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Conceptual Density Functional Theory Study of the Chemical Reactivity Properties and Bioactivity Scores of the Leu-Enkephalin Opioid Peptide Neurotransmitter

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Abstract

The SMD solvation model (Solvation Model based on the Density) and eight density functionals, CAM-B3LYP, LC-ωPBE, M11, MN12SX, N12SX, ωB97, ωB97X, and ωB97XD, were assessed in link with the Def2TZVP basis set for the calculation of the structure of the Leu-Enkephalin Opioid Peptide Neurotransmitter as well as their molecular properties. Through the Conceptual Density Functional Theory (CDFT), the entire chemical descriptors for the system were calculated. The active regions of the molecules necessary for electrophilic, nucleophilic and radical attacks were chosen through linking them with the corresponding Fukui functions. Furthermore, the prediction of the pKa value for the peptide is done with great accuracy as well as the ability of the studied molecule in acting as an efficient inhibitor of the formation of Advanced Glycation Endproducts (AGEs), which comprises of a useful knowledge for the development of drugs for preventing Alzheimer, Diabetes and Parkinson diseases. Lastly, the bioactivity scores for the studied peptides are predicted via various methodologies.

Keywords

Leu-Enkephalin, Opioid Neurotransmitters, Computational Chemistry, Conceptual DFT, Bioactivity Scores

1. Introduction

For the consideration of therapeutic peptides from the point of view of medicine,

it is necessary to know their molecular properties and their bioactivity. It is our belief that the bioactivity of these peptides is intimately related to their chemical reactivity from a molecular perspective. For this reason, we consider it essential to study the chemical reactivity of natural products that have the potential to become medicines through the tools provided by Computational Chemistry and Molecular Modeling. Probably the most powerful tool currently available to study the chemical reactivity of molecular systems from the point of view of Computational Chemistry and Molecular Modeling is the Conceptual DFT [1] [2], also called Chemical Reactivity Theory, which using a series of global and local descriptors allow to predict the interactions between molecules and understand the way in that chemical reactions proceed.

When one is working with Computational Chemistry and Molecular Modeling, there is not a universal methodology that could be applied to the entire spectra of known or unknown molecular systems. As it, also our own devised methodology cannot be considered useful for all the systems. The workaround that researchers in this field have found relies in studying with a particular methodology different but related families of molecules in order to see if the proposed methodology can be applied with the same degree of success to the different group of molecules and that the results obtained with a particular family of molecules are good not by chance or some kind of serendipity. Indeed, the larger the number of studies with different groups of molecules increases the validity of the used methodologies.

Considering that the knowledge of the chemical reactivity is essential for the development of new medicines, we have decided to study in this work the Leucine-Enkephalin which is an endogenous opioid peptide neurotransmitter that is found naturally in the brains of many animals and humans [3] [4] and that could be the foundation for the design of new therapeutic peptides by relying on a protocol that we have devised recently as a way to validate it with the study of the chemical properties of this important peptide.

Then, rather than employing the usual methodology in Medicinal Chemistry research based on Molecular Docking and QSAR and QSPR approximations, we prefer to rely on that mentioned protocol for our research on peptides. Thus, the objective of this work is to study the chemical reactivity of the Leu-Enkephalin opioid peptide neurotransmitter using the techniques of the Conceptual DFT, determining its global properties (of the molecule as a whole) as well as the local properties that allow to understand and predict active reaction sites, both electrophilic and nucleophilic by considering the recent methodology proposed by us [5]-[12]. Likewise, the pKa value of the peptide will be predicted based on a methodology previously developed by us [13], the ability of this potentially therapeutic peptide to act as inhibitor of the formation of Advanced Glycation Endproducts (AGEs) will be established according to our previous ideas [14], and the descriptors of bioavailability and bioactivity (Bioactivity Scores) will be calculated through different procedures described in the literature. Thus, The knowledge of the values of the global and local descriptors of the molecular reac-

tivity of the Leu-Enkephalin peptide studied could be useful in the development of new drugs based on this compound or some analogs.

