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SYNTHESIS OF A SERIES OF 2,4-DIOXABICYCLO[3.3.1]NONA-1(9),5,7-TRIENE DERIVATIVES AND THEORETICAL ACTIVITY EVALUATION ON BOTH μ AND κ-OPIOIDRECEPTORS

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Abstract
Opioids have been used for the treatment of chronic pain; however, some of these drugs may produce some side effects such as addiction, respiratory depressant, sedation, dizziness, nausea, vomiting and constipation. The aim of this study was to synthesize a series of 2,4-dioxabicyclo[3.3.1]nona-1(9),5,7-triene derivatives (compounds **2** to**10**)to evaluate theirtheoretical activity on both μ and κ-opiodreceptors using a Docking model.The preparation of **2** to**10** was carried out using a series of reactions which involves formylation,etherification, and addition. It is noteworthy that chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. The results showed that compound **4**to**10** could bind to different type of aminoacid residues involved in of 4djh 4dkl proteins surface compared anastrozole and exemestane; this phenomenon, may exert changes in the biological activity of both μ and κ-opiodreceptors. All data suggest that compound **9** or **10** could be an alternative therapeutic for treatment of the pain.

Keywords: Azete, steroid, derivative, docking model.

Introduction

For several years, some medications have been used for the treatment of pain such as codeine, fentanyl, buprenorphine, butorphanol[i,ii]. There are data indicating that these drugs can exert their effect through the activation of opioid receptors (μ, δ, κ, ε)[iii-vi]. However, some these drugs can cause some adverse effects such addiction[vii] respiratory depressant[viii], sedation, dizziness, nausea, vomiting, constipation[ix]. In the search ofnew therapeutic alternatives for treatment of pain, some drugs have been prepared; for example, a study showedthe synthesis of compound 14-Alkoxymorphinans.2.1(-)-JV-(Cyclopropylmethyl)-4,14-dimethoxy-morphinan-6-one with high affinity by μ-opioid receptorin an isolatedguineapigmusclepreparations[x]. In addition, an acetamidederivative(k-receptor agonist)was prepared to evaluate theiranalgesicactivity using a rat model[xi]. Other study showed that a k-receptor agonist (U-50,4H8) was synthetized and their biological activity was evaluated in a guinea pig model[xii]. Other data describes the synthesis of 2-[(Acylamino)ethyl]-l,4-benzodiazepines and their interaction with k-opioid receptor using a theoretical docking model[xiii]. Also, a report showed that both arylacetamide and benzomorphan derivatives could interact withk-opioidreceptor using a pharmacophoremodel[xiv]. Additionally, a study has shown the preparation and interaction of a piperidine analog withk-opioidreceptor using a docking model[xv]. Other data showed the preparation of a series from 4-(N, N-diarylamino) piperidines with high selectivity to the delta-opioid receptor using both 3D-QSAR and Docking models[xvi].All these data indicate that some drugs may interact with different types of opioid-receptors; this phenomenon could be due to different functional groups involved in the chemical structure or to diverse protocols used. The aim of this study was synthesizing a series of 2,4-dioxabicyclo[3.3.1]nona-1(9),5,7-triene derivatives to evaluate their theoretical interaction with both μ and k-opioidreceptors.

Results and Discussion

In this study were prepared a series of 2,4-dioxabicyclo[3.3.1]nona-1(9),5,7-triene derivatives using several strategies; the first stage was achieved for the synthesis of a 2-nitro-estrone-3-carbaldehyde (**2**). It is important to mention there are several reports on the oxidation of primary alcohols to form the corresponding aldehydes. These compounds can be prepared with some methods which are accomplished by stoichiometric amounts of metallic oxidants such as chromium(VI) palladium, rhodium or ruthenium and hydrogen peroxide reagents[xvii]. However, these reagents may induce risks of toxicity by generation of several substances involved on some reaction mixtures. In this study a previously methodreported[xviii] for oxidation of hydroxyl groups was used for formation of compound **2** via reaction of 2-nitroestrone (**1**) with DMSO (Figure 1). The ^{1}H NMR spectrum of the compound **2** showed several signals at 0.92 ppm for methyl group bound steroid nucleus; at 1,22-8.02 ppm for steroid moiety; at 10.80 ppm for aldehyde group. The ^{13}C NMR spectra display chemical shifts at 13.82 ppm for methyl group; at 21.70-151.75 ppm for steroid moiety; at 194.22 ppm for aldehyde group; at 219.76 ppm for ketone group. In addition, the mass spectrum from **2** showed a molecular ion (m/z) 327.14.

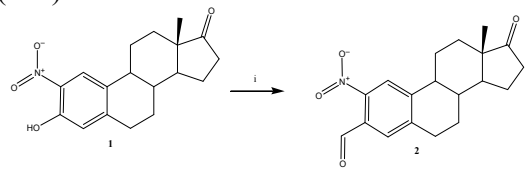

Figure 1.Preparation of 2-nitroestradiol carbaldehyde (**2**).Reaction of 2-nitroestradiol with dimethyl sulfoxide (i) to for the compound **2**.

Etherification reaction

There are several studies which showed the preparation of some ether derivatives via displacement of nitro group using methoxide as dipolar aprotic solvent[xix,xx]. In this study, the compound 1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene-7-carboxylic acid (**4**) was prepared by the reaction of ninhydrin with 3,5-dinitrobenzoic acid in presence of dimethyl sulfoxide at mild conditions (Scheme2). The ^{1}H NMR spectrum of the compound **4** showed several signals at 3.32-3.36 and 7.24-7.33 ppm for indene adduct; at 5.68 ppm for carboxyl group; at 6.10-6.64 ppm for phenyl group. The ^{13}C NMR spectra display chemical shifts at 44.20-67.10, 125.50-126.44 and 133.12 ppm for indene adduct; at 95.60-116.00, 128.12 and 150.62 ppm for phenyl group; at 168.74 ppm for carboxyl group. In addition, the mass spectrum from **4** showed a molecular ion (m/z) 268.07.

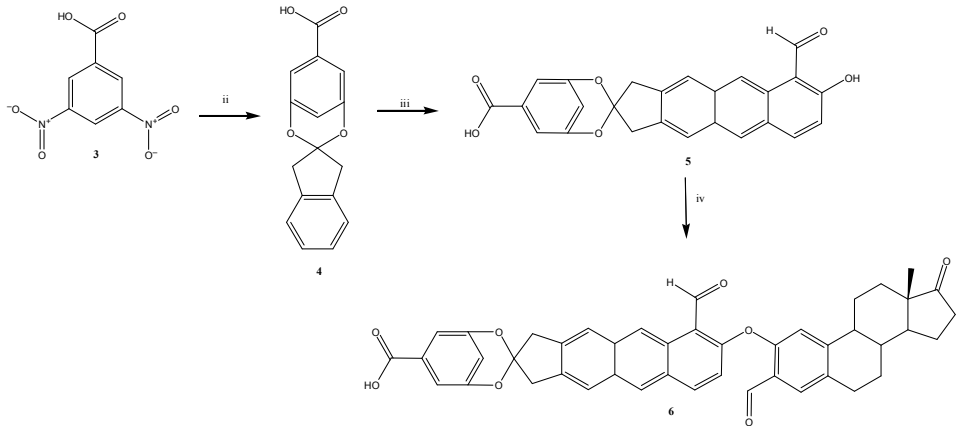

Figure 2. Preparation of formyl-oxo-cyclopenta[a]phenanthren-2,4-dioxaspiro-steroid-carboxylic acid derivative (**6**). Reaction of 3,5-dinitrobenzoic acid with ninhydrin [ii] to form a dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-carboxylic acid analog (**4**). Then, **4** reacted with 2-Hydroxy-naphthalene-1-carbaldehyde (iii) to synthesis of a 6'-formyl-7'-hydroxy-dioxaspiroanthracene-carboxylic acid derivative (**5**): Finally, **6** was prepared by the reaction of **5** with 2-nitroestradiol carbaldehyde (iv).

