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범밀도 함수법과 Molecular Descriptor를 이용한 모르핀 유도체에 대한 분자 모델링 연구

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Molecular Modeling Study on Morphine Derivatives Using Density Functional Methods and Molecular Descriptors

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요약. 마약인 모르핀, 헤로인, 코데인, 펜타조신 그리고, 버프레노파인에 대하여 범밀도함수이론에 근거하여 계산 연구를 수행하였다. 약물특이 분자단과 치환기의 기하학적 파라미터는 B3LYP/6-31+G(d) 레벨로 계산하였고, 전자의 구조는B3LYP/6-311++G(d,p) 레벨로 같은 혼성 범함수를 사용하여 계산하였다. 원자의 전하분포는 Mulliken 개체 수 분석에 의하여 구하였다. 보고된 생물학적 활성, 계산된 분배 계수, 전자 및 기하학적 분석을 토대로 펜타조신과 버프레노파인을 새로 제시된 유사화합물에 대한 모델화합물로 선택하였으며, 이들 유사화합물에 대하여 연구한 뒤, 모델화합물과 비교하였다. 본 연구 결과는 약물특이 분자단의 기하학적 구조와 전자 구조가 다른 치환기의 존재 하에서도 변함없이 유지된다는 것을 보여주었다. 제시된 유사화합물들도 모델 분자의 특성을 갖고 있기 때문에, 이들 유사화합물들도 생물학적 활성을 나타낼 것 같다.

주제어: 마약, DFT 계산, 약물특이 분자단

ABSTRACT. Computational studies were carried out on the opiates morphine, heroin, codeine, pentazocine, and buprenorphine, under the density functional theory. The geometric parameters of the pharmacophore and substituents were evaluated at the B3LYP/6-31+G(d) level of theory. The electronic structure calculations were performed using the same hybrid functional at the B3LYP/6-311++G (d,p) level of theory . The atomic charges were obtained by Mulliken population analysis. Given the reported biological activity, calculated partition coefficients, and electronic and geometric analysis, pentazocine and buprenorphine were chosen as models for proposed analogues. These analogues were then studied and compared with the model molecules. The study reveals that the geometry and electronic structure of the pharmacophore remains consistent in the presence of different substituents. Because the proposed analogues preserve the studied properties of the model molecules, it is likely that these analogues display biological activity.

Keywords: Opiates, DFT calculations, Pharmacophore

INTRODUCTION

Morphine is one of the most effective general analgesics currently available.[1-3] Despite its therapeutic benefits, morphine's use is limited by side effects such as tolerance, physical and psychological dependence, gastrointestinal and urinary disturbances, respiratory system depression, constipation, agitation, euphoria, nausea, and meiosis.

In order to reduce the harmful side effects, experimental methods have been used to alter morphine's chemical struc-

ture while preserving its pharmacophore (the part of the drug primarily responsible for the biological action by stereospecific interaction with the receptor), leading to the creation of numerous opiate families.[4] These experimental methods include variation of substituents, drug extension, rigidification, and simplification of structure.[5]

Structural modifications have been carried out primarily on a random basis depending on the ease of synthesis,[6] rather than by tracking patterns in a rational design. Now, however, thanks to the identification of opiate receptors and molecular modelization, these modifications may take place in a more consistent way,[7-10] providing very powerful tools for the design of new molecules with high affinity for a particular receptor.[11-12]

Several studies have been done on morphine and its derivatives, involving both experimental and computational work. Gilda H. Loew *et al.* carried out quantum-chemical studies on opiate drugs like morphine and oxymorphone, focusing on the effect of N-substituent changes,[13-14] as well as structure-activity studies of narcotic agonists and antagonists using semiempirical methods.[15] Other studies of structure-activity relationships[16] have been conducted on opiates with *ab initio* methods,[17] semiempirical[18] and molecular mechanics,[19-20] and molecular docking.[21]

This paper presents a theoretical study of morphine and some of its derivatives. Our hypothesis is that, if the pharmacophore is preserved and some related properties called molecular descriptors are kept,[22-25] the proposed derivatives will properly bind to the active site, increasing the probability of these molecules having a biological effect.

METHODOLOGY

A fast conformational search was carried out with the software Spartan'06, using the systematic approach and MMFF94 force field. The geometry optimization of the previously generated conformer was carried out using Gaussian 03W software[26] at the hybrid functional B3LYP with the basis set 6-31+G(d). The single point energies were calculated at the B3LYP/6-311++G(d,p) level of theory. provided by Gaussian. The calculated descriptors were electrostatic potential, HOMO and LUMO energies using Spartan'06 at the B3LYP/6-311++G(d,p) level of theory; dipole moment, Mulliken charges, interatomic distance, and volume using Gaussian 03W[26] at the B3LYP/6-311++G(d,p) level of theory; Log P using MOE 2001.01 by the MMFF94 force field. From the calculated descriptors, the geometric and electronic structure analysis of both the pharmacophore and the N-substituted molecules were performed. Based on this analysis, two new opiate analogues were proposed.

RESULTS AND DISCUSSION

Molecular geometry was assessed on the basis of bond distances, angles, and dihedrals adopted by the pharmacophore in morphine, heroin, codeine, pentazocine and buprenorphine (*Fig.* 1).

Table 1 reports the distances and dihedrals obtained for the pharmacophore at the B3LYP/6-31+G(d) level of theory and the reported experimental distances obtained by X-ray crystallography.[27-31] Most of the estimated bond lengths are slightly larger than the experimental distances, with deviations of the order of 0.010 Å, which are not significant. The theoretical model used reproduces satisfactorily the geometry of the studied molecules. The only significant deviation, 0.108 Å, was found in the RC9-N10 of heroin. Deviations may be due to the theoretical values of isolated molecules in the gas phase, whereas the experimental results come from molecules in the solid state.

