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Preparation of a hexynloxy-diazecin-naphtho-oxadiazocine derivative. Theoretical analysis of its interaction with the μ, δ, and κ opioid-receptors

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ABSTRACT

Some drugs have development with the purpose to evaluate its biological activity on opioid receptors; however, this phenomenon is not very clear, perhaps due to the established approach or to different types of chemical structures of each drug. The objective of this study was to synthesize a hexynloxy-diazecin-naphtho-oxadiazocine derivative (compound **6**) to evaluate its theoretical interaction on μ,δ, and κ opioid-receptors. The preparation of **6** was carried out using a series of reactions which involves; 1) addition/cyclization; 2) imination and 3) etherification. Chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. The following stage involved the theoretical evaluation on the interaction of compound **6** with the μ,δ,κ-opioid receptors surface using a docking model. The results showed that compound **6** can interact with different type of aminoacid residues of μ-opioid receptor (Thr_{111}, Phe_{114}, Val_{118}, Lys_{227}, Glu_{297}, Tyr_{312}) compared with the interaction with the δ and κ-opioid receptors. In conclusion all these data suggest that hexynloxy-diazecin-naphtho-oxadiazocine derivative is a particularly interesting, because involves higher interaction with μ-opioid receptor; these data indicate that compound **6** could be an alternative for the treatment of pain.

Keywords: *Oxadiazocine, etherification, aminoacid, opioid, receptor.*

1. INTRODUCTION

In the search for new pharmacological tools for the treatment of pain, several drugs have been developed since several years ago. There are studies which indicate that a diethylbenzamide derivative exert biological activity on guinea pig ileum via δ-opioid receptor activation [1]. Other report, describes the preparation and biological evaluation of some acetamide derivatives on opioid receptors (μ and κ) in a rat model [2]. In addition, other data has shown the synthesis of some arylacetamide derivatives as κ-receptor opioid agonist in an analgesia assay [3]. In addition, a report showed that other type of arylacetamide derivatives could be κ-receptor agonists using a Docking model [4]. Other data indicates that a fentanyl derivative active the μ-opioid receptor in an analgesia model [5]. In addition, one study showed that the naltrexamine derivative exerts its biological activity as μ-receptor antagonist in vitro assay [6]. Other data, describes the synthesis 2-[(Acylamino)ethyl]-1,4-benzodiazepines and their interaction with κ-receptor opioid using a theoretical docking model [7]. Another report showed that arylacetamide and benzomorphan derivatives can act as agonists of κ-opioid receptor using a model based on pharmacophores and coupling [8]. Other data showed the interaction of some piperazine-derivatives with μ-opioid receptor using a theoretical model [9]. In addition, a report indicates that several diazatricyclo-decanes can bind with μ-receptor opioid using a docking model [10]. These data suggest that several drugs can interact with different types of opioid-receptors; this phenomenon could be due to differences in their chemical structure or to the different chemical approaches used. Therefore, in this study a hexynloxy-diazecin-naphtho-oxadiazocine derivative was synthesized and their theoretical activity on μ,δ, κ-opiod receptors was evaluated.

2. EXPERIMENTAL SECTION

2.1. General methods. The reagents used in this study were purchased from Sigma-Aldrich Co. Ltd. The melting point was determined on an Electrothermal (900 model). ^{1}H and ^{13}C NMR spectrum were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

2.2. Preparation of 3-(2-Amino-ethyl)-1,5-dinitro-9-(3-oxo-butyl)-3-aza-bicyclo[3.3.1]non-6-ene-7-carboxylic acid (2)

A solution of 3,5-dinitrobenzoic acid (200 mg, 0.94 mmol) sodium ethoxide (64 mg, 0.94 mmol) and 5 ml of ethanol was stirred for 1 h at room temperature. Then, ethylenediamine (120 μl, 1.8 mmol) and 3 ml of formaldehyde were added; the mixture was stirring for 72 h to room temperature. Finally, the residue was purified by crystallization from methanol:water (4:1) yielding 52 % of product, m.p. 130-132 ^{o}C; IR (V_{max}, cm^{-1}): 3380,1722 and 1568; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.68-1.86 (m, 2H), 2.12 (s, 3H),

