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Design and Synthesis of Two Methylthiosteroid-Oxirenol Derivatives: Theoretical Evaluation of Their Interaction with B1-Cannabinoid Receptor

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Abstract

Several agonists and antagonists of B1 cannabinoid receptors have been synthesized for the treatment of several clinical pathologies such as psychosis, hyperalgesia, and drug addiction; however, some of these drugs may produce some side effects including higher intraocular pressure, hepatotoxicity, etc. The aim of this study was to synthesize two new methylthiosteroid-oxirenol derivatives (compounds **7** and **8**) to evaluate their theoretical interaction with B1 cannabinoid receptor (5gtz) using WIN-55,212-2, yangonin, cannabigerol, and tetrahydrocannabivarin drugs as controls in a docking model. The preparation of **7** and **8** were carried out using a series of reactions which involved nitration, etherification, hydrogenation-chlorination, and addition. The chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. The results showed that compound **7** or **8** could bind to different types of amino acid residues involved in 5gtz protein surface compared with the WIN 55,212-2, Yangonin, Cannabigerol, and Tetrahydrocannabivarin drugs. All data suggest that compound **7** or **8** may exert changes in the biological activity of B1 cannabinoid receptor.

Key words: Steroids, cannabinoid, receptor, cannabigerol,

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Introduction

tetrahydrocannabivarin

Drug addiction is a serious health problem worldwide. Drug addiction refers to physical dependence in which the body adapts to the chronic application of drugs (Fauzi et al. 2018), which affects different groups (Mansouri et al. 2017). It is the fourth issue of the crisis after the nuclear crisis, population explosion and environmental pollution (Feghhi et al. 2018). Drug dependence is considered a brain disease since drugs modify the brain (Sai et al. 2018). This clinical pathology is characterized by neurobiological changes in several systems such as adrenergic, dopaminergic, serotoninergic (Sofuoglu and Sewell, 2009), and cannabinoid (Maldonado et al., 2006). It is important to mention that cannabinoid system involves endogenous cannabinoids (e.g., anandamide and 2-arachidonoylglycerol), the enzymes responsible for the synthesis and degradation of endocannabinoids, and both CB1 and CB2 receptors (Lu and Mackie, 2016). Some data indicate that CB1 cannabinoid receptor activation has been correlated with an increase in addiction to amphetamine drugs (Su and Zhao, 2017) and marijuana (Huestis et al., 2001). Some CB1 antagonist drugs for treatment of drug addiction have been used such as rimonabant (Parolaro and Rubino, 2008; Mas-Nieto et al., 2001), AM251 (*N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide) (Xi et al., 2006), and cannabidiol (Adamczyk and Papp, 2016). However, some of these drugs can cause weight loss in obese patients, although it may also induce symptoms of anxiety and depression (Moreira and Crippa, 2009), ocular hypotensive (Colasanti et al., 1984) and others. In the previous researches, new therapeutic alternatives of some CB1-antagonists have been prepared; for example, the synthesis of a carboxamide derivative from a carboxylic acid analog and its biological evaluation as a CB1 antagonist using an animal model have been carried out (Murineddu et al., 2005). Another study showed the preparation of a cannabinoid antagonist (NESS 0327) with high selectivity for the cannabinoid CB_1 receptor using a mouse model (Ruiu et al., 2003). All these data have shown the synthesis of several cannabinoid CB1-receptor antagonists. However, their interaction with this biomolecule is very confusing. This phenomenon could be due to differences in the chemical structure of each drug. Therefore, in this investigation, two steroid derivatives were prepared using some strategies to

evaluate their theoretical interaction with cannabinoid CB_1 receptor using a Docking model.

Material and Methods

General methods

The reagents used in this investigation were acquired from Sigma-Aldrich Co., Ltd. Flash chromatography was performed on E. Merck (60230-400 mesh silica gel). Thin-layer chromatography was carried out on 0.25 mm silica gel plates (E. Merck, 60F254) and the methanol/hexane/ethyl acetate (3:1:2) system was used as eluent. The melting point for compounds was determined on an Electrothermal (900 models). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR300/5 FT NMR spectrometer at 300 MHz in $CDCl_3$ using TMS as the 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

Preparation of two nitro-steroids

In a round bottom flask (10 ml), 17α-ethynilestradiol (200 mg, 0.67 mmol), nitric acid (1 ml), and anhydride acetic (3 ml) were stirred to reflux for 6 h. The solution obtained, after reducing the pressure, was purified through flash chromatography on silica gel with the methanol/hexane/ethyl acetate system to provide the compounds **2** and 3.

(13S,17R)-17-ethynyl-13-methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclo-penta[a]phenanthre- ne-3,17-diol (2)

It yielded 66 % of product; m.p. 120-122 °C; IR (vmax, cm^{-1}) 3400, 2122, and 1344: ^1H NMR (300 MHz, Chloroform-*d*) δ_H: 1.04 (s, 3H), 1.22-1.88 (m, 8H), 2.00-2.92 (m, 7H), 3.34 (s, 1H), 6.66 (m, 1H), 7.25 (broad, 2H), 7.82 (m, 1H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 13.60, 22.82, 26.92, 27.22, 29.82, 32.93, 40.09, 40.22, 44.95, 46.96 49.49, 74.32, 80.72, 89.15, 114.05, 123.56, 132.33, 132.92, 145.09, 148.48 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, 70.30; H, 6.70.

(13S,17R)-17-ethynyl-13-methyl-4-nitro-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (3)

It yielded 12% of product; m.p. 128-130 °C; IR (vmax, cm^{-1}) 3400, 2120, and 1342: ^1H NMR (300 MHz, Chloroform-*d*) δ_H: 1.04 (s, 3H), 1.34-1.88 (m, 7H), 2.00-2.92 (m, 8H), 3.34 (s, 1H), 6.66 (m, 1H), 7.30 (m, 1H), 7.82 (broad, 2H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 13.60, 22.82, 24.42, 26.92, 29.50, 32.94, 40.09, 40.22, 44.94, 46.96 49.49, 74.32, 80.72, 89.15, 117.54, 127.44, 132.60, 132.92, 134.70, 145.56 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, 70.28; H, 6.72.

Preparation of an ether-steroid derivative

(1R,10aS)-1-ethynyl-10a-methyl-2,3,3a,3b,4,5,8b,9,10,10a-decahydro-1H-cyclopenta[7,8]phenanthro[2,3-b]oxiren-1-ol (4)

In a round bottom flask (10 ml), compound **2** (200 mg, 0.58 mmol), potassium carbonate (70 mg, 0.50 mmol) in dimethyl sulfoxide (5 ml) were stirred to reflux for 6 h. The solution obtained, after reducing the pressure, was purified through a crystallization using the methanol:water (3:1) system; yielding 44% of product; m.p. 138-140 °C; IR (vmax, cm^{-1}) 3400, 2120, and 1242: ^1H NMR (300 MHz, Chloroform-*d*) δ_H: 1.06 (s, 3H), 1.22-1.84 (m, 8H), 2.02-2.80 (m, 7H), 3.34 (s, 1H), 4.94 (broad, 1H), 6.30-6.32 (m, 2H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 13.62, 22.82, 26.92, 27.22, 29.80, 32.91, 40.12, 40.22, 45.44, 46.94, 49.50, 74.30, 80.70, 89.16, 108.84, 108.90, 130.34, 134.94, 147.40, 147.68 ppm. EI-MS m/z: 294.16. Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53; O, 10.87. Found: C, 81.56; H, 7.50.

