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Chemical reactivity and bioactivity properties of the Phallotoxin family of fungal peptides based on Conceptual Peptidology and DFT study

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ABSTRACT

A methodology based on the concepts that arise from Density Functional Theory (CDFT) was chosen for the calculation of the global and local reactivity descriptors of the Phallotoxin family of fungal peptides. The determination of the active sites for the molecules has been achieved by resorting some descriptors within Molecular Electron Density Theory (MEDT) like the Dual Descriptor and the Parr functions. Phallosacin has been found as the most reactive of the peptides on the basis of the calculated Global Reactivity Descriptors. The pKas of the seven studied peptides were established using a proposed relationship between this property and the calculated Global Hardness. The bioactivity properties of the peptides considered in this study were obtained by resorting to a homology model by comparison with the bioactivity of related molecules in their interaction with different receptors.

1. Introduction

Phallotoxins are heterodetic bicyclic peptides originated from Amanita phalloides that form, together with the Amatoxins, the main toxic components of these mushrooms. All phallotoxins are derived from the same cyclic Phalloin peptide backbone, and consist of seven amino acids, crosslinked by tryptathionine between residues 3 and 6 [1, 2].

The field of what we now refer to as Computational Peptidology encompasses the use of Computational Chemistry for the study and analysis of natural peptides and is becoming one of the key tools used in the pharmaceutical industry for the discovery of new drugs. All of the applications based on Computational Peptidology seek to make predictions about the biological activities of peptide-based molecules from a knowledge of (primarily) their chemical structures, and the computational modeling involved hence requires a tight coupling of chemical and biological information. The relationships between chemistry and biology characterized by Computational Chemistry are of outmost importance. Both the structure and the properties of a molecule can be regarded as different manifestations of the same underlying wave equation (or its associated electron density), and it is thus to be expected that molecular descriptors will indeed be related to property and the extent of the relationship will depend on the descriptors, the properties, and the sets of molecules [3, 4].

This study represents an attempt to assess the molecular and chemical reactivity properties of the seven members of the Phallotoxins family of fungal peptides through the application of the Density Functional Theory concepts or what is usually called Conceptual Density Functional Theory (CDFT). Understanding the chemical reactivity properties of these fungal peptides is important in their use of Fukui functions, the Condensed Dual Descriptor and the Parr functions to represent the peptides reactivity within the molecular systems in the process of the development of potential new drugs. Moreover, the knowledge of the pKas of the peptides as a basis for the understanding of the solubility of them and the bioactivity properties determined considering a homology modeling will be also pursued [5, 6, 7, 8].

2. Computational methodology

The generation of the tridimensional structures and the proposition of their respective low energy conformers in the prediction and calculation of the properties of the seven members of the Phallotoxin family of fungal peptides considered in this study was carried out using some ChemAxon Calculator Plugins available from MarvinSketch and Mar-

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vinView 17.15.0, 2017, ChemAxon (http://www.chemaxon.com). The molecules with the lowest energy conformations were selected and the DFTBA (Density Functional Tight Binding Model A) program available in the Gaussian 09 software [9] was used for a preoptimization of the conformers. The MN12SX/Def2TZVP model chemistry in the presence of water as the solvent was used in the reoptimization of the five conformers of each peptide having the lowest energy. Consequently, the global minimum approach was used for the confirmation of the optimized Phallotoxin structures through the application of the vibrational frequency analysis technique. The process of calculating the electronic properties necessaries for understanding the chemical reactivity of the fungal peptides involved the use of MN12SX/Def2TZVP/H2O model chemistry through the optimized molecular structures as it is explained in detail in the Results and Discussion section.

Considering the KID technique (for Koopmans in DFT) used on the previous studies being integrated into the finite difference approximation [10, 11, 12, 13, 14, 15, 16], the following expressions can be used to define the global reactivity descriptors [7, 8, 17, 18]:

Electronegativity $\chi = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\epsilon_L + \epsilon_H)$

Global Hardness $\eta = (I - A) \approx (\epsilon_L - \epsilon_H)$

Electrophilicity $\omega = \frac{\mu^2}{2\eta} = \frac{(I + A)^2}{4(I - A)} \approx \frac{(\epsilon_L + \epsilon_H)^2}{4(\epsilon_L - \epsilon_H)}$

Electrodonating Power $\omega^- = \frac{(3I + A)^2}{16(I - A)} \approx \frac{(3\epsilon_H + \epsilon_L)^2}{16\eta}$

Electroaccepting Power $\omega^+ = \frac{(I + 3A)^2}{16(I - A)} \approx \frac{(\epsilon_H + 3\epsilon_L)^2}{16\eta}$

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

being ϵ_H and ϵ_L the HOMO and LUMO energies associated to each molecule.

