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Interaction of NHC derivative molecules with vascular endothelial growth factor receptor-2: A computational analysis

Neslihan Şahın*[a] and Elvan Üstün[b]

[a]Department of Basic Education, Faculty of Education, Cumhuriyet University, 58140 Sivas, Turkey

[b]Department of Chemistry, Faculty of Art and Science, Ordu University, 52200 Ordu, Turkey

E-mail: neslihan4458@gmail.com

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NHCs, an important ligand in organometallic chemistry, and their metal complexes have been frequently studied owing to their bioactivities. One of the most important research topics related to NHCs is cancer, which is still a major health problem. The promising results obtained from the anticancer activity studies of these molecules have provided motivation for synthesizing and analyzing new molecules. Theoretical calculation methods, which constitute an important part of recent drug-design studies, offer many valuable information. In this study, global reactivity descriptors of optimized [1-(2-methyl-2-propenyl)-3-(4-methylbenzyl)benzimidazolium]$^+$ and [1-(2-methyl-2-propenyl)-3-(4-isopropylbenzyl)benzimidazolium]$^+$ molecules and their Ag complexes were calculated with HOMO/LUMO energies; and interactions of the molecules with VEGFR-2, which is known as an effective receptor in many cancer types, were analyzed by molecular docking method.

Keywords: N-Heterocyclic carbenes, VEGFR-2, silver complexes, molecular docking.

Introduction

The first N-heterocyclic carbene (NHC)-metal complex was reported by Öfele and Wanzlick in 1968[1]. Applications of NHC chemistry have been increased since the first free carbene was isolated by Arduengo in 1991[2]. These ligands are widely used in organometallic chemistry as catalysts[3]. NHCs are neutral ligands that are easy to synthesize and modify with two donor electron and could be bonded to both soft and hard metals. Recently, medical applications of stable metal-NHC complexes have been spreadly studied. The antimicrobial, antitumor, antifungal, and antibiotic effects of NHC complexes containing gold, rhodium, ruthenium, and palladium have been investigated[4]. Garrison and Young examined the antimicrobial activity of Ag-NHC complexes[5]. In addition, significant results were obtained in the researches about the activity of Ag(I)-NHC complexes in human cancer cell lines like ovarian, breast, and cervical[6].

Angiogenesis is crucial for tumor development since cancer cells need oxygen and nutrients for growing. The capillary and vascular network is the way of the nourishment for cell, as well as the tumor's metastasis and spread to other parts of the body. Vascular endothelial growth factor (VEGF) is a family of homodimeric glycoproteins that is critical for lymphatic system and embryonic development of the blood vascular system and the expression amount of VEGF is thought to play a role in pathological diseases such as tumor angiogenesis[7]. VEGF receptors (VEGFR) are divided into three main subtypes, numbered 1, 2 and 3. VEGFR-2 is known as Kinase Insert Domain Receptor and overexpression of this receptor is observed in different kinds of cancer, namely cervical cancer, renal carcinoma, breast cancer, non-small cell lung cancer, and likewise[8]. Thus, blocking the VEGFR-2 expression could be an emerging way for designing a selective anticancer agent by angiogenesis inhibition[9].

Recently, it is a frequently used method to support experimental results with theoretical calculations since the theoretical results provide useful information about the activity of molecules[10]. In addition, preliminary information about the reactivity of molecules is useful in making predictions about the synthesis of new molecules. On the other hand, molecu-

lar docking methods provide the opportunity to analyze the interaction mechanisms of molecules *in silico*[11]. In this study, synthesized and characterized [1-(2-methyl-2-propenyl)-3-(4-methylbenzyl)benzimidazolium]$^+$ (**L1**) and [1-(2-methyl-2-propenyl)-3-(4-isopropylbenzyl)benzimidazolium]$^+$ (**L2**) molecules and their Ag complexes (**M1** and **M2**) whose anticancer activities was previously analyzed[12], were evaluated with Global Reactivity Descriptors. Additionally, molecular interactions with VEGFR-2 were investigated using molecular docking methods.

