Computational Pharmacokinetics Report, ADMET Study and Conceptual DFT-Based Estimation of the Chemical Reactivity Properties of Marine Cyclopeptides

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Homophymines A–E and A1–E1 are bioactive natural cyclodepsipeptides with a complex molecular architecture. These molecules could have a potential use as antimicrobial, antiviral, and anticancer substances. We have carried out a computational study of the properties of this family of marine peptides using 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 cheminformatics tools. The latter can be used to estimate the associated physicochemical parameters and to improve the process of virtual screening through a similarity search. Using this approach, the ability of the peptides to behave as a potentially useful drugs can be investigated. An analysis of their bioactivity and pharmacokinetics indices related to the ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) features has also been carried out.

Introduction

Nature is one of the most important sources of pharmacologically active compounds in the search for drugs and biologically active compounds. Even though plants and terrestrial microorganisms have played as an important source for new drug candidates from nature, marine organisms such as tunicates, sponges, soft corals, sea horses, sea snakes, marine mollusks, seaweeds, nudibranches, sea slugs and marine microorganisms have been increasingly attracting attention in recent years. Marine organisms also have the potential to develop into future drugs against important diseases, such as cancer, a range of bacterial and viral diseases, malaria, and inflammations.[1]

Marine sponges have proven to be a significant source of biologically active cyclic peptides and depsipeptides. Cyclic peptides are polypeptide chains taking the shape of cyclic ring structures. There are many studies reporting that marine cyclodepsipeptides have a broad spectrum of biological functions, spanning from antitumor, anthelmintic, insecticidal, antibiotic, antifungal, immunosuppressant, anti-inflammatory, anti-HIV to anti-malarial activities.[2–9]

Homophymines A–E and A1–E1 are bioactive natural cyclodepsipeptides with a complex molecular architecture.[10–12] The main distinction between the members of this family is the length of the side chain. It was shown[10] that Homophymine A exhibited cytoprotective activity against HIV-1 infection while the biological data obtained in the study of Zampella and coworkers[11] strongly suggested antimicrobial, antiviral and anticancer effects of the whole family of Homophymine cyclopeptides.

In light of these potential therapeutic abilities, we have investigated the chemical and biological reactivity and bioactivity properties of the member of this family of marine cyclopeptides using a CDFT-based computational peptidology (CDFT-CP) methodology[13–20] that results from the combination of the chemical reactivity descriptors that arise from conceptual density functional theory (CDFT)[21–26] together with some cheminformatics tools.[27–34] These tools can be used to estimate the associated physicochemical parameters and to improve the process of virtual screening through a similarity search. An analysis of the bioactivity and pharmacokinetics indices related the ADMET (absorption, distribution, metabolism, excretion and toxicity) features has also been carried out.[35,36] In continuation to previous reports on several families of therapeutic peptides of marine origin,[13–20] here we have adopted a conceptual DFT-based computational peptidology approach complemented with the use of chemoinformatics tools.

Results and Discussion

The starting molecular structures of the marine cyclopeptides to be studied were obtained from ChemSpider (https://www.chemspider.com), which is a chemical structure database

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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. The graphical sketches of the molecular structures of the Homophymines A–E and A1–E1 are displayed in Figure 1.

Chemoinformatics and Bioactivity

A compact representation of the information related to bioavailability may be displayed in a graphic way through the so-called Bioavailability Radars which are shown in Figure 2 for the Homophymines family of antimicrobial marine cyclopeptides:

It can be appreciated that more important problems for the Homophymines family of antimicrobial marine cyclopeptides for their consideration as therapeutic drugs of easy availability are related to their size, polar character, and flexibility.

The Bioactivity Scores, that is a measure of the ability of the molecules to behave or interact with different receptors, for the Homophymines A–E and A1–E1 are presented in Table 1, while a graphical representation is displayed in Figure 3, as the corresponding Biological Targets.

