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# Synthesis and theoretical analysis of interaction from an adamantane-steroid derivative with both COX-1 and COX-2

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## ABSTRACT

Several inhibitors of cyclooxygenases (COX-1 and COX-2) have been prepared using different protocols; however, these methods use some reagents that require special conditions. The objective of this study was synthesize a new adamantane-steroid derivative to evaluate their theoretical activity against both COX-1 and COX-2 enzymes using either indomethacin and rofecoxib as controls in a docking method. Theorethical data showed that the adamantane-steroid derivative could have a higher affinity for COX-1; this interaction could produce changes on biological activity of COX-1 enzyme. In conclusion, the theoretical evaluation indicates that this steroid-derivative could be a good prospect as an inhibitor of COX-1

**Keywords:** *Cyclooxygenase, adamantane, steroid, docking, inhibitor.*

## 1. INTRODUCTION

Several studies indicate that cardiovascular disorders are some important factors health worldwid [1-3]. There are several drugs for the treatment of some of these clinical pathologies such as acetylsalicylic acid (ciclooxygenase inhibitor) [4], dazoxiben (thromboxane synthase inhibitor) [5], ridogrel (a dual thromboxane synthase blocker and receptor antagonist) [6], daltroban [7] and ramatroban (thromboxane A2 receptor antagonists) [8]. However, some these drugs can produce several secondary effects such as gastrointestinal erosions, hemorrhage and renal injury [9-14]. In search of new therapeutic alternatives, several drugs have been prepared; for example, the synthesis of *E*)-7-[4-[4-[[(4-cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyri dyl)hept-6-enoic acid (a dual thromboxane synthase inhibitor-thromboxane receptor antagonists) from a carboxamide [15]. In addition, a report showed the preparation of 5-(methoxy)-2-[(2-hydrox-6-pentadecylphenyl)-methyl]-thio]-1H-benzimidazole from 2-Hydroxy-6-pentadecyl- benzyl as a cyclooxygenase (COX) inhibitor [16]. In addition, a benzenesulfonamide as COX inhibitor was synthesized via the reaction of an imidazole derivative with hydrochloric acid [17]. Also, a study shown the preparation of a ketosulfone from an enamine derivative as COX-2 inhibitor [18]. In addition, a series of arylhydrazone derivatives were synthesized from 1-(4-chlorophenyl)-4,4,4-trifuorobutane-1,3-dione as COX-2 inhibitors [19]. Data above mentioned indicate that several drugs have been synthesized as COX inhibitors; however the use of some reagents requires some special conditions for their preparation. Therefore, in this study was prepared a new adamantane-steroid derivative with the aim to evaluate their theoretical activity against both COX-1 and COX-2.

## 2. MATERIALS AND METHODS

### 2.1. General methods.

The reagents involved in this investigation were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point for compounds was determinate using an Electrothermal (900 model). Infrared spectra (IR) were evaluated using i50 FT-IR Nicolet spectrometer.$^{1}$H and $^{13}$C NMR (nuclear magnetic resonance) spectra were determinate with a Varian VXR300/5 FT NMR spectrometer at 300 MHz (megahertz) in $CDCl_3$ (deuterated chloroform). EIMS (electron impact mass spectroscopy) spectra were evaluated using a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were evaluated from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

### 2.2. Chemical Synthesis.

**17-Ethynyl-13-methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-deca-hydro-6H-cyclopenta[a] phenanthrene-3,17-diol (2)**

In a round bottom flask (10 ml), 17α-Ethynylestradiol (200 mg, 0.67 mmol), 5 ml of anhydride acetic and 1 ml of nitric acid were stirred to reflux for 6 h. The solvent of mixture was reduced pressure and purified via a crystallization using the methanol:water (4:1) system; yielding 44% of product; m.p. 156-158 $^{o}$C; IR ($V_{max}$, $cm^{-1}$) 3400, 2124 and 1322: $^{1}$H NMR (300 MHz, Chloroform-*d*) $\delta_H$: 1.10 (s, 3H), 1.22-2.00 (m, 9H), 2.10-2.90 (m, 6H), 3.36 (s, 1H), 6.66 (m, 1H), 7.22 (broad, 2H), 7.82 (m, 1H) ppm. 13.62, 22.80, 26.92, 27.22, 29.82, 32.90, 40.10, 40.22, 44.94, 46.96, 49.52, 74.33, 80.70, 89.12, 114.02, 123.52, 132.30, 132.90, 145.12, 148.44 ppm. EI-MS m/z: 341.16. Anal. Calcd. for

$C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; O, 18.75. Found: C, 70.30; H, 6.72.

