Heterocyclic Letters
Vol. 12| No.4|697-708|Aug-Oct|2022
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

DESIGN AND SYNTHESIS OF THREE ESTER-HARMOL DERIVATIVES: THEORETICAL EVALUATION OF THEIR INTERACTION WITH B1-CANNABINOID RECEPTOR

López-Ramos Maria[1], Figueroa-Valverde Lauro[1,*], Díaz-Cedillo Francisco[22], Rosas-Nexticapa Marcela[3], Alvarez-Ramirez Magdalena[3], Mateu-Armad Maria Virginia[3], Cervantes-Ortega Catalina[3], Melgarejo-Guutierrez Montserrat[4], Lopez-Gutierrez Tomas[1], Priego-Delgado K[1].

[1] *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;*
[2] *Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, México, D.F. C.P. 11340;*
[3] *Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México;*
[4] *Facultad de Medicina, Universidad Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México;*
* *Correspondence: lfiguero@uacam.mx (F.V.L)*

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 three ester-harmon derivatives (compounds **4** to **6**) to evaluate their theoretical interaction with B1 cannabinoid receptor (5gtz) using tetrahydrocannabinol and AM-251 drugs as controls in a docking model. The preparation of **4** to **6** were carried out using a series of reactions which involved addition (2 +2), esterification, and an imino group formation. The chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. Other data showed that compounds **4** to **6** could bind to different types of amino acid residues involved in 5gtz protein surface compared with tetrahydrocannabinol and AM-251 drugs. All these data suggest that compounds **4** to **6** may exert changes in the biological activity of B1 cannabinoid receptor.

Keywords. Synthesis, ester, harmol, derivatives, B1-Cannabinoid Receptor.

Introduction

Opioids can produce tolerance and dependence, bringing as consequences neurobiological changes in several systems such as adrenergic, dopaminergic, serotoninergic[ii], and cannabinoid[iii]. In this way that cannabinoid system involves endogenous cannabinoids (e.g., anandamide and 2-arachidonoylglycerol), enzymes responsible for the synthesis and degradation of endocannabinoids, and CB1 and CB2 cannabinoid receptors[iv]. There are several data which suggest that CB1 cannabinoid receptor activation is correlated with an increase in addiction to amphetamine drugs[v] and marijuana[vi]. To try drug addiction several CB1 receptor antagonist have been used such as rimonabant[vii], AM251 (N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1Hpyrazole-3-carboxamide)[viii], and cannabidiol[ix]. However, some of these drugs can cause weight loss in obese patients, although it may also induce symptoms of anxiety and depression[x], ocular hypotensive[xi] and others. In the search a new drug for treatment of Drug dependence several compounds have been synthesized: for example, the preparation of Isothiocyanato-naphthalene derivative from an amino-naphthyl methanone analog and thiophosgene with affinity to CB1 cannabinoid receptor[xii]. In addition, a study showed the synthesis of a carboxamide derivative via reaction of **a** thiophene carboxylic acid derivative with trimethylacetyl chloride as CB1 cannabinoid receptor antagonist[xiii]. Other data display the reaction of an imidazol-4-one with Lawesson's reagent to form a 1,5-dihydro-imidazol-4-thione derivative which was used as a CB1 cannabinoid receptor Inverse Agonist[xiv]. Besides, two Methylthiosteroid-oxirenol derivatives were synthesized from 17-ethynilestradiol with higher affinity by CB1 cannabinoid receptor[xv]. Other study showed the reaction of preparation of 1-(5-fluoropentyl)-1H-indole-3-carboxylic acid with oxalyl chloride to form 1-(5-Fluoropentyl)-N-(2-phenylpropan-2-yl)-1H-indole-3-carboxamide which showed biological activity on CB1 cannabinoid receptor[xvi]. All these data show several protocols for preparation of compounds with biological activity on CB1 cannabinoid receptor. However, some of these methods use different reagents are dangerous and require special conditions such as different pH and higher temperature. In this research three harmol derivatives were synthesized using some chemical strategies to evaluate their theoretical interaction with CB1 cannabinoid receptor using a docking model.

Materials and Methods

General methods.

Starting materials were purchased from commercial suppliers (Sigma-Aldrich and AKos Consulting & Solutions). NMR spectra were recorded on a Varian VXR300/5 FT apparatus (300 MHz/$CDCl_3$) using tetramethylsilane as an internal standard. Electron Ionization mass spectrometry (EIMS) was recorder on a Finnigan PolarisQ ion trap mass spectrometer. Melting-point (m.p.) was determined on an electrothermal-900 model apparatus. The infrared spectrum (IR) was determined on a thermo-scientific iSOFT/IR device. Elemental analysis was determined using a PerkinElmer apparatus (Ser. II CHNS / 02400).

Chemical synthesis.

(1-Methyl-2,9-dihydro-b-carbolin-7-ylidene)-prop-2-ynyl-amine4-Hydroxy-N-[3-(tetra-hydro-furan-2-yl)-allyl]-benzamide **(2)**

In a round bottom flask (10 ml), harmol (100 mg, 0.50 mmol), propargylamine (70 mg. 0.64 mmol), boric acid (50 mg, 0.80 mmol) and methanol (5 ml) were stirring for 12 h at room temperature. Then the solvent was evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system; yielding 65% of product; IR (V_{max}, cm^{-1}) 3444, 3320 and 1212. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.12 (s, 3H), 2.30 (s, 1H), 3.94 (m, 2H), 6.44-7.60 (m, 5H), 9.02 (broad, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 14.70, 46.22,

68.40, 77.50, 92.00, 106.34, 112.70, 113.77, 124.50, 126.00, 131.00, 134.50, 152.12, 152.36, 169.40 ppm. EI-MS m/z: 235.11. Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.54; H, 5.53.