Preparation of chloromethylthio vinyl-nitro steroid derivative

13S,17S)-17-((E)-1-chloro-2-(methylthio)vinyl)-13-methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenan- threne-3,17-diol (5)

In a round bottom flask (10 ml), compound **2** (200 mg, 0.58 mmol), and hydrochloric acid (1ml) in dimethyl sulfoxide (10 ml) were stirred to reflux for 12 h. The solution obtained, after reducing the pressure, was purified through a crystallization using the methanol:water: hexane (3:1:1) system; yielding 44% of product; m.p. 152-154 °C; IR (vmax, cm^{-1}) 3400, 2492, 1342 and 744: ^1H NMR (300 MHz, Chloroform-*d*) δ_H: 1.06 (s, 3H), 1.22-1.90 (m, 8H), 2.02-2.35 (m, 4H), 2.44 (s, 3H), 2.76-2.90 (m, 3H), 4.44 (broad, 1H), 6.36 (d, 1H, J = 0.34 Hz), 6.66 (m, 1H), 7.00 (broad, 2H), 7.82 (m, 1H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 15.36, 16.40, 22.42, 24.96, 27.72, 29.80, 31.88, 36.14, 40.70, 44.98, 47.80, 50.94, 88.26, 112.72, 114.02, 123.56, 132.34, 133.10, 145.10, 148.46, 151.20 ppm. EI-MS m/z 423.12. Anal. Calcd. for $C_{21}H_{26}ClO_4S$: C, 59.49; H, 6.18; Cl, 8.36; N, 3.30; O, 15.10; S, 7.56. Found: C, 59.42; H, 6.12.

Preparation of an ether-chloromethylsulfanyl-vinyl-steroid derivative

(1S,10aS)-1-((E)-1-chloro-2-(methylthio)vi-nyl)-10a-methyl-2,3,3a,3b,4,5,8b,9,10,10a-decahydro-1H-cyclo-penta[7,8]phenanthro [2,3-b]oxiren-1-ol (6)

Method A:

In a round bottom flask (10 ml), compound **4** (200 mg, 0.68 mmol), and hydrochloric acid (1ml) in dimethyl sulfoxide (10 ml) were stirred to reflux for 12 h. The solution obtained, after reducing the pressure, was purified through a crystallization using the methanol:water: hexane (3:1:2) system; yielding 56% of product; m.p. 118-120 °C; IR (vmax, cm^{-1}) 3430, 2490, 1242, and 742: ^1H NMR (300 MHz, Chloroform-*d*) δ_H: 1.06 (s, 3H), 1.22-1.90 (m, 8H), 2.02-2.35 (m, 4H), 2.44 (s, 3H), 2.44-2.80 (m, 3H), 4.44 (broad, 1H), 6.30-6.32 (m, 2H), 6.40 (d, 1H, J = 0.34 Hz) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 15.36, 16.40, 22.42, 24.96, 27.72, 29.80, 31.88, 36.14, 40.70, 45.40, 47.80,

50.94, 87.26, 108.84, 108.92, 119.72, 130.34, 135.10, 143.62, 147.40, 147.64 ppm. EI-MS m/z: 376.12. Anal. Calcd. for $C_{21}H_{25}ClO_2S$: C, 66.91; H, 6.69; Cl, 8.36; N, 9.41; O, 8.49; S, 8.51. Found: C, 66.87; H, 6.64.

Method B:

In a round bottom flask (10 ml), compound **5** (200 mg, 0.47 mmol), and potassium carbonate (70 mg, 0.50 mmol) in dimethyl sulfoxide (5 ml) were stirred. The solution obtained, after reducing the pressure, was purified through a crystallization using the methanol: water (3:1) system; yielding 38% of product. Similar signals of both ^{1}HNMR and ^{13}CNMR spectra were found in comparison with Method A.

Preparation of a methylthiosteroid-oxirenol derivative

(1S,10aS)-1-((Z)-8-hydroxy-1-(methylthio)oct-1-en-3-yn-2-yl)-10a-methyl-2,3,3a,3b,4,5,8b,9,10,10a-decahy- dro-1H-cyclopenta [7,8]phenanthro[2,3-b]oxiren-1-ol (7)

In a round bottom flask (10 ml), compound **6** (200 mg, 0.53 mmol), 5-hexyn-1-ol (80 µl, 0.72 mmol), Copper (II) chloride anhydrous (70 mg, 0.52 mmol), and methanol (5 ml) were stirred to reflux for 12 h. The solution obtained, after reducing the pressure, was purified through a crystallization using the methanol:water (3:1) system; yielding 65% of product; m.p. 165-167 ℃; IR (vmax, cm^{-1}) 3400, 2490, 2120 and 1240: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 1.00 (s, 3H), 1.22-1.32 (m, 4H), 1.56-1.58 (m, 4H), 1.66-2.12 (m, 6H), 2.14 (m, 2H), 2.18-2.28 (m, 2H), 2.35 (s, 3H), 2.44-2.80 (m, 3H), 2.90 (broad, 2H), 3.64 (m, 2H), 6.12 (d, 1H, J = 0.34 Hz), 6.30-6.34 ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 16.00, 18.00, 18.94, 23.80, 24.94, 25.20, 27.96, 29.82, 31.82, 33.02, 36.62, 40.70, 45.40, 49.70, 51.36, 62.12, 76.12, 86.32, 108.84, 108.90, 112.84, 118.50, 130.34, 135.12, 143.16, 147.39, 147.67 ppm. EI-MS m/z: 438.22. Anal. Calcd. for $C_{27}H_{34}O_3S$: C, 73.93; H, 7.81; O, 10.94; S, 7.31. Found: C, 73.90; H, 7.78.

Synthesis of a steroid- oxirenol derivative

((1S,10aS)-1-((1Z,3E)-6-hydroxy-1-(methylthio)-6-phenylhexa-1,3-dien-2-yl)-10a-me-thyl-2,3,3a,3b,4,5,8b,9, 10,10a-decahydro-1H-cyclopenta[7,8]phenanthro[2,3-b]oxi-ren-1-ol (8)

In a round bottom flask (10 ml), compound **7** (200 mg, 0.53 mmol), 4-Phenyl-1-buten-4-ol (100 µl, 0.67 mmol), Copper (II) chloride anhydrous (70 mg, 0.52 mmol), and methanol (5 ml) were stirred to reflux for 12 h. The solution obtained, after reducing the pressure, was purified through a crystallization using the methanol:water:benzene (3:1:1) system; yielding 63% of product; m.p. 64-66 ℃; IR (vmax, cm^{-1}) 3430, 3400, and 1480: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 1.00 (s, 3H), 1.22-2.00 (m, 10H), 2.12-2.28 (m, 2H), 2.34 (s, 3H), 2.38 (m, 1H), 2.44 (m, 1H), 2.46 (m, 1H), 2.76-2.80 (m, 2H), 3.09 (broad, 2H), 4.40 (m, 1H), 5.15 (d, 1H, J = 0.87 Hz), 6.30-6.32 (m, 2H), 6.34 (d, 1H, J = 0.34 Hz), 6.62 (d, 1H, J = 0.93 Hz), 7.30-7.36 (m, 5H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 14.90, 17.90, 22.84, 24.92, 27.96, 29.83, 32.10, 36.92, 40.70, 43.00, 45.40, 50.04, 52.18, 73.70, 84.23, 108.84, 108.90, 124.12, 126.64, 127.66, 128.22, 128.66, 130.34, 131.10, 135.04, 140.92, 143.68, 147.41, 147.64 ppm. EI-MS m/z: 488.23. Anal. Calcd. for $C_{31}H_{36}O_3S$: C, 76.19; H, 7.43; O, 9.82; S, 6.56. Found: C, 76.14; H, 7.40.

