

Computational Study of the Chemical Reactivity and Bioactivity Rates of Marine Peptides Hemiasterlin and Its A and B Derivatives Used in the Cancer Treatment through Conceptual Density Functional Theory

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Abstract

This study involved the assessment of the MNI2SX/Def2TZVP/H2O model chemistry to enhance the understanding of the structural composition of the marine peptide Hemiasterlin and its derivatives A and B used in cancer treatment. The Conceptual Density Functional theory was used in the calculation of molecular properties of the system chemical descriptors during the study. Integration of the active molecular regions into their respective Fukui functions was used in the selection of electrophilic and nucleophilic attacks. Additionally, the proposed correlation between global hardness and the pKa was used as the basis of deriving accurate predictions for the pKa values while a homology technique was used in the prediction of bioactivity and bioavailability scores of the peptides under investigation.

Keywords

Hemiasterlins, Computational Chemistry, Conceptual DFT, Bioavailability, Bioactivity Scores

1. Introduction

The structural diversity of numerous biologically active metabolites that are found in the marine ecosystems has been used in the development of new categories of agents that can be used in anticancer therapies. The successful devel-

opment of the anticancer agents has overcome the challenges experienced in the development of drugs from natural resources due to the structural complexity of the agent sourcing process. Despite the challenges several anticancer drugs derived from the marine life agents have been tested and approved as highly effective therapeutic interventions within the past few years. Research reveals that marine life forms contain diverse clinical and preclinical compounds that are potentially vital in the development of new drug formulas for the treatment of human health complications. Researchers have carried out numerous studies to understand the structural and biosynthetic assembling of the marine agents through re-engineering techniques, interdisciplinary development processes, and innovative manipulation within the gene clusters of these agents. These processes are key in enhancing the pharmaceutical properties of the marine agents when compared to the utilization of the natural products directly in the development of human medicine [1] [2].

A wide range of marine species contains bioactive products known as peptides, which contain high amounts of nutraceutical and medicinal agents based on their diverse bioactivities. Pharmacists and medical scientists have leveraged the antimicrobial, neuroprotective, antiviral, immunomodulatory, antioxidative, antidiabetic, analgesic, antiatherosclerotic, cardioprotective, and anxiolytic properties to create drugs that have been used as effective treatments for human diseases. The chemical derivatives of some marine peptides are known to have high demand and commercial value in the pharmaceutical industry due to their important roles in improving patient outcomes in various clinical and preclinical stages of disease treatment. A linear tripeptide known as Hemiasterlin is composed of unique amino acids and cytotoxic properties that are vital in the treatment of leukemia. These properties of Hemiasterlin enhance the clinical treatment of leukaemia by inhibiting the formation of mitotic spindle thus inducing apoptosis and mitotic arrest, which results in tubulin depolymerization [3]-[8].

The oceanic environment provides habitat for many organisms which are important agents in the manufactured medicine. According to clinical trials that have been carried out to develop medications for cancer, a wide range of marine peptides have been found to have important anti-cancer properties that inhibit growth or kill cancer cells through activities that inhibit different angiogenesis process as well as the tubulin-microtubule balance. The advantage of marine peptides as anticancer agents over the traditional chemotherapeutic interventions is that they do not have extreme side effects on the immune system. Therefore, the use of marine peptides in the development of anticancer peptides is the ideal solution to chemotherapy side effects such as multi-drug resistance, which are common in the use of traditional treatment methods [9]. A wide range of naturally occurring molecules focuses on microtubules as the key drug targets in the treatment of cancer. Combining the marine peptides with the terrestrial anticancer agents such as vinca alkaloids and taxes forms an effective clinical agent that produce tubulin-binding molecules to inhibit the growth of cancer cells [10]. The isolation of cytotoxic peptides from marine sponges results in the

formation of Hemiasterlins A and B, which are composed of a wide range of unique amino acids such as trimethyltryptophan, N-methyl homovinylogous valine, and tert-leucine. These amino acids contain antimitotic properties which are used in the treatment of different types of cancer [11] [12] [13].

