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Research Article

A CDFT-Based Computational Peptidology (CDFT-CP) Study of the Chemical Reactivity and Bioactivity of the Marine-Derived Alternaramide Cyclopentadepsipeptide

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Alternaramide is a cyclic pentadepsipeptide isolated from marine sources that has been shown to present weak antibiotic activity against *Bacillus subtilis* and *Staphylococcus aureus* as well as inhibitory effects on inflammatory mediator expressions. Thus, this work reports the results of a computational study of the chemical reactivity and bioactivity properties of this cyclopentadepsipeptide considering a CDFT-based computational peptidology (CDFT-CP) methodology that results from the combination of the chemical reactivity descriptors that arise from conceptual density functional theory (CDFT) together with some cheminformatics tools that can be used to estimate the associated physicochemical parameters, to improve the process of virtual screening through a similarity search, and to identify the ability of the peptide to behave as a potential useful drug, complemented with an analysis of its bioactivity and pharmacokinetics indices related to the ADMET (absorption, distribution, metabolism, excretion, and toxicity) features. The results represent a new confirmation of the superiority of the MN12SX density functional in the fulfilment of the Janak and ionization energy theorems through the proposed KID procedure. This has been useful for the accurate prediction of the CDFT reactivity descriptors that help in understanding the chemical reactivity. The computational pharmacokinetics study revealed the potential ability of alternaramide as a therapeutic drug by interacting with GPCR ligands and protease inhibitors. The ADMET indices confirm this assertion through the absence of toxicity and good absorption and distribution properties.

1. Introduction

There are many studies showing that marine cyclodepsipeptides have a broad spectrum of biological functions, spanning from antitumor, anthelmintic, insecticidal, antibiotic, antifungal, immunosuppressant, anti-inflammatory, anti-HIV to antimalarial activities [1–8].

Alternaramide is a cyclic pentadepsipeptide that has been isolated from an extract of the marine-derived fungus *Alternaria* spp. SF-5016 whose structure was determined by analysis of the NMR spectroscopic data. It has been shown that alternaramide present weak antibiotic activity against *Bacillus subtilis* and *Staphylococcus aureus* [9]. Another study demonstrated that the alternaramide cyclopentadepsipeptide displays inhibitory effects on inflammatory mediator expressions [10].

The first synthesis of alternaramide was presented by Horton and coworkers using solution phase coupling protocols and macrolactonization and macrolactamization routes while its structure was determined by single crystal X-ray analysis [11].

In light of these potential therapeutic properties, we present the results of a computational study of the chemical reactivity and bioactivity properties of this cyclopentadepsipeptide using a CDFT-based computational peptidology (CDFT-CP) methodology [12–20], which is

based on the combination of chemical reactivity descriptors derived from conceptual density functional theory (CDFT) [21–26], together with some cheminformatics tools [27–34] that can be used to estimate the associated physicochemical parameters, to improve the process of virtual screening through a similarity search, and to identify the ability of the peptide to behave as a potential useful drug, complemented with an analysis of its bioactivity and pharmacokinetics indices related the ADMET (absorption, distribution, metabolism, excretion, and toxicity) features [35, 36].

2. Materials and Methods

2.1. Density Functional Theory (DFT) Calculations. The Kohn–Sham (KS) methodology entails determining the molecular energy, electronic density, and orbital energies of a given system, particularly the frontier orbitals HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital), which are intrinsically linked to the chemical reactivity of molecules [37–40]. This methodology is convenient when thinking of quantitative qualities related with conceptual DFT descriptors [21–26]. The definitions for the global reactivity descriptors are as follows [21–26]: electronegativity as $\chi = 1/2(\varepsilon_L + \varepsilon_H)$, global hardness as $\eta = (\varepsilon_L - \varepsilon_H)$, and electrophilicity as $\omega = (\varepsilon_L + \varepsilon_H)^2/4(\varepsilon_L - \varepsilon_H)$. In these definitions, ε_H and ε_L represent the HOMO and LUMO energies related to the marine cyclopentadepsipeptide studied through this research. In turn, the electrodonating power is defined as $\omega^- = (3\varepsilon_H + \varepsilon_L)^2/16\eta$ and the electroaccepting power is defined as $\omega^+ = (\varepsilon_H + 3\varepsilon_L)^2/16\eta$ while the net electrophilicity is a combination of the previous reactivity descriptors defined as $\Delta\omega^{\pm} = \omega^+ + \omega^-$.

These global reactivity descriptors arising from conceptual DFT [21–26] are complemented by a new nucleophilicity index N which was established [41–45] considering the value of the HOMO energy obtained by means of the KS scheme using an arbitrary shift of the origin with tetracyanoethylene (TCE) as a reference.