Results and discussion

DFT-based global reactivity descriptors have been used for analyzing structure/property correlations of inorganic compounds. Ionization potential (IP), electron affinity (EA), and electronegativity (χ) of the molecules were calculated from HOMO and LUMO energies of optimized molecules. While the highest IP and EA values were calculated for **M2**, the highest χ values were calculated for **M1**. Global softness (S) and chemical hardness (η) are used as indicators for the reactivity of the molecules. The stability of a molecule decreases with increasing global softness. Chemical hardness is just the reciprocal of global softness, so the higher the hardness, the lower the reactivity. It could be seen in Table 1 that the most reactive molecule is **M1** while the most stable one is **M2**. Electrophilicity index (ω) is regarded as an indication of the electrophilic force of the molecular system against a nucleophile. Among the calculated molecules included in this study, the highest electrophilic molecule is **M1**, while the highest nucleophilic one is **L2**.

NHCs (**L1** and **L2**) and Ag-NHC complexes (**M1** and **M2**) were docked to VEGFR-2 by using AutoDockTools 4.2. While **L1** molecule has the best conformation with –6.8 kcal/mol binding energy, –7.11 kcal/mol binding energy was calculated for **L2**. Both **L1** and **L2** were interacted with the same part of the target molecule. Ligands formed alkylic interactions with Ile886, Val896, Leu1017, Cys1022, and His1024, π-anionic interactions with Glu883 and Asp1044; and also, π-amide stacked with Cys1043. The interaction length between the ligands and VEGFR-2 target molecule is 4.47 Å for π-amide stacked while the interaction lengths are ranging between 4.11 Å and 4.66 Å for alkylic interactions, 4.12 Å and 5.02 Å for π-anion interactions. Molecular docking has been also performed for **M1** and **M2** which are Ag-NHC complexes of **L1** and **L2**, respectively. Both complexes were interestingly interacted within the same region of the VEGFR-2. Unlike the ligands, Ile890 is interacted with **M1** and **M2**. Moreover, Ile886 is interacted with chlorine of the complexes while it was interacted with benzylic part of the ligands. The interaction lengths between the ligands and VEGFR-2 target molecule are also close to each other ranging between 4.05 Å and 6.38 Å for alkylic interactions, and between 4.04 Å and 4.96 Å for π-anion interactions, while it is determined as 4.69 Å for π-amide stacked (Fig. 1).

Table 1. Calculated global reactivity descriptors of the molecules

	L1	L2	M1	M2
Ionization potential (IP)	9.246	9.208	9.312	9.313
Electron affinity (EA)	5.566	5.498	5.716	5.580
Electronegativity (χ)	7.406	7.353	7.514	7.446
Chemical potential (μ)	–7.406	–7.353	–7.514	–7.446
Global softness (S)	0.272	0.269	0.278	0.268
Chemical hardness (η)	1.840	1.855	1.798	1.866
Electrophilicity index (ω)	14.919	14.544	15.696	14.859

Calculation and docking method

DFT/TDDFT calculations for full unconstrained geometry optimizations tricarbonyl complexes were carried out with ORCA version 3.0.3 using the exchange functional according to Becke and the correlation functional suggested by Perdew hereafter called BP, with the resolution-of-the-identity (RI) approximation, a TZVP basis set, and the tightscf and grid4 options[13]. To speed up the calculations, TZVP/J auxiliary basis set was used. Global reactivity descriptors were also calculated by using HOMO and LUMO energies of optimized molecules.

Molecular docking was performed using AutoDock 4.2 with crystal structure of VEGFR-2 enzyme from RCSB protein data bank (PDB code: 1YWN). Water in the proteins were removed and polar hydrogen atoms and Kollman charges were evaluated for target molecules in the docking process. Gasteiger charges, randomized starting positions, optimizations, and torsions have been evaluated for ligand molecules. The genetic algorithm population was used as 150 while applying Lamarkian genetic algorithms.