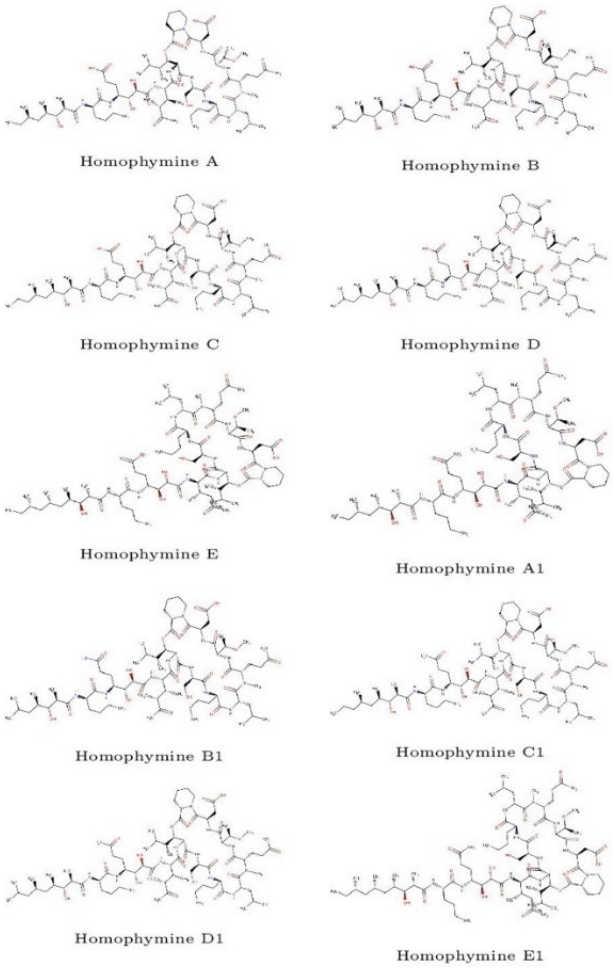

Figure 1. Graphical sketches of the molecular structures of the Homophymines Family of Antimicrobial Marine Cyclopeptides.

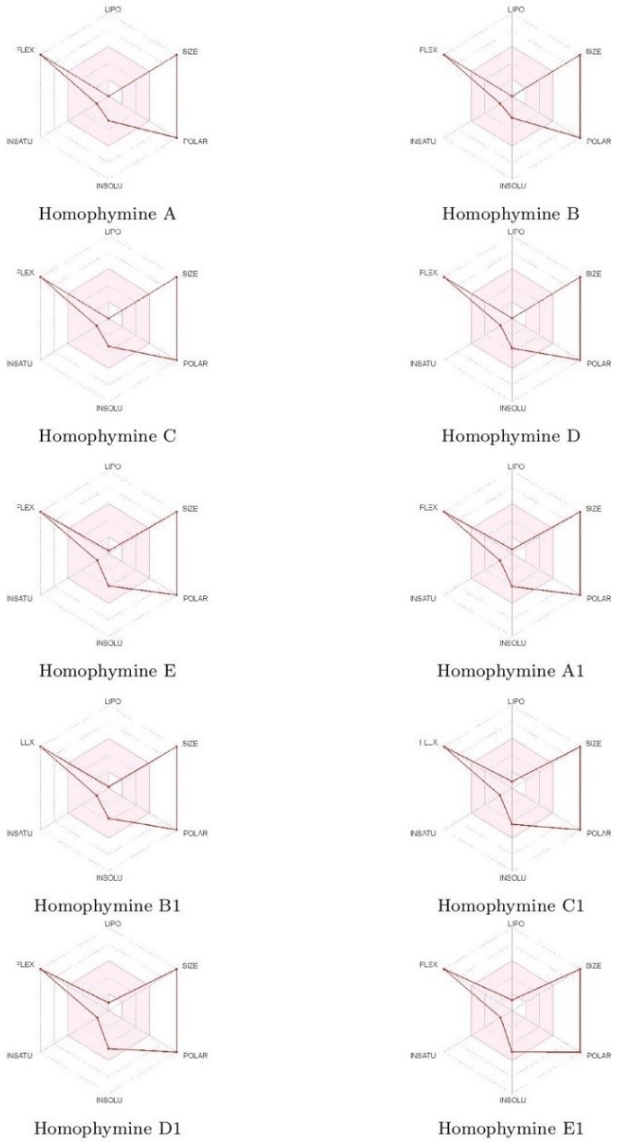

Figure 2. Bioavailability radars of the Homophymine Family of Antimicrobial Marine Cyclopeptides.

