Ordu Üniversitesi Bilim ve Teknoloji Dergisi
Ordu Üniv. Bil. Tek. Derg.

Ordu University Journal of Science and Technology
Ordu Univ. J. Sci. Tech.

E-ISSN: 2146-6459 2023, 13(1), 15-23 Araştırma Makalesi / Research Article
https://doi.org/10.54370/ordubtd.1206005

Synthesis, Characterization, and Molecular Docking Analysis of A Novel NHC Salt and Its Palladium-PEPPSI Complex

Neslihan Şahin[1], Elvan Üstün[2]

[1]Cumhuriyet University, Faculty of Education, Department of Mathematics and Science Education, Sivas
[2] Ordu University, Faculty of Art and Science, Department of Chemistry, Ordu

Geliş Tarihi / Received Date: 16.11.2022 Kabul Tarihi / Accepted Date: 30.01.2023

Abstract

PEPPSI type Pd complexes have wide applications in recent years. Serum albumin carries very important molecules such as oleic and linoleic acids, nitric oxide, vitamin B6, thyroid and so do many drugs. In this study, a novel NHC molecule and its Pd-PEPPSI complex were synthesized and characterized. Both the ligand and the complex were optimized by DFT-based calculation methods. The binding properties of the molecules with HSA were analyzed by molecular docking methods. Binding affinity of -8.04 kcal/mol and inhibition constant of 1.29 µM were determined for NHC salt while the binding affinity was calculated as -7.04 kcal/mol and the inhibition constant as 6.92 µM for Pd-PEPPSI complex.

Keywords: N-Heterocyclic carbene, benzimidazole, molecular docking, DFT, PEPPSI

Yeni Bir NHC Tuzunun ve Palladyum-PEPPSI Kompleksinin Sentezi, Karakterizasyonu ve Moleküler Doking Analizi

Öz

PEPPSI tipi Pd kompleksleri son yıllarda geniş uygulama alanına sahiptir. Serum albümini oleik ve linoleik asitler, nitrik oksit, vitamin B6, tiroid gibi çok önemli molekülleri ve pek çok ilacı taşır. Bu çalışmada, yeni NHC molekülü ve onun Pd-PEPPSI kompleksi sentezlendi ve karakterize edildi. Hem ligand hem de kompleks, DFT tabanlı hesaplama yöntemleriyle optimize edildi. Moleküllerin HSA ile bağlanma özellikleri moleküler doking yöntemleri ile analiz edildi. NHC tuzu için -8.04 kcal/mol bağlanma afinitesi ve 1.29 uM inhibisyon sabiti belirlenirken, Pd-PEPPSI kompleksi için bağlanma afinitesi -7.04 kcal/mol ve inhibisyon sabiti 6.92 uM olarak hesaplandı.

Anahtar Kelimeler: N-Heterosiklik karben, benzimidazol, moleküler doking, DFT, PEPPSI

Sorumlu Yazar / Corresponding Author: Neslihan Şahin neslihan@cumhuriyet.edu.tr

Introduction

Palladium-based organometallic complexes draw the attention of chemists because of their catalytic and bioactivity properties (Hussaini et al., 2019; Netherton & Fu, 2005; Scattolin et al., 2021;). Many important studies about Pd-based complexes with NHC ligands which have unique electronic and structural properties have been published (Fowler et al., 2019; Kaloğlu et al., 2021; Meng & Szostak, 2018). PEPPSI (Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation) type Pd complexes, which have wide application in recent years, are one of them. In addition to catalytic activities in C-C bond formation reactions, these compounds have also been recorded as significant enzyme inhibitors (Akkoç et al., 2016; Akkoç et al., 2017; Daşgın et al., 2021; Kaloğlu & Özdemir, 2019; Slimani et al., 2021). Moreover, new Pd-complexes were synthesized by using the ligand-exchange method instead of pyridine part of PEPPSIs, and these new complexes were diversified with different substitutions.

Serum albumin is one of the most important transport components of human blood. It carries both very important molecules such as oleic and linoleic acids, nitric oxide, vitamin B6, thyroid and steroid hormones and therapeutic agents for many drugs such as cancer, diabetes, Alzheimer Disease (Carter & Ho, 1994; Peters, 1985; Rabbani & Ahn, 2019). Therefore, binding properties of bioactivity candidate molecules with serum albumin must analyze. The strong binding with drug candidates can be either an advantage or a disadvantage. Weak affinity could be a problem about transportation, while strong interactions could inhibit to releasing of the agent in the target tissue (Al-Harthi et al., 2019; Tayyab & Feroz, 2021; Wani et al., 2021).

In this study, novel 1-isopropyl-3-(2,3,5,6-tetramethylbenzyl)-5,6-dimethylbenzimidazolium chloride, dichloro[1-isopropyl-3-(2,3,5,6-tetramethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]pyridinepalladium(II) complex were synthesized and characterized by ^{1}H NMR and ^{13}C{^{1}H} NMR (Figure 1). Both the ligand and the complex were optimized by DFT-based calculation methods. The binding properties of the molecules with HSA (Human Serum Albumin) were analyzed by molecular docking methods.

