Medicinal Chemistry

Flores-Holguín et al., Med Chem (Los Angeles) 2019, 9:3
DOI: 10.4172/2161-0444.1000530

Research Article Open Access

An Alternative Approach to Computational Peptidology Based on Conceptual DFT and Empirical Bioactivity Scores

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Abstract

This work presents the results of a study of the global and local chemical reactivity of the antineoplastic Elisidepsin and Plitidepsin marine drugs based on the calculation of descriptors coming from Conceptual DFT for their consideration as a tool to explain the molecular interactions, and as a useful complement to those approximations based on Molecular Docking. The knowledge of the values of the global and local descriptors of the molecular reactivity of the Elisidepsin and Plitidepsin molecules obtained through our proposed methodology could be useful in the development of new drugs based on these compound or some analogs relying in the chemical interaction between these peptides and their biological receptors of protein kind. It can be concluded that the Conceptual DFT approximation to the global and local chemical reactivity based on the descriptors can provide interesting information for the consideration of both molecules a potential drugs. This is complemented with a study on AGEs inhibition by comparison with the usual molecular systems considered for that task. Finally, the bioactivity scores for Elisidepsin and Plitidepsin are predicted by considering similarity searches of compounds with structures that can be compared to those that are being studied whose pharmacological properties are well known.

Keywords: Elisidepsin; Plitidepsin; Conceptual DFT; Global chemical reactivity; Local chemical reactivity properties; AGEs inhibition ability; Bioactivity scores

Introduction

There has been an increasing interesting during the last years on the study of cyclic peptides (CP), specially those that can be obtained from marine sources, because of their potential pharmacological applications to fi t several diseases. Elisidepsin and Plitidepsin are cyclodepsipeptides, that is, peptides in which one or more of its amide, groups are replaced by the corresponding ester. In particular, Elisidepsin is a synthetic cyclodepsipeptide derived from a marine metabolite that exhibits antineoplastic properties. Thus, Elisidepsin and Plitidepsin represent nice examples of marine drugs that could be incorporated in the practice of Medicinal Chemistry.

From the medicinal chemistry point of view, peptides exert their action by interacting with the active sites of their respective receptors which are generally proteins. These processes are theoretically studied through the recently presented fi of Computational Peptidology whose some of their techniques have been already described and discussed [1,2].

One of these techniques is called Molecular Docking which has been proven as a useful and indispensable tool in Medicinal Chemistry [3,4]. However, it has already found that this process can only be performed accurately for peptides not exceeding three amino acids long [1,2], making it necessary to resort to some other techniques acting not as a replacement of Molecular Docking but as complementary ones.

Within Computational Chemistry and Molecular Modelling practice, it is common to resort to Conceptual DFT [5,6], 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. For this reason, we have been studying with great success the chemical reactivity properties of a series of carbohydrates involved in the Maillard reaction, some small peptides, several melanoidinic colorants [7-13] and lately, a family of anticancer peptides of marine origin [14]. In all these studies, a search was performed to fi the most well behaved density functional by resorting to a procedure proposed by the authors [7-14].

Thus, the objective of this work is to perform a comparative study the chemical reactivity of the Elisidepsin and Plitidepsin cyclodepsipeptides of marine origin by resorting to Conceptual DFT, in addition to an investigation of their potential AGEs inhibition abilities. Moreover, the bioactivity scores for Elisidepsin and Plitidepsin are predicted 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.

Settings and Computational Methods

In the same way as we have proceded in our recent studies [7-14], the computational tasks in this work have been done by considering the popular Gaussian 09 software [15]. Following the conclusions obtained from those studies, the MN12SX density functional [16] is chosen again because it can be considered a well-behaved according to our proposed mentioned criteria. Accordingly, the calculation of the electronic properties used a model chemistry based on the mentioned deensity functional in connection with the Def2TZVP basis set while a smaller Def 2SVP was considered for the pre- diction of the most stable structures [17,18]. In order to obtain accurate results, all calculations were performed using water as the solvent simulated with the SMD model [19].