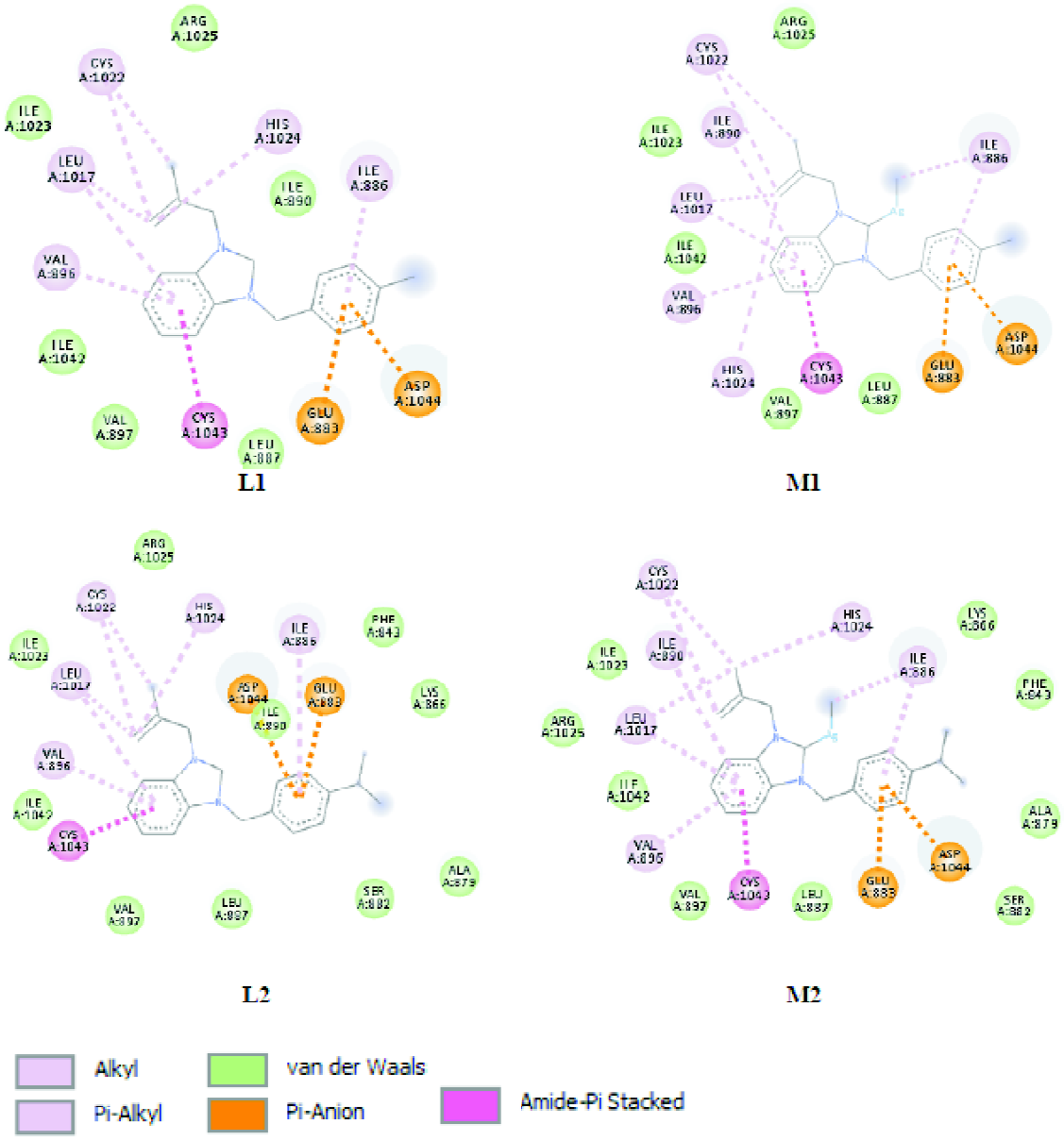

Fig. 1. Selected interactions of molecules with VEGFR-2 enzyme.