Addition reaction

Several compounds have been prepared through of addition reactions using some reagents such as palladium[xxi], zinc trifluoromethanesulfonate[xxii], CuBr[xxiii], CuLi[xxiv] and others. In this investigation, was prepared a 2,4-dioxaspiro[bicyclo[3.3.1]nonane-carboxylic acid derivative (**5**) via 2+2 addition of 2-Hydroxy-naphthalene-1-carbaldehyde to compound **4** using Copper(II) as catalyst. The ^{1}H NMR spectrum of the compound **5** showed several signals at 2.26-5.40 and 6.64-7.02 ppm for tetrahydro-1H-cyclopenta[b]anthracene fragment; at 6.10-6.62 ppm for phenyl group bound to carboxyl group; at 8.12 ppm for both carboxyl and hydroxyl group; at 9.92 ppm for aldehyde group. The ^{13}C NMR spectra display chemical shifts at 41.66-68.51, 111.12-113.16, 118.30-128.27, 131.00-152.00 and 167.02 ppm for tetrahydro-1H-cyclopenta[b]anthracene fragment; at 95.32, 115.72, 128.65 and 153.82 ppm for phenyl group bound to carboxyl; at 168.74 ppm for carboxyl group; at 187.78 ppm for aldehyde group. In addition, the mass spectrum from **5** showed a molecular ion (m/z) 414.11.

Second etherification reaction

A new etherification was carried out via reaction of **5** withthe 2-nitroestronecarbaldehide derivative (**2**). The ^{1}H NMR spectrum of the compound **6** showed several signals at 0.92 ppm for methyl group bound to steroid nucleus; at 1.22-2.22, 2.45-2.56, 2.84-2.86 and 7.02-7.78 ppm for steroid moiety; at 2.24, 2.76, 3.20-5.40, 6.54 and 7.00 ppm for tetrahydro-1H-cyclopenta[b]anthracene fragment; at 5.68 ppm for carboxyl group; at 6.08 and 6.64 ppm for phenyl group bound to carboxyl group; at 10.02-10.22 ppm for both aldehyde groups. The

^{13}C NMR spectra display chemical shifts at 13.80 ppm for methyl group; at 21.80-37.52, 48.10-50.40, 112.77, 122.53, 130.63-131.07, 149.56 and 155.75 ppm for steroid moiety; at 41.68-46.34, 68.53, 111.15, 118.82, 123.80-124.69, 136.47-140.50, 150.26 and 172.40 ppm for tetrahydro-1H-cyclopenta[b]anthracene fragment; at 95.29, 115.72, 128.62 and 153.82 ppm for phenyl bound to carboxyl group; at 168.74 ppm for carboxyl group; at 185.00-190.70 ppm for aldehyde groups; at 220.70 ppm for ketone group. In addition, the mass spectrum from **6** showed a molecular ion (m/z) 694.25.

Thirdetherification reaction

The compound **8** was prepared via etherification of 3,4-dinitrofluorobenzene with ninhydrin in presence of dimethylsulfoxideat mild conditions. The ^{1}H NMR spectrum of the compound **8** showed several signals at 3.32-3.40 and 7.24-7.33 ppm for indene adduct; at 5.66-7.00 ppm for phenyl group. The ^{13}C NMR spectra display chemical shifts at 44.20-67.04 and 125.50-132.10 ppm indene adduct; at 98.40-114.84 and 146.33-149.93 ppm for phenyl group. In addition, the mass spectrum from **8** showed a molecular ion (m/z) 242.07.

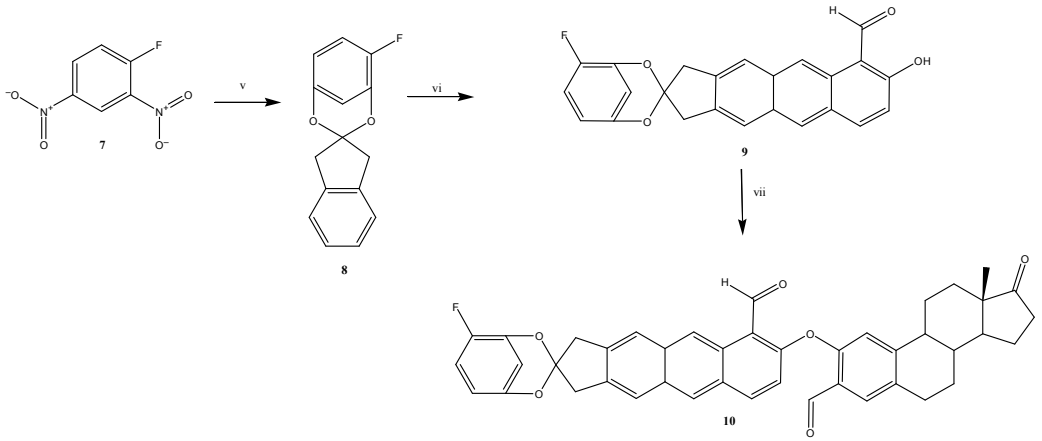

Figure 3.Synthesis of formyl-oxo-cyclopenta[a]phenanthren-8-fluoro-2,4-dioxaspiro-steroid-carbaldehyde derivative (**10**). Reaction of 2,4-dinitrofluorobenzene with ninhydrin [v] to form 8-fluoro-1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene **(8)**. Then, **8**reacted with 2-Hydroxy-naphthalene-1-carbaldehyde (vi) to synthesis of 8-fluoro-7'-hydroxy-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-cyclopenta[b]anthracene]-1(9),5,7-triene-6'-carbaldehyde (**9**). Finally, **10**was prepared by the reaction of **9** with 2-nitroestradiol carbaldehyde (vii).

Second addition reaction

The compound **9** was prepared via 2+2 addition of 2-Hydroxy-naphthalene-1-carbaldehyde to **8**. The ^{1}H NMR spectrum of the compound **9** showed several signals at 2.20-5.40 and 6.64-7.10 ppm for tetrahydro-1H-cyclopenta[b]anthracene fragment; at 5.62-6.46 ppm for phenyl group bound to fluoride; at 9.92 ppm for aldehyde group; at 10.52 for hydroxyl group. The ^{13}C NMR spectra display chemical shifts at 41.64-68.10, 113.17, 115.44-140.52, 152.00 and 167.02 ppm for tetrahydro-1H-cyclopenta[b]anthracene fragment; at 98.10-108.46, 115.30, 149.40-149.52 and 153.10 ppm for phenyl bound to fluoride; at 187.74 ppm for aldehyde group. In addition, the mass spectrum from **9** showed a molecular ion (m/z) 388.11.