2. Computational Methodology

Consistent with our previous work [5]-[12], the computational studies were performed with the Gaussian 09 [15] series of programs that implement density functional methods. The basis set Def2SVP was used in this work for geometry optimization and frequency determination, while the Def2TZVP basis set was used for calculating electronic properties [16] [17]. All calculations were performed in the presence of water as solvent under the Solvation Model Density (SMD) parameterization of the Integral Equation Formalism-Polarized Continuum Model (IEF-PCM) [18].

To calculate the molecular structure and properties of the studied system, we have chosen eight density functionals known to consistently provide satisfactory results for several structural and thermodynamic properties:

CAM-B3LYP	Long-range-corrected B3LYP by the CAM method	[19]
LC-ωPBE	Long-range-corrected ωPBE density functional	[20]
M11	Range-separated hybrid meta-GGA	[21]
MN12SX	Range-separated hybrid nonseparable meta-NGA	[22]
N12SX	Range-separated hybrid NGA	[22]
*ω*B97	Long-range corrected density functional	[23]
*ω*B97X	Long-range corrected density functional	[23]
*ω*B97XD	*ω*B97X version including empirical dispersion	[24]

In these functionals, GGA denotes the generalized gradient approximation, in which the density functional depends on the up/down spin densities and their reduced gradient, and NGA denotes the nonseparable gradient approximation, which is similar to GGA but also adopts a nonseparable form.

The SMILES notation of the studied compound was fed in the online Molinspiration software from Molinspiration Cheminformatics (www.molins.piration.com) for the calculation of the molecular properties (Log P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds, etc.) and for the prediction of the bioactivity score for different drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors). The bioactivity scores were compared with those obtained through the use of other software like MolSoft from Molsoft L.L.C. (http://molsoft.com/mprop/) and ChemDoodle Version 9.02 from iChemLabs L.L.C. (www.chemdoodle.com).

3. Results and Discussion

3.1. Geometry Optimization and Global Reactivity Descriptors Calculation

The molecular structure of Leu-Enkephalin, which graphical sketch is shown in Figure 1, was preoptimized in the gas phase by considering the DFTBA model

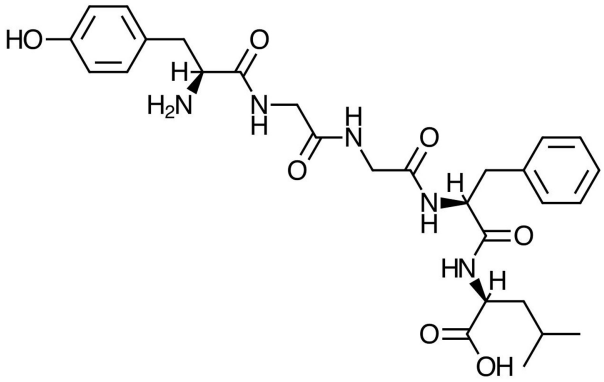


Figure 1. Graphical sketch of the Leu-Enkephalin molecule.

available in Gaussian 09 and then reoptimized using the eight density functionals mentioned in the previous section together with the Def2SVP basis set and the SMD solvent model using water as the solvent. After verifying that each of the structures corresponded to the minimum energy configurations through a frequency calculation analysis, the electronic properties were determined by using the same model chemistry but with the Def2TZVP basis set instead of that used for the geometry optimization.