**Preparation of 1-Adamantan-1-yl-4-(3,17-dihydroxy-13-methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-but-3-yn-1-one (3)**

In a round bottom flask (10 ml), compound **2** (200 mg, 58 mmol), 1-Adamantyl bromomethyl ketone (154 mg, 0.60 mmol), Copper(II) chloride anhydrous (100 mg, 0.74 mmol) and 10 ml of methanol were stirred to room temperature for 72 h. The solvent of mixture was reduced pressure and purified via a crystallization using the methanol:water:hexane (4:1:2) system; yielding 55% of product; m.p. 110-112 $^oC$; IR ($V_{max}$, $cm^{-1}$) 3402, 2196, 1722 and 1324: $^1H$ NMR (300 MHz, Chloroform-*d*) $\delta_H$: 0.92 (s, 3H), 1.22-1.50 (m, 4H), 1.58-1.64 (m, 6H), 1.70-1.74 (m, 2H), 1.78 (m, 3H), 1.83 (m, 1H), 1.84 (m, 3H), 1.87 (m, 1H), 1.92 (m, 3H), 2.10-2.90 (m, 7H), 4.08 (m, 2H), 6.66 (m, 1H), 7.61 (broad, 2H), 7.82 (m, 1H) ppm. $^{13}C$ NMR (300 Hz, $CDCl_3$) $\delta_C$: 12.82, 22.82, 26.92, 27.22, 28.32, 29.42, 29.83, 32.94, 37.94, 39.00, 39.50, 40.10, 44.96, 47.22, 47.37, 49.40, 81.72, 82.00, 97.47, 114.02, 123.54, 132.30, 132.92, 145.12, 148.44, 204.92 ppm. EI-MS m/z: 517.28. Anal. Calcd. for $C_{32}H_{39}NO_5$: C, 74.25; H, 7.59; N, 2.71; O, 15.45. Found: C, 74.20; H, 7.52.

**1-Adamantan-1-yl-4-(17-hydroxy-13-methyl-6,8,9,11,12,13,14,15,16,17-decahydro-7H-20-oxa-cyclopropa[2,3]cyclopenta[a]phenanthren-17-yl)-but-3-yn-1-one (4)**

In a round bottom flask (10 ml), compound **3** (200 mg, 0.38 mmol), potassium carbonate anhydrous (100 mg, 0.72 mmol) and 10 ml of dimethyl sulfoxide were stirred to room temperature for 72 h. The solvent of mixture was reduced pressure and purified via a crystallization using the methanol:water (3:1) system; yielding 67% of product; m.p. 50-52 $^oC$; IR ($V_{max}$, $cm^{-1}$) 3400, 1722 and 1172: $^1H$ NMR (300 MHz, Chloroform-*d*) $\delta_H$: 0.92 (s, 3H), 1.22-1.50 (m, 4H), 1.58-1.64 (m, 6H), 1.70-1.74 (m, 2H), 1.78 (m, 3H), 1.83 (m, 1H), 1.84 (m, 3H), 1.87 (m, 1H), 1.92 (m, 3H), 2.10-2.80 (m, 7H), 4.08 (m, 2H), 5.72 (broad, 1H), 6.30-6.33 (m, 2H) ppm. $^{13}C$ NMR (300 Hz, $CDCl_3$) $\delta_C$: 12.83, 22.82, 26.92, 27.20, 28.32, 29.42, 29.83, 32.94, 37.94, 39.00, 39.52, 40.10, 45.44, 47.24, 47.35, 49.50, 81.70, 82.00, 97.45, 108.90, 108.92, 130.34, 134.90, 147.42, 147.64, 204.92 ppm. EI-MS m/z: 470.28. Anal. Calcd. for $C_{32}H_{38}O_3$: C, 81.66; H, 8.14; O, 10.20. Found: C, 81.60; H, 8.10.