2.64 (m, 1H), 3.04 (m, 1H), 3.05 (m. 2H), 3.10 (m, 2H), 3.20-3.52 (m, 2H), 3.66-4.22 (m, 4H), 5.04 (broad, 3H), 8.46 (m, 1H), ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 18.90, 29.62, 38.48, 39.42, 40.83, 56.72, 58.25, 58.82, 59.08, 93.00, 98.13, 128.08, 142.10, 167.72, 209.10 ppm. EI-MS *m/z* 370.14 Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13; O, 30.24. Found: C, 48.58; H, 5.90.

(Z)-6-methyl-9,12a-dinitro-3,4,7,8,8a,9,10,12a-octahydro-1H-2,9-methanobenzo[f][1,4]diazecine-11-carboxylic acid (3)

A solution of **2** (200 mg, 0.54 mmol), boric acid (52 mg, 0.84 mmol) in 5 ml of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:hexane:water (4:1:1) yielding 64 % of product, m.p. 96-98 ^{o}C; IR (V_{max}, cm^{-1}): 3320,1720 and 1570; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.50 (m, 1H), 2.12 (s, 3H), 2.82 (m, 2H), 3.12-3.52 (m, 3H), 3.66 (m, 1H), 3.84 (m, 2H), 3.86-4.22 (m, 4H), 5.70 (m, 2H), 8.46 (d, 1H), 13.04 (broad, 1H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 16.94, 21.26, 29.66, 38.50, 48.95, 53.66, 58.82, 59.07, 92.25, 97.43, 128.10, 142.12, 158.84, 167.72 ppm. EI-MS *m/z* 352.13 Anal. Calcd. for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90; O, 27.25. Found: C, 51.08; H, 5.68.

2-formylnaphthalen-1-yl(Z)-6-methyl-9,12a-dinitro-3,4,7,8,8a,9,10,12a-octahydro-1H-2,9-methanobenzo[f][1,4]diazecine-11-carboxylate (4)

A solution of **3** (200 mg, 0.57 mmol), 2-hydroxy-1-naphthaldehyde (100 mg, 0.58 mmol) and potassium carbonate anhydrous (50 mg, 0.36 mmol) in 5 ml of dimethyl sulfoxide was stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:hexane:water (4:2:1) yielding 48 % of product, m.p. 112-114 ^{o}C; IR (V_{max}, cm^{-1}): 33202, 1570 and 1120; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.54 (m, 2H), 2.12 (s, 3H), 2.83 (m, 2H), 3.06 (m, 1H), 3.18-3.52 (m, 2H), 3.62-3.80 (m, 2H), 3.84 (m, 2H), 3.96-4.16 (m, 2H), 4.16 (m, 2H), 5.70 (m, 2H), 7.14-8.18 (m, 5H), 8.38 (d, 1H, J = 1.82 Hz), 8.50 (m, 1H), 10.66 (s, 1H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 16.96, 21.28, 29.62, 36.44, 48.95, 53.66, 54.83, 59.06, 59.37, 91.53, 96.62, 122.80, 124.84, 125.53, 126.73, 128.38, 128.68, 130.00, 131.33, 133.63, 137.98, 139.62, 156.12, 158.20, 158.84, 189.00 ppm. EI-MS *m/z* 506.18 Anal. Calcd. for $C_{26}H_{26}N_4O_7$: C, 61.65; H, 5.17; N, 11.06; O, 22.11. Found: C, 61.60; H, 5.10.