Comparing the pharmacophore structure of each compound with morphine, the highest deviation is 0.033 Å, corresponding to the distance RN10-C16 in the molecule of pentazocine. This is probably due to the effects of the proximity of a double bond and the bulkiness of the chain attached to the nitrogen. The same applies to buprenorphine, in which the distance RN10-C16 is influenced by the nitrogen substituent. The deviations mentioned above are not significant, indicating that the pharmacophore structure keeps the geometric relationships in the molecules under study.

Evaluated dihedrals are those associated with the T-shaped characteristic structure of morphine and the piperidine ring conformation. Calculated dihedral angles are consistent with those experimentally determined,[27-31] with no significant deviations to influence the adopted conformation by the pharmacophore.

Comparing the dihedrals of each molecule with those of morphine, it is easily seen that the largest dihedral change (6.7°) lies in DC1-C6-C7-C8 of pentazocine. While numerically the deviation is relatively large, it does not represent

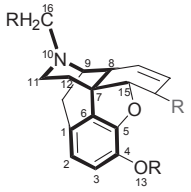

***Fig.* 1.** Pharmacophore numbering

***Table* 1.** Pharmacophore bond distances in Angstroms and dihedrals, obtained from X-ray crystallography and calculations at the B3LYP/6-31+G(d) level of theory.

	Morphine		Heroin		Codeine		Pentazocine		Buprenorphine	
	Exp.	B3LYP/ 6-31+G(d)	Exp.	B3LYP/ 6-31+G(d)	Exp.	B3LYP/ 6-31+G(d)	Exp.	B3LYP/ 6-31+G(d)	Exp.	B3LYP/ 6-31+G(d)
RC1-C2	1.390	1.406	1.420	1.405	1.396	1.405	1.392	1.405	1.396	1.407
RC1-C6	1.360	1.386	1.360	1.384	1.392	1.386	1.398	1.407	1.367	1.385
RC2-C3	1.410	1.399	1.400	1.400	1.380	1.396	1.380	1.388	1.420	1.401
RC3-C4	1.390	1.406	1.390	1.401	1.394	1.410	1.381	1.400	1.373	1.407
RC4-C5	1.380	1.393	1.410	1.392	1.385	1.400	1.377	1.397	1.408	1.395
RC4-O13	1.370	1.360	1.400	1.384	1.367	1.357	1.364	1.363	1.372	1.362
RC5-C6	1.370	1.380	1.380	1.385	1.359	1.386	1.391	1.405	1.367	1.381
RC6-C7	1.500	1.508	1.510	1.507	1.500	1.509	1.523	1.538	1.492	1.492
RC7-C15	1.550	1.559	1.550	1.558	1.547	1.557	1.530	1.541	1.532	1.544
RC7-C12	1.540	1.549	1.520	1.549	1.520	1.549	1.542	1.559	1.535	1.550
RC7-C8	1.550	1.551	1.520	1.548	1.536	1.551	1.542	1.559	1.542	1.544
RC11-C12	1.520	1.526	1.550	1.525	1.492	1.526	1.503	1.524	1.516	1.528
RC8-C9	1.550	1.553	1.530	1.553	1.554	1.550	1.515	1.537	1.525	1.556
RN10-C11	1.510	1.520	1.450	1.522	1.479	1.519	1.497	1.513	1.502	1.528
RC9-N10	1.530	1.548	1.440	1.548	1.477	1.548	1.511	1.539	1.518	1.544
RN10-C16	1.490	1.502	1.460	1.502	1.478	1.502	1.509	1.535	1.486	1.525
DC7,C8,C9,N10	-	65.5	66.0	65.4	64.9	65.6	63.3	63.2	-	65.5
DC1,C6,C7,C8	-	-36.1	-34.0	-34.5	-33.3	-35.1	-28.0	-29.4	-	-41.3
DC1,C6,C7,C12	-	83.2	-	84.9	-	84.4	-	87.4	-	81.9
DC7,C12,C11,C10	-	-51.4	-	-51.1	-52.8	-51.4	-53.5	-53.2	-	-48.5

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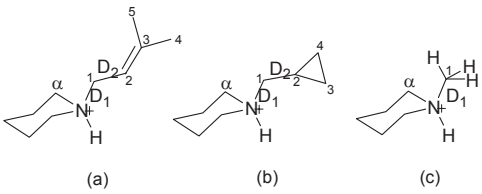

***Fig*. 2.** Numbering and dihedrals (D) evaluated for: (a) Pentazocine (b) Buprenorphine (c) Morphine, Heroin, and Codeine (α corresponds to carbon 9 in *Fig*. 1).

a significant change in pharmacophore geometry.

In morphine, heroin, and codeine, the N-substituent is a methyl group, which has not been taken into account due to its simplicity, while the substituents of pentazocine and buprenorphine are included in this study because more geometric variables need to be taken into account (*Fig*. 2).

Table 2 reports the geometric parameters for the N-substituents of pentazocine and buprenorphine. It can be seen that the calculated values are consistent with experimental data,[27-31] showing only slight deviations.

The electronic characteristics considered for the pharmacophore and substituents are expressed in terms of Mulliken charges, electrostatic potential, dipole moment, and frontier orbitals. The charges arising from the pharmacophore Mulliken population analysis showed that most of the atomic charges are negative, focusing mainly on the C4 of morphine, codeine and buprenorphine, C5 of heroin, and C12 of pentazocine. C6 and C7 form a positive charge center in all molecules.

***Table* 2.** Geometric parameters for the pentazocine and buprenorphine *N*-substituents obtained by X-ray crystallography and B3LYP/6-31+G(d)calculations.