**2.3. Physicochemical parameters evaluation.**

Some electronic factors of compounds **3** and **4** such as $M_V$ (molar volume, $M_R$ (molar refractivity), 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 PSA (polar surface area) were evaluated using both ACD/Chem Sketch and SPARTAN'06 programs [20, 21].

**2.4. Pharmacophore evaluation.**

The 3D pharmacophore method for the compounds **3** and **4** was evaluated using LigandScout 4.08 software [22, 23].

**2.5. Theoretical interaction of compound 4 with both COX-1 and COX-2.**

The binding of compound **4** with both COX1-1 (2OYU) and COX-2 (3LN1) [28] was evaluated with the DockingServer program [24].

## 3. RESULTS

**3.1. Chemical synthesis.**

Several nitro derivatives have prepared using some reagents such as $Fe(NO_2)_3$ [25], sodium hydride [26], aryllithium [27], Iodine(III) [28] and others. In this study a bis-steroid-tetracyclodione derivative was synthesized; the first stage involved the reaction of ethinylestradiol with the nitric acid/anhydride acetic system (Figure 1).

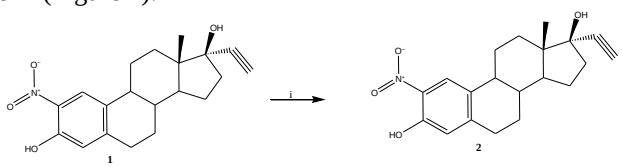


**Figure 1.** Synthesis of 17α-Ethynyl-13-methyl-2-nitro-steroid-3,17-diol (**2**). Reaction of 2-nitro-17α-Ethynylestradiol with nitric acid (i) to form **2**.

The $^1H$ NMR spectra for **2** showed several signals at 1.10 ppm for methyl group bound to steroid nucleus; at 1.22-2.90, 6.66 and 7.82 ppm for steroid moiety; 3.36 ppm for alkyne group; at 7.22 ppm for hydroxyl group. $^{13}C$ NMR spectra for **2** showed several signals at 13.62 ppm for methyl group; at 22.80-49.52, 80.70 and 114.02-148.44 ppm for steroid moiety; at 74.33 and 89.12 ppm for alkyne group. Additionally, the mass spectrum from **2** showed a molecular ion (m/z) 341.16.

Then, **2** reacted with 1-Adamantyl bromomethyl ketone to form an adamantanyl-steroid-butynone derivative (**3**) in the presence of Copper(II) chloride as catalyst (Figure 2) using a previous method reported (29). The $^1H$ NMR spectra for **3** showed several signals at 0.92 ppm for methyl group bound to steroid nucleus; at 1.22-1.50, 1.70, 1.74, 1.83, 1.87, 2.10-2.90, 6.66 and 7.82 ppm for steroid moiety; at 1.58-1.64, 1.78, 1.84 and 1.92 ppm for adamantane ring; at 7.61 ppm for both hydroxyl groups; at 4.08 ppm for methylene bound to both alkyne and ketone groups. $^{13}C$ NMR spectra for **3** showed several signals at 12.82 ppm for methyl group bound to steroid nucleus; at 22.82-27.22, 29.83-32.94, 39.00, 40.10-47.22, 49.96, 82.00 and 114.02-148.44 ppm for steroid moiety; at 28.32 ppm for methylene bound to both alkyne and ketone groups; 29.42, 37.94-39.50 and 47.37 ppm for adamantane ring; at 81.72 and 97.47 ppm for alkyne group; at 204.92 for ketone group. In addition, the mass spectrum from **3** showed a molecular ion (m/z) 517.28.

Finally, an adamantane-steroid ether derivative (**4**) was prepared using a previous method reported [29] through an internal intramolecular reaction, through of displacement of the nitro group by hydroxyl group involved in the chemical structure of compound **3** under mild conditions (Figure 2). The $^1H$ NMR spectra for **3** (Figure 3) showed several signals at 0.92 ppm for methyl group bound to steroid nucleus; at 1.22-1.50, 1.70-1.74,

1.82, 1.87, 2.10-2.80 and 6.30-6.33 ppm for steroid moiety; at 1.58-1.64, 1.78, 1.84 and 1.92 ppm for adamantane ring; at 4.08 ppm for methylene bound to both alkyne and ketone groups; at 5.72 ppm for hydroxyl group.