The analysis of the results obtained in the study aimed at verifying that the KID procedure was fulfilled. On doing it previously, several descriptors associated with the results that the HOMO and LUMO calculations obtained are related with results obtained using the vertical I and A following the ΔSCF procedure. A link exists between the three main descriptors and the simplest conformity to the Koopmans' theorem by linking ϵ_H with-I, ϵ_L with-A, and their behavior in describing the HOMO-LUMO gap as $J_I = \left|\epsilon_H + E_{gs}(N-1) - E_{gs}(N)\right|$, $J_A = \left|\epsilon_L + E_{gs}(N) - E_{gs}(N+1)\right|$, and $J_{HL} = \sqrt{J_I^2 + J_A^2}$. Notably, the J_A descriptor consists of an approximation that remains valid only when the HOMO that a radical anion has (the SOMO) shares similarity with the LUMO of the neutral system. Consequently, we decided to design another descriptor ΔSL, to guide in verifying the accuracy of the approximation [5]-[11]. The results of this analysis are presented in **Table 1**.

As can be seen from **Table 1**, the results for the descriptors show values that are consistent with our previous findings for the case of the melanoidins [5]-[11], that is, only the MN12SX and N12SX density functionals are capable of giving HOMO and LUMO energies that allow verifying the agreement with the approximate Koopmans' theorem. This is not only true because the J_{HL} values are almost zero, but due to the fact that the ΔSL descriptor, which relates to the difference between the LUMO of the neutral and the HOMO of the anion, is also close to zero. Indeed, these values cannot be exactly equal to zero, but the small differences mean that errors in the prediction of the global reactivity descriptors will be negligible. Moreover, it can be seen from **Table 1** that the MN12SX and N12SX density functionals are the only ones that predict negative values for the LUMO energies which will represent positive values of the electron affinity A.

Table 1. Electronic energies of the neutral, positive, and negative molecular systems (in au) of Leu-Enkephalin; the HOMO, LUMO, and SOMO orbital energies (in eV); and the J_I, J_A, J_{HL} and ΔSL descriptors calculated with the eight density functionals and the Def2TZVP basis set using water as the solvent simulated with the SMD parametrization of the IEF-PCM model.

	Eo	E+	E−	HOMO	LUMO
CAM-B3LYP	−1887.46	−1887.25	−1887.49	−7.46	0.83
LC-*ω*PBE	−1887.19	−1886.97	−1887.22	−8.78	1.77
M11	−1887.32	−1887.09	−1887.34	−8.60	1.58
MN12SX	−1886.67	−1886.44	−1886.70	−6.16	−0.83
N12SX	−1887.50	−1887.29	−1887.53	−5.88	−0.68
*ω*B97	−1888.09	−1887.87	−1888.12	−8.66	1.89
*ω*B97X	−1887.93	−1887.71	−1887.96	−8.47	1.73
*ω*B97XD	−1887.91	−1887.59	−1887.94	−8.08	1.37
	SOMO	J_I	J_A	J_{HL}	ΔSL
CAM-B3LYP	−2.20	1.49	1.50	2.12	3.03
LC-*ω*PBE	−3.51	2.63	2.62	3.71	5.28
M11	−3.12	2.41	2.33	3.36	4.71
MN12SX	−0.87	0.01	0.02	0.03	0.04
N12SX	−0.78	0.00	0.05	0.05	0.11
*ω*B97	−3.30	2.62	2.57	3.67	5.19
*ω*B97X	−3.14	2.43	2.51	3.42	4.87
*ω*B97XD	−2.81	2.06	2.07	2.92	4.18

An opposite and incorrect (unphysical) behavior is observed from **Table 1** for the other density functionals considered in this work.

By taking into account the KID procedure presented in our previous works together with the finite difference approximation, the global reactivity descriptors can be expressed as:

Electronegativity $$\chi = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\epsilon_L + \epsilon_H)$$ [1] [2]

Global Hardness $$\eta = (I - A) \approx (\epsilon_L - \epsilon_H)$$ [1] [2]

Electrophilicity $$\omega = \frac{\mu^2}{2\eta} = \frac{(I + A)^2}{4(I - A)} \approx \frac{(\epsilon_L + \epsilon_H)^2}{4(\epsilon_L - \epsilon_H)}$$ [25]

Electrodonating Power $$\omega^- = \frac{(3I + A)^2}{16(I - A)} \approx \frac{(3\epsilon_H + \epsilon_L)^2}{16\eta}$$ [26]

Electroaccepting Power $$\omega^+ = \frac{(I + 3A)^2}{16(I - A)} \approx \frac{(\epsilon_H + 3\epsilon_L)^2}{16\eta}$$ [26]

Net Electrophilicity $$\Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^-$$ [27]

where ϵ_H and ϵ_L are the energies of the HOMO and LUMO, respectively.