Results and Discussion

The molecular structures of the Elisidepsin and Plitidepsin

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Received February 25, 2019; **Accepted** March 11, 2019; **Published** March 18, 2019

Citation: Flores-Holguín N, Frau J, Glossman-Mitnik D (2019) An Alternative Approach to Computational Peptidology Based on Conceptual DFT and Empirical Bioactivity Scores. Med Chem (Los Angeles) 9: 020-023. doi: 10.4172/2161-0444.1000530

cyclodepsipep- tides, which are depicted in Figure 1, were preoptimized in the gas phase by resorting to the Density Functional Theory Tight Binding (DFTBA) model available in Gaussian 09. The resulting conformers were processed as it is customary within Computational Chemistry to obtain the desired calculated properties acoording to the techniques mentioned in the previous section.

As previously stated, the first step was to verify that the model chemistry considered in this study corresponded to a well-behaved density functional and for this objective we resorted to several descriptors proposed by us [7-14] that can help in the verification of our designed procedure. The results of this analysis are presented in Table 1.

From Table 1, the results for the descriptors show values that are con- sistent with our previous fi for the case of the melanoidins [7-13] and peptides of marine origin [14], that is, the MN12SX density functional is capable of giving HOMO and LUMO energies that allow to verify the agreement with the approximate Koopmans' theorem.

After that verification, the values of the chemical reactivity descriptors coming from Conceptual DFT and whose definitions are provided as the electronegativity $\chi=-1\backslash 2(I+A) \approx 1\ (E_L+E_H)$ [5,6], the global hardness $\eta=(I-A) \approx (E_L+E_H)$ [5,6], the electrophilicity $\omega=\mu^2/2\eta=(I+A)^2/4(I-A) \approx (E_L+E_H)^2/4(E_L-E_H)$ [20], the electrodonating power $\omega^-=(3I+A)2/16(I-A)\approx(3E_H+E_L)^2/16\eta$ [21], the electroaccepting power $\omega^+=(I+3A)^2/16(I-A) \approx (E_H+3_{EL})^2/16\eta$ [21], and the net electrophilic- ity $\Delta\omega^{\pm}=\omega^+-(-\omega^-)=\omega^++\omega^-$ [22], where EH and EL are the energies of the HOMO and LUMO, respectively, which results for the Elisidepsin and Plitidepsin cyclodepsipeptides are presented in Table 2.

If we now focus on the local reactivity descriptors coming from Conceptual DFT, then the definitions will be: Nucleophilic Fukui Function $f^+(r)=\rho N+1(r)-\rho N\ (r)$ [5,6], Electrophilic Fukui Function $f-(r)=\rho N\ (r)-\rho N-1(r)$ [5,6]. Dual Descriptor $\Delta f\ (r)=(\partial\ f\ (r)/\partial\ N)\upsilon(r)$ [23-28], where $\rho N+1(r)$, $\rho N\ (r)$, and $\rho N-1(r)$ are the electronic densities at point r for a system with N+1, N, and N-1 electrons, respectively.

Figures 2 and 3 display the graphical sketches of the HOMO and LUMO of the Elisidepsin and Plitidepsin cyclodepsipeptides as approximation to the electrophilic and nucleophilic Fukui functions examples of the local reactivity descriptors.

For the consideration of natural products to be useful for applications in Medicinal Chemistry, the knowledge of their pK is very important. For large molecules like the peptides studied in this work, the experimental de- termination of the pKa is sometimes difficult. However, we have already shown that the pKa of a peptide can be predicted by applying a relationship with the global hardness η [29]. Thus, the values of the pKas of Elisidepsin and Plitidespin determined through that relationship are presented in Table 3.

It is our belief that these results could be of interest for the processes that involve drug design and development using these peptides.

The Maillard reaction is, in fact, a collection of chained chemical reactions that start from the interaction between a reducing carbonyl and the free amino group of a peptide or protein. This chain of reactions leads to a fi group of molecules known as Advanced Glycation Endproducts or AGEs which are considered as the main reasons for the developing of some diseases, such as Diabetes, Alzheimer and Parkinson [30].