It can be concluded that the main interaction for all the members of the Homophymine family of antimicrobial marine cyclopeptides will be behaving as protease inhibitors with little differences between them.

An ADMET study is the assessment of pharmacokinetics of a drug which stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of the fate of a drug and the effects caused by a drug inside the body, such as how much drug is absorbed if administered orally and how much is absorbed in the gastrointestinal tract, is an indispensable part of drug discovery. In a similar way, if the absorption is poor, its distribution and metabolism would be affected, which can lead to causing neurotoxicity and nephrotoxicity. Ultimately, the study is to understand the disposition of a drug molecule

Table 1. Bioactivity Scores of the Homophymines Family of Antimicrobial Marine Cyclopeptides Calculated based on the GPCR Ligand, Ion Channel Modulator, Nuclear Receptor Ligand, Kinase Inhibitor, Protease Inhibitor, and Enzyme Inhibitor Interactions.

Property	A	B	C	D	E	A1	B1	C1	D1	E1
GPCR Ligand	−3.99	−3.99	−3.99	−4.00	−4.00	−3.99	−3.99	−3.99	−4.00	−4.00
Ion Channel Modulator	−4.04	−4.03	−4.04	−4.04	−4.05	−4.04	−4.03	−4.04	−4.04	−4.05
Nuclear Receptor Ligand	−4.05	−4.05	−4.06	−4.06	−4.06	−4.05	−4.05	−4.06	−4.06	−4.06
Kinase Inhibitor	−4.05	−4.05	−4.06	−4.06	−4.06	−4.06	−4.05	−4.06	−4.06	−4.06
Protease Inhibitor	−3.94	−3.93	−3.94	−3.95	−3.95	−3.94	−3.93	−3.94	−3.95	−3.95
Enzyme Inhibitor	−3.99	−3.99	−4.00	−4.00	−4.01	−4.00	−3.99	−4.00	−4.00	−4.01

Figure 3. Predicted biological targets of the Homophymines family of antimicrobial marine cyclopeptides.

within an organism. Thus, ADMET study is one of the most essential parts of computational drug design.

The computed ADMET properties of the Homophymines family of antimicrobial marine cyclopeptides are presented in Table 2.

The Caco-2 cell monolayer is commonly employed as an in vitro model of the human intestinal mucosa to predict medication absorption when given orally. A compound is considered to have a high Caco-2 permeability has a Papp $>8\times10^{-6}$ cm/s. Thus, high Caco-2 permeability would translate in predicted values >0.90, presenting the Homophymines A–E and A1–E1 values much lower than the ideal one. The Intestine is normally the primary site for absorption of a drug from an orally administered solution and the Intestinal Absorption (IA) parameter predicts the percentage of a drug absorbed through the human intestine. An absorbance of less than 30% is considered poor. From Table 2, all the Homophymines A–E and A1–E1 will not be absorbed. P-glycoprotein functions as a biological barrier by extruding toxins and xenobiotics out of cells. The model predicts whether a given compound is likely to be a substrate of Pgp or not. The prediction is in the positive direction for Homophymines A and A1–E1 and negative for Homophymines B–E. Modification of P-glycoprotein- mediated transport has significant pharmacokinetic consequences for Pgp substrates, which might be employed for specific therapeutic benefits or create contraindications.

Thus, this study predicts that all the antimicrobial peptides considered in this study will not act as P-glycoprotein I and II inhibitors. Also, it can be predicted whether a given compound is likely to be skin permeable. If a compound's log Kp is more than −2.5, it is said to have low skin permeability. It means that all cyclopeptides could be of interest for the development of transdermal drug delivery.[36]

