Heterocyclic Letters
Vol. 9| No.3|213-223|May-July|2019
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

DESIGN AND SYNTHESIS OF TWOADAMANTANYL-2-OXOSTEROID-DIONE DERIVATIVES USING SOME CHEMICAL TOOLS

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Abstract
Several oxo-steroid derivatives have been synthesized using several protocols; however, some reagents used in the preparation are expensive and difficult to handle. The aim of this study was to synthetize two adamantanyl-2-oxosteroid-dione derivatives using some reactions such as *i*) nitration; *ii*) etherification; *iii*) cycloaddition and *iv*) esterification. The structure of the compounds obtained was confirmed through elemental analysis, spectroscopy and spectrometry data. The proposed method offers some advantages such as simple procedure, low cost, and ease of workup.

Introduction
For several years, both chemical and pharmaceutical industry has shown interest in the preparation of oxo-derivatives[i-ii].For example, the synthesis of an oxo-chromanone via a hydroxylation-oxo-addition of alkyne groups[iii]. Other data showed an oxo-hydroxy-acyloxylation of alkenes and enol-esters using iodide as catalyst[iv]. In addition, a study indicates the oxo-Amination of alkenes and enol ethers with N-bromosuccinimide-dimethyl sulfoxide[v]. Also, a report showed the preparation of a γ-Oxo-β-amino ester using a multicomponent system (alkyne, ester and azide) in presence of CuI/RhII[vi].
On the other hand, a series of steroid derivatives have been prepared using different protocols; for examplethe synthesis of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one from cholesteryl acetate and m-CPBA[vii]. Other data showed that some 6-oxo-estrogens derivatives can be synthetized via oxidation with chromic anhydride-3,5-dimethylpyrazole[viii]. Other

report indicates the synthesis of 5α-androstan-3β-olderivative by reaction of 5α-androstane-3β,17β-diolwithTHF/H_2SO_4[ix]. Additionally, a study had shown a stereospecific synthesis of 16-alpha.-hydroxy-17-oxo steroids by controlled alkaline hydrolysis of corresponding 16-bromo-17-ketones[x]. All these data indicate that some methods are available for synthesis of several oxo-steroids; nevertheless, expensive reagents and special conditions are required. Therefore, in this study, two adamantanyl-2-oxosteroid-dione derivativeswere synthesized using some strategies.

METHODOLOGY

The compounds used in this investigation were acquired from Sigma-Aldrich Co., Ltd. The melting point for compounds was determined on an Electrothermal (900 model). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer.^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR300/5 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 Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

Chemical Synthesis

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

In a round bottom flask (10 ml), compound **1**(200 mg, 0.63 mmol), nitric acid (1 ml), and anhydride acetic (5ml) were stirred to reflux for 12 h. The solution obtained was reduced pressure and purified through a crystallization using the methanol:water (4:1) system; yielding 65% of product; m.p. 156-158 ^{o}C;IR (V_{max}, cm^{-1}) 3400, 2122 and 1352: IR (V_{max}, cm^{-1}) 156-158 ^{o}C;IR (V_{max}, cm^{-1}) 3400, 2122 and 1352: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 1.04 (s, 3H), 1.20-1.84 (m, 8H), 2.00-2.90 (m, 7H), 3.32 (s, 1H), 6.68 (m, 1H), 7.22 (broad, 2H), 7.82 (m, 1H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 12.32, 23.66, 26.92, 27.70, 29.83, 34.88, 36.12, 37.88, 44.96, 48.42, 52.80, 74.72, 80.72, 88.56, 114.00, 123.58, 132.30, 132.90, 145.12, 148.52 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, 79.40; H, 5.92.