(2Z,5Z)-2-((Z)-6-methyl-9,12a-dinitro-3,4,7,8,8a,9,10,12a-octahydro-1H-2,9-methanobenzo[f][1,4]diazecin-11-yl)-4H-naphtho[2,1-g][1,3,5]oxadiazocine (5)

A solution of **4** (200 mg, 0.39 mmol) ethylenediamine (50 µl, 0.74 mmol) and boric acid (52 mg, 0.84 mmol) in 5 ml of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water (4:1) yielding 45 % of product, m.p. 96-98 ^{o}C; IR (V_{max}, cm^{-1}): 3320, 1568 and 1122; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.52 (m, 2H), 1.92 (m, 1H), 2.12 (s, 3H), 2.26 (m, 1H), 2.82 (m, 2H), 3.16-3.70 (m, 2H), 3.82 (m, 2H), 3.90-4.26 (m, 3H), 5.32 (m, 2H), 5.70 (m, 2H), 7.60-8.28 (m, 6H), 8.48 (d, 1H, J = 1.82 Hz), 8.62 (m, 1H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 16.96, 21.27, 29.65, 36.70, 48.95, 53.65, 54.89, 58.63, 58.88, 71.83, 92.70, 97.50 125.23, 125.53, 126.21, 126.33, 127.08, 127.88, 128.00, 128.34, 136.34, 138.22, 143.54, 155.54, 155.85, 158.80, 198.90 ppm. EI-MS *m/z* 516.21 Anal. Calcd. for $C_{27}H_{28}N_6O_5$: C, 62.78; H, 5.46; N, 16.27; O, 15.49. Found: C, 62.70; H, 5.40.

(2Z,5Z)-2-((Z)-9-(hex-5-yn-3-yloxy)-6-methyl-12a-(pent-1-yn-3-yloxy)-3,4,7,8,8a,9,10,12a-octahydro-1H-2,9-methanobenzo[f][1,4]diazecin-11-yl)-4H-naphtho[2,1-g][1,3,5]oxadiazocine (6).

A solution of **5** (200 mg, 0.39 mmol) 5-hexyn-3-ol (80 µl, 0.72 mmol), potassium carbonate anhydrous (50 mg, 0.36 mmol) in 5 ml of dimethyl sulfoxide was stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After, the residue was purified by crystallization from methanol:water (3:1) yielding 66 % of product, m.p. 122-124 ^{o}C; IR (V_{max}, cm^{-1}): 3322, 2122, 1122 and 664; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.88 (s, 3H), 1.00 (s, 3H), 1.54 (m, 1H), 1.58 (m, 1H), 1.66-1.78 (m, 3H), 2.00 (s, 1H), 2.08 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.32 (m, 1H), 2.34 (s, 1H), 2.36 (m, 2H), 2.52 (m, 1H), 2.56 (m, 1H), 2.66 (m, 2H), 2.76-3.32 (m, 4H), 3.34 (m, 2H), 3.38-3.94 (m, 2H), 5.34 (m, 2H), 5.70 (m, 2H), 7.32 (d, 1H), 7.60-8.62 (m, 7H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 9.62, 11.06, 16.92, 22.84, 24.53, 27.53, 29.14, 33.22, 38.28, 48.95, 54.85, 57.19, 57.93, 64.16, 67.10, 67.84, 70.00, 71.83, 80.25, 80.61, 81.24, 81.54, 86.63, 125.20, 125.53, 126.24, 126.30, 127.10, 127.84, 128.00, 128.30, 136.42, 139.74, 142.64, 150.84, 155.83, 158.80, 174.64 ppm. EI-MS *m/z* 604.34 Anal. Calcd. for $C_{38}H_{44}N_4O_3$: C, 75.47; H, 7.33; N, 9.26; O, 7.94. Found: C, 75.38; H, 7.26.

2.9. Docking Server. Docking calculations were carried out using Docking Server [11, 12, 16, 17]. Theoretical calculations were carried out using some protein models such as 4DKL [13], 4RWD [14] and 4DJH [15].

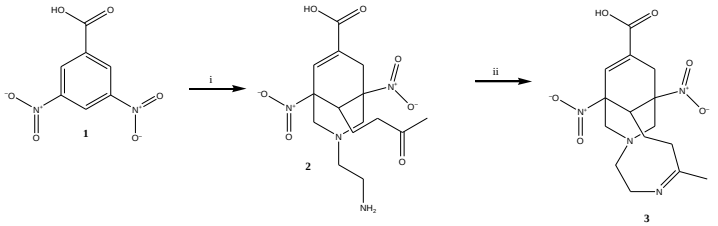
2.11. Toxicity analysis. The evaluation of theoretical toxicity of an oxadiazocine-derivative (compound **6**) was determinate using PASSonline [18].