Applying the same ideas as before, the definitions for the local reactivity descriptors will be [7, 8]:

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

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

which are relationships between the electronic densities of the neutral, positive and negative species.

The Parr functions can be expressed as [19, 20]:

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

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

where $\rho_s^{rc}(\mathbf{r})$ and $\rho_s^{ra}(\mathbf{r})$ are related to the atomic spin density of the radical cation or anion of the considered system, respectively [21].

The open bioactivity prediction online-site like Molinspiration has been used for the determination of the molecular properties and bioactivity scores. Molinspiration, a proficient system for the calculation of drug-likeness information, allows predicting G-Protein Coupled Receptor (GPCR) ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and other enzyme targets (http://www.molinspiration.com/cgi-bin/properties).

3. Results and discussion

The corresponding ChemAxon Calculator Plugins were used in the process of deriving the molecular structures and the bioactivity properties of the conformers. The preoptimization of the lowest energy conformers was carried out using the DFTBA program while the reoptimizations were performed with the MN12SX/DefTZVP/H2O model chemistry as mentioned in the Computational Methodology section. The graphical sketches of the optimized molecular structures of the Phallotoxins are shown in Fig. 1.

Table 1
Electronic energies of the neutral molecular systems (in au) of the Phallotoxins, 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/Def2TZVP/H2O model chemistry.

Molecule	Total Electronic Energy	HOMO	LUMO	HOMO-LUMO Gap	λ_{max}
Phallacidin	-3249.4534	-5.3332	-1.0147	4.3184	287
Phallacin	-3174.5001	-5.2981	-0.9451	4.3530	285
Phallisacin	-3324.7074	-5.2907	-1.0531	4.2376	293
Phallisin	-3097.1661	-5.1318	-0.8528	4.2790	290
Phalloidin	-3022.0902	-5.1459	-0.8860	4.2599	291
Phalloin	-2946.9608	-5.6700	-1.2944	4.3756	283
Prophalloin	-2871.8195	-5.6303	-1.2550	4.3753	283

The Density Functional Tight-Binding method was used in the predetermination of the optimized molecular structures while the MN12SX density functional method combined with the SMD (for Solvent Model Density) solvent model and the DefTZVP basis which were used in the reoptimization of the molecular structures using water as the solvent. The MN12SX/DefTZVP/H2O model chemistry was used in the determination of the electronic properties of each molecular structure after using calculation analysis procedures to determine whether all the molecular structures correspond to their respective minimum energy requirements.

According to Becke, that the adiabatic connection and the ideas of Hohenberg, Kohn, and Sham apply only to electronic ground states is a common misconception [22]. Baerends et al. state that the level of energy excitation within a KS system can be used as an effective measure of the optimization to the molecular optical gap [23]. Thus, the HOMO-LUMO gap of the KS model is used to approximate the excitation energy [24]. Ground state calculations are used in the determination of the optimal maximum absorption wavelength that belongs to the fungal peptides of the Phallotoxin family based on the selected density functional to find the respective λ_{max} values through the application of theoretical models which allow to establish the HOMO-LUMO gaps (HL). Therefore, the calculation of the maximum wavelength absorption of the Phallotoxins fungal peptides involved conducting ground-state calculations at the same level of model chemistry and determining the HOMO–LUMO gap and $\lambda_{max} = 1240/\text{HL}$ as can be seen in Table 1.

3.1. Calculation of the global reactivity descriptors of the phallotoxins

According to Frau and Glossman-Mitnik, the results from the previous evaluation of some peptides and other molecules like the melanoidins in the generation of HOMO and LUMO energies that are required for the estimation of the agreement with the estimated Koopmans' approximation based on MN12SX/Def2TZVP/H2O model chemistry justifies the application of the proposed KID technique [10, 11, 12, 13, 14, 15, 16].