[3-[[(E)-(1-methyl-2,9-dihydropyrido[3,4-b]indol-7-ylidene)amino]methyl]cyclobut-2-en-1-yl]-phenyl-methanol (3)

In a round bottom flask (10 ml), compound **2** (100 mg, 0.59 mmol), 1-Phenyl-prop-2-en-1-ol (70 µl, 0.57 mmol), Copper(II) chloride anhydrous (70 mg, 0.52 mmol) and methanol (5 ml) were stirring for 72 h at room temperature. Then the solvent was evaporated on a rotary evaporator and the product is separated using the chloroform: water (3:1) system; yielding 44% of product; IR (V_{max}, cm^{-1}) 3478, 3444 and 3320. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.12 (s, 3H), 2.52-3.60 (m, 3H), 3.80 (m, 2H), 4.50 (m, 1H), 6.20 (m, 1H), 6.30 (m, 1H), 6.64-6.86 (m, 2H), 6.92 (broad, 3H), 7.12-7.38 (m, 5H), 7.60-7.64 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 14.70, 28.94, 43.00, 47.52, 81.40, 97.45, 106.34, 112.70, 119.17, 126.00, 126.44, 127.12, 127.22, 129.16, 133.60, 134.50, 134.82, 140.00, 140.15, 152.12, 154.32, 160.36 ppm. EI-MS m/z: 369.18. Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37; O, 4.33. Found: C, 78.00; H, 6.24.

[[3-[[(E)-(1-methyl-2,9-dihydropyrido[3,4-b]indol-7-ylidene)amino]methyl]cyclobut-2-en-1-yl]-phenyl-methyl] benzoate (4)

In a round bottom flask (10 ml), compound **3** (200 mg, 0.63 mmol), benzoic acid (80 mg. 0.65 mmol), *N*,*N´*-dicyclohexylcarbodiiimide (150 mg, 0.73 mmol) and methanol (5 ml) were stirring for 72 h at room temperature. Then the solvent was evaporated on a rotary evaporator and the product is separated using the chloroform:water (4:1) system; yielding 54% of product; IR (V_{max}, cm^{-1}) 3440, 3322 and 1732. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.12 (s, 3H), 3.02-3.60 (m, 3H), 3.80 (m, 2H), 6.20 (m, 1H), 6.30 (m, 1H), 6.50 (m, 1H), 6.64-6.86 (m, 2H), 7.22-7.30 (m, 5H), 7.40-7.54 (m, 3H), 7.56-7.62 (m, 2H), 8.06 (m, 2H), 9.02 (broad, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 14.70, 28.84, 41.10, 47.52, 83.96, 97.45, 106.34, 112.70, 119.17, 126.00, 127.12, 127.82, 128.50, 129.16, 130.10, 131.78, 132.08, 132.70, 133.60, 134.50, 138.72, 141.90, 152.12, 154.32, 160.36, 165.70 ppm. EI-MS m/z: 473.21. Anal. Calcd. for $C_{31}H_{27}N_3O_2$: C, 78.62; H, 5.75; N, 8.87; O, 6.76. Found: C, 78.60; H, 5.72.

[[3-[[(E)-(1-methyl-2,9-dihydropyrido[3,4-b]indol-7-ylidene)amino]methyl]cyclobut-2-en-1-yl]-phenyl-methyl] 3,5-dinitrobenzoate (5)

In a round bottom flask (10 ml), Compound **4** (200 mg, 0.42 mmol), 3,5-dinitrobenzoic acid (90 mg. 0.42 mmol), *N*,*N´*-dicyclohexylcarbodiiimide (86 mg, 0.42 mmol) and methanol (5 ml) were stirring for 72 h at room temperature. Then the solvent was evaporated on a rotary evaporator and the product is separated using the chloroform:hexane:water (4:1:1) system; yielding 76% of product; IR (V_{max}, cm^{-1}) 3444, 3322, 1732 and 1350. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.12 (s, 3H), 3.02-3.60 (m, 3H), 3.80 (m, 2H), 6.20 (m, 1H), 6.30 (m, 1H), 6.50 (m, 1H), 6.64-6.86 (m, 2H), 7.22-7.30 (m, 5H), 7.54-7.60 (m, 2H), 9.02 (broad, 2H), 9.16 (m, 3H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 14.70, 28.84, 41.10, 47.52, 83.96, 97.45, 106.34, 112.70, 119.17, 122.30, 126.00, 127.12, 127.82, 128.50, 129.16, 129.60, 132.10, 133.60, 134.50, 135.22, 138.72, 141.90, 148.40, 152.12, 154.32, 159.14, 160.36, ppm. EI-MS m/z: 563.18. Anal. Calcd. for $C_{31}H_{25}N_5O_6$: C, 66.07; H, 4.47; N, 12.43; O, 17.03. Found: C, 66.04; H, 4.43.