Fourth etherification reaction

The compound **10** was synthetized via etherification of **9** with 2-nitroestronecarbaldehide derivative (**2**) in presence of dimethylsulfoxideat mild conditions. The ^{1}H NMR spectrum of the compound **10** showed several signals at 0.92 ppm for methyl group bound to steroid nucleus; at 1.22-2.220, 2.46-2.56, 2.84-2.86, 7.02 and 7.76 ppm for steroid moiety; at 2.22-2.28, 2.78, 3.20-5.40 and 6.54-7.00 ppm for tetrahydro-1H-cyclopenta[b]anthracene

fragment; at 5.62-6.46 and 7.10 ppm for phenyl group bound to fluoride; at 10.02-10.22 for aldehyde groups. The ^{13}C NMR spectra display chemical shifts at 13.80 ppm for methyl group bound to steroid nucleus; at 21.70-37.42, 46.88-50.22, 112.74, 122.52-124.69, 130.62, 131.02-140.50, 149.59 and 155.72 ppm for steroid moiety; at 41.68-46.34, 68.53, 115.48, 123.12, 136.47, 150.23 and 172.40 ppm for tetrahydro-1H-cyclopenta[b]anthracene fragment; at 98.12-108.49, 115.31, 149.40-149.52 and 153.10 ppm for phenyl group bound to fluoride; at185.00-190.70 ppm for aldehyde groups; at 220.20 ppm for ketone group. In addition, the mass spectrum from **9** showed a molecular ion (m/z) 668.25.

Electronic parameters

Molecular orbitals and frontier electron density have been used to predict the most reactive position in some electron system on several types of reactions which are translated as changes in the biological activity produced of several compounds against some biomolecules[xxv,xxvi].

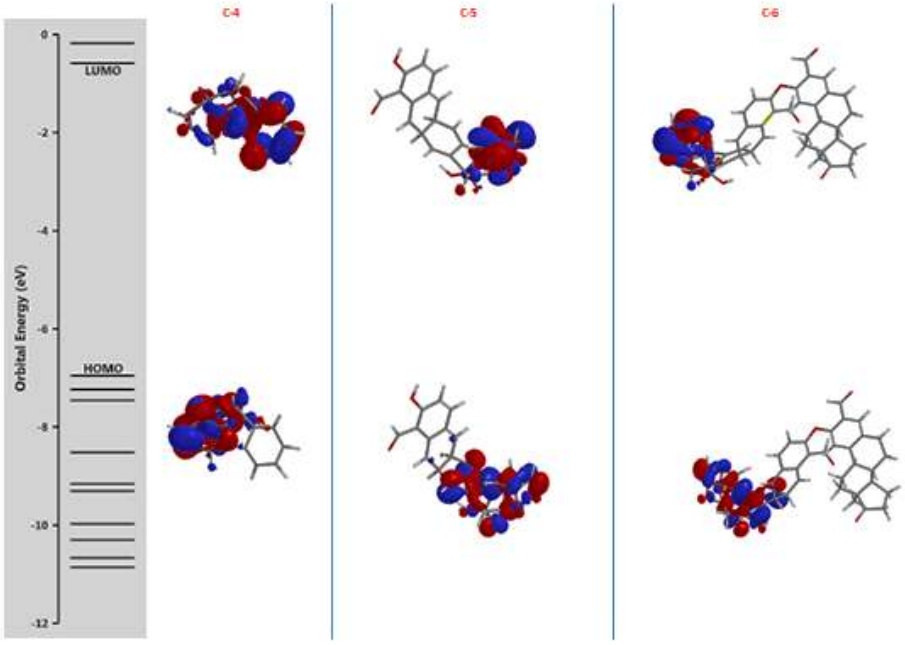

Figure 4. Molecular orbitals (HOMO and LUMO) involved in the compounds **4** (C-4), **5** (C-5) and**6**(C-6). Visualized with SPARTAN'06 software

These studies indicate that values of highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) and their energy gap reflect the chemical activity of a molecule[xxvii]. 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, a study showed the determination of frontier molecular orbitals (HOMO-LUMO gap) from some steroid using MINDO and ZINDO models[xviii,xix]. Other report indicates that 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) have been used to determinate both HOMO and LUMO orbitals of some compounds. Therefore, in this study these parameters were evaluated for either compounds **4** to **10** (Figure 4 and 5; Table 1) using Spartan'06 V112 program[xxx].

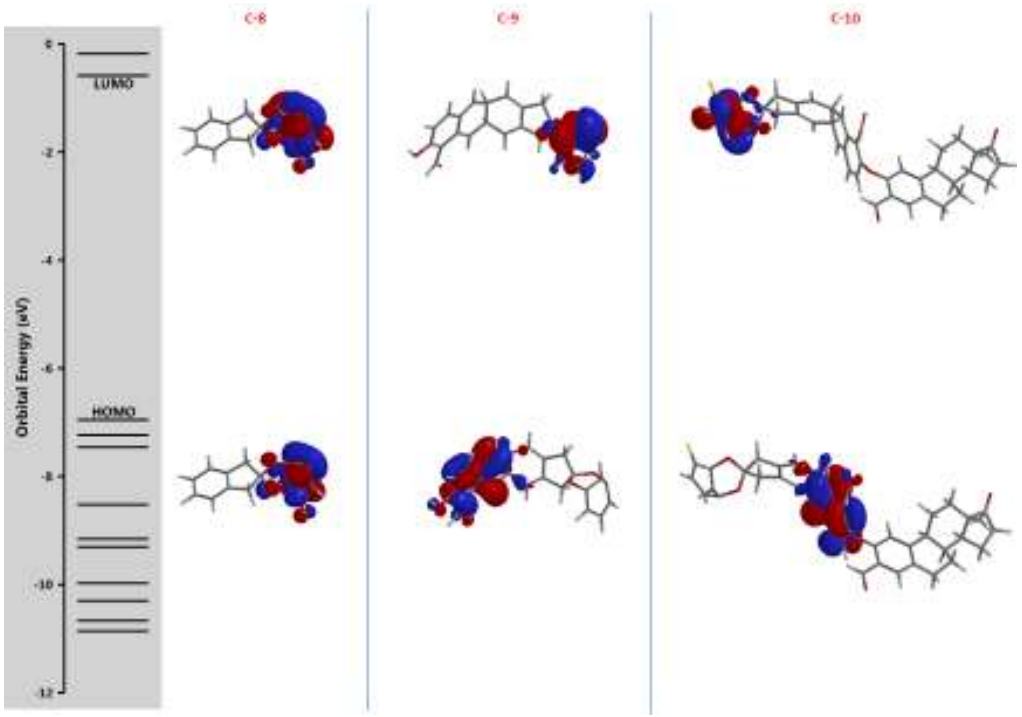

Figure 5. Molecular orbitals (HOMO and LUMO) involved in the compounds **8** (C-8), **9** (C-9) and **10** (C-10). Visualized with SPARTAN'06 software

Table 1. Physicochemical parameters involved chemical structure of compounds **8** and **9**. The values were calculated using both ACDLabs and Spartan software.