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

In a round bottom flask (10 ml), compound **2**(200 mg, 0.58 mmol), 1-adamantyl bromomethyl ketone(150 mg, 0.58 mmol), Copper(II) chloride (78 mg 0.58 mmol) and 5 ml of methanol were stirred to reflux for 12 h. The solution obtained was reduced pressure and purified through a crystallization using the methanol:bencene (4:1) system; yielding 68% of product; m.p.50-52^{o}C;IR (V_{max}, cm^{-1}) 3400, 2122, 1712 and 1352: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.20-1.50 (m, 4H), 1.56-1.62- (m, 6H), 1.70-1.74 (m, 2H), 1.78 (m, 3H), 1.80-1.84 (m, 4H), 1.86 (m, 1H), 1.90 (m, 3H), 2.08-2.12 (m, 2H), 2.30-2.90 (m, 5H), 4.10 (m, 2H), 6.66 (m, 1H), 7.66 (broad, 2H), 7.80 (m, 1H) ppm.^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 12.34, 23.72, 26.92, 27.70, 28.32, 29.42, 29.82, 34.90, 36.56, 37.84, 37.92, 39.50, 44.94, 47.34, 48.14, 52.80, 81.56, 81.86, 97.32, 114.00, 123.52, 132.36, 132.94, 145.12,148.48, 204.96 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, 79.40; H, 5.92.

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, 0.39 mmol), potassium carbonate (30 mg, 0.22 mmol), and 5 ml of dimethyl sulfoxidewere stirred to reflux for 12 h. The solution obtained was reduced pressure and purified through a crystallization using the

methanol:bencene (4:2) system; yielding 44% of product; m.p. 88-90 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 2120, 1714, 1352 and 1212: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.90 (s, 3H), 1.20-1.50 (m, 4H), 1.56-1.62 (m, 5H), 1.70-1.74 (m, 2H), 1.76 (m, 3H), 1.80 (m, 1H), 1.84 (m, 3H), 1.86 (m, 1H), 1.90 (m, 3H), 2.08-2.80 (m, 7H), 4.10 (m, 2H), 5.70 (broad, 1H), 6.30-6.34 (m, 2H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C:12.34, 23.70, 26.90,27.72, 28.34, 29.42, 29.82, 34.94, 36.62, 37.84, 37.90, 39.50, 45.40, 47.34, 48.16, 52.80, 81.54, 81.86, 97.35, 108.85, 108.90, 130.32, 134.90, 147.36, 147.62, 204.94 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, 81.58; H, 8.08.

1-Adamantan-1-yl-2-[2-(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)-3-(hydroxy-phenyl-methyl)-cyclobutadienyl]-ethanone(5)

In a round bottom flask (10 ml), compound **4**(200 mg, 0.42 mmol), 1-phenyl-prop-2-yn-1-ol (72 µl, 0.50 mmol), Copper(II) chloride (78 mg 0.58 mmol)and 5 ml of methanol were stirred to reflux for 12 h. The solution obtained was reduced pressure and purified through a crystallization using the methanol:bencene (4:1) system; yielding 56% of product; m.p.120-122^{o}C; IR (V_{max}, cm^{-1}) 3400, 1714, 1580 and 1212: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.76 (s, 3H), 1.12-1.36 (m, 3H), 1.50 (m, 3H), 1.52 (m, 2H), 1.58-1.66 (m, 9H), 1.69-1.86 (m, 4H), 1.90 (m, 3H), 1.92-2.80 (m, 6H), 3.24 (m, 2H), 3.74 (broad, 2H), 5.50 (m, 1H), 5.80 (d, 1H, J = 1.30 Hz), 6.28-7.32 (m, 7H) ppm. ^{13}C NMR (500 MHz, Chloroform-*d*) δ_C:20.94, 24.50, 25.94, 27.79, 29.44, 29.84, 30.70, 35.74, 37.94, 38.12, 38.64, 40.50, 42.82, 45.38, 47.92, 51.32, 77.82, 84.12, 108.88, 108.96, 127.92, 128.42, 129.42, 129.40, 130.36, 134.94, 136.32, 140.14, 141.12, 147.44, 147.60, 147.72, 210.52 ppm. EI-MS m/z: 602.33. Anal. Calcd. for $C_{41}H_{46}O_4$: C, 81.69; H, 7.69;; O, 10.62. Found: C, 81.60; H, 7.60.