Many compounds have been devised as drugs to achieve the goal of in- hibiting the formation of AGEs which include Pyridoxamine, Aminoguani- dine, Carnosine, Metformin, Pioglitazone and Tenilsetam [31,32]. We have already proposed that peptides having amino and amido groups could be thought as potential therapeutic drugs for preventing the formation of AGEs, because they could react in the Maillard reaction with reducing carbohy- drates before the peptides and proteins of our body [33]. Our previous results lead us to conclude that the inverse of the net electrophilicity $\Delta\omega\ \pm$ represents a good defi for the nucleophilicity N [34], which, in turn, could be a good descriptor for the AGEs inhibition ability.

If we consider that this relationship is valid, then based on the calcu- lated global descriptors for Elisidepsin and Plitidepsin, it should be possible to predict their AGEs inhibition ability by comparison with the mentioned drugs:

ALT946>Aminoguanidine>Metformin>Carnosine>>Tenilsetam> Pyridoxamine>Pioglitazone>>Elisidepsin>Plitidepsin.

This qualitative trend is representative of the known pharmacological properties of the studied AGEs inhibitors [31,32] and it can be seen that the studied peptides possess AGEs Inhibitor Abilities which are lower to that of other molecular systems already in the market.

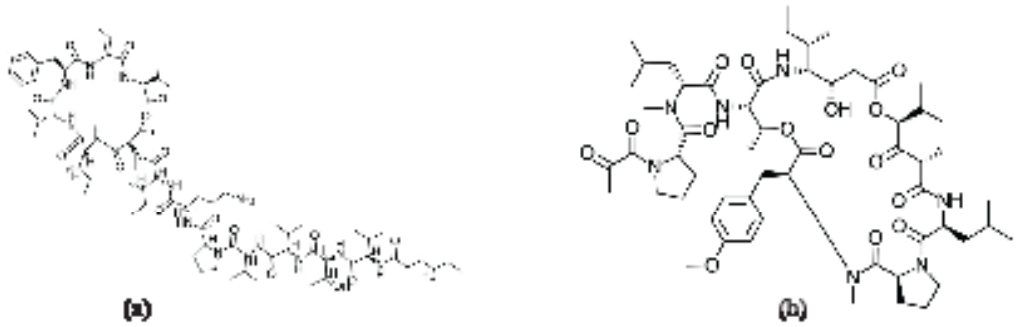
When looking for the potential therapeutic capacities of new molecules, an interesting approach is based on considering similarity searches in the chemical space of compounds with structures that can be compared to those that are being studied and with known pharmacological properties. These values are known as Bioactivity Scores and can be easily estimated by re- sorting to the free online Molinspiration software as shown in Table 4.

	Eo	E+	E-	HOMO	LUMO
Elisidepsin	-4900.910	-4900.675	-4900.971	-6.539	-1.576
Plitidepsin	-3734.627	-3734.403	-3734.710	-6.128	-2.199
	SOMO	JI	JA	JHL	ΔSL
Elisidepsin	-1.714	0.134	0.069	0.151	0.138
Plitidepsin	-2.340	0.048	0.078	0.091	0.141

Table 1: Total and orbital electronic energies as well as the accuracy descriptors for Elisidepsin and Plitidepsin calculated acoording to our proposed methodology.