	Pentazocine		Buprenorphine	
Bond distance (Å)	Exp.	B3LYP/ 6-31+G(d)	Exp.	B3LYP/ 6-31+G(d)
RN-C1	1.511	1.535	1.486	1.525
RC1-C2	1.490	1.497	1.524	1.505
RC2-C3	1.300	1.349	1.480	1.520
RC2-C4	-	-	1.480	1.514
RC3-C4	1.512	1.508	1.480	1.504
RC3-C5	1.466	1.508	-	-
Dihedrals (°)				
Dα-N-C1-C2	-163.8	-153.9	-67.8	-63.1
DN-C1-C2-C3	-118.6	-114.2	-142.8	-143.1
Bond angles (°)				
AC1-N-α	113.2	114.4	115.8	115.6
AN-C1-C2	110.7	111.3	113.8	112.7
AC1-C2-C3	126.8	127.3	119.6	119.9
AC1-C2-C4	-	-	120.9	118.8
AC2-C3-C4	125.0	125.4	59.1	60.1
AC2-C3-C5	120.3	120.1	-	-
AC3-C2-C4	-	-	60.4	59.4
AC4-C3-C5	114.7	114.6	-	-

One interesting finding is that five of the six atoms forming the piperidine ring are negatively charged, the exception being C7 (part of the strong positive charge center), while the nitrogen atom of buprenorphine shows a slight positive charge. In addition, C4 and C5 on the benzene ring have

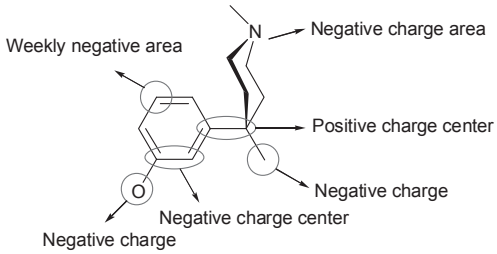

***Fig*. 3.** Pharmacophore Mulliken charge distribution.

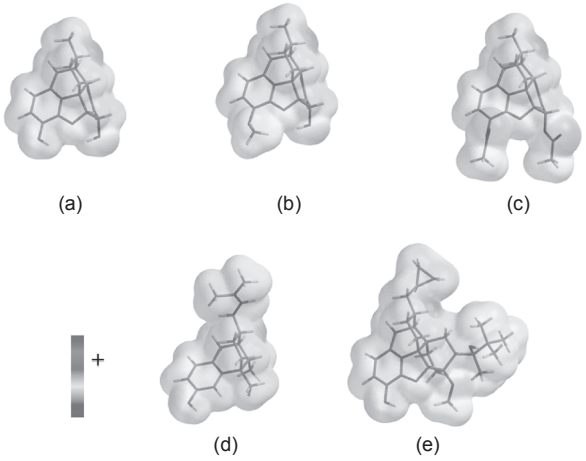

***Fig*. 4.** Electrostatic potential map in the Van der Waals surface: (a) Morphine (b) Codeine (c) Heroin (d) Buprenorphine (e) Pentazocine.

significant negative charges. *Fig*. 3 gives a general outline of the charge distribution in the studied molecules.

The electrostatic potential map (*Fig*. 4) shows all molecules to have a strong positive charge at the periphery of the protonated amine group. Morphine has the highest charge intensity, with a potential energy of 153.49 kcal/mol (*Table* 3).

The phenolic oxygen is the center of maximum negative charge in buprenorphine and pentazocine, whereas in morphine and codeine the phenolic oxygen has energy values of approximately -19.00 to -20.00 kcal/mol. Heroin, with an electron attractor substituent, has lower charge intensity than in previous molecules, with an approximate value of

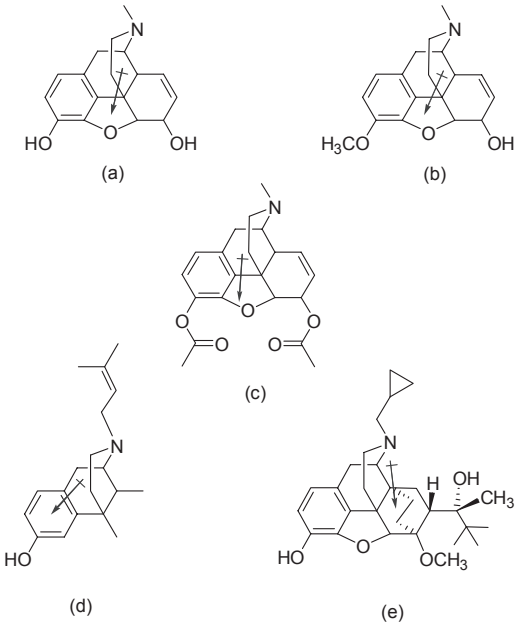

***Fig*. 5.** Dipole moment orientation calculated at the B3LYP/6-311++G(d,p) level of theory: (a) Morphine (b) Codeine (c) Heroin (d) Pentazocine (e) Buprenorphine

-27.00 kcal/mol. The electrostatic potential on the aromatic ring has values of -57 to -60 kcal/mol for molecules of morphine, heroin, codeine, and pentazocine. For buprenorphine, the value is -45.73 kcal/mol, indicating a greater negative charge compared with the four above-mentioned molecules.

The dipole moment presented significantly high values, as shown in *Table* 3. Morphine, heroin, and codeine have a dipole in approximately the same orientation, while buprenorphine and pentazocine show a different orientation, as can be seen in *Fig*. 5.

The Mulliken charges of N-substituents reveal a pattern in their distribution (*Fig*. 6). Even though the geometric and chemical characteristics differ from one substituent to another due to the bond types, it appears that the sum of the Mulliken charges for all the studied molecules is close to 0.320, and that the carbon adjacent to the nitrogen atom develops a negative charge.

***Table* 3.** Electrostatic potential energy in kcal/mol and dipole moment in Debye, energies in au and volume in $Å^3$ calculated obtained at the B3LYP/6-311++G(d,p) level of theory and Log *P* by MMFF94 force field.

