

# Synthesis of a Bis-oxabicyclo[5.4.0] Derivative and their Theoretical Evaluation as a Dopamine, Serotonin Transporters Inhibitor

López-Ramos Maria <sup>1</sup>, Figueroa-Valverde Lauro <sup>1,\*</sup>, Díaz-Cedillo Francisco <sup>2</sup>, Rosas-Nexticapa Marcela <sup>3</sup>, Mateu-Armad Maria Virginia <sup>3</sup>, Garcimarrero Alejandara <sup>4</sup>, Gutierrez-Lopez Tomas <sup>1</sup>, Alvarez-Ramirez Magdalena <sup>3</sup>, Ortiz-Ake Yazmin <sup>1</sup>, Cauch-Carrillo Regina <sup>1</sup>

<sup>1</sup> Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp., México

<sup>2</sup> Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, D.F. C.P. 11340, México

<sup>3</sup> Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontólogos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México

<sup>4</sup> Facultad de Medicina, Universidad Veracruzana, Médicos y Odontólogos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México

\* Correspondence: lauro\_1999@yahoo.com; lfiguero@uacam.mx;

Scopus Author ID 55995915500

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**Abstract:** The aim of this investigation was to synthesize a bis-oxabicyclo[5.4.0] derivative (compound 6) was prepared from Fluoro-2,4-dinitrobenzene. The chemical structure of the compounds was determined using nuclear magnetic resonance spectra. Besides, the theoretical activity of compound 6 on either dopamine (4m48 protein) or serotonin (5i6z protein) transporters was evaluated using fluoxetine and altoprone as controls in a Docking model. The data found indicate a higher interaction of 6 with 5i6z protein compared with fluoxetine. In addition, 6 could have lower affinity by 4m48 protein in comparison with altoprone. All data showed that compound 6 could be good dopamine, serotonin transporters inhibitor.

**Keywords:** oxabicyclo; synthesis; dopamine; serotonin.

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## 1. Introduction

For several years, have been synthesized several dopamine and serotonin transporter inhibitors [1-3]; for example, a series of gamma-amino alcohols were prepared from cyanide and some aldehyde derivatives as dopamine and serotonin inhibitors [4]. Besides, a study showed the synthesis of some thiophene derivatives from several tropane analogs to evaluate their biological activity on catecholamine transporters [5]. Other data indicate the synthesis of some phenyltropane derivatives via reaction of cyclic ketoesters with aryl boronates; it is noteworthy that phenyltropane derivatives were used as dopamine and serotonin transporter inhibitors [6]. In addition, a report showed the synthesis of some cyclopropane analogs from sulfonium ylide as a serotonin transporter inhibitor [7]. Another study showed the preparation of a 3,7-dimethylimipramine via reaction of 3,7-dihydroxymethyl imipramine and Palladium with biological activity on serotonin transporter [8]. All these reports indicate that several compounds have been prepared with biological activity on both dopamine and serotonin

transporters. Analyzing these data, the objective of this investigation was to prepare a bis-oxabicyclo[5.4.0] derivative to evaluate their theoretical activity on either dopamine or serotonin transporters using a docking model.

## 2. Materials and Methods

### 2.1. General.

All reagents used in this research were acquired from Sigma-Aldrich Co., Ltd. The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were evaluated with a Thermo Scientific iSOFT-IR spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded using a Varian VXR300/5 FT NMR spectrometer at 300 MHz in  $\text{CDCl}_3$  using TMS as an internal standard. EIMS spectra were obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

#### 2.1.1. Synthesis.

##### **6-(2,4-Dinitro-phenyl)-hex-5-yn-1-ol (2)**

In a round bottom flask (10 ml), 1-Fluoro-2,4-dinitrobenzene (100  $\mu\text{l}$ , 0.79 mmol), 5-hexyn-1-ol (100  $\mu\text{l}$ , 0.90 mmol), and Copper(II) chloride anhydrous (110 mg, 0.99 mmol) were stirred to room temperature at 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:agua (4:1) system; yielding 54% of product; m.p. 132-134  $^\circ\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2190 and 1542;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -*d*)  $\delta_{\text{H}}$ : 1.56-1.60 (m, 4H), 1.94 (broad, 1H), 2.26-3.64 (m, 4H), 7.96-8.36 (m, 3H) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.64, 25.76, 31.82, 62.21, 80.65, 88.70, 120.50, 123.04, 128.00, 137.62, 149.52, 155.03 pm. EI-MS *m/z*: 264.07. Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_5$ : C, 54.55; H, 4.58; N, 10.60; O, 30.28. Found: C, 54.52; H, 4.54.

