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Synthesis of Two Testosterone Derivatives and their Theoretical Evaluation as Serotonin Reuptake Transporter Inhibitors

Lauro Figueroa-Valverde [1,*], Magdalena Alvarez-Ramirez [2], Marcela Rosas-Nexticapa [2], Francisco Díaz-Cedillo [3], Maria López-Ramos [1], Maria Virginia Mateu-Armad [2], Tomas Lopez-Gutierrez [1], Regina Cauich-Carrillo [1]

[1] Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Humberto Lanz Cárdenas S/N, Colonia Ex Hacienda Kalá, C.P. 24085, Campeche, Mexico
[2] 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
[3] Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontologos 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: This investigation aimed to synthesize two testosterone derivatives (4 and 7) from either testosterone 3-oxime or testosterone 3-(O-carboxymethyl)oxime. The chemical structure of the compounds was determined using nuclear magnetic resonance spectra. Besides, testosterone derivatives' theoretical activity on serotonin transporter (5i6z protein) was evaluated using fluoxetine as a control in a Docking model. The results showed a higher interaction of both compounds 4 and 7 with a 5i6z protein surface compared with fluoxetine. In conclusion, it's noteworthy that reagents used in this investigation no require special conditions. Also, the theoretical study showed that either compounds 4 or 7 could be good serotonin transporter inhibitors.

Keywords: testosterone; synthesis; serotonin; protein.

1. Introduction

Biogenic amine reuptake inhibitors have been used as an antidepressant; for example, fluoxetine (serotonin reuptake inhibitor selective) [1, 2], imipramine (noradrenaline and reuptake inhibitor non-selective), vanoxerine (dopamine reuptake inhibitor selective) [4], moclobemide (monoamine oxidase inhibitor) [5]; however, some of these drugs can produce some adverse effects such as tiredness [6], psychomotor retardation [7], increases body weight [8] and others. In the search for some alternative therapeutic, some drugs have been developed for the treatment of depression as amine reuptake inhibitors; in this way, the hydroxynorketamine was prepared from 1-Chloro-2-cyclohex-1-enyl-benzene [9]. In addition, other studies display the preparation of paroxetine via reaction of arene-diazonium tetrafluoroborate salt with an ester derivative [10]. Besides, a study displayed an indole analog reaction with *N*-Boc-piperidinone to form an indol-isoquinoline derivative [11]. Other data showed cyclic ketoesters' reaction with arylboronates to the synthesis of some phenyltropane analogs [12]. In addition, a report displayed the preparation of several cyclopropane analogs

from sulfonium-ylide [13]. Another study showed the synthesis of an imipramine derivative from dihydroxymethyl imipramine and palladium [14]. All these reports use different protocols that require several reagents that require special conditions such as differences in the heat and pH. Analyzing these data, in this investigation, two testosterone analogs were prepared using some chemical reactions. Besides, the theoretical interaction of two testosterone derivatives on reuptake serotonin transporter was evaluated.

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}H and ^{13}C NMR spectra were recorded using a Varian VXR300/5 FT NMR spectrometer at 300 MHz in $CDCl_3$ 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.

(3E,10R,13S,17S)-3-(2-hydroxyethoxyimino)-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-ol (2)

A solution of testosterone 3-(O-carboxymethyl)oxime (200 mg, 0.55 mmol), sodium borohydride (40 mg, 0.63 mmol) in ethanol was stirring for 72 h at room temperature. 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 54% of product; m.p. 186-188 ^{o}C; IR (V_{max}, cm^{-1}) 3400, and 3320: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.82 (s, 3H), 0.96-1.02 (m, 2H), 1.04 (s, 3H), 1.07-1.88 (m, 12H), 2.10-3.64 (m, 6H), 3.71 (m, 2H), 3.95 (broad, 2H), 4.08 (m, 2H), 5.70 (d, 1H, J = 0.70 Hz) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.10, 17.73, 20.94, 23.34, 29.22, 30.30, 31.32, 31.42, 31.70, 35.26, 35.33, 36.50, 42.82, 50.54, 50.60, 62.92, 73.76, 80.82, 114.90, 152.41, 157.40 ppm. EI-MS m/z: 347.24. Anal. Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03; O, 13.81. Found: C, 72.56; H, 9.54.