The objective of this work is to study the chemical reactivity of the Hemiasterlin and the Hemiasterlin A and B derivatives using the techniques of the Conceptual DFT [14] [15] [16], 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, with the aid of the calculated Parr functions [17] [18]. Similarly, the pKa values for each of the peptides will be predicted based on a methodology previously developed by us [19]. Finally, the bioavailability of these compounds and their potential bioactivity will be predicted by using some online available software designed for this purpose. This research can be considered as providing new insights into the knowledge of the chemical reactivity and bioactivity properties of peptides of marine origin with potential therapeutic properties in the same line as our previous work on the field [20]-[25].

2. Computational Methodology

This study obtained the molecular structures of Hemiasterlin and its A and B derivatives from PubChem (<https://pubchem.ncbi.nlm.nih.gov>), a website that serves as the public repository for information pertaining to chemical substances, along with their associated biological activities. The resulting geometries were optimized by means of the DFTBA (Density Functional Tight Binding Approximation) module available within Gaussian 09 [26].

Consistent with our previous work [20]-[25] [27]-[34], the calculation of the electronic properties needed for the determination of the chemical reactivity descriptors within the KID (Koopmans in DFT) procedure were obtained by resorting to the MN12SX/Def2TZVP/H2O model chemistry [35] [36] [37] under the Solvation Model Density (SMD) parameterization of the Integral Equation Formalism-Polarized Continuum Model (IEF-PCM) [38].

3. Results and Discussion

The molecular structures of the optimized members of the Hemiasterlins obtained as mentioned in the Computational Methodology section are displayed in **Figure 1**.

Following Becke's ideas [39] and the studies by Baerends *et al.* concluding that the HOMO-LUMO gap of the Kohn-Sham (KS) system can be used as an effective measure of the molecular optical gap [40] [41], ground state calculations were used for the determination of the maximum absorption wavelength that belongs to the Hemiasterlins to find the respective λ_{\max} values through the application of chosen model chemistry to determine the HOMO-LUMO gaps. Therefore, the results for the calculation of the electronic properties of the Hemiasterlins are displayed in **Table 1**.

Table 1. Electronic energies of the neutral molecular systems (in au) of Hemiasterlin and its A and B derivatives, the HOMO and LUMO orbital energies as well as the HOMO-LUMO gap (in eV), and the maximum absorption wavelengths λ_{\max} (in nm) calculated with the MN12SX density functional and the Def2TZVP basis set using water as solvent simulated with the SMD parametrization of the IEF-PCM model.

Molecule	Total Electronic Energy	HOMO	LUMO	HOMO-LUMO Gap	λ_{\max}
Hemiasterlin	-1690.078	-5.452	-1.907	3.545	350
Hemiasterlin A	-1650.793	-5.542	-1.907	3.635	341
Hemiasterlin B	-1611.505	-5.471	-1.927	3.544	350