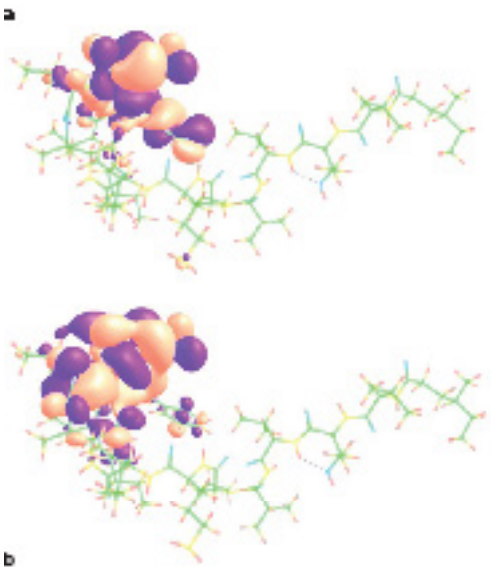
	Electronegativity (χ)	Chemical Hardness (η)	Electrophilicity (ω)
Elisidepsin	4.0576	4.9647	1.6581
Plitidepsin	4.1636	3.9310	2.2050
	Electrodonating Power (ω^-)	Electroaccepting Power (ω^+)	Net Electrophilicity ($\Delta\omega^{\pm}$)
Elisidepsin	5.6554	1.5977	7.2531
Plitidepsin	6.7375	2.5739	9.3114

Table 2: Global reactivity descriptors for the Elisidepsin and Plitidepsin molecules calcu- lated with the MN12SX density functional with the Def2TZVP basis set and the SMD solvation model using water as the solvent.



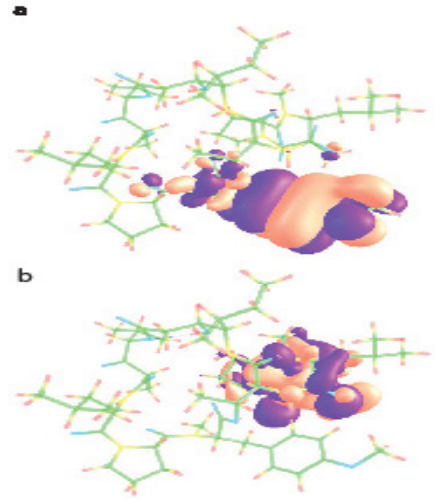
a: Elisidepsin. **b:** Plitidepsin.

Figure 1: Graphical sketches of the molecular structures of the cyclodepsipeptides: a) Elisidepsin and b) Plitidepsin.



a: HOMO. **b:** LUMO.

Figure 2: Graphical sketches of the HOMO and LUMO of the Elisidepsin cyclodepsipeptide as approximations to the electrophilic and nucleophilic Fukui functions.



a: HOMO. **b:** LUMO.

Figure 3: Graphical sketches of the HOMO and LUMO of the Plitidepsin cyclodepsipeptide as approximations to the electrophilic and nucleophilic Fukui functions.

Molecule	pKa
Elisidepsin	12.2
Plitidepsin	13.06

Table 3: pKas of the Elisidepsin and Plitidepsin.

Peptide	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor
Elisidepsin	-3.97	-4.02	-4.03
Plitidepsin	-3.75	-3.85	-3.88
Peptide	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
Elisidepsin	-4.03	-3.91	-3.98
Plitidepsin	-3.85	-3.59	-3.76

Table 4: Empirical Bioactivity Scores for the Elisidepsin and Plitidepsin molecules.

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

Table 5: Factors for Evaluation of the Empirical Bioactivity Scores.

The results from Table 4 can be interpreted by considering the factors for evaluation of the Bioactivity Scores that are shown in Table 5.

Conclusions

In this paper we have presented the results of a study of the chemical reactivity of two peptides of marine origin with potential therapeutic proper- ties, Elisidepsin and Plitidepsin, by resorting to Conceptual DFT and some empirical relationships for the prediction of the pKa values, for their AGEs inhibition abilities and for the prediction of the Bioactivity Scores. All these computed values could be of interest for the design and development of new pharmaceutical drugs as well as for the practice of Medicinal Chemistry.

Acknowledgements

Daniel Glossman-Mitnik conducted this work while a Visiting Lecturer at the University of the Balearic Islands from which support is gratefully acknowledged. Norma Flores-Holguin and Daniel Glossman-Mitnik are researchers of CIMAV and CONACYT and acknowledge both institutions for partial support. This work was cofunded by the Ministerio de Econom´ıa y Competitividad (MINECO) and the European Fund for Regional Develop- ment (FEDER) (CTQ2014-55835-R).

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