##### **12-nitro-2-oxabicyclo[7.4.0]trideca-1(13),9,11-trien-7-yne (3)**

In a round bottom flask (10 ml), compound 2 (100 mg, 0.38 mmol), potassium carbonate anhydrous (50 mg, 0.36 mmol) and 5 ml of dimethyl sulfoxide were stirred to room temperature at 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:agua (3:1:1) system; yielding 45% of product; m.p. 166-168  $^\circ\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 2190, 1542 and 1242;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -*d*)  $\delta_{\text{H}}$ : 1.00-3.90 (m, 8H), 7.43-7.70 (m, 3H) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 20.34, 29.80, 32.50, 67.30, 76.72, 97.12, 111.32, 117.42, 117.48, 134.70, 149.70 pm. EI-MS *m/z*: 217.07. Anal. Calcd. for  $\text{C}_{12}\text{H}_{11}\text{NO}_3$ : C, 66.35; H, 5.10; N, 6.45; O, 22.10. Found: C, 66.32; H, 5.08.

##### **2-oxabicyclo[7.4.0]trideca-1(13),9,11-trien-7-yn-12-amine (4)**

In a round bottom flask (10 ml), compound 3 (100 mg, 0.46 mmol) sodium borohydride (30 mg, 0.79 mmol) and 5 ml of ethanol were stirred to room temperature at 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:agua (3:1) system; yielding 68% of product; m.p. 144-146  $^\circ\text{C}$ ; IR ( $V_{\text{max}}$ ,  $\text{cm}^{-1}$ ) 3380, 2192 and 1242;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ -*d*)  $\delta_{\text{H}}$ : 1.00-3.90 (m, 8H), 4.84 (broad, 1H), 6.17-6.84 (m, 3H) ppm.  $^{13}\text{C}$  NMR (300 Hz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 20.34, 29.80, 32.50, 67.30, 76.72, 97.12, 100.22, 105.62, 110.92, 131.14, 150.50 pm. EI-MS *m/z*: 187.09. Anal. Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}$ : C, 76.98; H, 7.00; N, 7.48; O, 8.54. Found: C, 76.95; H, 7.00.

**1-[(E)-2-oxabicyclo[7.4.0]trideca-1(13),9,11-trien-7-yn-12-yliminomethyl]-naphthalen-2-ol (5)**

In a round bottom flask (10 ml), compound 4 (100 mg, 0.53 mmol) 2-hydroxynaphthalene-1-carbaldehyde (100 mg, 0.58 mmol), boric acid (35 mg, 0.56 mmol) and 5 ml of methanol were stirred to room temperature at 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:agua (4:1) system; yielding 45% of product; m.p. 182-184 °C; IR ( $V_{max}$ ,  $cm^{-1}$ ) 3400, 3332, 2190 and 1240:  $^1H$  NMR (300 MHz,  $CDCl_3-d$ )  $\delta_H$ : 1.00-3.90 (m, 8H), 4.84 (broad, 1H), 6.56-6.76 (m, 2H), 6.92 (m, 1H), 7.17 (m, 1H), 7.58-8.54 (m, 5H), 8.90 (m, 1H), 14.78 (broad, 1H) ppm.  $^{13}C$  NMR (300 Hz,  $CDCl_3$ )  $\delta_C$ : 20.34, 29.80, 32.50, 67.30, 76.72, 97.12, 104.90, 105.96, 108.30, 114.18, 121.10, 122.73, 123.80, 127.06, 128.60, 128.86, 133.32, 135.50, 136.23, 153.50, 160.94, 163.36 ppm. EI-MS  $m/z$ : 341.14. Anal. Calcd. for  $C_{23}H_{19}NO_2$ : C, 80.92; H, 5.61; N, 4.10; O, 9.37. Found: C, 80.90; H, 5.58.