The total dose of a drug requires a volume to be uniformly in blood plasma which is named VDss. The drug will be more distributed in the tissue rather than in the plasma for higher VDss. VDss is estimated low when log VDss <-0.15 and high when log VDss >-0.45) implying that for the Homophymines A–E the values for VDss are high while they are low for the Homophymines A1–E1. The degree to which a medicine binds proteins in the blood can impair its efficacy, as the more bound it is, the less efficiently it can pass cellular membranes or diffuse. The Fraction Unbound predicts the fraction that will be unbound in plasma resulting in the values shown in Table 2. The ability of a medicine to pass the blood-brain barrier is an important feature to examine to avoid side effects and toxicities. The logarithmic ratio of brain to plasma drug concentrations is used to calculate permeability. A logBB >-0.3 indicates that a substance can easily penetrate the blood-brain barrier, whereas molecules with a logBB >-1 are poorly distributed to the brain. Another measurement is the blood-brain permeability-surface area product (logPS) or CNS Permeability. It is predicted that the Homophymines A–E and A1–E1 will be unable to penetrate the CNS.[36]

Because it oxidizes xenobiotics to promote excretion, Cytochrome P450 is a key detoxification enzyme in the body, primarily found in the liver. Many medicines are destroyed, and

Table 2. Computed ADMET Properties of the Homophymines Family of Antimicrobial Marine Cyclopeptides.

Property	Absorption A	B	C	D	E	A1	B1	C1	D1	E1
Caco-2 Permeability	−0.31	−0.79	−0.62	−0.82	−0.68	−0.39	−0.58	−0.48	−0.47	−0.40
Intestinal Absorption	0	0	0	0	0	0	0	0	0	0
Skin Permeability	−2.74	−2.74	−2.74	−2.74	−2.74	−2.74	−2.74	−2.74	−2.74	−2.74
P-glycoprotein Substrate	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes
P-glycoprotein I Inhibitor	No	No	No	No	No	No	No	No	No	No
P-glycoprotein II Inhibitor	No	No	No	No	No	No	No	No	No	No
Property	**Distribution A**	**B**	**C**	**D**	**E**	**A1**	**B1**	**C1**	**D1**	**E1**
VDss	−0.45	−0.53	−0.51	−0.46	−0.45	−0.30	−0.33	−0.30	−0.35	−0.31
Fraction Unbound	0.29	0.33	0.33	0.34	0.34	0.34	0.33	0.35	0.33	0.34
BBB Permeability	−3.60	−4.47	−4.38	−4.53	−4.43	−3.63	−4.04	−3.70	−3.80	−3.83
CNS Permeability	−6.47	−6.63	−6.62	−6.66	−6.61	−6.76	−6.65	−6.82	−6.55	−6.64
Property	**Metabolism A**	**B**	**C**	**D**	**E**	**A1**	**B1**	**C1**	**D1**	**E1**
Substrate										
CYP2D6	No	No	No	No	No	No	No	No	No	No
CYP3A4	No	No	No	No	No	No	No	No	No	No
Inhibitor										
CYP1A2	No	No	No	No	No	No	No	No	No	No
CYP2C19	No	No	No	No	No	No	No	No	No	No
CYP2C9	No	No	No	No	No	No	No	No	No	No
CYP2D6	No	No	No	No	No	No	No	No	No	No
CYP3 A4	No	No	No	No	No	No	No	No	No	No
Property	**Excretion A**	**B**	**C**	**D**	**E**	**A1**	**B1**	**C1**	**D1**	**E1**
Total Clearance	−2.17	−1.94	−1.85	2.27	−2.05	−2.09	−1.94	−2.23	−2.30	2.24
Renal OCT2 Substrate	No	No	No	No	No	No	No	No	No	No
Property	**Toxicity A**	**B**	**C**	**D**	**E**	**A1**	**B1**	**C1**	**D1**	**E1**
AMES Toxicity	No	No	No	No	No	No	No	No	No	No
MRTD	0.45	0.44	0.43	0.44	0.44	0.47	0.46	0.47	0.46	0.467
hERG I Inhibitor	No	No	No	No	No	No	No	No	No	No
hERG II Inhibitor	No	No	No	No	No	No	No	No	No	No
ORAT	2.48	2.48	2.48	2.48	2.48	2.48	2.48	2.48	2.48	2.48
ORCT	6.29	6.91	6.77	7.13	6.97	6.97	7.37	6.54	7.84	6.9
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Skin Sensitisation	No	No	No	No	No	No	No	No	No	No
T. Pyriformis Toxicity	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29

some are activated by the cytochrome P450 iso- forms. As a result, determining a compound's capacity to inhibit cytochrome P450 is critical. If the concentration required to achieve 50% inhibition for each isoform is less than 10 μM, the substance is termed a cytochrome P450 inhibitor. As can be seen from Table 2, all the cyclopeptides are predicted as not being P450 inhibitors for any isoform. It is al important to know if a given compound is likely to be a cytochrome P450 substrate. The prediction indicate that this will be not the case for any of the cyclopeptides.[36]

