Chapter

Chemical Reactivity Properties and Bioactivity Scores of the Angiotensin II Vasoconstrictor Octapeptide

Norma Flores-Holguín, Juan Frau and Daniel Glossman-Mitnik

Abstract

Eight density functionals, CAM-B3LYP, LC-ωPBE, M11, MN12SX, N12SX, ωB97, ωB97X, and ωB97XD, in connection with the Def2TZVP basis set were assessed together with the SMD solvation model for the calculation of the molecular and chemical reactivity properties of the angiotensin II vasoconstrictor octapeptide in the presence of water. All the chemical reactivity descriptors for the systems were calculated via conceptual density functional theory (CDFT). The potential bioavailability and druggability as well as the bioactivity scores for angiotensin II were predicted through different methodologies already reported in the literature which have been previously validated during the study of different peptidic systems.

Keywords: angiotensin II, conceptual DFT, chemical reactivity, drug-likeness features, bioactivity scores

1. Introduction

In order to consider peptides and related compounds as the starting point for the development of medical drugs, it is mandatory to acquire a knowledge about their chemical reactivity properties as well as the bioactivity associated with them. From the basics of medicinal chemistry, it is known that drugs exert their effect by interacting with the active site of a receptor which is generally a protein [1]. These interactions rely on the different kinds of bindings between the pharmacophore and the chemical groups present in the active site and thus intimately related to their chemical reactivity from a molecular perspective [2, 3]. One of the most powerful tools to understand the chemical reactivity of interacting molecular systems within computational chemistry is probably the conceptual density functional theory (CDFT) [4, 5], also called chemical reactivity theory, which allows to accomplish this task by resorting to several global and local descriptors which are in turn related to variations in the electronic densities of the studied systems.

On the basis of the previous considerations, the objective of this work is to study the chemical reactivity of an octapeptide known as angiotensin II that acts

constricting the blood vessels and retaining the fluid in the kidneys [1], using the techniques of the conceptual DFT, determining their global reactivity properties, that is, of the molecule as a whole. Moreover, during the process of the development of new drugs, there is a need to learn about the drug-like properties of the involved molecular systems [6]. Thus, the descriptors of bioavailability and bioactivity (bioactivity scores) will be calculated through different procedures described in the literature [7, 8] trying to relate them with the calculated conceptual DFT descriptors.

2. Computational methodology

In the same way as we have proceeded in our recent studies [9–16], the computational tasks in this work have been done by considering the popular Gaussian 09 software [17]. Following the conclusions obtained from those studies, eight density functionals have been chosen, CAM-B3LYP, LC-ωPBE, M11, MN12SX [18], N12SX, ωB97, ωB97X, and ωB97XD, because they can be considered to be well-behaved for our purposes according to our proposed KID (for Koopmans in DFT) criteria [19–23] related to the approximate validity of the Koopmans' theorem within DFT [19–23]. For the calculation of the electronic properties, several model chemistries have been considered, based on the mentioned density functionals in connection with the Def2TZVP basis set, while a smaller Def2SVP was considered for the prediction of the most stable structures [24, 25]. In order to obtain accurate results, all calculations were performed using water, which is the universal biological solvent, simulated with the SMD model [26].

3. Results and discussion

The molecular structures of the conformers of the angiotensin II vasoconstrictor octapeptide graphically presented in **Figure 1** were optimized in the gas phase by means of the DFTBA model available in the software and then reoptimized with the eight density functionals described previously, the Def2SVP basis set, and water as the solvent. The calculation of the electronic properties was performed by using the same model chemistries but changing the basis set with the Def2TZVP one.

In order to verify the fulfillment of our proposed KID procedure, it is necessary to perform a comparison of the orbital energies with the results obtained by means of the vertical I and A through the ΔSCF criterium. To this end, the three main descriptors are linked by ε_H with $-I$, ε_L with $-A$, and their behavior in describing the HOMO-LUMO gap as $J_I = |\varepsilon_H + E_{gs}(N-1) - E_{gs}(N)|$,