**(E)-N-(2-oxabicyclo[7.4.0]trideca-1(13),9,11-trien-7-yn-12-yl)-1-[2-(2-oxabicyclo[7.4.0]trideca-1(13),9,11-trien-7-yn-12-yloxy)-1-naphthyl]methanimine (6)**

In a round bottom flask (10 ml), compound 3 (65 mg, 0.30 mmol), compound 5 (100 mg, 0.29 mmol) compound (100 mg, 0.58 mmol), potassium carbonate anhydrous (50 mg, 0.36 mmol) and 5 ml of dimethyl sulfoxide were stirred to room temperature at 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:agua (4:1) system; yielding 45% of product; m.p. 208-210 °C; IR ( $V_{max}$ ,  $cm^{-1}$ ) 3330, 2190 and 1242:  $^1H$  NMR (300 MHz,  $CDCl_3-d$ )  $\delta_H$ : 1.00-3.90 (m, 16 H), 6.54-7.16 (m, 5H), 7.24 (m, 1H), 7.46 (m, 1H), 7.66-8.80 (m, 5H), 9.04 (m, 1H) ppm.  $^{13}C$  NMR (300 Hz,  $CDCl_3$ )  $\delta_C$ : 20.34, 29.80, 32.50, 67.30, 76.72, 97.12, 104.02, 104.90, 105.62, 108.12, 109.92, 110.12, 113.26, 118.48, 122.92, 123.90, 124.12, 125.72, 127.22, 128.44, 133.42, 134.90, 135.50, 150.41, 157.63, 162.80, 163.78, 165.80, 171.54 ppm. EI-MS  $m/z$ : 511.21. Anal. Calcd. for  $C_{35}H_{29}NO_3$ : C, 82.17; H, 5.71; N, 2.74; O, 9.38. Found: C, 82.14; H, 5.68.

### 2.1.2. Pharmacophore analysis

The 3D pharmacophore model for compound 6 was determined using LigandScout 4.08 software [9].

### 2.2. Theoretical evaluation.

The interaction of compound 6 with either dopamine (4m48) [10] or serotonin (5i6z) [11] transporter proteins was evaluated using the DockingServer software [12]. In addition, fluoxetine (serotonin transporter inhibitor) [13] and reboxetine (dopamine transporter inhibitor) [14] were used as controls.

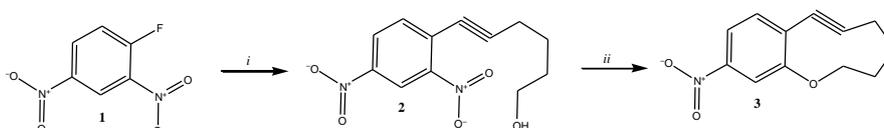
## 3. Results and Discussion

Several dopamine and serotonin transporters inhibitors have been synthesized [4-8]; however, several protocols use some reagents which require special conditions. In this research, the compound bis-oxabicyclo[5.4.0] derivative was prepared, and their theoretical activity as dopamine and serotonin transporters inhibitor was evaluated. The first stage was achieved as follows:

### 3.1. Chemistry.

#### 3.1.1 Preparation of an alkyne derivative.

There are several reports for the displacement of halides through nucleophilic substitution using some reagents such as polymer-supports [15], potassium *tert*-butoxide [16], Ru(II)OAc [17], Pt(II) [18], others. In this investigation, compound **2** was synthesized from 5-hexyn-1-ol and Copper(II) chloride (Figure 1). The <sup>1</sup>H NMR spectrum from **2** showed several signals at 1.56-1.60 and 2.26-3.64 ppm for methylene groups linked to both alkyne and hydroxyl groups; at 1.94 ppm for hydroxyl group; at 7.96-8.36 ppm for phenyl group. <sup>13</sup>C NMR spectra display chemical shifts at 19.64-62.21 ppm for methylene groups linked to both alkyne and hydroxyl groups; at 80.65-88.70 ppm for alkyne group; at 120.50-155.03 ppm for phenyl group. Besides, the mass spectrum from **2** showed a molecular ion (m/z) 260.07.



