Chapter

Computational Chemistry Study of Natural Apocarotenoids and Their Synthetic Glycopeptide Conjugates as Therapeutic Drugs

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Abstract

The objective of the research to be presented in the chapter is the determination of the chemical reactivity properties of some natural apocarotenoids and their synthetic glycopeptide conjugates that could have the ability to inhibit SARS-CoV-2 replication. The study will be based on the consideration of the Conceptual DFT branch of Density Functional Theory (DFT) through the consideration of particular successful model chemistry which has been demonstrated as satisfying the Janak and Ionization Energy theorems within Generalized Gradient Approximation (GGA) theory. The research will be complemented by a report of the ADMET and pharmacokinetic properties hoping that this information could be of help in the development of new pharmaceutical drugs for fighting COVID-19.

Keywords: natural Apocarotenoids, glycopeptide conjugates, computational chemistry, SARS-CoV-2, COVID-19, chemical reactivity, conceptual DFT

1. Introduction

Cyclic peptides have several desirable qualities, including high binding affinity, target selectivity, and low toxicity, which make them a promising therapeutic development approach. Antimicrobial peptides (AMPs), also known as host defense peptides, are short, positively charged peptides found in a wide range of life forms, including microbes and humans. The majority of AMPs are capable of directly killing microbial infections, whereas some operate indirectly by altering the host defensive mechanisms [1].

Teicoplanin, a therapeutically utilized glycopeptide antibiotic, has surfaced as a possible antiviral in the context of the global COVID-19 pandemic, with its potency being increased with lipophilic modifications. Teicoplanin was obtained from *Actinoplanes teichomyceticus*, which was recovered from a soil sample collected in Nimodi Village, Indore, India, for the first time in 1978. Teicoplanin's structure was discovered in 1984. Teicoplanin has been identified as a lipoglycopeptide antibiotic. This antibiotic is made up of a heptapeptide made up of seven aromatic amino acids,

sugar residues, and a lipid chain that is nonribosomal. It is made up of five identical chemicals that differ in their fatty acid side chains and are generated by bacteria [2]. This glycopeptide antibiotic typically used to treat Gram-positive bacterial infections has been demonstrated to diminish SARS-CoV-1 and MERS-CoV infection [3].

Lipophilic modifications have been shown to improve the antiviral spectrum and efficacy of glycopeptide antibiotics, which improve antiviral activity against coronaviruses, HIV, flavivirus, and influenza viruses with the drawback of being associated with substantial cytotoxicity [4–13]. To obtain efficient glycopeptide antibiotics by increasing their lipophilicity and avoiding the cytotoxicity problems, recent research has been presented with a study of the structural and biochemical properties of new lipophilic apocarotenoid conjugates of Teicoplanin and its pseudoaglycone [14].

Inspired by this latest research and as a follow up of our previous studies on the chemical reactivity properties of carotenoids [15–19] and cyclopeptides [20–24], we think that it is worth reporting the physicochemical and bioactivity properties of some of these apocarotenoid conjugates of Teicoplanin as well as to predict and understand their chemical reactivity properties considering a methodology developed by our research group. This will be done as a means of further validation of the procedure and for assessing the behavior of the MN12SX density functional in the fulfillment of the Janak theorem and the Ionization Energy Theorem, which is a corollary of the former [25–29].

Thus, the objective of this work is to report the results of a computational study of the bioactivity properties and chemical reactivity of three apocarotenoid conjugates of Teicoplanin based on the CDFT-based Computational Peptidology (CDFT-CP) methodology [20–24]. These three molecules will be designed by considering the Teicoplanin A3–1 variant (PubChem CID 15122170) and the apocarotenoids Bixin, Methylcrocetin and -apo-8'-Carotenoic Acid. The methodology will be based on the combination of the chemical reactivity descriptors from Conceptual Density Functional Theory (CDFT) [30–35] with some Cheminformatics tools [36–43] which may be utilized to assess the associated physicochemical properties. This will be complemented by the detection of the ability of the three molecules to act as possible useful drugs through an analysis of their bioactivities and pharmacokinetics characteristics linked to the ADMET features [44–46].