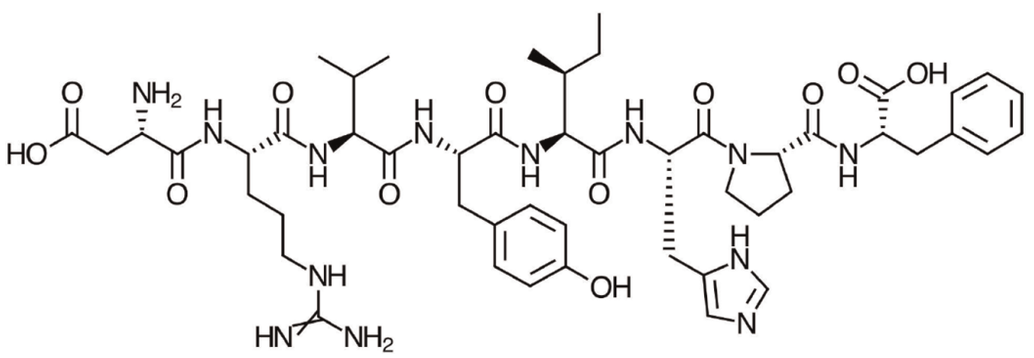

Figure 1.
Graphical sketch of the angiotensin II molecule.

	Eo	E+	E−	HOMO	LUMO
CAM-B3LYP	−1887.465	−1887.246	−1887.489	−7.462	0.828
LC-wBPE	−1887.192	−1886.966	−1887.223	−8.786	1.767
M11	−1887.317	−1887.090	−1887.345	−8.601	1.582
MN12SX	−1886.668	−1886.440	−1886.699	−6.164	−0.832
N12SX	−1887.505	−1887.288	−1887.531	−5.881	−0.679
ωB97	−1888.093	−1887.871	−1888.118	−8.658	1.890
ωB97X	−1887.933	−1887.711	−1887.959	−8.474	1.724
ωB97XD	−1887.814	−1887.592	−1887.840	−8.087	1.374
	SOMO	J_I	J_A	J_{HL}	**ΔSL**
CAM-B3LYP	−2.205	1.497	1.498	2.117	3.033
LC-wBPE	−3.509	2.635	2.619	3.715	5.276
M11	−3.124	2.412	2.333	3.356	4.706
MN12SX	−0.869	0.021	0.017	0.028	0.038
N12SX	−0.785	0.000	0.053	0.053	0.106
ωB97	−3.303	2.619	2.575	3.673	5.192
ωB97X	−3.144	2.432	2.410	3.424	4.868
ωB97XD	−2.809	2.059	2.073	2.922	4.183

Table 1.
Total electronic energies of angiotensin II (in au) for the neutral and charged species, the corresponding orbital energies (in eV), and the KID-related descriptors obtained with the five density functionals, the Def2TZVP basis set, and water as the solvent.

$J_A = |\varepsilon_L + E_{gs}(N) - E_{gs}(N+1)|$, and $J_{HL} = \sqrt{{J_I}^2 + {J_A}^2}$. Another descriptor, ΔSL (the difference between the SOMO and the LUMO), was also designed to guide in verifying the accuracy of the approximation [9–15]. The results of this analysis are presented in **Table 1**.

The overall conclusion that can be extracted from the inspection of the results presented in **Table 1** is that, in agreement with our previous studies on melanoidins and peptides, the model chemistries involving the MN12SX and N12SX density functionals are the best for verifying our proposed criteria of well-behavior.

3.1 Calculation of the global reactivity descriptors

By taking into account the KID procedure presented in our previous works together with the finite difference approximation, the global reactivity descriptors can be expressed as

Electronegativity	$\chi = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H)$	[4, 5]
Global hardness	$\eta = (I - A) \approx (\varepsilon_L - \varepsilon_H)$	[4, 5]
Electrophilicity	$\omega = \frac{\mu^2}{2\eta} = \frac{(I+A)^2}{4(I-A)} \approx \frac{(\varepsilon_L+\varepsilon_H)^2}{4(\varepsilon_L-\varepsilon_H)}$	[27]
Electrodonating power	$\omega^- = \frac{(3I+A)^2}{16(I-A)} \approx \frac{(3\varepsilon_H+\varepsilon_L)^2}{16\eta}$	[28]
Electroaccepting power	$\omega^+ = \frac{(I+3A)^2}{16(I-A)} \approx \frac{(\varepsilon_H+3\varepsilon_L)^2}{16\eta}$	[28]
Net electrophilicity	$\Delta\omega^{\pm} = \omega^+ - (-\omega^-) = \omega^+ + \omega^-$	[29]

where I is the ionization potential and A the electronic affinity, while ε_H and ε_L are the energies of the HOMO and LUMO, respectively.