3. RESULTS SECTION

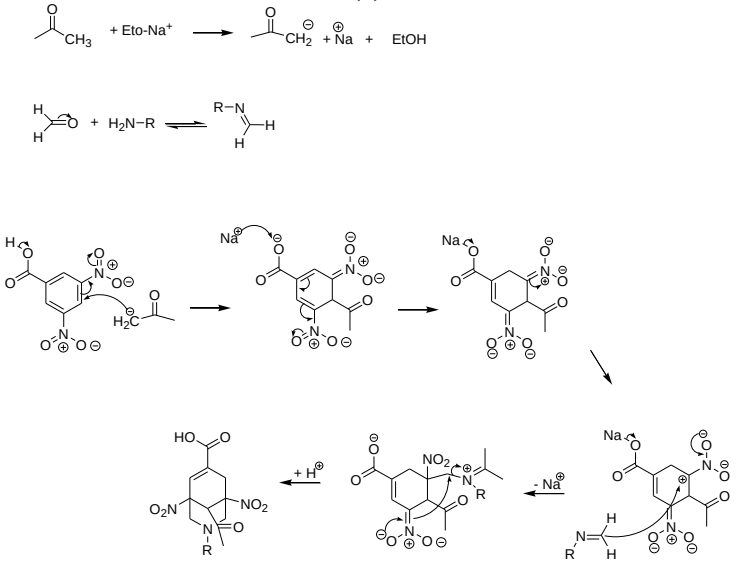
Chemical synthesis. In this study a hexynloxy-diazecin-naphtho-oxadiazocine derivative (compound **6**) was synthesized using some chemical strategies.

3.1. Preparation of an aza-bicyclo-carboxylic acid derivative (2). There are reports which indicate the preparation of diverse bicyclic analogs; nevertheless, some reagents require special conditions [19-22]. In this study a straightforward route is reported the synthesis of an azabicyclo derivative (Scheme 1 and 2) using a multicomponent system (3,5-dinitrobenzoic acid, sodium ethoxide, ethylendiamine and formaldehyde) in acid medium. The ^{1}H NMR spectrum of **2** shows signals at 1.68-1.86 and 3.05 ppm for methylene groups bound to both bicycle ring and ketone group; at 2.12 ppm for methyl group; at 2.64 and 3.08 ppm for methylene groups bound to both bicycle ring and amino groups; at 3.44, 3.18-4.22 and 8.46 ppm for bicycle ring; at 5.04 ppm for both amino and carboxyl groups. The ^{13}C NMR spectrum display chemical shifts at 18.90 and 40.83-56.72 ppm for methylene groups involved in the arm bound to bicycle ring; at 29.62 ppm for

methyl group; at 38.48, 58.82 and 142.10 ppm for bicycle ring; at 39.42 and 58.25 ppm for methylene groups bound to bicycle ring; at 167.72 ppm for carboxyl group; at 209.19 ppm for ketone group. In addition, **2** was confirmed showed a molecular ion at 370.14.

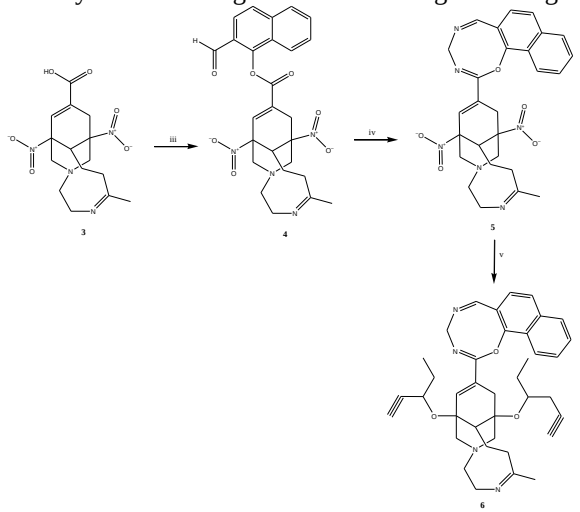


Scheme 1. Preparation of dinitro-diazecine-carboxylic acid (**3**). Reaction of 3,5-dinitrobenzoic acid (**1**), dimethyl ketone, ethylendiamine and formaldehyde (i) to form an aza-bicyclo-carboxylic acid derivative (**2**). Then, **2** was reacted with boric acid (ii) to form **3**.