2. Methodology

2.1 Density functional theory calculations

The Kohn-Sham (KS) methodology approach to Density Functional Theory (DFT) involves the determination of the electronic density, the molecular energy, and the orbital energies of a specific system, in particular, the HOMO and LUMO frontier orbitals which are intrinsically related to the chemical reactivity of the molecules [47–50]. The definitions for the global reactivity descriptors that form the core of Conceptual DFT are [30–35]:

$$\text{Electronegativity} \quad \chi \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H) \tag{1}$$

$$\text{Global Hardness} \quad \eta \approx (\varepsilon_L - \varepsilon_H) \tag{2}$$

$$\text{Electrophilicity} \quad \omega \approx (\varepsilon_L + \varepsilon_H)^2/4(\varepsilon_L - \varepsilon_H) \tag{3}$$

$$\text{Electrodonating Power} \quad \omega^- \approx (3\varepsilon_H + \varepsilon_L)^2/16\eta \tag{4}$$

$$\text{Electroaccepting Power} \quad \omega^+ \approx (\varepsilon_H + 3\varepsilon_L)^2/16\eta \tag{5}$$

$$\text{Net Electrophilicity} \quad \Delta\omega^{\pm} = \omega^+ + \omega^- \tag{6}$$

being ε_H and ε_L the frontier orbital energies related to the molecular systems considered in this research. These global reactivity descriptors that arise from Conceptual DFT [30–35], have been complemented by the estimation of the Nucleophilicity Index N [51–55] that takes into account the value of the HOMO energy obtained using the KS scheme using an arbitrary shift of the origin with tetracyanoethylene (TCE) as a reference.

Conformational analysis of the studied molecules has been achieved using MarvinView 17.15 from ChemAxon [http://www.chemaxon.com], which was applied to undertake Molecular Mechanics calculations considering the MMFF94 force field [56–60]. This was followed in each case by a geometry optimization and frequency calculation using the Density Functional Tight Binding (DFTB) methodology [61]. This last step was required for the verification of the absence of imaginary frequencies as a confirmation of the stability of every optimized structure as being a minimum in the energy surface. The determination of the electronic properties and the Conceptual DFT reactivity descriptors of the studied molecules was addressed through the MN12SX/Def2TZVP/H2O model chemistry [62–64] because it has been previously shown that it verifies the KID procedure fulfiling the Ionization Energy Theorem, with the help of the Gaussian 16 software [61] and the context of the SMD solvation model [65]. The charge of all the molecules was taken as equal to zero whereas the radical anion and cation were considered in the doublet spin state. The SMD solvation model was chosen because it has been shown that it provides atomic charges of the Hirshfeld kind that are almost independent of the basis set and which are usually recommended for calculations within Conceptual Density Functional Theory.

2.2 Computational pharmacokinetics and ADMET report

The SMILES notation of each studied molecule was generated through the Online SMILES Translator and Structure File Generator [https://cactus.nci.nih.gov/translate/], and then was fed into the online program Chemicalize from ChemAxon [http://www.chemaxon.com], which was considered to get a glimpse of the potential therapeutic properties of the studied molecular systems (accessed: January 2022).

A similarity search in the chemical space of compounds with molecular structures that could be compared to the ones being studied, with already known biological and pharmacological properties, was achieved through the online Molinspiration software from Molinspiration Cheminformatics [https://www.molinspiration.com/] (accessed, January 2022).

Pharmacokinetics is a procedure that involves determining the likely fate of a medicinal molecule in the body, which is critical information in the creation of new medicine. Individual indices named Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) factors have typically been used to analyze the associated consequences. Chemicalize and the internet available pkCSM, a software for the prediction of small-molecule pharmacokinetic properties using SMILES, was also used to obtain additional information regarding the Pharmacokinetics parameters and ADMET indices [45].

3. Results and discussion

3.1 Conceptual DFT-based computational peptidology

The optimized molecular structures of the three apocarotenoid glycopeptide conjugates considered through this research through the methodology presented before are displayed in **Figure 1**:

The quality of the chosen density functional may be realized by comparing its results with results from high-level computations or experiential values. Nevertheless, this comparison is not always computationally practicable because of the large size of the molecules or the lack of experimental results for the chemical methods being explored. Our research group has developed a methodology known as KID [20–24], as an aid to evaluating a particular density functional about its internal coherence. It is evident that within the Generalized Kohn-Sham (GKS) version of DFT, some relationships exist between the KID methodology and the Ionization Energy Theorem, which is a corollary of Janak theorem [25–29]. This is done by connecting ε_H to -I and ε_L to -A, through

