# Computational Peptidology Assisted by Conceptual Density Functional Theory for the Study of Five New Antifungal Tripeptides

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ABSTRACT: A well-behaved model chemistry previously validated for the study of the chemical reactivity of peptides was considered for the calculation of the molecular properties and structures of a group of five new antifungal tripeptides, namely (2*R*)-2-[(2*S*)-2-[(2*S*)-2-amino-3-phenylpropanamido]propanamido]-5-[(diaminomethylidene)amino]pentanoic acid, (2*S*)-2-[(2*S*)-2-[(2*S*)-2-amino-3-phenyl propanamido]propanamido]-3-(4-hydroxyphenyl)propanoic acid, (2*S*)-2-[(2*S*)-2-[(2*S*)-2-amino-3-phenylpropanamido]-3-methylbutanamido]-3-(4-hydroxyphenyl)-propanoic acid, (2*R*)-2-[(2*S*)-2-[(2*S*)-2-amino-3-phenylpropanami-do]-3-(1*H*-indol-3-yl)propanamido]-3-sulfanylpropanoic acid, and (2*S*)-2-[(2*S*)-2-[(2*S*)-2-amino-3-phenylpropanamido]-3-(1*H*-indol-3-yl)propanamido]-3-(4-hydroxyphenyl)propanoic acid, according to their amino acid sequences. A methodology based on conceptual density functional theory was chosen for the determination of the reactivity descriptors. The molecular active sites were associated with the active regions of the molecules that were associated with the nucleophilic, electrophilic, and radical Fukui functions. Additionally, the pK_a values for the different peptides are predicted with great accuracy, which constitutes a useful knowledge for the process of drug design. Finally, the bioactivity scores for the new antifungal peptides are predicted through a homology methodology relating them with the calculated reactivity descriptors.
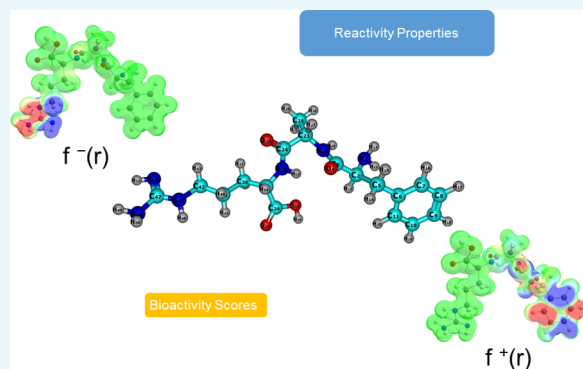
INTRODUCTION

It is well known nowadays that, within medicinal chemistry research, the design and development of new pharmaceutical drugs have a preponderant place. These drugs act by producing changes in some physiological process or function, exerting their effect by interacting specifically with some macromolecular structure of an organism which is called the receptor. In this way, the interaction of each drug with its respective receptor or site of action initiates the biochemical and physiological changes that are characteristic of that drug.[1−3]

Starting from the knowledge of the receptor associated to each disease, a protocol composed of a series of steps, generally known as computer-aided drug design, has been devised by researchers in this field over the past decades allowing us to understand the way by which the potential drugs interact with the corresponding sites of action, leading to the name of druggable receptors. Computers play a significant role in this protocol and, together with their associated software, have become an indispensable tool for performing these tasks with a guarantee of success.[1−3]

There are actually two variants of this protocol depending on whether the molecular structure of the druggable receptor is or is not known. When the structure of the receptor is already known, the following process is called structure-based drug design and has a long-standing record of already developed pharmaceutical drugs. However, when this knowledge is not available, the process is called ligand-based drug design, and it is associated with some computer-related techniques like pharmacophore modeling, quantitative structure activity relationship (QSAR), and three-dimensional (3D)-QSAR.