(3E,10R,13S,17S)-3-(2-hydroxyethoxyimino)-10,13-dimethyl-4-nitro-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-ol (3)

A solution of compound 2 (200 mg, 0.57 mmol), acetic anhydride (3 ml) and nitric acid (5 ml) was stirring for 8 h at reflux. 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. 146-148 ^{o}C; IR (V_{max}, cm^{-1}) 3402, 3320 and 1542: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.82 (s, 3H), 0.96-1.10 (m, 2H), 1.14 (s, 3H), 1.16-1.88 (m, 12H), 2.04-3.64 (m, 6H), 3.71 (m, 2H), 3.95 (broad, 2H), 4.08 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.10, 19.00, 20.94, 23.28, 25.22, 26.84, 30.12, 30.90, 32.18, 35.33, 36.50, 40.16, 42.78, 49.66, 50.60, 62.92, 73.76, 80.52, 144.76, 148.90, 150.00 ppm. EI-MS m/z: 392.23. Anal. Calcd. for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14; O, 20.38. Found: C, 64.22; H, 8.20.

(1R,5S,6S)-1,5-dimethyl-15,18-dioxa-19-azapentacyclo[11.9.0.02,10.05,9.014,20]docosa-13,19-dien-6-ol (4)

A solution of compound 3 (200 mg, 0.50 mmol), potassium carbonate (85 mg, 0.6 mmol) in 5 ml of dimethyl sulfoxide was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:agua (4:1:1) system; yielding 65% of product; m.p. 222-224 ºC; IR (V_{max}, cm^{-1}) 3400, 3380 and 1208: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.82 (s, 3H), 0.96-1.05 (m, 3H), 1.07 (s, 3H), 1.10-1.96 (m, 13H), 2.66-3.12 (m, 3H), 3.18-3.23 (m, 2H), 3.66 (m, 1H), 3.92-4.02 (m, 2H), 6.22 (broad, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.10, 20.90, 20.94, 22.02, 23.28, 29.90, 30.12, 30.98, 31.70, 35.33, 36.50, 38.58, 42.78, 49.96, 50.60, 65.49, 70.56, 80.52, 128.55, 145.00, 161.10 ppm. EI-MS m/z: 345.23. Anal. Calcd. for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.05; O, 13.89. Found: C, 73.00; H, 9.02.

(10R,13S,17S)-17-hydroxy-10,13-dimethyl-4-nitro-1,2,6,7,8,9,11,12,14,15,16,17-dodeca-hydrocyclopenta[a]phenanthren-3-one oxime (6)

A solution of compound testosterone-3-oxime (200 mg, 0.66 mmol), acetic anhydride (3 ml) and 5 ml of nitric acid were stirring for 8 h at reflux. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:agua (4:1) system; yielding 70% of product; m.p. 222-224 ºC; IR (V_{max}, cm^{-1}) 3400, 3320 and 1540: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.82 (s, 3H), 0.96-1.10 (m, 2H), 1.12 (s, 3H), 1.18-1.90 (m, 12H), 2.06-3.66 (m, 1H), 3.92-4.02 (m, 6H), 6.94 (broad, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.10, 19.00, 20.94, 22.02, 23.28, 24.90, 26.80, 30.12, 30.92, 31.32, 35.33, 36.50, 40.18, 42.78, 49.66, 50.60, 80.52, 143.96, 151.50, 156.02 ppm. EI-MS m/z: 348.20. Anal. Calcd. for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04; O, 18.37. Found: C, 65.46; H, 8.08.