Scheme 2. Reaction mechanism involved in the synthesis of the aza-bicyclo-carboxylic acid derivative (2).

3.2. Preparation of dinitro-diazecine-carboxylic acid (3). The following stage was achieved by synthesis of an imino group; it is noteworthy, that there are some methods for the preparation of imino groups which have been previously reported [23]. In this study, the compound **2** reacted with boric acid to form **3**. Boric acid is an easy to handle reagent and is not dangerous reagent [24].



Scheme 3. Preparation of the hexynloxy-diazecin-naphtho-oxadiazocine derivative (**6**). Reaction of **3** with 2-hydroxy-1-naphthaldehyde (iii) to form an ether-derivative (**4**). Then **4** was reacted with ethylenediamine (iv) to form an oxodiaza derivative (**5**): Finally, **6** was synthesized by the reaction of **5** with 1-hexyn-3-ol (v).

The ^{1}H NMR spectrum of **3** display signals at 2.12 ppm for methyl group; at 2.54 and 2.82-5.70 ppm for diazabicyclo-dodecene ring; at 8.46 ppm for cyclohexane ring; at 13.04 ppm for carboxyl group. The ^{13}C NMR spectra showed chemical shifts at 16.94 ppm methyl group; at 21.26-29.66 and 48.95-59.07 ppm for diazabicyclo-dodecene ring; at 38.50 and 92.25-142.12 ppm for cyclohexane ring; at 158.84 ppm for imino group; at 167.72 ppm for carboxyl group. In addition, the compound **3** showed a molecular ion at m/z*:* 352.13.

3.3. Preparation of an ether derivative. There are several reports to preparation of ether groups via displacement of nitro groups using some reagents such as methoxy groups [25], fluoride ion [26], nitropropane or nitrocyclohexanone [27], sodium phenoxide [28], nitrobenzamide in DMSO [29] and others. In this study, an ether derivative (**4**) was synthesized by the reaction of **3** with 2-hydroxy-1-naphthaldehyde (Figure 3) using previously reports for preparation of ether groups [30]. ^{1}H NMR spectrum of **4** showed signals at 2.12 ppm for methyl group; at 1.54, 2.83, 3.06 and 3.62-5.70 ppm for diazabicyclo-dodecene ring; at 3.18-3.52 and 8.38 ppm for cyclohexene ring; at 7.14-8.18 and 8.50 ppm for phenyl groups; at 10.66 ppm for aldehyde group. The ^{13}C NMR spectra display chemical shifts at 16.96 ppm for methyl group; at 21.28-29.62 and 48.95-59.37 ppm for diazabicyclo-dodecene ring; at 36.44, 91.53-96.62, 126.73 and 139.62 ppm for cyclohexene ring; at 122.80-125.53, 128.38-137.98 and 156.12 ppm for phenyl groups; at 158.84 ppm for imino group; at 189.00 ppm for aldehyde group. In addition, the presence of **4** showed a molecular ion at m/z*:* 506.18.