Hepatic clearance and renal clearance combine to form drug clearance (Cltot) (excretion via the kidneys). It has something to do with bioavailability and is crucial in setting dose rates. The predicted Total Clearance Cltot for the Homophymines A–E and A1–E1 are given in log(ml/min/kg). OCT2 is a renal uptake transporter that plays an important role in disposition and renal clearance of drugs. It is predicted that all the cyclopeptides considered in this study will not behave as an OCT2 substrate.[36]

The AMES test is a widely used bacteria-based method for determining a compound's mutagenic potential. A positive test indicates that the substance is mutagenic and so could cause cancer. All of the compounds under investigation have unfavorable predictions. The maximum recommended tolerated dose (MRTD) is a measure of a chemical's hazardous dosage threshold in humans. The MRTD is low for all the Homophymines A–E and A1–E1. The Inhibition of the potassium channels encoded by hERG are the principal causes for the development of acquire long QT syndrome, thus leading to fatal ventricular arrhythmia. The predictions indicate that all the cyclopeptides are unlikely to be a hERG I or II inhibitor. The lethal dosage values (LD50) are a standard measurement of acute toxicity and is defined as the amount of a compound that causes the death of 50% of a group of test animals. The predicted values are given in mol/kg. Chronic studies are designed to determine the

lowest dose of a chemical that causes an unfavorable impact (LOAEL) and the highest dose at which no adverse effects are seen (NOAEL). In this case, the predicted values are given in log (mg/kg-bw/lday). Drug-induced liver injury is a major safety concern for drug development and a significant cause of drug attrition. Thus, Hepatoxicity is associated with disrupted normal function of the liver and the predicted values for all the cyclopeptides are positive. On the other hand, the predicted values for Skin Sensitization are negative. T. Pyriformis is a protozoa bacterium, with its toxicity often used as a toxic endpoint. For the Homophymines A–E and A1–E1, the plGC50, which is the negative logarithm of the concentration required to block 50% growth (a value > -0.5 log μg/L is considered hazardous), has been predicted.[36]

Conceptual DFT Calculations

The optimized molecular structures of the Homophymines A–E and A1–E1 marine cyclopeptides calculated according to the procedure presented in the Materials and Methods section are displayed in Figure 4.

By considering an in-house software tool for the estimation of the the KID parameters of the Homophymines A–E and A1–E1 cyclopeptides on the basis of the electron densities generated through the high-level calculations, the global reactivity descriptors (including the Nucleophilicity N) have been determined which results are displayed in Table 3.

It can be concluded from the results in Table 3 that the chemical reactivity of the Homophymines family of antimicrobial marine cyclopeptides will be almost the same for all the calculated global DFT descriptors.

The global DFT 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 Fukui functions[21–23] and the Dual Descriptor[37–42] are some of these local reactivity descriptors. Although the Fukui functions are of great help and have been successfully used for the identification of reactive sites, it has been mentioned that the Dual Descriptor (DD) $\Delta f(r)$, can describe simultaneously the nucleophilic and electrophilic sites within a molecule without ambiguities.[42] Figures 5 and 6 display graphical sketches of the DD for the Homophymines