(2R,16S,17S)-2,17-dimethyl-7-oxa-6-azapentacyclo[10.7.0.02,9.05,8.013,17]nonadeca-5,8-dien-16-ol (7)

A solution of compound 6 (200 mg, 0.57 mmol), potassium carbonate (85 mg, 0.60 mmol) in 5 ml of dimethyl sulfoxide were stirring for 72 h at room temperature. 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. 135-137 ºC; IR (V_{max}, cm^{-1}) 3400, 3322 and 1242: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.82 (s, 3H), 0.96-1.04 (m, 3H), 1.06 (s, 3H), 1.10-1.98 (m, 13H), 2.60-3.66 (m, 4H), 6.23 (broad, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.10, 20.22, 20.94, 21.60, 23.28, 30.12, 30.92, 30.16, 30.22, 30.90, 35.33, 36.50, 37.42, 42.78, 50.44, 50.60, 80.52, 129.96, 142.76, 169.60 ppm. EI-MS m/z: 301.20. Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65; O, 10.62. Found: C, 75.68; H, 9.00.

2.2. Theoretical evaluation.

The interaction of both compounds 4 and 7 with serotonin (5i6z) [15] transporter protein was evaluated using the DockingServer software [16]. Besides, fluoxetine (serotonin transporter inhibitor) [17] was used as a control.

3. Results and Discussion

Several Biogenic amine reuptake inhibitors have been synthesized using different protocols [9,14]; in this research, two testosterone derivatives were synthesized from either testosterone 3-(O-carboxymethyl)oxime or 3-oxime testosterone as follows:

3.1. Chemistry.

3.1.1. Reduction reaction.

There are several reports for the reduction of carboxyl groups using several reagents such as sodium borohydride/samarium chloride [18], disiamylborane [19], borohydride [20], sodium borohydride and diborane [21], lithium borohydride [22], cyanuric chloride/sodium borohydride [23], and others. In this investigation, the carboxyl group of compound 1 was reduced in the presence of sodium borohydride to form compound 2 (Figure 1). The ^{1}H NMR spectrum from 2 display some bands signals at 0.82 and 1.04 ppm for methyl groups; at 0.96-1.02, 1.07-3.64 and 5.70 ppm for steroid moiety; at 3.71 and 4.08 ppm for methylene groups linked to both hydroxyl and oxime groups; at 3.95 ppm for hydroxyl groups. ^{13}C NMR spectra showed chemical shifts at 11.10-17.73 ppm for methyl groups; at 20.94-50.60 and 80.82-157.40 ppm for steroid moiety; at 62.92-73.76 ppm for methylene groups linked to both hydroxyl and oxime groups. Besides, the mass spectrum from 2 displayed a molecular ion (m/z) 347.24.

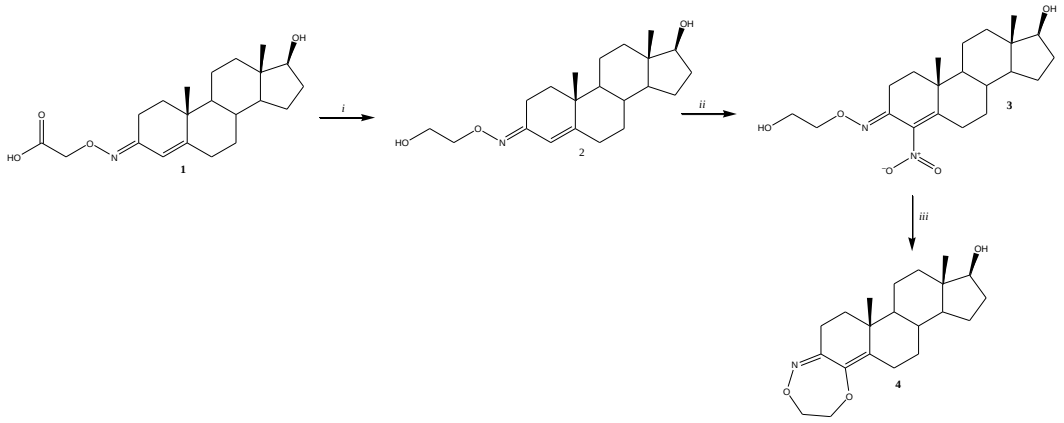

Figure 1. Synthesis of an ether-steroid derivative (4). *Reagents and conditions*: *i* = sodium cyanoborohydride, room temperature, 12 hs; *ii* = acetic anhydride, nitric acid, reflux 8 h; *iii* = potassium carbonate, dimethyl sulfoxide, room temperature, 72h.

