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Computational Chemistry and Molecular Modeling Techniques for the Study of Micropeptin EI-964: Insights into Its Chemical Reactivity and Potential Pharmaceutical Properties

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Graphical Abstract

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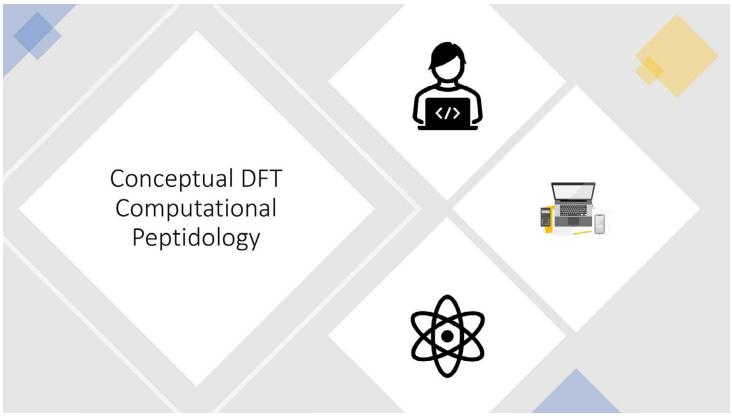

Abstract

Micropeptin EI-964 is a cyclic peptide compound isolated from a marine cyanobacterium with potent inhibitory activity against serine proteases, particularly chymotrypsin and trypsin. It has shown promising activity against various cancer cell lines, making it a candidate for drug development. The

unique structure and activity of Micropeptin EI-964 make it a promising lead compound for the development of novel serine protease inhibitors and anti-cancer drugs. Computational Chemistry and Molecular Modeling techniques can provide valuable insights into the chemical reactivity and pharmaceutical properties of Micropeptin EI-964, guiding the design and development of new compounds with enhanced bioactivity and improved drug-like properties.

Keywords

Micropeptin EI-964, Chemical Reactivity, Conceptual DFT, Computational Pharmacokinetics, Pharmaceutical Drugs

Highlights

Computational Chemistry and Molecular Modeling Techniques for the Study of Micropeptin EI-964: Insights into its Chemical Reactivity and Potential Pharmaceutical Properties

- Micropeptin EI-964 is a cyclic peptide compound isolated from a marine cyanobacterium of the genus Lyngbya.
- It is a potent inhibitor of serine proteases, specifically chymotrypsin and trypsin, which are important enzymes involved in various physiological processes.
- Micropeptin EI-964 has shown promising activity against cancer cell lines, inhibiting growth and inducing apoptosis in breast and pancreatic cancer cells.
- Its unique and complex structure includes three unusual amino acids, giving it potent inhibitory activity against serine proteases.
- Computational Chemistry and Molecular Modeling techniques can be used to optimize the structure of Micropeptin EI-964 for enhanced bioactivity and predict its potential toxicity and pharmacokinetics.
- Micropeptin EI-964 represents a promising lead compound for the development of novel serine protease inhibitors and anti-cancer drugs, but further studies are needed to determine its safety and efficacy *in vivo*.

1. Introduction

Micropeptin EI-964 is a cyclic peptide compound that has been isolated from a marine cyanobacterium of the genus Lyngbya. It is a potent inhibitor of serine proteases, specifically chymotrypsin and trypsin, which are important enzymes involved in the regulation of various physiological processes. Micropeptin EI-964 has also shown promising activity against cancer cell lines and has potential therapeutic applications in cancer treatment [1].

The structure of Micropeptin EI-964 is characterized by a cyclic heptapeptide backbone, with a thiazoline and a thiazole ring, and three unusual amino acids,

including (2S, 3S, 5S)-3-amino-2,5-dimethyl-4-hydroxyheptanoic acid (ADH) and (2S, 3S, 4S)-4-amino-2,3,4-trihydroxy-5-methylhexanoic acid. The presence of these unusual amino acids gives Micropeptin EI-964 a unique and complex structure [2] [3].