The quality of a density functional can be determined by comparing the results it produces with experimental values or results produced from high-level computations. However, due to lack of experimental results for the chemical systems under investigation or the large size of the molecules, this comparison is not always computationally feasible. A methodology called KID (Koopmans in DFT) has been developed by our research group [12–20] for the validation of a given density functional in terms of its internal coherence. It has been shown that within the generalized Kohn–Sham (GKS) version of DFT, there are some relations between the KID indices and the Koopmans and ionization energy theorems, by connecting ε_H to –I, ε_L to –A, and a combination of both orbital energies through the formulas $J_I = |\varepsilon_H + E_{gs}(N-1) - E_{gs}(N)|$, $J_A = |\varepsilon_L + E_{gs}(N) - E_{gs}(N+1)|$, and $J_{HL} = \sqrt{J_I^2 + J_A^2}$. An additional KID descriptor ΔSL amounting to the difference in energies between the SOMO (equivalent to the HOMO of the radical anion) and the LUMO of the neutral system has been designed to help in the verification of the accuracy of this methodology [12–20].

The conformers of the peptide studied in this study were determined using MarvinView 17.15 from ChemAxon (http://www.chemaxon.com), which was used to perform molecular mechanics calculations using the overall MMFF94 force field [46–50]. Following that, the density functional tight binding (DFTBA) methodology was used to optimize the geometry and calculate the frequency [51]. This final step was required to ensure that there were no imaginary frequencies as a check for the optimized structures' stability as a minimum in the energy landscape. The electronic properties and the chemical reactivity descriptors of the alternaramide marine cyclopentadepsipeptide considered the MN12SX/Def2TZVP/H2O model chemistry [52–54] on its optimized molecular structure, owing to the fact that has been previously proved that it verifies the "Koopmans in DFT" (KID) procedure [13–20, 55–62], with the aid of the Gaussian 16 software [51] and the SMD solvation model [63]. This model chemistry considers the MN12SX screened-exchange density functional [52] together with the Def2TZVP basis set [53, 54] and the charge of the molecule being equal to zero while the radical anion and cation have been considered in the doublet spin state.

2.2. In Silico Pharmacokinetics Analysis and ADMET Study. The first step in understanding the potential therapeutic properties of the considered marine cyclopentadepsipeptide was to feed its SMILES (simplified molecular input line entry specification), which was obtained through ChemDoodle 11.3.0 software, into Chemicalize, by ChemAxon (http://www.chemaxon.com), which was used for the prediction of several properties related to cheminformatics (http://chemicalize.com/) (accessed March 2021).

The online Molinspiration software from Molinspiration Cheminformatics (https://www.molinspiration. com/) (accessed March 2021) was used to search the chemical universe for molecules having molecular structures that are comparable to the one being analyzed for similarity with already known biological and pharmacological properties for the prediction of the bioactivity scores for the different drug targets.

SwissTargetPrediction is a useful tool that is available online for the efficient prediction of protein targets of small molecules and has been considered for the determination of the potential bioactivity of the marine cyclopentadepsipeptide considered in this study [64]. The associated website allows the estimation of the most probable macromolecular targets of a small molecule, assumed as bioactive.

Pharmacokinetics is the process associated with the knowledge of the possible fate of a therapeutic compound in the organism which is very important knowledge within the process of development of a new drug. This has been usually done by analyzing the associated effects through individual indices that are called absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters. In this research, some ADMET parameters were estimated with the aid of Chemicalize and the SwissADME software available online [35]. Additional information about the

pharmacokinetics parameters and the ADMET properties were obtained by resorting to pkCSM [36], a software application for the prediction of small-molecule pharmacokinetic properties using SMILES that can be accessed through its associated web page (https://biosig.unimelb.edu.au/pkcsm/) (accessed March 2021).

3. Results and Discussion

The starting molecular structure of the marine cyclopentadepsipeptide to be studied was obtained from ChemSpider (https://www.chemspider.com), which is a chemical structure database available online that provides fast structure search access to millions of structures from many data sources, with information related to physical, chemical, and biological properties, interactive spectra, and literature references. A graphical sketch of the molecular structure of alternaramide is shown in Figure 1.

3.1. Names, Identifiers, and Physicochemical Properties. The names, identifiers, and basic properties of the alternaramide marine cyclopentadepsipeptide are presented in Table 1 while its geometrical, structural, and physicochemical properties are given in Table 2.

This information could it be of interest for future QSAR studies based on the peptide as well as for potential derivatives designed for therapeutical purposes using peptidomimetics.

3.2. Conceptual DFT Calculations. The optimized molecular structure of alternaramide marine cyclopentadepsipeptide calculated according to the procedure presented in the Materials and Methods section is shown in Figure 2, while Figure 3 shows a schematic representation of the cyclopeptide showing an internal H-bond formed between O (5) and the H atom attached to N (9).