According to our previous discussion, the results for the calculated global reactivity descriptors based on the values of the HOMO and LUMO energies

according to the previous definitions will be significative only for the MN12SX and N12SX density functionals. Thus, these results are presented in **Table 2**.

As expected from the molecular structure of this species, its electrodonating ability is more important that its electroaccepting character. There is no significative differences between the values obtained by using either of the density functionals for the calculation of the global reactivity descriptors. Notwithstanding, after an inspection of **Table 1** it can be said that the MN12SX density functional is a somewhat better that the N12SX density functional in verifying the approximate Koopmans behavior. Thus, only the MN12SX density functional will be considered for the remaining of this work.

3.2. Local Reactivity Descriptors Calculation

Applying the same ideas as before, the definitions for the local reactivity descriptors will be:

Nucleophilic Fukui Function	$f^{+}(\mathbf{r}) = \rho_{N+1}(\mathbf{r}) - \rho_{N}(\mathbf{r})$	[1] [2]
Electrophilic Fukui Function	$f^{-}(\mathbf{r}) = \rho_{N}(\mathbf{r}) - \rho_{N-1}(\mathbf{r})$	[1] [2]
Dual Descriptor	$\Delta f(\mathbf{r}) = \left(\frac{\partial f(\mathbf{r})}{\partial N}\right)_{\upsilon(\mathbf{r})}$	[28]-[33]
Nucleophilic Parr Function	$P^{-}(\mathbf{r}) = \rho_{s}^{rc}(\mathbf{r})$	[34] [35]
Electrophilic Parr Function	$P^{+}(\mathbf{r}) = \rho_{s}^{ra}(\mathbf{r})$	[34] [35]

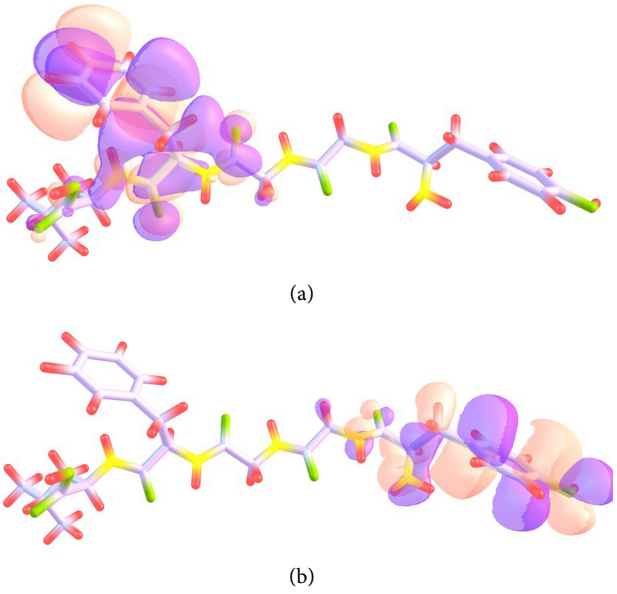
where $\rho_{N+1}(\mathbf{r})$, $\rho_{N}(\mathbf{r})$, and $\rho_{N-1}(\mathbf{r})$ are the electronic densities at point $\mathbf{r}$ for a system with $N+1$, N, and $N-1$ electrons, respectively, and $\rho_{s}^{rc}(\mathbf{r})$ and $\rho_{s}^{ra}(\mathbf{r})$ are related to the atomic spin density (ASD) at the $\mathbf{r}$ atom of the radical cation or anion of a given molecule, respectively [36].