	Morphine	Heroin	Codeine	Pentazocine	Buprenorphine
Positive charge center	153.49	150.18	152.88	138.12	130.11
Negative charge center	12.53	6.70	10.88	17.29	12.13
Dipole Moment	12.808	13.830	13.366	6.387	9.673
E	-940.26	-1245.66	-979.57	-870.88	-1486.13
V	314.740	406.090	335.360	360.870	542.740
Log *P*	0.937	1.767	1.201	3.716	4.825

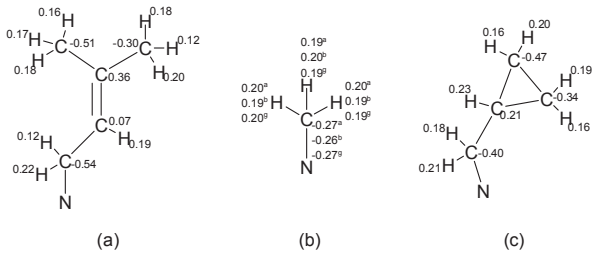

***Fig*. 6.** Mulliken charges for the *N*-Substituents of: (a) Pentazocine (bα) Morphine (bβ) Heroin (bγ) Codeine (c) Buprenorphine

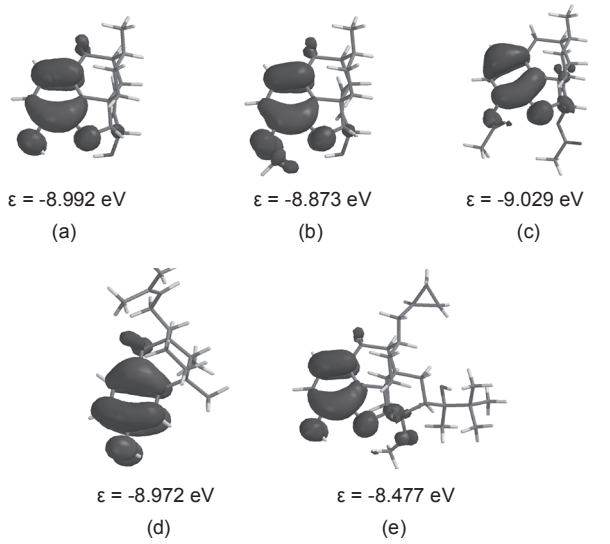

***Fig*. 7.** HOMO surface calculated at the B3LYP/6-311++G(d,p) level of theory: (a) Morphine (b) Codeine (c) Heroin (d) Pentazocine (e) Buprenorphine

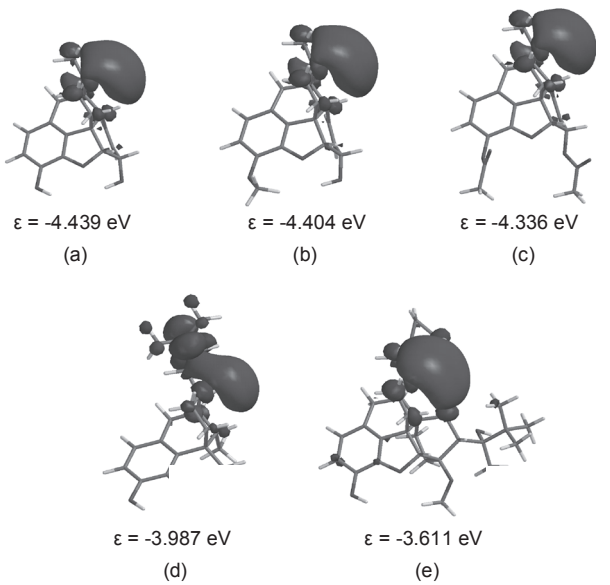

***Fig*. 8.** LUMO calculated at the B3LYP/6-311++G(d,p) level of theory: (a) Morphine (b) Codeine (c) Heroin (d) Pentazocine (e) Buprenorphine

The shape and energy of the calculated frontier molecular orbitals are shown in *Figs*. 7 and 8. The HOMO for all studied molecules shows that the electronic cloud is located on the aromatic ring. In morphine, codeine, and buprenorphine, the electronic cloud has the same nodal plane, while in heroin and pentazocine the plane has a different orientation.

In addition, a portion of this orbital is located on the phenolic oxygen, indicating that this is an electron donor group. This is consistent with the Mulliken population analysis. The LUMO for each of the molecules is located on the piperidine ring nitrogen atom, indicating that it is the most susceptible site to nucleophilic attack, which is consistent with data from the electrostatic potential map.

Other parameters taken into account for the analysis were energy (a measure of stability), volume (a key parameter for the receptor coupling), and log P (a solubility index of the ability to cross biological barriers and reach the receptor). *Table* 3 also shows the energies and volumes obtained at the B3LYP/6-311++G (d, p) level of theory and log P calculated by the MMFF94 force field. Buprenorphine has a larger volume and a greater log P than the other molecules studied because of the hydrophobic regions that confer lipophilicity to this molecule.

Analogues proposal

Taking into account the biological activity and the electronic and geometric analysis conducted on morphine, heroin, codeine, pentazocine, and buprenorphine, the latter two were selected as models to design two new analogues.

Ten analogues of each model molecule were proposed by varying the substituents. Each analogue underwent a similar conformational MMFF94 study in order to determine the geometry of minimum energy conformers, which were then optimized at the semiempirical-PM3 level of theory. From this study, we selected five analogues for pentazocine (*Fig*. 9) and four for buprenorphine (*Fig*. 10), based on conformation similarity with the model molecules.

To obtain a more detailed comparative analysis of the adopted geometry, the selected analogues were structurally superpositioned onto their model molecules (*Fig*. 11).

After the structural superposition, an analogue of each molecule was selected based on similarity with the model molecule. The chosen analogues were number five (5) for pentazocine and number one (1) for buprenorphine. These were then submitted to electronic and geometric property studies at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) level of theory.