Prameters	**C-4**	**C-5**	**C-6**	**C-8**	**C-9**	**C-10**
Molar Refractivity (cm^3)	71.02	109.58	1.88.96	64.85	103.41	182.79
Molar Volume(cm^3)	184.20	266.80	480.40	178.60	261.40	475.30
PSA ($Å^2$)	41.15	73.30	90.16	47.12	14.51	63.90
Dipole Moment (debyete)	10.72	10.69	6.85	6.79	2.06	5.85
Polarizability	60.19	71.13	94.54	69.78	58.66	93.19
Parachor (cm^3)	532.50	798.10	1406.70	479.40	745.00	1353.50
Surface Tension (dyne/cm)	69.70	80.00	73.50	51.80	65.90	65.70
Density (g/cm^3)	1.45	1.55	1.44	1.35	1.48	1.40
E. HOMO (Ev)	-6.29	-6.95	-7.06	-7.12	-7.57	-7.34
E. LUMO (Ev)	-0.17	-0.58	-0.67	0.68	0.54	0.47
HBD	1	2	1	1	0	0
HBA	3	5	7	4	2	6
LogP	3.46	0.97	5.40	1.57	4.06	6.00

The results showed differences in both HOMO and LUMO values for the compounds **4** to **10**; this phenomenon could be conditioned by the difference in π orbitals density located in their chemical structure of either compounds **4** to **10**.

Pharmacophore ligand model

Several chemical models have been used to determine the three-dimensional orientation adopted by the functional groups of a molecule to predict its interaction with some biomolecules[xxxi]; 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[xxxii]. Therefore, in this investigation, a pharmacophore model for compounds **4** to **10**(Figures6 and 7)was determinate using the LigandScoutprogram[xxxiii].The results showed that functional groups involved in the chemical

structure of either compounds **4** to **10** may interact via hydrophobic contacts or as hydrogen bond acceptors or as hydrogen bond donor with some biomolecules.

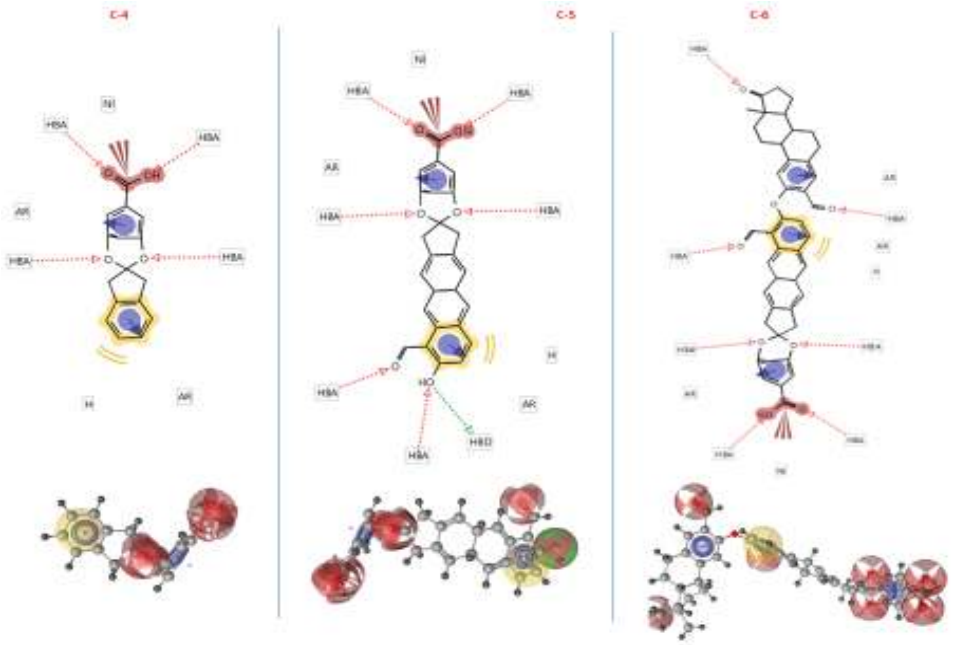

Figure 6. Scheme represents a pharmacophore from both compounds **4** (C-4), **5** (C-5)and**6** (C-6)using the LigandScout 4.0 software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, green).

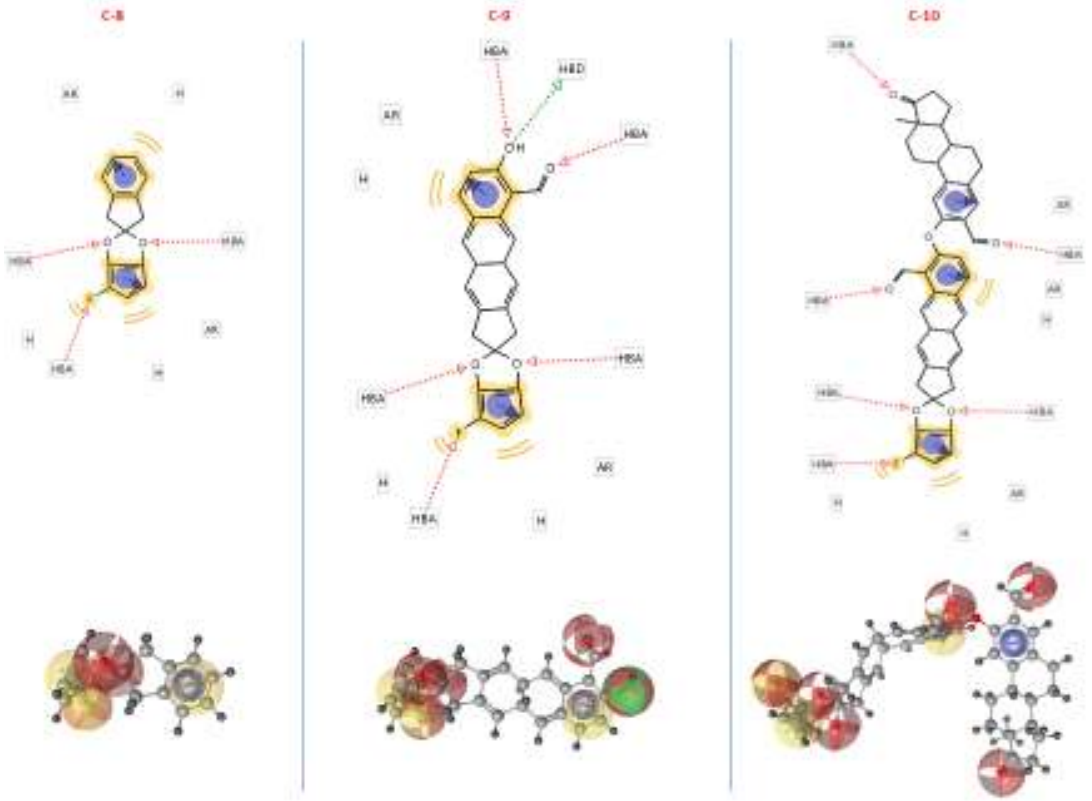

Figure 7. Scheme represents a pharmacophore from the compounds **8** (C-8), **9** (C-9)and**10** (C-10)using the LigandScout 4.0 software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red) and hydrogen bond donor (HBD, green).