Studies have shown that Micropeptin EI-964 inhibits chymotrypsin and trypsin with an IC50 value of 1.2 nM and 0.14 nM, respectively, making it one of the most potent inhibitors of these enzymes. The mechanism of inhibition is thought to involve binding of Micropeptin EI-964 to the active site of the enzyme, thereby preventing substrate binding and catalysis [4].

In addition to its activity against serine proteases, Micropeptin EI-964 has also shown promising activity against various cancer cell lines. Studies have shown that Micropeptin EI-964 inhibits the growth of human breast cancer cells and induces apoptosis, or programmed cell death, in these cells. It has also been shown to inhibit the growth of pancreatic cancer cells and to sensitize them to chemotherapy [4].

The unique structure and potent activity of Micropeptin EI-964 make it an attractive candidate for drug development. However, further studies are needed to determine its safety and efficacy *in vivo*, as well as to investigate its potential as a therapeutic agent for cancer treatment. Overall, Micropeptin EI-964 represents a promising lead compound for the development of novel serine protease inhibitors and anti-cancer drugs [4].

Computational Chemistry and Molecular Modeling techniques can provide valuable insights into the chemical reactivity and potential pharmaceutical properties of Micropeptin EI-964. Computational Chemistry can be used to study the electronic and structural properties of Micropeptin EI-964, providing information on its stability, solubility, and potential interactions with other molecules. This information can be used to optimize the structure of the compound for enhanced bioactivity, as well as to predict its potential toxicity and bioavailability [5] [6] [7] [8] [9].

Molecular Modeling can be used to explore the potential anticancer activity of Micropeptin EI-964, as for studying its pharmacokinetics properties [5]-[10]. Overall, Computational Chemistry and Molecular Modeling techniques are powerful tools that can be used to obtain information about the chemical reactivity and potential pharmaceutical properties of Micropeptin EI-964 [5]-[10]. These insights can be used to guide the design and development of new compounds with enhanced bioactivity and improved drug-like properties, as well as to optimize the potential therapeutic use as a pharmaceutical drug of Micropeptin EI-964 whose starting molecular structure has been taken from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) and is displayed in **Figure 1**.

2. Methodology

Using the Conceptual DFT (CDFT) method [11]-[17], we performed calculations to determine the molecular energies, electronic densities, and orbital energies of the ligands under investigation. The Highest Occupied Molecular Orbital

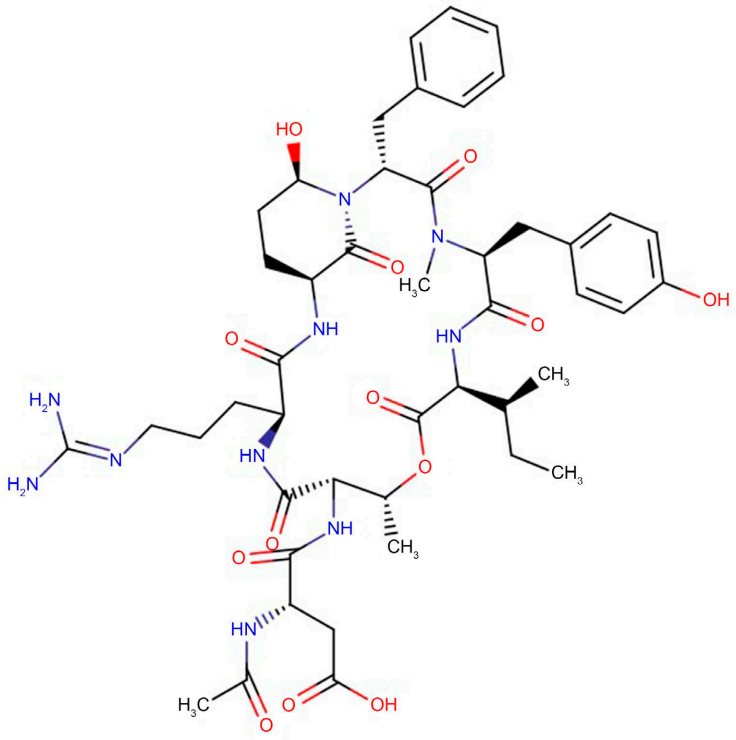

Figure 1. Graphical sketch of the molecular structure of the Micropeptide-EI964.

(HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) were specifically analyzed. To identify the conformers of the compounds studied, Molecular Mechanics (MM) calculations were conducted. The entire MMFF94 force field in MarvinView 17.15 from ChemAxon [http://www.chemaxon.com] was employed [18] [19] [20] [21] [22]. Initially, an optimization of the molecular geometry and frequency calculation was performed using the Density Functional Tight Binding (DFTBA) method [23]. This was followed by a second round of geometry optimization, frequency analysis, and computation of electronic properties and chemical reactivity descriptors using the MN12SX/Def2TZVP/H2O model chemistry [24] [25] [26] on the optimized molecular structures. The Def2TZVP basis set [25] [26] was utilized with the molecule's charge set to zero, considering the doublet spin state for the radical anion and cation. The MN12SX screened-exchange density functional [24] was incorporated into this model chemistry. The absence of imaginary frequencies served as a criterion to ensure the optimized structure represented a minimum in the energy landscape. The Gaussian 16 program [23] and the SMD solvation model [27] were employed for this purpose.

Understanding the pharmacokinetics, which refers to the behavior of a chemical once it enters the body, is crucial for the development of a new therapeutic drug [10]. To fulfill this purpose, Chemicalize, a tool developed by ChemAxon (http://www.chemaxon.com), was considered. Molinspiration software (https://www.molinspiration.com/) (accessed in March 2023) was employed to

calculate the molecular characteristics and predicted bioactivity score of drug targets such as enzymes, nuclear receptors, kinase inhibitors, GPCR ligands, and ion channel modulators.

3. Results and Discussion

The assessment of a given density functional's effectiveness is typically done by comparing its outcomes with experimental values or with results obtained from post Hartree-Fock calculations such as MP2, MP4, or CCSD. However, this approach may not always be feasible due to the unavailability of experimental data for the studied molecular systems or the computational impracticality of accurate methodologies for large molecules. To address this limitation, we have devised a validation protocol called KID (Koopmans in DFT) [5] [6] [7] [8] [9] that aims to evaluate a density functional's internal consistency. In our previous work, we identified several descriptors associated with the HOMO and LUMO calculations, which are linked to the results obtained through the vertical I and A using the ΔSCF technique (Self-Consistent Field). These descriptors demonstrate a connection between adherence to Koopmans' theorem or the Ionization Energy theorem within the Generalized Kohn-Sham (GKS) version of DFT. This relationship is established by connecting ε_H to -I, ε_L to -A, and through the definition of the HOMO-LUMO gap (HL), $J_I = \left|\varepsilon_H + E_{gs}(N-1) - E_{gs}(N)\right|$, $J_A = \left|\varepsilon_L + E_{gs}(N) - E_{gs}(N+1)\right|$, and $J_{HL} = \sqrt{J_I^2 + J_A^2}$. It is important to acknowledge that the J_A descriptor is an approximation valid only when the radical anion's HOMO (SOMO) resembles the neutral system's LUMO. To ensure the accuracy of this approximation, another descriptor ΔSL has been developed by our research group [5] [6] [7] [8] [9]. While the Koopmans'-compliant behavior of the MN12SX density functional has been previously demonstrated for peptides [5] [6] [7] [8] [9], we believe it is valuable to conduct further validation for the molecule under study. This validation was performed using our in-house CDFT software tool and also the MultiWFN package [28] [29], while the analysis results are presented in **Table 1**:

Table 1. The frontier energy orbitals HOMO and LUMO, the HL Gap and the KID descriptors of the Micropeptin EI964 Marine Cyclopeptide (all in eV).