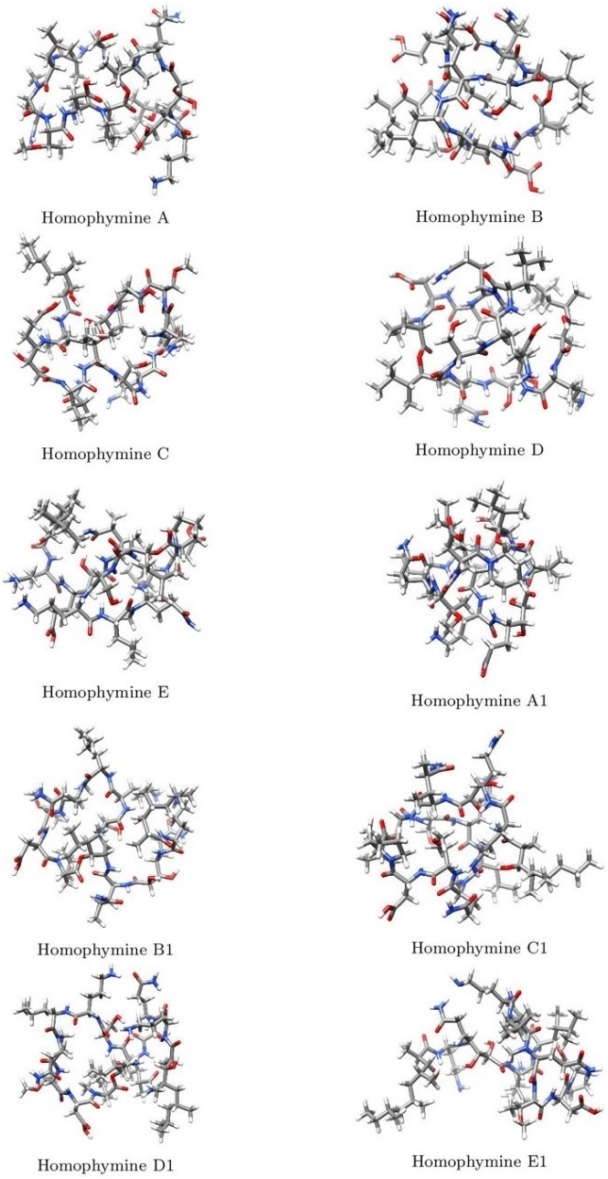

Figure 4. Optimized molecular structures of the Homophymines family of antimicrobial marine cyclopeptides.

Table 3. Global Reactivity Descriptors for the Homophymines family of antimicrobial marine cyclopeptides (all in eV, with the exception of S expressed in eV^{-1}).

Molecule	χ	η	ω	S	N	$\omega-$	$\omega+$	$\Delta\omega^{\pm}$
Homophymine A	3.719	5.263	1.314	0.190	2.442	4.817	1.098	5.915
Homophymine B	3.827	5.655	1.295	0.177	2.138	4.856	1.029	5.885
Homophymine C	3.746	5.143	1.364	0.194	2.475	4.923	1.177	6.100
Homophymine D	3.626	5.265	1.248	0.190	2.534	4.638	1.013	5.651
Homophymine E	3.534	4.833	1.293	0.207	2.842	4.654	1.120	5.774
Homophymine A1	3.703	5.214	1.315	0.192	2.483	4.807	1.104	5.910
Homophymine B1	3.437	5.001	1.181	0.200	2.855	4.394	0.957	5.350
Homophymine C1	3.570	5.085	1.253	0.197	2.680	4.610	1.039	5.649
Homophymine D1	3.531	5.132	1.215	0.195	2.695	4.516	0.985	5.501
Homophymine E1	3.955	5.015	1.560	0.199	2.330	5.410	1.455	6.866