Interaction theoretical (protein-ligand)

Several studies indicate 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[xxxiv]. Analyzing these data, a theoretical analysis was carried out on the interaction of either compounds **4** to **10** with the both 4djh (μ-opioidreceptor) [43] and 4dkl (κ-opioidreceptor)[xxxv] proteins using some drugs such as morphine (μ-opioid receptor agonist)[xxxvi], fentanyl (μ and κ-opioid receptor agonist)[xxxvii], naloxone (non-selective opioid receptors antagonist)[xxxviii], butorphanol (opioid-receptors agonist/antagonist)[xxxix], salvorin-A (κ-opioid receptor antagonist)[XL] [49] and pentazocina (opioid-receptors agonist/antagonist) [50] as chemical tools in a Docking model[XLi] [24]. The data (Tables 2 and 3) showed differences in the interaction of both compounds **4** to **10** with some aminoacid residues involved in both 4dkl and 4djh proteins surface. In addition, other data suggest that there is another type of aminoacid residues in the interaction of morphine, fentanyl, naloxone, Butorphanol, Salvorin-A and Pentazocina with either both 4dkl and 4djh proteins. This phenomenon could be conditioned by the different conformations adopted by the compounds **4** to **10** or the length of bound between the steroid-derivatives and the aminoacid residues involved in both 4dkl and 4djh proteins surface.

Table 2.Aminoacid residues involved in the interaction ofmorphine, butherphenol, naloxone, fentanyl and compounds **4**to**10**with4dkl protein surface.

Morphine	Butherphenol	Naloxone	Fentanyl	C-4	C-5	C-6	C-7	C-8	C-10
Ile_{144} Asp_{147} Tyr_{148} Met_{151} Leu_{219} Val_{236} Trp_{293} Ile_{296} His_{297} Val_{300} Tyr_{326}	Ile_{144} Asp_{147} Tyr_{148} Met_{151} Leu_{219} Trp_{293} Val_{300} Ile_{322} Tyr_{326}	Asp_{147} Tyr_{148} Met_{151} Trp_{293} Ile_{296} Val_{300} Ile_{322} Tyr_{326}	Gln_{124} Tyr_{128} Val_{143} Ile_{144} Asp_{147} Met_{151} Val_{236} Ile_{296} His_{297} Ile_{322} Tyr_{326}	Val_{108} Trp_{111} Asp_{138} Asn_{141} Trp_{287} Ile_{316} Tyr_{320}	Asp_{147} Tyr_{148} Met_{151} Trp_{293} Ile_{296} Val_{300} Trp_{318} Ile_{322}	Gln_{124} Val_{143} Ile_{144} Asp_{147} Tyr_{148} Met_{151} Ile_{296} Val_{300} Tyr_{326}	Asp_{147} Met_{151} Trp_{293} Ile_{296} His_{297} Val_{300} Ile_{322} Tyr_{326}	Asp_{147} Tyr_{148} Met_{151} Trp_{293} Ile_{296} Val_{300} Ile_{322}	Gln_{124} Asn_{127} Trp_{1133} Ile_{144} Asp_{147} Tyr_{148} Cys_{217} Lys_{233} Ile_{298} Val_{300} Trp_{318} Ile_{322}

Table 3.Aminoacid residues involved in the interaction ofmorphine, butherphenol, naloxone, fentanyl and compounds **4** to**10**with 4djh protein surface.

Morph	Butherph	Naloxone	Fentanyl	Salvinorin	Pentazocina	C-4	C-5	C-6	C-8	C-9	C-10
Thr_{111} Gln_{115} Trp_{124} Val_{134} Leu_{135} Asp_{138} Tyr_{312} Ile_{316} Tyr_{320}	Asp_{138} Tyr_{139} Met_{142} Lys_{227} Val_{230} Trp_{287} Ile_{290} His_{291} Ile_{294} Ile_{316}	Asp_{138} Tyr_{139} Met_{142} Ser_{211} Leu_{2212} Ile_{294} Tyr_{312} Ile_{294} Ile_{316}	Val_{108} Thr_{111} Gln_{115} Asp_{138} Asn_{141} Met_{142} Val_{230} Trp_{287} Ile_{290} His_{291} Ile_{294}	Thr_{111} Gln_{115} Val_{118} Leu_{135} Asp_{138} Ile_{194} Tyr_{312} Tyr_{313} Tr_{320}	Val_{108} Thr_{111} Asp_{138} Tyr_{139} Met_{142} Lys_{227} Trp_{287} Ile_{290} Ile_{294} Tyr_{312} Ile_{316} Tyr_{320}	Asp_{147} Met_{151} Trp_{293} Ile_{296} Ile_{322} Tyr_{326}	Val_{108} Thr_{111} Asp_{138} Asn_{141} Trp_{287} Ile_{316} Tyr_{320}	Gln_{115} Leu_{135} Asp_{138} Tyr_{139} Met_{142} Val_{230} Trp_{287} Ile_{290} His_{291} Ile_{294} Tyr_{312} Ile_{316}	Thr_{111} Phe_{114} Gln_{115} Trp_{124} Val_{134} Leu_{135} Asp_{138} Cys_{210} Tyr_{320}	Thr_{111} Gln_{115} Trp_{124} Val_{134} Leu_{135} Asp_{138} Cys_{210} Tyr_{312} Tyr_{320}	Val_{108} Thr_{111} Gln_{115} Trp_{124} Val_{134} Leu_{135} Asp_{138} Tyr_{139} Ser_{211} Asp_{223} Lys_{227} Ile_{294} Tyr_{312} Tyr_{320}

Morph= morphine; Butherph = butherphenol

Thermodynamicparameters

It is noteworthy that some studies indicate that some thermodynamic factors such as free energy of binding, electrostatic energy; total intermolecular energy and Van der Waals (vdW) + hydrogen bond (Hbond) + desolvation energy can be involved in the interaction of several compounds with the proteins or enzymes; in this study, these thermodynamic parameters were determinate using DockigServer[XLi]. Theoretical results (Tables4 and 5) indicate that there are differences in the thermodynamic parameters of morphine, fentanyl, naloxone, Butorphanol, Salvorin-A and Pentazocincompared with either compounds **4** to **10**. Finally, other data showed that inhibition constant (Ki) involved in the interaction of either compounds **4** to **10** with both 4dkl and 4djh proteins surface was different compared with the controls. In addition, the interaction of compounds **4**, **8** and **10** with 4kdl protein surface showed a Ki value similar at morphine. On the other hand, the binding of compounds **4**, **8** and **10** with 4djh protein surface display a Ki value similar atbutherphenol.This phenomenon could be translated as a higher affinity of compounds **4**, **8** and **10** both μ and κ-opioid receptors; however, it is important to mention that it would be interesting to carry out additional experiments in some biological models to know if compounds **4**, **8** and **10** could act as agonists or antagonists of eitherμ κ-opioid receptors.