QSAR is one of the most important methodologies that can be used in the process of drug design and development.[4−6] Its utility resides in the idea that the biological activity of a given molecule candidate, to be considered as a potential drug, can be expressed in the form of a mathematical formula relating this activity with a series of parameters called descriptors. Although there are hundreds of descriptors available from the specialized literature, for the objectives of the present work, we will be more interested in those properly called chemical reactivity descriptors which arise naturally from the conceptual density functional theory (CDFT), which allow to understand the interaction between molecules as well to have a comprehensive picture on the way that chemical reactions proceed.[7−9]
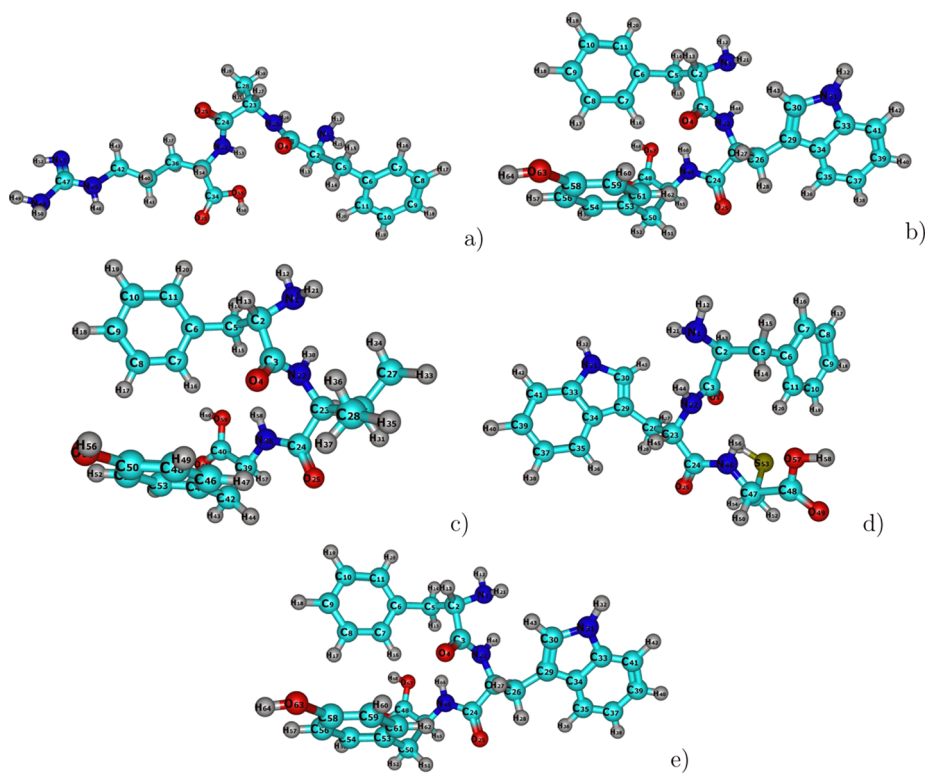
Figure 1. Graphical sketches of the molecular structures of the five antifungal tripeptides showing the numbering of the atoms: (a) FAR; (b) FAY; (c) FVY; (d) FWC; and (e) FWY, where green is used for C, red for O, blue for N, and gray for H.

The reasons for this election are based on the assumption that relates the potential bioactivity of drugs with their chemical reactivity from the molecular point of view[10,11] and also that when a group of descriptors cannot be cast in a QSAR mathematical formulation because of the limited availability of information, the knowledge of the chemical reactivity of a small group of molecules may still provide useful results that can serve as a guide for the purpose of the research.

One of the most important groups of molecules which have arisen during the last years as potential candidates to be considered as pharmaceutical drugs are that of peptides of marine origin. Although there have been some controversies in the literature about the possibilities of considering small peptides as drugs because of their limited bioavailability, it is also true that there has been an explosion of research in this field since the beginning of the 21st century because of the potential importance that peptides may have in the practice of medicinal chemistry.[12–14]