Theoretical analysis

- *Physicochemical properties of both compound 7 and 8*

Some theoretical electronic properties, such as HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) energy, orbital coefficients distribution, molecular dipole moment, HBD (hydrogen bond donor groups), HBA (hydrogen bond acceptor groups), and TPSA (topological polar surface area) involved in the chemical structure of both compounds **7** and **8** were evaluated using SPARTAN'06 software (Obi-Egbedi and Obo, 2011). Additionally, other physicochemical factors such as molecular refractivity (MR), and volume reactivity (VR) were determined using Chemsketch program (Şahin and Sacan, 2018; Tahir et al., 2017).

- *Pharmacophore evaluation*

The 3D pharmacophore model for both compounds **7** and **8** was determinate using LigandScout 4.08 software (Réau et al., 2018)

- *Docking evaluation*

Interaction of both compounds **7** and **8** with B1-Cannabinoid receptor el was determinate using 5tgz protein from protein data bank as control, and DockingServer software (Sapundzhi et al., 2018; Suresh et al., 2018).

Results and Discussion

In this study, two steroid derivatives were prepared from 17α-ethinylestradiol using some chemical strategies as follows:

Synthesis of two nitro-steroid analogs (compounds 2 and 3)

In the literature several methods have been reported for preparation of nitro derivatives using some reagents such as dimethyldioxirane (Murray et al., 1986), $NaNO_2$ (Foroumadi et al., 2003), HNO_3 (Chuvière et al., 2003), NOF (Boswell, 1968), $HNO_3/(CH_3CO)_2O$ (Cornelis et al., 1983) and others. In this study, 17α-ethynyl-2-nitroestradiol (**2**) was prepared from 17α-ethynylestradiol in presence of $HNO_3/(CH_3CO)_2O$. It is important to mention that considering the possibility that the nitration could be produced in the carbons C-2 (compound **2**) or C-4 (compound **3**) of the steroid nucleus (Figure 1), the mixture of the reaction was subjected to flash chromatography on silica gel with the methanol/hexane/ethyl acetate system to provide the compounds **2** (66% yield) and **3** (15% yield).

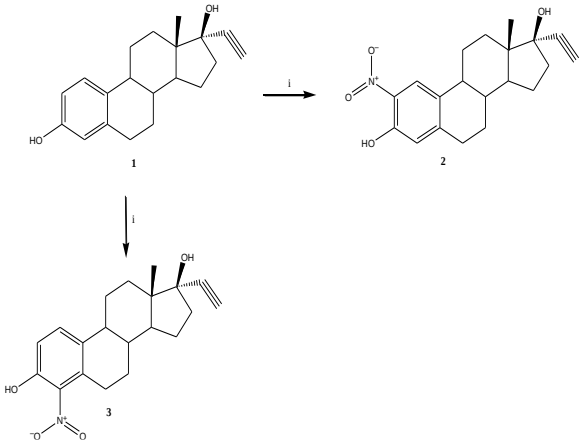

Figure 1. Nitration of 17α-ethynilestradiol with nitric acid/anhydride acetic (i) to form the compounds 2-nitro-17α-ethynilestradiol (compound **2**) or 2-nitro-17α-ethynilestradiol (compound **3**).

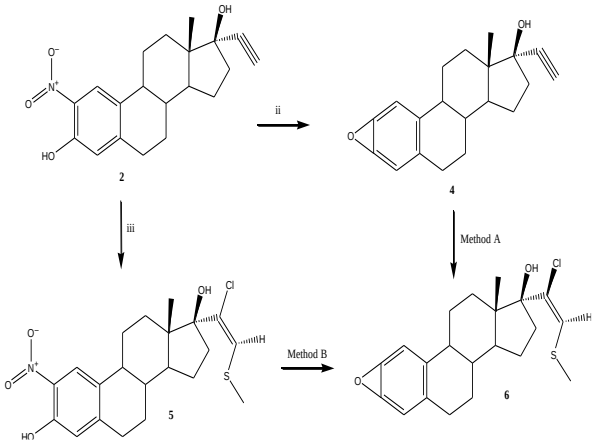

Figure 2. Preparation of an ether-chloromethylthiovinyl-nitrosteroid (**6**). Etherification of 2-nitro-17α-ethynilestradiol (**2**) with dimethyl sulfoxide/potassium carbonate (ii) to form an oxirenol-steroid derivative (**4**). Then, nitro-chloromethylthiovinyl-steroid derivative (**5**) was prepared from compound **2** and HCl/dimethyl sulfoxide (iii). Finally, **6** was synthesized using two methods; method A was achieved via etherification of compound **4** in the presence of dimethyl sulfoxide/potassium carbonate. Also, compound **6** was prepared from **5** dimethyl sulfoxide/potassium carbonate (Method B).

The ^{1}H NMR spectrum of the compound **2** showed several signals at 1.04 ppm for methyl bound to steroid nucleus; at 1.22-2.92 and 26.66 and 7.84 ppm for steroid moiety; at 3.34 ppm for alkyne group; at 7.25 ppm for both hydroxyl groups. The ^{13}C NMR spectra display chemical shifts at 13.60 ppm for methyl group bound to steroid nucleus; at 22.82-49.49, 80.72 and 114.05-148.48 ppm for steroid moiety; at 74.32 and 89.15 ppm for alkyne group. In addition, the mass spectrum from compound **2** showed a molecular ion (m/z) 341.16.

The signals involved in the ^{1}H NMR spectrum for compound **3** displays several signals at 1.04 ppm for methyl bound to steroid nucleus; at 1.34-2.92and 6.6-7.30 ppm for steroid moiety; at 3.34 ppm for alkene group; at 7.82 ppm for both hydroxyl groups. The ^{13}C NMR spectra display chemical shifts at 13.60 ppm for methyl bound to steroid nucleus; at 22.82-49.49, 80.92 and 117.54-145.56 ppm for steroid moiety; at 74.32 and 89.15 ppm for alkyne group. In addition, the mass spectrum from compound **3** showed a molecular ion (m/z) 341.16.

Preparation of an ether-steroid derivative (compound 4)

There are some studies that indicate the preparation of some ether derivatives via displacement of the nitro group using methoxide as dipolar aprotic solvent (Figueroa-Valverde et al., 2015). In this study, the compound **4** was synthesized by an intermolecular reaction through the displacement of the nitro group by the hydroxyl involved in the chemical structure of compound **2** in the presence of dimethyl sulfoxide under mild conditions (Figure 2).

The ^{1}H NMR spectrum of the compound **4** showed several signals 1.06 ppm for methyl group bound to steroid nucleus; at 1.22-2.80 and 6.30-6.32 ppm for steroid moiety; at 3.34 ppm for alkyne group; at 4.94 ppm for the hydroxyl group. The ^{13}C NMR spectra display chemical shifts at 13.62 ppm for methyl group bound to steroid nucleus; at 22.82-49.50, 80.70 and 108.84-147.68 ppm for steroid moiety; at 74.30 and 89-16 ppm for alkyne group. In addition, the mass spectrum from compound **4** showed a molecular ion (m/z) 294.16.

Synthesis of a disubstituted alkene-steroid (compound 5)

Several disubstituted-alkenes have been synthesized using several reagents such as sulfone/aldehyde (Blakemore et al., 1998), BH/I_2 (Zweifel et al., 1967), Ni(0) (Shimizu et al., 2005), Pd$(OAc)_2$, HBr (Karki and Magolan, 2015), and others. In this study, a disubstituted alkene-steroid derivative (compound **5**) was prepared via the reaction of compound **2** with dimethyl sulfoxide in the presence of hydrochloric acid. It is important to mention that in this study a regioselective anti-sulfurchlorination reaction of the unactivated alkyne is reported which involves a mechanism of chlorination/demethylation (Figures 2 and 3). The ^{1}H NMR spectrum of the compound **5** showed several signals at 1.06 ppm for methyl group bound to steroid nucleus; at 1.22-2.35, 2.76-2.92, 6.66 and 7.82 ppm for steroid moiety; at 2.44 ppm for methyl bound to sulfur; at 6.36 ppm for alkene group; at 7.00 ppm for both methyl groups. The ^{13}C NMR spectra displayed chemical shifts at 15.36 ppm for methyl group; at 16.40 ppm for methyl bound sulfur; at 22.42-88.26 and 114.02-148.46 ppm for steroid moiety; at 112.72 and 151.20 ppm for alkene group. In addition, the mass spectrum from compound **5** showed a molecular ion (m/z) 423.12.