KID Descriptor	Value
HOMO	−5.8260
LUMO	−1.1268
SOMO	−1.1467
HL gap	4.6991
J_I	0.0336
J_A	0.0110
J_{HL}	0.0353
ΔSL	0.0199

The outcomes presented in Table 1 reveal that all the KID descriptors' values are extremely close to zero. This suggests that the selected MN12SX density functional exhibits a Koopmans-compliant behavior. Consequently, the MN12SX/Def2TZVP/H2O model chemistry has been extensively validated and deemed highly suitable for the specific objectives of this research.

The optimized molecular structure of the Micropeptin EI964 cyclopeptide using the methodology previously presented is displayed in Figure 2:

Considering the KID methodology incorporated in previous studies and its integration into the finite difference approximation [5] [6] [7] [8] [9], the subsequent definitions can be employed to describe global characteristics that aid in comprehending the chemical reactivity of molecular systems [11] [12] [13] [30] [31]. The electronegativity can be expressed as $\chi = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H)$, the global hardness as $\eta = I - A \approx \varepsilon_L - \varepsilon_H$, the electrophilicity as $\omega = \mu^2/2\eta = (I + A)^2/4(I - A) \approx (\varepsilon_L + \varepsilon_H)^2/4(\varepsilon_L - \varepsilon_H)$, the electrodonating power as $\omega^- = (3I + A)^2/16(I - A) \approx (3\varepsilon_H + \varepsilon_L)^2/16\eta$, the electroaccepting power as $\omega^+ = (I + 3A)^2/16(I - A) \approx (\varepsilon_H + 3\varepsilon_L)^2/16\eta$, and the net electrophilicity as $\Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^-$. As mentioned earlier, ε_H and ε_L denote the HOMO and LUMO energies associated with the cyclopeptide investigated in this study. It is important to note that the global indices' chemical power is directly linked to the electronic density, as well as the corresponding Hohenberg-Kohn functional [32].

Also, Domingo and colleagues [33] [34] [35] [36] [37] introduced an Nucleophilicity index, denoted as N, by evaluating the HOMO energy using the KS scheme with a modified origin, using tetracyanoethylene (TCE) as a reference molecule. Using the aforementioned CDFT software tool, the electronic property calculations of the Micropeptin EI964 cyclopeptide were analyzed, enabling the determination of various global reactivity descriptors, including the Nucleophilicity N. The obtained values are presented in Table 2:

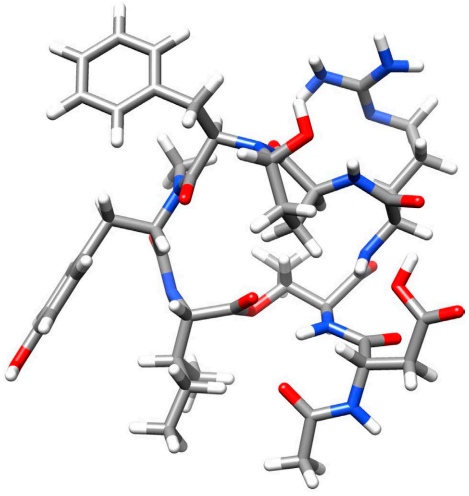

Figure 2. Optimized molecular structure of the Micropeptin-EI964 Marine Cyclopeptide.

Table 2. Conceptual DFT global reactivity descriptors of the Micropeptin EI964 Marine Cyclopeptide (all in eV).

KID Descriptor	Value
Electronegativity χ	3.4764
Global Hardness η	4.6991
Electrophilicity ω	1.2859
Nucelophilicity Index N	2.2952
Electrodonating Power ω^{-}	4.6037
Electroaccepting Power ω^{+}	1.1273
Net Electrophilicity $\Delta\omega^{\pm}$	5.7310

In DFT, the dual descriptor DD is a powerful tool used to study the reactivity of molecules. It provides a measure of both the nucleophilic and electrophilic character of a molecule, making it a valuable tool in predicting chemical reactivity. The dual descriptor has many applications in chemistry, including in the design of new catalysts, the prediction of chemical reactions, and the study of chemical reactivity. It provides a useful tool for understanding the electronic structure of molecules, and for predicting their behavior in chemical reactions [38] [39] [40] [41].