Assuming that an understanding of the chemical interactions is essential for the development of new pharmaceutical drugs, several recently synthesized small tripeptides have been chosen as the object of this study by considering that they could be the basis for the development of new therapeutic antifungal peptides.[15] Thus, in this work, we will be studying the reactivity properties of five new antifungal tripeptides, namely (2R)-2-[(2S)-2-[(2S)-2-amino-3-phenylpropanamido]-propanamido]-5-[(diaminomethylidene)amino]pentanoic acid, (2S)-2-[(2S)-2-[(2S)-2-amino-3-phenyl propanamido]-propanamido]-3-(4-hydroxyphenyl)propanoic acid, (2S)-2-[(2S)-2-[(2S)-2-amino-3-phenylpropanamido]-3-methylbuta-namido]-3-(4-hydroxyphenyl)propanoic acid, (2R)-2-[(2S)-2-[(2S)-2-amino-3-phenylpropanamido]-3-(1H-indol-3-yl)-propanamido]-3-sulfanylpropanoic acid, and (2S)-2-[(2S)-2-

[(2S)-2-amino-3-phenylpropanamido]-3-(1H-indol-3-yl)-propanamido]-3-(4-hydroxyphenyl)pro-panoic acid, by resorting to the CDFT methodology, which will allow the determination of the global properties as well as the local properties for the prediction of the active reaction sites, both electrophilic and nucleophilic. The corresponding short names for these tripeptides are FAR, FAY, FVY, FWC, and FWY. In a similar way, the pK_a values for each of the tripeptides will be calculated by resorting to a methodology previously considered by us,[16] and the descriptors of bioactivity (bioactivity scores) will be established through a procedure described in the literature,[17,18] trying to relate them with the global and local CDFT reactivity descriptors that result from a calculation protocol based on DFT already validated by our group in previous research.[19–26]

COMPUTATIONAL METHODOLOGY

Following the methodology considered in our previous works,[19–26] similar computations have been performed in this work by resorting to the Gaussian 09 software.[27] The full methodological procedure is explained in detail at the beginning of the Results and Discussion section. In a similar way as it was done in the referenced works, the MN12SX density functional[28] was considered because of the fact that it is a well-behaved density functional for our purposes according to our proposed KID (for Koopmans in DFT) criteria,[19–26] related to the approximate validity of the Koopmans theorem within DFT.[29–33] For the calculation of the electronic properties, a model chemistry has been considered on the basis of the MN12SX density functional associated to the Def2TZVP basis set, whereas a smaller Def2SVP was considered for the prediction of the most stable structures.[34,35] All calculations were performed using water, which is the

universal biological solvent, simulated with the Solvent Model Density (SMD) model.[36]

RESULTS AND DISCUSSION

The molecular structures of the antifungal tripeptides FAR, FAY, FVY, FWC, and FWY drawn by scratch, as depicted in Figure 1, were optimized in gas phase by resorting to the Density Functional Tight Binding Model A (DFTBA) model, through the consideration of the five most stable conformers chosen from a preoptimization accomplished by means of molecular mechanics techniques[37−41] using the conformer search engine available in the Marvin View 17.15 program, which can be regarded as an advanced chemical viewer (https://www.chemaxon.com). All the resulting conformers were processed, as is customary within computational chemistry, by means of a new reoptimization with the MN12SX density functional mentioned before, together with the Def2SVP basis set and the SMD solvent model, using water as the solvent. Once it has been verified that every structure belonged to the minimum energy conformation by means of a frequency calculation analysis, the corresponding electronic properties were calculated with the Def2TZVP basis set instead of that used for the geometry optimization.

As it has been mentioned recently by Becke[42] and also by Baerends et al.,[43] it can be said that the lowest excitation energy can be associated with the highest occupied molecular orbital (HOMO)−lowest unoccupied molecular orbital (LUMO) gap of the ground state.[44] Therefore, in this work, the determination of the maximum wavelength absorption of the five antifungal tripeptides was done by conducting ground-state calculations with the aforementioned density functional at the same level of model chemistry and theory and then determining the HOMO−LUMO gaps from which the maximum absorption wavelengths λ_{max} were obtained (Table 1).

