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Synthesis of an Adamantyl Derivative and their Theoretical Interaction with both COX-1 and COX-2 Enzymes

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Abstract: Various drugs have been used to treat pain; nevertheless, several drugs can produce side effects such as bronchospasm, thinning, and angioedema. In the search for new therapeutic alternatives, some drugs have been elaborated using different reagents that are difficult to handle and require special conditions such as different pH and higher temperatures. Therefore, this research aimed to prepare an adamantyl derivative (compound 4) from 1-Adamantyl bromomethyl ketone using some chemical strategies. Besides, a theoretical evaluation of the interaction of compound 4 with both cyclooxygenase enzymes (COX-1 and COX-2) was evaluated using either 4cox or 5jw1 proteins as theoretical models. In addition, both indomethacin and celecoxib drugs were used as controls in a docking model. The results showed that compound 4 has a higher affinity by both 4cox and 5jw1 proteins surface compared with either indomethacin or celecoxib drugs. In conclusion, these data suggest that 4 could be a good candidate for pain treatment.

Keywords: Adamantyl; synthesis; docking; pain.

1. Introduction

Pain is a main public health problem worldwide [1-4]; it is important to mention that non-steroidal anti-inflammatory [5,6] and opioid drugs are used for the treatment of pain [7-9]; however, some of these drugs could produce several adverse effects such as bronchospasm, vasomotor thinitis, and angioedema [10], renal dysfunction, meningeal syndrome, and bone marrow depression, headache, vertigo, [11-13]. In search of new therapeutic alternatives, some compounds have been synthesized to treat the pain; for example, the preparation of a piperazinyl-ethanone from a tosyl derivative for treating pain [14]. Besides, a pyrrolidine-carboxamide analog was synthesized via reaction of a lactam derivative with hydroxybenzotriazole/histamine as a possible drug to treat pain [15]. Another study showed the synthesis of a naphthalene-chalcone derivative from Phenyl-ethanone and Naphthalene-1-carbaldehyde with analgesic activity [16]. Additionally, a report showed the preparation of 4-

(6-(benzylideneamino)-7-cyano-2,3-dihydro-1H-pyrrolizine-5-carbo-xamido)benzoate by the reaction of a benzoate derivative and benzaldehyde for treatment of pain [17].

On the other hand, some 1,4-disubstituted adamantyl analogs have been prepared as an analgesic and anti-inflammatory reagents from adamantyl and methylbenzylamine[18]. Besides, several arylamides of N-1-2-)adarnantyl-azacycloalkanecarboxylic acids were prepared via reaction of 1-(or 2-)aminoadamantane and mesidide α-bromo-ω-chlorovaleric acid with anesthetic activity [19]. Therefore, this study aimed to prepare an adamantyl derivative to evaluate their theoretical activity on both cyclooxygenase enzymes (COX-1 and COX-2) involved in the pain.

2. Materials and Methods

2.1. General methods.

Starting materials were purchased from commercial suppliers (Sigma-Aldrich and AKos Consulting & Solutions). NMR spectra were recorded on a Varian VXR300/5 FT apparatus (300 MHz/$CDCl_3$) using tetramethylsilane as an internal standard. Electron Ionization mass spectrometry (EIMS) was recorded on a Finnigan PolarisQ ion trap mass spectrometer. Melting-point (m.p.) was determined on an electrothermal-900 model apparatus. The infrared spectrum (IR) was determined on a thermo-scientific iSOFT/IR device. Elemental analysis was determined using a PerkinElmer apparatus (Ser. II CHNS / 02400).

2.2. Synthesis of 1-(1-adamantyl)-7-hydroxy-hept-2-yn-1-one (2).

In a round bottom flask (10 ml), 1-Adamantyl bromomethyl ketone (200 mg, 0.78 mmol), 5-hexyn-1-ol (100 µl, 92 mmol), Copper(II) chloride (105 mg, 0.78 mmol) and 5 ml of methanol were stirred at reflux for 48 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 56% of product; IR (V_{max}, cm^{-1}) 3400, 2190 and 1712: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.52 (m, 6H), 1.58-1.64 (m, 4H), 1.66 (m, 6H), 1.92 (m, 4H), 1.96 (broad, 1H), 2.24-3.64 (m, 4H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 18.82, 25.42, 27.80, 31.83, 36.66, 40.12, 46.44, 62.12, 81.40, 95.82, 194.20 ppm. EI-MS m/z: 260.17. Anal. Calcd. for $C_{17}H_{24}O_2$. C, 78.42; H, 9.29; O, 12.29. Found: C, 78.40; H, 9.26.