(10a'S)-13-(2-((3S,5S,7S)-adamantan-1-yl)-2-oxoethyl)-10a'-methyl-9-phenyl-2',3',3a',3b',4',5',8b',9',10',10a'-decahydro-3,8-dioxaspiro[bicyclo[9.2.0]tridecane-2,1'-cyclopenta[7,8]phenanthro[2,3-b]oxirene]-1(13),11-diene-4,7-dione (6)

In a round bottom flask (10 ml), compound **5**(200 mg, 0.33 mmol), succinic acid (59 mg, 0.50 mmol), andboric acid (31 mg, 0.50 mmol) and 5 ml of methanol were stirred to reflux for 12 h. The solution obtained was reduced pressure and purified through a crystallization using the methanol:water (4:1) system; yielding 68% of product; m.p.156-158^{o}C;IR (V_{max}, cm^{-1}) 1725, 1714, 1580 and 1212: ^{1}H NMR (500 MHz, Chloroform-*d*) δ_H: 0.70 (s, 3H), 1.12-1.44 (m, 3H), 1.50-1.56 (m, 6H), 1.58 (m, 1H), 1.60-1.66 (m, 6H), 1.68-1.86 (m, 2H), 1.90 (m, 3H), 1.92-2.10 (m, 5H), 2.30 (m, 2H), 2.34 (m, 2H), 2.44 (m, 2H), 2.48 (m, 2H), 2.76-2.80 (m, 2H), 3.20 (m 2H), 5.30 (m, 1H), 5.64 (d, 1H, J = 0.56 Hz), 6.30-6.34 (m, 2H), 7.20-7.30 (m, 5H) ppm.^{13}C NMR (500 MHz, Chloroform-*d*) δ_C: 19.54, 24.40, 25.80, 27.70, 28.14, 29.42, 29.82, 30.70, 30.84, 35.62, 37.92, 38.60, 38.64, 40.34, 42.52, 44.78, 45.42, 47.92, 51.22, 76.64, 80.80, 108.84, 108.90, 122.90, 126.52, 127.64, 127.84, 129.15, 130.32, 132.84, 135.68, 137.6, 142.26, 147.42, 147.68, 173.00, 173.12, 210.54 ppm. ppm. EI-MS m/z: 698.36. Anal. Calcd. for $C_{46}H_{50}O_6$: C, 79.05; H, 7.21; O, 13.74. Found: C, 79.00; H, 7.16.

Physicochemical parameters evaluation

Some electronic parameters such as 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 the SPARTAN'06 software[xi]. In

addition, to determinate both logP (LogKow) and π parameters, the KOWWIN program wasused[xii-xii].

Results and Discussion

Several steroid-dioneanalogs have prepared using some reagents such as glycol[xiv], lithium aluminium[xv], CrO_3[xvi], pyridiniumchlorochromate[xvii]and others. In this study anadamantanyl-steroid-oxirene-dionederivative (compound **6**)was synthesized using some chemical strategies. The first stage was achieved by the nitration of 17α-ethynylestradiolunderacid conditions to form the compound **2**(Figure 1). The ^{1}HNMR showed several signals for **2**at 1.04 ppm for methyl group bound to steroid nucleus; at 1.20-2.90, 6.668 and 7.84 ppm for steroid moiety; at 3.32 and 88.56 ppm for alkyne group. The ^{13}CNMR display some signals at 12.32 ppm for methyl group linked to steroid nucleus; at 23.66-52.80, 80.72 and 114.00-146.52 ppm for steroid moiety; at 74.72 and 88.56 ppm for alkyne group. In addition, the mass spectrum from **2** showed a molecular ion (m/z) 341.16.

The second stage involved the preparation of an adamantanyl-steroid-butynone (**3**) via reaction of **2** with 1-adamantyl bromomethyl ketoneusing Copper(II) as catalyst. The ^{1}HNMR showed several signals for **3** at 0.90 ppm for methyl bound to steroid nucleus; at 1.20-1.50, 1.70-1.74, 1.80, 1.86, 2.08-2.80 and 6.66 ppm for steroid moiety; at 1.56-1.62, 1.78, 1.84 and 1.90 ppm for amantadyl fragment; at 4.10 ppm for methylene group bound to both alkyne and ketone groups; at 7.66 ppm for hydroxyl group. The ^{13}CNMR display some signals at 12.34 ppm for methyl group; at 23.72-27.70, 28.82-37.84, 44.94, 48.14-81.56 and 114.00-148.48 ppm for steroid moiety; 28.32 ppm for methylene group bound to both alkyne and ketone groups; at 29.42, 37.92-39.50 and 47.34 ppm for amantadyl fragment; at 81.86-97.32 ppm for alkyne group. Finally, the mass spectrum from **3** showed a molecular ion (m/z) 517.28.