Table 1. HOMO and LUMO Orbital Energies (in eV), the HOMO−LUMO Gap (Also in eV), and the Maximum Absorption Wavelengths λ_{max} (in nm) of the Five Antifungal Tripeptides, FAR, FAY, FVY, FWC, and FWY, Predicted by the MN12SX/Def2TZVP/H2O Model Chemistry

	HOMO	LUMO	HOMO−LUMO gap	λ_{max}
FAR	−7.051	−2.838	4.213	294
FAY	−6.223	−3.285	2.938	422
FVY	−6.254	−1.753	4.501	275
FWC	−5.634	−1.733	3.901	318
FWY	−5.634	−3.184	2.450	506

Calculation of Global Reactivity Descriptors. According to the results obtained when studying melanoidins[19−25] as well as peptides from marine sources,[26] it can be said that the calculations performed with the MN12SX density functional render HOMO and LUMO energies that satisfy the approximate Koopmans theorem. Thus, the application of the KID procedure will be justified. The global reactivity descriptors, electronegativity χ,[7,9] global hardness η,[7,9] electrophilicity ω,[45] electrodonating power ω^-,[46] electroaccepting power ω^+,[46] and net electrophilicity $\Delta\omega^{\pm}$[47] were calculated by resorting to the HOMO and LUMO energies determined with the MN12SX density functional, with the results being presented in Table 2. The interested reader in the mathematical formulations of these reactivity descriptors is

referred to the original works and to our previous research on the field.[19−26]

Table 2. Global Reactivity Descriptors of the Five New Antifungal Tripeptides FAR, FAY, FVY, FWC, and FWY (in eV), Calculated with the MN12SX/Def2TZVP/H20 Model Chemistry

molecule	electronegativity	global hardness	electrophilicity
FAR	4.945	4.212	2.902
FAY	4.754	2.938	3.846
FVY	4.003	4.501	1.780
FWC	3.683	3.901	1.739
FWY	4.409	2.450	3.968

molecule	electrodonating power	electroaccepting power	net electrophilicity
FAR	8.540	3.595	12.135
FAY	10.252	5.498	15.750
FVY	5.844	1.840	7.684
FWC	5.563	1.880	7.442
FWY	10.294	5.885	16.178

As expected from the molecular structure of these species, their electrodonating ability is more important than their electroaccepting character as can be seen from the values of the electrodonating and electroaccepting powers and their comparison through the net electrophilicity. However, an interesting comparison can be performed by taking into account the values for the global hardness which is a measure of the deformability of the molecular electron density and, hence, of the chemical reactivity. In this case, it can be observed that FVY and FWC are much more reactive than the other tripeptides. This is corroborated by the lower values of the global electrophilicity, that is, the balance between the chemical electronegativity and the global hardness, for those peptides.

Local Reactivity Descriptor Calculation. We now turn our attention to the local descriptors of chemical reactivity, namely the electrophilic Fukui function $f^-(\mathbf{r})$,[7−9] the nucleophilic Fukui function $f^+(\mathbf{r})$,[7−9] and the dual descriptor (DD) $\Delta f(\mathbf{r})$.[48−52] As for the case of the global reactivity descriptors, the interested reader in the mathematical formulations of these reactivity descriptors is referred to the original works and to our previous research on the field.[19−26]

The electrophilic Fukui functions $f^-(\mathbf{r})$ and nucleophilic Fukui functions $f^+(\mathbf{r})$ for the five new antifungal tripeptides FAR, FAY, FVY, FWC, and FWY are shown in Figure 2.

Martínez-Araya has explained in a recent research[52] that the condensed expression for DD as Δf_k 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.[53,54] through the consideration of atomic spin densities that result from the Mulliken population analysis (MPA).