[[3-[[(E)-(1-methyl-2,9-dihydropyrido[3,4-b]indol-7-ylidene)amino]methyl]cyclobut-2-en-1-yl]-phenyl-methyl] hex-5-ynoate (6)

In a round bottom flask (10 ml), compound **5** (200 mg, 0.35 mmol), 1-hexynoic acid (80 µl, 0.75 mmol), *N,N´*-dicyclohexylcarbodiiimide (86 mg, 0.42 mmol) and methanol (5 ml) were stirring for 72 h at room temperature. Then the solvent was evaporated on a rotary evaporator and the product is separated using the chloroform:hexane:water (4:1:1) system; yielding 65% of product; IR (V_{max}, cm^{-1}) 3440, 3322, 2110 and 1730. ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.60 (m, 2H), 2.07 (s, 1H), 2.12 (s, 3H), 2.30-2.34 (m, 4H), 3.02-3.60 (m, 3H), 3.80 (m, 2H), 6.20 (m, 1H), 6.30 (m, 1H), 6.44 (m, 1H), 6.64-6.86 (m, 2H), 7.16-7.30 (m, 5H), 7.54-7.60 (m, 2H), 9.02 (broad, 2H), 9.06 (m, 3H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 14.70, 17.85, 23.66, 28.84, 33.40, 41.10, 47.52, 69.16, 82.92, 83.22, 97.45, 106.34, 112.70, 119.17, 126.00, 126.10, 127.10, 127.82, 129.16, 132.10, 133.60, 134.50, 138.02, 141.90, 152.12, 154.32, 159.14, 160.36, 168.72 ppm. EI-MS m/z: 463.22. Anal. Calcd. for $C_{30}H_{29}N_3O_2$: C, 77.73; H, 6.31; N, 9.06; O, 6.90. Found: C, 77.70; H, 6.28.

Pharmacophore analysis

Pharmacophore model for compounds **4**-**6** was developed using LigandScout 4.08 software Docking[xvii].

Protein-ligand interaction

Interaction of compounds **4**-**6** with B1-Cannabinoid receptor was determinate using 5tgz protein[xviii] from protein data bank as control, and Achilles blind docking server[xix].

Results and Discussion

In this investigation three harmon-ester derivatives (compounds **4** to **6)** were prepared using some chemical strategies as follows:

Synthesis of an imino derivative (2). This stage was achieved through of synthesis of an imino group involved in compound **2**; it is noteworthy that some methods have been used for preparation of imino analogs[xx-xxiii]; nevertheless, in this study boric acid was used as catalyst (Figure 1), because it is not an expensive reagent and special conditions for its use are not required[xxiv]. The ^{1}H NMR spectrum from 2 shows signals at 2.12 ppm for methyl group; at 2.30 ppm for alkyne group; at 3.94 ppm for methylene group bound to both imino and alkyne groups; at 6.44-7.60 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 9.02 ppm for amino groups. ^{13}C NMR spectrum of **2** showed several chemical shifts at 14.70 ppm for methyl group; at 46.22 ppm for methylene group linked to both imino and alkyne groups; at 68.40-77.50 ppm for alkyne group; at 92.00-152.36 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 169.40 ppm for imino group. The presence of **2** was further confirmed from the mass spectrum which showed a molecular ion at m/z 235.11.

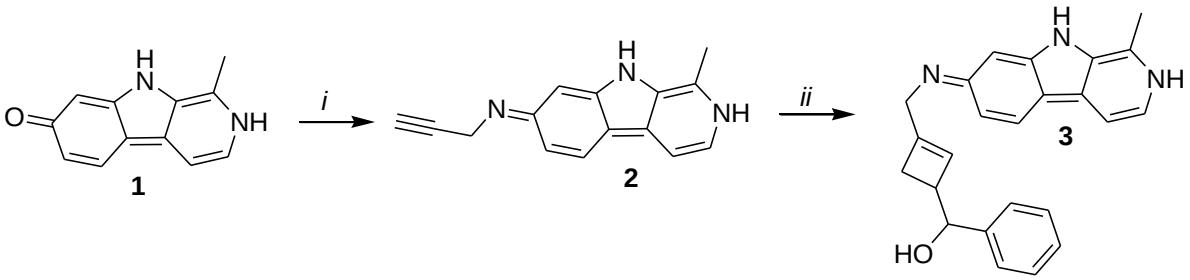

Figure 1. Synthesis of a cyclobut-2-enyl}-phenyl-methanol derivative (3). Conditions and reagents: *i* = propargylamine, boric acid, MeOH, 12, h, rt; *ii* = 1-Phenyl-prop-2-en-1-ol, Copper(II) chloride, MeOH, 72 h, rt. rt = room temperature.

Synthesis of a cyclobutene derivative. It is noteworthy that several cyclobutene have been prepared using reagents such as organolithium derivative[xxv], rhodium[xxvi], palladium[xxvii], nickel[xxviii], cobalt complexes[xxix], Copper(I)[xxx]. In this study, a cyclobutene derivative (compound 3) was prepared via [2+2] addition of an alkene derivative to **2** using Copper(II) as catalyst (Figure 1). In this research, **2** reacted with 1-Phenyl-prop-2-en-1-ol using Cooper II chloride as catalyst to form the compound **3**. The ^{1}H NMR spectrum from **3** displayed several signals at 2.12 ppm for methyl group; at 2.52-3.60 and 6.30 ppm for cyclobutene ring; at 3.80 ppm for methylene group bound to both cyclobutene ring and imino group; at 4.50 ppm for methylene group linked to hydroxyl group; at 6.20 and 6.64-6.86 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 6.92 ppm for imino and hydroxyl groups; at 7.12-7.38 ppm for phenyl bound to methanol fragment. ^{13}C NMR spectrum of **3** showed some bands at 14.70 ppm for methyl group; at 28.94-43.00, 134.82 and 140.15 ppm for cyclobutene ring; at 47.52 ppm for methylene group linked to both cyclobutene ring and imino group; at 81.40 ppm for methylene group bound to hydroxyl group; at 97.45-126.00, 127.12, 133.60-134.50 and 152.12-154.32 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 126.44, 127.22-129.16 and 140.00 ppm for phenyl bound to methanol fragment. Besides, the mass spectrum for **3** showed a molecular ion at m/z 369.18.