It has been proved in our previous research on peptides [12–20] that the MN12SX density functional presents a Koopmans-compliant behavior. However, we consider that it is worth to perform further validation for the marine cyclopentadepsipeptide under study. This determination has been done by considering the in-house developed CDFT software tool including a comparison with the results that can be obtained using other density functionals. It has been shown for small molecules that long-range corrected density functionals are the best for reproducing the behavior prescribed by Janak's theorem [65] and its corollary, the ionization energy theorem. A recent study [66] has compared this behavior for a group of density functionals that includes the usual B3LYP [67–69] and PBE0 [70, 71] density functionals, the local density functionals BLYP [68, 69, 72, 73] and PBE [74] together with their long-range corrected counterparts, LC-BLYP and LC-PBE [75], three modern long-range corrected density functionals, CAM-B3LYP [76], LC-ωHPBE [77], and ωB97XD [78], and three recently proposed variants of the PBE0 density functional, RSX-PBE, RSX-PBE0, and RSX-PBE0-1/3 [79]. For the sake of completeness, we are presenting in Table 3 a comparison of the

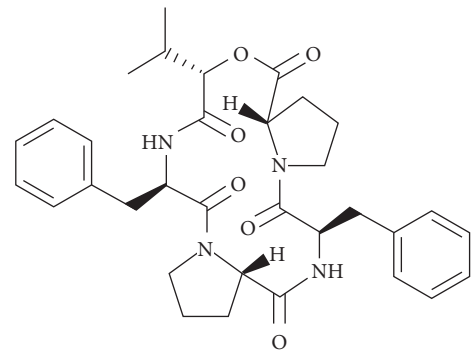


Figure 1: Graphical sketch of the molecular structure of the alternaramide marine cyclopentadepsipeptide.

fulfilment of the ionization energy theorem between the mentioned density functionals and the screened-exchange MN12SX density functional that has been considered in this and previous research for the study of peptides.

According to a recent study [66], the precise vertical ionization energy (VIE) may be obtained using both the SCF approach or the HOMO energy if one possesses the exact exchange-correlation functional. It can be derived from this assertion that a given approximate density functional will be more closer to the exact one as the values of the VIE that it renders from both methodologies will not differ. This is precisely what the KID procedure allows to verify for every tested density functional. From Table 3, the values for the KID descriptors are all very close to zero meaning that the MN12SX density functional has a Koopmans-compliant behavior (or the fulfilment of the Janak and ionization energy theorems) further justifying that the MN12SX/Def2TZVP/H2O is a model chemistry very adequate for the purpose of this research. Although some other density functionals have been shown to approximately fullfil those theorems for the case of small molecules, the results from this and previous research have demonstrated that this not the case for peptides and cyclopeptides [12–20]. The MN12SX density if the only one that allows the verification of these theorems not only for the case of the VIE but also for the vertical electron affinity thus rendering very accurate HOMO-LUMO gaps.

The values of the defined global reactivity descriptors (including the nucleophilicity N) for the alternaramide marine cyclopentadepsipeptide obtained using the mentioned CDFT tool are given in Table 4.

The global descriptors are an indication of the chemical reactivity of each molecule as a whole, and due to this, local reactivity descriptors have been designed for an estimation of the differences in the chemical reactivity between the regions within the molecule. The nucleophilic and electrophilic Fukui functions (NFF and EFF) [21–23] and the dual descriptor (DD) [80–85] are some of these local reactivity descriptors. They have been defined as follows: $\mathrm{NFF} = \rho_{N+1}(r) - \rho_N(r)$, $\mathrm{EFF} = \rho_N(r) - \rho_{N-1}(r)$, and $\mathrm{DD} = \Delta f(r) = (\partial f(r)/\partial N)_{v(r)}$, establishing connections between the electronic densities of different species as well as between the NFF and EFF.

Table 1: Names, identifiers, and basic properties of the studied molecular system.

Property	Value
Common name	Alternaramide
PubChem CID	44605719
Molar mass	588.705 g/mol
Exact mass	588.294785024 Da
Formula	$C_{33}H_{40}N_4O_6$
Composition	C (67.33%), H (6.85%), N (9.52%), O (16.31%)
IUPAC name	(3R,6S,12R,15S,18S)-3,12-Dibenzyl-15-(propan-2-yl)-16-oxa-1,4,10,13-Tetraazatricyclo[16.3.0.0^{6,10}]henicosane-2,5,11,14,17-Pentone
SMILES	CC(C)[C@@H]1OC(=O)[C@@H]2CCCN2C(=O)[C@@H](CC2=CC=CC=C2)NC(=O)[C@@H]2CCCN2C(=O)[C@@H](CC2=CC=CC=C2)NC1=O
InChIKey	IZCWSRIIMBIBGB-MASCHLQQSA-N

Table 2: Geometrical, structural, and physicochemical properties of the studied molecular system.