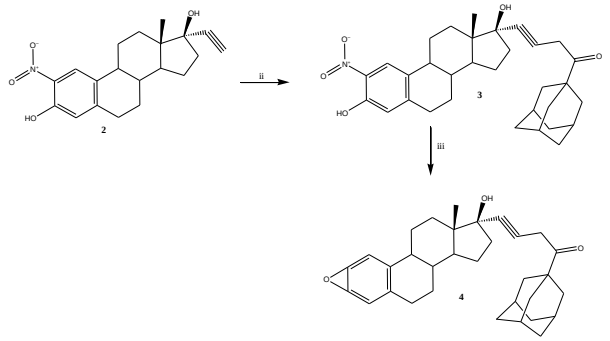

**Figure 2.** Preparation of an adamantane-steroid derivative (**4**). Reaction of 17α-Ethynyl-13-methyl-2-nitro-steroid-3,17-diol (**2**) with 1-Adamantyl bromomethyl ketone (ii) to form the adamantanyl-2-nitro-steroid-butynone complex (**3**). Then, **4** was prepared by an internal-intramolecular reaction via displazament of nitro by hydroxyl group of **3** using DMSO / K2CO3 (iii).

Finally, an adamantane-steroid ether derivative (**4**) was prepared using a previous method reported [29] through an internal intramolecular reaction, through of displacement of the nitro group by hydroxyl group involved in the chemical structure of compound **3** under mild conditions (Figure 2). The $^{1}$H NMR spectra for **3** (Figure 3) showed several signals at 0.92 ppm for methyl group bound to steroid nucleus; at 1.22-1.50, 1.70-1.74, 1.82, 1.87, 2.10-2.80 and 6.30-6.33 ppm for steroid moiety; at 1.58-1.64, 1.78, 1.84 and 1.92 ppm for adamantane ring; at 4.08 ppm for methylene bound to both alkyne and ketone groups; at 5.72 ppm for hydroxyl group.

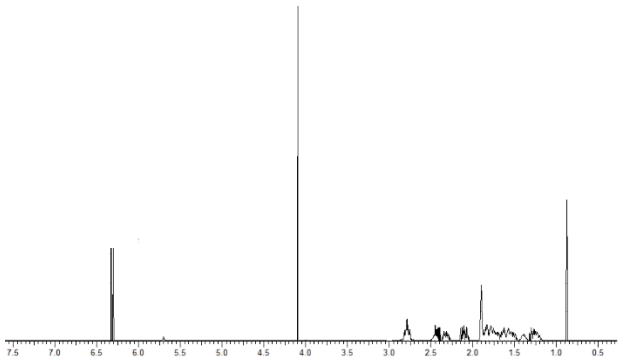

**Figure 3**. The scheme shown $^{1}$H NMR spectrum from compound **4**. Analyzed with a Varian VXR300/5 FT NMR apparatus at 300 MHz in CDCl3. Axis abscissa (ppm); ppm = parts per million.

$^{13}$C NMR spectra for **4** showed several signals at 12.83 ppm for methyl group bound to steroid nucleus; at 22.82-27.20, 29.83-32.94, 39.00, 40.10-47.24, 49.50, 82.00 and 108.90-147.64 ppm for steroid moiety; at 28.32 ppm for methylene group bound to both alkyne and ketone groups; at 29.42, 32.94, 39.52 and 47.35 ppm for adamantane ring; at 81.70 and 97.45 ppm for alkyne group; at 204.92 ppm for ketone group. Finally, the mass spectrum from **4** showed a molecular ion (m/z) 470.28.