First Reaction esterification

Several reagents are available for producing ester derivatives[xvii, xviii]; nevertheless, most conventional methods have found only limited use for this purpose; here it is important to mention that some carbodiimides and, especially, N,N´-dicyclohexylcarbodiimide have attracted increasing attention as condensing agents in ester synthesis[xix, xx]. In this way, compound **4** was prepared via esterification of the hydroxyl group of **3** with benzoic acid using *N*,*N*´-dicyclohexylcarbodiimide as catalyst (Figure 2). The ^{1}H NMR spectrum from **4** showed several bands at 2.12 ppm for methyl group; at 3.02-3.60 and 6.30 ppm for cyclobutene ring; at 3.80 ppm for methylene group linked to both cyclobutene ring and imino group; at 6.20, 6.64-6.86 and 7.56-7.62 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 6.50 ppm for methylene group bound to ester group; at 7.22-7.54 and 8.10 ppm for phenyl group linked to methyl ester fragment; at 9.02 for amino groups. ^{13}C NMR spectrum of **4** showed some signals at 14.70 ppm for methyl group; at 28.40-41.10, 132.08 and 141.90 ppm for cyclobutene ring; at 47.52 ppm for methylene group bound to both cyclobutene ring and imino group; at 83.96 ppm for methylene group linked to both phenyl and ester groups; at 97.45-119.17, 127.12, 133.60-134.50 and 152.12-154.32 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 126.00, 127.82-131.78, 132.70 and 138.72 ppm for phenyl group linked to methyl ester fragment; at 160.36 ppm for imino group; at 165.70 ppm for ester group. In addition, the mass spectrum for **4** showed a molecular ion at m/z 473.21.

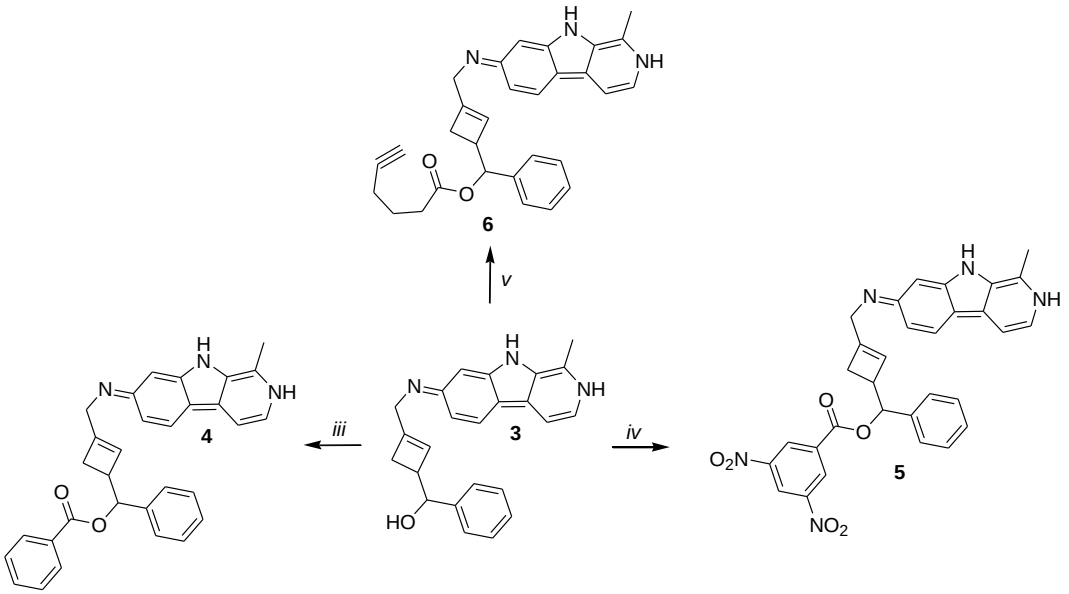

Figure 2. Synthesis of three ester-harmol derivatives (**4**-**6**). Reagents and Conditions: *iii* = benzoic acid, *N*,*N*´-dicyclohexylcarbodiimide, MeOH, 72 h, rt: *iv* = 3,5-dimitrobenzoic acid, *N*,*N*´-dicyclohexylcarbodiimide, MeOH, 72 h, rt: 1-hexynoic acid, *N*,*N*´-dicyclohexylcarbodiimide, MeOH, 72 h, rt.
rt = room temperature.

Second reaction esterification

The compound **4** reacted with 3,5-dinitrobenzoic acid in the presence of *N*,*N*´-dicyclohexylcarbodiimide to form **5** (Figure 2). The ^{1}H NMR spectrum from **5** showed several bands at 2.12 ppm for methyl group; at 3.02-3.60 and 6.30 ppm for cyclobutene ring; at 3.80 ppm for methylene group linked to both cyclobutene ring and imino group; at 6.20, 6.64-6.86 and 7.54-7.60 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 6.50 ppm for methylene group bound to ester group; at 7.22-7.30 and 9.16 ppm for phenyl group linked to methyl ester fragment; at 9.02 for amino groups. ^{13}C NMR spectrum of **5** showed some signals at 14.70 ppm for methyl group; at 28.84-41.10, 132.10 and 141.90 ppm for cyclobutene ring; at 47.52 ppm for methylene group bound to both cyclobutene ring and imino group; at 83.96 ppm for methylene group linked to both phenyl and ester groups; at 97.45-119.17, 127.12, 133.60-134.50 and 152.12-154.32 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 122.30-126.00, 127.82-129.60, 135.22-138.72, 148.40 ppm for phenyl group linked to methyl ester fragment; at 159.14 ppm for ester group; at 160.36 ppm for imino group. Besides, the mass spectrum for **5** showed a molecular ion at m/z 563.18.