Table 4. Thermodynamic parameters involve in the interaction of morphine, butherphenol, naloxone, fentanyl and compounds **4** to**10**with4dkl protein surface

Compound	**Est. Fee Energy of Binding (kcal/mol)**	**Est. Inhi-bition Constant, Ki (μM)**	**cdW + Hbond + desolv Energy**	**Electrost. Energy**	**Total Inter-molec. Energy**	**Interact. Surface**
Morphine	-3.46	2.93	-5.38	-0.78	-6.16	889.13
Butherphenol	-6.74	11.43	-7.67	-0.24	-7.91	780.44
Naloxone	-7.08	6.43	-7.42	-0.51	-7.93	693.17

C-4	-7.77	2.01	-7.89	-0.18	-8.07	583.37
C-5	-8.43	666.13	-8.80	-0.22	-9.02	642.96
C-6	-13.21	207.91	-13.30	-0.21	-13.50	942.88
C-8	-7.55	2.93	-7.64	0.09	-7.55	560.81
C-9	-8.33	781.66	-8.75	-0.17	-8.92	611.18
C-10	-11.84	2.09	-12.74	-0.22	-12.96	945.18
Fentanyl	-7.12	6.05	-7.90	-0.90	-8.81	862.28

Table 5. Thermodynamic parameters involve in the interaction of morphine, butherphenol, naloxone, fentanyl and compounds **4** to**10** with 4djh protein surface

Compound	**Est. Fee Energy of Binding (kcal/mol)**	**Est. Inhi-bition Constant, Ki (µM)**	**cdW + Hbond + desolv Energy**	**Electrost. Energy**	**Total Inter-molec. Energy**	**Interact. Surface**
Morphine	-6.18	29.71	-6.27	-0.63	-6.90	622.16
Butherphenol	-7.09	6.37	-7.18	-1.02	-8.20	765.93
Naloxone	-5.70	66.34	-5.52	-1.34	-6.86	730.88
Pentazocina	-7.64	2.49	-7.30	-1.19	-8.49	780.31
C-4	-7.08	6.48	-7.76	0.38	-7.38	558.48
C-5	-7.36	4.00	-8.34	0.40	-7.94	618.20
C-6	-10.46	21.57	-13.25	0.30	-12.95	1049.25
C-8	-7.16	5.62	-7.14	-0.02	-7.16	527.95
C-9	-8.56	527.64	-9.16	-0.02	-9.18	574.32
C-10	-11.29	5.30	-12.35	-0.04	-12.39	1065.47
Salvinorin-A	-5.92	45.46	-6.81	-0.24	-7.06	1088.13
Fentanyl	-7.83	1.83	-8.20	-1.27	--9.47	982.83

Conclusions

In this study, is reported a facile synthesis of a series of 2,4-dioxabicyclo[3.3.1]nona-1(9),5,7-triene derivatives with theoretical activity on both µ and κ-opiodreceptors which can be translated as good candidates for their evaluation in some biological model to pain.

Acknowledgements

None

Material and Methods

General methods

The reagents 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 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

2-Nitro-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3-carbaldehyde (2)

In a round bottom flask (10 ml), 2-nitroestrone (200 mg, 0.66 mmol), and dimethyl sulfoxide (5 ml)were stirred to reflux for 6 h. The solvent of the reaction mixture was evaporated under reduced pressure and purified through a chloroform/hexane/water (3:1:1) system to provide compound **2** (yielding 66 %); m.p. 120-122 ^{o}C; IR (V_{max}, cm^{-1}) 1740, 1712 and 1412: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 0.92 (s, 3H), 1.22-1.92 (m, 7H), 2.10-2.86 (m, 7H), 3.04-8.02 (m, 3H), 10.80 (s, 1H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C:13.82, 21.70, 25.52, 27.52, 29.61, 31.02, 35.00, 37.22, 46.40, 48.34, 50.10, 122.55, 126.24 126.49, 145.40,

150.88, 151.75, 194.22,219.76 ppm.EI-MS m/z: 327.14. Anal.Calcd.for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28, O, 19.55. Found: C, 69.68; H, 6.44.

1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene-7-carboxylic acid(4)

In a round bottom flask (10 ml), 3,5-dinitrobenzoic acid (160 mg, 0.75 mmol), ninhydrin (135 mg, 0.75mmol),dimethyl sulfoxide (5 ml) and ethanol (3 ml)were stirred to reflux for 6 h. The solvent of the reaction mixture was evaporated under reduced pressure and purified through a acetonitrile/chloroform/water (1:3:1) system to provide compound **4** (yielding 73 %);m.p. 76-78; IR (V_{max}, cm^{-1}) 1608, and 1240: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H:3.32 (m, 2H), 3.36 (m, 2H), 5.68 (broad, 1H), 6.10-6.64 (m, 3H), 7.24-7.33 (m, 4H) ppm.^{13}C NMR (300 MHz, Chloroform-*d*) δ_C:44.20, 46.23, 67.10, 95.60, 116.00, 125.50, 126.44, 128.12, 133.12, 150.62, 168.74 ppm. EI-MS m/z: 268.07. Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51; O, 23.86. Found: C, 71.60; H, 4.48.

6'-formyl-7'-hydroxy-1',3',4'a,10'a-tetrahydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-cyclopenta[b]anthracene]-1(9),5,7-triene-7-carboxylic acid (5)

In a round bottom flask (10 ml), compound **4** (200 mg, 0.48 mmol), 2-hydroxy-naphthalene-1-carbaldehyde (85 mg, 0.49 mmol) and Copper(II) chloride anhydrous (65 mg, 0.48 mmol)in 5 ml of methanol were stirred to room temperature for 48 h The solvent of the reaction mixture was evaporated under reduced pressure and purified through a chloroform/hexane/water (3:1:1) system to provide compound **5** (yielding 66 %); m.p. 176-178^{o}C; IR (V_{max}, cm^{-1}) 3400, 1740, 1608 and 1240: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H:2.26 (m, 4H), 2.78-5.40 (m, 6H), 6.10-6.62 (m, 3H), 6.64-7.02 (m, 2H), 8.12 (broad, 2H), 9.92 (s, 1H) ppm.^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 41.66, 45.72, 46.31, 68.51, 95.32, 111.12, 113.16, 115.72, 118.30, 118.8, 124.02, 124.20, 128.27, 128.65, 131.00, 137.34, 140.52, 152.00, 153.82, 167.02, 168.74, 187.78 ppm. EI-MS m/z: 414.11. Anal. Calcd. for $C_{25}H_{18}O_6$: C, 72.46; H, 4.38; O, 23.16. Found: C, 72.40; H, 4.32.