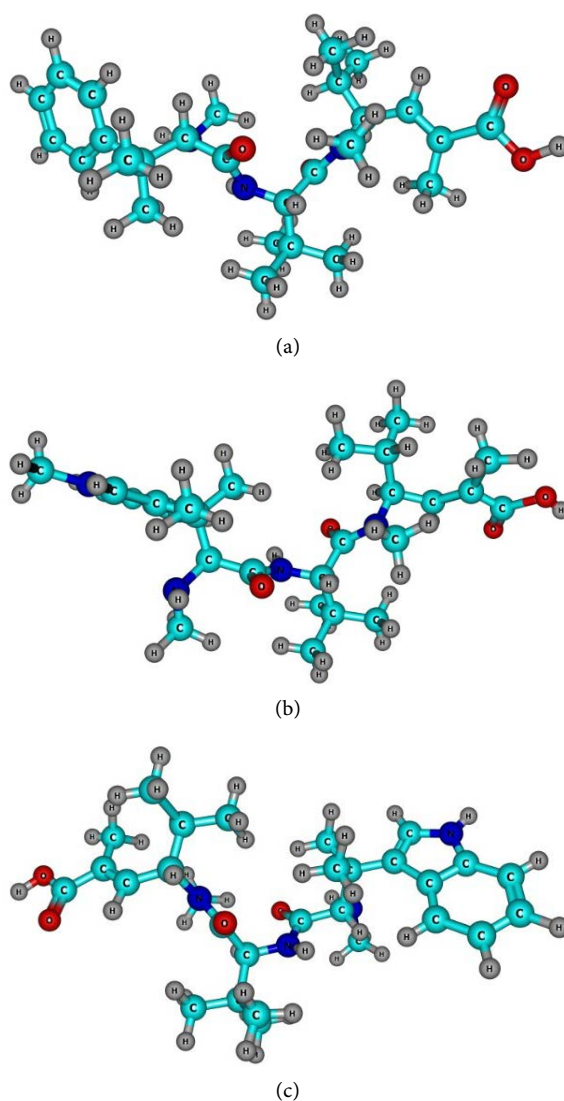


Figure 1. Part (a) shows the graphical representation of the molecular structure of Hemiasterlin, while parts (b) and (c) show the molecular structures of Hemiasterlin A and B, respectively.

3.1. Computation of the Global Reactivity Descriptors

According with our previous findings for the case of the melanoidins [27]-[33]

and peptides of marine origin [20]-[25] [34], the MN12SX density functional is capable of giving HOMO and LUMO energies that allow to verify the agreement with the approximate Koopmans' theorem. Thus, the application of the KID procedure will be justified. By taking into account the KID procedure presented in those previous works together with the finite difference approximation, the global reactivity descriptors can be expressed as [14] [15] [16] [42] [43] [44]:

$$\text{Electronegativity } \chi = -0.5(I + A) \approx 0.5(\varepsilon_H + \varepsilon_L)$$

$$\text{Global Hardness } \eta = (I - A) \approx (\varepsilon_L - \varepsilon_H)$$

$$\text{Electrophilicity } \omega = 0.5 \chi^2 / \eta$$

$$\text{Electrodonating Power } \omega^- = (3I + A)^2 / 16(I - A)$$

$$\text{Electroaccepting Power } \omega^+ = (I + 3A)^2 / 16(I - A)$$

$$\text{Net Electrophilicity } \Delta\omega^\pm = \omega^+ + \omega^-$$

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

Thus, the results for the global reactivity descriptors based on the values of the HOMO and LUMO energies calculated with the MN12SX/Def2TZVP/H2O model chemistry are presented in **Table 2**.

The electrophilicity ω index encompasses the balance between the tendency of an electrophile to acquire an extra amount of electron density and the resistance of a molecule to exchange electron density with the environment [45]. By studying the electrophilicity of a series of reagents involved in Diels-Alder reactions [46], through a quantitative characterization of the global electrophilicity pattern of some reagents involved in 1,3-dipolar cycloaddition reactions [47] and by means of the understanding of the mechanism of polar Diels-Alder reactions [48], Domingo *et al.* were allowed to establish an electrophilicity ω scale for the classification of organic molecules as strong electrophiles with $\omega > 1.5$ eV, moderate electrophiles with $0.8 < \omega < 1.5$ eV and marginal electrophiles with $\omega < 0.8$ eV [46]. By inspection of **Table 2**, it can be seen that all the peptides considered in this study can be regarded as strong electrophiles. Besides the electrophilicity classification, an electrophilicity scale for these anticancer peptides can be displayed as: Hemiasterlin B > Hemiasterlin > Hemiasterlin A.

The nucleophilicity N is another important chemical reactivity descriptor.

Table 2. Global reactivity descriptors of Hemiasterlin and its A and B derivatives, calculated with the MN12SX/Def2TZVP/H2O model chemistry.

Molecule	Electronegativity	Global Hardness	Electrophilicity
Hemiasterlin	3.679	3.545	1.909
Hemiasterlin A	3.724	3.635	1.908
Hemiasterlin B	3.699	3.544	1.931
Molecule	Electrodonating Power	Electroaccepting Power	Net Electrophilicity
Hemiasterlin	5.880	2.200	8.080
Hemiasterlin A	5.906	2.181	8.087
Hemiasterlin B	5.932	2.233	8.165