The results for the global reactivity descriptors for the angiotensin II octapeptide based on the values of the HOMO and LUMO energies calculated with the MN12SX and N12SX density functionals are presented in **Table 2**.

As expected from the molecular structure of this peptide, its electrodonating ability is more important that its electroaccepting character. It can be seen that MN12SX and N12SX density functionals (which verify the KID criteria) give results different than those obtained from the calculation with the other three density functionals.

3.2 Bioactivity scores

The molecular properties that are related to the concept of drug-likeness and in particular those associated with the criteria proposed by Lipinski et al. [30, 31] for the prediction of oral bioavailability have been calculated by feeding the corresponding SMILES notations into the Molinspiration software readily available online (Slovensky Grob, Slovak Republic: https://www.mol inspiration.com). The results are presented in **Table 3**.

However, what the Lipinski's rule of five really measures is the oral bioavailability of a potential drug because this is the desired property for a molecule having drug-like character. Then, a different approach was followed by considering similarity searches in the chemical space of compounds with structures that can be

	Electronegativity (χ)	**Chemical hardness (η)**	**Electrophilicity (ω)**
MN12SX	3.3286	4.9685	1.1150
N12SX	3.1472	4.7664	1.0391
	Electrodonating power (ω^-)	**Electroaccepting power (ω^+)**	**Net electrophilicity ($\Delta\omega^{\pm}$)**
MN12SX	2.4725	1.1286	3.6011
N12SX	2.3225	1.0468	3.3693

Table 2.
Global reactivity descriptors for the angiotensin II molecule calculated with the MN12SX and N12SX density functionals with the Def2TZVP basis set and the SMD solvation model using water as the solvent.

Molecule	**Angiotensin II**
miLogP	−3.91
TPSA	406.33
nAtoms	75
nON	25
nOHNH	16
nviol	3
nrotb	30
volume	955.57
MW	1046.20

Table 3.
Molecular properties of the angiotensin II peptide calculated to verify the Lipinski's rule of five.

Molecule	Angiotensin II
GPCR ligand	−3.59
Ion channel modulator	−3.74
Kinase inhibitor	−3.78
Nuclear receptor ligand	−3.85
Protease inhibitor	−3.25
Enzyme inhibitor	−3.67

Table 4.
Bioactivity scores of the angiotensin II molecule calculated on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, and enzyme inhibitor interactions.

compared to those that are being studied and with known pharmacological properties. The same software was used for the calculation of the bioactivity scores which are a measure of the ability of the potential drug to interact with the different receptors, that is, to act as GPCR ligands or kinase inhibitors, to perform as ion channel modulators, or to interact with enzymes and nuclear receptors. The values of the bioactivity scores for angiotensin II are presented in **Table 4**.

These bioactivity scores for organic molecules can be interpreted as active (when the bioactivity score > 0), moderately active (when the bioactivity score lies between −5.0 and 0.0), and inactive (when the bioactivity score < −5.0). The angiotensin II peptide was found to be moderately bioactive toward the protease inhibitor and the GPCR ligand considered in the study.

4. Conclusions

In this chapter we have presented a new study performed on the chemical reactivity of the angiotensin II vasoconstrictor octapeptide based on the conceptual DFT as a tool to explain the molecular interactions.

The knowledge of the values of the global descriptors of the molecular reactivity of angiotensin II could be useful in the development of new drugs based on this compound or some analogs.

Finally, the molecular properties related to bioavailability and drug-likeness have been predicted using a proven methodology already described in the literature, and the descriptors used for the quantification of the bioactivity allowed to characterize the studied molecule as being moderately bioactive toward the protease inhibitor and the GPCR ligand considered in this study.

Acknowledgements

Norma Flores-Holguín and Daniel Glossman-Mitnik are researchers of CIMAV and CONACYT from which partial support is gratefully acknowledged. Daniel Glossman-Mitnik conducted this work while being a visiting lecturer at the University of the Balearic Islands. This work was also cofunded by the Ministerio de Economía y Competitividad (MINECO) and the European Fund for Regional Development (FEDER).