7'-{[(11aS)-7-formyl-11a-methyl-1-oxo-2H,3H,3aH,3bH,4H,5H,9bH,10H,11H-cyclopenta[a]phenanthren-8-yl]oxy}-6'-formyl-1',3',4'a,10'a-tetrahydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-cyclopenta[b]anthracene]-1(9),5,7-triene-7-carboxylic acid(6)

In a round bottom flask (10 ml), compound **5** (200 mg, 0.48 mmol), compound **2** (155 mg, 0.47 mmol), potassium carbonate (50 mg, 0.36 mmol) and dimethyl sulfoxide (5 ml) were stirred to reflux for 6 h. The solvent of the reaction mixture was evaporated under reduced pressure and purified through a methanol/hexane/water (3:1:1) system to provide compound **6** (yielding 84 %);m.p. 212.214^{o}C; IR (V_{max}, cm^{-1}) 1742, 1712, 1610 and 1242:^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 0.92 (s, 3H), 1.22-2.22 (m, 11H), 2.24 (m, 4H), 2.46-2.56 (m, 2H), 2.76 (m, 1H), 2.84-2.86 (m, 2H), 3.20-5.40 (m, 5H), 5.68 (broad, 1H), 6.08 (m, 1H), 6.54 (m, 1H), 6.64 (m 2H), 7.00 (m, 1H), 7.02-7.76 (m, 2H), 10.02 (s, 1H), 10.22 (s, 1H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C:13.80, 21.80, 25.82, 27.52, 29.61, 31.50, 35.40, 37.52, 37.88, 41.68, 45.71, 46.34, 48.10, 50.40, 68.53, 95.29, 111.15, 112.77, 115.72, 118.82, 122.52, 123.80, 124.02, 124.09, 124.11, 124.69, 128.62, 130.62, 131.07, 136.47, 136.48, 140.50, 149.56, 150.26, 153.82, 155.75, 168.74, 172.40, 185.00, 190.70, 220.70 ppm. EI-MS m/z: 694.25. Anal. Calcd. for $C_{44}H_{38}O_8$: C, 76.06; H, 5.51; O, 18.42. Found: C, 76.00; H, 5.48.

8-fluoro-1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene (8)

In a round bottom flask (10 ml), 2,4-dinitrofluorobenzene (140 mg, 0.75 mmol), ninhydrin (135 mg, 0.75mmol), dimethyl sulfoxide (5 ml) and ethanol (3 ml)were stirred to reflux for 8 h. The solvent of the reaction mixture was evaporated under reduced pressure and purified

through a chloroform/water (3:1) system to provide compound **8** (yielding 54 %);m.p. 68-70^{o}C; IR (V_{max}, cm^{-1}) 1600 and 1240: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 3.32-3.34 (m, 2H), 3.36 (m, 2H), 3.40 (m, 1H), 5.66-700 (m, 3H), 7.24-7.33 (m, 4H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 44.20, 46.22, 67.04, 98.40, 108.82, 114.84, 125.50, 126.44, 132.10, 146.33, 149.72, 149.93 ppm. EI-MS m/z: 242.07. Anal.Calcd.for $C_{15}H_{11}FO_2$: C, 74.37; H, 4.58; F, 7.84; O, 13.21. Found: C, 74.30; H, 4.52.

8-fluoro-7'-hydroxy-1',3',4'a,10'a-tetrahydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-cyclopenta[b]anthracene]-1(9),5,7-triene-6'-carbaldehyde (9)

In a round bottom flask (10 ml), compound **8** (120 mg, 0.49 mmol), 2-hydroxy-naphthalene-1-carbaldehyde (85 mg, 0.49 mmol) and Copper(II) chloride anhydrous (65 mg, 0.48 mmol)in 5 ml of methanol were stirred to room temperature for 48 h The solvent of the reaction mixture was evaporated under reduced pressure and purified through a chloroform/hexane/water (3:1:1) system to provide compound **5** (yielding 66 %);m.p. 118-120^{o}C; IR (V_{max}, cm^{-1}) 3400 and 1740: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 2.20 (m, 2H), 2.28 (m, 2H), 2.76-5.40 (m, 6H), 5.62-6.46 (m, 2H), 6.64-7.10 (m, 3H), 9.92 (s, 1H), 10.52 (broad, 1H) ppm.^{13}C NMR (300 MHz, Chloroform-*d*) δ_C:41.64, 45.70, 46.32, 68.50, 98.10, 108.46, 113.17, 115.30, 115.44, 118.33, 123.12, 124.02, 124.24, 128.28, 130.94, 137.34, 140.52, 149.40, 149.52, 152.00, 153.10, 167.02, 187.74 ppm.EI-MS m/z: 388.11. Anal.Calcd.for $C_{24}H_{17}FO_4$: C, 74.22; H, 4.41; F, 4.89; O, 16.48. Found: C, 74.18; H, 4.38.

7'-{[(11aS)-7-formyl-11a-methyl-1-oxo-2H,3H,3aH,3bH,4H,5H,9bH,10H,11H-cyclopenta[a]phenanthren-8-yl]oxy}-8-fluoro-1',3',4'a,10'a-tetrahydro-2,4-dioxaspiro [bicyclo[3.3.1]nonane-3,2'-cyclopenta[b]anthracene]-1(9),5,7-triene-6'-carbaldehyde (10)

In a round bottom flask (10 ml), compound **9** (200 mg, 0.48 mmol), compound **2** (155 mg, 0.47 mmol) potassium carbonate (50 mg, 0.36 mmol) and dimethyl sulfoxide (5 ml) were stirred to reflux for 6 h. The solvent of the reaction mixture was evaporated under reduced pressure and purified through a methanol/hexane/water (3:1:1) system to provide compound **6** (yielding 84 %); m.p. 198-200^{o}C; IR (V_{max}, cm^{-1}) 1742, 1712 and 1242: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 0.92, 1.22-2.20 (m, 11H), 2.22-2.28 (m, 4H), 2.46-2.56 (m, 2H), 2.78 (m, 1H), 2.84-2.86 (m, 2H), 3.20-5.40 (m, 5H), 5.62-6.46 (m, 2H), 6.54-7.00 (m, 2H), 7.02 (m, 1H), 7.10 (m, 1H), 7.76 (m, 1H), 10.02 (s, 1H), 10.22 (s, 1H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C:13.80, 21.70, 25.70, 27.66, 29.61, 31.34, 35.32, 37.42, 41.68, 45.71, 46.34, 46.88, 48.12, 50.22, 68.53, 98.12, 108.49, 112.74, 115.31, 115.48, 122.52, 123.12, 123.82, 124.02, 124.09, 124.14, 124.69, 130.62, 131.02, 136.47, 136.49, 140.50, 149.40, 149.52, 149.59, 150.23, 153.10, 155.72, 172.40, 185.00, 190.70, 220.30ppm. EI-MS m/z: 668.25. Anal.Calcd.for $C_{42}H_{35}FO_6$: C, 77.23; H, 5.58; F, 2.84; O, 14.35. Found: C, 77.20; H, 5.54.

Theoretical analysis

Physicochemical properties of compounds4 to 10

Some theoretical electronic properties, 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 TPSA (topological polar surface area) involved in the chemical structure of compounds **4**to**10**were evaluated using SPARTAN'06 software; additionally, other physicochemical factors such as logP (logKowin), molecular refractivity (MR), volume reactivity (VR) were determined using Chemsketchprogram$^{x_L ii\text{-}x_L iv}$.

Pharmacophore evaluation

The 3D pharmacophore model for compounds **4** to**10** was determinate using LigandScout 4.08 software[xLv,xLvi].