There are several definitions of nucleophilicity available in the literature of Conceptual DFT, and the interested reader is referred to the recent work of Domingo and Pérez [49]. However, those indices fail for more complex molecules which display concurrently both electrophilic and nucleophilic behaviors and in these cases the value of the electrophilicity ω does not correlate well with their expected nucleophilicity [45]. This has compelled Domingo and his collaborators [45] [48] [49] [50] to propose a new nucleophilicity index N simply based on the highest occupied molecular orbital (HOMO) energy obtained within the Kohn-Sham scheme with an arbitrary shifting of the origin with tetracyanoethylene (TCE) taken as a reference. The corresponding definition for the nucleophilicity N index is [45] [48] [49] [50]: $N(\text{Nu}) = \text{EHOMO}(\text{Nu}) - \text{EHOMO}(\text{TCE})$, and the results for the calculation of this index for the anticancer peptides are: Hemiasterlin = 3.34 eV, Hemiasterlin A = 3.25 eV and Hemiasterlin B = 3.32 eV. On the basis of the previous definition and the scale established in the mentioned study [50], it can be concluded that the Hemiasterlins can be regarded as strong nucleophiles because their values are greater than 3 eV.

3.2. Computation of the Local Reactivity Descriptors

The expressions for the local reactivity descriptors are shown below [14] [15] [16] [51]-[55]:

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

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

$$\text{Dual Descriptor } \Delta f(r) = f^+(r) - f^-(r)$$

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.

Figure 2 shows the Electrophilic and the Nucleophilic Fukui functions $f^-(r)$ and $f^+(r)$ for the respective Hemiasterlins.

3.3. Computation of the Marine Anticancer Peptides pKas

Following the methodology of our previous work [19], where we have developed a simple QSAR relationship for the prediction of the pKa of peptides with the form $\text{pKa} = 16.3088 - 0.8268\eta$, in this study we have considered the optimized molecular structure of each Hemiasterlin and we have applied it to the calculation of the pKa of these molecules, making use of the η values presented in **Table 3** being the results as follows.

The resulting pKas must be seen within the context of our previous study [19],

Table 3. The pKa value representation of Hemiasterlin with its derivatives A and B.

Molecule	pKa
Hemiasterlin	13.38
Hemiasterlin A	13.30
Hemiasterlin B	13.38

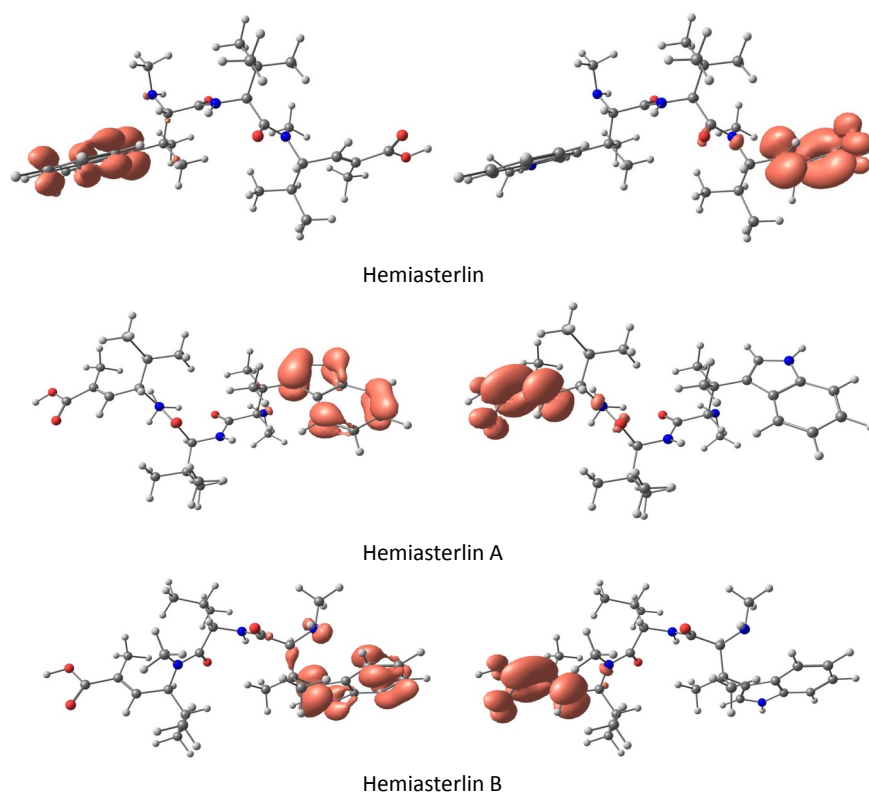


Figure 2. The right column represents the Nucleophilic Fukui function while the left column represents the Electrophilic Fukui function of Hemiasterlin and its A and B derivatives.

and it is our belief that they could be of interest during the process of the development of pharmaceuticals starting from these peptides which could enable an explanation of the mechanisms of action and the drug delivery procedures within the pH where these actions take place.