Geometric Analysis of selected analogues

In comparing each analogue with its model molecule

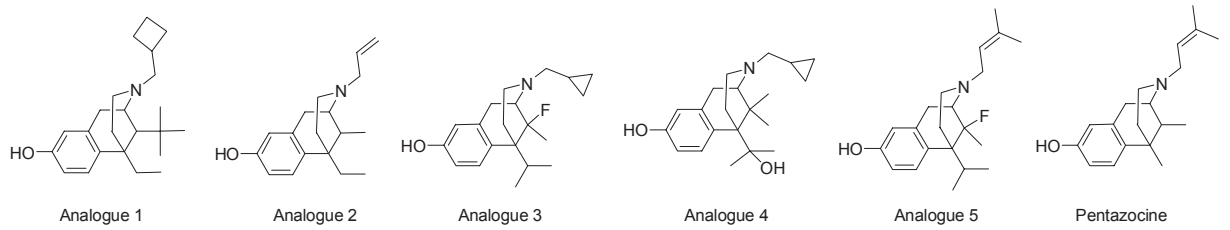

***Fig*. 9.** Pentazocine and selected analogues

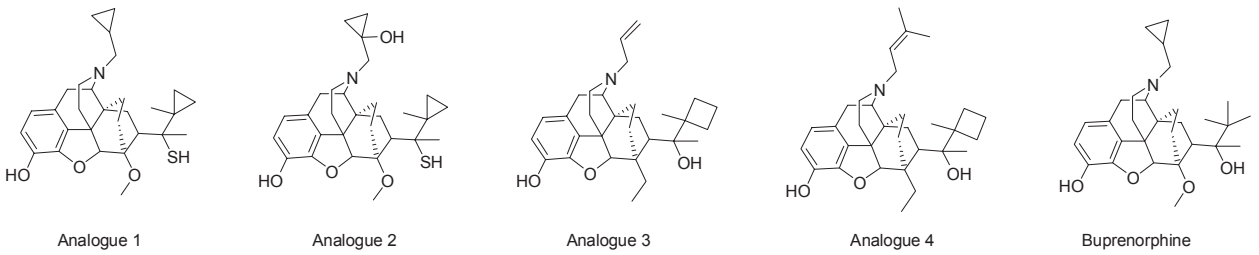

***Fig*. 10.** Buprenorphine and selected analogues

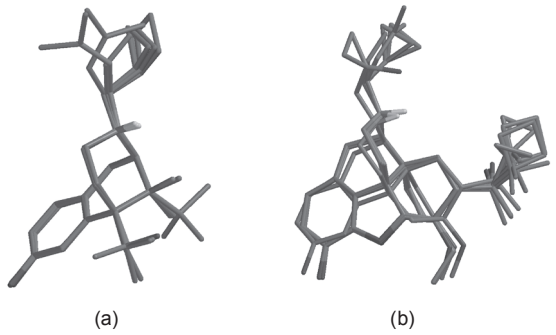

***Fig*. 11.** Structural superpositioning of (a) Pentazocine analogues and (b) Buprenorphine analogues.

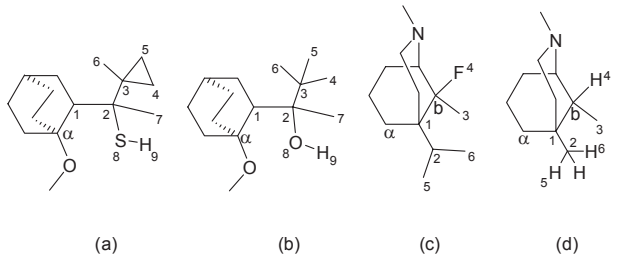

***Fig*. 12.** Numbering of modified substituents for: (a) Analogue 1 (b) Buprenorphine (c) Analogue 5 (d) Pentazocine (α and β correspond to reference carbons for dihedral measurements)

(*Table* 4), it is evident that the geometry of the pharmacophores is consistent with the values obtained for the model molecules. The largest deviation, with a value of 0.041 Å, is in the distance for C7-C15, which is expected because the methyl group in pentazocine has been replaced by an isopropyl alkyl group. For the conformation, the largest deviation is 4.8°, in the dihedral DC1-C6-C7-C8.

The geometric analysis of the N-substituents was carried out with the numbering used in *Fig*. 2, while the evaluated parameters for the remaining substituents are based on the numbering in *Fig*. 12.

Table 5 contains the geometrical parameters (bond distances, angles, and dihedrals) for the N-substituent in pentazocine, buprenorphine, and analogues. It can be seen that, in general, the calculated values are consistent with data obtained for the model molecules. The pentazocine analogue does differ considerably from the dihedral parameters, but without affecting the double bond position.

Table 6 shows the geometric parameters of pentazocine and its analogue. These results show that the analogue parameters are consistent with those of pentazocine, showing only negligible changes in geometry.

For the buprenorphine analogue (*Table* 7), bond lengths showed no significant divergence from the model molecule. The largest deviation was in the bond distance RC2-X8, caused by an oxygen atom being replaced by sulfur, which has a much larger Van der Waals radius. There were some deviations for the dihedrals and bond angles, but the spatial arrangement of atoms remained similar.

Analysis of the electronic structure of selected analogues

The atomic charges obtained from the pharmacophore Mulliken population analysis have a very similar distribution for all studied structures.

***Table* 4.** Geometric parameters of the pharmacophore for the chosen analogues and the model molecules, obtained at the B3LYP/6-31+G(d) level of theory.

Bond Distance (Å)	Pentazocine	Analogue 5	Deviation	Buprenorphine	Analogue 1	Deviation
RC1-C2	1.405	1.402	-0.003	1.407	1.406	-0.001
RC1-C6	1.407	1.411	0.004	1.385	1.387	0.003
RC2-C3	1.388	1.390	0.002	1.401	1.401	0.000
RC3-C4	1.400	1.399	-0.001	1.407	1.406	-0.001
RC4-C5	1.397	1.397	-0.001	1.395	1.395	0.000
RC4-O13	1.363	1.363	0.000	1.362	1.362	-0.001
RC5-C6	1.405	1.403	-0.002	1.381	1.381	0.001
RC6-C7	1.538	1.553	0.014	1.492	1.497	0.005
RC7-C15	1.541	1.582	0.041	1.544	1.559	0.014
RC7-C12	1.559	1.565	0.006	1.550	1.550	-0.001
RC7-C8	1.559	1.562	0.003	1.544	1.552	0.009
RC11-C12	1.524	1.526	0.002	1.528	1.526	-0.001
RC8-C9	1.537	1.537	0.000	1.556	1.557	0.001
RN10-C11	1.513	1.513	0.000	1.528	1.513	-0.014
RC9-N10	1.539	1.530	-0.009	1.544	1.544	0.000
RN10-C16	1.535	1.535	-0.001	1.525	1.525	0.001
Dihedrals (^{o})						
DC7,C8,C9,N10	63.2	62.6	-0.6	65.5	65.1	-0.4
DC1,C6,C7,C8	-29.4	-24.6	4.8	-41.3	-41.2	0.1
DC1,C6,C7,C12	87.4	89.8	2.4	81.9	80.9	-1.0
DC7,C12,C11,C10	-53.2	-53.0	0.2	-48.5	-50.0	-1.5

***Table* 5.** Geometric parameters for the *N*-Substituents in pentazocine, buprenorphine, and analogues, obtained at the B3LYP/6-31+G(d) level of theory.