Third reaction esterification

The compound **3** reacted with 1-hexynoic acid using *N*,*N*´-dicyclohexylcarbodiimide as catalyst to form **6** (Figure 2). The ^{1}H NMR spectrum from **6** showed several bands at 2.07 ppm for alkyne group; at 2.12 ppm for methyl group; at 1.60 and 2.30-2.34 ppm for methylene groups bound to both alkyne and ester groups; at 3.02-3.60 and 6.30 ppm for cyclobutene ring; at 3.80 ppm for methylene group linked to both cyclobutene ring and imino group; at 6.20, 6.64-6.86 and 7.54-7.60 ppm for 1-Methyl-7,9-dihydro-2H-b-carboline fragment; at 6.44 ppm for methylene group bound to ester group; at 7.16-7.30 and 9.06 for phenyl group linked to methyl ester fragment; at 9.02 for amino groups. ^{13}C NMR spectrum of **6** showed some bands at 14.70 ppm for methyl group; at 17.85, 23.66 and 33.40 ppm for methylene groups linked to both alkyne and ester groups; at 28.84, 41.10, 132.10 and 141.90 ppm for cyclobutene ring; at 47.52 ppm for methylene group bound to both cyclobutene ring and imino group; at 69.16 and 83.22 for alkyne group; at 82.92 ppm for methylene group linked to both phenyl and ester groups; at 97.45-119.17, 126.10-127.10, 133.60-134.50 and 152.12-160.36 ppm for 1-Methyl-

7,9-dihydro-2H-b-carboline fragment; at 122.82-129.16 and 138.02 ppm for phenyl group linked to methyl ester fragment; at 160.36 ppm for imino group; at 168.72 ppm for ester group;. Besides, the mass spectrum for **6** showed a molecular ion at m/z 463.22.

Pharmacophore model

There are some methods to predict the three-dimensional orientation adopted by the functional groups of different molecules in order to evaluate their interaction with some biomolecule[xxxi, xxxii]. In this way, in this research, a pharmacophore model for compounds **4** to **6** was determinate using the LigandScout software[xxxiii-xxxv]. The results (Figure 3) showed functional different groups involved in the chemical structure **4** to **6**, which could interact through of hydrophobic contacts or as hydrogen bond acceptors or as hydrogen bond donor with some biomolecules.

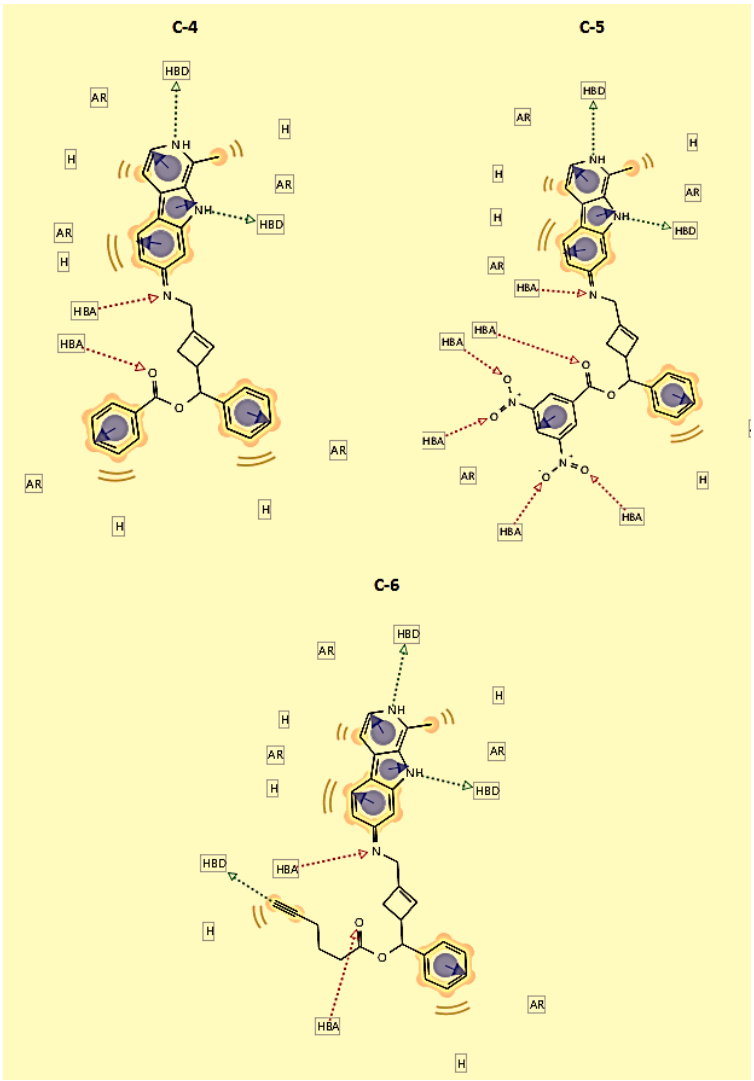

Figure 3. Theoretical pharmacophore from both compounds 4 (C-4), 5 (C-6) and 6 (C-6) using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, green).