3.1.2. Synthesis of a nitro-steroid derivative.

There are several methods for the synthesis of nitro derivatives using some reagents such as dimethyldioxirane [24], $NaNO_2$ [25], HNO_3 [26], NOF [27], $HNO_3/(CH_3CO)_2O$ [28], and others. In this investigation, 3 was prepared from compound 2, nitric acid, and anhydride acetic (Figure 1). The ^{1}H NMR spectrum from 3 showed several signals at 0.82 and 1.14 ppm for methyl groups; at 0.96-1.10, 1.16-3.64 and 5.70 ppm for steroid moiety; at 3.71 and 4.08 ppm for methylene groups linked to both hydroxyl and oxime groups; at 3.95 ppm for a hydroxyl group. ^{13}C NMR spectra showed chemical shifts at 11.10-19.00 ppm for methyl groups; at 20.94-50.60 and 80.82-150.02 ppm for steroid moiety; at 62.92-73.76 ppm for methylene groups linked to both hydroxyl and oxime groups. Besides, the mass spectrum from 3 displayed a molecular ion (m/z) 392.23.

3.1.3. Preparation of an ether-steroid derivative.

Several ether analogs have been synthesized using different reagents such as Ta/Al_2O_3 [29], palladium [30], tert-Butyl Nitrite [31], Ceric Ammonium Nitrate [32]. Some reports also showed the preparation of ether derivatives through the nitro group's displacement using dipolar aprotic solvents such as dimethyl sulfoxide [33]. In this way, an ether-steroid analog (4) was prepared from compound 3, dimethyl sulfoxide, and sodium carbonate (Figure 1). The ^{1}H NMR spectrum from 4 showed several signals at 0.82 and 1.07 ppm for methyl groups; at 0.96-1.05, 1.10-3.12 and 3.66 ppm for steroid moiety; at 3.18-3.23 and 3.92-4.02 ppm for 6,7-Dihydro-4H-[1,5,2]dioxazepine ring; at 6.22 ppm for a hydroxyl group. ^{13}C NMR spectra showed chemical shifts at 11.10-20.90 ppm for methyl groups; at 20.94-50.60 and 80.52-161.10 ppm for steroid moiety; at 65.49-70.56 ppm for 6,7-Dihydro-4H-[1,5,2] dioxazepine ring. Additionally, the mass spectrum from 4 showed a molecular ion (m/z) 345.23.

3.1.4. Preparation of a 4-nitro-testosterone oxime.

This stage was achieved via nitration of 3-oxime testosterone in the presence of nitric acid and anhydride acetic. The ^{1}H NMR spectrum from **6** showed several signals at 0.82 and 1.07 ppm for methyl groups; at 0.96-1.05, 1.10-3.12 and 3.66 ppm for steroid moiety; at 3.18-3.23 and 3.92-4.02 ppm for 6,7-Dihydro-4H-[1,5,2]dioxazepine ring; at 6.22 ppm for a hydroxyl group. ^{13}C NMR spectra showed chemical shifts at 11.10-20.90 ppm for methyl groups; at 20.94-50.60 and 80.52-161.10 ppm for steroid moiety; at 65.49-70.56 ppm for 6,7-Dihydro-4H-[1,5,2] dioxazepine ring. Additionally, the mass spectrum from **6** displayed a molecular ion (m/z) 345.23.