Bond Distance (Å)	Pentazocine	Analogue 5	Deviation	Buprenorphine	Analogue 1	Deviation
RN-C1	1.535	1.535	0.000	1.544	1.525	-0.018
RC1-C2	1.497	1.499	0.002	1.505	1.505	-0.001
RC2-C3	1.349	1.350	0.001	1.520	1.521	0.000
RC2-C4	-	-	-	1.514	1.515	0.000
RC3-C4	1.508	1.508	0.000	1.504	1.504	0.000
RC3-C5	1.508	1.508	0.000	-	-	-
Dihedrals (^{o})						
Dα-N-C1-C2	-153.9	-160.7	-6.8	-63.1	-60.3	2.8
DN-C1-C2-C3	-114.2	-262.5	-148.3	-143.1	-143.9	-0.8
Bond angles (^{o})						
AC1-N-α	114.3	113.8	-0.6	115.6	115.8	0.2
AN-C1-C2	111.3	112.1	0.8	112.7	113.0	0.4
AC1-C2-C3	127.3	126.1	-1.2	119.9	120.0	0.0
AC1-C2-C4	-	-	-	118.8	118.6	-0.1
AC2-C3-C4	125.4	125.2	-0.1	60.1	60.1	0.01
AC2-C3-C5	120.0	120.1	0.0	-	-	-
AC3-C2-C4	-	-	-	59.4	59.4	-0.0
AC4-C3-C5	114.6	114.6	0.0	-	-	

The sum of Mulliken charges in the aromatic ring of both analogues is more intensely negative than for the previously studied molecules. Buprenorphine and its analogue have a similar charge distribution in the pharmacophore, but displayed some differences in the substituents. In general, both analogues retain the original charge distribution shown in *Fig*. 3.

The charges obtained for the N-substituents are shown in *Fig*. 13. For the pentazocine analogue, despite possessing the same substituent, the charge distribution is different in sp^2 hybridized carbons, introducing a charge intensity diminution in carbon 3, while carbon 2 went from a slightly

***Table* 6.** Geometric parameters for pentazocine and its analogue, obtained at the B3LYP/6-31+G(d) level of theory.

Bond Distances (Å)	Pentazocine	Analogue 5	Deviation
RC1-C2	1.541	1.582	0.042
Rβ-C3	1.538	1.524	-0.015
Rβ-X4	1.103	1.437	0.335
RC2-H6	1.097	1.544	0.447
RC2-H5	1.094	1.546	0.452
Dihedrals (°)			
Dα-C1-C2-C6	171.2	179.6	8.4
DC2-C1-β-C3	56.9	52.8	-4.1
DC2-C1-β-X4	-61.8	-67.5	-5.8
Dβ-C1-C2-C5	-72.7	-74.8	-2.0
Bond angles (°)			
Aα-C1-C2	113.2	112.2	-1.0
Aβ -C1-C2	109.8	114.7	4.9
AC1-C2-C6	110.3	115.7	5.4
AC3-β-X4	106.9	106.4	-0.6
AC5-C2-C6	108.1	108.5	0.4

***Table* 7.** Geometric parameters for buprenorphine and its analogue, obtained at the B3LYP/6-31+G(d) level of theory.

Bond Distances (Å)	Buprenorphine	Analogue 1	Deviation
RC1-C2	1.593	1.585	-0.008
RC2-C3	1.602	1.577	-0.025
RC3-C6	1.545	1.534	-0.012
RC2-X8	1.450	1.876	0.426
RC2-C7	1.541	1.543	0.003
RC3-C4	1.549	1.520	-0.029
RC3-C5	1.546	1.524	-0.023
Dihedrals (°)			
Dα-C1-C2-C3	211.1	172.0	-39.1
DC1-C2-X8-H9	-167.4	-74.5	92.9
Dα-C1-C2-C7	-24.2	-66.4	-42.7
Dα-C1-C2-X8	92.8	53.6	-39.2
Bond angles (°)			
AC2-X8-H9	108.4	95.0	-13.4
Aα-C1-C2	118.3	121.1	2.8
AC2-C3-C6	113.0	118.8	5.8
AC5-C3-C6	107.9	115.0	7.1
AC1-C2-X8	104.9	112.2	7.3
AC2-C3-X8	109.6	106.3	-3.3

positive charge to a charge of -0.305. The N-substituent of the buprenorphine analogue has a similar charge distribution to the model molecule. The sum of Mulliken charges on this substituent was 0.280, which is slightly lower than for the morphine analogues, heroin, codeine, pentazocine, and buprenorphine, but not significantly so. The carbon atom adjacent to nitrogen is also negatively charged.