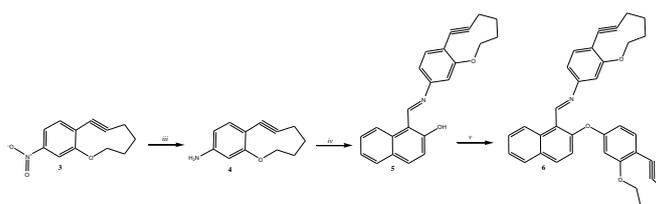
**Figure 1.** Synthesis of 12-nitro-2-oxabicyclo[7.4.0]trideca-1(13),9,11-trien-7-yne (**3**). Conditions and reagents: *i* = 5-hexyn-1-ol, Copper(II) chloride anhydrous, room temperature, 72 h; *ii* = potassium carbonate anhydrous, dimethyl sulfoxide, room temperature, 72 h.

#### 3.1.2. Synthesis of an ether-derivative.

There are methods for the synthesis of ether derivatives, which use some reagents such as Ta/Al<sub>2</sub>O<sub>3</sub> [19], palladium [20], *tert*-Butyl Nitrite [21], Ceric Ammonium Nitrate [22]. In addition, some reports showed the preparation of ether derivatives through the displacement of the nitro group using dipolar aprotic solvents such as dimethyl sulfoxide [23]. In this way; in this research, an ether analog (**3**) was prepared from compound **2**, dimethyl sulfoxide, and potassium carbonate (Figure 1). The <sup>1</sup>H NMR spectrum from **3** display several signals at 1.00-3.90 ppm for 1-oxacyclonon-6-yne ring; at 7.43-7.70 ppm for phenyl group. <sup>13</sup>C NMR spectra showed chemical shifts at 20.36-67.30 ppm for 1-oxacyclonon-6-yne ring; at 76.72-97.12 ppm for alkyne group; at 111.32-149.70 ppm for phenyl group. Besides, the mass spectrum from **3** showed a molecular ion (m/z) 217.07.

#### 3.1.3. Reduction reaction.

Some methods have used to nitro reduction using some reagents such as stannous chloride [24] TiO<sub>2</sub> [25], Be<sub>2</sub>[OH]<sub>4</sub> [26], graphitic carbon nitride [27], CuFe<sub>2</sub>O<sub>4</sub> [28], NiFe<sub>2</sub>O<sub>4</sub>/γ-Fe<sub>2</sub>O<sub>3</sub> [29]. In this research, compound **4** was prepared via reduction of the nitro group from **3** in the presence of sodium borohydride (Figure 1).



**Figure 2.** Synthesis of a bis-oxabicyclo[5.4.0] derivative (**6**). Conditions and reagents: *iii* = sodium borohydride, EtOH, room temperature, 72 h; *iv* = 2-hydroxynaphthalene-1-carbaldehyde, boric acid, MeOH, room temperature, 72 h; *v* = compound **3**, potassium carbonate anhydrous, dimethyl sulfoxide, room temperature, 72 h.

The  $^1\text{H}$  NMR spectrum from 4 showed several signals at 1.00-3.90 ppm for 1-oxacyclonon-6-yne ring; at 4.84 ppm for the amino group; at 6.17-6.84 ppm for phenyl group.  $^{13}\text{C}$  NMR spectra showed chemical shifts at 20.34-67.30 ppm for 1-oxacyclonon-6-yne ring; at 76.72-97.12 ppm for alkyne group; at 100.22-150.50 ppm for phenyl group. Additionally, the mass spectrum from 4 displays a molecular ion ( $m/z$ ) 187.09.