2.2.1. 1-adamantyl(2,3,4,5-tetrahydrooxepin-7-yl)methanone (3).

In a round bottom flask (10 ml), compound 2 (200 mg, 0.77 mmol) and Copper(II) chloride (105 mg, 0.78 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:water (4:1) system; yielding 52% of product; IR (V_{max}, cm^{-1}) 1712, 1602 and 1104: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.30-1.66 (m, 4H), 1.74-1.98 (m, 2H), 2.04 (m, 2H), 2.08 (m, 3H), 2.10-6.34 (m, 4H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 25.00, 26.60, 27.68, 31.44, 37.00, 41.40, 51.82, 72.81. 123.94, 160.00, 201.90 ppm. EI-MS m/z: 260.17. Anal. Calcd. for $C_{17}H_{24}O_2$. C, 78.42; H, 9.29; O, 12.29. Found: C, 78.39; H, 9.26.

2.2.2. (*E*)-1-(1-adamantyl)-N-prop-1-ynyl-1-(2,3,4,5-tetrahydrooxepin-7-yl)methanimine (4).

In a round bottom flask (10 ml), compound 3 (200 mg, 0.77 mmol), Prop-2-ynylamine (75 mg, 0.82 mmol), boric acid (50 mg, 0.80 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 68% of product; IR (V_{max}, cm^{-1}) 3330, 2112, 1604 and 1102: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.36-1.44 (m, 2H), 1.56-1.62 (m, 12H), 1.64-2.10 (m, 3H), 2.16 (m, 3H), 2.18 (m, 1H), 3.20 (s, 1H), 3.72-5.30 (m, 3H), ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 25.08, 26.70, 27.92, 28.96, 37.24, 37.78, 42.40, 72.60, 77.30, 82.62, 112.84, 156.34, 165.50 ppm. EI-MS m/z: 283.19. Anal. Calcd. for $C_{19}H_{25}NO$. C, 80.52; H, 8.89; N, 4.94; O, 5.65. Found: C, 80.50; H, 8.86.

2.3. Ligand-protein interaction.

The interaction of the adamantyl derivative with either cox-1 or cox-2 enzymes was evaluated using both 4cox and 5jw1 proteins as theoretical models [20,21]. In addition, to evaluate binding energy involved in the interaction of adamantyl derivatives with either 4cox or 5jw1 proteins surface, either indomethacin or celecoxib were used as controls on a docking server software [22].

2.4. Pharmacokinetics parameter.

Some pharmacokinetic factors were determined using the SwissADME software [23].

3. Results and Discussion

Several drugs have been developed the treat the pain; however, the interaction with some biomolecules is very confusing; perhaps, this phenomenon could be to the different structure chemicals of each compound reagent [14-19]. Analyzing these data, in this research, an adamantyl derivative (compound 4) was prepared using some chemical strategies as follows.

3.1. Synthesis of an alkynol.

Some alkynol analogs have been synthesized using different methods, which use some reagents such as trimethylsilyl trifluoromethanesulfonate [24], zinc trifluoromethane-sulfonate [25], Copper(I) [26]. In this investigation (Figure 1), 1-Adamantyl bromomethyl ketone reacted with 5-hexyn-1-ol in the presence of Copper(II) chloride to form an alkynol derivative (**2**). The ^{1}H NMR spectrum of **2** showed several signals at 1.52, 1.66, and 1.92 ppm for adamantane fragment; at 1.58-1.64 and 2.24-3.64 ppm for methylene groups bound to both alkyne and hydroxyl groups; at 1.96 ppm for a hydroxyl group. The ^{13}C NMR spectra display chemical shifts at 18.82-25.42, 31.83, and 62.12 ppm for methylene groups bound to alkyne and hydroxyl groups; at 27.80 and 36.66-46.44 ppm for adamantane fragment; at 81.40-95.82 ppm for alkyne group; at 194.20 ppm for ketone group. Besides, the mass spectrum from **2** showed a molecular ion (m/z) at 260.17.