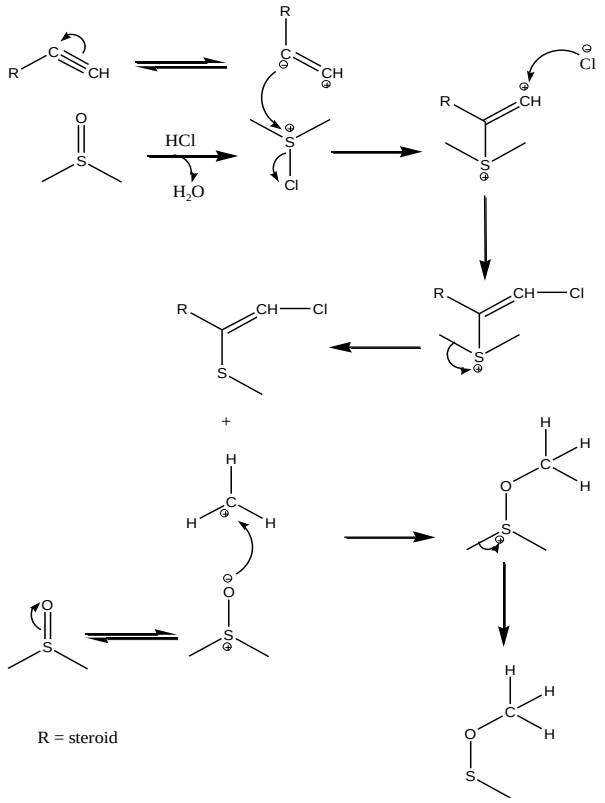

Figure 3. Reaction mechanism involved in the synthesis of an ether-chloromethylthiovinyl-nitrosteroid derivative (compound **5**).

Synthesis of an ether-disubstituted alkene derivative (*compound* 6)

A new ether-disubstituted alkene derivative was prepared using two methods; in Method A, compound **4** reacted with dimethyl sulfoxide in the presence of hydrochloric acid to form compound **6**. The ^{1}H NMR spectrum of the compound **6** showed several signals at 1.06 ppm for methyl group bound to steroid nucleus; at 1.22-2.35, 2.44-2.80 and 6.30-6.32 ppm for steroid moiety; at 2.44 ppm for methyl bound to sulfur; at 4.44 ppm for hydroxyl group; at 6.40 for alkene group. The ^{13}C NMR spectra displayed chemical shifts at 15.36 ppm for methyl group; at 16.40 ppm for methyl group bound to sulfur; at 22.42-108.92, 130.34-135.10 and 147.40-147.64 ppm for steroid moiety; at 119.72 and 143.62 ppm for alkene group. In addition, the mass spectrum from compound **6** showed a molecular ion (m/z) 376-12.

Method B.

In this stage, compound **6** was prepared via intra-molecular etherification using $KsCO_3$/DMSO. Similar ^{1}H NMR and ^{13}C NMR data were obtained compared to those of Method-A product. However, in this pathway lower yield was obtained, most probably due to reaction conditions.

Preparation of propargylic-alcohol-steroid derivative (compound 7)

Several studies have been reported for the synthesis of propargylic-alcohols using some reagents such as disulfide-oxazolidine (Braga et al., 2002), Ti(O-i-Pr)$_4$-BINOL complex (Marshall and Bourbeau, 2003), chiral diamine-coordinated tin(II) triflate (Mukaiyama et al., 1991), $P(PhCH_2NCH_2CH_2)_3N$ (Wadhwa et al., 2009) and others. However, some of these reagents are difficult to handle and require special conditions. In this study, the compound **6** reacted with 5-hexyn-1-ol using Copper(II) as a catalyst (Figure 4) to form a propargylic-alcohol-steroid derivative (compound **7**). The ^{1}H NMR spectrum (Figure 5) of the compound **7** showed several signals at 1.00 ppm for methyl group bound to steroid nucleus; at 2.35 ppm for methyl bound to sulfur; at 1.22-1.32, 1.66-2.12, 2.18-2.28, 2.44-2.80, 6.30-6.32 ppm for steroid moiety; at 1.56-1.58, 2.84 and 3.64 ppm for arm bound to both alkyne and hydroxyl groups; at 2.88 ppm for hydroxyl group; at 6.12 ppm for alkene group.

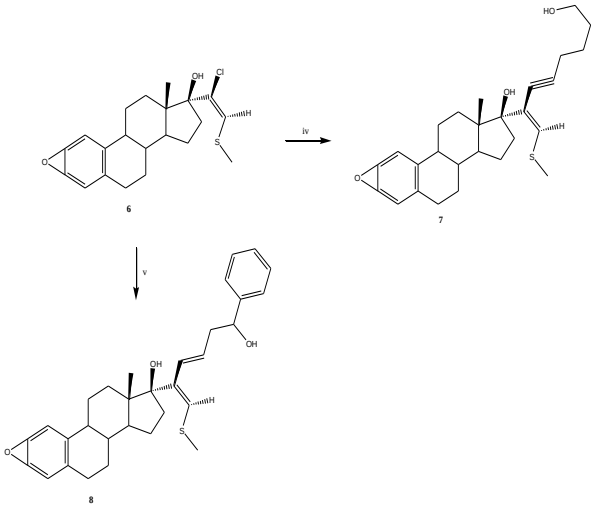

Figure 4. Preparation of two methylthiosteroid-oxirenol analogs (**7** or **8**). Reaction of the ether-chloromethylthiovinyl-nitrosteroid derivative (compound **6**) with 5-hexyn-1-ol (iv) to form the 8-hydroxymethylthio-steroid-oxirenol derivative **(7).** Finally, compound **8** was prepared from compound **6** and 4-Phenyl-1-buten-4-ol (v).

The ^{13}C NMR spectra displayed chemical shifts at 16.00 ppm for methyl group; at 18.94 ppm for methyl bound to sulfur; at 18.00, 23.80-24.94, 27.98-29.82, 33.02-51.36, 86.32-108.90, 130.34-135.12 and 147.39-147.67 ppm for steroid moiety; at 25.20, 31.82 and 62.12 ppm for arm bound to both alkyne and hydroxyl groups; at 76.12 and 112.84 ppm for alkyne group; at 118.50 and 143.16 ppm for alkene group. In addition, the mass spectrum from compound **7** showed a molecular ion (m/z) 438.22.

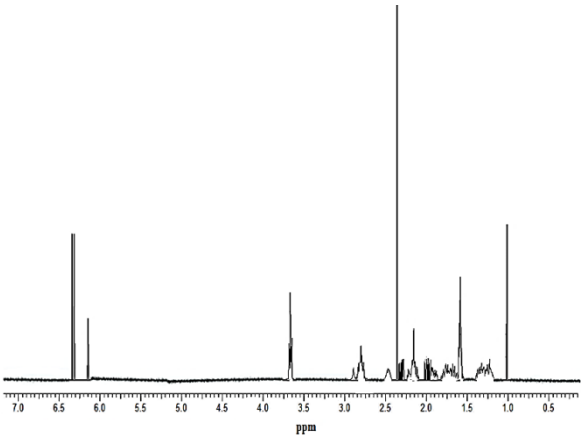

Figure 5. The scheme showing the ^{1}HNMR spectrum from compound **7** analyzed with a Varian VXR300/5 FT NMR apparatus at 300 MHz in CDCl3. Axis abscissa (ppm). ppm = parts per million.