Property	Value
Atom count	83
Non-hydrogen atom count	43
Asymmetric atom count	5
Rotatable atom count	5
Ring count	5
Aromatic ring count	2
Hetero ring count	3
FSP3	0.48
Hydrogen bond donor count	2
Hydrogen bond acceptor count	5
Formal charge	0
van der Waals volume (Å^3)	546.61
van der Waals surface area (Å^2)	870.17
Solvent accessible surface area (Å^2)	769.98
Topological polar surface area (Å^2)	125.12
Polarizability (Å^3)	62.04
Molar refractivity (cm^3/mol)	158.15

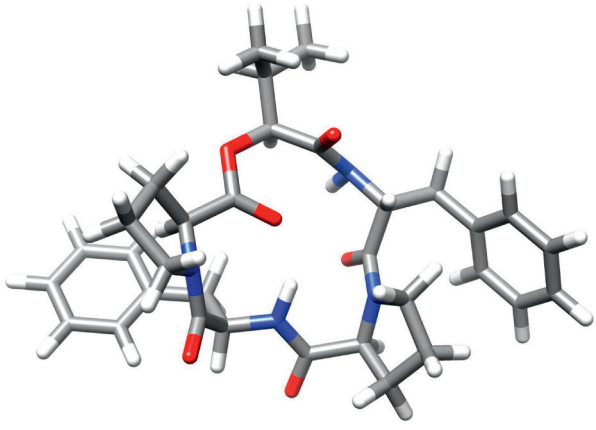


Figure 2: Optimized molecular structure of alternaramide.

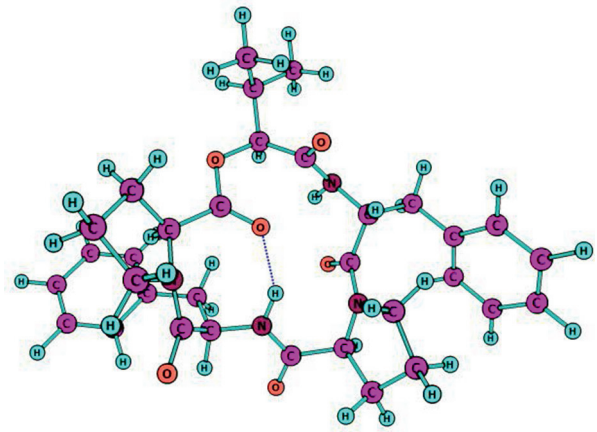


Figure 3: Molecular structure of alternaramide showing the internal H-bond.

Table 3: HOMO, LUMO, and SOMO energies, HOMO-LUMO gap, and the KID descriptors (all in eV) for the alternaramide marine cyclopentadepsipeptide.

DF	HOMO	LUMO	SOMO	HL gap	J_I	J_A	J_{HL}	ΔSL
BLYP	−5.31	−1.42	−0.78	3.89	0.29	0.41	0.50	0.63
PBE	−5.51	−1.62	−1.02	3.89	0.29	0.38	0.48	0.60
B3LYP	−6.63	−0.80	−1.12	5.83	0.21	0.16	0.26	0.32
PBE0	−6.93	−0.63	−1.33	6.30	0.35	0.36	0.51	0.70
LC-BLYP	−9.52	1.92	−2.48	11.44	2.76	2.18	3.52	4.40
LC-PBE	−9.78	1.68	−2.75	11.47	2.77	2.20	3.54	4.43
CAM-B3LYP	−8.11	0.64	−2.48	8.75	1.47	1.55	2.14	3.12
LC-ωHPBE	−9.47	1.72	−2.59	11.19	2.64	2.14	3.40	4.31
ωB97XD	−8.11	0.64	−2.48	8.75	1.47	1.55	2.14	3.12
RSX-PBE	−9.73	1.65	−2.74	11.38	2.72	2.18	3.48	4.39
RSX-PBE0	−9.73	1.70	−2.73	11.43	2.77	2.19	3.54	4.43
RSX-PBE0-1/3	−9.74	1.72	−2.73	11.46	2.80	2.20	3.57	4.45
MN12SX	−6.72	−1.03	−1.02	5.69	0.01	0.01	0.01	0.02

Table 4: Global reactivity descriptors for the alternaramide marine cyclopentadepsipeptide (all in eV).

