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Article

Virtual Screening of Marine Natural Compounds by Means of Chemoinformatics and CDFT-based Computational Peptidology

Norma Flores-Holguín [1,†], Juan Frau [2,†], and Daniel Glossman-Mitnik [1,†*],

[1] Laboratorio Virtual NANOCOSMOS, Departamento de Medio Ambiente y Energía, Centro de Investigación en Materiales Avanzados, Chihuahua, Chih 31136, Mexico; norma.flores@cimav.edu.mx (N.F.H.); daniel.glossman@cimav.edu.mx (D.G.M.)

[2] Departament de Química, Universitat de les Illes Balears, Palma de Malllorca. E-07122, Spain; juan.frau@uib.es (J.F.)

* Correspondence: daniel.glossman@cimav.edu.mx; Tel.: +52 614 4391151 (D.G.M.)

† These authors contributed equally to this work.

Abstract: This work presents the results of a computational study of the chemical reactivity and bioactivity properties of the members of the Theopapuamides A-D family of marine peptides by making use of our own proposed methodology named Computational Peptidology (CP) that has been successfully considered in previous studies of this kind of molecular systems. CP allowed for the determination of the global and local descriptors that come from Conceptual Density Functional Theory (CDFT) that can give an idea of the chemical reactivity properties of the marine natural products under study which are already known to be related to their bioactivity. At the same time, the validity of the procedure based on the adoption of the KID (Koopmans in DFT) technique as well as the MN12SX/Def2TZVP/H_2O model chemistry has been successfully verified. Together with several Chemoinformatic tools that can be used for the improvement of process of Virtual Screening, some additional properties of these marine peptides were identified related to their ability to behave as useful drugs. With the further object of analyzing their bioactivity some parameters of usefulness for future QSAR studies, their predicted biological targets and the the ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) parameters related to the Theopapuamides A-D pharmacokinetics are also reported.

Keywords: Theopapuamides A-D; Virtual Screening; Chemoinformatics; Conceptual DFT; Computational Peptidology; Bioavailability; Bioactivity Scores; ADMET

1. Introduction

Drug Design can be pursued following a methodology driven by advancement and innovation breakthroughs including a combination of experimental and computational strategies. Computational strategies play a pivotal part in advanced therapeutic chemistry, displaying a special potential for changing the early stages in the process of drug discovery, especially in terms of time and cost savings.

Bioactive peptides are short amino acid chains that are inactive within the sequence of the parent protein and can be activated through gastrointestinal digestion, food processing, storage or in vitro hydrolysis by proteolytic enzymes. Since bioactive peptides have the ability to impart a biological effect resulting in a positive impact on body functions or conditions, their application is of relevance for food industry. Computational Chemistry and Molecular Modeling tools provide methodologies to identify peptide sequences and their 3D molecular structure. Using in silico modeling, these molecular structures can be related to biological activity and targets of interest. These in silico targeted

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discovery approaches are well known and frequently used in drug discovery in pharmaceutical industry. Computational Chemistry methodologies are based on a broad palette of experience in pharmaceutical drug discovery, and application of this knowledge towards medicinal chemistry research may lead to new insights through elucidation of the mechanistic knowledge on potential ingredients such as bioactive peptides.

Peptides are present in many marine species, and the extensive research that has been conducted on them has shown that they most often found in sponges, as occurred with polyketides, peptides can be also produced by commensal or symbiotic bacteria or fungi. Due to the great potential that these peptides offer as an aid in the treatment of many diseases, they are commonly referred to as therapeutic peptides. As a consequence, there is a lot of current research in this field [1]. By considering these therapeutic peptides from the viewpoint of a medicinal angle, a detailed knowledge of their bioactivity as well as their chemical reactivity properties at the molecular level is of great interest.

Since the structure of molecules defines the chemical, physical and biological properties of matter, this information is crucial for understanding, explaining and predicting chemical reactions and biochemical processes, developing new drugs and provideing crucial insights into the nature of the interactions between drug targets and ligands, which allows predictive models that are suitable for lead discovery and optimization to be constructed. There are numerous reports in the literature showing that from a molecular viewpoint, the bioactivity and the chemical reactivity properties of these peptides are intimately related [2,3]. For this reason, we are currently doing exhaustive research in this field by studying different families of marine peptides (mainly cyclodepsipeptides) trying to find the relationships that could help in the development of new medical drugs for fighting several diseases.

It then follows that it is of the utmost importance to study the chemical reactivity of the natural products (in this case of marine origin), because it is likely to help with the development of some medicines by with the aid of tools displayed through Computational and Theoretical Chemistry as well as Molecular Modeling. In a very special way, Conceptual Density Functional Theory (DFT) [4–6] is one of the most powerful tools within those that are available for the study, understanding and comprehension of the chemical reactivity of molecular systems. Conceptual DFT, sometimes called as Chemical Reactivity Theory, is able to help in the prediction of the relationships between the bioactivity and the chemical reactivity properties by considering a series of global and local descriptors that arise from the fundamentals of the method [7–9].

As a part of an ongoing project for the development of new pharmaceutical drugs of marine origin, we are curently investigating new families of peptides obtained from marine sources hoping that this could be the starting point for the design of potentially helpful therapeutic peptides [1]. Thus, the objective of this study is to report the global and local chemical reactivity descriptors of the Theopapuamides A-D family of marine peptides [10–13] by making use of the Conceptual DFT methodology. It also involves the determination the determination of the potential reaction sites for the cases of nucleophilic and electrophilic attacks and though the consideration of a methodology that we have developed and validated before, also the prediction of the pKa values for each peptide has been attained [14]. The study has been complemented by considering the report of some additional properties that could be useful in QSAR involving several methodologies addressed in the literature [15,16], as well as a detailed study of bioactivity radars that can give an idea of the drug-like behavior of the studied peptides, the predicted biochemical targets on the basis of an homology methodology and the values associated to pharmacokinetics. By following this approach that we have coined as Conceptual DFT-based Computational Peptidology, as a branch of Computational Chemistry dedicated to the study of peptides, the current study acts as a follow-up to previously published results on some families of therapeutic peptides of marine origin [17–21].