Hydrogenation-chlorination

There are several reports to hydrogenation/chlorination which use some reagents such as Molybdenum(V)Chloride (Filippo and Sowinski et al., 1975), sulfur tetrachloride (Riley et al., 1962), and *N*-chlorosuccinimide (Shi et al., 2015) and others. The ^{1}H NMR spectrum (Figure 6) of the compound **8** showed several signals at 1.00 ppm for methyl group bound to steroid nucleus; at 2.34 ppm for methyl bound to sulfur; at 1.22-2.28, 2.44, 2.76-2.80 and 6.30-6.32 ppm for steroid moiety; at 3.09 ppm for both hydroxyl groups; at 5.15 and 6.34-6.62 ppm for alkene groups; at 7.30-7.36 ppm for phenyl group. The ^{13}C NMR spectra displayed chemical shifts at 14.90 ppm for methyl group; at 17.90 ppm for methyl bound to sulfur; at 22.84-40.70, 45.40-52.18, 84.23-108.90, 130.34, 135.04 and 147.41-147.64 ppm for steroid moiety; at 43.00 and 73.70 ppm for methylene groups bound to both alkene and hydroxyl groups; at 124.12-126.64, 131.10 and 140.92 ppm for alkene group; at 127.66-128.66 and 143.68 ppm for phenyl group. In addition, the mass spectrum from compound **8** showed a molecular ion (m/z) 488.23.

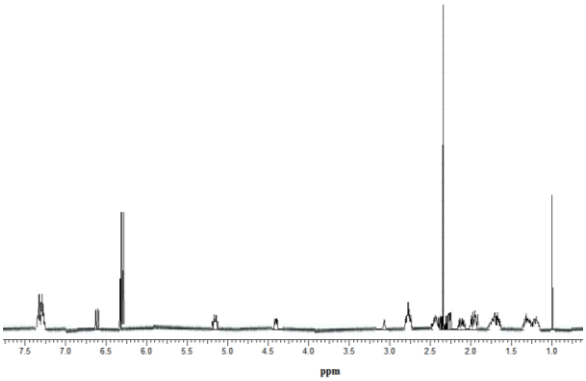

Figure 6. The scheme showing the ^{1}HNMR spectrum from compound **8**, analyzed with a Varian VXR300/5 FT NMR apparatus at 300 MHz in CDCl3. Axis abscissa (ppm). ppm = parts per million.

Physicochemical parameters

There are studies that suggest that several physicochemical parameters such as molar volume (MV) and molar refractory (MR) could condition the biological activity of different biomolecules. It is important to mention that these physicochemical factors depend on the characteristics of substituents attached to a constant reaction center of each molecule (Figueroa-Valverde et al., 2019). Therefore, both MV and MR parameters involved in the chemical structure of both compounds **7** and **8** were evaluated using a previously reported method (Figueroa-Valverde et al., 2011). The theoretical results (Table 1) showed that MV and MR were higher for compound **8** compared with compound **7**. These data suggest that steric hindrance, conformational preferences, and internal rotation could influence the biological activity of both compounds **7** or **8** on some biological models. However, other reports suggest that other types of electronic factors could condition change in biological activity exerted by some compounds against some biomolecules (Figueroa-Valverde et al., 2019).

Table 1. Physicochemical parameters involved in the chemical structure of compounds **7** and **8**. The values were calculated using both ACDLabs and Spartan software.

Parameters	**7**	**8**
Molar Refractivity (cm^3)	126.51	143.79
Molar Volume (cm^3)	355.10	393.90
PSA ($Å^2$)	47.63	45.20
Dipole Moment (debyete)	4.71	6.30
Polarizability	76.60	80.77
Parachor (cm^3)	976.10	1078.10
Surface Tension	57.00	56.10
Density (g/cm^3)	1.23	1.24
E. HOMO (Ev)	-7.54	-7.33
E. LUMO (Ev)	3.27	3.24
HBD	2	2
HBA	4	4
LogP	4.54	5.77
Sovation E. Kj/mol	-34.44	-19.51

- *Electronic parameters*

Analyzing the above-mentioned hypothesis and some studies indicate that molecular orbitals and frontier electron density are used to predict the most reactive position in some electron systems on several types of reactions which are translated as changes in the biological activity of some compounds (Walter and Ruback, 1982; Houk, 1975). These reports suggest that values of highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) and their energy gap reflect the chemical activity of a molecule (Ess and Houk, 2008). It is noteworthy, that some methods have been used to evaluate the relation between HOMO and LUMO with biological activity of some compounds; for example, there are some data which show the evaluation of the frontier molecular orbitals (HOMO-LUMO gap) from some steroids using MINDO and ZINDO models (Prasad et al., 2008; Latosińska et al., 2000). In this study, the Hartee-Fock method (method of approximation for the determination of the wave function and the energy of a quantum many-body system in a stationary state) was used to determinate

both HOMO and LUMO orbitals of either compounds **7** and **8** (Figure 7 and Table 1) with Spartan'06 V112 program (Figueroa-Valverde et al., 2012).

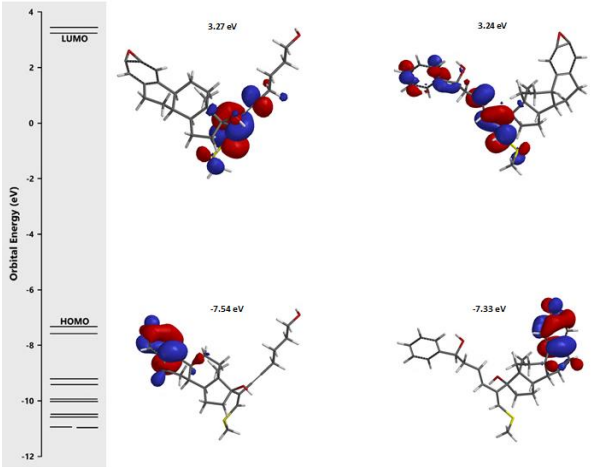

Figure 7. Molecular orbitals (HOMO and LUMO) involved in the compounds **7** (left) and **8** (right), visualized with SPARTAN'06 software

The results showed changes in both HOMO and LUMO values for compound **7** compared with compound **8**. This phenomenon could be conditioned by the difference in π orbitals density located in their chemical structure of either compounds **7** or **8**.

- *Pharmacophore ligand model*

It is noteworthy that some chemical models have been used to determine the three-dimensional orientation adopted by the functional groups of a molecule to predict its interaction with several biomolecules (Schneider et al., 1999); for example, the use of a pharmacophore model can furnish a new insight to design novel molecules that can enhance or inhibit the function of a biological target which can be useful in new drug discovery (Patel et al., 2018).

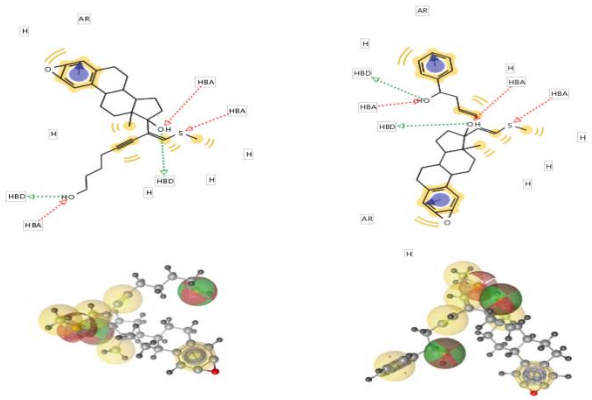

Figure 8. The scheme representing a pharmacophore from both compounds **7** (left) and **8** (right) using the LigandScout 4.0 software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, green).