***Electronic parameters.*** Molecular orbitals HOMO and LUMO for both compounds **3** and **4** were determinate using SPARTAN´06 software (Figure 4), with Hartee-Feck method at 321-G level [21]. The results showed that LUMO was higher for the compound **4** compared with **3**; this phenomenon could condition other type of physicochemical factors involved in the chemical structure of **4.**

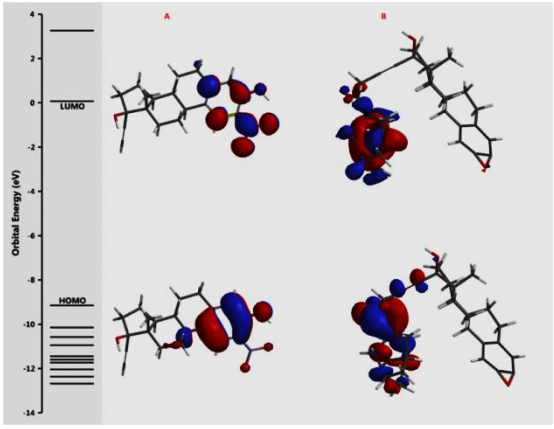


**Figure 4**. In the scheme are shown both HOMO and LUMO for either **3** (A) or **4 (B)**. The figure was visualized with SPARTAN´06 software.

***Physicochemical parameters of both compounds 3 and 4.*** To evaluate the hypothesis above mentioned, several reports were analyzed which indicate that physicochemical parameters such as molar volume ($M_V$) and molar refractory ($M_R$) could be correlated with different biological properties. Analyzing these data in this investigation, both $M_V$ and $M_R$ descriptors were determinate using a previous method reported [30]. The data found indicate that $M_V$ and $M_R$ were higher for **3** compared with **4** (Table 1). These results suggest that steric hindrance, conformational preferences, and internal rotation could be two factors which influence the biological activity to exert by **3** compared with **4** on some biological model. Nevertheless, it is noteworthy that also other physiochemical factors such as hydrogen bond donor groups (HBD) and hydrogen bond acceptor groups (HBA), topological polar surface area (TPSA) can exert changes on biologica activity in some system [31]. Therefore, these physicochemical parameters of compounds **2**-**4** were determinate using Spartan 6.0 software.

**Table 1.** Physicochemical parameters of the compounds **3** and **4**. The values were calculated using both ACDLabs and Spartan programs.

| Parameters | 3 | 4 |
|---|---|---|
| **Molar Refractivity (cm$^3$)** | 142.01 | 134.13 |
| **Molar Volume (cm$^3$)** | 390.10 | 368.70 |
| **Polarizability (cm$^3$)** | 56.29 | 53.17 |
| **Parachor (cm$^3$)** | 1115.10 | 1030.10 |
| **Index of refraction** | 1.64 | 1.64 |
| **Surface Tension (dyne/cm)** | 66.70 | 60.80 |
| **PSA Å$^2$** | 88.67 | 44.03 |
| **Density g/cm$^3$** | 1.32 | 1.27 |
| **HBD** | 2 | 1 |
| **HBA** | 5 | 2 |
| **HOMO (eV)** | -6.31 | -7.57 |
| **LUMO (eV)** | 0.03 | 2.96 |

The results showed that the HBA value was <5 and the HBD value was <6 for both compounds **3** and **4**, these data suggest that these compounds may be well absorbed such happening with another type of systems [32]. In addition, other results showed that polar surface area (PSA) for either **3** or **4** was < 100 Å values; here, it is noteworthy that some studies indicate that PSA<140 Å values could condition a good absorption of each drug [33].

***Pharmacophore asses.*** Several reports have shown that the pharmacophore model can be very useful to design new molecules with pharmacological activity. [34]. In this investigation, LigandScout software [14] was used to develop two pharmacophores from both compounds **3** and **4**. The results showed in Figures 5 indicated that several functional groups of compounds 3 and 4 could interact with some biomolecules through hydrophobic contacts or as hydrogen bond acceptors or as hydrogen bond donor.

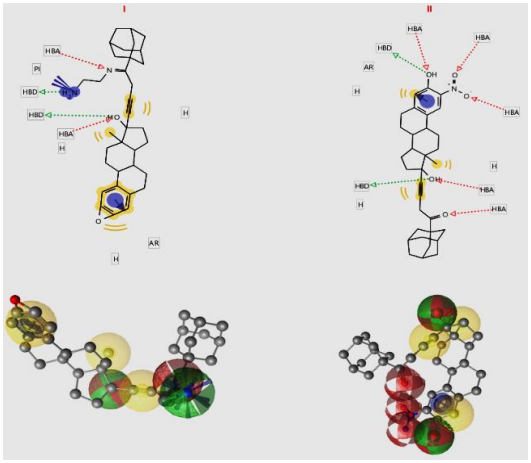

**Figure 5.** Scheme represents a pharmacophore from both compounds **3** (I) and **4** (II) using the LigandScout software. The model involves a hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, green).