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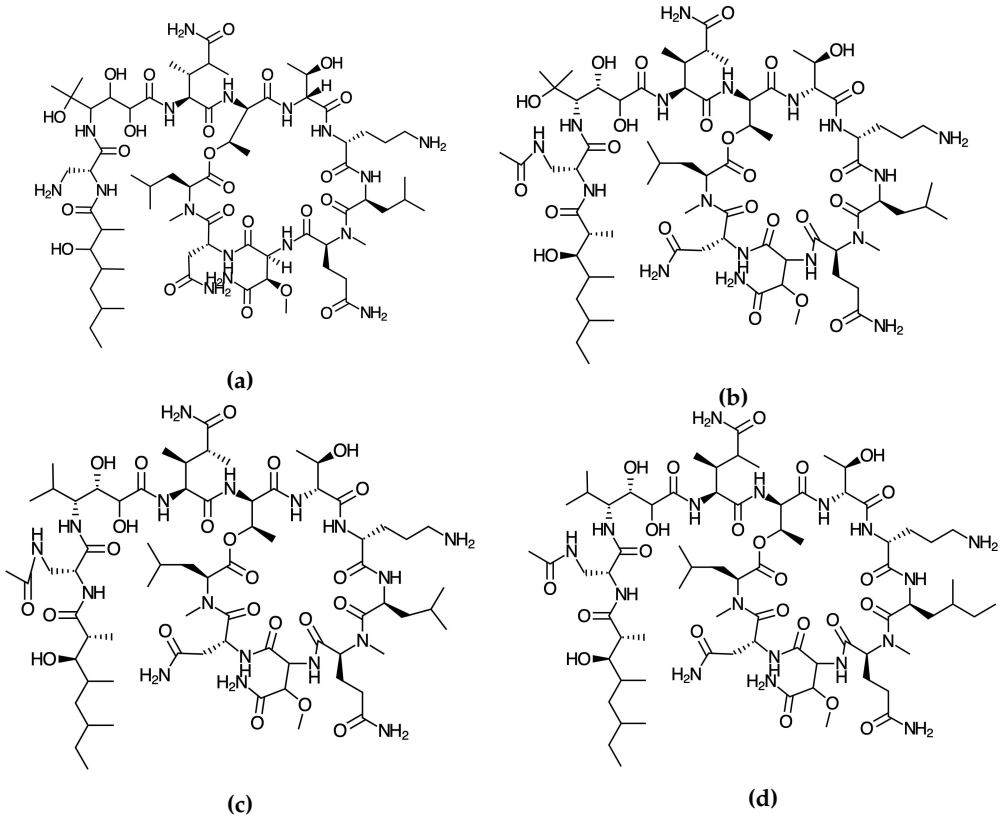

Figure 1. Graphical sketches of the molecular structure of a) Theopapuamide A , b) Theopapuamide B, c) Theopapuamide C and d) Theopapuamide D

2. Theoretical Background and Computational Details

Kohn-Sham (KS) methodology includes the estimation of the molecular energy and density of a given system, as well as the orbital energies, explicitly connected with the frontier orbitals including the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) [22–25]. This methodology is convenient when thinking of quantitative qualities related with Conceptual DFT descriptors. At present, the utilization of range-separated (RS) exchange-correlation density functionals in Kohn-Sham DFT is of extraordinary concern [26–29]. It is essential to the development of these density functionals to think about the partitioning of the exchange and the $\frac{-1}{12}$ operator into long-and short-ranged parts partnering with a range-separation ω parameter that controls the rate at which long-range behavior is obtained. The estimation of ω can either be fixed or "tuned" by utilization of a molecule-by-molecule procedure by adhering to some tuning principles. The ideal tuning methodology depends on having the KS HOMO energy related to vertical ionization potential (IP) which is an estimation of the energy difference, E(N-1)-E(N). For the instance of the Generalized KS theory appropriate to an N-electron molecular system, we should have -IP(N) = ϵ_H(N), which can be considered as the DFT counterpart of the well-known Koopmans' theorem. In reality, this is valid only for the exact density functionall. For the situation where, for pragmatic reasons, we have to consider an approximated density functional, there will be possibly some critical distinction between -IP(N) and ϵ_H(N), Thus, ideal tuning involves setting up ω, system-specific range-separation parameter, by a nonempirical approach and having a RSE useful density functional [30–37]. Indeed, even with the absence of an equal methodology that can be utilized for the correlation of the electron affinity (EA) combined with the energy of the LUMO, it can be drawn that ϵ_H((N+1)= -EA(N) is conceivable. This makes the acquisition of the optimized ω value easier, provided that the differences between ϵ_L(N) and ϵ_H(N+1) are small. Through this, the forecast of the Conceptual DFT descriptors expectation is upgraded for a given optimized density functional. The concurrent prescription is

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dubbed as the "KID procedure" (for Koopmans in DFT), this being in reference to the relationship it has with Koopmans' theorem that has been previously quoted [17–21].

Following the methodology considered in our previous studies [17–21], we have done the computational determinations by using the Gaussian 09 series of programs [38] for the implementation of the density functional needed for the development of this work. The Def2SVP basis set [39,40] was chosen for the geometry optimizations and in the verification that the optimized structures corresponded to the minimal ones through the calculation of the associated frequencies. As a larger basis set is usually needed for the calculation and analysis of the electronic properties, the Def2TZVP basis set was chosen [39,40] as a constituent of our standard methodology. According to our previous studies on this kind of molecular systems, water was selected as the solvent through the Solvation Model Density (SMD) parameterization of the Integral Equation Formalism-Polarized Continuum Model (IEF-PCM) [41] for all the DFT calculations. For the determination of the molecular structures and their associated electronic properties of the studied peptides, the MN12SX density functional was chosen because it is already well known that it is capable of giving very good results for several structural and thermodynamic properties [42]. The resulting model chemistry, MN12SX/Def2TZVP/H20, was then considered model chemistry due to the excellent behavior that our previous research has demonstrated owing to the fact that the MN12SX behaves as as a Koopmans-complaining density functional which is very useful for obtaining accurate HOMO and LUMO orbital energies, thus avoiding the determination of the energies of the cationic and anionic systems for which convergence is usually hard to obtain for the somewhat large molecules as peptides are [17–21].

3. Results and Discussion

The starting molecular structures of the Theopapuamides A-D peptides to be studied were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov), which is a website that acts a online free resource of information related to physical, chemical and biological properties, interactive spectra and literature references. In order to get a glimpse of the potential therapeutic properties of the considered peptides, Simplified Molecular Input Line Entry Specification (SMILES) notations for the molecular systems under consideration were fed into the online Molinspiration software from Molinspiration Cheminformatics (Slovensky Grob, Slovak Republic) allowing for the estimation of several molecular properties that are known to be related related to druggability and that could be useful in QSAR studies that are commonplace in the process of drug design and development. The results of this determination are presented in Table 1:

Table 1. Predicted parameters useful for QSAR studies for the Theopapuamides A-D marine cyclopeptides: ΔG of Solvation (in Kcal/mol), pKa, logP, TPSA (Å^2) and Molecular Volume (Å^3)

	ΔG of Solvation	pKa	logP	TPSA	Molecular Volume
Theopapuamide A	-92.97	11.77	-5.58	663.60	1455.23
Theopapuamide B	-91.59	11.99	-5.50	666.78	1491.89
Theopapuamide C	-93.67	11.82	-5.27	646.45	1484.20
Theopapuamide D	-87.85	11.54	-5.20	646.45	1501.00

The values of the pKas of the Theopapuamides A-D displayed in Table 1 have been calculated by resorting to a methodology proposed by our research group [14] which has been proven to be successfull for this task in the study of several families of peptides of marine origin [17–21].