Conclusions

DFT-based global reactivity descriptors have been successfully applied to NHCs and Ag-NHC complexes for estimating structure/property correlations. From the molecular docking studies, it was found that some π-anion and alkylic interactions were involved in the binding of NHCs and Ag-NHC complexes to VEGFR-2. It was concluded that the global reactivity descriptor could be used for comparing the activities of the NHCs and Ag-NHC complexes. Moreover, the weak interactions between the molecules and the VEGFR-2 is compatible with the experimental results.

References

1. (a) H. W. Wanzlick and H. J. Schönherr, *Angew. Chem. Int. Ed.*, 1968, **7(2)**, 141; (b) K. Öfele, *J. Organomet. Chem.*, 1968, **12(3)**, P42.
2. A. J. Arduengo III, R. L. Harlow and M. J. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361.

3. (a) N. Ortega, D. T. D. Tang, S. Urban, D. Zhao and F. Glorius, *Angew. Chem. Int. Ed.*, 2013, **52(36)**, 9500; (b) H. Van Rensburg, R. P. Tooze, D. F. Foster and A. M. Slawin, *Inorg. Chem.*, 2004, **43(8)**, 2468; (c) D. Munz, C. Allolio, D. Meyer, M. Micksch, L. Roessner and T. Strassner, *J. Organomet. Chem*., 2015, **794**, 330; (d) J. Yang, L. L. Zong, X. T. Zhu, X. Y. Zhu and J. Y. Zhao, *Appl. Organomet. Chem*., 2020, 5985.
4. (a) T. V. Serebryanskaya, A. A. Zolotarev and I. Ott, *Med. Chem. Commun.*, 2015, **6(6)**, 1186; (b) P. V. Simpson, C. Schmidt, I. Ott, H. Bruhn and U. Schatzschneider, *Eur. J. Inorg. Chem*., 2013, **2013(32)**, 5547; (c) L. Boubakri, A. Chakchouk-Mtibaa, A. S. Al-Ayed, L. Mansour, N. Abutaha, A. H. Harrath, L. Mellouli, I. Özdemir, S. Yasar and N. Hamdi, *RSC Adv*., 2019, **9(59)**, 34406; (d) C. R. Shahini, G. Achar, S. Budagumpi, H. Müller–Bunz, M. Tacke and S. A. Patil, *J. Organomet. Chem*., 2018, **868**, 1; (e) T. Zou, C. N. Lok, P. K. Wan, Z. F. Zhang, S. K. Fung and C. M. Che, *Current Op. Chem. Biolog*., 2018, 43, 30.
5. J. C. Garrison and W. J. Youngs, *Chem. Rev*., 2005, **105(11)**, 3978.
6. (a) M. Marinelli, M. Pellei, C. Cimarelli, H. R. Dias, C., Marzano, F. Tisato and C. Santini, *J. Organomet. Chem*., 2016, **806**, 45; (b) S. Ray, R. Mohan, J. K. Singh, M. K. Samantaray, M. M. Shaikh, D. Panda and P. Ghosh, *J. Am. Chem. Soc*., 2007, **129(48)**, 15042; (c) T. Fatima, R. A. Haque, M. A. Iqbal, A. Ahmad, L. E. A. Hassan, M. Taleb-Agha and M. R. Razali, *J. Organomet. Chem*., 2017, **853**, 122.
7. (a) L. Morbidelli, S. Donnini, S. Filippi, L. Messori, F. Piccioli, P. Orioli, G. Sava and M. Ziche, *British J. Cancer*, 2003, **88(9)**, 1484; (b) G. Neufeld, T. Cohen, S. Gengrinovitch and Z. Poltorak, *The FASEB Journal*, 1999, **13(1)**, 9; (c) N. Ferrara, *Endocrine Reviews*, 2004, **25(4)**, 581; (d) D. J. Hicklin and L. M. Ellis, *Journal of Clinical Oncology*, 2005, **23(5)**, 1011; (e) M. Klagsbrun and P. A. D'Amore, *Cytokine & Growth Factor Reviews*, 1996, **7(3)**, 259; (f) N. Ferrara, K. A. Houck, L. B. Jakeman, J. Winer and D. W. Leung, *Journal of Cellular Biochemistry*, 1991, **47(3)**, 211.