$$J_I = \varepsilon_H + E_{gs}(N-1) - E_{gs}(N) \tag{7}$$

$$J_A = \varepsilon_L + E_{gs}(N) - E_{gs}(N+1) \tag{8}$$

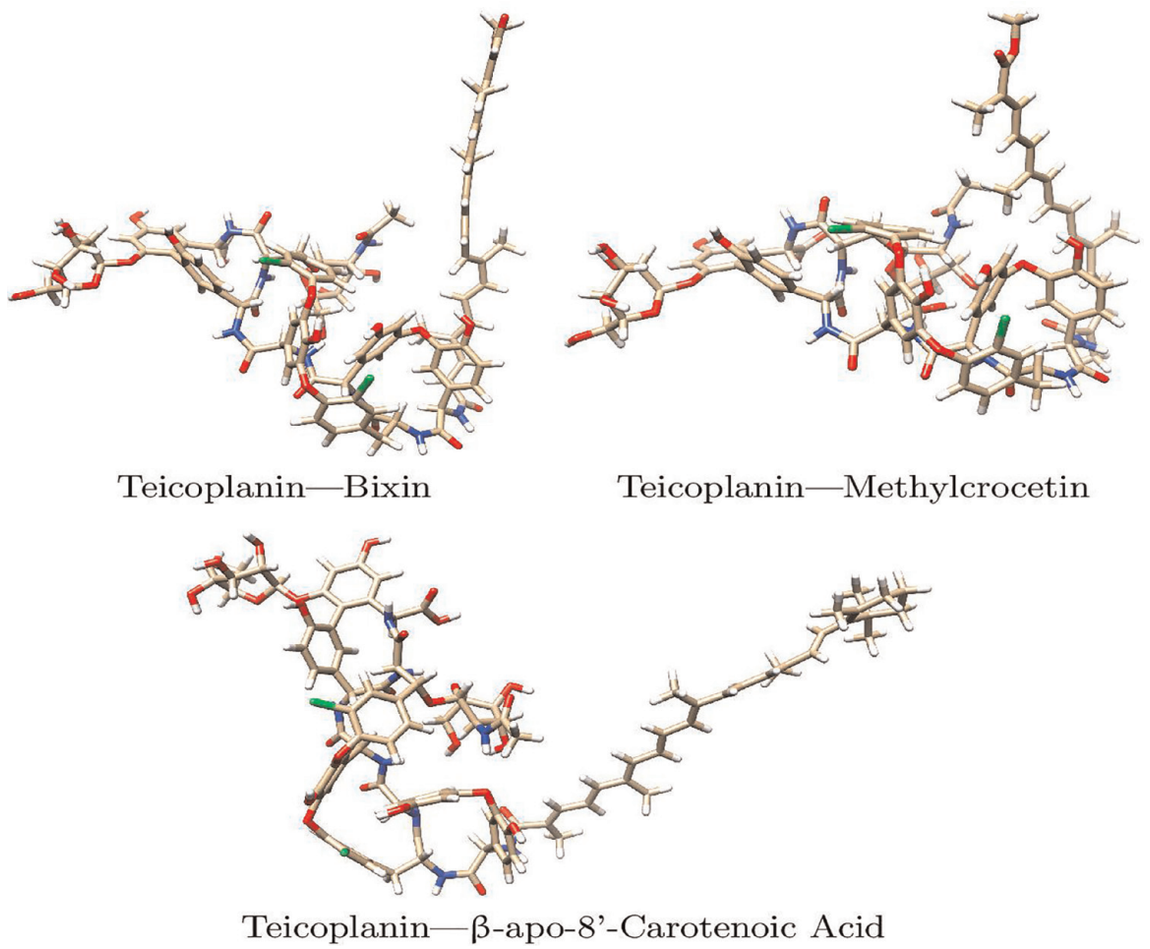

Figure 1.
Optimized molecular structures of three apocarotenoid glycopeptide conjugates (Brown: C, blue: N, red: O, green: Cl, and white: H).

$$J_{HL} = \sqrt{J_I{}^2 + J_A{}^2} \tag{9}$$

Another KID descriptor ΔSL related to the difference in energies between the SOMO and the LUMO of the neutral system has been devised to aid in the verification of the accuracy of the methodology.

The MN12SX density functional has been shown to have a Koopmans-compliant behavior in earlier studies of the chemical reactivity of diverse molecular systems. However, for further validation of this model chemistry in the prediction of the chemical reactivity properties of the apocarotenoid glycopeptides conjugates considered here, additional research is necessary. The CDFT software tool was used to make this determination, and the findings are shown in **Table 1**:

The results from **Table 1** are very interesting because they show that there is an almost perfect fulfillment of the Janak and Ionization Energy theorems for the MN12SX/Def2TZVP/H2O model chemistry employed in this work.

Having verified that the MN12SX/Def2TZVP/H2O is the most adequate one for obtaining accurate results for the Conceptual DFT global reactivity descriptors, the estimated values for the Global Reactivity Descriptors (including the Nucleophilicity N) for the three molecular systems acquired utilizing the mentioned CDFT tool are displayed in **Table 2**:

The electronegativity (χ) and global hardness (η) are absolute values for the chemical reactivity that have not a known experimental counterpart. Indeed, they can be estimated by resorting to the experimental vertical ionization energy (I) and vertical electron affinity (A) but these values are not known for the molecule under study. A different thing can be said about electrophilicity ω and Nucleophilicity (N). The electrophilicity ω index involves a compromise between the tendency of an electrophile to acquire extra electron density and its resistance to exchange electron

Molecule	HOMO	LUMO	SOMO	H-L Gap	J(I)	J(A)	J(HL)	ΔSL
1	−5.246	−2.693	−2.701	2.553	0.001	0.004	0.005	0.008
2	−5.262	−2.711	−2.717	2.552	0.003	0.005	0.005	0.007
3	−5.073	−2.377	−2.389	2.696	0.002	0.007	0.008	0.012

1: Teicoplanin-Bixin; 2: Teicoplanin-Methylcrocetin; 3: Teicoplanin-β-apo-8′-Carotenoic Acid.