***Interaction theoretical.*** There are several theoretical models to predict the binding of some drugs with protein or enzymes [35]. In this investigation, a theoretical analysis from the interaction of compound **4** with either COX1-1 (2OYU) and COX-2 (3LN1) was evaluated in a Docking model [24] using both indomethacin and rofecoxib as controls. The data (Table 3) showed differences in the interaction of either indomethacin or compound **4** on 2OYU protein surface. It is important to mention that only $Pro_{35}$ (red) could act in a similar form with both **4** and indomethacin.

**Table 3**. Aminoacid residues involved between the interaction of the interaction of compound **4** and indomethacin and 2OYU protein surface.

| Indomethacin | Compound 4 |
|---|---|
| **$Pro_{35}$** | $Val_{33}$ |
| **$Arg_{54}$** | $Pro_{35}$ |
| **$Tyr_{55}$** | $Tyr_{38}$ |
| **$Pro_{67}$** | $Pro_{40}$ |
| | $Tyr_{55}$ |

Other theoretical (Table 4) results showed a similar interaction between both rofecoxib and compound **4** with some $Ser_{23}$, $GLn_{27}$ and $Tyr_{40}$ amino acid residues (red) of COX-2 (3LN1).

**Table 4**. Aminoacid residues involved between the interaction of compounds 3, 4 and rofecoxib and 3LN1 protein surface.

| Rofecoxib | Compound 4 |
|---|---|
| **$Ser_{23}$** | $Cys_{22}$ |
| **$Pro_{25}$** | $Ser_{23}$ |
| **$Gln_{27}$** | $Gln_{27}$ |
| **$Tyr_{40}$** | $Tyr_{40}$ |
| **$Asn_{53}$** | $Val_{151}$ |
| **$Lys_{152}$** | |

All these data suggest that there are several differences between the interactions of compound **4** with either COX-1 or COX-2 enzymes could be translated as a different biological activity.

***Evaluation of drug binding to aminoacids residues of both COX enzymes.*** To evaluate the affinity of the functional groups of compound **4** on both COX-1 and COX-2 enzymes; in this study, the distances that may be produced between compound **4** and some amino acid residues that involved in both 2OYU and 3LN1 protein surface were determined using the SeeSAR software [36]. The results showed that hydroxyl group could be a factor determinate to bind to both COX-1 and COX-2 compared with ketone and ether groups (Figure 6, Table 5 and 6).

**Table 5.** Distance involve in the interaction of functional groups of **4** with aminoacid residues of COX-1 enzyme (2OYU).

| Aminoacid residues | Hydroxyl (Å) | Ketone (Å) | Ether (Å) |
|---|---|---|---|
| **$Val_{33}$** | 69.29 | 73.55 | - |
| **$Pro_{35}$** | 65.05 | 60.46 | - |
| **$Tyr_{38}$** | 61.61 | - | - |
| **$Pro_{40}$** | 57.40 | 57.40 | 53.59 |
| **$Tyr_{55}$** | 59.69 | | |

**Table 6.** Distance involve in the interaction of functional groups of **4** with aminoacid residues of COX-2 enzyme (3LN1).

| Aminoacid residues | Hydroxyl (Å) | Ketone (Å) | Ether (Å) |
|---|---|---|---|
| **$Val_{33}$** | 69.29 | 73.55 | - |
| **$Pro_{35}$** | 65.05 | 60.46 | - |
| **$Tyr_{38}$** | 61.61 | - | - |
| **$Pro_{40}$** | 57.40 | 57.40 | 53.59 |
| **$Tyr_{55}$** | 59.69 | | |

However, is noteworthy that some reports indicate that interaction of some compounds with several proteins involve another type of energetic parameters which could affect some biological system [37].