#### 3.1.4. Preparation of an imino group.

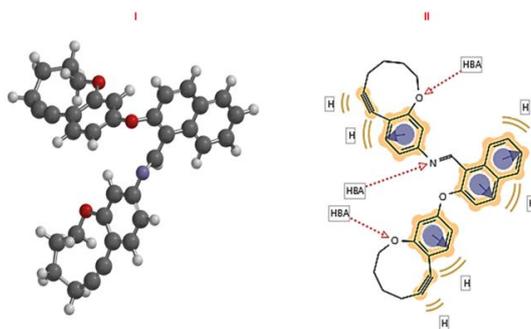
There are several protocols for preparation of imino groups using some reagents such as Gold(I) [30], AgF [31], chloroacetyl acid [32], tert-Butyl hypochlorite [33], dirhodium tetraacetate [34] and others. In this investigation, an imino derivative was prepared from compound 4 and 2-hydroxynaphthalene-1-carbaldehyde to form compound 5 in the presence of boric acid (Figure 2). The  $^1\text{H}$  NMR spectrum from 5 showed several signals at 1.00-3.90 ppm for 1-oxacyclonon-6-yne ring; at 6.56-6.76 and 7.17 ppm for phenyl group; at 6.92 and 7.58-8.54 ppm for naphthalene fragment; at 8.90 ppm for imino group; at 14.78 ppm for a hydroxyl group.  $^{13}\text{C}$  NMR spectra display chemical shifts at 20.34-67.30 ppm for 1-oxacyclonon-6-yne ring; at 76.72-97.12 ppm for alkyne group; at 104.90, 108.30-114.18, 135.50 and 153.50 ppm for phenyl group; at 105.96, 121.10-133.32, 136.23 and 160.94 ppm for naphthalene fragment; at 163.36 ppm for imino group. Besides, the mass spectrum from 5 showed a molecular ion ( $m/z$ ) 341.14.

#### 3.1.5. Synthesis of a second ether group.

This stage was achieved *via* a reaction of 3 with 5 to form compound 6. The  $^1\text{H}$  NMR spectrum from 6 showed several signals at 1.00-3.90 ppm for 1-oxacyclonon-6-yne ring; at 6.54-6.16 and 7.46 ppm for phenyl group; at 7.24 and 7.66-8.80 ppm for naphthalene fragment; at 9.04 ppm for imino group; at 14.78 ppm for a hydroxyl group.  $^{13}\text{C}$  NMR spectra display chemical shifts at 20.34-67.30 ppm for 1-oxacyclonon-6-yne ring; at 76.72-97.12 ppm for alkyne group; at 104.02-110.12, 134.90-150.41, 162.80 and 165.80-171.54 ppm for phenyl group; at 113.26-133.42 and 157.63 ppm for naphthalene fragment; at 163.78 ppm for imino group. Finally, the mass spectrum from 6 showed a molecular ion ( $m/z$ ) 511.21.

#### 3.1.6. Pharmacophore model.

Several pharmacophore models have been used to predict the interaction of some drugs with different biomolecules in some biological models [35, 36]; In this way. In this investigation, a pharmacophore was prepared for compound 6 (Figure 3, Table 1) using the LigandScout software [9].



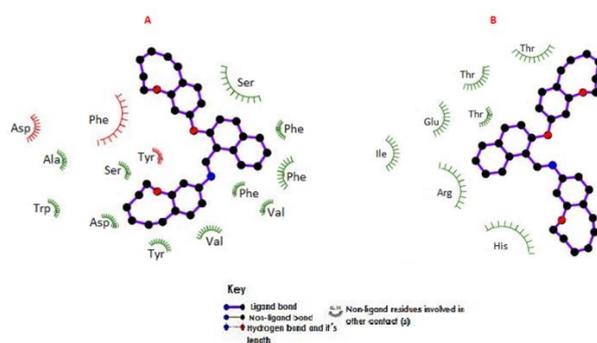
**Figure 3.** Scheme represents a pharmacophore from compound 6 using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red).

**Table 1.** Physicochemical parameters of compound 6.

Molecular weight	511.61 g/mol
Num. heavy atoms	39
Num. arom. heavy atoms	22
Fraction C (sp <sup>3</sup> )	0.23
Num. rotatable bonds	4
Num. H-bond acceptors	4
Num. H-bond donors	0
Molar Refractivity	157.63
TPSA	40.05 Å <sup>2</sup>

3.1.7. Teorethical evaluation.

Several studies have been used to evaluate the ligand-protein interaction of some compounds using different theoretical analysis [35]. In this way, a study was carried out to determine the interaction of compound 6 with DA (4m8m protein) and 5HT (5i6z protein) transporter using DockingServer software (Figure 4).