Table 1.
Frontier orbital energies, H-L gap and the KID indices (all in eV) were used for the verification of the ionization energy theorem behavior of the MN12SX density functional in the study of the chemical reactivity of the synthetic conjugates of the glycopeptide Teicoplanin with several apocarotenoids.

Molecule	χ	η	ω	S	N	ω^-	ω^+	$\Delta\omega\pm$
1	3.970	2.553	3.086	0.392	3.546	8.316	4.346	12.662
2	3.987	2.552	3.114	0.392	3.530	8.380	4.394	12.774
3	3.725	2.696	2.574	0.371	3.720	7.178	3.453	10.632

1: Teicoplanin-Bixin; 2: Teicoplanin-Methylcrocetin; 3: Teicoplanin-β-apo-8′-Carotenoic Acid.

Table 2.
Global reactivity descriptors for the synthetic conjugates of the glycopeptide Teicoplanin with several apocarotenoids: Electronegativity (χ), hardness (η), Electrophilicity (ω) (all in eV), softness S (in eV^{-1}), Nucleophilicity N, Electrodonating power (ω^-), Electroaccepting power (ω^+) and net Electrophilicity ($\Delta\omega\pm$) (also in eV).

density with the environment [55]. By considering a group of Diels-Alder reactions and the electrophiles involved in them [53, 66, 67], classification of organic compounds as strong, moderate, or marginal electrophiles, that is an electrophilicity ω scale, was established, with ω larger than 1.5 eV for the first instance, with ω between 0.8 and 1.5 eV for the second case, and ω smaller than 0.8 eV for the final case [53, 66, 67]. By checking **Table 2**, it can be said that the three molecules may be regarded as strong electrophiles. Domingo and his collaborators [51–55] have also proposed a Nucleophilicity index N through the consideration of the HOMO energy obtained through the KS scheme with an arbitrary shift of the origin taking the molecule of tetracyanoethylene (TCE) as a reference. An analysis of a series of common nucleophilic species participating in polar organic reactions allowed them to establish a further classification of organic molecules as strong nucleophiles with $N > 3.0$ eV, moderate nucleophiles with $2.0 < N < 3.0$ eV and marginal nucleophiles with
$N < 2.0$ eV. By checking again **Table 2**, it can be concluded that the three molecular systems may be considered also as strong nucleophiles.

It is interesting to see that in comparison with similar research with peptides [20–24], the MN12SX/Def2TZVP/H2O model chemistry retains its predictive ability even when the glycopeptides are conjugated with carotenoids, as in the present case. An important point is that the conjugates are predicted to be strong nucleophiles and electrophiles while the computed behavior for isolated peptides depicts them as moderate or even marginal nucleophiles and electrophiles.

3.2 Computational pharmacokinetics and ADMET report

The majority of medicinal drugs work by attaching to target protein molecules while at the same time modifying their functions. The Bioactivity Scores, which are a measure of the capacity of the molecules to act or coordinate with distinct receptors, are listed in **Table 3** for the three apocarotenoid glycopeptide conjugates:

These bioactivity scores for organic molecules can be interpreted as active (when the bioactivity score is greater thanÂ 0), moderately active (when the bioactivity score lies between −5.0 and 0.0) and inactive (when the bioactivity score is lower than −5.0).

The pharmacokinetics of a drug is evaluated through ADMET research, which is acronymous for Absorption, Distribution, Metabolism, Excretion, and Toxicity. If absorption is unsatisfactory, the distribution and metabolism of the drug would be changed, potentially resulting in nephrotoxicity and neurotoxicity. As a result, ADMET analysis is one of the most important aspects of computational drug design. In addition to the previous Conceptual DFT-based Computational Peptidology and Pharmacokinetics results, we are complementing this study with a report of the computed ADMET features as shown in **Table 4**:

Molecule	GPCR ligand	Ion channel modulator	Nuclear receptor ligand	Kinase inhibitor	Protease inhibitor	Enzyme inhibitor
1	−4.08	−4.11	−4.12	−4.11	−4.07	−4.08
2	−4.08	−4.10	−4.11	−4.10	−4.06	−4.07
3	−4.08	−4.09	−4.13	−4.11	−4.08	−4.08

1: Teicoplanin-Bixin; 2: Teicoplanin-Methylcrocetin; 3: Teicoplanin-β-apo-8'-Carotenoic Acid.