The Electrophilic Fukui function $f^{-}(\mathbf{r})$ and Nucleophilic Fukui function $f^{+}(\mathbf{r})$ for the Leu-Enkephalin molecule are shown in **Figure 2(a)** and **Figure 2(b)**, respectively.

As it has been stated by Martínez-Araya in some recent works [31] [32] [33], while the Fukui function is a nice descriptor to understand the local reactivity of the molecules, it can be demonstrated that the Dual Descriptor in its condensed form Δf_k will perform better for the prediction of the preferred sites for the electrophilic and nucleophilic attacks. For this reason, we have decided to

Table 2. Global reactivity descriptors for the Leu-Enkephalin molecule calculated with the MN12SX and N12SX density functionals with the Def2TZVP basis set and the SMD solvation model using water as the solvent.

	Electronegativity (χ)	Chemical Hardness (η)	Electrophilicity (ω)
MN12SX	3.4976	5.3321	1.1471
N12SX	3.2797	5.2015	1.0340
	Electrodonating Power (ω^{-})	Electroaccepting Power (ω^{+})	Net Electrophilicity ($\Delta\omega^{\pm}$)
MN12SX	4.3763	0.8787	5.2551
N12SX	4.0328	0.7532	4.7860



(a)

(b)

Figure 2. (a) Electrophilic Fukui function $f^{-}(\mathbf{r})$ and (b) Nucleophilic Fukui function $f^{+}(\mathbf{r})$ for the Leu-Enkephalin molecule.

present the results for the Condensed Dual Descriptor Δf_k as calculated from either Mulliken Population Analysis (M) or Natural Population Analysis (N) in comparison with the Nucleophilic Parr Function P_k^+ and Electrophilic Parr Function P_k^- proposed by Domingo *et al.* [34] [35] considering atomic spin densities coming from the mentioned Mulliken Population Analysis (M) or from Hirshfeld Population Analysis (H).

The results for the calculation of these local reactivity descriptors for the Leu-Enkephalin molecule are presented in **Table 3**. It must be noted that we are presenting only the results for those atomic sites where the Δf_k (which is itself multiplied by 100) are greater than 1. Also, the H atoms are not shown.

As can be seen from **Table 3**, the local reactivity descriptors calculated from the different formulations are able to recognize the nucleophilic and electrophilic sites for chemical reactivity with great accuracy. Moreover, there is an impressive agreement between the results coming from the Condensed Dual Descriptor Δf_k and the Nucleophilic and Electrophilic Parr Functions P_k^+ and P_k^- which means that their use in this and future works related to the study of therapeutic peptides will be a warranty of success.

3.3. Determination of pKa Value of the Peptide

We have recently presented a study of the computational prediction of the pKas of small peptides through Conceptual DFT descriptors [13]. In that work, we concluded that the relationship pKa = 16.3088 - 0.8268η could be a valuable starting point for the prediction of the pKa of larger peptides of interest for the development of AGE inhibitors.

Table 3. Local reactivity descriptors for the Leu-Enkephalin molecule calculated with the MN12SX density functional with the Def2TZVP basis set and the SMD solvation model using water as the solvent: Condensed Dual Descriptor Δf_k, Nucleophilic Parr Function P_k^+ and electrophilic parr function P_k^-; M stands for mulliken population analysis, N corresponds to natural population analysis and h means hirshfeld population analysis.