The calculated values for these global reactivity descriptors using the MN12SX/Def2TZVP/H2O model chemistry are displayed in Table 2.

Although the calculated values for the chemical reactivity descriptors are of the same magnitude for all the studied peptides, two conclusions can be drawn from the analysis fo the results. The first is that the electrodonating power is more important than the electroaccepting power for all the peptides, which is the expected results for this kind of molecules. The second is that on the basis of the values of the Global Hardness, Phallisacin will be the most reactive of the considered peptides. This result can be correlated with the λ_{max} value presented in Table 1 for Phallisacin because in our formulation in terms of the KID technique, the Global Hardness equals the HOMO-LUMO gap.

3.2. Calculation of the pKas of the phallatoxin family of fungal peptides

A previous publication focused on the application of the Conceptual DFT descriptors to evaluate the pKas of some peptides where it was es-

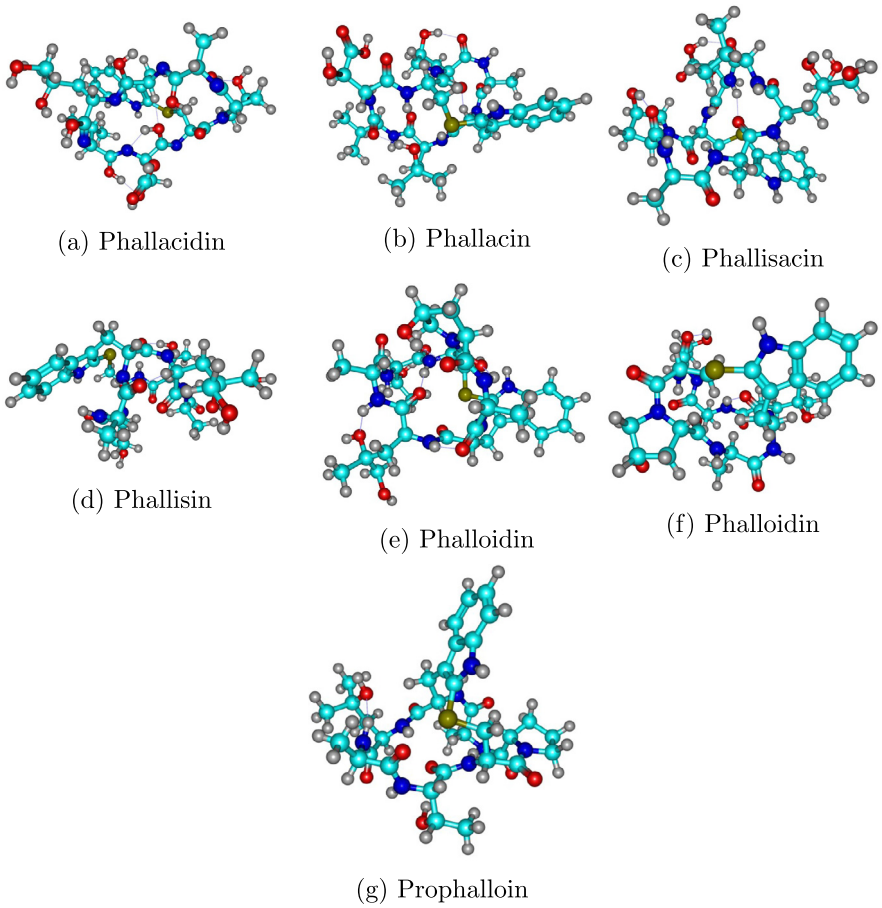

Fig. 1. Graphical sketches of the molecular structures of a) Phallacidin; b) Phallacin; c) Phallisacin; d) Phallisin; e) Phalloidin, f) Phalloin and g) Prophalloin.

Table 2
Global reactivity descriptors of the Phallotoxins calculated with the MN12SX/Def2TZVP/H2O model chemistry.