Table 3.
Bioactivity scores of the synthetic conjugates of the glycopeptide Teicoplanin with several apocarotenoids.

Property	MOL 1	MOL 2	MOL 3
		Absorption	
Water Solubility (log mol/L)	−2.892	−2.892	−2.892
Caco2 Permeability (log Papp 10^{-6} cm/s)	−0.965	−0.915	−0.748
Gastrointestinal Absorption (human) (% Absorbed)	8.189	6.874	25.006
Skin Permeability (log Kp)	−2.735	−2.735	−2.735
P-glycoprotein Substrate	Yes	Yes	Yes
P-glycoprotein I Inhibitor	No	No	No
P-glycoprotein II Inhibitor	No	No	No
		Distribution	
VDss (human) (log L/kg)	0.052	0.042	0.045
Fraction Unbound (human) (Fu)	0.363	0.368	0.367
BBB Permeability (log BB)	−5.180	−5.192	−4.950
CNS Permeability (log PS)	−7.097	−7.187	−6.499
		Metabolism	
CYP2D6 Substrate	No	No	No
CYP3A4 Substrate	No	No	No
CYP1A2 Inhibitor	No	No	No
CYP2C19 Inhibitor	No	No	No
CYP2C9 Inhibitor	No	No	No
CYP2D6 Inhibitor	No	No	No
CYP3A4 Inhibitor	No	No	No
		Excretion	
Total Clearance (log ml/min/kg)	−0.989	−1.037	−1.319
Renal OCT2 Substrate	No	No	No
		Toxicity	
AMES Toxicity	No	No	No
Max. Tolerated Dose (human) (log mg/kg/day)	0.438	0.438	0.438
hERG I inhibitor	No	No	No
hERG II inhibitor	No	No	No
Oral Rat Acute Toxicity (LD50) /mol/kg)	2.482	2.482	2.482
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg-bw/day)	17.306	17.065	17.008
Hepatotoxicity	No	No	No
Skin Sensitization	No	No	No
T. Pyriformis Toxicity (log g/L)	0.285	0.285	0.285
Minnow Toxicity (log mM)	25.665	26.019	24.477

1: Teicoplanin-Bixin; 2: Teicoplanin-Methylcrocetin; 3: Teicoplanin-β-apo-8'-Carotenoic Acid.

Table 4.
Computed ADMET features of the synthetic conjugates of the glycopeptide Teicoplanin with several apocarotenoids.

It is important to note that all the members of the group of studied molecules display positive values for the Human Gastrointestinal Absorption (HI), in particular for MOL3, and negative values for the AMES toxicity and Hepatotoxicity. All the molecular systems will be P-glycoprotein inhibitors (P-gp), being also P-gp substrates. None of the apocarotenoid glycopeptide conjugates will be inhibitors of the molecules related to cytochrome P450, displaying also a negative behavior as substrates of the CYP2D6 and CYP3A4 variants. Finally, all the molecular systems considered here will display a negative result regarding their behavior as hERG inhibitors. These results are comparatively similar to those presented within the study of the structural and biochemical properties of lipophilic apocarotenoid conjugates of Teicoplanin and its pseudoaglycone that inspired this research [14].

4. Conclusions

The chemical reactivities of three apocarotenoid glycopeptide conjugates have been thoroughly investigated by optimizing their structures using the DFTB methodology and calculating their electronic properties using high-quality model chemistry, namely MN12SX/Def2TZVP/H2O. This model chemistry was already used in previous research, demonstrating its utility for this type of calculation. However, an involved estimation of the KID descriptors for all the molecules demonstrated the ability of the MN12SX density functional for the accurate estimation of the frontier orbital energies based on the KID procedure methodology. The fact that the energy of the LUMO and the SOMO (or the HOMO energy of the anion) are almost the same, which is reflected in the KID accuracy descriptor ΔSL being very close to zero, is an indication that the derivative discontinuity is negligible for the chosen density functional. This is translated as the ability of the LUMO energy to reflect with precision the Electron Affinity of the molecule, implying that the chemical reactivity parameters obtained by considering this density functional will be very accurate. This is a very important result because it allowed the estimation of the accuracy of the results based only on the fulfillment of some intrinsic requirements (like the Janak and Ionization Energies) without the need to resort to the comparison with experimental results that could not be available, as in the present case.

By considering our suggested Conceptual DFT-based Computational Peptidology methodology, the three apocarotenoid glycopeptide conjugates have been studied by applying certain techniques generally used in the procedure of drug discovery and development, showing that these molecular systems may be regarded as potential therapeutic drugs. The biological targets, physicochemical attributes, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) indices associated with their bioavailability and pharmacokinetics were forecasted and analyzed as descriptors that could be useful in future drug development research.