Conflict of interest

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

Author details

Norma Flores-Holguín[1†], Juan Frau[2†] and Daniel Glossman-Mitnik[1*†]

1 Centro de Investigación en Materiales Avanzados, Departamento de Medio Ambiente y Energía, Laboratorio Virtual NANOCOSMOS, Chihuahua, Mexico

2 Departament de Química, Universitat de les Illes Balears, Palma de Mallorca, Spain

*Address all correspondence to: daniel.glossman@cimav.edu.mx

†These authors contributed equally.

References

[1] Patrick GL. An Introduction to Medicinal Chemistry. Oxford, UK: Oxford University Press; 2013

[2] Rekka EA, Kourounakis PN. Chemistry and Molecular Aspects of Drug Design and Action. Boca Raton: CRC Press; 2008

[3] N'aray-Szabó G'a, Warshel A. Computational Approaches to Biochemical Reactivity. New York: Kluwer Academic Publishers; 2002

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

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

[6] Stromgaard K, Krogsgaard-Larsen P, Madsen U. Textbook of Drug Design and Discovery. Boca Raton, FL: CRC Press/Taylor and Francis Group; 2017

[7] Gupta GK, Kumar V. Chemical Drug Design. Berlin: Walter de Gruyter GmbH; 2016

[8] Gore M, Jagtap UB. Computational Drug Discovery and Design. New York: Springer Science+Business Media, LLC; 2018

[9] Frau J, Glossman-Mitnik D. Molecular reactivity and absorption properties of melanoidin blue-G1 through conceptual DFT. Molecules. 2018;**23**(3):559-515

[10] Frau J, Glossman-Mitnik D. Conceptual DFT study of the local chemical reactivity of the dilysyldipyrrolones A and B intermediate melanoidins. Theoretical Chemistry Accounts. 2018; **137**(5):1210

[11] Frau J, Glossman-Mitnik D. Conceptual DFT study of the local chemical reactivity of the colored BISARG melanoidin and its protonated derivative. Frontiers in Chemistry. 2018;**6**(136):1-9

[12] Frau J, Glossman-Mitnik D. Molecular reactivity of some Maillard reaction products studied through conceptual DFT. Contemporary Chemistry. 2018;**1**(1):1-14

[13] Frau J, Glossman-Mitnik D. Computational study of the chemical reactivity of the blue-M1 intermediate melanoidin. Computational and Theoretical Chemistry. 2018;**1134**:22-29

[14] Frau J, Glossman-Mitnik D. Chemical reactivity theory applied to the calculation of the local reactivity descriptors of a colored Maillard reaction product. Chemical Science International Journal. 2018;**22**(4):1-14

[15] Frau J, Glossman-Mitnik D. Blue M2: An intermediate melanoidin studied via conceptual DFT. Journal of Molecular Modeling. 2018;**24**(138): 1-13

[16] Frau J, Flores-Holguín N, Glossman-Mitnik D. Chemical reactivity properties, pKa values, AGEs inhibitor abilities and bioactivity scores of the mirabamides A–H peptides of marine origin studied by means of conceptual DFT. Marine Drugs. 2018; **16**(9):302-319

[17] Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian 09 Revision E.01. Wallingford, CT: Gaussian Inc.; 2016

[18] 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

[19] Borghi G, Ferretti A, Nguyen NL, Dabo I, Marzari N. Koopmans-compliant functionals and their performance against reference molecular data. Physical Review B. 2014;**90**(7):1

[20] Dabo I, Ferretti A, Poilvert N, Li Y, Marzari N, Cococcioni M. Koopmans' condition for density-functional theory. Physical Review B. 2010;**82**(11):115121

[21] 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

[22] Salzner U, Baer R. Koopmans' springs to life. The Journal of Chemical Physics. 2009;**131**(23):231101

[23] Vanfleteren D, Van Neck D, Ayers PW, Morrison RC, Bultinck P. Exact ionization potentials from wavefunction asymptotics: The extended Koopmans' theorem, revisited. The Journal of Chemical Physics. 2009;**130**(19):194104

[24] 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

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

[26] 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;**113**:6378-6396

[27] Parr RG, Szentpaly LV, Liu SB. Electrophilicity index. Journal of the American Chemical Society. 1999;**121**: 1922-1924

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

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

[30] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews. 2001;**46**:3-26

[31] Leeson P. Drug discovery: Chemical beauty contest. Nature. 2012;**481**(7382): 455-456