Atom	Δf_k (M)	Δf_k (N)	P_k^+ (M)	P_k^- (M)	P_k^+ (H)	P_k^- (H)
1 O	2.89	3.66	0.0347	0.0000	0.0366	0.0000
7 O	−16.41	−15.13	0.0000	0.2070	0.0000	0.1927
8 N	1.24	1.51	0.0020	0.0000	0.0088	0.0000
12 N	−2.17	−1.95	0.0000	0.0328	0.0000	0.0246
16 C	2.28	0.31	0.0275	0.0000	0.0233	0.0000
19 C	5.74	3.94	0.0670	0.0000	0.0566	0.0000
20 C	1.95	0.68	−0.0068	0.0000	0.0258	0.0000
22 C	16.48	9.77	0.2391	0.0000	0.1465	0.0000
23 C	1.55	1.74	0.0151	0.0000	0.0118	0.0000
25 C	22.74	20.32	0.3209	0.0000	0.2011	0.0000
27 C	−1.92	−0.43	0.0000	0.0174	0.0000	0.0251
28 C	−1.20	−2.31	0.0000	−0.0331	0.0000	0.0240
29 C	20.17	17.13	0.2860	0.0000	0.1837	0.0000
31 C	−24.58	−20.24	0.0000	0.4101	0.0000	0.2325
33 C	17.36	12.95	0.2005	0.0000	0.1483	0.0000
36 C	−5.57	−3.43	0.0000	−0.0296	0.0000	0.0395
37 C	−5.02	−2.65	0.0000	−0.0423	0.0000	0.0324
38 C	−10.13	−8.39	0.0000	0.0953	0.0000	0.0927
39 C	−11.33	−9.63	0.0000	0.1159	0.0000	0.1052
40 C	−18.27	−12.77	0.0000	0.2203	0.0000	0.1863

Thus, we have now applied the mentioned relationship to the calculation of the pKa of the Leu-Enkephalin molecule giving a result of 11.90. This result could be of interest when designing pharmaceutical drugs starting from these peptide allowing to explain the mechanisms of action and the drug delivery procedures.

3.4. Quantification of the AGEs Inhibitor Ability

The Maillard reaction between a reducing carbonyl and the amino group of a peptide or protein leads to the formation of a Schiff base which through a series of steps renders different molecules known as Advanced Glycation Endproducts or AGEs. It is believed that the presence of these AGEs is one of the main reasons for the developing of some diseases like Diabetes, Alzheimer and Parkinson.

Among several strategies that have been considered for the prevention of the formation of AGEs, it is worth to mention the use of compounds presenting amino groups in their structure capable of interacting with the reducing car-

bonyl of carbohydrates and being competitive with the amino acids, peptides and proteins present in our body. Many compounds have been devised as drugs to achieve this goal and to name a few, we can include Pyridoxamine, Aminoguanidine, Carnosine, Metformin, Pioglitazone and Tenilsetam.

It can be proposed that peptides having amino and amido groups could be thought as potential therapeutic drugs for preventing the formation of AGEs. In a previous work, we have studied the ability of a group of proposed molecules to act as inhibitors of the formation of AGEs by quantifying their behavior in terms of Conceptual DFT reactivity descriptors [14]. It was concluded that the key factor in the study of the chemical reactivity of the potential AGEs inhibitors was on their nucleophilic character and although there are several definitions of nucleophilicity [37], our results suggested that the inverse of the net electrophilicity $\Delta\omega^{\pm}$ could be a good definition for the nucleophilicity N. On the basis of the mentioned analysis, we were able to find some qualitative trends for the studied molecular systems.

In this work, we will extend this correlation to the Leu-Enkephalin peptide in order to see if it can be considered as a precursor of therapeutic drugs for the inhibition of the formation of AGEs. As the model chemistry employed in both works is the same, the comparison is straightforward:

Aminoguanidine > Metformin > Carnosine > Leu-Enkephalin > Tenilsetam > Pyridoxamine > Pioglitazone

This qualitative trend is representative of the known pharmacological properties of the studied AGEs inhibitors [38] [39] and it can be seen that Leu-Enkephalin possesses better AGEs Inhibitor Ability that Tenilsetam and Pyridoxamine, but lower than Aminoguanidine, Metformin and Carnosine.