It may be concluded that the results coming from the present study may be of importance for the pharmaceutic industry because they show that the proposed three apocarotenoid glycopeptide conjugates fulfilled the objective of increasing the lipophilicity while at the same time avoiding the risk of the associated toxicity.

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Conflict of interest

The authors declare no conflict of interest regarding the publication of this manuscript.

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References

[1] Mahlapuu M, Håkansson J, Ringstad L, Björn C. Antimicrobial peptides: An emerging category of therapeutic agents. Frontiers in Cellular and Infection Microbiology. 2016;**6**:194

[2] Vimberg V. Teicoplanin – A new use for an old drug in the COVID-19 era? Pharmaceuticals. 2021;**14**(12):1227

[3] Schütz D, Ruiz-Blanco YB, Münch J, Kirchhoff F, Sanchez-Garcia E, Müller JA. Peptide and peptide-based inhibitors of SARS-CoV-2 entry. Advanced Drug Delivery Reviews. 2020;**167**:47-65

[4] Balzarini J, Keyaerts E, Vijgen L, Egberink H, De Clercq E, Van Ranst M, et al. Inhibition of feline (FIPV) and human (SARS) coronavirus by semisynthetic derivatives of Glycopeptide antibiotics. Antiviral Research. 2006;**72**(1):20-33

[5] Szűcs Z, Naesens L, Stevaert A, Ostorházi E, Batta G, Herczegh P, et al. Reprogramming of the antibacterial drug vancomycin results in potent antiviral agents devoid of antibacterial activity. Pharmaceuticals. 2020;**13**(7):139

[6] Bereczki I, Csávás M, Szűcs Z, Rőth E, Batta G, Ostorházi E, et al. Synthesis of antiviral perfluoroalkyl derivatives of teicoplanin and vancomycin. ChemMedChem. 2020; **15**(17):1661-1671

[7] Balzarini J, Pannecouque C, De Clercq E, Pavlov AY, Printsevskaya SS, Miroshnikova OV, et al. Antiretroviral activity of semisynthetic derivatives of glycopeptide antibiotics. Journal of Medicinal Chemistry. 2003;**46**(13): 2755-2764

[8] De Burghgraeve T, Kaptein SJF, Ayala-Nunez NV, Mondotte JA, Pastorino B, Printsevskaya SS, et al. An analogue of the antibiotic teicoplanin prevents flavivirus entry in vitro. PLoS One. 2012;**7**(5):e37244

[9] Naesens L, Vanderlinden E, Rőth E, Jekö J, Andrei G, Snoeck R, et al. Anti-influenza virus activity and structure-activity relationship of aglycoristocetin derivatives with cyclobutenedione carrying hydrophobic chains. Antiviral Research. 2009;**82**(1):89-94

[10] Pintér G, Batta G, Kéki S, Mándi A, Komáromi I, Takács-Novák K, et al. Diazo transfer-click reaction route to new, lipophilic teicoplanin and ristocetin aglycon derivatives with high antibacterial and anti-influenza virus activity: An aggregation and receptor binding study. Journal of Medicinal Chemistry. 2009;**52**(19):6053-6061

[11] Sipos A, Máté G, Rőth E, Borbás A, Batta G, Bereczki I, et al. Synthesis of fluorescent ristocetin aglycon derivatives with remarkable antibacterial and antiviral activities. European Journal of Medicinal Chemistry. 2012;**58**:361-367

[12] Bereczki I, Kicsák M, Dobray L, Borbás A, Batta G, Kéki S, et al. Semisynthetic teicoplanin derivatives as new influenza virus binding inhibitors: Synthesis and antiviral studies. Bioorganic & Medicinal Chemistry Letters. 2014;**24**(15):3251-3254

[13] Szűcs Z, Kelemen V, Le Thai S, Csávás M, Rőth E, Batta G, et al. Structure-activity relationship studies of lipophilic teicoplanin pseudoaglycon derivatives as new anti-influenza virus agents. European Journal of Medicinal Chemistry. 2018;**157**:1017-1030

[14] Bereczki I, Papp H, Kuczmog A, Madai M, Nagy V, Agócs A, et al. Natural

apocarotenoids and their synthetic glycopeptide conjugates inhibit SARS-CoV-2 replication. Pharmaceuticals. 2021;**14**(11):1111

[15] Flores-Holguín N, Frau J, Glossman-Mitnik D. Chemical reactivity properties, solubilities, and bioactivity scores of some pigments derived from carotenoids of marine origin through conceptual DFT descriptors. Journal of Chemistry. 2019;**1–12**:2019

[16] Flores-Hidalgo M, Torres-Rivas F, Monzón-Bensojo J, Escobedo-Bretado M, Glossman-Mitnik D, Barraza-Jiménez D. Electronic structure of carotenoids in natural and artificial photosynthesis. In: Cvetkovic DJ, Nikolic GS, editors. Carotenoids. Rijeka: InTech; 2017. pp. 17-33