Molecule	Electronegativity	Global Hardness	Electrophilicity
Phallacidin	3.1739	4.3184	1.1664
Phallacin	3.1216	4.3530	1.1192
Phallisacin	3.1719	4.2376	1.1871
Phallisin	2.9923	4.2790	1.0463
Phalloidin	3.0160	4.2599	1.0676
Phalloin	3.4822	4.3756	1.3856
Prophalloin	3.4426	4.3753	1.3544
Molecule	Electrodonating Power	Electroaccepting Power	Net Electrophilicity
Phallacidin	4.1896	1.0157	5.2053
Phallacin	4.0713	0.9498	5.0211
Phallisacin	4.2250	1.0531	5.2781
Phallisin	3.8561	0.8638	4.7199
Phalloidin	3.9095	0.8935	4.8030
Phalloin	4.7859	1.3036	6.0895
Prophalloin	4.7036	1.2609	5.9645

tablished that the pKa = 16.3088–0.8268 η relationship would play an important role in the determination of this property for larger peptides which could be of importance in the manufacture of medical drugs [25]. Given the biological level of pH, the peptides considered in this study exist as neutral molecules and are still considered to be neutral during the pKa computations [25]. The pKa relationship is also important in the optimization of the molecular structure of every conformer as well as the computation of the pKa values for all molecules given the η values shown in Table 2. The computed results of the pKa values for the seven members of the Phallotoxin family of fungal peptides are shown in Table 3:

Table 3
pKas of the Phallatoxin family of fungal peptides.

Molecule	pKa
Phallacidin	12.74
Phallacin	12.71
Phallisacin	12.81
Phallisin	12.77
Phalloidin	12.79
Phalloin	12.69
Prophalloin	12.69

The pKa values shown in Table 3 indicate that the computational methodology used is effective in the differentiation of the respective pKa values for all the peptide molecules irrespective of the significance of the difference. The same comment presented in the previous section can be applied for the case of the value of pKa being the greatest for Phallisacin because in our previously developed formula, the smaller the Global Hardness corresponds to a largest pKa. The knowledge of the pKa values of these peptides could be important in the manufacture of pharmaceutical drugs by explaining the procedures used in drug delivery and their respective action mechanisms.

3.3. Local reactivity descriptors calculation

The Electrophilic Fukui functions $f^{-}(\mathbf{r})$ and Nucleophilic Fukui functions $f^{+}(\mathbf{r})$ for the Phallotoxin peptides are shown in Fig. 2:

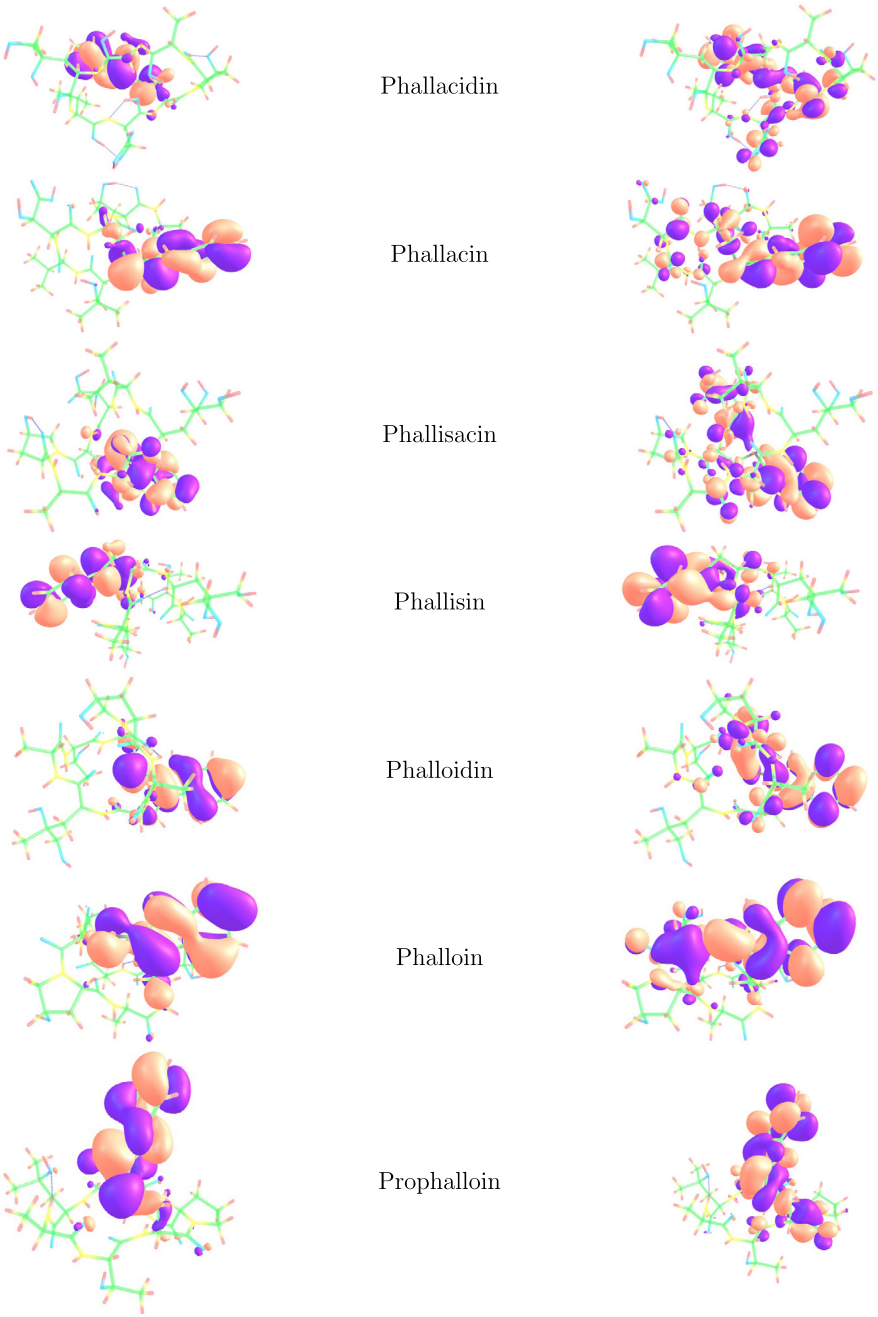

Fig. 2. Graphical representation of the Electrophilic Fukui function $f^{-}(\mathbf{r})$ (left column) and Nucleophilic Fukui function $f^{+}(\mathbf{r})$ (right column) of the Phallotoxins.

Martínez-Araya has explained in a recent research [26] that the condensed expression for the Dual Descriptor, namely Δf_k, as the difference between the Electrophilic and Nucleophilic Fukui functions will be more useful for the prediction of the preferred sites of reaction than the condensed Fukui functions alone. For this reason, we have decided to present the results for the Condensed DD Δf_k in comparison with the Nucleophilic and Electrophilic Parr functions, P_k^+ and P_k^-, proposed by Domingo et al. [19, 20] through the consideration of atomic spin densities that result from a Mulliken Population Analysis (MPA).

The results for the calculation of these local reactivity descriptors for the seven members of the Phallotoxins family of fungal peptides are presented in Table 4 where the Condensed Dual Descriptor Δf_k has been determined by localizing the corresponding Fukui functions over the atomic sites employing a charge scheme based on the MPA as it was done for the Parr functions. It must be noticed that we are presenting only the results for those atomic sites where the Δf_k are maxima in absolute value. The values for Δf_k are multiplied by 100 for easier comparison.

As can be seen from Table 4, there is a nice agreement between the results that come from the Condensed Dual Descriptor Δf_k and those obtained through the Nucleophilic and Electrophilic Parr functions P_k^+ and P_k^-. Thus it can be expected that the methodology used in this work could be the basis for the study of the chemical reactivity of peptides larger in size. Moreover, by comparing the results from Table 4 and the graphics in Fig. 2, it can be concluded that there is a nice match for both kind of analysis.

3.4. Bioactivity properties of the Phallotoxins

The degree of oral bioavailability of molecules that can be potentially used in the manufacture of drugs is measured using the Lipinski Rule of Five by determining the molecules that possess drug-like prop-

Table 4
Local reactivity descriptors condensed to atoms for the seven members of the Phallotoxins family calculated with the MN12SX/Def2TZVP/H2O model chemistry: Dual Descriptor Δf_k, Nucleophilic Parr function P_k^+ and Electrophilic Parr function P_k^-.