3.5. Bioactivity Scores

When considering a given molecular system as a potential therapeutic drug, it is customary to check if the considered species follows the Lipinsky Rule of Five which is used to predict whether a compound has or not has a drug-like character [40]. The molecular properties related to the drug-like character were calculated with the aid of the MolSoft and Molinspiration software and are presented in **Table 4** where miLogP represents the octanol/water partition coefficient, TPSA is the molecular polar surface area, natoms is the number of atom of the molecule, nON and nOHNH are the number of hydrogen bond acceptors and hydrogen bond donors respectively, nviol is the number of violations of the

Table 4. Molecular properties of the Leu-Enkephalin peptide calculated to verify the Lipinsky Rule of Five.

Molecule	miLogP	TPSA	nAtoms	nON	nOHNH
Leu-Enkephalin	−0.85	199.94	40	12	8
Molecule	nviol	nrotb	volume	MW	
Leu-Enkephalin	3	15	511.75	555.63	

Lipinsky Rule of Five, nrotb is the number of rotatable bonds, volume is the molecular volume, and MW is the molecular weight of the studied system.

However, what the Lipinsky Rule of Five really measures is the oral bioavailability of a potential drug because this is desired property for a molecule having drug-like character. Indeed, this criteria cannot be applied to peptides, even when they are small, as we can see from Table 4, due to the inherent molecular weight and number of hydrogen bonds.

In a more recent work, Martin [41] have developed what she called "A Bioavailability Score" (ABS) for avoiding these problems. The rule for the ABS established that the Bioavailability Score for neutral organic molecules must be 0.55 if they pass the Lipinsky Rule of Five and 0.170 if they fail. The ABS value for all the Leu-Enkephalin peptide considered in this work have been calculated by using the ChemDoodle software and the result was equal to 0.170.

Then, a different approach was followed by considering similarity searches in the chemical space of compounds with structures that can be compared to those that are being studied and with known pharmacological properties.

As has been mentioned in the Settings and Computational Methods section, this task can be accomplished using the online Molinspiration software for the prediction of the bioactivity score for different drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors). The results are named Bioactivity Scores and the values for the Leu-Enkephalin are presented in Table 5.

These bioactivity scores for organic molecules can be interpreted as active (when the bioactivity score > 0), moderately active (when the bioactivity score lies between −5.0 and 0.0) and inactive (when the bioactivity score < −5.0) as it is summarized in Table 6. The Leu-Enkephalin peptide was found to be bioactive towards the Protease Inhibitor and the GPCR Ligand considered in the study.

Table 5. Bioactivity scores of the Leu-Enkephalin molecule calculated on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor intteractions.

Molecule	GPCR	Ion Channel	Kinase
	Ligand	Modulator	Inhibitor
Leu-Enkephalin	0.38	−0.05	−0.10
Molecule	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
Leu-Enkephalin	0.06	0.59	0.18

Table 6. Factors for evaluation of bioactivity.

Active	Moderately Active	Inactive
>0	Between −5.0 and 0.0	<−5.0

4. Conclusions

In this paper, we have presented the results of a study of the chemical reactivity of the Leucine-Enkephalin opioid neurotransmitter peptide based on the Conceptual DFT as a tool to explain the molecular interactions.

The knowledge of the values of the global and local descriptors of the molecular reactivity of the Leu-Enkephalin peptide studied could be useful in the development of new drugs based on this compound or some analogs.

In a similar manner, the pKa value for the potentially therapeutic peptide has been predicted by resorting to the value of the chemical hardness following a previously proposed methodology and the information that resulted would be helpful in understanding not only the chemical reactivity but other important properties like the water solubility.

A point of special interest has been the quantification of the ability of the peptide to act as an inhibitor in the formation of AGEs and this could be of importance for the design of medicines for fighting diseases like Diabetes, Alzheimer or Parkinson.

Finally, the molecular properties related to bioavailability have been predicted using different methodologies already described in the literature, and the descriptors used for the quantification of the bioactivity allowed characterizing the studied peptide as being bioactive towards the Protease Inhibitor and the GPCR Ligand considered in the study. In this way, our work is on the same line as previous studies on the bioactivity of organic molecules [42] [43] with the novelty of being applied to a peptide of great therapeutic importance.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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