Following, **4**was prepared through a etherification reaction; here, it is important to mention that there are several reagents to synthesis of ether derivatives such as 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone[xviii], amorphous silica-alumina[xix], proton exchange membranes[xx], $(CuOTf)_2PhMe$[xxi] and others. In this study, **4**was synthesizedvia intramolecular displazament of nitro group by thehydroxyl group bound to A-ring. The ^{1}HNMR showed several signals for **4**at 0.90 ppm for methyl group bound to steroid nucleus; at 1.20-1.50, 1.70-1.74, 1.80, 1.86, 2.08-2.80 and 6.30-6.34 ppm for steroid moiety; at 1.567-1.62, 1.76, 1.84 and 1.90 ppm for adamantly fragment; at 4.10 ppm for methylene group bound to both alkyne and ketone groups; at 5.70 ppm for hydroxyl group. The ^{13}CNMR display some signals at 12.34 ppm for methyl group, at 23.70-27.72, 29.82-37.84, 45.40, 48.16-81.54 and 108.85-147.62 ppm for steroid moiety; at 28.34 ppm for methylene group bound to both alkyne and ketone groups; at 29.42, 37.90-39.50 and 47.34 ppm for amantadyl fragment; at 81.86-97.35 ppm for alkyne group; at 204.94 for ketone group. Additionally, the mass spectrum from **4** showed a molecular ion (m/z) 470.98.

On the other hand, a 1-Adamantan-steroid-cyclobutadienylethanone (compound **5**) was prepared. It is noteworthy that several reagents have used to synthesis of cyclobutadiene rings such as pyrrolidinederivative[xxii], Cu_2O/pyridine[xxiii]chloro(pentamethylcyclopentadie-nyl)(cycloocta- diene)ruthenium(II)[xxiv], and others. In this study **5** reacted with 1-Phenyl-prop-2-yn-1-ol through a 2 + 2 cycloaddition using Coppre(II) as catalyst (Figure 2). The ^{1}HNMR showed several signals for **5**at 0.76 ppm for methyl group; at 1.12-1.36, 1.56, 1.69-1.86, 1.92-2.80 and 6.30-6.32 ppm for steroid moiety; at 1.50, 1.58-1.66 and 1.90 ppm for amantadyl fragment; at 3.24 ppm for methylene group bound to cyclobutadiene ring and ketone group; at 3.74 ppm for hydroxyl groups; at 5.50 ppm for methylene group bound to both phenyl and hydroxyl groups; at 5.80 ppm for cyclobutadiene ring; at 7.28-7.54 ppm for phenyl group. The ^{13}CNMR display some signals at20.94 ppm for methyl group; at 24.50-27.79, 29.84-35.74, 38.12, 42.82-45.38, 51.32, 84.12-108.85, 130.36-134.94 and 147.44-

147.72 ppm for steroid moiety; at 29.44, 37.94, 38.64 and 47.92 ppm for amantadyl fragment; at 40.50 ppm for methylene group bound to cyclobutadiene ring and ketone group; at 77.70 ppm for methylene group bound to both phenyl and hydroxyl groups; at 127.92-129.40 and 140.14 ppm for phenyl group; at 129.42, 136.32, 141.12 and 147.60 ppm for cyclobutadiene ring. In addition, the mass spectrum from **5** showed a molecular ion (m/z) 608.33.