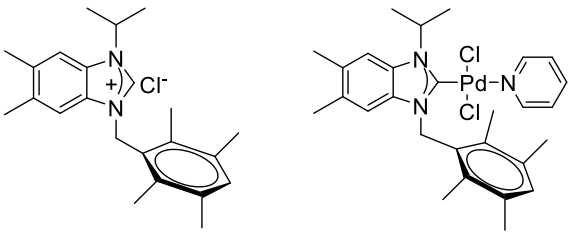

Figure 1. NHC Salt (left side) and Palladium-PEPPSI Complex (Right Side)

Material and Method

Experimental

Standard Schlenk line techniques were used for all synthesis procedures under argon atmosphere with flame-dried glassware. All reagents are Sigma Aldrich (Dorset, UK). Purification of all solvents was done by distillation methods over the drying agents, and they were transferred to the reaction matrix under Argon. Electrothermal 9100 was used for melting point detection by capillary tubes. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were taken using a Bruker As 400 Mercury spectrometer operating at 400 MHz (^{1}H), 100 MHz (^{13}C{^{1}H}) in $CDCl_3$ with tetramethylsilane as the internal reference.

Synthesis of 1-isopropyl-3-(2,3,5,6-tetramethylbenzyl)-5,6-dimethylbenzimidazolium Chloride

5,6-Dimethylbenzimidazole (10 mmol) was added slowly to a solution of NaH (11 mmol) in tetrahydrofuran (20 mL) in a Schlenk tube and the solution was mixed at room temperature for 1 h. Then, isopropyl bromide (10.1 mmol) was added to the mixture and the solution was stirred for 24 h at 60 ^{o}C. The solution was cooled to room temperature and tetrahydrofuran was evaporated under

the vacuum. Dichloromethane (50 mL) was added to the resulting solid. The last solution was distilled and 1-isopropyl-5,6-dimethylbenzimidazole was obtained. The 1-isopropyl-5,6-dimethylbenzimidazole (1 mmol) and 2,3,5,6-tetramethylbenzyl chloride (1 mmol) were mixed in DMF (5 mL) for 24 h at 80 ^{o}C. At the end of this period, white solid was precipitated. It was filtered and rinsed out with diethyl ether and dried under the vacuum. Yield: 83%; m.p. 183-184 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.79, 1.81 (s, 6H, NCH(C*H*$_3$)$_2$), 2.25 (s, 12H, CH_2C_6H(C*H*$_3$)$_4$-2,3,5,6), 2.25, 2.40 (s, 6H, NC_6H_2N(C*H*$_3$)$_2$-5,6), 5.05 (hept., 1H, NC*H*(CH$_3$)$_2$, *J*= 8 Hz), 5.97 (s, 2H, C*H*$_2C_6H$(CH$_3$)$_4$-2,3,5,6), 6.82 (s, 1H, Ar-*H*), 7.06 (s, 1H, Ar-*H*), 7.46 (s, 1H, Ar-*H*), 11.24 (s, 1H, NC*H*N). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 16.1 (NCH(*C*H$_3$)$_2$), 20.7, 20.8 (NC_6H_2N(*C*H$_3$)$_2$-5,6), 20.6, 22.2 (CH_2C_6H(*C*H$_3$)$_4$-2,3,5,6), 48.0 (N*C*H(CH$_3$)$_2$), 51.7 (*C*H$_2C_6H$(CH$_3$)$_4$-2,3,5,6), 113.1, 113.8, 128.4, 129.3, 130.4, 133.2, 133.9, 134.1, 134.8, 135.0, 136.7, 136.8 (Ar-*C*), 141.1 (N*C*HN).

Synthesis of Dichloro[1-isopropyl-3-(2,3,5,6-tetramethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]pyridinepalladium(II)

