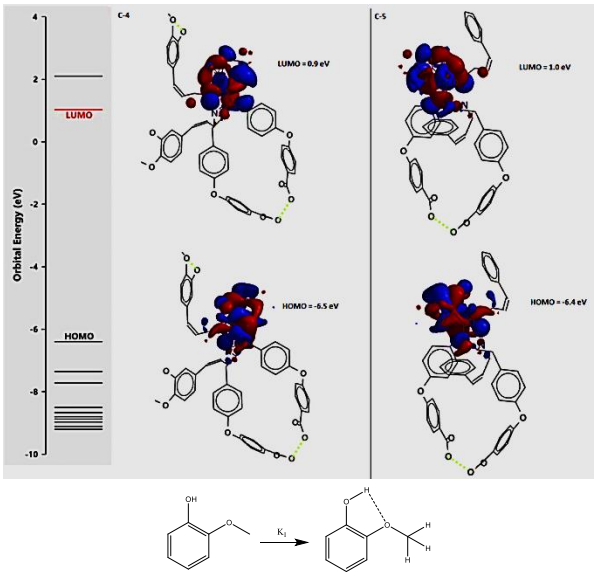

Fig. 5. In the scheme I are showed the electronic parameters such as HOMO and LUMO for both compounds 4 (C-4) and **5** (C-5), visualized with Spartan 6.0 software. In addition, is showed the possible intramolecular interaction (Ki) between both methoxy and hydroxyl groups.

Other data showed that HBD and HBA values were different for two compounds (Table 1), all these results suggest that **5** have a different electron donation ability compared to **4**; this phenomenon may be conditioned by both methoxy and hydroxyl grups bound to phenyl groups of **4**.

Physicochemical parameters of both compounds 4 and 5

Some physicochemical parameters have used to predictors of lipophilicity degree of some compounds such as logP and π [35]; in this sense, a theoretical analysis on lipophilicity degree of compound **4** and **5** was evaluated using the parameters *logP* and π. It is noteworthy that *logP* (logKow) determinate the lipophilicity degree; in addition, therefore, logKow represents the lipophilic effects of all molecule [35]. The results shown in Table 1 indicated that logKow and π were higher for compound **5** compared to **4**, which translates to more lipophilicity.

Table 1. Physicochemical factors (logKow and π) involved in the compounds 7 and 8.

Compound	Fragment	Value
4	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2$ [aliphatic carbon]	2.4555
	-CH [aliphatic carbon]	3.6140
	=CH- or =C< [olefinc carbon]	1.5344
	-N< [aliphatic attach]	-3.6646
	Aromatic Carbon	10.5840
	-OH [hydroxy, aromatic attach]	-0.9604
	-O- [oxygen, one aromatic attach]	-0.9328
	-O- [aliphatic O, two aromatic attach]	0.5846
	-C(=O)- [carbonyl, aliphatic attach]	-3.1172
	-COOH [acid, aromatic attach]	-0.2372
	Fused aliphatic ring unit correction	-1.3684
	Internal aliphatic fused-ring ketone cor.	0.7044
	Benzene to -C-C-N- correction	-0.4452
	Ring reaction -> alkyloxy ortho to –OH	-0.5120
	-N-C-C(=O)-carbon structure correction	0.7616
	Equation Constant	0.2290
	π	0.1643
	Log Kow	10.3243
5	$-CH_2$ [aliphatic carbon]	2.4555
	-CH [aliphatic carbon]	3.6140
	=CH- or =C< [olefinc carbon]	1.5344
	-N< [aliphatic attach]	-3.6646
	Aromatic Carbon	10.5840
	-O- [aliphatic O, two aromatic attach]	0.5846
	-C(=O)- [carbonyl, aliphatic attach]	-3.1172
	-COOH [acid, aromatic attach]	-0.2372
	Fused aliphatic ring unit correction	-1.3684
	Internal aliphatic fused-ring ketone cor.	0.7044
	Benzene to -C-C-N- correction	-0.4452
	-N-C-C(=O)-carbon structure correction	0.7616
	Equation	0.2290
	π	1.3106
	Log Kow	11.6349

This phenomenon could be conditioned by other physicochemical parameters of **4** or **5** 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 parameters are tools that can relate different chemical properties that depend on the characteristics of the substituents of compounds 4 or 5. To evaluate both M_V and M_R descriptors in this study, a previously method reported was used [36]. The theoretical results showed (Table 1) that M_V and M_R were higher for **4** compared with **5**. These data suggest that steric hindrance, conformational preferences, and internal rotation could be factors that influence the biological activity by compound **4** on some biological model. Analyzing these data and a study which indicate that some physiochemical factors of several drugs such as hydrogen bond donor groups (HBD) and hydrogen bond acceptor groups (HBA), topological polar surface area (TPSA) are used to predict the effect exerted by some compounds on biological targets using several theoretical models [37]; in this study these physicochemical parameters (Table 1) were evaluated using the Spartan 6.0 software. The results indicate that HBA was < 15 and < 10 HBD and values these data indicate that both compounds **4**

and **5** could be well absorbed such happening with another type of compounds [38].

Table 2. Electronic parameters involved in the compound 7 and 8.