Finally, anadamantanyl-steroid-oxirene-dione derivative (**6**) was prepared through of an esterification reaction. It is noteworthy that in the literature there are several protocols for preparation of ester derivatives; however, some protocols use reagents expensive and difficult to handle[xxv,xxvi]. In addition, another report showed the synthesis of ester groups using boric acid as a catalyst[xxvii]; therefore, in this study, the compound **6**was synthesized via reaction of **6** with succinic acid in presence of boric acid.The ^{1}HNMR showed several signals for **6**at 0.70 ppm for methyl group bound to steroid nucleus; at 1.12-1.44, 1.58, 1.68-1.86, 1.92-2.10, 2.44, 2.76-2.80 and 6.30-6.34 ppm for steroid moiety; at 1.50-1.56, 1.60-1.66 and 1.90 ppm for amantadyl fragment; at 2.30-2.34 and 2.48 ppm for 1,6dioxa-cycloundecane-2,5-dione ring; at 3.20 ppm for group bound to cyclobutadiene ring and ketone group; at 5.30 ppm for methylene group bound to both phenyl and hydroxyl groups; at 5.64 ppm for cyclobutadiene ring; at 7.20-7.30 ppm for phenyl group. The ^{13}CNMR display some signals at 19.54 ppm for methyl bound to steroid nucleus; at 24.40-28.14, 29.82, 35.62, 38.64, 42.56, 45.42, 51.22, 80.80-108.90, 130.32, 135.68 and 140.42-147.68 ppm for steroid moiety; at 29.42, 37.92-38.60 and 47.92 ppm for amantadyl fragment; at 30.70-30.84 and 44.78 ppm for 1,6-dioxa-cycloundecane-2,5-dione ring; at 40.34 ppm for group bound to cyclobutadiene ring and ketone group; at 76.64 ppm for methylene group bound to both phenyl and hydroxyl groups; at 122.90-126.52, 132.84 and 137.62 ppm for cyclobutadiene ring; at 127.64-129.15 and 142.26 ppm for phenyl group; at 173.00-173.12 ppm for ester groups; at 210.54 ppm for ketone group. Finally, the mass spectrum from **6** showed a molecular ion (m/z) 698.36.

Electronic parameters evaluation (HOMO and LUMO).

The molecular orbitals HOMO and LUMO for the compounds **2**-**6** were theoretically evaluated with SPARTAN'06 software, using Hartree-Fock method at 321-G level[xxviii]. Datadeterminateindicate (Figure 3) that LUMO value was higher for the compound **6** compared with **2**-**5**; in addition, HBD and HBA values for **6**were similar to **5**; however, different for **2**-**4**(Table 1), these data indicate that both **5** and **6** have a different electron donation ability compared to **2**-**4**.

Physicochemical parameters of both compounds 7 and 8

Since several years ago, the lipophilicity degree have been evaluate using sometheoreticalparameters such as*logP* and π .These physicochemical parameters were determinate to evaluate the lipophilicity degree of **2**-**6**using logKowanalysis[xxix].The theoretical data indicate that logKow and π were higher for compound **6**compared to **2**-**5**(Table 2 and 3), which translates to more lipophilicity. Analyzing these data, also other physicochemical parameters involved in the chemical structure of **2**-**6**such as molar volume (M_V) and molar refractory (M_R). Here it is important to mention that these physicochemical factors are tools that correlate with different biological properties which may depend on the characteristics of each substituent involved in the chemical structure of a molecule. Therefore, in this study, both M_V and M_R descriptors were determinate usinga previously method reported[xxx]. The theoretical results showed (Table 1) that M_V and M_R were higher for **6**compared with **2**-**5**. This phenomenon suggest that steric hindrance, conformational preferences, and internal rotation may be two factors which influence the biological activity exert by **6**on some biological model. However, other type of physiochemical factors such as hydrogen bond donor groups (HBD) and hydrogen bond acceptor groups (HBA), topological

polar surface area (TPSA) has been used to predict the biological activity of some compounds in several theoretical models[xxxi]. These physicochemical parameters (Table 1) were determinate using the Spartan 6.0 software; the theoretical data showed that the HBA value was <10 and the HBD value was <5 for compounds **2**-**6**, this phenomenon suggest that these compounds may be well absorbed such happening with another type of compounds[xxxii]. Other results showed that polar surface area (PSA) for **2**-**6** was < 100 Å values; it is noteworthy that some reports suggests that PSA < 140 Å values may condition the ability of some drugs to a good oral absorption and exhibit some biological activity[xxxii].

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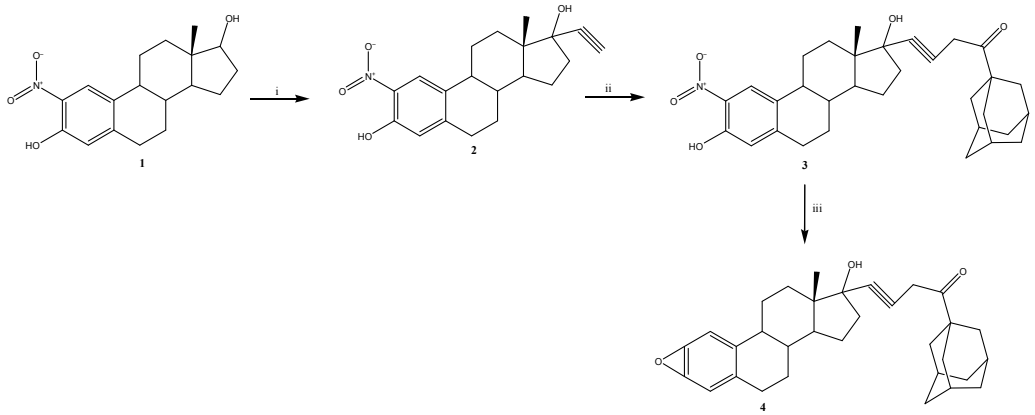