Fig. 14 shows the Mulliken charge distribution in the modified substituents. Despite the great structural similarity,

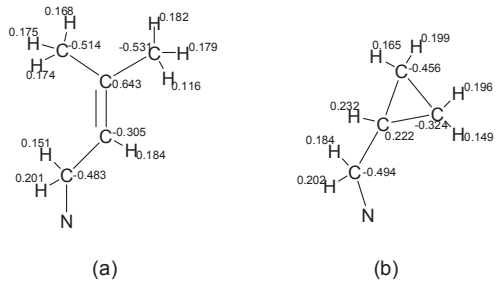

***Fig*. 13.** Mulliken charges for the *N*-Substituents: (a) Pentazocine analogue (b) Buprenorphine analogue.

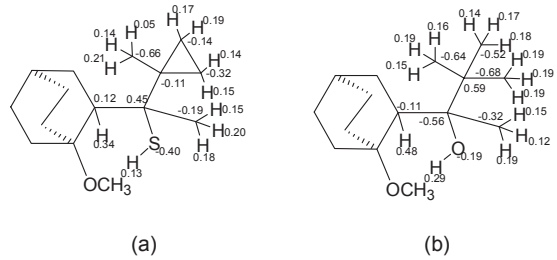

***Fig*. 14.** Mulliken charges for substituents: (a) Buprenorphine analogue (b) Buprenorphine.

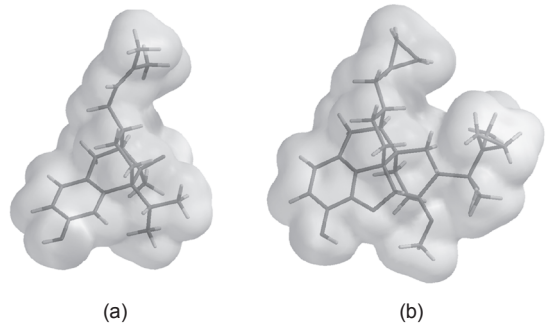

***Fig*. 15.** Electrostatic potential map on the Van der Waals surface: (a) Pentazocine analogue (b) Buprenorphine analogue.

buprenorphine carbons C1 and C2 have positive charge, while the analogue's carbon C2 has a charge difference of 1.010 with respect to buprenorphine. This deviation, which is the largest, may be due to the replacement of an oxygen atom with sulfur in the analogue, as well as the differences in charge distribution between the t-butyl and 1-methylciclopropyl groups.

The greatest difference in charge distribution between the t-butyl and 1-methylciclopropyl groups is that the substituent carbon C5 in the analogue has a negative charge, while in buprenorphine it has a value of 0.590. The electrostatic potential maps for the analogues are illustrated in *Fig*. 15. In both analogues, the area with strong positive charge on the periphery of the nitrogen is retained, albeit with a slight reduction

***Table* 8.** Electrostatic potential energy in kcal/mol, dipole moments in Debye, energies in au and volume in Å^3 obtained at the B3LYP/6-311++G(d,p) level of theory and Log *P* by MMFF94 force field for pentazocine, buprenorphine, and analogues.

	Pentazocine	Analogue 5	Buprenorphine	Analogue 1
Positive charge center	138.12	125.80	130.11	133.26
Negative charge center	17.29	21.38	12.13	13.50
Dipole Moment (Debye)	6.387	5.940	9.673	10.451
E	-870.88	-1048.79	-1486.13	-1807.85
V	360.870	404.530	542.740	546.850
Log *P*	3.716	4.359	4.825	5.648

in the pentazocine analogue. This reduction is probably due to the presence of the fluorine atom, which exhibits a slightly negative charge.

Compared with the model molecules, the electrostatic potential energy of the positively charged area is 12.32 kcal/mol less for the pentazocine analogue and 3.15 kcal/mol greater for the buprenorphine analogue (*Table* 8). The phenol oxygen group remains as the maximum negative charge center in both analogues, with deviation from the model molecules at 4.09 kcal/mol for the pentazocine analogue and 1.37 kcal/mol for the buprenorphine analogue.

On the aromatic ring, the analogues have slightly higher electrostatic potential values than the model molecules, with deviations of about 3.80 kcal/ mol, resulting in a small decrease in the negative charge in this area.

The dipole moment (*Table* 8) observed for the pentazocine analogue is 0.447 Debye lower than that of the pentazocine, whereas the buprenorphine analogue presents an increase of 0.778 Debye compared to the buprenorphine.

Fig. 16 shows that the dipoles of buprenorphine and its analogue have the same orientation, but the pentazocine analogue has a changed dipole orientation due to the new negative charge introduced by the substituent modification.

Figs. 17 and 18 show the shape and energy of the analogues' molecular orbitals.

The HOMOs of the pentazocine and buprenorphine analogues showed similar distributions to those of the model molecules: electronic cloud located on the aromatic ring, same nodal plane, and a portion of this orbital located on the phenol oxygen. However, in the buprenorphine analogue, a small portion of this orbital is also found on sulfur. The energy values obtained for the selected analogues are listed in *Table* 8.

The partition coefficient values calculated for the analogues show an increase of 0.643 and 0.823 for pentazocine and buprenorphine respectively, indicating a higher lipophilicity. The volume of the pentazocine analogue increased by 43.660 Å^3 due to the difference in the size of the substituents, while the buprenorphine analogue grew 4.110 Å^3 despite losing two hydrogens.

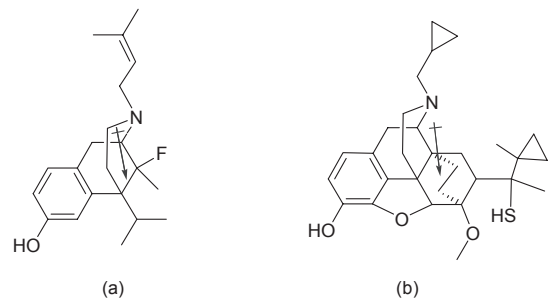

***Fig*. 16.** Dipole moment orientation calculated at the B3LYP/6-311++G(d,p) level of theory: (a) Pentazocine analogue (b) Buprenorphine analogue.

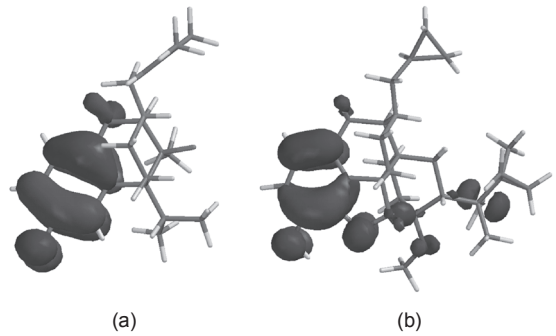

***Fig*. 17.** Calculated HOMO at the B3LYP/6-311++G(d,p) level of theory: (a) Pentazocine analogue (b) Buprenorphine analogue.