***Thermodynamic parameters***. To evaluate the hypothesis above mentioned, In this investigation some thermodynamic factors were determinate such as; 1) binding-free energy that indicates the energy requirements that a molecule needs to bind to a protein; 2) electrostatic energy that involves electric charge and electrostatic potential; 3) total intermolecular energy and 4) van der Waals forces (vdW) + hydrogen bond (Hbond) + desolvation energy (Desolv Energy), which are factors that can influence the movement of molecules [37].

Theoretical data found (Table 7 and 8) showed several differences in the thermodynamic parameters of compound **4** compared to either indomethacin or rofecoxib. This phenomenon suggests that **4** could induce changes in the biological activity of either COX-1 (2OYU) or COX-2 (3LN1) in comparison with indomethacin and rofecoxib.

**Table 7.** Thermodynamic parameters involve in the interaction of compounds 3, 4 and indomethacin with COX-1 enzyme (2OYU).

| Compound | Est. Fee Energy of Binding (kcal/mol) | Est. Inhi-bition Constant, Ki (μM) | cdW + Hbond + desolv Energy | Electrost. Energy | Total Inter-molec. Energy | Interact. Surface |
|---|---|---|---|---|---|---|
| **Indomethacin** | -5.32 | 126.53 | -6.24 | -0.19 | -6.43 | 576.69 |
| **4** | -7.79 | 1.95 | -9.01 | -0.02 | -9.03 | 685.53 |

**Table 8.** Thermodynamic parameters involve in the interaction of compounds 3, 4 and rofecoxib with COX-2 enzyme (3LN1).

| Compound | Est. Fee Energy of Binding (kcal/mol) | Est. Inhi-bition Constant, Ki (μM) | cdW + Hbond + desolv Energy | Electrost. Energy | Total Inter-molec. Energy | Interact. Surface |
|---|---|---|---|---|---|---|
| **Rofecoxib** | -3.78 | 1.69 | -4.90 | 0.18 | -4.73 | 557.62 |
| **4** | -5.56 | 84.47 | -6.32 | -0.04 | -6.37 | 691.41 |

In addition, theoretical data indicate that inhibition constant (Ki) was lower compared with indomethacin; however, the value of Ki was higher to compound **4** compared with rofecoxib (Tables 4 and 5). Theoretical results indicate that compound 4 (adamantane-steroid derivative) could interact with higher affinity against COX-1.

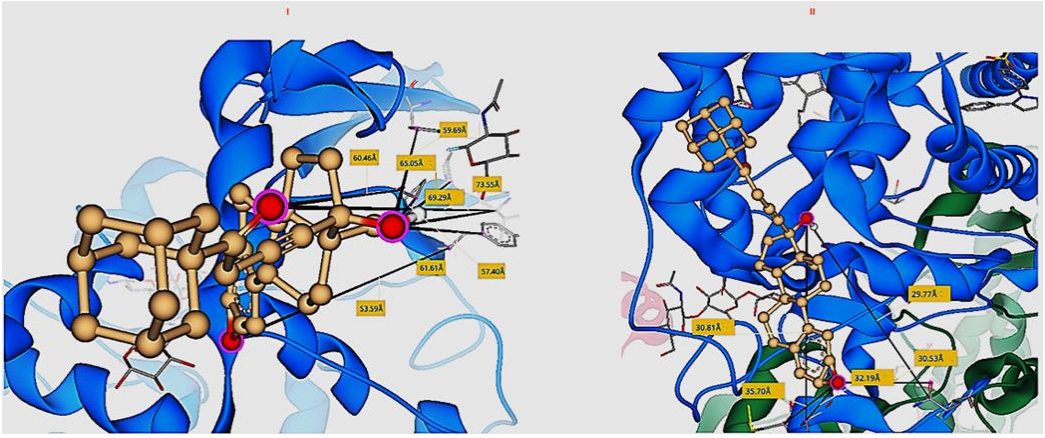


**Figure 6**. The scheme shows the distance between functional groups of **4** with some aminoacid residues involved on both 2OYU (I]) and 3LN1 (II) proteins surface. The visualization was carried out using SeeSar 8.1 software.

## 4. CONCLUSIONS

In this study a facile synthesis of a new adamantane-steroid derivative was prepared. In addition, the theoretical evaluation indicates that this steroidal derivative could be a good prospect as an inhibitor of COX-1 which is traslated as a possible drug for treatment of pain.

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