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[xxxvi]. In this research, a theoretical analysis was carried out to evaluate the interaction of compounds **4** to **6** with 5tgz protein surface (Figure 9 and 10) using some drugs such as tetrahydrocannabinol (cannabinoid receptor agonist)[xxxvii] and AM-251 (B1 cannabinoid receptor antagonist)[xxxviii] in a Docking model[xix]. The results showed differences in the interaction of compounds **4** to **6** with some amino acid residues involved in the 5tgz protein surface (Figure 4 and Tables 1 and 2) compared with both tetrahydrocannabinol and AM-251 drugs. It is noteworthy that some amino acid residues could interact with compounds **4** (Hist178), **5** (Ile105), and **6** (His 178) through hydrogen bonds. In addition, the results showed that these interactions require lower binding energy compared with both tetrahydrocannabinol and AM-251 drugs; this phenomenon can result in changes in the biological activity of B1-Cannabinoid Receptor.

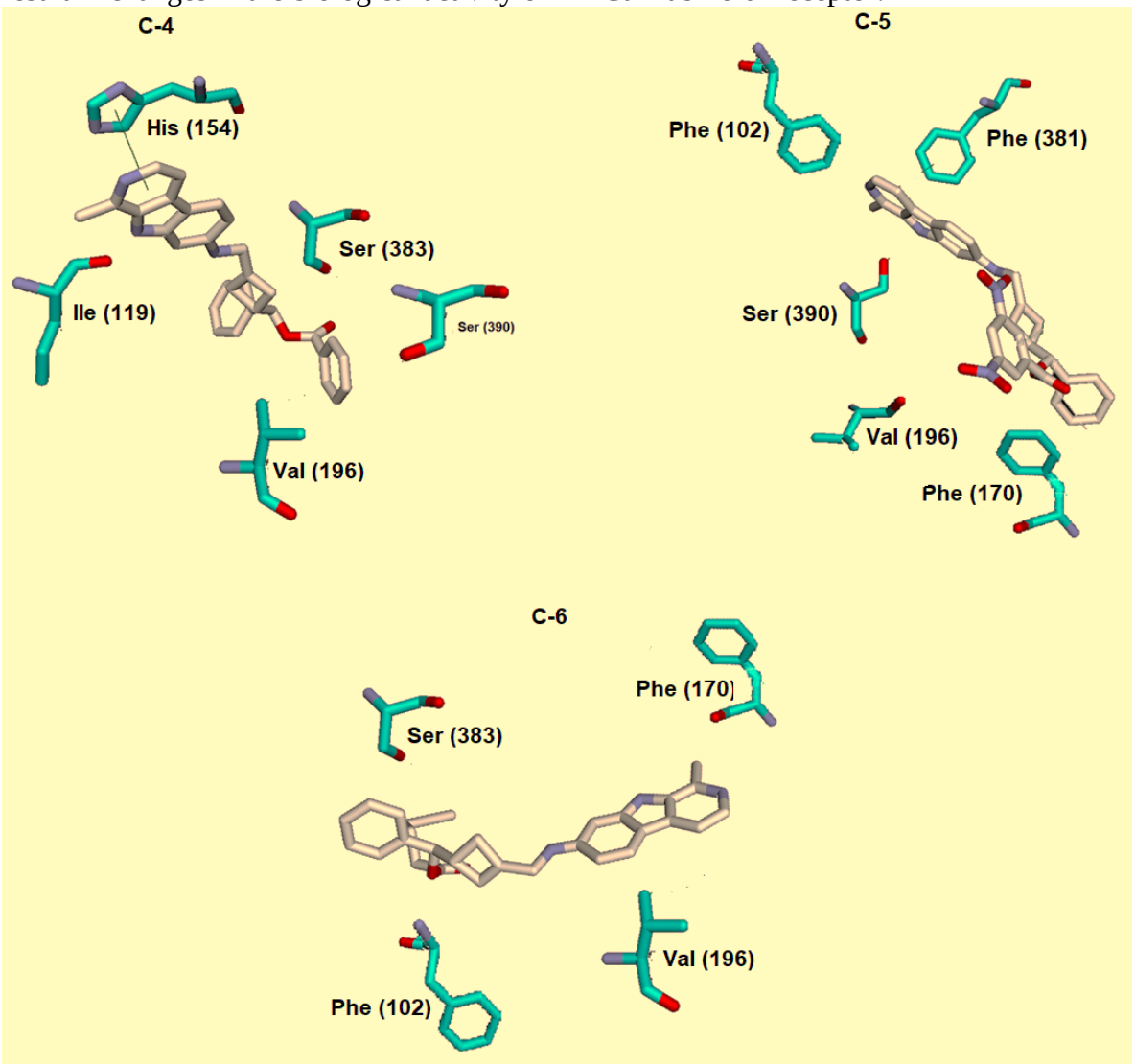

Figure 4. the scheme shows the binding sites of compound 4 (C-4), 5 (C-5) and 6 (C-6) with some aminoacid residues involved on 5tgz protein surface. The visualization was carried out using Achilles blind docking server[xix].

Table 1. Hydrophobic Interactions of Tetrahydrocannabinol, AM-251 and compounds **4**-**6** with 5tgz protein surface.