The dual descriptor DD is calculated as the product of the difference between the HOMO and LUMO energy levels, being thus related to the HOMO-LUMO gap. The dual descriptor DD can be used to predict the reactivity of a molecule towards nucleophilic or electrophilic attack. A high positive value of the dual descriptor indicates that the molecule is a good electrophile, while a high negative value indicates that it is a good nucleophile [38] [39] [40] [41].

A graphical representation of the dual descriptor DD for the Micropeptin EI-964 is displayed in **Figure 3**, where the nucelophilic and electrophilic regions can be distinguished:

As a complement of the information obtained about the chemical reactivity of the Micropeptin-EI964 marine cyclopeptide by considering a CDFT analysis, **Table 3** provides bioactivity scores for the studied peptide against various targets, including GPCR ligands, ion channel modulators, nuclear receptor ligands, kinase inhibitors, protease inhibitors, and enzyme inhibitors. These scores provide valuable insights into the potential therapeutic applications of these compounds [10].

GPCRs are a class of proteins that play a key role in cell signaling and are involved in a wide range of physiological processes. The bioactivity scores presented in **Table 3** suggest that Micropeptin-EI964 has potential as GPCR ligands. Its moderate score as a GPCR ligand indicates that it may be able to selectively bind to and activate specific GPCRs involved in disease processes. This could make it an effective drug or therapy for treating conditions such as inflammation or cancer.

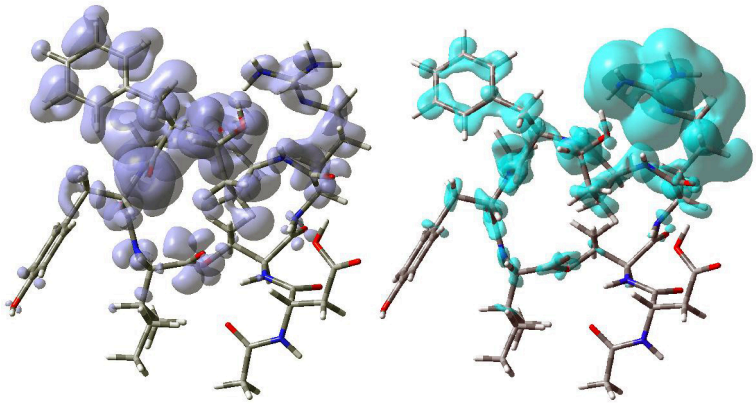

Figure 3. Graphical representation of the Dual Descriptor DD of the Micropeptin-EI964 Marine Cyclopeptide. Left: DD > 0, Right: DD < 0.

Table 3. Bioactivity scores of the Micropeptin-EI964 Marine Cyclopeptide calculated on the basis of the different interactions.

Property	Value
GPCR Ligand	−0.81
Ion Channel Modulator	−2.00
Nuclear Receptor Ligand	−1.58
Kinase Inhibitor	−1.65
Protease Inhibitor	−0.28
Enzyme Inhibitor	−1.33

Ion channels are another class of proteins involved in cell signaling and are important targets for drug development. The bioactivity scores presented in Table 3 suggest that Micropeptin-EI964 has a low potential as ion channel modulator.

The same conclusion can be obtained for the case of the interaction with nuclear receptor ligands and as a kinase inhibitor. Nuclear receptors are a class of proteins that play a key role in gene expression and are important targets for drug development. In turn, kinases are a class of enzymes involved in cell signaling and are important targets for drug development.