In this sense, in this study, a pharmacophore model for both compounds **7** and **8** was determinate using the LigandScout program (Obi-Egbedi et al., 2011) (Figure 8). The results showed that functional groups involved in the chemical structure of either compounds **7** or **8** could interact via hydrophobic contacts or as hydrogen bond acceptors or as hydrogen bond donor with some biomolecules.

- *Interaction theoretical*

Analyzing the hypothesis mentioned above and some studies suggest that the formation of binary complexes between some compounds that act as ligands with several target biomolecules could induce changes in many activities of some biological systems (Seeliger and Groot, 2010). In this study, a theoretical analysis was carried out on the interaction of either compounds **7** or **8** with the 5tgz protein surface (Figure 9 and 10) using some drugs such as WIN 55,212-2, Yangonin [B1 cannabinoid receptor agonists] (Lauckner et al., 2005; Ligresti et al., 2012), and cannabigerol or tetrahydrocannabivarin [B1 cannabinoid receptor inhibitors] (Thomas et al., 2005; Thomas et al., 2007) as chemical tools in a Docking model (Foroumadi et al., 2003).

The data showed differences in the interaction of both compounds **7** and **8** with some amino acid residues involved in the 5tgz protein surface (Table 2). In addition, other data suggest that there is another type of amino acid residue in the interaction of Yangonin, cannabigerol, and tetrahydrocannabivarin with 5tgz (Tables 2 and 3).

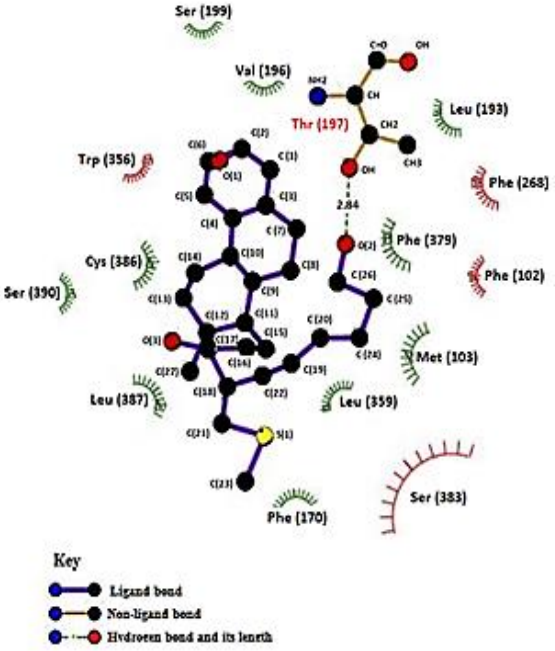

Figure 9. The scheme showing the interaction of compound **7** with the 5tgz protein surface. Theoretical analysis was carried out using the Docking-server.

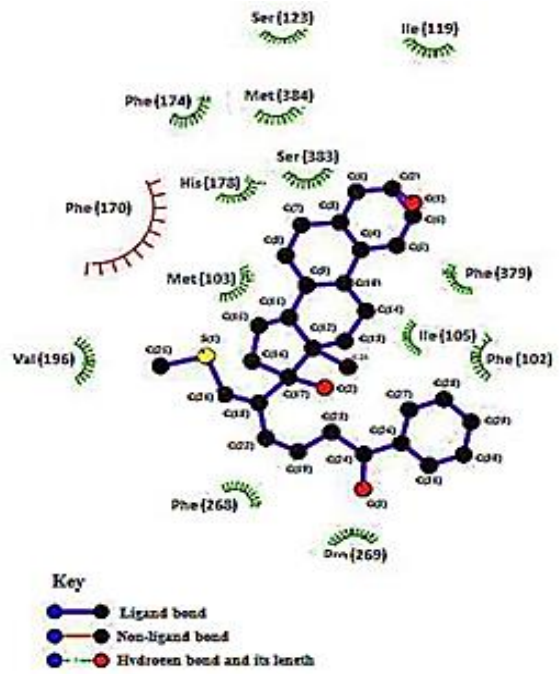

Figure 10. Interaction between compound **8** and the 5tgz protein surface. Theoretical analysis was carried out using the Docking-server.

Table 2. Amino acid residues involved in the interaction of WIN 55,212-2, Yangonin, and Cannabigerol with 5tgz protein surface.

Tetrahydrocannabivarin	C-7	C-8
Phe_{102}	Phe_{102}	Phe_{102}
Met_{103}	Met_{103}	Met_{103}
Asp_{104}	Phe_{170}	Ile_{105}
Ile_{105}	Leu_{193}	Ile_{1119}
Phe_{268}	Val_{196}	Ser_{123}
Pro_{269}	Thr_{197}	Phe_{170}
Phe_{379}	Ser_{199}	His_{178}
	Phe_{268}	Val_{196}
	Trp_{356}	Phe_{268}
	Leu_{359}	Pro_{269}
	Phe_{379}	Phe_{379}
	Ser_{383}	Ser_{383}
	Cys_{386}	Met_{384}
	Leu_{387}	
	Ser_{390}	

Table 3. Amino acid residues involved in the interaction of WIN 55,212-2, Yangonin, and Cannabigerol with 5tgz protein surface.

WIN 55,212-2	Yangonin	Cannabigerol
Met_{103}	Phe_{102}	Phe_{102}
Ile_{105}	Ile_{105}	Met_{103}
Ile_{169}	Glu_{106}	Ile_{105}
Phe_{170}	Phe_{170}	Phe_{170}
Phe_{174}	Val_{196}	Phe_{174}
Val_{196}	Phe_{268}	His_{178}
Phe_{268}	Pro_{269}	Val_{196}
Leu_{269}	Phe_{379}	Ser_{199}
Ser_{383}	Ser_{383}	Trp_{356}
Met_{384}		Leu_{359}
Cys_{386}		Ser_{383}
		Met_{384}
		Cys_{386}
		Leu_{387}
		Ser_{390}

This phenomenon could be conditioned by different conformations adopted by both compounds **7** and **8** or the length of the bound between the steroid derivatives and the amino acid residues involved in the 5tgz protein surface. However, it is important to mention that some reports suggest that other thermodynamic factors such as free energy of binding, electrostatic energy; total intermolecular energy and Van der Waals (vdW) + hydrogen bond (H-bond) + desolvation energy can be involved in the interaction of several compounds with the proteins or enzymes (Figueroa-Valverde et al., 2019).

- *Thermodynamic parameters*

In this study, by analyzing the above-mentioned hypothesis, some thermodynamic parameters were determinate using DockigServer. Theoretical data (Tables 4 and 5) indicate that there are differences in the thermodynamic parameters of WIN 55,212-2, Yangonin, Cannabigerol, and Tetrahydrocannabivarin compared with both compounds **7** and **8**.

Table 4. Thermodynamic parameters involved in the interaction of WIN55,212-2, Yangonin, Cannabigerol, Tetrahydrocannabivarin, and compounds 7 (C-7) and 8 (C-8).

Compound	Est. Fee Energy of Binding (kcal/mol)	Est. Inhibition Constant, Ki (μM)	cdW + Hbond + desolvation Energy
WIN55,212-2	-9.64	82.45	-10.70
Yangonin	-6.83	9.85	-7.91
Cannabigerol	-6.70	12.22	-9.86
Tetrahydrocannabivarin	-6.59	14.73	-6.84
C-7	-6.68	12.69	-8.52
C-8	-3.58	2.38	-8.25

Table 5. Thermodynamic factors involved in the interaction of WIN55,212-2, Yangonin, Cannabigerol, Tetrahydrocannabivarin, and compounds 7 (C-7) and 8 (C-8).