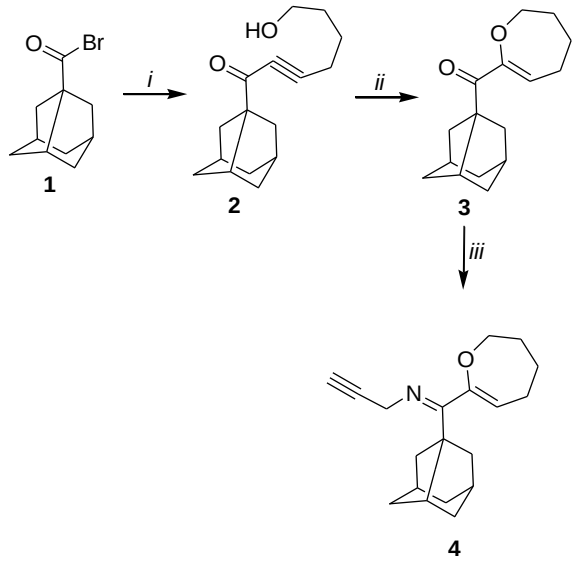

Figure 1. Synthesis of (*E*)-1-(1-adamantyl)-N-prop-1-ynyl-1-(2,3,4,5-tetrahydrooxe-pin-7-yl)methanimine (4). *Reagents and conditions*: *i* = 5-hexyn-1-ol, Copper(II) chloride, methanol, rt, 48 h; *ii* = Copper(II) chloride, methanol, rt, 72 h; *iii* = Prop-2-ynylamine, methanol, boric acid, rt, 72h.

3.2. Cyclization of two alkyn-alcohol derivatives.

Several studies have shown the cyclization of alkyn-alcohol analogs using some reagents such as gold chloride [27], ruthenium [28], diphenyl ether [29], palladium(II) chloride [30], and *N*-bromosuccinamide/silver nitrate [31]. In this research, a Tetrahydro-oxepine derivative (3) was prepared via a cyclization internal of alkyn-alcohol (**2**) in the presence of Copper(II) chloride (Figure 1). The ^{1}H NMR spectrum of **3** showed several signals at 1.30-1.66, 2.04, and 2.10-6.34 ppm for Tetrahydro-oxepine ring; at 1.74-1.98 and 2.08 ppm for adamantane fragment. The ^{13}C NMR spectra display chemical shifts at 25.00-26.60, 31.44, 72.81-160.00 for Tetrahydro-oxepine ring; at 27.68 and 37.00-51.82 ppm for adamantane fragment; at 201.90 ppm for ketone group. In addition, the mass spectrum from **3** showed a molecular ion (m/z) at 260.17.

3.3. Synthesis of an imino derivative.

There are several reports in the literature on the synthesis of some imine analogs [32-34]. In this research, compound **4** was prepared via reaction of **3** with Prop-2-ynylamine (75 mg, 0.82 mmol) using boric acid as a catalyst. The ^{1}H NMR spectrum for **4** at 1.36-1.44, 1.64-2.10, and 2.18 ppm for Tetrahydro-oxepine ring; at 1.56-1.62, 2.16 and 3.72-5.30 ppm for adamantane fragment; at 3.20 ppm for alkyne group. ^{13}C NMR spectra display chemical shifts at 25.08-27.92, 72.60, and 112.84-156.34 ppm for Tetrahydro-oxepine ring; at 28.96-42.40 ppm for adamantane fragment; at 77.30-82.62 ppm for alkyne group; at 165.50 ppm for imino group. Finally, the mass spectrum from **4** showed a molecular ion (m/z) at 283.19.

3.4. Ligand-protein interaction.

There are several methods to predict drug binding on the surface of some protein or enzyme. Furthermore, these techniques showed that free binding and solvation energies are involved in the ligand-biomolecule interaction [35]. In this way, in this investigation, a theoretical analysis was carried out to evaluate the interaction of compound **4** with either COX-1 or COX-2 enzymes using both 4cox and 5jw1 proteins as theoretical models. The results

(Figures 2 and 3; Table 1 and 2) showed different amino acid residues involved in the interaction of compound **4** with either 4cox or 5jw1 proteins surface compared with either indomethacin or celecoxib drugs; this phenomenon could be due to differences in their chemical structure.

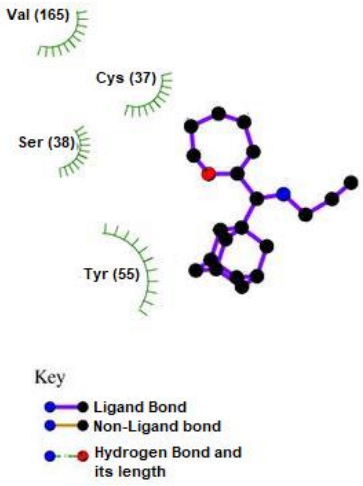

Figure 2. Interaction of compound 4 with 4cox-protein surface using docking server.