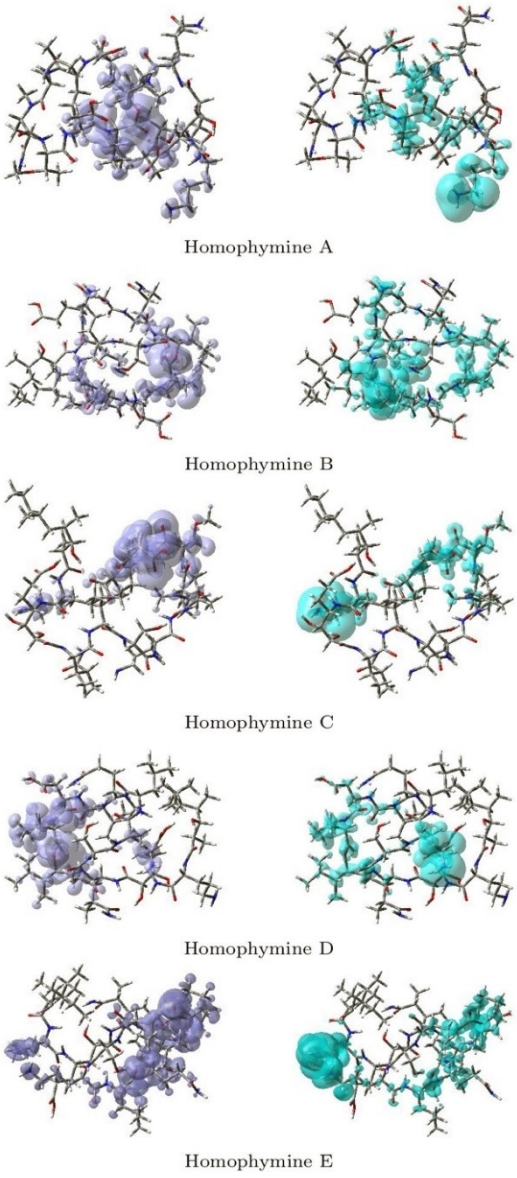

Figure 5. Graphical Sketches of the Dual Descriptor DD of the Homophymines A–E. Left: DD > 0, Right: DD < 0.

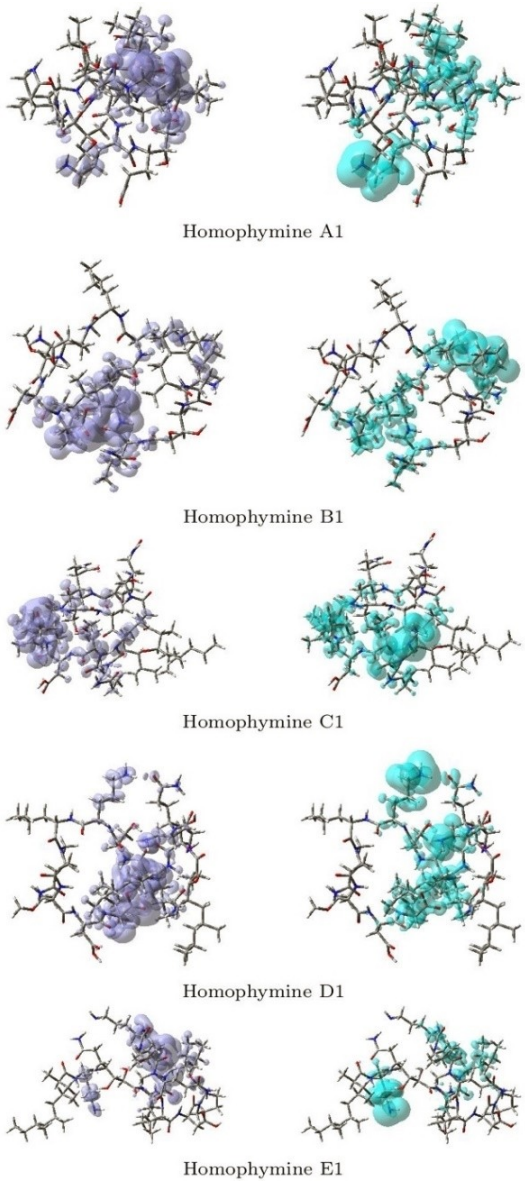

Figure 6. Graphical Sketches of the Dual Descriptor DD of the Homophymines A1–E1. Left: DD > 0, Right: DD < 0.

A–E and A1–E1, highlighting the locations inside the molecules where DD > 0 and DD < 0 for a better understanding of the local chemical reactivity of these compounds.

Although there is some overlapping between the different reactivity zones within the cyclopeptides, it is in all cases possible to distinguish between the nucleophilic regions where DD is positive from those places where DD is lower than zero meaning that they are electrophilic regions.