Parameter	Compound 4	Compound 5
M_R (cm^3)	286.06 ± 0.3	264.94 ± 0.3
M_V (cm^3)	745.80 ± 0.3	700.90 ± 6.0
Energy (kcal/mol)	-3329.69	-2954.31
Energy HOMO (ev)	-6.4	-6.5
Energy LUMO (ev)	0.9	1.0
Energy-gap = E. HOMO - E. LUMO (ev)	-7.4	-7.4
TPSA ($Å^2$)	150.87	102.26
HBD	4	2
HBA	12	8

Another result showed that TPSA for **4** was higher compared the compound **5**; it is important to mention, 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 [39].

Theoretical analysis.

To evaluate the interaction of both compounds **4** and **5** with BRCA1 protein (1N5O) [23] a docking model was used [23]. The results showed (Figure 6 and 7) that **4** could interaction with some amino acid residues of BRCA1 protein such as Ile_{1680}, Leu_{1701}, Lys_{1702}, Tyr_{1703}, Phe_{1704}, Leu_{1705}, Ile_{1707}, Ala_{1708}, Lys_{1711}, Val_{1713}, Val_{1736}, Asp_{1739}, Asn_{1742}, Pro_{1749}, Lys_{1759}, Phe_{1772}, Arg_{1775}, leu_{1780}, Met_{1783}, Leu_{1786}, Val_{1809}, Arg_{1835}, Val_{1838}, Leu_{1839} and Val_{1842}.

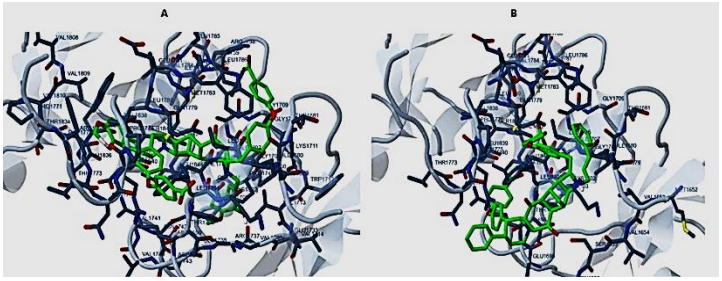

Fig. 6. The scheme indicates the interaction of compounds **4** (A) or **5** (B) with BRCA1 protein surface. Visualized with GL mol Viewer, dockingserver.

Other theoretical data indicates that compound **5** could bound to several amino acid residues of BRCA1 protein such as Ser_{1655}, Ile_{1680}, Arg_{1699}, Thr_{1700}, Leu_{1701}, Lys_{1702}, Tyr_{1703}, Phe_{1704}, Leu_{1705}, Ile_{1707}, Ala_{1708}, Asn_{1774}, Arg_{1775}, Gln_{1779}, Trp_{1782}, Met_{1783}, Leu_{1786}, Cys_{1787}, Leu_{1839}, Val_{1842} and Ala_{1843}.

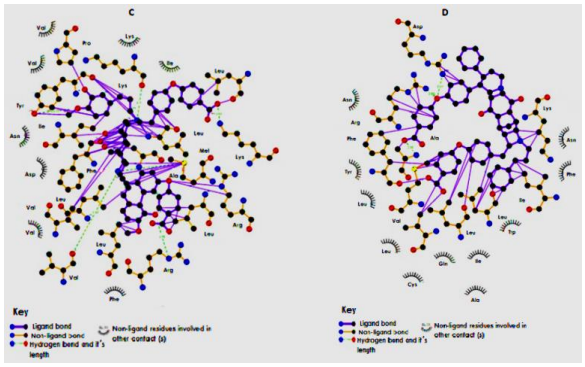

Fig. 7. The scheme indicates the binding site of some amino acid residues of BRCA1 protein with compounds **4** (C) or **5** (D). Visualized with GL mol Viewer, dockingserver.

These data indicate that interaction of compound **4** or **5** involves a different type of aminoacid residues involved in the BRCA1 protein surface; this phenomenon could be due to both methoxy and hydroxyl groups bound to phenyl groups from **4** compared with **5**.

Nevertheless, it is noteworthy that some studies suggest that several thermodynamic parameters could be evidence for confirming the interaction drug-protein [40]. Analyzing this hypothesis, in this study a theoretical study 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 + desolv. energy and inhibition constant.

Table 3. Electronic parameters involved in both compounds 4 and 5.

Comp.	Est. Free Energy of Binding (kcal/ mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrost. Energy (kcal/ mol)	Total Intermol. Energy (kcal/ mol)	Interact. Surface
4	$6.38e^{+04}$	$6.29e^{+04}$	-1.18	$6.29e^{+04}$	1401.645
5	$1.13e^{+04}$	$1.01e^{+04}$	1.05	$1.01e^{+04}$	1200.054

The results showed differences in the intramolecular energy involved in the interaction for compound **4** or **5** (Table 3) with the BRCA1 protein. These data suggest that **4** needs a higher contact with the protein surface, which translates as an increase in the binding energy compared with compound **5**.

4. CONCLUSIONS

All this data suggests that both compounds **4** or **5** could interact in a manner different with amino acids residues on the surface of BRCA1 protein which could be the result of differences in the chemical structure of compounds of this study.

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