Figure 1.Synthesis of an adamantanyl-17-hydroxy-20-oxa-steroid-butyne (**4**). Preparation of 2-nitroestradiol-17-ethynyl (**2**) from 2-nitro estradiol (**1**) in basic conditions (i). Then **2** reacted with 1-adamantyl bromomethyl ketone (ii) to form an adamantanyl-3,17-dihydroxy-2-nitro-steroid-butynone (**3**). Finally, **4**was prepared via reaction of **3** with DMSO/K_2CO_3 (iii).

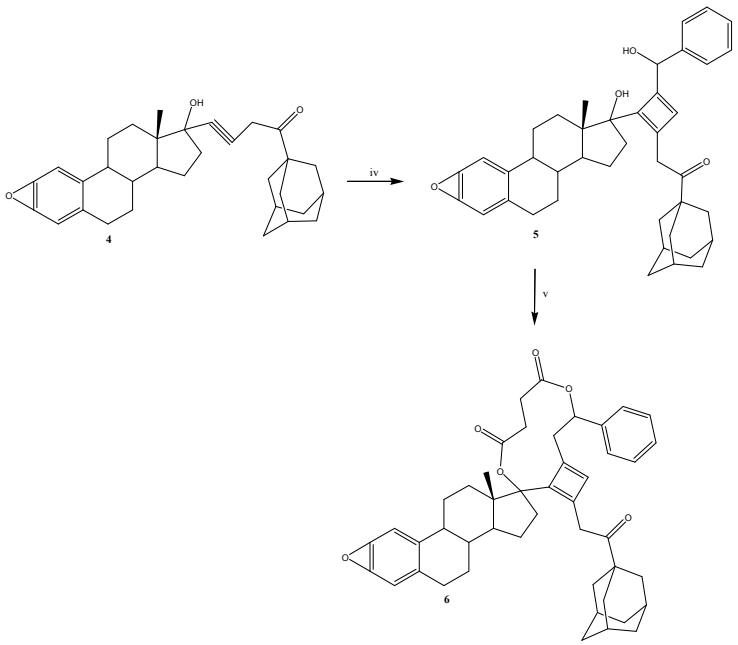

Figure 2.Preparation of an adamantanyl-2-oxosteroid-dione derivative (**6**). Reaction of adamantanyl-17-hydroxy-20-oxa-steroid-butyne (**4**) with 1-Phenyl-prop-2-yn-1-ol (iv) to form a 1-Adamantan-steroid-cyclobutadienylethanone (**5**). Then, **5** reacted with succinic acid (v) to synthesis of **6**.