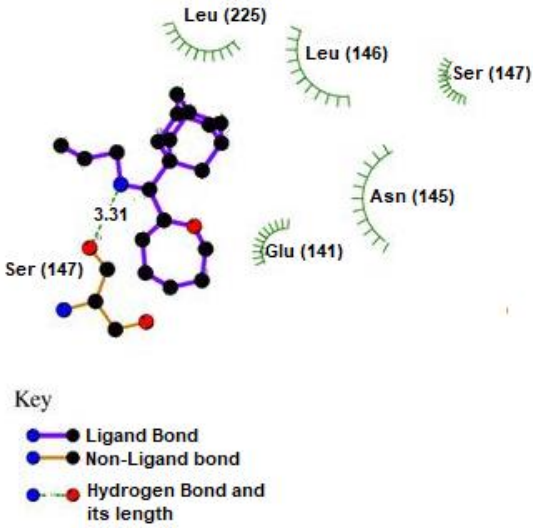

Figure 3. Interaction of compound 4 with 5jw1-protein surface using docking server.

Table 1. Interaction of compound 4 and indomethacin (control) with 4cox-protein surface.

Indomethacin	**Compound 4**
Ser_{38}	Cys_{37}
Pro_{40}	Ser_{38}
Gln_{42}	Tyr_{55}
Asp_{53}	Val_{165}
Tyr_{55}	
Asn_{68}	
Glu_{465}	

Table 2. Interaction of compound 4 and celecoxib (control) with 5jw1-protein surface.

Celecoxib	**Compound 4**
Asn_{145}	Glu_{141}
Ser_{147}	Ser_{144}
Tyr_{148}	Asn_{145}
Arg_{217}	Leu_{146}
Phe_{221}	Ser_{147}
	Leu_{225}

On the other hand, to evaluate some thermodynamic parameters involved in the interaction of compound 4 with either 4cox or 5jw1 proteins surface, the docking server software was used. The results showed (Table 3 and 4) differences in the thermodynamic parameters on the interaction of compound 4 with either 4cox or 5jw1 proteins surface compared with the controls (indomethacin and celecoxib). Besides, the inhibition constant (Ki) for compound **4** was lower than either indomethacin or celecoxib drugs. These phenomena suggest that compound **4** could have higher biological activity against pain.

Table 3. Thermodynamic parameters involved in the interaction of compound 4 and control (indomethacin) with 4cox-protein surface.

Compound	Est. Free energy of Binding	Est. Inhibition Constant (Ki)	vdW + H-bond + desolv Energy	Electrostatic Energy	Total Interm. Energy	Interact Surface
Indomethacin	-3.62	2.23	-4.89	0.10	-4.79	496.37
4	-3.64	2.15	-5.11	0.00	-5.10	512.69

Table 4. Thermodynamic parameters involved in the interaction of compound **4** and control (indomethacin) with 4cox-protein surface.

Compound	Est. Free energy of Binding	Est. Inhibition Constant (Ki)	vdW + H-bond + desolv Energy	Electrostatic Energy	Total Interm. Energy	Interact Surface
Celecoxib	-2.67	11.03	-4.11	-0.09	-4.20	369.11
4	-3.85	1.50	-4.81	-0.07	-4.88	418.10

3.5. Pharmacokinetic evaluation.

Several studies have reported the evaluation of some pharmacokinetic parameters of different drugs using theoretical models such as PKQuest [36], PharmPK [37], SwissADME [38]. In this way, in this study, some pharmacokinetic parameters involved in compound 4 were determined using the SwissADME software. The results in Tables 5, and 6 suggest that these compounds could have different gastrointestinal absorption and, consequently, their metabolism could involve different types of CYP enzymes (Cytochrome P450 system). This phenomenon could depend on their chemical structure and lipophilicity degree.

Table 5. The pharmacokinetics properties of the Fluoro-2,4dioxaspiro[bicyclo[3.3.1]indene derivative. The values were determinate using the SwissADME software

Parameter	Compound 4
GI absorption	high
BBB permanent	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
$LogK_p$ (cm/s)	-5.00

Table 6. Values of lipophilicity degree for compound 4 using SwissADME software.

iLOGP	3.75
XLOGP3	4.38
WLOGP	4.44
MLOGP	3.73
SILICOS-IT	5.01
Consensus Log Po/w	4.26

4. Conclusions

In this study, an easy synthesis of an adamantyl derivative (compound 4) is reported using some chemical strategies. Furthermore, the theoretical analysis showed a greater affinity of compound 4 for the surface of either 4cox or 5jw1 proteins compared to indomethacin and celecoxib drugs. These data suggest that compound 4 may be a good candidate for the treatment of pain.

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Conflicts of Interest

We declare that this manuscript does not have any conflict of financial interests (political, personal, religious, ideological, academic, intellectual, commercial, or otherwise) for its publication.

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