Descriptor	Value
Electronegativity χ	3.8787
Hardness η	5.6894
Electrophilicity ω	1.3222
Softness S	0.1751
Nucleophilicity N	2.3978
Electrodonating power ω^-	4.9392
Electroaccepting power ω^+	1.0605
Net electrophilicity $\Delta\omega^\pm$	5.9998

The NFF determines the sites of a molecular that are more susceptible to nucleophilic attacks while the EFF is an indication of regions that are more susceptible to electrophilic attacks. These local reactivity descriptors have been successfully used for the identification of the reactive sites. However, it has been found that the dual descriptor $\Delta f(r)$ or DD can describe simultaneously the nucleophilic and electrophilic sites within a molecule without ambiguities [85]. A graphical sketch of the dual descriptor (DD) for the alternaramide marine cyclopentadepsipeptide is presented in Figure 4 showing the regions where DD > 0 and DD < 0 for a better understanding of the local chemical reactivity of these molecules.

Table 5 presents a comparison of several reactivity descriptors: condensed electrophilicity ω_k, condensed nucleophilicity N_k, and condensed dual descriptor Δf_k, over selected atoms of the alternaramide cyclopentadepsipeptide in relation with the molecular structure shown in Figure 5.

3.3. Chemoinformatics and Bioactivities. A compact representation of the parameters related to bioavailability can be displayed in a graphic way through the so called bioavailability radar shown in Figure 6 for the alternaramide marine cyclopentadepsipeptide.

It can be appreciated that the only problem for the alternaramide marine cyclopentadepsipeptide to be considered as therapeutic drug of easy availability is related to their size which is a bit greater than the ideal one.

The bioactivity score, that is, the measure of the ability of a given molecule to behave or interact with different receptors, for the alternaramide marine cyclopentadepsipeptide is presented in Table 6, while a graphical representation is shown in Figure 7, as the corresponding biological targets.

A chemical with a bioactivity score more than 0 is predicted to have significant biological activities, while values between −0.50 and 0.00 are moderately active. The molecular system is considered inactive if the bioactivity score is less than −0.50. The findings clearly show that drug complexes' physiological activities may be mediated by many pathways, including interactions with GPCR ligands, protease inhibitors, and other enzymes. These bioactivity scores from Table 6 and Figure 6 suggest considerable interaction of the alternaramide cyclopeptide with GPCR ligands and protease inhibitors, while showing moderate interactions with the other receptors.

The pharmacokinetics of a drug are assessed in an ADMET research, which stands for absorption, distribution, metabolism, excretion, and toxicity. Predicting a medication's fate and effects inside the body, such as how much of a drug is absorbed if taken orally versus how much is absorbed in the gastrointestinal tract, is an essential element of drug development. Similarly, if absorption is poor, the distribution and metabolism of the drug would be altered, potentially leading to neurotoxicity and nephrotoxicity. The goal of the research is to figure out how a drug molecule behaves within an organism. As a result, one of the most important aspects of computational drug design is an ADMET analysis.

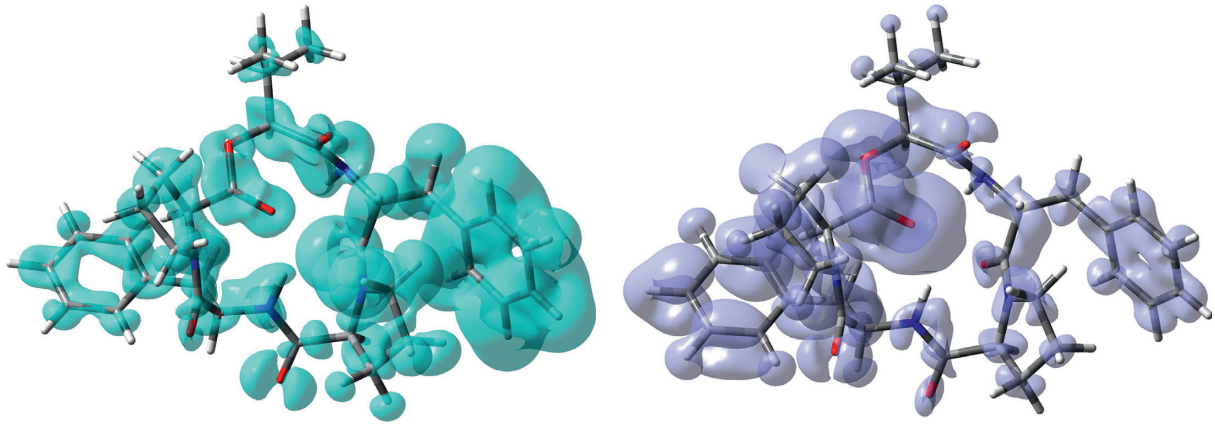
If a substance is injected into the bloodstream, it can reach a tissue. A medicine is typically delivered through mucous surfaces such as the digestive tract, i.e., intestinal absorption, before being taken up by target cells. Poor substance solubility, difficulty to permeate the intestinal wall, and chemical instability in the stomach are all factors that contribute to drug absorption being reduced following oral delivery. Absorption is crucial since it influences a compound's bioavailability. Oral delivery, such as inhalation or intravenously, is less desirable for drugs with limited absorption [36, 86].