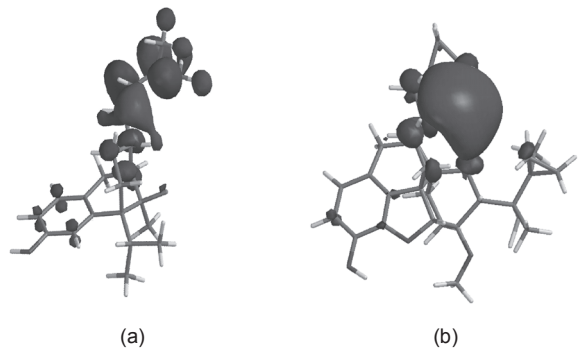

***Fig*. 18.** Calculated LUMO at the B3LYP/6-311++G(d,p) level of theory: (a) pentazocine analogue (b) Buprenorphine analogue

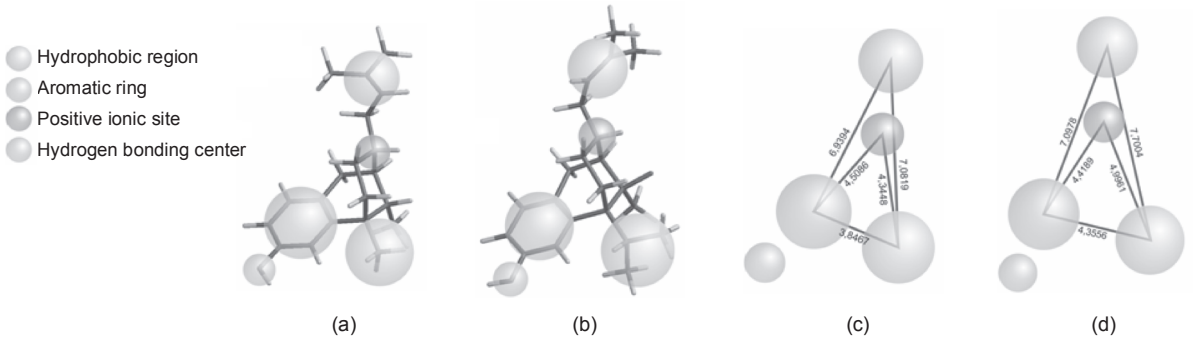

***Fig*. 19.** Possible sites of receptor interaction: (a) Pentazocine (b) Pentazocine analogue. Spatial arrangement: (c) Pentazocine (d) Pentazocine analogue.

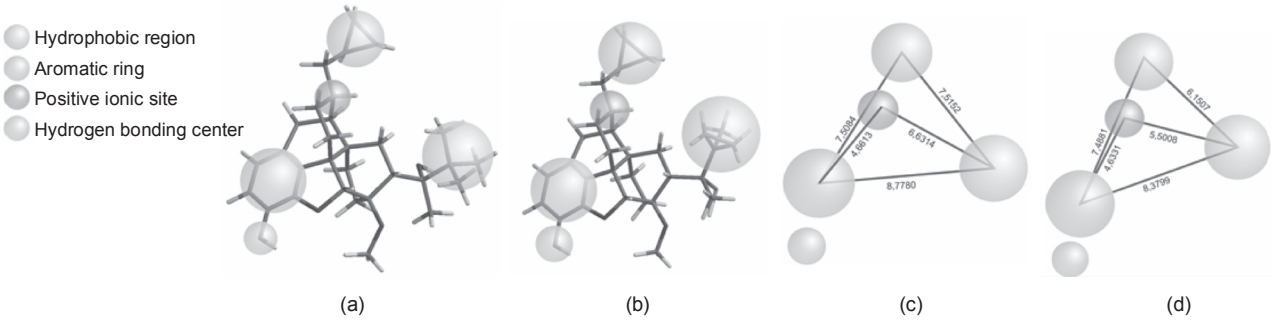

***Fig*. 20.** Possible sites of interaction: (a) Buprenorphine (b) Buprenorphine analogue. Spatial arrangement: (c) Buprenorphine (d) Buprenorphine analogue.

The possible sites of receptor interaction that the model molecules and the analogues had in common were two hydrophobic regions, a protonated amine group, an aromatic ring, and a phenol hydroxyl group (*Figs*. 19 and 20). The spatial arrangement of these potential interaction sites is very similar for the analogues and the model molecules.

In the pentazocine analogue, the distances between the possible sites of interaction were slightly larger than those exhibited by pentazocine, except for the distance between the aromatic ring and the protonated amino group. This is because of the isopropyl alkyl group, which places its hydrophobic region a little farther away due to its higher volume, and also because the N-substituent has adopted a different conformation.

The hydrophobic region in the buprenorphine analogue is found closer to the other sites of possible interaction than in buprenorphine, due to the adopted conformation by the methylciclopropyl group.

CONCLUSIONS

The method used for calculations reproduces the geometry of the studied molecules satisfactorily, as the found deviations from the experimental data were not significant. Therefore, the chemical model B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) is a good approximation of the physical reality of the studied molecules, meaning that the obtained data is reliable and recommended for the study of such structures.

Each molecule studied has a different affinity for a particular receptor (μ, δ, and κ), while maintaining the pharmacophore properties almost intact. This indicates that the selectivity of the studied molecules for different receptors depends on the geometry and electronic structure of the substituents, and not on the geometry and electronic properties of the pharmacophore. In the proposed analogues, the partition coefficients have higher values than in the model molecules, indicating their efficiency in crossing biological barriers and reaching their receptor sites.

Because the model molecules and their proposed analogues exhibit similar geometry, electronic properties, Log P, and spatial arrangement of possible interaction sites, it is likely that these analogues exhibit some kind of biological activity.

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