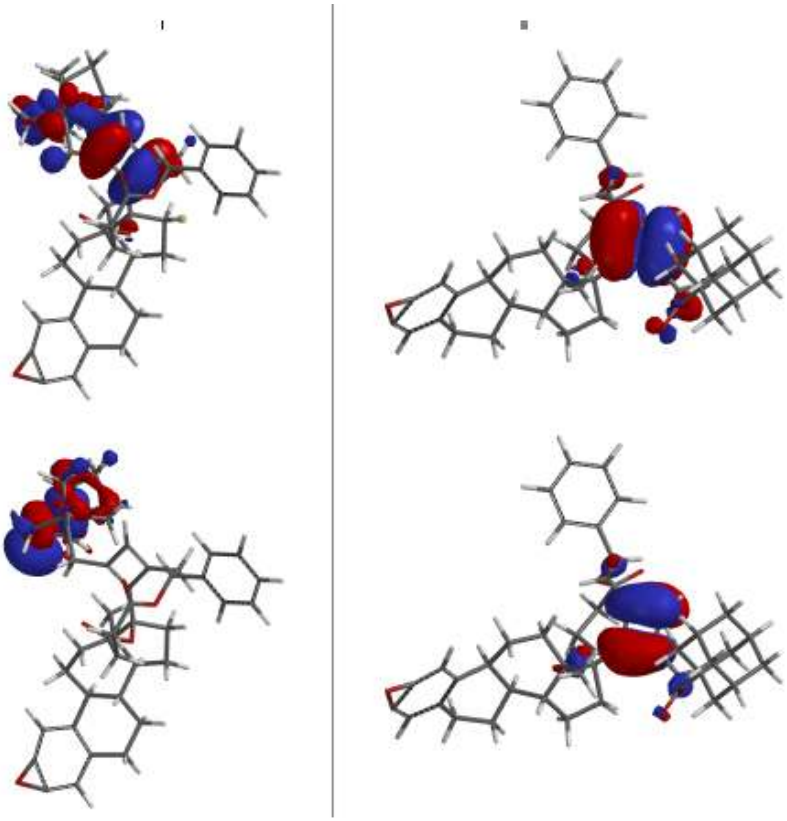

Figure 3.In the scheme are showed the electronic parameters such as HOMO and LUMO for both compounds **5** (I) and **6** (II), visualized with Spartan 6.0 software.

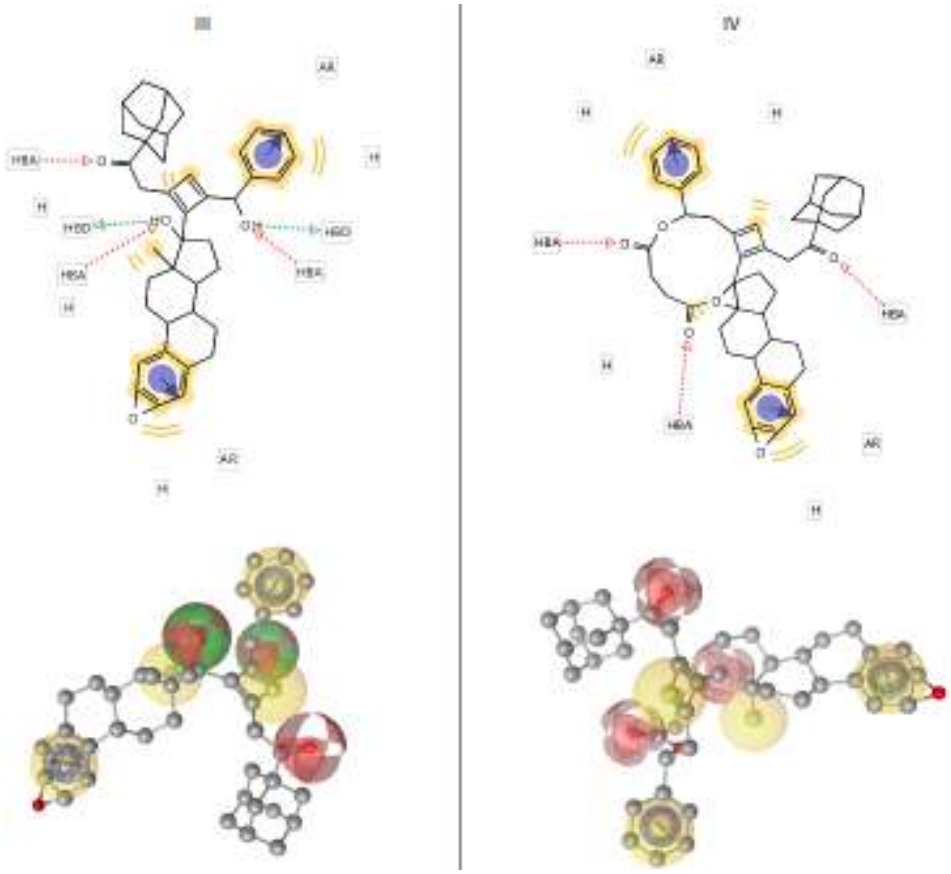

Figure 4. Scheme represents a pharmacophore model from both compounds 5(III) and 6(IV) using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, green).

Table 1. Physicochemical parameters of compounds **2**-**6**. The values were calculated using both ACDLabs and Spartan softwars.