The computed absorption properties of the alternaramide marine cyclopentadepsipeptide are presented in Table 7.

A given compound is considered to have a high Caco-2 permeability through the human intestinal mucosa for predicted values > 0.90, presenting the alternaramide marine cyclopentadepsipeptide a value similar to the ideal one. The intestine is normally the primary site for absorption of a drug from an orally administered solution. The intestinal absorption predicts the percentage of a compound to be absorbed through the human intestine considering an absorbance of less than 30% to be poorly absorbed. From Table 7, the alternaramide marine cyclopentadepsipeptide is predicted to be well absorbed. Toxins and xenobiotics are extruded from cells by the P-glycoprotein, which acts as a biological barrier. The model predicts whether or not a given substance will be a P-glycoprotein substrate. The alternaramide marine cyclic pentadepsipeptide has a promising future. Modulation of P-glycoprotein-mediated transport has substantial pharmacokinetic implications for P-glycoprotein substrates, which can be used for specific therapeutic benefits or cause contraindications. Thus, this study predicts that the alternaramide marine cyclopentadepsipeptide considered in this study will not act as P-glycoprotein I and II inhibitors. It is also possible to forecast if a certain substance will be skin permeable. If a compound's log Kp is more than −2.5, it is said to have low skin permeability. It suggests that alternaramide may be useful in the development of transdermal medication delivery systems [36].

The computed distribution properties of the alternaramide marine cyclopentadepsipeptide are presented in Table 8.

The total dose of a drug requires a volume to be uniform in blood plasma which is named VDss. The drug will be more distributed in the tissue rather than in the plasma for higher VDss. From Table 8, a low value of VDss is found for the alternaramide marine cyclopentadepsipeptide. The efficacy of a given drug may be affected by the degree to which



(a) (b)

Figure 4: Graphical representation of the dual descriptor (DD) of the alternaramide marine cyclopentadepsipeptide. (a) DD > 0. (b) DD < 0.

Table 5: Comparison of several reactivity descriptors: condensed electrophilicity ω_k, condensed nucleophilicity N_k, and condensed dual descriptor Δf_k, over selected atoms of the alternaramide cyclopentadepsipeptide (H atoms are not shown).

Alternaramide			
Atom	ω_k	N_k	Δf_k
1 (O)	0.0828	0.0087	0.0591
2 (O)	0.0143	0.0612	−0.0146
3 (O)	0.0315	0.0120	0.0189
4 (O)	0.0134	0.1182	−0.0391
5 (O)	0.1673	0.0033	0.1255
6 (O)	0.0364	0.0490	0.0072
7 (N)	0.0035	0.0957	0.0373
8 (N)	0.0057	0.0061	0.0018
9 (N)	0.0036	0.0169	−0.0043
10 (N)	0.0130	0.0596	−0.0158
C (11)	0.0025	0.0212	−0.0069
C (12)	0.0019	0.0160	−0.0053
C (13)	0.0358	0.0028	0.0259
C (14)	0.0016	0.0276	−0.0103
C (15)	0.0015	0.0507	−0.0200
C (16)	0.0212	0.0017	0.0154
C (17)	0.0076	0.0022	0.0049
C (18)	0.0098	0.0016	0.0067
C (19)	0.0022	0.0052	−0.0006
C (20)	0.0094	0.0218	−0.0020
C (21)	00158	0.0037	0.0105
C (22)	0.0067	0.0306	−0.0077
C (23)	0.0041	0.0341	−0.0111
C (24)	0.2202	0.0063	0.1644
C (25)	0.0098	0.0025	0.0064
C (26)	0.0172	0.0064	0.0103
C (27)	0.0031	0.0047	−0.0173
C (28)	0.0053	0.0035	0.0025
C (29)	0.0130	0.0205	0.0013
C (30)	0.0223	0.0007	0.0166
C (31)	0.0001	0.1484	−0.0618
C (32)	0.0042	0.0028	0.0020
C (33)	0.0051	0.0018	0.0031
C (34)	0.0326	0.0018	0.0240
C (35)	0.0236	0.0012	0.0174

Table 5: Continued.