3.4. Preparation of an oxodiaza derivative. Several reagents have used for synthesis of oxadiaza derivatives such as acylhydrazines [31], polymer-supported reagents [32], 4-bromobenzhydrazid [33] and other. In this study the compound **4** was reacted with ethylenediamine in the presence of boric acid to form the oxadiaza- derivative (**5**). ^{1}H NMR spectrum for the compound **5** showed signals at 1.52, 2.82 and 5.70 ppm for diazabicyclo-dodecene ring; at 1.92, 2.26-4.26 and 8.48 ppm for cyclohexene ring; at 3.50 ppm for oxadiazocine ring; at 2.12 ppm for methyl group; at 7.60-8.28 and 8.62 ppm for phenyl groups. The ^{13}C NMR spectra showed chemical shifts at 21.27, 48.95 and 58.88 ppm for diazabicyclo-dodecene ring; at 36.70, 92.70-97.50 and 138.22-143.54 ppm for cyclohexane ring; at 71.83 and 155.54 ppm for oxadiazocine ring; at 125.23 -136.34 ppm for phenyl groups; at 158.85-198.90 ppm for imino groups. In addition, the compound **5** display a molecular ion at m/z*:* 516.21.

3.4. Preparation of an ether derivative (Compound 6). In this study, the compound **5** was reacted with 5-hexyn-3-ol in basic medium to form **6**. ^{1}H NMR spectrum of **6** showed signals at 0.88-1.00 ppm for methyl groups bound to both ether and alkyne groups; at 2.14 ppm for methyl group linked to diazabicyclo-dodecene ring; at 1.54, 2.08 and 7.32 ppm for cyclohexene ring; at 1.58-1.78, 2.32, 2.52 and 3.38-3.94 ppm for methylene groups involved in the arms bound to diazabicyclo-dodecene ring; at 2.00 and 2.34 ppm for alkyne groups; at 2.36, 2.56-3.34 and 5.70 ppm for diazabicyclo-dodecene ring; at 7.60-8.62 ppm for phenyl groups. The ^{13}C NMR spectra display chemical shifts at 9.62-11.06 ppm for methyl groups bound to ether group; at 16.92 ppm for methyl group bound to diazabicyclo-dodecene ring; at 22.84, 33.22, 44.55-57.93 and 67.84 ppm for diazabicyclo-dodecene ring; 24.53-29.14, 70.00 and 80.25 ppm for methylene involved in the arm bound to both ether and alkyne groups; at 38.28, 81.54-86.63 and 139.74-142.64 ppm; at 64.16-67.10 and 80.61-81.24 ppm for alkyne groups; 71.83 ppm diazabicyclo-dodecene ring; at 125.20-136.42 and 150.84 ppm for phenyl groups; at 155.83-174.64 ppm

for imino groups. In addition, the compound **6** showed a molecular ion at m/z: 604.34.

3.9. Docking evaluation. Analyzing the reports which indicates that some compounds exert their biological activity via opioid receptors; in this study was evaluated the possibility that a oxadiazocine-derivative could interact with opioid receptors such as μ (4DKL) [13], δ (4RW) [14], κ (4DJH) [15] using a docking model [11]. The results (Figure 4, Table 1) show the possible interaction of oxadiazole-derivative with several amino acid residues involved in the structure of μ-opioid receptor such as Gln_{115}, Val_{118}, Trp_{124}, Val_{134}, Leu_{135}, Asp_{138}, Tyr_{139}, Met_{142}, Cys_{210}, Asp_{223}, Lys_{227}, Ile_{290}, Ile_{294}, Tyr_{312}, Tyr_{313}, Ile_{316}.

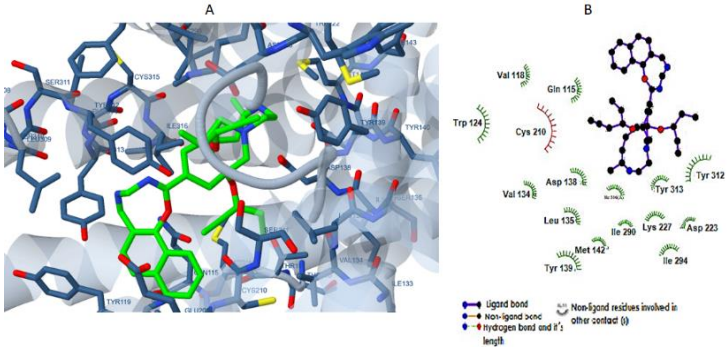


Figure 4. The scheme shown the contact site of amino acid residues involved in the interaction of μ-opioid receptor (4DKL) with the compound **6**. Visualized with GL mol Viewer (A) after docking analysis with one-click docking (B).