A further and complementary step can be performed by resorting to SwissADME [43] which is an online free tool that allows the evaluation of drug-likeness though a graphical representation of the properties of interest called Bioavailability Radar which is obtained for every peptide by with the aid of its SMILES representation and where the pink area exhibits the zone with the optimal range for a particular property, as shown in Fig. 2:

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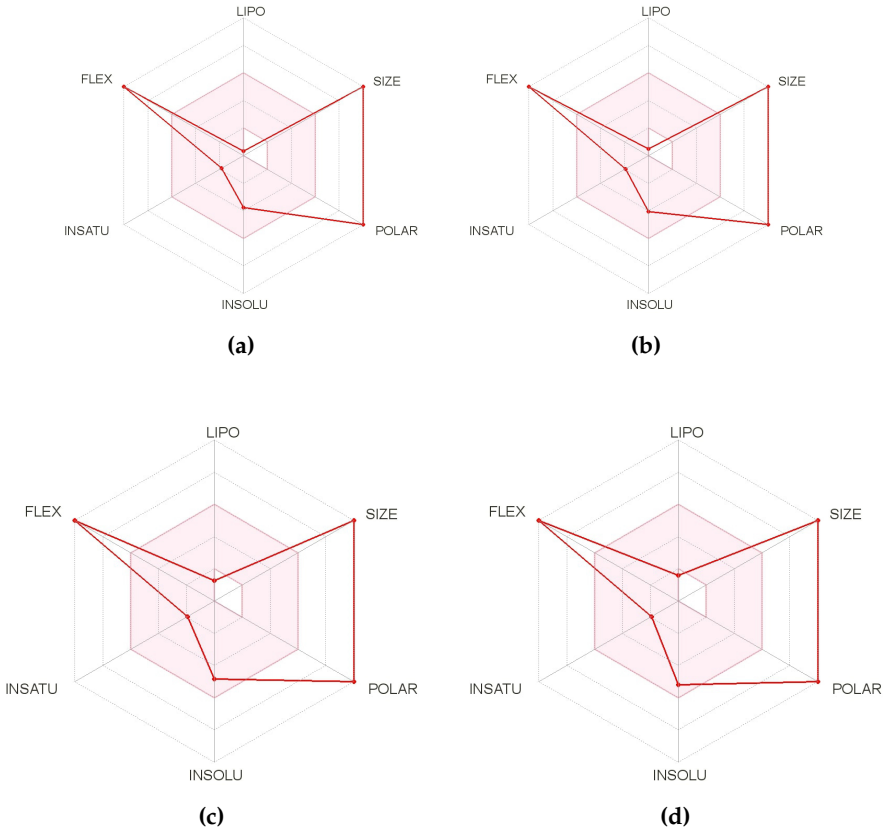

Figure 2. Bioactivity Radars of the a) Theopapuamide A, b) Theopapuamide B, c) Theopapuamide C and d) Theopapuamide D molecules

It can be appreciated from Fig. 2 that the major drawbacks for these peptides to be considered as potential drugs are related to their large size and flexibility. This are very common features of peptides that could prevent for their consideration as therapeutic drugs. However, these problems coould be overcome considering Peptidomimetics studies and the finding of alternative ways for faciliting the drug delivery process.

Another information that can be obtained from the precedent study is that related to the pharmacokinetic properties of the potential therapeutic peptides, that is, how the living organism will interact with the drugs since they are delivered to the body up to when they or their metabolites are finally excreted. These information is collectively known as ADMET properties and the experimental evaluation of ADMET is still costly and time consuming. Thus, the development of computer science and modeling has become a useful tool to predict ADMET properties and this important information in the process of drug discovery is presented in Table 2 for the Theopapuamides A-D marine peptides:

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Table 2. Absorption, Distribution, Metabolism, and Excretion (ADME) parameters related to Theopapuamides A-D pharmacokinetics

	Theopapuamides			
	A	**B**	**C**	**D**
GI absorption	Low	Low	Low	Low
BBB permeant	No	No	No	No
P-gp substrate	Yes	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	No
CYP2D6 inhibitor	No	No	No	No
CYP3A4 inhibitor	No	No	No	No
Log K_p (skin permeation) (cm/s)	-19.30	-19.37	-18.28	-17.98

Indeed, the efficacy of a given therapeutic drug will be highly dependent of the way it interacts with a given receptor in the cells, which in turn with the diseases that the medicines will be designed to fight. This can be predicted beforehand by resorting to an homology procedure using databases of known molecules of similar and related structures to the ones under study. This is an important tool in the drug discovery process and has been used in this work to analyze the Theopapuamides A-D family of peptides by resorting to the free online SwissTargetPrediction software [44] with the results for the predicted biological targets presented in Fig. 3:

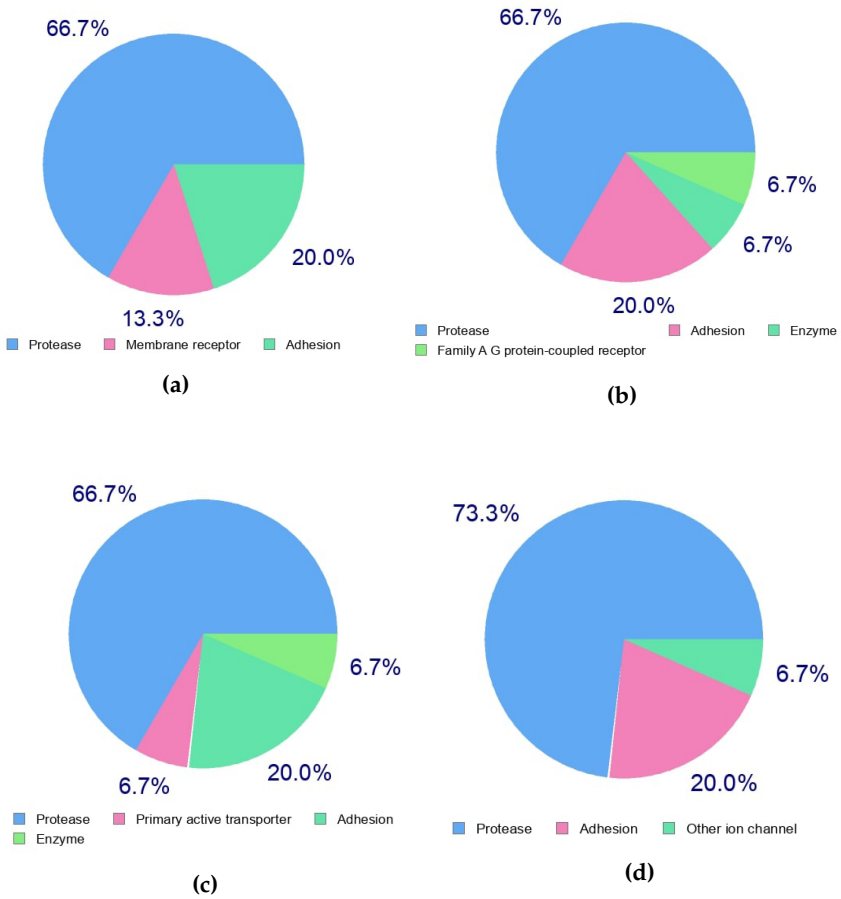

Figure 3. Predicted biological targets of the a) Theopapuamide A, b) Theopapuamide B, c) Theopapuamide C and d) Theopapuamide D molecules