Docking evaluation

Interaction of compounds **4**to**10**with μ and κ-opioid receptors was determinate using both 4dkl and 4djh proteins as control from protein data bank[xLvii-xLix] and DockingServersoftware[xLi].

References

i. J. Mao,*Pain*.100, 213 (2002).
ii. W. Ling, L. Mooney, M.Hillhouse,*Drug Alcohol Rev*.30, 300 (2011).
iii. S.Yekkirala, E. Kalyuzhny, S. Portoghese,*ACSChemNeuros*.1, 146 (2009).
iv. C. Mignat, U. Wille, A. Ziegler,*Life Sci*.56, 793, (1995).
v. W.Sadee, S. Rosenbaum, A.Herz, J. *Pharm. Exp. Therap*.223, 157 (1982).
vi. S. Commiske, L. Fan, K. Ho, W.Rockhold,*J Pharm. Sci*. 98, 109 (2005).
vii. M. Cepeda,H.Alvarez, O. Morales, D.Carr,*Pain*. 107, 41 (2004).
viii. F. Benedetti, M. Amanzio, S. Baldi, C. Casadio, G. Maggi, *Eur. J. Neur*. 11, 625 (1999).
ix. R. Buenaventura, R. Adlaka, M. Sehgal,*PainPhysician*. 11, S105 (2008).
x. H.Schmidhammer, W. Burkard, L. Eggstein, C. Smith, *J. Med. Chem*.32, 418 (1989).
xi. C. Clark, P. Halfpenny, R. Hill, D. Horwell, J. Hughes, T. Jarvis,*J. Med. Chem*.31, 831 (1988).
xii. P. Vonvoigtlander, R. Lahti, J. Ludens, *J. Pharmacol. Exp. Ther*.224, 7 (1983).
xiii. A. Cappelli, M. Anzini, S. Vomero, M. Menziani, P. De-Benedetti, M. Sbacchi, L. Mennuni, *J. Med. Chem*. 39, 860 (1996).
xiv. C. De-Ranter, C. Verlinde, N. Blaton, O. Peeters, *Neuropeptides*.5, 209 (1984).
xv. B. Largent, A. Gundlach, S. Snyder,*J. Pharmacol. Exp. Ther*. 238, 739 (1986).
xvi. B.Podlogar, G.Poda, D. Demeter, S. Zhang, J. Carson, L. Neilson, D. Ferguson,*LettDrug Des Discov*. 17, 34 (2000).
xvii. A.Dijksman, M. González, A. Payeras,I.Arends, R. Sheldon,*J. Am. Chem. Soc*. 123, 6826 (2001).
xviii. L. Figueroa, F. Diaz, L. Hau, E. García, M. Rosas, E. Pool, A. Camacho, R. García,Lopéz, *Lett. Org. Chem*. 13, 22 (2015).
xix. L. Figueroa, F.Diaz, M. Rosas, V. Mateu, E. Montano,L.Hau, A. Alonso, *Asian J. Green Chem*. 3, 216 (2019).
xx. L. Figueroa, F. Diaz, M. Rosas, E. García, E. Pool, M. Chan, M, *Lett. Org. Chem*. 12, 394 (2015).
xxi. G. Zeni, C. Larock, *Chem Rev*.106, 4644 (2006).
xxii. E. Frantz, R. Fässler, M. Carreira, *J. Am. Chem. Soc*.122, 1806 (2000).
xxiii. C.Koradin,K.Polborn,P.Knochel,*Ang. Chem. Int. Ed*.41, 2535 (2002).
xxiv. J.Corey,A.Katzenellenbogen,*J. Am. Chem. Soc*.91, 1851 (1969).
xxv. W.Walter,W.Ruback,*Liebigs Ann. Chem*. 647, 231 (1982).
xxvi. K. Houk,*Acc. Chem. Res*.8, 361 (1975).
xxvii. D. Ess,K.Houk,*J. Am. Chem. Soc*.130, 10187 (2008).
xxviii. Y. Prasad, P. Kumar, D. Smiles, P.Babub,*Arkivok*. 11, 266 (2008).
xxix. J.Latosińska, J. Kasprzak,Z.Kazimierczuk, *J. Mol. Struc-THEOCHEM*.530, 217 (2000).
xxx. L. Figueroa, F. Diaz, E. Garcia, *J. Chem*. 9, 27 (2012).

xxxi. S. Sagdinc, S. Bayari, *J. Mol. Struc-THEOCHEM*.668, 93 (2004).
xxxxii. C. Patel, J. Georrge, K. Modi, J. Narechania, D. Patel, F. Gonzalez, H. Pandya, H, *J. Biomol. Struct.Dyn*.36, 3938 (2018).
xxxiii. N. Obi, I. Obot, M. El-Khaiary, S. Umoren, E. Ebenso, *Int. J. Electrochem. Sci*. 6, 5649 (2011).
xxxiv. D. Seeliger, B. De-Groot, *J. Computer. Aided. Mol. Des*. 24, 417 (2010).
xxxv. A.Goldfeld, R. Murphy, B. Kim, L. Wang, T. Beuming,R.Abel,A.Friesner,*J. Phys. Chem*.119, 824 (2014).
xxxvi. F.Wieberneit, A. Korste, B. Albada, N. Metzler-Nolte, R. Stoll, *Dalton Trans*.42, 9799 (2013).
xxxvii. L. Martini,l.Whistler,*Curr. Neur*.17, 556 (2007).
xxxviii. P. Armenian, T. Vo,J. Barr-Walker,L. Lynch,*Neuropharmacology*.134, 121 (2018).
xxxix. R. Hutchinson, Y. Zhang.K. Brown,D.Coats,M.Shridhar,W.Sholar,C. Rice,*Eur. J. Neur*.28, 20 (2008).
xL. H. Gomes, L. Oliveira, L. Marques, M. Coelho, F. Silva, *Vet. Anaesth.Anal*. 45, 68 (2018).
xLi. J.Roach,A.Shenvi,Bioorg.*Med. Chem. Lett*.28, 1436 (2018).
l. M.Hiramatsu,T. Hoshino,*Brain*. 1057, 72 (2005).
xLii. A. Şahin, M. Saçan, *SAR QSAR Environ. Res*. 29, 117 (2008).
xLiii. M. Tahir, M. Khalid, A. Islam, S. Mashhadi, A. Braga, *J. Mol. Struct*.127, 766 (2016).
xLiv. A. Hartman, A. Hirsch,*Eur. J. Med. Chem*.136, 573 (2017).
xLv. M.Réau,F.Langenfeld,J.Zagury,M. Montes,*J. Computer-Aided. Mol. Des*.32, 231 (2018).
xLvi. G.Wolber, T. Langer,*J. Chem. Inf. Model*. 45, 160 (2006).
xLvii. S. Noha, H.Schmidhammer, M.Spetea, *ACS Chem.Neur*.8, 1327 (2017).
xLviii. J. Loo, A.Emtage, K. Ng, A. Yong, S. Doughty, *J. Mol.Grap.Model*.80, 38 (2018).
xLix. P.Suresh,N.Divya,S.Nidhi,R.Rajasekaran,*Spectrochim. ActaA Mol. Biomol. Spectrosc*.193, 523 (2018).

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