[17] Ruiz-Anchondo T, Glossman-Mitnik D. Computational molecular characterization of the β,β-carotene molecule. Journal of Molecular Structure: THEOCHEM. 2009;**913**:215-220

[18] Ruiz-Anchondo T, Flores-Holguín N, Glossman-Mitnik D. Natural carotenoids as precursors of nanomaterials for molecular photovoltaics: A computational DFT study. Molecules. 2010;**15**(7): 4490-4510

[19] Payán-Gómez SA, Flores-Holguín N, Pérez-Hernández A, Pinón-Miramontes M, Glossman-Mitnik D. Computational molecular characterization of the flavonoid morin and its Pt(II), Pd(II) and Zn(II) complexes. Journal of Molecular Modeling. 2011;**17**(5):979-985

[20] Flores-Holguín N, Frau J, Glossman-Mitnik D. A fast and simple evaluation of the chemical reactivity properties of the Pristinamycin family of antimicrobial peptides. Chemical Physics Letters. 2020;**739**:137021

[21] Flores-Holguín N, Frau J, Glossman-Mitnik D. Conceptual DFT-based computational peptidology of marine natural compounds: Discodermins A–H. Molecules. 2020;**25**(18):4158

[22] Flores-Holguín N, Frau J, Glossman-Mitnik D. Virtual screening of marine natural compounds by means of chemoinformatics and CDFT-based computational peptidology. Marine Drugs. 2020;**18**(9):478

[23] Norma Flores-Holguín, Juan Frau, and Daniel Glossman-Mitnik. Conceptual DFT as a helpful chemoinformatics tool for the study of the Clavanin family of antimicrobial marine peptides. In Sergio Ricardo De Lazaro, Luis Henrique Da Silveira Lacerda, and Renan Augusto Pontes Ribeiro, editors, Density Functional Theory, Chapter 3. London,UK: Intech Open; 2021. pp. 57-67

[24] Flores-Holguín N, Frau J, Glossman-Mitnik D. A CDFT-based computational peptidology (CDFT-CP) study of the chemical reactivity and bioactivity of the marine-derived alternaramide cyclopentadepsipeptide. Journal of Chemistry. 2021;**1–11**:2021

[25] Janak JF. Proof that $\partial E/\partial n_i = \varepsilon$ in density functional theory. Physical Review B. 1978;**18**:7165-7168

[26] Kar R, Song J-W, Hirao K. Long-range corrected functionals satisfy Koopmans' theorem: Calculation of correlation and relaxation energies. Journal of Computational Chemistry. 2013;**34**(11):958-964

[27] Tsuneda T, Song J-W, Suzuki S, Hirao K. On Koopmans' theorem in density functional theory. The Journal of Chemical Physics. 2010;**133**(17):174101

[28] Tsuneda T, Hirao K. Long-range correction for density functional theory.

Wiley Interdisciplinary Reviews: Computational Molecular Science. 2014; **4**(4):375-390

[29] Kanchanakungwankul S, Truhlar DG. Examination of how well long-range-corrected density functionals satisfy the ionization energy theorem. Journal of Chemical Theory and Computation. 2021;**17**(8):4823-4830

[30] Parr RG, Yang W. Density-Functional Theory of Atoms and Molecules. New York: Oxford University Press; 1989

[31] Chermette H. Chemical reactivity indexes in density functional theory. Journal of Computational Chemistry. 1999;**20**:129-154

[32] Geerlings P, De Proft F, Langenaeker W. Conceptual density functional theory. Chemical Reviews. 2003;**103**:1793-1873

[33] Gázquez JL, Cedillo A, Vela A. Electrodonating and electroaccepting powers. Journal of Physical Chemistry A. 2007;**111**(10):1966-1970

[34] Chattaraj PK, Chakraborty A, Giri S. Net electrophilicity. Journal of Physical Chemistry A. 2009;**113**(37):10068-10074

[35] Geerlings P, Chamorro E, Chattaraj PK, De Proft F, Gázquez JL, Liu S, et al. Conceptual density functional theory: Status, prospects, issues. Theoretical Chemistry Accounts. 2020;**139**(2):36

[36] Engel T, Gasteiger J, editors. Applied Chemoinformatics : Achievements and Future Opportunities. Weinheim, Germany: Wiley-VCH; 2018

[37] Engel T, Gasteiger J, editors. Chemoinformatics: Basic Concepts and Methods. Weinheim: Wiley-VCH; 2018

[38] Bajorath J, editor. Chemoinformatics for Drug Discove. Hoboken, New Jersey: WILEY, A John Wiley & Sons Publication; 2014

[39] Varnek A, Tropsha A, editors. Chemoinformatics Approaches to Virtual Screening. Cambridge, UK: Royal Society of Chemistry; 2008