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All the presented results for the potential therapeutic activity of the Theopapuamides A-D family of peptides are an indication that the chemical reactivity of these molecules is an area worth to be explored. As we did in the past [17–21]. a methodology called Conceptual DFT-based Computational Peptidology developed in our research group will be considered now for the calculation and analysis of the chemical reactivity properties of these interesting molecules. The starting point consists in a search for the most stable conformers of each peptide on the basis of the molecular structures taken from the PubChem webpage by resorting to the MarvinView 17.15 program (ChemAxon, Budapest, Hungary) relying on the overall MMFF94 force field [45–49].

The most stable conformer for each peptide obtained through the described procedure were then subjected to a geometry optimization in the gas phase by considering the Density Functional Tight-Binding Approximation (DFTBA) model that is accessible in Gaussian 09 [38]. As it was mentioned in the Theoretical Background and Computational Details section, the resultant structures were subsequently reoptimized by considering the MN12SX/Def2SVP/H2O model chemistry that have proven to be adequate for this purpose [17–21]. Upon verification that every optimized structure corresponded to a minimum in the energy potential curve by employing the frequency-calculation analysis technique, the electronic properties were calculated by resorting to a similar model chemistry but considering the Def2TZVP basis set instead of the Def2SVP one because it has been demonstrated [17–21] that this is a better choice for the prediction and analysis of the HOMO and LUMO orbItals and of the chemical reactivity properties derived from them.

A graphical display of the tridimensional optimized molecular structures of the Theopapuamides A-D peptides obtained with the aid of the UCSF Chimera Visualization System [50] are presented in Fig. 4:

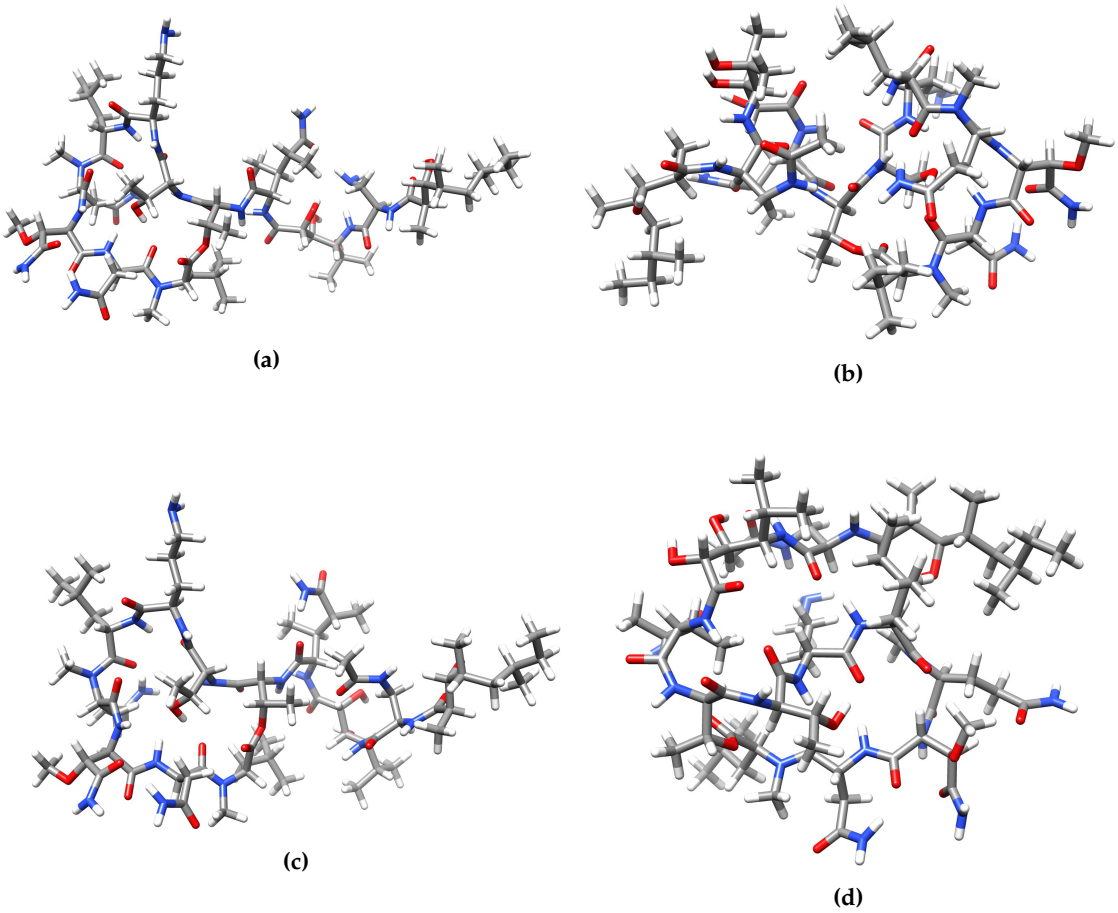

Figure 4. Optimized molecular structures of a) Theopapuamide A, b) Theopapuamide B, c) Theopapuamide C and d) Theopapuamide D.