Compound	Electrostatic Energy	Total Inter-molecular Energy	Interact. Surface
WIN55,212-2	-0.4	-10.74	1030.82
Yangonin	-0.10	-8.01	902.48

Cannabigerol	-0.02	-9.58	1023.36
Tetrahydrocannabivarin	-0.05	-6.89	822.56
C-7	-0.01	-8.52	948.52
C-8	0.06	-8.20	1230.67

In addition, other results showed that inhibition constant (Ki) involved in the interaction of both compounds **7** and **8** with the 5tgz protein surface was different compared with the controls. All these data could be translated as a higher affinity of either compound **7** or **8** by the B1-cannabinoid receptor; however, it is important to mention that it would be interesting to carry out additional experiments in some biological models to know if compounds **7** and **8** could act as agonists or antagonists of B1-cannabinoid receptor.

Discussion

In this study, the facile synthesis of two steroid derivatives (compounds **7** or **8**) is reported using several chemical strategies. In addition, the theoretical analysis suggests that both compounds could interact with B1-cannabinoid receptor which can be translated as good candidates for their evaluation in some biological models.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Adamczyk, P., & Papp, M. (2016). On the Role of the Endocannabinoid System in Cocaine Addiction. In *Neuropathology of Drug Addictions and Substance Misuse* (pp. 48-62). Academic Press..

Blakemore, P. R., Cole, W. J., Kocieński, P. J., & Morley, A. (1998). A stereoselective synthesis of trans-1, 2-disubstituted alkenes based on the condensation of aldehydes with metallated 1-phenyl-1H-tetrazol-5-yl sulfones. *Synlett*, *1998*(01), 26-28.

Boswell Jr, G. A. (1968). Reaction of nitrosyl fluoride and selected steroid enes. New synthesis of. DELTA. 5-4-keto steroids. *The Journal of organic chemistry*, *33*(10), 3699-3713.

Braga, A. L., Appelt, H. R., Silveira, C. C., Wessjohann, L. A., & Schneider, P. H. (2002). Facile and practical enantioselective synthesis of propargylic alcohols by direct addition of alkynes to aldehydes catalyzed by chiral disulfide–oxazolidine ligands. *Tetrahedron*, *58*(52), 10413-10416.

Chauvière, G., Bouteille, B., Enanga, B., de Albuquerque, C., Croft, S. L., Dumas, M., & Périé, J. (2003). Synthesis and biological activity of nitro heterocycles analogous to megazol, a trypanocidal lead. *Journal of medicinal chemistry*, *46*(3), 427-440.

Colasanti, B. K., Craig, C. R., & Allara, R. D. (1984). Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol. *Experimental eye research*, *39*(3), 251-259.

Cornelis, A., Laszlo, P., & Pennetreau, P. (1983). Clay-supported reagents. 5. Nitration of estrone into 2-nitroestrone by clay-supported ferric nitrate. *The Journal of Organic Chemistry*, *48*(24), 4771-4772.

Ess, D. H., & Houk, K. N. (2008). Theory of 1, 3-dipolar cycloadditions: distortion/interaction and frontier molecular orbital models. *Journal of the American Chemical Society*, *130*(31), 10187-10198.

Fauzi, N. F. A. M., Bakar, N. H. A., Mohamad, N., Hadzrullathfi, S., Omar, S., Ismail, M. Z., ... & Mustafa, N. S. Nigella sativa Effects on Neurotransmitter Systems: Potential Treatment for Drug Tolerance and Dependence. *International Journal of Pharmaceutical Research & Allied Sciences*, *7*(1), 196-200.

Feghhi, F., & Malekzadeh, M. (2018). Nurses' Attitude Towards the Care of Narcotic Patients in Yasuj in 2014. *International Journal of Pharmaceutical and Phytopharmacological Research*, *8*(3), 55-58.

Figueroa-Valverde, L., Díaz-Cedillo, F., & Garcia-Cervera, E. (2012). Synthesis of two steroids derivatives and its relationship with some physicochemical parameters. *Journal of Chemistry*, *9*(1), 27-34.

Figueroa-Valverde, L., Diaz-Cedillo, F., Ramos, M. L., & Cervera, E. G. (2011). Synthesis of pregnenolone–danazol–ethylendiamine conjugate: relationship between descriptors log P, π, R m, and V m and its antibacterial activity in S. aureus and V. cholerae. *Medicinal Chemistry Research*, *20*(7), 847-853.

Foroumadi, A., Mansouri, S., Kiani, Z., & Rahmani, A. (2003). Synthesis and in vitro antibacterial evaluation of N-[5-(5-nitro-2-thienyl)-1, 3, 4-thiadiazole-2-yl] piperazinyl quinolones. *European journal of medicinal chemistry*, *38*(9), 851-854.

Houk, K. N. (1975). Frontier molecular orbital theory of cycloaddition reactions. *Accounts of Chemical Research*, *8*(11), 361-369.

Huestis, M. A., Gorelick, D. A., Heishman, S. J., Preston, K. L., Nelson, R. A., Moolchan, E. T., & Frank, R. A. (2001). Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Archives of general psychiatry*, *58*(4), 322-328.

Karki, M., & Magolan, J. (2015). Bromination of Olefins with HBr and DMSO. *The Journal of organic chemistry*, *80*(7), 3701-3707.

Latosińska, J. N., Kasprzak, J., & Kazimierczuk, Z. (2000). Effects of chlorination and deoxiribose substitution on electron density distribution in indazole molecule studied by 35Cl NQR spectroscopy and ab initio calculations. *Journal of Molecular Structure: TheocheM*, *530*(1-2), 217-222.

Lauckner, J. E., Hille, B., & Mackie, K. (2005). The cannabinoid agonist WIN55, 212-2 increases intracellular calcium via CB1 receptor coupling to Gq/11 G proteins. *Proceedings of the National Academy of Sciences*, *102*(52), 19144-19149.

Lauro, F. V., Francisco, D. C., Marcela, R. N., Guadalupe, M. V., Elodia, G. C., Eduardo, P. G., ... & Marissa, C. S. (2015). Design and synthesis of some carbamazepine derivatives using several strategies. *Letters in Organic Chemistry*, *12*(6), 394-401.

Lauro, F. V., Francisco, D. C., Marcela, R. N., Virginia, M. A., Elizabeth, M. T., Lenin, H. H., ... & Alondra, A. J. (2019). Design and synthesis of two steroid derivatives from 2-nitroestrone and theoretical evaluation of their interaction with BRCA-1. *Asian Journal of Green Chemistry*, *3*(2. pp. 125-287), 216-235.

Ligresti, A., Villano, R., Allarà, M., Ujváry, I., & Di Marzo, V. (2012). Kavalactones and the endocannabinoid system: the plant-derived yangonin is a novel CB1 receptor ligand. *Pharmacological Research*, *66*(2), 163-169.

Lu, H. C., & Mackie, K. (2016). An introduction to the endogenous cannabinoid system. *Biological psychiatry*, *79*(7), 516-525.

Maldonado, R., Valverde, O., & Berrendero, F. (2006). Involvement of the endocannabinoid system in drug addiction. *Trends in neurosciences*, *29*(4), 225-232.

Mansouri, M., Taheri, A. R., & Maghsoudi, J. (2018). Effect of Enable Consultation on Addicts' Hope and Happiness. *International Journal of Pharmaceutical and Phytopharmacological Research*, *8*(1), 90-97.

Marshall, J. A., & Bourbeau, M. P. (2003). Synthesis of enantioenriched propargylic alcohols related to polyketide natural products. A comparison of methodologies. *Organic letters*, *5*(18), 3197-3199.