3.4. Bioavailability and Bioactivity Scores

The bioavailability of pharmaceuticals is intimately related to the concept of drug-likeness for which several criteria have been proposed by Lipinski *et al.* [56] [57]. The resulting descriptors can be easily calculated by feeding the corresponding SMILES notations into the readily available online MolInspiration software (Slovensky Grob, Slovak Republic (www.molinspiration.com)). The results for this determination are presented in **Table 4**.

Indeed, the Lipinsky Rule of Five measures the oral bioavailability of a potential drug and it is usual that peptides fail to pass it, mostly due to their volume and molecular weight (MW). As we can see from **Table 4**, this is true also for the case of small peptides like those considered in this work. An alternative approach can be followed by resorting similarity searches in the chemical space for similar compounds of known pharmacological properties.

Molinspiration was considered again for the calculation of the bioactivity scores which are a measure of the ability of the potential drug to act as GPCR li-

gands or Kinase inhibitors, to perform as Ion Channel modulators, or to interact with Enzymes and Nuclear receptors. The determination of these bioactivity scores has been performed by feeding the SMILES notation for each peptide into the online Molinspiration software from Molinspiration Cheminformatics (www.molinspiration.com) for the prediction of the bioactivity score for different drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors). The values of the bioactivity scores for the Hemiasterlins are presented in **Table 5**.

As it can be seen from the previous table, the Hemiasterlin family of marine peptides will behave mostly as protease inhibitors, and also as enzyme inhibitors and as GPCR ligands.

4. Conclusions

This paper describes a study carried out to investigate the reactivity properties of Hemiasterlin and its derivatives using the density functional theory to explain how the molecular interactions of these marine peptides can be used in anti-cancer drugs.

The development of new pharmaceutical drugs, especially in cancer treatment requires extensive knowledge of the molecular bioactivity scores of different global and local peptides. Similarly, the values of the chemical hardness of some

Table 4. Molecular properties of the Hemiasterlin family of anticancer peptides of marine origin calculated to verify the Lipinski Rule of Five.

Molecule	milogP	TPSA	nAtoms	nON	NOHNH
Hemiasterlin	4.65	103.67	38	8	3
Hemiasterlin A	4.58	114.52	37	8	4
Hemiasterlin B	4.00	114.52	36	8	4
Molecule	Nviol	Nrotb	Volume	MW	
Hemiasterlin	1	11	525.87	526.72	
Hemiasterlin A	1	11	508.92	512.70	
Hemiasterlin B	0	11	492.69	498.67	

Table 5. Bioactivity scores of the Hemiasterlin family of marine peptides.

Molecule	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor
Hemiasterlin	0.51	0.02	0.01
Hemiasterlin A	0.56	0.13	0.04
Hemiasterlin B	0.49	0.12	0.06
Molecule	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
Hemiasterlin	0.19	0.62	0.43
Hemiasterlin A	0.18	0.68	0.45
Hemiasterlin B	0.13	0.58	0.35

therapeutic peptides have been used as the basis of determining their respective pKa values as proposed in the computational methodology. This information that is obtained enhances the understanding of properties such as the chemical reactivity and the water solubility of the peptides.

Moreover, prediction of the molecular properties of the peptides using various methodologies as described in the literature can also be used in the computation of the bioavailability values. As a result, the bioactivity levels can be quantified on the basis of their respective descriptors in the characterization process of the peptide bioactivity with the GPCR Ligand and the protease inhibitors.

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Conflicts of Interest

The authors declare that no conflict of interest exists regarding the publication of this paper.

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