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It is usually assumed that the goodness of a given density functional can be estimated by comparing the results that it gives with the experimental values that are trying to be reproduced or with the results that can be obtained through post Hartree-Fock calculations like MP2, MP4 or CCSD. However, this is not always possible due to the lack of experimental results for the molecular systems that are being studied or the large size of the molecules that keep some accurate methodologies to be computationally practical. For this reason, we have developed a protocol named KID (Koopmans in DFT) [17–21], which is an attempt to validate a given density functional in terms of its internal coherence. Within the KID protocol four descriptors have been defined where it has been shown that there is a connection between those descriptors and the simplest conformity to the theorem of Koopmans or the Ionization Energy theorem, which is its equivalent within the Generalized Kohn-Sham (GKS) version of DFT, by connecting ϵ_H to -I, ϵ_L to -A, and their actions through the HOMO – LUMO gap as $J_I = |\epsilon_H + E_{gs}(N-1) - E_{gs}(N)|$, $J_A = |\epsilon_L + E_{gs}(N) - E_{gs}(N+1)|$ and $J_{HL} = \sqrt{{J_I}^2 + {J_A}^2}$. An additional descriptor ΔSL has been designed [17–21]to help in the verification of the accuracy of the KID approximation by comparing the HOMO energy of the radical anion with the energy of the LUMO of the neutral species. Although the Koopmans'-complaining behavior of the MN12SX density functional has been proven previously for the case of peptides [17–21], we think that it is worth to perform a further validation for the case of the molecules considered in the present study. This determination has been achieved by making use of the in-house developed CDFT software tool and the results of this analysis are shown in Table 3:

Table 3. HOMO, LUMO and SOMO orbital energies, HOMO-LUMO gap and the KID descriptors (all in eV) tested in the verification of the Koopmans-like behavior of the MN12SX density functional for the Theopapuamides A-D marine cyclopeptides

	HOMO	LUMO	SOMO	H-L Gap	*J(I)*	*J(A)*	*J(HL)*	ΔSL
Theopapuamide A	-6.3114	-0.8210	-0.8169	5.4904	0.041	0.000	0.041	0.004
Theopapuamide B	-6.2907	-1.0710	-1.0675	5.2197	0.042	0.002	0.043	0.004
Theopapuamide C	-6.3125	-0.8893	-0.8838	5.4232	0.042	0.000	0.042	0.005
Theopapuamide D	-6.6760	-0.9040	-0.8879	5.7721	0.003	0.010	0.011	0.016

As can be seen from the results in Table 3, the values for the KID descriptors are all very close to zero which is an indication that the chosen MN12SX density functional behaves as a Koopmans-complaining one and that for this reason the MN12SX/Def2TZVP/H2O is a model chemistry that has been further demonstrated very adequate for the purpose of this research.

Taking into account the KID methodology considered in the previous research being integrated into the finite difference approximation [17–21], the following definitions can be used for the global descriptors that help in the understanding of the chemical reactivity of the molecular systems [4–6,51, 52]:

Electronegativity	$\chi = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\epsilon_L + \epsilon_H)$
Global Hardness	$\eta = (I - A) \approx (\epsilon_L - \epsilon_H)$
Electrophilicity	$\omega = \frac{\mu^2}{2\eta} = \frac{(I+A)^2}{4(I-A)} \approx \frac{(\epsilon_L+\epsilon_H)^2}{4(\epsilon_L-\epsilon_H)}$
Electrodonating Power	$\omega^- = \frac{(3I+A)^2}{16(I-A)} \approx \frac{(3\epsilon_H+\epsilon_L)^2}{16\eta}$
Electroaccepting Power	$\omega^+ = \frac{(I+3A)^2}{16(I-A)} \approx \frac{(\epsilon_H+3\epsilon_L)^2}{16\eta}$
Net Electrophilicity	$\Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^-$

being ϵ_H and ϵ_L the HOMO and LUMO energies associated to each of the peptides considered in this work.

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As a complement of these global reactivity descriptors that arise from Conceptual DFT [4–6,51, 52], Domingo and his collaborators [53–57] have proposed a Nucleophilicity index N through the consideration of the HOMO energy obtained through the KS scheme with an arbitrary shift of the origin taking the molecule of tetracyanoethylene (TCE) as a reference.

By making use of the mentioned CDFT software tool applied to the results of the calculation of the electronic properties of the Theopapuamides A-D peptides, the values of the defined global reactivity descriptors (including the Nucleophilicity N) could be obtained and they are displayed in Table 4:

Table 4. Global reactivity descriptors for the Theopapuamides A-D marine cyclopeptides: Electronegativity (χ), Hardness (η), Electrophilicity (ω) (all in eV), Softness S (in eV^{-1}), Nucleophilicity N, Electrodonating Power (ω^-), Elctroaccepting Power (ω^+) and Net Electrophilicity ($\Delta\omega^\pm$) (also in eV)

	χ	η	γ	S	N	ω^-	ω^+	$\Delta\omega^\pm$
Theopapuamide A	3.5662	5.4904	1.1582	0.1808	2.8098	4.4426	0.8764	5.3190
Theopapuamide B	3.6809	5.2197	1.2979	0.1900	2.8305	4.7624	1.0815	5.8439
Theopapuamide C	3.6009	5.4232	1.1954	0.1830	2.8087	4.5303	0.9294	5.4597
Theopapuamide D	3.7900	5.7721	1.2443	0.2012	3.2174	4.7443	0.9543	5.6986

The Global Hardness η can be seen as a measure of the resistance of the electronic density to be deformed and thus as an indication low reactivity fo a given molecular system. From the results of Table 4, it can be concluded that theopapuamide B will be the more reactive peptide in this family, while Theopapuamide B will be the less reactive ones, being the chemical reactivity of the other peptides approximately the same. A analog behavior is observed for the Electrophilicity ω descriptor which encompasses the balance between the tendency of an electrophile to acquire an extra amount of electrons and the resistance of a molecule to exchange electrons with the environment. As expected from the molecular structure of these species, their electrodonating ability is more important that their electroaccepting character, possessing an Theopapuamides B and D an electrodonating power larger than the others but not very different. On the basis of the previous definition and the scale established by these authors [54], it can be concluded that Theopapuamide D can be regarded as a strong nucleophile because the values for the Nucleophilicity N is greater than 3 eV, while the other peptides can be considered as moderate nucleophiles.

The presented global descriptors are a representation of the chemical reactivity of a molecule as a whole. However, local reactivity descriptors have been developed that can give an idea of the differences between the reactivity of each of the atoms that form the molecule. One of the most important groups of such reactivity descriptors are the Fukui functions [4–6] and the Dual Descriptor [58–63], which has been defined as:

$$\text{Nucleophilic Fukui Function} \qquad f^+(\mathbf{r}) = \rho_{N+1}(\mathbf{r}) - \rho_N(\mathbf{r})$$

$$\text{Electrophilic Fukui Function} \qquad f^-(\mathbf{r}) = \rho_N(\mathbf{r}) - \rho_{N-1}(\mathbf{r})$$

$$\text{Dual Descriptor} \qquad \Delta f(\mathbf{r}) = \left(\frac{\partial f(\mathbf{r})}{\partial N}\right)_{v(\mathbf{r})}$$

which are relationships between the electronic densities of the neutral, positive and negative species as well as between the Nucleophilic and Electrophilic Fukui functions.