Table 1. Aminoacid residues involved between the interactions of compound **6** with μ-opioid receptor (4DKL) surface.

Polar	Hydrophobic	pi-pi	Others
Asn_{127}	Ile_{144}	Tyr_{128}	Asn_{127}
Asp_{216}	Tyr_{148}	His_{319}	Tyr_{128}
	Cys_{217}		Asp_{147}
	Leu_{219}		Tyr_{148}
	Trp_{318}		Asp_{216}
			Cys_{217}
			Thr_{218}
			Glu_{229}
			Lys_{223}

Other data showed (Figure 5, Table 2) the bond of oxadiazole-derivative (compound **6**) with δ-opioid receptor which involves several amino acid residues such as Thr_{111}, Phe_{114}, Gln_{115}, Val_{118}, Trp_{124}, Leu_{135}, Asp_{138}, $Tyrt_{139}$, Ser_{211}, Lys_{227}, Ile_{290}, Ile_{294}, Glu_{297}, Tyr_{312}, Ile_{316} and Tyr_{320}.

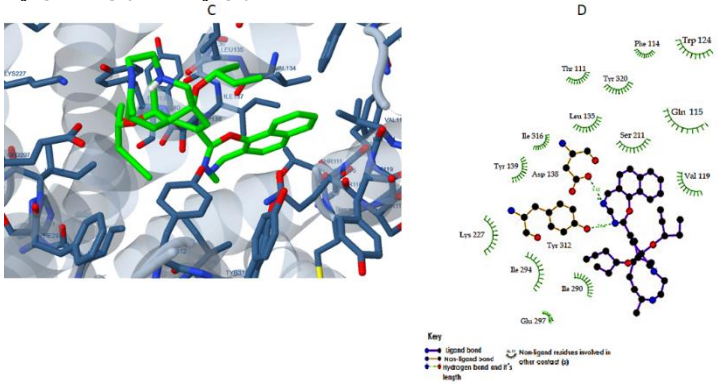
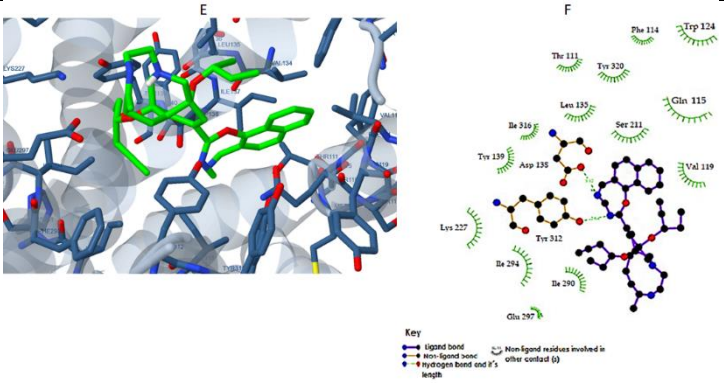


Figure 5. The scheme shown the contact site of amino acid residues involved in δ-opioid receptor (4RWD) with the compound **6**. Visualized with GL mol Viewer (C) after docking analysis with one-click docking (D).

Table 2. Aminoacid residues involved between the interaction of compound **6** with δ-opioid receptor (4RWD) surface.

Hidrogen bonds	Polar	Polar	pi-pi	Others
Gln_{115}	Asp_{138}	Trp_{124}	Trp_{287}	Gln_{115}
Tyr_{320}		Val_{134}	Tyr_{320}	Asp_{138}
		Leu_{135}		Tyr_{139}
		Tyr_{139}		Ser_{211}
		Cys_{210}		Tyr_{312}
		Ile_{290}		
		Ile_{294}		
		Ile_{316}		



Scheme 6. The scheme shown the contact site of amino acid residues involved in the interaction of κ-opioid receptor (4DJH) with the compound **6**. Visualized with GL mol Viewer (E) after docking analysis with one-click docking (F).