Alternaramide Atom	ω_k	N_k	Δf_k
C (36)	0.0010	0.0640	−0.0260
C (37)	0.0015	0.1879	−0.0772
C (38)	0.0227	0.0015	0.0166
C (39)	0.0289	0.0020	0.0211
C (40)	0.0015	0.1644	−0.0675
C (41)	0.0015	0.0024	−0.0321
C (42)	0.0468	0.0024	0.0345
C (43)	0.0017	0.2123	−0.0873

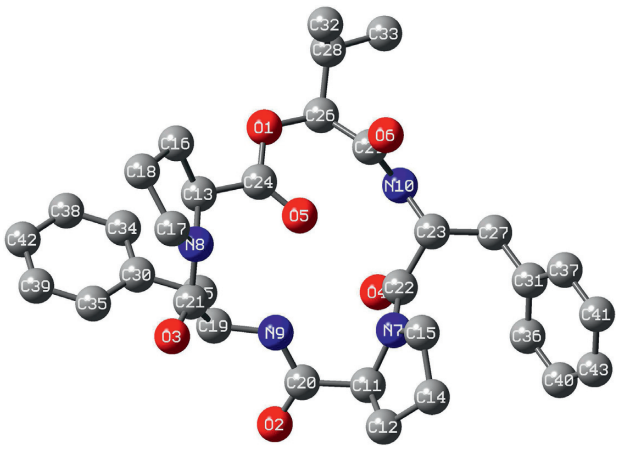


Figure 5: Molecular structure of alternaramide showing the labelling over the atoms. H atoms are not shown.

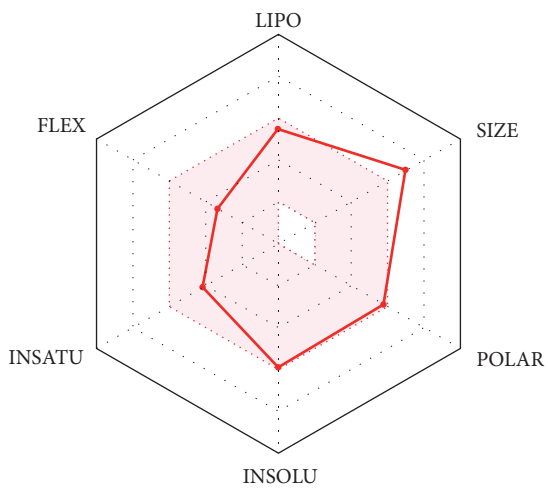


Figure 6: Bioactivity radar of the alternaramide marine cyclopentadepsipeptide.

it binds proteins within blood. The fraction unbound forecasts the fraction of plasma that will be unbound, giving the value in Table 8. The ability of a drug to cross into the brain is an important descriptor to be known because it can help to reduce side effects and toxicities and is measured using the blood-brain permeability parameter. A logBB

Table 6: Bioactivity scores of the alternaramide marine cyclopentadepsipeptide calculated for its biological target interactions.

Property	Value
GPCR ligand	0.16
Ion channel modulator	−0.49
Nuclear receptor ligand	−0.40
Kinase inhibitor	−0.35
Protease inhibitor	0.51
Enzyme inhibitor	−0.17

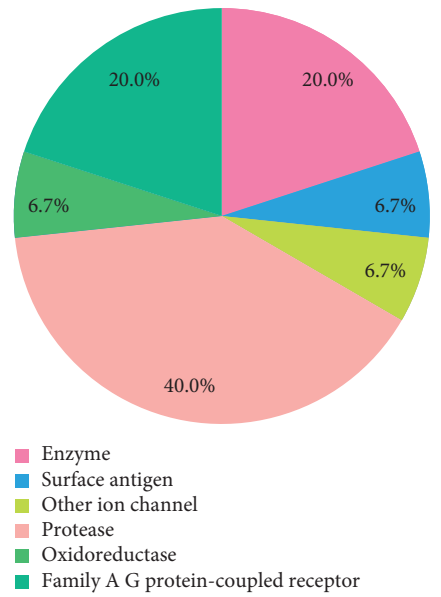


Figure 7: Predicted biological targets of alternaramide marine cyclopentadepsipeptide.

Table 7: Absorption properties of the alternaramide marine cyclopentadepsipeptide.

Property	Value
Water solubility	−4.518
Caco-2 permeability	0.907
Intestinal absorption	74.153
Skin permeability	−2.737
P-glycoprotein substrate	+
P-glycoprotein I inhibitor	—
P-glycoprotein II inhibitor	—

Table 8: Distribution properties of the alternaramide marine cyclopentadepsipeptide.

Property	Value
VDss	−0.141
Fraction unbound	0.016
BBB permeability	−0.610
CNS permeability	−2.971

score of > -0.3 indicates that a possible therapeutic treatment will easily penetrate the blood-brain barrier, whereas a logBB value of > -1 indicates that the medicine will be poorly dispersed to the brain. Another measurement is the CNS permeability with a value of −2.971 predicted for the alternaramide marine cyclopentadepsipeptide meaning that this drug will be unable to penetrate the central nervous system (CNS) [36].