The Nucleophilic Fukui function, $f^+(\mathbf{r})$, reveals the sites on a molecular system that are susceptible to nucleophilic attacks and the Electrophilic Fukui function, $f^+(\mathbf{r})$, describes those sites that are more susceptible to electrophilic attacks. These local reactivity descriptors are very useful and has been used successfully for the identification of reactive sites. However, some times there is an overlap between the results of both descriptors and no conclusions can be accurately obtained. Instead, the Dual Descriptor $\Delta f(\mathbf{r})$ or DD, can described unambiguously nucleophilic and electrophilic sites within a molecule [63]. Thus, a graphical representation of the DD for the Theopapuamide marine peptides is

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presented in Fig. 5 showing clearly the areas within the molecules where DD > 0 and DD < 0 for a better understanding of the local chemical reactive of these molecules:

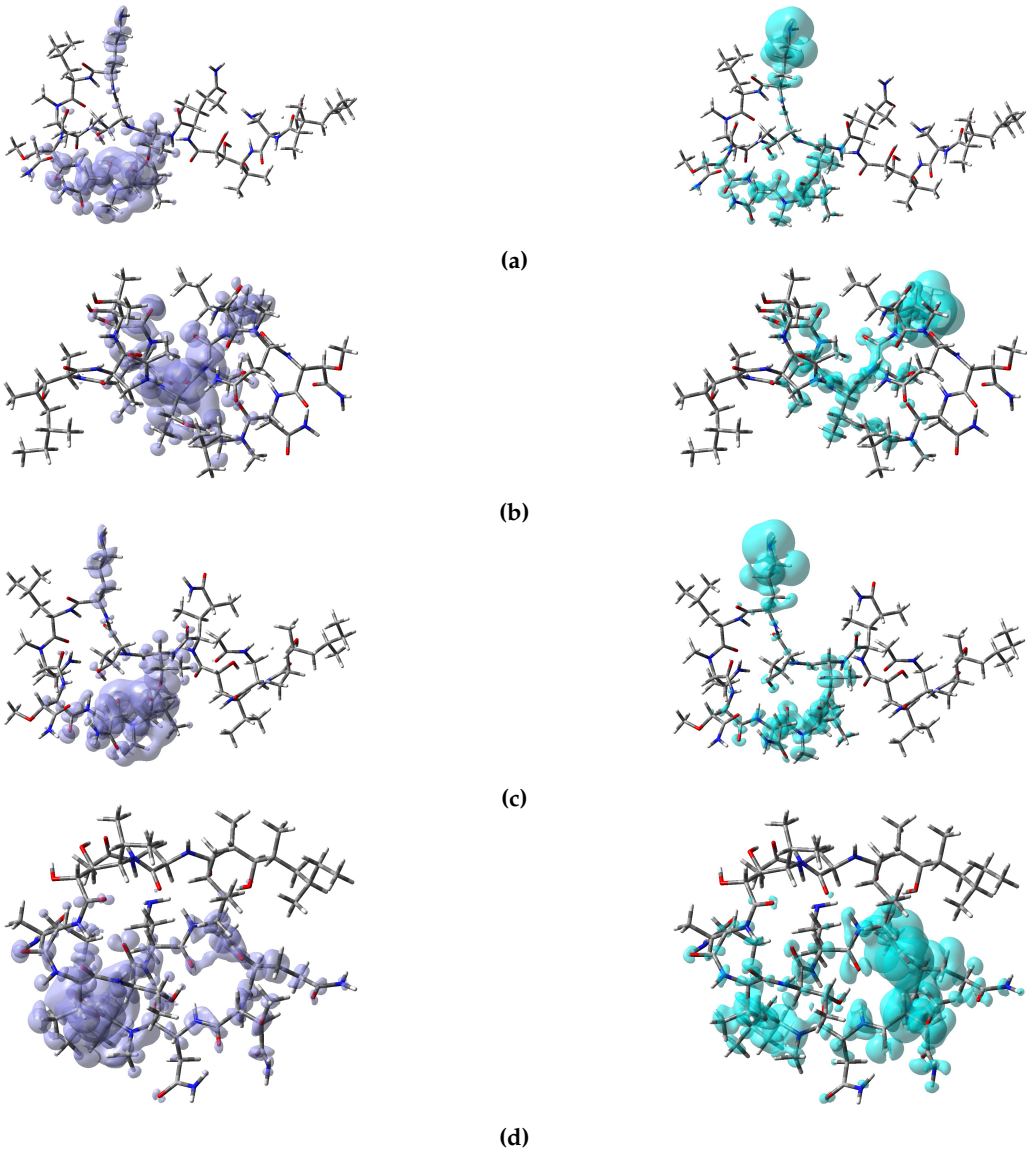

Figure 5. Graphical representation of the Dual Descriptor DD of the a) Theopapuamide A, Theopapuamide B, Theopapuamide C and b) Theopapuamide D molecules. Left: DD > 0, Right: DD < 0

Another local reactivity descriptors are the Parr functions [64,65] that can be considered as an alternative to the Fukui functions for describing sites or areas within the molecules where nucleophilic or electrophilic attacks will be favored. The Parr functions can be expressed as [64,65]:

$$\text{Nucleophilic Parr Function} \quad P^{-}(\mathbf{r}) = \rho_s^{rc}(\mathbf{r})$$

$$\text{Electrophilic Parr Function} \quad P^{+}(\mathbf{r}) = \rho_s^{ra}(\mathbf{r})$$

where $\rho_s^{rc}(\mathbf{r})$ and $\rho_s^{ra}(\mathbf{r})$ are related to the atomic spin density of the radical cation or anion of the considered system, respectively [57].

In order to perform a comparison between the results that can be obtained form either formulations, the predictions for the specific reactions sites coming from the Electrophilic and Nucleophilic Fukui functions analysis for each peptide have been compiled in a series of tables that are presented as an Appendix to this work together with the values that are the outcome of the

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Parr functions analysis. The Radical Fukui function $f^0(\mathbf{r})$, which can be considered as an average of $f^+(\mathbf{r})$ and $f^-(\mathbf{r})$, and denotes the favorable sites for a radical attack, has also been included for the sake of completeness. In a complementary way to the tables, a graphical representation of these descriptors have been included as a series of figures such as the comparison between the results coming for both kind of studies can be done accurately.

By looking at the numerical and graphical results presented in Tables A1 to A4 and Figures A1 to A4, it can be concluded that there is a very nice agreement between the values coming from both representations. Considering the the numerical values, it can be seen that there is a complete agreement between the reactive sites predicted by the Fukui functions or the Parr functions. It can also be noted that the numerical results for the Parr functions are greater than those for the Fukui functions which is an indication that the first ones are better defined than the others. The same conclusions can be obtained by looking at the graphical representations of the Fukui and the Parr functions, where they are extended over the same surface within the molecules, but it can be seen that the Parr functions are more compact than the Fukui functions. This nice agreement, that have been also found in the study of other families of peptides of marine origin, could led to the conclusion that if the Dual Descriptor DD can be built as the difference between both Fukui functions, a new reactivity descriptor could be defined in terms of the difference between both Parr functions in an analog way to the Dual Descriptor giving the same information and being the starting point for further research on the field of Conceptual DFT-based Computational Peptidology.