In addition, also was evaluated the possibility of that oxadiazole-derivative may interact with κ-opioid-receptor. The results showed the interaction with several amino acid residues such as Glu_{115}, Trp_{124}, Val_{134}, Leu_{135}, Asp_{138}, Tyr_{139}, Cys_{210}, Ser_{211}, Trp_{287}, Ile_{290}, Ile_{294}, Tyr_{312}, Ile_{316} and Tyr_{320} involved in structure of κ-opioid receptor.

Table 3. Aminoacid residues involved between the interaction of compound **6** with κ-opioid receptor (4DJH) surface.

Hidrogen bonds	Polar	Polar	pi-pi	Others
asp_{138}	Gln_{115}	Val_{118}	Phe_{114}	Thr_{111}
Tyr_{312}	Tyr_{312}	Leu_{135}	Trp_{124}	Gln_{115}
		Tyr_{139}	Trp_{124}	Asp_{138}
		Cys_{210}		Tyr_{139}
		Ile_{290}		Ser_{211}
		Ile_{294}		Lys_{227}
		Tyr_{312}		Ile_{294}
		Ile_{316}		Glu_{297}

All these data indicate oxadiazocine could interact with the same type of amino acids such as Glu_{115}, Trp_{124}, Val_{134}, Leu_{135}, Asp_{138}, Tyr_{139}, Cys_{210}, Ile_{290}, Ile_{294}, Tyr_{312} and Ile_{316} for the opioid-receptors (μ, δ, κ). However, The compound **6** interact in a manner different with other type of amino acids (Figure 4-6) on surface of μ, δ and κ opioid-receptors. This phenomenon could involve other type intramolecular interactions due to changes in the energy levels.

Table 4. Intramolecular parameters involved between of interaction of the compound **6** and μ, δ, κ-opioid receptors.

Receptor	Free Energy (Kcal/mol)	Inhibition Constant (Ki, μM)	vdW + H-bond + desolv Energy
μ	-6.44	19.06	-9.70
δ	-8.58	514.95	-11.02
κ	-5.28	133.90	-9.04

In addition the inhibition constant (Ki) for δ and κ-opioid receptors was higher in comparison with the interaction of compound **6** with μ-opioid receptor; these data indicate a higher interaction of the compound **6** with μ-opioid receptor.

Evaluation of some physicochemical parameters. Analyzing this hypothesis, in this study were evaluated some type of energies. The results showed a less intramolecular energy involved in the interaction of compound **6** with the μ-opioid receptor compared with the interaction with the δ and κ-opioid receptors.

Table 5. Physicochemical factors involved between of interaction of the compound **6** and μ, δ, κ-opioid receptors.

Receptor	Electrostatic Energy	Total Intermol Ec. Energy	Interact. Surface
μ	0.20	-9.51	1384.11
δ	-0.48	-11.51	1308.85
κ	-8.89	-9.94	1428.61

The results found show interesting data that could be used to evaluate the biological activity and toxicity degree of compound **6** in some biological system.

Analysis of theoretical toxicity. Analyzing the hypothesis above mentioned, in this study also was evaluated the theoretical toxicity induced by the compound **6** (hexynloxy-diazecin-naphtho-oxadiazocine derivative) using the GUSAR software [34]. The results showed in the table 6 that toxicity could higher by intraperitoneal administration compared with intravenose, oral, and subcutaneous.

Table 6. Theoretical analyses of LD_{50} of compound **6** using the GUSAR software.

Rat ip, median dose lethal (LD_{50}; mg/Kg)	Rat iv, median dose lethal (LD_{50}; mg/Kg)	Rat oral, median dose lethal (LD_{50}; mg/Kg)	Rat sc, median dose lethal (LD_{50}; mg/Kg)
131.500	18.540	54.700	13.530

intraperitoneal administration (ip); intravenose (iv); subcutaneous (sc).

4. CONCLUSIONS

The compound **6** (hexynloxy- diazecin- naphtho- oxa-diazocine derivative) is a particularly interesting, because involves the interaction with μ, δ and κ-opioid receptor. Therefore, these results indicate that compound **6** could be used as an therapeutic alternative for pain.

5. REFERENCES

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