[40] Guha R, Bender A, editors. Computational Approaches in Cheminformatics and Bioinformatics. Hoboken, N.J: Wiley; 2012

[41] Benjamin B. Basic Principles of Drug Discovery and Development. Amsterdam Netherlands: Academic Press; 2015

[42] Medina-Franco JL, Saldívar-González FI. Cheminformatics to characterize pharmacologically active natural products. Biomolecules. 2020; **10**(11):11

[43] Firdaus Begam B, Satheesh Kumar J. A study on cheminformatics and its applications on modern drug discovery. Procedia Engineering. 2012; **38**:1264-1275

[44] Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017;**7**(1): 42717

[45] Pires DEV, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. Journal of Medicinal Chemistry. 2015;**58**(9): 4066-4072

[46] Chakraborty A, Pan S, Chattaraj PK. Biological activity and toxicity: A conceptual DFT approach. In: Structure

and Bonding. Berlin Heidelberg: Springer; 2012. pp. 143-179

[47] Lewars E. Computational Chemistry - Introduction to the Theory and Applications of Molecular and Quantum Mechanics. Dordrecht: Kluwer Academic Publishers; 2003

[48] Young DC. Computational Chemistry - A Practical Guide for Applying Techniques to Real-World Problems. New York: John Wiley & Sons; 2001

[49] Jensen F. Introduction to Computational Chemistry. 2nd ed. Chichester, England: John Wiley & Sons; 2007

[50] Cramer CJ. Essentials of Computational Chemistry - Theories and Models. 2nd ed. Chichester, England: John Wiley & Sons; 2004

[51] Domingo LR, Chamorro E, Perez P. Understanding the reactivity of captodative ethylenes in polar cycloaddition reactions. A theoretical study. The Journal of Organic Chemistry. 2008;**73**(12):4615-4624

[52] Jaramillo P, Domingo LR, Chamorro E, Pérez P. A further exploration of a nucleophilicity index based on the gas-phase ionization potentials. Journal of Molecular Structure: Theochem. 2008;**865**(1–3): 68-72

[53] Domingo LR, Sáez JA. Understanding the mechanism of polar Diels-Alder reactions. Organic and Biomolecular Chemistry. 2009;**7**(17): 3576-3583

[54] Domingo LR, Perez P. The nucleophilicity N index in organic chemistry. Organic and Biomolecular Chemistry. 2011;**9**:7168-7175

[55] Domingo LR, Ríos-Gutiérrez M, Pérez P. Applications of the conceptual density functional theory indices to organic chemistry reactivity. Molecules. 2016;**21**:748

[56] Halgren TA. Merck molecular force field. I. Basis, form, scope, parameterization, and performance of MMFF94. Journal of Computational Chemistry. 1996;**17**(5–6):490-519

[57] Halgren TA. Merck molecular force field. II. MMFF94 van der Waals and electrostatic parameters for intermolecular interactions. Journal of Computational Chemistry. 1996;**17**(5–6): 520-552

[58] Halgren TA. MMFF VI. MMFF94s option for energy minimization studies. Journal of Computational Chemistry. 1999;**20**(7):720-729

[59] Halgren TA, Nachbar RB. Merck molecular force field. IV. Conformational energies and geometries for MMFF94. Journal of Computational Chemistry. 1996;**17**(5–6):587-615

[60] Halgren TA. Merck molecular force field. V. Extension of MMFF94 using experimental data, additional computational data, and empirical rules. Journal of Computational Chemistry. 1996;**17**(5–6):616-641

[61] Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian 16 Revision C.01. Wallingford CT: Gaussian Inc; 2016

[62] Peverati R, Truhlar DG. Screened-exchange density functionals with broad accuracy for chemistry and solid-state physics. Physical Chemistry Chemical Physics. 2012;**14**(47):16187-16191

[63] Weigend F, Ahlrichs R. Balanced basis sets of Split valence, triple zeta

valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. Physical Chemistry Chemical Physics. 2005;**7**: 3297-3305

[64] Weigend F. Accurate coulomb-fitting basis sets for H to R. Physical Chemistry Chemical Physics. 2006;**8**: 1057-1065

[65] Marenich AV, Cramer CJ, Truhlar DG. Universal solvation model based on solute electron density and a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. Journal of Physical Chemistry B. 2009;**18**(1): 6378-6396

[66] Domingo LR, José Aurell M, Pérez P, Contreras R. Quantitative characterization of the global electrophilicity power of common diene/dienophile pairs in Diels-Alder reactions. Tetrahedron. 2002;**58**(22):4417-4423

[67] Pérez P, Domingo LR, José Aurell M, Contreras R. Quantitative characterization of the global electrophilicity pattern of some reagents involved in 1,3-dipolar cycloaddition reactions. Tetrahedron. 2003;**59**(17): 3117-3125