8. (a) S. J. Modi and V. M. Kulkarni, *Med. Drug Discov.*, 2019, **2**, 100009; (b) I. Kim, A. M. Ryan, R. Rohan, S. Amano, S. Agular, J. W. Miller and A. P. Adamis, *Invest Ophthalmol Vis Sci*., 1999, **40**, 2115; (c) V. Joukov, K. Pajusola, A. Kaipainen, D. Chilov, I. Lahtinen, E. Kukk, O. Saksela, N. Kalkkinen and K. Alitalo, *EMBO J*., 1996, **15**, 290; (d) N. Ferrara, *European Journal of Cancer*, 1996, **32(14)**, 2413; (e) H. F. Dvorak, L. F. Brown, M. Detmar and A. M. Dvorak, *Am. J. Pathol.*, 1995, **146(5)**, 1029; (f) L. F. Brown, B. Berse, R. W. Jackman, K. Tognazzi, A. J. Guidi, H. F. Dvorak, D. R. Senger, J. L. Connolly and S. J. Schnitt, *Human Pathology*, 1995, **26(1)**, 86.
9. (a) K. Holmes, O. L. Roberts A. M. Thomas and M. J. Cross, *Cellular Signalling*, 2007, **19(10)**, 2003; (b) S. R. Silva, K. A. Bowen, P. G. Rychahou, L. N. Jackson, H. L. Weiss, E. Y. Lee, C. M. Townsend and B. M. Evers, *Int. J. Cancer*, 2011, **128**, 1045; (c) K. J. Kim, B. Li, J. Winer, M. Armanini, N. Gillett, H. S. Phillips and N. Ferrara, *Nature*, 1993, **362**, 841; (d) N. Ferrara, *The Oncologist*, 2004, **9**, 2; (e) K. Jin, Y. Zhu, Y. Sun, X. O. Mao, L. Xie and D. A. Greenberg, *PNAS*, 2002, **99(18)**, 11946.
10. (a) M. Musthafa, K. N. Aneesrahman, B. Perumalsamy, T. Ramasamy, R. Ganguly and A. Sreekanth, *J. Mol. Struct*., 2019, **1180**, 585; (b) J. A. Franze, T. F. Carvalho, C. Gaglieri, F. J. Caires, G. Bannach, R. C. Castro, O. Treu-Filho, M. Ionashiro and R. A. Mendes, *J. Therm. Anal. Calorim*., 2017, **127**, 1393; (c) L. M. Novena, S. S. Kumar and S. Athimoolam, *J. Mol. Struct*., 2016, **1116(15)**, 45; (d) P. Krawczyk, M. Bratkowska, T. Wybranowski, I. Hołyńska-Iwan, P. Cysewski and B. Jędrzejewska, *J. Mol. Liq.*, 2020, **314**, 113632; (e) Y. Maa, Y. Fengb, T. Diaoa, W. Zeng and Y. Zuo, *Journal of Molecular Structure*, 2020, **1204**, 127509; (f) P. Rajkumar, S. Selvaraj, R. Suganya, D. Velmurugan, S. Gunasekaran and S. Kumaresan, *Chemical Data Collections*, 2018, **15-16**, 10.
11. M. Berry, B. Fielding and J. Gamieldien, "Practical Considerations in Virtual Screening and Molecular Docking", Elsevier Inc., 2015.
12. S. Şahin-Bölükbaþý and N. Þahin, *J. Organomet. Chem*., 2019, **891**, 78.
13. (a) F. Neese, *Wiley Interdiscip. Rev. Comput. Mol. Sci*., 2012, **2**, 73; (b) L. Goerigk and S. Grimme, *Phys. Chem. Chem. Phys*., 2011, **13**, 6670; (c) P. J. Aittala, O. Cramariuc, T. I. Hukka, M. Vasilescu, R. Bandula and H. Lemmetyinen, J. *Phys. Chem. A*, 2010, **114(26)**, 7094.