4. Conclusions

The Theopapuamides A-D family of cyclodepsipeptides of marine origin has been studied by resorting to some techniques of common use in the process of drug discovery and development showing that these kind molecules can be regarded as potential therapeutic drugs. Some Chemoinformatics tools have been to obtain information about the potential therapeutic properties of these peptides in the form of Bioactivity Radars, Biological Targets and ADMET values.

With this knowledge in mind, the chemical reactivity of the studied peptides has been exhaustively analyzed through the optimization of their structures using a MN12SX/Def2SVP/H2O model chemistry and the determination of their electronic properties by means of a larger model chemistry, namely MN12SX/Def2TZVP/H20, already used in previous works for the study of peptides, validating their usefulness for this kind of calculations.

The chemical reactivity of the considered molecular systems was subject to an analysis based on a particular methodology developed by our research group named Conceptual DFT-based Computational Peptidology being the use of the MN12SX density functional validated once again by resorting to the KID procedure and the in-house software tool CDFT.

The analysis of the global and local reactivity descriptors arising from Conceptual DFT together with some proposals like the Nucleophilicity N and the Parr functions allowed for a complete understanding of the chemical reactivity of the studied peptides, by distinguishing the different chemical reactivities through the analysis of the global descriptors and the further identification of the reaction sites or regions within the molecules by resorting to Fukui and Parr functions as well as the Dual Descriptor.

Finally, a nice agreement was found between the outcome of the numerical and graphical analysis of the Fukui and Parr functions on each peptide leading to the conclusion that it could be possible to define a new chemical reactivity descriptor analog to the Dual Descriptor on the basis of the difference between the Parr functions which could act as an additional tool for the study of the chemical reactivity of molecular systems through Conceptual DFT-based Computational Peptidology.

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Abbreviations

The following abbreviations are used in this manuscript:

DFT	Density Functional Theory
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
SOMO	Single Occupied Molecular Orbital
KID	Koopmans in DFT
SMD	Solvation Model Density
QSAR	Quantitative Structure Activity Relationships
IEF-PCM	Integral Equation Formalism-Polarized Continuum Model
IP	Ionization Potential Energy
EA	Electronic Affinity
DFTBA	Density Functional Tight-Binding Approximation
DD	Dual Descriptor

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Appendix A

Table A1. Condensed local reactivity descriptors for Theopapuamide A denoting the reactivity sites: Electrophilic Fukui Function f^-, Nucleophilic Fukui Function f^+, Radical Fukui Function f^0, Electrophilic Parr Function $P-$ and Nucleophilic Parr Function $P+$

	f^-	f^+	f^0	$P-$	$P+$
Theopapuamide A	N37 (0.41)	C78 (0.11)	N37 (0.20)	N37 (0.78)	C78 (0.23)

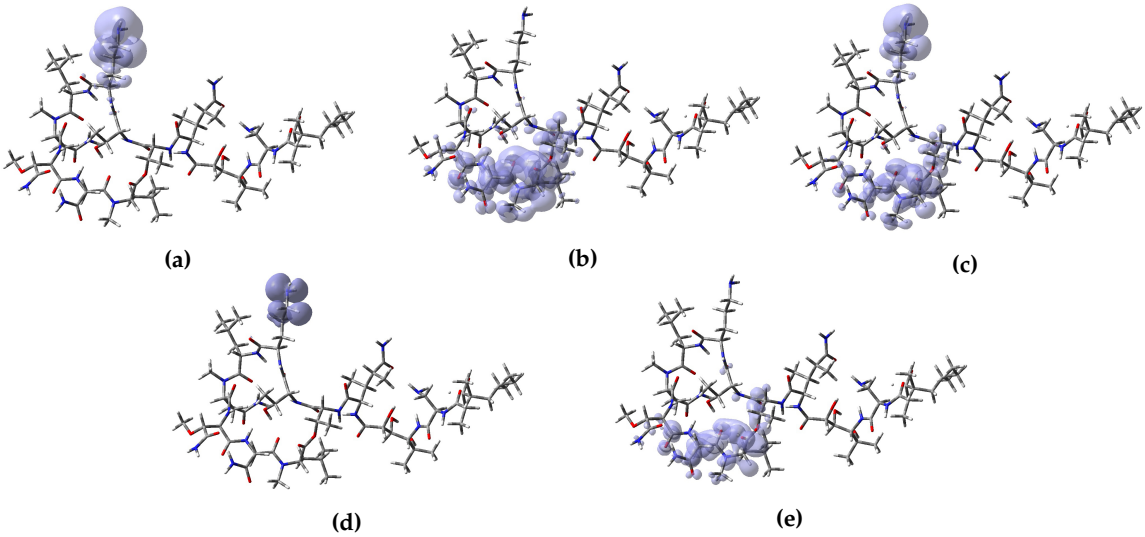

Figure A1. Graphical sketches of the local reactivity descriptors for Theopapuamide A showing the reactivity regions: a) Electrophilic Fukui Function f^-, b) Nucleophilic Fukui Function f^+, c) Radical Fukui Function f^0, d) Electrophilic Parr Function $P-$ and e) Nucleophilic Parr Function $P+$

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Table A2. Condensed local reactivity descriptors for Theopapuamide B denoting the reactivity sites: Electrophilic Fukui Function f^-, Nucleophilic Fukui Function f^+, Radical Fukui Function f^0, Electrophilic Parr Function $P-$ and Nucleophilic Parr Function $P+$

	f^-	f^+	f^0	$P-$	$P+$
Theopapuamide B	N38 (0.41)	C73 (0.09)	N38 (0.20)	N38 (0.78)	C73 (0.19)