3.1.5. Synthesis of an azete-steroid derivative.

In this investigation, an azete-steroid derivative was prepared the compound **7** from an intramolecular reaction of **6** in the presence of dimethylsulfoxide/potassium carbonate (Figure 2). The ^{1}H NMR spectrum from **7** showed several signals at 0.82 and 1.06 ppm for methyl groups; at 0.96-1.04 and 1.10-3.66 ppm for steroid moiety; at 6.23 ppm for a hydroxyl group. ^{13}C NMR spectra showed chemical shifts at 11.10-20.22 ppm for methyl groups; at 20.94-142.76 ppm for steroid moiety; 169.60 ppm for imino group. Besides, the mass spectrum from **7** displayed a molecular ion (m/z) 301.20.

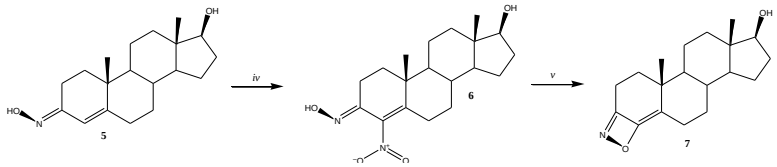

Figure 2. Synthesis of an azete-steroid derivative (**7**). Reagents and conditions: i = acetic anhydride, nitric acid, reflux 8 h.

3.1.6. Teorethical evaluation.

In the literature, some studies have been used to evaluate the ligand-protein interaction of some drugs [34-36]. In this way, compounds 4 and 7 were used to determine their interaction with serotonin transporter (5i6z protein) in DockingServer software (Figures 3 and 4).

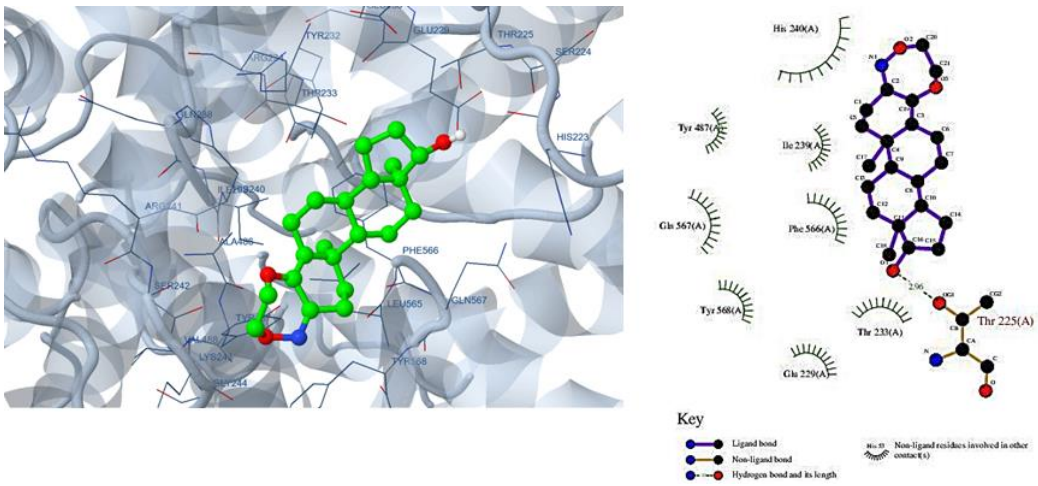

Figure 3. Interaction of compound **4** with 5i6z protein surface using Dockingserver software.