Compound	Chain A	Distance
Tetrahydrocannabinol	Phe_{363}	3.63
	Glu_{133}	3.45
	Leu_{136}	3.65
	Val_{137}	3.97
	Val_{140}	3.56
	Ile_{395}	3.94
	Ala_{398}	3.52
	Lu_{404}	3.89
	Phe_{408}	3.64
AM-251	Gln_{115}	3.59
	Ile_{119}	3.75
4	Ile_{141}	3.98
	Arg_{148}	3.97
	Val_{161}	3.83
	Leu_{165}	3.51
	Trp_{241}	3.37
	Thr_{242}	3.64
	Ile_{245}	3.48
5	Ile_{119}	3.79
	Ala_{120}	3.60
	His_{178}	3.84
	Ala_{380}	3.65
	Phe_{381}	3.82
6		

Table 2. Hydrogen Interactions of Tetrahydrocannabinol, AM-251 and compounds **4**-**6** with 5tgz protein surface.

Compound	Chain A	Distance
Tetrahydrocannabinol	Pro_{394}	2.20
AM-251	His_{178}	3.18
4	His_{154}	3.78
5	Ile_{105}	2.36
	His_{178}	2.37
6	His_{178}	3.78

CONCLUSIONS

In this research an easy method for the preparation of three ester-harmol amide derivatives (compounds **4** to **6**) using some chemical strategies is reported; It is noteworhy that the yielding obtained is good. On the other hand, other data showed that compounds **4** to **6** could bind to different types of amino acid residues involved in 5gtz protein surface compared with tetrahydrocannabinol and AM-251 drugs. All these data suggest that compounds **4** to **6** may exert changes in the biological activity of B1 cannabinoid receptor.

ACKNOWLEDGEMENT

None

REFERENCES

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

ii. Sofuoglu, M.; Sewell, R.; Norepinephrine and stimulant addiction; Addiction biology; 2009, **14**(2), 119.

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

iv. Lu, H.; Mackie, K.; An introduction to the endogenous cannabinoid system; Biological psychiatry; 2016, **79**(7), 516.

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

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

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

viii. Xi, Z.; Gilbert, J.; Peng, X.; Pak, A.; Li, X.; Gardner, E.; Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-primed relapse in rats: role of glutamate in the nucleus accumbens; Journal of Neuroscience; 2006, **26**(33), 853.

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

x. Moreira, F.; Crippa, J.; The psychiatric sideeffects of rimonabant; Brazilian Journal of Psychiatry; 2009, **31**(2), 145.

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

xii. Yamada, K.; Rice, K.; Flippen-Anderson, J.; Eissenstat, M.; Ward, S.; Johnson, M.; Howlett, A.; (Aminoalkyl) indole isothiocyanates as potential electrophilic affinity ligands for the brain cannabinoid receptor; *Journal of medicinal chemistry*; 1996, **39**(10), 1967.

xiii. Tseng, S.; Hung, M.; Chang, C.; Song, J.; Tai, C.; Chiu, H.; Shia, K.; Bioisosteric replacement of the pyrazole 5-aryl moiety of N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-1 H-pyrazole-3-carboxamide (SR141716A). A novel series of alkynylthiophenes as potent and selective cannabinoid-1 receptor antagonists; Journal of medicinal chemistry; 2008, **51**(17), 5397.

xiv. Wu, C.; Hung, M.; Song, J.; Yeh, T.; Chou, M.; Chu, C.; Shia, K.; (2009). Discovery of 2-[5-(4-Chloro-phenyl)-1-(2, 4-dichloro-phenyl)-4-ethyl-1 H-pyrazol-3-yl]-1, 5, 5-trimethyl-1, 5-dihydro-imidazol-4-thione (BPR-890) via an Active Metabolite. A Novel, Potent and Selective Cannabinoid-1 Receptor Inverse Agonist with High Antiobesity Efficacy in DIO Mice; Journal of medicinal chemistry; 2009, **52**(14), 4496.

xv. Figueroa- Valverde, L.; Diaz-Cedillo, F.; Rosas-Nexticapa, M.; Mateu-Armand, V.; Lopez-Ramos, M.; Estrella, R.; Design and Synthesis of Two Methylthiosteroid-Oxirenol Derivatives: Theoretical Evaluation of Their Interaction with B1-Cannabinoid Receptor; Journal of Biochemical Technology; 2019, **10**(4), 29.

xvi. Banister, S.; Adams, A.; Kevin, R.; Macdonald, C.; Glass, M.; Boyd, R.; Gerona, R.; Synthesis and pharmacology of new psychoactive substance 5F-CUMYL-P7AICA, a scaffold-hopping analog of synthetic cannabinoid receptor

agonists 5F-CUMYL-PICA and 5F-CUMYL-PINACA; Drug testing and analysis; 2019, **11**(2), 279.

xvii. Figueroa-Valverde, L.; Díaz-Cedillo, F.; Rosas-Nexticapa, M.; Mateu-Armad, M; López-Ramos, M.; Lopez-Gutierrez, T.; Alvarez-Ramirez, M.; Cervantes-Ortega, C.; Cauich-Carrillo, R.; Design and Synthesis of Two Azete Derivatives Using some Chemical Strategies; Biointerface Research in Applied Chemistry; 2022, **12**(4), 5567.

xviii. Figueroa- Valverde, L.; Diaz-Cedillo, F.; Rosas-Nexticapa, M.; Mateu-Armand, V.; Lopez-Ramos, M.; Estrella, R.; Design and Synthesis of Two Methylthiosteroid-Oxirenol Derivatives: Theoretical Evaluation of Their Interaction with B1-Cannabinoid Receptor; Journal of Biochemical Technology; 2019, **10**(4), 29.

xix. Sánchez-Linares,I.; Pérez-Sánchez, H.; José, C.; García, J.; High-throughput parallel blind virtual screening using BINDSURF; BMC Bioinformatics; 2012, **13**, S13.