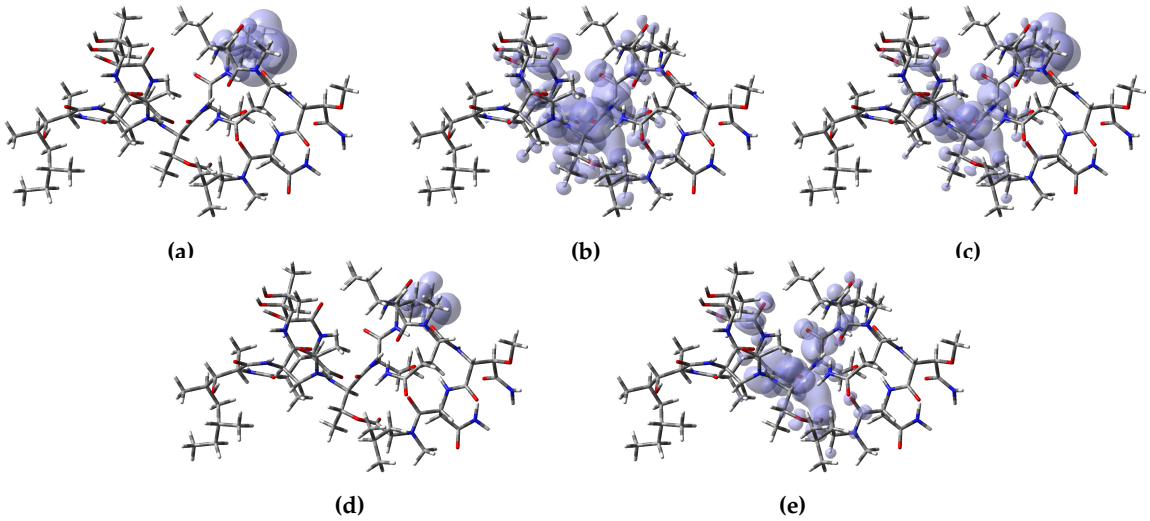

Figure A2. Graphical sketches of the local reactivity descriptors for Callipeptin B showing the reactivity regions: a) Electrophilic Fukui Function f^-, b) Nucleophilic Fukui Function f^+, c) Radical Fukui Function f^0, d) Electrophilic Parr Function $P-$ and e) Nucleophilic Parr Function $P+$

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Table A3. Condensed local reactivity descriptors for Theopapuamide C denoting the reactivity sites: Electrophilic Fukui Function f^-, Nucleophilic Fukui Function f^+, Radical Fukui Function f^0, Electrophilic Parr Function $P-$ and Nucleophilic Parr Function $P+$

	f^-	f^+	f^0	$P-$	$P+$
Theopapuamide C	N37 (0.41)	C78 (0.13)	N37 (0.20)	N37 (0.78)	C78 (0.25)

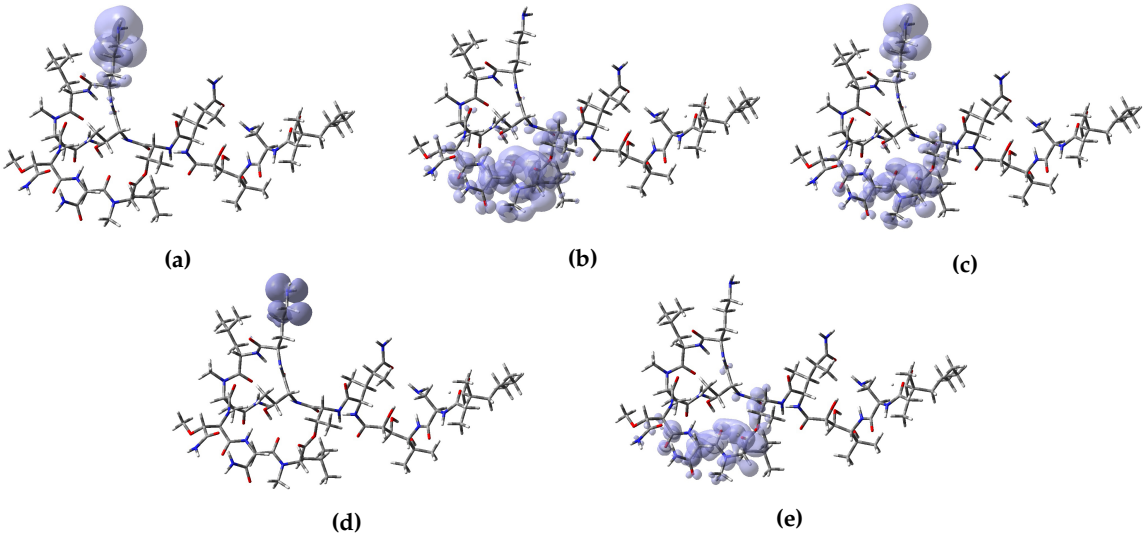

Figure A3. Graphical sketches of the local reactivity descriptors for Theopapuamide C showing the reactivity regions: a) Electrophilic Fukui Function f^-, b) Nucleophilic Fukui Function f^+, c) Radical Fukui Function f^0, d) Electrophilic Parr Function $P-$ and e) Nucleophilic Parr Function $P+$

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Table A4. Condensed local reactivity descriptors for Theopapuamide D denoting the reactivity sites: Electrophilic Fukui Function f^-, Nucleophilic Fukui Function f^+, Radical Fukui Function f^0, Electrophilic Parr Function $P-$ and Nucleophilic Parr Function $P+$

	f^-	f^+	f^0	$P-$	$P+$
Theopapuamide D	N30 (0.11)	C84 (0.10)	C84 (0.10)	N30 (0.27)	C84 (0.38)

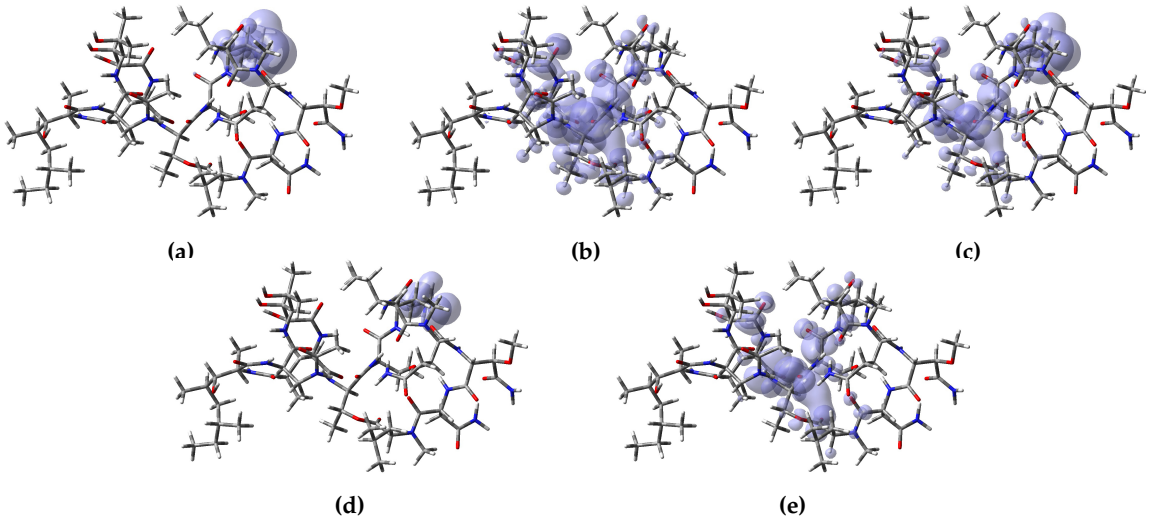

Figure A4. Graphical sketches of the local reactivity descriptors for Theopapuamide D showing the reactivity regions: a) Electrophilic Fukui Function f^-, b) Nucleophilic Fukui Function f^+, c) Radical Fukui Function f^0, d) Electrophilic Parr Function $P-$ and e) Nucleophilic Parr Function $P+$