Conclusion

Ten antimicrobial cyclopeptides isolated from marine sources, Homophymines A–E and A1–E1, have been studied by resorting to some techniques of common use in the process of drug discovery and development through our proposed Computational Peptidology methodology showing that these kinds of molecules can be regarded as potential therapeutic drugs.

The physicochemical properties, their predicted biological targets, and the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters related to the bioavailability and pharmacokinetics of these marine cyclopeptides under study were predicted and analyzed with the additional goal of analyzing their bioactivity.

With this knowledge, the chemical reactivity of the studied Homophymines family of antimicrobial marine cyclopeptides has been thoroughly investigated by optimizing their structures using the DFTBA methodology, followed by geometry re-optimization, frequency analysis, and determination of their electronic properties using an improved model chemistry,

namely MN12SX/Def2TZVP/H2O, which has already been used in previous studies.

Materials and Methods

Computational Pharmacokinetics Analysis and ADMET Study

To get a glimpse of the potential therapeutic properties of the considered cyclodepsipeptides, the SMILES (Simplified Molecular Input Line Entry Specification) notation of the every studied compound, which was obtained by access- ing ChemDoodle 11.3.0 software, was fed into the online program Chemicalize, a software developed by ChemAxon (http://www.chemaxon.com), which was used for naming, molecular fingerprints, structure generation and the prediction of several properties related to Chemoinformatics (http://chemicalize.com/) (accessed March 2021).

Using Molinspiration Cheminformatics' online Molinspiration program (https://www.molinspiration.com/) (accessed, March 2021), a similarity search in the chemical space of compounds having molecular structures with known bio- logical and pharmacological features that could be compared to the ones being examined was performed 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 cyclodepsipeptides considered in this study.[43] 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 in- dices 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 online available SwissADME software.[35] Additional information about the Pharmacokinetics parameters and the ADMET properties were obtained by resorting to pkCSM,[36] a software for the prediction of small-molecule pharmacokinetic properties using SMILES and that can be accessed through it associated webpage (https://biosig.unimelb.edu.au/pkcsm/) (accessed, March 2021).

Density Functional Theory (DFT) Calculations

The Kohn-Sham (KS) methodology includes the determination of the molecular energy, the electronic density and the orbital energies of a given system and the frontier orbitals HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) which are intrinsically related to the chemical reactivity of the molecules.[44–47] This methodology is convenient when thinking of quantitative qualities related with Conceptual DFT descriptors.[21–26] As a complement of these global reactivity descriptors that arise from Conceptual DFT,[21–26] a new Nucleophilicity Index N has been established[48–52] 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 goodness of a given density functional can be determined through a comparison of the results that it renders with the experimental values or with the results that can be obtained by means of high-level calculations. However, the lack of experimental results for the molecular systems under study or the large size of the molecules sometimes render this comparison as computationally impractical. A methodology called KID (Koopmans in DFT) has been developed by our research group,[13–20] for the validation of a given density functional in terms of its internal coherence.

The evaluation of the many conformers of the cyclopeptides peptides studied through this research was performed by resorting to MarvinView 17.15 available from ChemAxon (http://www.chemaxon.com) by doing Molecular Mechanics calculations through the overall MMFF94 force field.[53–57] This was followed by a geometry optimization by means of the Density Functional Tight Binding (DFTBA) methodology[58] and a later geometry re-optimization and frequency calculation considering the MN12SX/Def2TZVP/H2O model chemistry.[59–61] This last step was required for the verification of the absence of imaginary frequencies as a check for the stability of the optimized structures as being a minimum in the energy landscape. The electronic properties and the chemical reactivity descriptors of the Homophymines A–E and A1–E1 were estimated by the MN12SX/Def2TZVP/H2O model chemistry[62–69] on their optimized molecular structures, owing to the fact that it has been previously proved that it verifies the 'Koopmans in DFT' (KID) procedure,[14–20,62–69] with the aid of the Gaussian 16 software[58] and the SMD solvation model.[70] This model chemistry considers the MN12SX screened-exchange density functional[59] together with the Def2TZVP basis set[60,61] and the charge of the molecules being equal to zero while the radical anions and cations have been considered in the doublet spin state.

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Conflict of Interest

The authors declare no conflict of interest.

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