Phallacidin			
Atom	Δf_k	P_k^+	P_k^-
27 C	10.61	0.120	0.000
32 C	-20.01	0.011	0.396
Phallacin			
Atom	Δf_k	P_k^+	P_k^-
55 C	14.01	0.217	0.015
34 C	-21.10	0.013	0.441
Phallisacin			
Atom	Δf_k	P_k^+	P_k^-
39 C	10.70	0.209	0.029
1 S	-36.30	0.010	0.330
Phallisin			
Atom	Δf_k	P_k^+	P_k^-
52 C	20.32	0.290	0.050
1 S	-27.99	0.004	0.308
Phalloidin			
Atom	Δf_k	P_k^+	P_k^-
52 C	15.44	0.212	0.043
1 S	-24.82	0.006	0.288
Phalloin			
Atom	Δf_k	P_k^+	P_k^-
50 C	7.28	0.187	0.066
31 C	-17.71	0.055	0.413
Prophalloin			
Atom	Δf_k	P_k^+	P_k^-
49 C	7.16	0.160	0.038
30 C	-17.09	0.046	0.391

erties. However, this technique cannot be applied in measuring the bioavailability of the peptides due to the existence of hydrogen bonds and high molecular weight properties [27, 28].

In this study we applied a different technique in the evaluation of the chemical structure of other compounds that were predicted to possess similar bioactivity properties as the Phallotoxins peptides under study. As illustrated in the Computational Methodology section, the evaluation of the pharmacological properties of different compounds in the process of determining the Bioactivity Properties can be carried out using Molinspiration software based on the variability of the drug targets as shown in Table 5. According to the table, the peptides whose Bioactivity Scores is less than zero are considered to be active while the organic molecules whose bioactivity score are between zero and negative five are considered to be moderately active and the organic molecules with a score of less than negative five are considered to be inactive. All peptides that were studied during this study were found to have moderate Bioactivity Scores to interact as a Protease Inhibitor.

4. Conclusions

In this work, the chemical reactivity of a group of seven fungal peptides of the Phallotoxins family, Phallacidin, Phallacin, Phallisacin, Phallisin, Phalloidin, Phalloin and Prophalloidin, was studied by resorting to the Conceptual DFT as a tool to explain the molecular interactions.

The information about the global and local reactivity descriptors of the fungal peptides adcquired in this work could be helpful to assist in the design of new pharmaceutical drugs based on these compounds.

Although Phalloin is the molecule with the highest Electrophilicity and also with the highest Net Electrophilicity (the comparison between the Electrodonating and Electroaccepting Powers), the most reactive species is Phallosacin because displays the lowest value for the Global Hardness which is a measure of the resistance to deformation of the electron density.

Table 5
Bioactivity Scores of the Phallotoxins calculated on the basis of GPCR Ligand, Ion Channel Modulator, Nuclear Receptor Ligand, Kinase Inhibitor, Protease Inhibitor and Enzyme Inhibitor interactions.

Molecule	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor
Phallacidin	-1.74	-3.13	-2.81
Phallacin	-1.48	-3.00	-2.61
Phallisacin	-2.14	-3.36	-3.09
Phallisin	-1.13	-2.62	-2.07
Phalloidin	-0.94	-2.39	-1.84
Phalloin	-0.76	-2.19	-1.66
Prophalloin	-0.64	-1.97	-1.50
Molecule	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
Phallacidin	-3.06	-0.97	-2.33
Phallacin	-2.75	-0.75	-2.11
Phallisacin	-3.16	-1.44	-2.63
Phallisin	-2.37	-0.56	-1.72
Phalloidin	-2.12	-0.39	-1.51
Phalloin	-1.84	-0.26	-1.34
Prophalloin	-1.62	-0.15	-1.18

Among the many descriptors that could be useful for the development of new medicines with a repurposing criteria, the pKa is of paramount importance because it is related to the water solubility of the peptides. Thus, when the experimental values of the pKa are unknown, the approximate QSAR relationship employed in this work could be considered as a useful predictive tool for the determination of the pKas of small and large peptides. The largest value of pKa corresponds to Phallisacin which is correlated with the result of having the longest λ_{max} and being the most reactive of the studied peptides.

Finally, the molecular descriptors used for the quantification of the bioactivity allowed the characterization of the studied peptides establishing some relationships between the bioactivity properties and the calculated global reactivity descriptors.

Declarations

Author contribution statement

Daniel Glossman-Mitnik: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Norma Flores-Holguín, Juan Frau: Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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