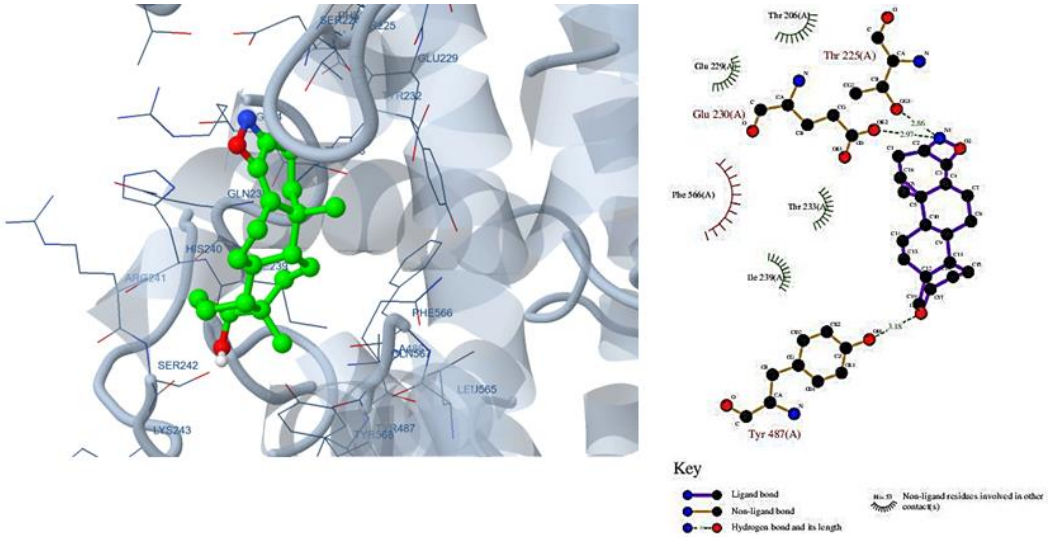

Figure 4. Interaction of compound **7** with either 5i6z protein surface using Dockingserver software.

The results showed differences in the type of amino acid residues involved in the interaction of fluoxetine and compound 4 and 7 with the 5i6z protein surface (Table 1 and 2). These data could be due to the energy differences involved in the interaction of compounds 4 and 7 with the 5i6z protein surface.

Table 1. Interaction of either compound **4** or fluoxetine with 5i6z protein.

Compound	Aminoacid residues
4	Thr_{225} Glu_{229} Thr_{233} Ile_{239} His_{240} Tyr_{487} Phe_{566} Gln_{567} Tyr_{568}
Fluoxetine	Thr_{206} Asn_{208} $Hist_{223}$ Thr_{225} Glu_{230} Ile_{239} His_{240} Tyr_{487}

Table 2. Interaction of either compound 7 or fluoxetine with 5i6z protein.

Compound	Aminoacid residues
7	Thr_{206} Thr_{225} Glu_{229} Glu_{230} Thr_{233} Ile_{239} Tyr_{487} Phe_{566}
Fluoxetine	Phe_{43} Ala_{44} Asp_{46} Val_{113} Ile_{116} Ala_{117} Val_{120} Asp_{121} Tyr_{124} Ser_{320} Leu_{321}

To evaluate the energies involved in the interaction of either compounds **4** or **7** with 5i6z protein surface was used the Dockingserver software (Table 3).

Table 3. Energy levels involved in the interaction of either compounds **4** or **7** or fluoxetine with 5i6z protein.

Compound	Est. Free energy of Binding (Kcal/mol)	Est. Inhibition Constant (Ki) [μM]	vdW + HBond + Desolv. Energy (Kcal/mol)	Electrostatic Energy (Kcal/mol)	Total Inter-molec. Energy (Kcal/mol)	Interact. Surface
4	-6.68	12.65	-7.12	0.14	-6.98	654.45
7	-5.87	50.01	-6.19	0.02	-6.17	582.38
Fluoxetine	-4.48	519.97	-5.12	0.09	-5.03	476.66

The results showed several differences in the energy levels involved in the interaction for either compounds 4, 7, and fluoxetine with 5i6z protein surface (Tables 3). Other data showed that the Ki value (inhibition constant) was lower for 4 compared with both compound 7 and fluoxetine; however, the Ki for 7 was higher in comparison with fluoxetine. All these data indicate that either compounds 4 or 7 could have a higher affinity for the 5i6z protein than fluoxetine, which could translate as a decrease in the serotonin transporter protein's biological activity.

4. Conclusions

In this investigation, the synthesis of two testosterone derivatives is reported using some chemical strategies. It's noteworthy that reagents used in this investigation no require special conditions. This study's theoretical study showed that either compounds 4 or 7 could be good serotonin transporters inhibitors.

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Conflicts of Interest

The authors declare no conflict of interest.

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