Parameters	**2**	**3**	**4**	**5**	**6**
Molar Refractivity (cm^3)	92.29	142.01	134.13	173.20	195.09
Molar Volume(cm^3)	255.60	390.10	368.70	460.50	529.10
PSA ($Å^2$)	86.32	41.88	59.04	60.92	61.17
DipoleMoment (debyete)	7.57	5.06	2.60	5.61	3.40
Polarizability	82.96	80.28	91.09	98.18	97.65
E. HOMO (Ev)	-6.33	-6.34	-6.77	-6.22	-6.74
E. LUMO (Ev)	0.11	1.99	1.57	1.70	1.69
HBD	2	1	2	0	0
HBA	6	3	4	4	4

Table 2. Physicochemical factors (logKow and π) involved in both compounds **2** and **3**.

Compound	Fragment	Value
	-CH3 [aliphatic carbon]	0.5473
	-CH2- [aliphatic carbon]	2.9466
	-CH [aliphatic carbon]	1.0842
	#C [acetylenic carbon]	0.2668
	-OH [hydroxy, aliphatic attach]	-1.4086
	Aromatic Carbon	1.7640
2	-OH [hydroxyl aromatic attach]	-0.4802
	-NO2 [nitro, aromatic attach]	-0.1823
	-tert Carbon [3 or more carbon attach]	0.5352
	Ring reaction -> -NO2 with –OH/amino/azo	0.5777
	Fused aliphatic ring unit correction	-1.3684
	Equation Constant	0.2290
	π	4.1214
	Log Kow	8.4614
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	-CH3 [aliphatic carbon]	0.5473
	-CH2- [aliphatic carbon]	6.3843
	-CH [aliphatic carbon]	2.1684
	#C [acetylenic carbon]	0.2688
	-OH [hydroxy, aliphatic attach]	-1.4086
	Aromatic Carbon	1.7640
3	-OH [hydroxyl aromatic attach]	-0.4802
	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	-NO2 [nitro, aromatic attach]	-0.1823
	-tert Carbon [3 or more carbon attach]	0.8028
	Ring reaction -> -NO2 with –OH/amino/azo	0.5777
	Fused aliphatic ring unit correction	-1.0263
	Equation Constant	0.2290
	π	-0.4184
	Log Kow	8.0430

Table 3. Physicochemical parameters (logKow and π) involved in the compounds **4** to **6**.

Compound	Fragment	Value
	-CH3 [aliphatic carbon]	0.5473
	-CH2- [aliphatic carbon]	6.3843
	-CH [aliphatic carbon]	2.1684
	#C [acetylenic carbon]	0.2668
	-OH [hydroxy, aliphatic attach]	-1.4086
4	Aromatic Carbon	1.7640
	-O- [aliphatic O, two aromatic attach]	0.2923
	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	-tert Carbon [3 or more carbon attach]	0.8028
	Fused aliphatic ring unit correction	-1.0263
	Equation Constant	0.2290
	π	0.4184
	Log Kow	8.4614
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	-CH3 [aliphatic carbon]	0.5473
	-CH2- [aliphatic carbon]	6.3843
	-CH [aliphatic carbon]	2.5298
	=CH- or =C< [olefinc carbon]	1.5344
	-OH [hydroxy, aliphatic attach]	-2.8172
	Aromatic Carbon	3.5280
5	-O- [aliphatic O, two aromatic attach]	0.2923

	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	-tert Carbon [3 or more carbon attach]	0.8028
	Multi-alcohol correction	0.4064
	Fused aliphatic ring unit correction	-1.0263
	Equation Constant	0.2290
	π	2.3908
	Log Kow	10.8522
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	-CH3 [aliphatic carbon]	0.5473
	-CH2- [aliphatic carbon]	7.8576
	[aliphatic carbon]	2.5298
	C [aliphatic carbon - No H, not tert]	1.9446
	=CH- or =C< [olefinc carbon]	0.7672
	Aromatic Carbon	3.5280
6	-O- [aliphatic O, two aromatic attach]	0.2923
	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	-C(=O)O [ester, aliphatic attach]	-1.9010
	-tert Carbon [3 or more carbon attach]	0.8028
	Cyclic ester correction	-2.1154
	Fused aliphatic ring unit correction	-1.0263
	Equation Constant	0.2290
	π	1.0451
	Log Kow	11.8973

Received on February 5, 2019.