The computed metabolism properties of the alternaramide marine cyclopentadepsipeptide are presented in Table 9.

Because it oxidizes xenobiotics to promote excretion, cytochrome P450 is a key detoxification enzyme in the body, primarily found in the liver [36]. As can be seen from Table 6, the alternaramide marine cyclopentadepsipeptide is predicted as not being an inhibitor for all the P450 cytochrome isoforms with the exception of CYP3A4. It is also crucial to know whether or not a medicine is a cytochrome P450 substrate. According to the forecast, this will not be the case for CYP2D6, but it will be for CYP3A4.

The computed excretion properties of the alternaramide marine cyclopentadepsipeptide are presented in Table 10.

Drug clearance occurs as a combination of hepatic clearance and renal clearance, and it is related to bioavailability, thus important for determining dosing rates. The predicted total clearance of the alternaramide marine cyclopentadepsipeptide is given in log (ml/min/kg). OCT2 is a renal uptake transporter that plays a key role in drug disposition and clearance in the kidneys. The cyclopentadepsipeptide used in this investigation is unlikely to act as an OCT2 substrate [36].

The computed toxicity properties of the alternaramide marine cyclopentadepsipeptide are presented in Table 11.

The AMES toxicity test uses bacteria to check a compound's mutagenesis potential. A positive test indicates that the substance is mutagenic and so could cause cancer. The predictions are negative for the cyclopentadepsipeptide under study. The maximum recommended tolerated dose (MRTD) provides an estimate of the toxic dose threshold of chemicals in humans. The MRTD is low for the alternaramide marine cyclopentadepsipeptide. The inhibition of the potassium channels encoded by hERG is the principal cause for the development of acquiring long QT syndrome, thus leading to fatal ventricular arrhythmia. The predictions indicate that alternaramide cyclopentadepsipeptide is unlikely to be a hERG I inhibitor, but it is the opposite for hERG II. The lethal dosage values (LD50) are a common measure of acute toxicity, and they are defined as the amount of a substance that kills 50% of a set of test animals. The ORAT (oral rat acute toxicity) and ORCT (oral rat chronic toxicity) metrics can be used to assess this. Drug-induced liver injury is a prominent source of medication attrition and a critical safety concern for drug development. As a result, hepatoxicity is linked to a disruption in the liver's normal function, and alternaramide has a favorable prognosis. Skin sensitisation, on the other hand, has a negative outlook. *T. pyriformis* is a protozoan bacterium whose toxicity is frequently employed as a hazardous endpoint. Toxicity is defined as a predicted value of > -0.5 for a given chemical [36].

Table 9: Metabolism properties of the alternaramide marine cyclopentadepsipeptide.

Property	Value
CYP2D6 substrate	−
CYP3A4 substrate	+
CYP1A2 inhibitor	−
CYP2C19 inhibitor	-
CYP2C9 inhibitor	−
CYP2D6 inhibitor	−
CYP3A4 inhibitor	+

Table 10: Excretion properties of the alternaramide marine cyclopentadepsipeptide.

Property	Value
Total clearance	0.670
Renal OCT2 substrate	—

Table 11: Toxicity properties of the alternaramide marine cyclopentadepsipeptide.

Property	Value
AMES toxicity	—
MRTD	−0.442
hERG I inhibition	—
hERG II inhibition	+
ORAT	3.665
ORCT	2.890
Hepatotoxicity	+
Skin sensitisation	—
T. pyriformis toxicity	0.285

4. Conclusion

Through our proposed computational peptidology methodology, the alternaramide marine cyclopentadepsipeptide isolated from marine sources was studied using some techniques commonly used in the process of drug discovery and development, demonstrating that this peptide can be considered a potential therapeutic drug.

Some useful descriptors for future QSAR studies, the physicochemical properties, its biological targets, and the ADMET (absorption, distribution, metabolism, excretion, and toxicity) indices related to the bioavailability and pharmacokinetics of these marine cyclopentadepsipeptide under study were predicted and analyzed.

With this knowledge in mind, the chemical reactivity of the studied alternaramide marine cyclopentadepsipeptide has been exhaustively analyzed through the optimization of their structures using the DFTBA methodology and the calculation of their electronic properties with the consideration of a best quality model chemistry, that is, MN12SX/Def2TZVP/H20, which has been already used in previous research for the study of cyclic peptides, showing its usefulness for this kind of calculations being complemented with the calculation of the conceptual DFT global and local reactivity descriptors.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

NFH and JF were responsible for research and data analysis. DGM was responsible for research, data analysis, and writing the manuscript.

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