Mas-Nieto, M., Pommier, B., Tzavara, E. T., Caneparo, A., Nascimento, S. D., Fur, G. L., ... & Noble, F. (2001). Reduction of opioid dependence by the CB1 antagonist SR141716A in mice: evaluation of the interest in pharmacotherapy of opioid addiction. *British journal of pharmacology*, *132*(8), 1809-1816.

Moreira, F. A., & Crippa, J. A. S. (2009). The psychiatric side-effects of rimonabant. *Brazilian Journal of Psychiatry*, *31*(2), 145-153.

Mukaiyama, T., Furuya, M., Ohtsubo, A., & Kobayashi, S. (1991). Highly enantioselective synthesis of propargylic alcohols by way of the asymmetric aldol reaction. *Chemistry Letters*, *20*(6), 989-992.

Murineddu, G., Ruiu, S., Loriga, G., Manca, I., Lazzari, P., Reali, R., ... & Pinna, G. A. (2005). Tricyclic Pyrazoles. 3. Synthesis, Biological Evaluation, and Molecular Modeling of Analogues of the Cannabinoid Antagonist 8-Chloro-1-(2 ‘, 4 ‘-dichlorophenyl)-N-piperidin-1-yl-1, 4, 5, 6-tetrahydrobenzo [6, 7] cyclohepta [1, 2-c] pyrazole-3-carboxamide. *Journal of medicinal chemistry*, *48*(23), 7351-7362.

Murray, R. W., Jeyaraman, R., & Mohan, L. (1986). A new synthesis of nitro compounds using dimethyldioxirane. *Tetrahedron letters*, *27*(21), 2335-2336.

Obi-Egbedi N, Obot I, El-Khaiary M, Umoren S, & Ebenso E (2011). Computational Simulation and Statistical Analysis on the Relationship Between Corrosion Inhibition Efficiency and Molecular Structure of Some Phenanthroline Derivatives on Mild Steel Surface. *Int J Electrochem Sci. 6*, 5649-5675.

Obi-Egbedi, N. O., & Obot, I. B. (2011). Inhibitive properties, thermodynamic and quantum chemical studies of alloxazine on mild steel corrosion in H2SO4. *Corrosion Science*, *53*(1), 263-275.

Parolaro, D., & Rubino, T. (2008). the role of the endogenous cannabinoid system in drug addiction. *Drug news & perspectives*, *21*(3), 149-157.

Patel, C. N., Georrge, J. J., Modi, K. M., Narechania, M. B., Patel, D. P., Gonzalez, F. J., & Pandya, H. A. (2018). Pharmacophore-based virtual screening of catechol-o-methyltransferase (COMT) inhibitors to combat Alzheimer’s disease. *Journal of Biomolecular Structure and Dynamics*, *36*(15), 3938-3957.

Prasad, Y. R., Kumar, P. R., Smiles, D. J., & Babu, P. A. (2008). QSAR studies on chalcone derivatives as antibacterial agents against Bacillus pumilis. *Arkivoc*, *11*, 266-276.

Réau, M., Langenfeld, F., Zagury, J. F., & Montes, M. (2018). Predicting the affinity of Farnesoid X Receptor ligands through a hierarchical ranking protocol: a D3R Grand Challenge 2 case study. *Journal of computer-aided molecular design*, *32*(1), 231-238.

Riley, R. F., Flato, J., & Bengels, D. (1962). Addition of selenium and sulfur tetrachlorides to alkenes and alkynes. *The Journal of Organic Chemistry*, *27*(7), 2651-2653.

Ruiu, S., Pinna, G. A., Marchese, G., Mussinu, J. M., Saba, P., Tambaro, S., ... & Pani, L. (2003). Synthesis and characterization of NESS 0327: a novel putative antagonist of the CB1 cannabinoid receptor. *Journal of Pharmacology and Experimental Therapeutics*, *306*(1), 363-370.

Şahin, A. D., & Saçan, M. T. (2018). Understanding the toxic potencies of xenobiotics inducing TCDD/TCDF-like effects. *SAR and QSAR in Environmental Research*, *29*(2), 117-131.

San Filippo Jr, J., Sowinski, A. F., & Romano, L. J. (1975). Chlorination of alkenes and alkynes with molybdenum (V) chloride. *Journal of the American Chemical Society*, *97*(6), 1599-1600.

Sandhya, S. T., Thangavelu, L., & Roy, A. (2018). Awareness of Drug Abuse among Teenagers. *International Journal of Pharmaceutical and Phytopharmacological Research*, *8*(6), 18-21.

Sapundzhi, F. I., Dzimbova, T. A., Pencheva, N. S., & Milanov, P. B. (2018). Molecular docking experiments of cannabinoid receptor. *Bulg Chem Commun*, *50*, 44-48.

Schneider, G., Neidhart, W., Giller, T., & Schmid, G. (1999). "Scaffold-hopping" by topological pharmacophore search: a contribution to virtual screening. *Angewandte Chemie International Edition*, *38*(19), 2894-2896.

Seeliger, D., & de Groot, B. L. (2010). Ligand docking and binding site analysis with PyMOL and Autodock/Vina. *Journal of computer-aided molecular design*, *24*(5), 417-422.

Shi, D., Liu, Z., Zhang, Z., Shi, W., & Chen, H. (2015). Silver-Catalyzed Synthesis of 1-Chloroalkynes Directly from Terminal Alkynes. *ChemCatChem*, *7*(9), 1424-1426.

Shimizu, K., Takimoto, M., Sato, Y., & Mori, M. (2005). Nickel-catalyzed regioselective synthesis of tetrasubstituted alkene using alkylative carboxylation of disubstituted alkyne. *Organic letters*, *7*(2), 195-197.

Sofuoglu, M., & Sewell, R. A. (2009). Norepinephrine and stimulant addiction. *Addiction biology*, *14*(2), 119-129.

Su, H., & Zhao, M. (2017). Endocannabinoid mechanism in amphetamine-type stimulant use disorders: A short review. *Journal of Clinical Neuroscience*, *46*, 9-12.

Suresh, P. K., Divya, N., Nidhi, S., & Rajasekaran, R. (2018). Phenytoin-Bovine Serum Albumin interactions-modeling plasma protein–drug binding: A multi-spectroscopy and in silico-based correlation. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *193*, 523-527.

Tahir, M. N., Khalid, M., Islam, A., Mashhadi, S. M. A., & Braga, A. A. (2017). Facile synthesis, single crystal analysis, and computational studies of sulfanilamide derivatives. *Journal of Molecular Structure*, *1127*, 766-776.

Thomas, A., Baillie, G. L., Phillips, A. M., Razdan, R. K., Ross, R. A., & Pertwee, R. G. (2007). Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *British journal of pharmacology*, *150*(5), 613-623.

Thomas, A., Stevenson, L. A., Wease, K. N., Price, M. R., Baillie, G., Ross, R. A., & Pertwee, R. G. (2005). Evidence that the plant cannabinoid Δ9-tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist. *British journal of pharmacology*, *146*(7), 917-926.

Wadhwa, K., Chintareddy, V. R., & Verkade, J. G. (2009). P (PhCH2NCH2CH2) 3N: An Efficient Lewis Base Catalyst for the Synthesis of Propargylic Alcohols and Morita− Baylis− Hillman Adducts via Aldehyde Alkynylation. *The Journal of organic chemistry*, *74*(17), 6681-6690.

Xi, Z. X., Gilbert, J. G., Peng, X. Q., Pak, A. C., Li, X., & Gardner, E. L. (2006). Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-primed relapse in rats: role of glutamate in the nucleus accumbens. *Journal of Neuroscience*, *26*(33), 8531-8536.

Zweifel, G., Arzoumanian, H., & Whitney, C. C. (1967). A convenient stereoselective synthesis of substituted alkenes via hydroboration-iodination of alkynes. *Journal of the American Chemical Society*, *89*(14), 3652-3653.