The definitions for the Parr functions are as follows:
Nucleophilic Parr function[53,54]

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

Electrophilic Parr function[53,54]

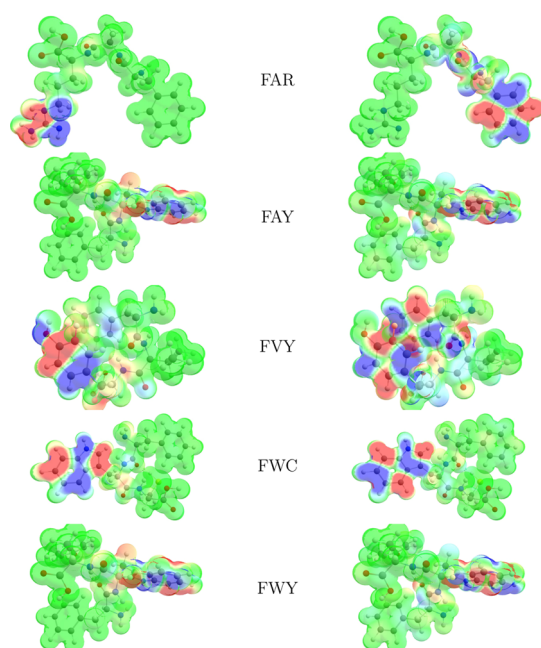$$P^+(\mathbf{r}) = \rho_s^{ra}(\mathbf{r})$$

Figure 2. Graphical representation of the electrophilic Fukui functions $f^-(\mathbf{r})$ (left column) and nucleophilic Fukui functions $f^+(\mathbf{r})$ (right column) of the five antifungal tripeptides.

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.[55]

The results for the calculation of these local reactivity descriptors for the five antifungal tripeptides FAR, FAY, FVY, FWC, and FWY are presented in Table 3 where the condensed

Table 3. Local Reactivity Descriptors for the Antifungal Tripeptides FAR, FAY, FVY, FWC, and FWY, Calculated with the MN12SX/Def2TZVP/H2O Model Chemistry: Condensed DD Δf_k, Nucleophilic Parr Function P_k^+, and Electrophilic Parr Function P_k^-

atom	Δf_k	P_k^+	P_k^-
FAR			
11C	26.62	0.383	0.000
51N	−51.22	0.000	0.713
FAY			
29C	−22.96	0.013	0.459
41C	12.68	0.316	0.126
FVY			
8C	8.23	0.145	0.002
45C	−23.25	0.038	0.384
FWC			
29C	−22.55	0.001	0.434
41C	15.14	0.325	0.084
FWY			
29C	−22.96	0.013	0.459
41C	12.68	0.316	0.126

DD Δf_k has been determined by localizing the corresponding Fukui functions over the atomic sites, employing a charge scheme based on MPA as it was done for the Parr functions. It must be noticed that we are presenting the results only for those atomic sites where Δf_k are maxima in absolute value. The values of Δf_k are multiplied by 100 for easier comparison.

As can be seen from Table 3, there is a good agreement between the results that come from the condensed DD 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 therapeutic peptides of larger size. Moreover, by comparing the results from Table 3 and the graphics in Figure 2, it can be concluded that there is a perfect match for both kinds of analysis.

Calculation of the pK_a's of the Five Antifungal Tripeptides. In a recent work, the relationship between the pK_a's of small peptides and the chemical hardness was developed in our group,[16] leading to the conclusion that it represented a starting point for the prediction of the pK_a of bigger peptides which could be of interest for the development of new therapeutic drugs.

According to the methodology employed in our previous work, we have applied the mentioned relationship of the form pK_a = 16.3088 − 0.8268η to the calculation of the pK_a of the new tripeptides, with the η values presented in Table 4.

Table 4. pK_a's of the Antifungal Tripeptides FAR, FAY, FVY, FWC, and FWY

molecule	pK_a
FAR	12.83
FAY	13.88
FVY	12.59
FWC	13.08
FWY	11.44

It is good to see from these results that this approximate relationship allows us to discriminate between the pK_a results for the tripeptides. This could be of interest for the development of pharmaceutical drugs starting from these molecules, enabling at the same time to obtain an explanation about the mechanisms of action and drug delivery procedures. Moreover, they can be shown as an additional application of the results of the calculation of the global reactivity descriptors to the new field of computational peptidology[56] and as a possible basis for explaining the solubilities of the peptides.