xx. Shirayev A.; Moiseev I.; Karpeev, S.; Synthesis and cis/trans isomerism of N-alkyl-1,3-oxathiolane-2imines; Arkivok; 2005, **4**, 199.

xxi. Bhowon M.; Solventless synthesis of imines derived from dyphenyldisulphide diamine or p-Vanilin; E-journal of Chemistry; 2009, **6**(S1), 195.

xxii. Hania, M.; Synthesis of some imines and investigation of their biological activity; E-journal of Chemistry; 2009, **6**(3), 629.

xxiii. Eftekhari-Sis, B.; Zirak, M.; α-Imino esters in organic synthesis: recent advances; Chemical Review*s*; 2017, **117**(12), 8326.

xxiv. Figueroa-Valverde, L.; Diaz-Cedillo, F.; García-Cervera, E.; Gómez, P.; Rosas-Nexticapa, M.; López-Ramos, M.; May-Gil, I.; Design and Synthesis of an Aromatic-steroid Derivative; Oriental Journal of. Chemistry; 2013, **29**, 465.

xxv. Reed, M.; Pollart, D.; Perri, S.; Foland, L.; Moore, H.; Synthesis of 4-substituted-3-alkoxy-3-cyclobutene-1,2-diones; The Journal of Organic Chemistry; 1988, **53**(11), 2477.

xxvi. Xu, H.; Zhang, W.; Shu, D.; Werness, J.; Tang, W.; Synthesis of cyclobutenes by highly selective transition-metal-catalyzed ring expansion of cyclopropanes; Angewandte Chemie International Edition; 2008, **47**(46), 8933-8936.

xxvii. Frébault, F.; Luparia, M.; Oliveira, M.T.; Goddard, R.; Maulide, N.; A versatile and stereoselective synthesis of functionalized cyclobutenes; Angewandte Chemie International Edition; 2010, **49**(33), 5672.

xxviii. Huang, D.; Rayabarapu, D.; Li, L.; Sambaiah, T.; Cheng, C.; Nickel-catalyzed cycloaddition of alkynes with activated cyclic alkenes: synthesis and novel ring expansion studies of cyclobutene products; Chemistry-A European Journal; 2000, **6**(20), 3706.

xxix. Chao, K.; Rayabarapu, D.; Wang, C.; Cheng, C.; Cross [2+2] cycloaddition of bicyclic alkenes with alkynes mediated by cobalt complexes: A facile synthesis of cyclobutene derivatives; The Journal of Organic Chemistry; 2001, **66**(26), 8804.

xxx. Barluenga, J.; Riesgo, L.; López, L.; Rubio, E; Tomas, M.; Discrimination of Diazo Compounds Toward Carbenoids: Copper (I)-Catalyzed Synthesis of Substituted Cyclobutenes; Angewandte Chemie; 2009, **12***1*(41), 7705.

xxxi. Jiang, H.; Fan, M.; Wang, J.; Sarma, A.; Mohanty, S.; Dokholyan, N.; Kandemir, M.; Guiding Conventional Protein–Ligand Docking Software with

Convolutional Neural Networks; Journal of Chemical Information and Modeling; 2020, **60**(10), 4594.

xxxii. Tao, X.; Huang, Y.; Wang, C.; Chen, F.; Yang, L.; Ling, L.; Chen, X.; Recent developments in molecular docking technology applied in food science: a review. International Journal of Food Science & Technology; 2020, 55(1), 33.

xxxiii. Figueroa-Valverde, Lauro; Díaz-Cedillo, F.; López-Ramos, M.; Rosas-Nexticapa, M.; Alvarez-Ramirez, M.; Mateu-Armad, M.; Lopez-Gutierrez, T.; Cervantez-Ortega, C.; Benitez-Coeto, L.; Cauch-Carrillo, R.; Synthesis of an Adamantyl Derivative and their Theoretical Interaction with both COX-1 and COX-2 Enzymes; 2022, **12**(5), 5884.

xxxiv. Figueroa-Valverde, L.; Alvarez-Ramirez, A.; Rosas-Nexticapa, M.; Díaz-Cedillo, F.; López-Ramos, T.; Mateu-Armad, V.; Lopez-Gutierrez, T.; Cauich-Carrillo R.; Synthesis of Two Testosterone Derivatives and their Theoretical Evaluation as Serotonin Reuptake Transporter Inhibitors; Biointerface Research in Applied Chemistry; 2020, **11**(5), 12462.

xxxv. López-Ramos, M.; Figueroa-Valverde, L.; Díaz-Cedillo, F.; Rosas-Nexticapa, M.; Mateu-Armad, M.; Garcimarrero, A.; Gutierrez-Lopez, T.; Alvarez-Ramirez, M.; Ortiz-Ake, Y.; Cauich-Carrillo, Regina.; Synthesis of a Bis-oxabicyclo[5.4.0] Derivative and their Theoretical Evaluation as a Dopamine, Serotonin Transporters Inhibitor; Biointerface Research in Applied Chemistry; 2021, **11**(3) , 10746.

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

xxxvii. Yu, J.; Xue, Y.; Wang, Y.; Liu, C.; Chen, L.; In vivo Bidirectional Modulation of Cannabinoid on the Activity of Globus Pallidus in Rats; Neuroscience; 2021, **468**, 123.

xxxviii. Ruiz, C.; Torrens, A.; Castillo, E.; Perrone, C.; Cevallos, J.; Inshishian, V.; Mahler, S.; Pharmacokinetic, behavioral, and brain activity effects of Δ9-tetrahydrocannabinol in adolescent male and female rats; Neuropsychopharmacology; 2021, **46**(5), 959.

Received on 5 July 2022.