**Figure 4.** Interaction of compound 6 with either 4m48 (A) or 5i6z (B) proteins surface using Dockingserver software.

The data indicated differences in the interaction of fluoxetine, altoprone, and compound 6 with either 5i6z and 4m48 proteins surface (Table 2 and 3). These data could be due to the energy differences involved in the interaction of compound 6 with either 4m48 or 5i6z proteins.

**Table 2.** Interaction of either compound 6 or fluoxetine with 5i6z protein.

Compound	Aminoacid residues
6	Thr <sub>206</sub>
	Thr <sub>225</sub>
	Glu <sub>229</sub>
	Thr <sub>233</sub>
	Arg <sub>234</sub>
	Ile <sub>239</sub>
	His <sub>240</sub>
Fluoxetine	Thr <sub>206</sub>
	Asn <sub>208</sub>
	Hist <sub>223</sub>
	Thr <sub>225</sub>
	Glu <sub>230</sub>
	Ile <sub>239</sub>
	His <sub>240</sub>
Tyr <sub>487</sub>	

To evaluate the hypothesis above mentioned, a theoretical analysis of energies involved in the interaction of compound 6 with either 4m48 or 5i6z proteins using the Dockingserver software. The results showed (tables 4 and 5) differences in the energies values. Furthermore,

the  $K_i$  value (inhibition constant) was lower for compound 6 compared with fluoxetine; these data suggest that compound 6 could have a higher affinity for the 5i6z protein compared to fluoxetine, which could translate as a decrease in the biological activity of the serotonin transporter protein.

**Table 3.** Interaction of either compound 6 or altropone with 4m48 protein.

Compound	Aminoacid residues
6	Thr <sub>206</sub>
	Thr <sub>225</sub>
	Glu <sub>229</sub>
	Thr <sub>233</sub>
	Arg <sub>234</sub>
	Ile <sub>239</sub>
His <sub>240</sub>	
Fluoxetine	Phe <sub>43</sub>
	Ala <sub>44</sub>
	Asp <sub>46</sub>
	Val <sub>113</sub>
	Ile <sub>116</sub>
	Ala <sub>117</sub>
	Val <sub>120</sub>
	Asp <sub>121</sub>
	Tyr <sub>124</sub>
	Ser <sub>320</sub>
	Leu <sub>321</sub>

On the other hand, the interaction of compound 6 with protein 4m48 showed that the  $K_i$  of compound 6 was higher compared with altropone, which indicates that 6 could exert a lesser effect on the activity of protein 4m48 compared to altropone.

**Table 4.** Energy levels involved in the interaction of compound 6 and fluoxetine with 5i6z protein.

Compound	Est. Free energy of Binding (Kcal/mol)	Est. Inhibition Constant ( $K_i$ ) [ $\mu$ M]	vdW + HBond + Desolv. Energy (Kcal/mol)	Electrostatic Energy (Kcal/mol)	Total Inter-molec. Energy (Kcal/mol)	Interact. Surface
6	-6.24	26.65	-6.29	-0.04	-6.33	869.60
Fluoxetine	-4.48	519.97	-5.12	0.09	-5.03	476.66

**Table 5.** Type of energies involved in the interaction of compound 6 and altropone with 4m48 protein.

Compound	Est. Free energy of Binding (Kcal/mol)	Est. Inhibition Constant ( $K_i$ ) [ $\mu$ M]	vdW + HBond + Desolv. Energy (Kcal/mol)	Electrostatic Energy (Kcal/mol)	Total Inter-molec. Energy (Kcal/mol)	Interact. Surface
6	-10.96	9.28	-10.94	0.05	-10.89	1061.16
Altropone	-7.74	2.13	-8.87	-0.93	-9.80	700.78

## 4. Conclusions

In this study, the synthesis of a bis-oxabicyclo[5.4.0] derivative was reported using some strategies chemical. It's is noteworthy that reagents used in this investigation no require special conditions. Besides, theoretical data showed that compound 6 could be good dopamine, serotonin transporters inhibitor.

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## Conflicts of Interest

The authors declare no conflict of interest.

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