Bioactivity Scores. The properties of the molecules that are identified with the idea of their ability to behave as a pharmaceutical drug are those which are related to the proposal by Lipinski et al.[57,58] for the prediction of druggability and have been determined by associating the SMILES notations corresponding to each tripeptide with the MolInspiration software which is readily available online (Slovensky Grob, Slovak Republic https://www.molinspiration.com).

Indeed, this criterion which is called the Lipinski Rule of Five, or Ro5 for short, does not apply to peptides. Then, a homology modeling approach was considered by searching for structures with known pharmacological properties that could be compared with those that are the object of our study. Thus, a series of descriptors called bioactivity scores which are an indication of the capacity of the potential drugs to interact with different receptors, such as G protein-coupled receptor (GPCR) ligands or kinase inhibitors, to act as ion channel modulators, or to interact with enzymes and nuclear receptors. It must be recalled that GPCRs are the largest family of signaling receptors in the human genome and also are the largest class of targets of approved drugs. The values of the

Table 5. Bioactivity Scores of the Antimicrobial Peptides FAR, FAY, FVY, FWC, and FWY Calculated on the Basis of the GPCR Ligand, Ion Channel Modulator, Nuclear Receptor Ligand, Kinase Inhibitor, Protease Inhibitor, and Enzyme Inhibitor Interactions

molecule	GPCR ligand	ion channel modulator	kinase inhibitor	nuclear receptor ligand	protease inhibitor	enzyme inhibitor
FAR	0.42	0.24	0.08	0.08	0.64	0.47
FAY	0.35	0.18	0.10	0.17	0.67	0.38
FVY	0.32	0.15	0.07	0.15	0.67	0.36
FWC	0.43	0.29	0.09	0.07	1.09	0.51
FWY	0.39	0.21	0.07	0.11	0.78	0.35

bioactivity scores for the five antimicrobial peptides are presented in Table 5.

The interpretation of the bioactivity scores is based on a scheme that tends to classify them as active, moderately active, or inactive, depending on the obtained values. If the bioactivity score is >0, it will correspond to the first case; if the bioactivity score lies between −5.0 and 0.0, it will belong to the second case; and if the bioactivity score is <−5.0, it will be assigned to the third case. It can be seen that although the antifungal tripeptides considered in this work may act as GPCR ligands and as ion channel modulators, their main bioactivity is related to their ability to act as protease inhibitors. It is also evident that for the FWC peptide, this ability is larger than for the other tripeptides. Although this behavior cannot be cast into a QSAR equation because the number of results is low, it can be however related to the values of the global descriptors for this particular tripeptide. From Table 2, it can be seen that for FWC, the values of the electronegativity χ, the electrophilicity ω, the electrodonating and electroaccepting powers, ω^- and ω^+, and the net electrophilicity $\Delta\omega^{\pm}$ attain minimum values. Thus, it can be said that, as an approximation, the protease inhibition ability for these antifungal tripeptides has a behavior related to the inverse of the mentioned global reactivity descriptors.

CONCLUSIONS

In this work, the chemical reactivity of a group of five recently synthesized antifungal tripeptides with therapeutic potential, FAR, FAY, FVY, FWC, and FWY, was studied by resorting to CDFT as a tool to explain the molecular interactions.

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

Among the many descriptors that could be useful for the development of new medicines, pK_a is of paramount importance because it is related to the water solubility of the drugs. Thus, when the experimental values of pK_a are unknown, the approximate QSAR relationship employed in this work could be a useful predictive tool for the determination of the pK_a's of small and large peptides.

Finally, the molecular properties related to the bioavailability and the descriptors used for the quantification of the bioactivity allowed the characterization of the studied antifungal tripeptides, establishing some relationships between the bioactivity properties and the calculated global reactivity descriptors.

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Author Contributions
D.G.-M. conceived and designed the research and headed, wrote, and revised the manuscript, and J.F. and N.F.-H. contributed to the writing and the revision of the article.

Notes
The authors declare no competing financial interest.

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