Finally, it could be appreciated from Table 3, that the main activity of the Micropeptin-EI964 molecule will be as a protease inhibitor. A protease inhibitor is a type of molecule that can block the activity of a protease enzyme, which is a type of protein that plays a key role in the breakdown of other proteins in the body.

Proteases are involved in many biological processes, such as protein digestion, blood clotting, and immune response. Aberrant protease activity has been linked to a variety of diseases, including viral infections, cancer, and inflammation. When a protease inhibitor binds to a protease, it blocks its ability to cleave target proteins, effectively stopping downstream signaling pathways. This can prevent the replication of viruses, the progression of cancer, and the activation of

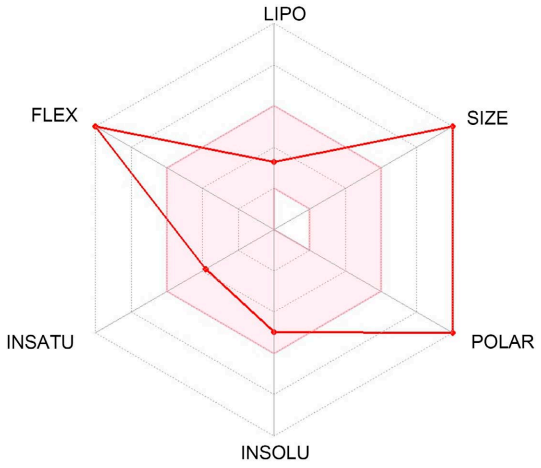

Figure 4. Bioavailability radar of the Micropeptin-EI964 Marine Cyclopeptide.

inflammatory pathways, leading to therapeutic effects. Protease inhibitors are important targets for drug discovery and development, as they have the potential to selectively target and inhibit specific proteases involved in disease processes, leading to more effective and less toxic treatments. Many antiviral drugs, such as HIV protease inhibitors, are protease inhibitors that have shown significant clinical success.

Another common analysis when considering molecules as potential drugs is the verification of the so called Lipinski's rules. This kind of studies was proposed several years ago with the objective of predicting if the drug could be orally deriverable [42]. With this idea in mind, the subjects of the study were small molecules. However, it has been shown many times that the Lipinski's rules do not apply for the case of cyclic peptides, which in spite of being larger in size and volume, and with less solubility, they can be delivered orally. Thus, this is not a problem for the consideration of cyclic peptides as potential pharmacological drugs [43]. The interplay between these properties for the Micropeptin-EI964 marine cyclopeptide considered in this research can be appreciated graphically through the so called Bioactivity Radar, which is shown in **Figure 4**. It can be concluded that the major deviations from the ideal behavior are due to their size, polarity and flexibility.

4. Conclusions

Conceptual Density Functional Theory (CDFT) is an established theoretical framework utilized for investigating the characteristics of atoms and molecules through the computation of their electronic density. By interpreting the electronic density within the context of chemical principles, DFT offers valuable insights into the behavior of molecules and materials, enabling the prediction and comprehension of chemical reactions and material properties. Prominent experts in this field have emphasized the significance of CDFT not only for comprehending and validating experimental findings but also as an exceptional tool

for the advanced anticipation of unexplored properties in molecular systems.

Theoretical and computational approaches related to DFT and CDFT have been applied to forecast the chemical reactivity of Micropeptin-EI964 marine cyclopeptides, offering valuable insights into their electronic structure, molecular characteristics, and reactivity indicators. Furthermore, a thorough investigation and computational projection of the pharmacokinetic properties of this peptide have been conducted. The acquired knowledge is expected to assist in the design of novel derivatives with improved properties or the exploration of potential therapeutic agents.

CRediT Authorship Contribution Statement

Norma Flores-Holguín: Theoretical Calculations and Analysis; Juan Frau: Theoretical Calculations and Analysis; Daniel Glossman-Mitnik: Conceptualization, Methodology, Software, Theoretical Calculations and Analysis; Writing—Original Draft.

Data Availability

All generated data is available from the authors under request.

Conflicts of Interest

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

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