1-Isopropyl-3-(2,3,5,6-tetramethylbenzyl)-5,6-dimethylbenzimidazolium chloride (1 mmol), $PdCl_2$ (1 mmol) and K_2CO_3 (5 mmol) in pyridine (5 mL) were stirred at 80 ^{o}C for 4 h. After the reaction was finished, pyridine was removed under vacuum. To the resulting solid mixture, CH_2Cl_2 (10 mL) was added and filtered through a silica gel and celite layer in order to remove unreacted $PdCl_2$. The solvent in the reaction medium was removed under vacuum and dried. Crude product was crystallized in CH_2Cl_2/pentane and bright yellow dichloro[1-isopropyl-3-(2,3,5,6-tetramethylbenzyl)-5,6-dimethylbenzimidazole-2-ylidene]pyridinepalladium was obtained. Yield: 79%; m.p. 271-273 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.73, 1.74 (s, 6H, NCH(C*H*$_3$)$_2$), 2.17 (s, 12H, CH_2C_6H(C*H*$_3$)$_4$-2,3,5,6), 2.03, 2.23 (s, 6H, NC_6H_2N(C*H*$_3$)$_2$-5,6), 6.02 (s, 2H, C*H*$_2C_6H$(CH$_3$)$_4$-2,3,5,6), 6.35 (hept., 1H, NC*H*(CH$_3$)$_2$, *J*= 8 Hz), 6.21 (s, 1H, Ar-*H*), 7.01 (s, 1H, Ar-*H*), 7.23 (s, 1H, Ar-*H*), 7.27 (tt, 1H, Ar-*H*, *J* = 4 Hz), 7.67 (tt, 1H, Ar-*H*, *J* = 4 Hz), 8.86 (td, 1H, Ar-H, *J* = 4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 16.5 (NCH(*C*H$_3$)$_2$), 20.3, 20.4 (NC_6H_2N(*C*H$_3$)$_2$-5,6), 20.6, 21.2 (CH_2C_6H(*C*H$_3$)$_4$-2,3,5,6), 49.7 (N*C*H(CH$_3$)$_2$), 54.7 (*C*H$_2C_6H$(CH$_3$)$_4$-2,3,5,6), 112.0, 112.4, 124.4, 130.9, 131.0, 131.2, 131.6, 132.3, 134.2, 134.6, 135.2, 137.9, 151.2 (Ar-*C*), 160.2 (N*C*N).

Calculation Method

ORCA Package (version 4.2) was used for the optimizations of the molecules by DFT-based calculation methods (Neese, 2020; Neese, 2012; Neese et al., 2020). BP86 correlation functional that was suggested by Becke and Perdew was also used with the resolution-of-the-identity (RI) approximation and KDIIS, SOSCF. def2-SVP/J auxiliary basis set was used for speeding up the calculation which were carried out with def2-SVP basis set (Becke, 1988; Perdew, 1986; Neese, 2007; Serdaroğlu et al., 2021).

The crystal structure of the Human Serum Albumin was downloaded from RCSB protein data bank (https://www.rcsb.org/) with PDB ID:1bm0 (Sugio et al., 1999). Molecular docking performances were carried out with AutoDockTools 4.2 (Trott & Olson, 2010; Morris et al, 2008). Default number of torsions and the aromaticity criterions were used for ligand molecule. Additionally, Gastegier charges and randomized starting positions were used for the ligand. Polar hydrogens and Kollman charges were evaluated for the target molecule and also the waters were extracted from the HSA (Çelik et al., 2022; Üstün et al., 2022). Also, Lamarckian genetic algorithms with 150 populations were utilized (Bucur et al, 2022). Discovery Studio 4.1.0 were used for illustrations (https://www.3ds.com/).

Result and Discussion

Preparation and Characterization of NHC Salt and Its Pd-PEPPSI Complex

The synthetic route for the synthesis of NHC salt is shown in Figure 2. First, 5,6-dimethylbenzimidazole was reacted with isopropyl bromide. In the second step, obtained 1-isopropyl-5,6-dimethylbenzimidazole was reacted with 2,3,5,6-tetramethylbenzyl chloride.

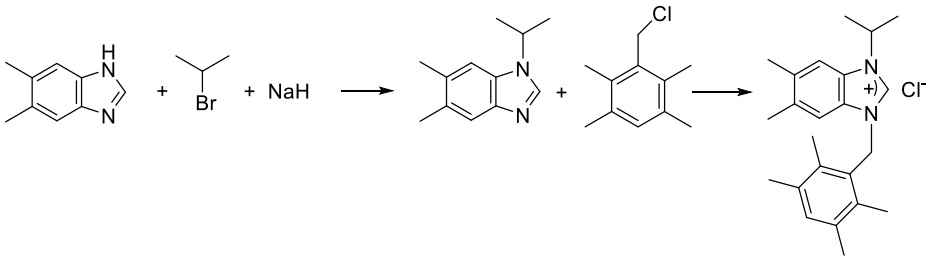

Figure 2. Synthesis of NHC Salt

The synthetic route of Pd-PEPPSI complex is shown in Figure 3. Pd-PEPPSI complex was synthesized from $PdCl_2$, the NHC salt obtained in the previous step and pyridine in the presence of K_2CO_3 as a base.

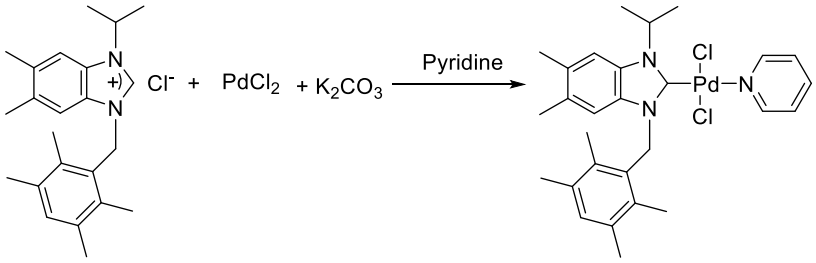

Figure 3. Synthesis of Pd-PEPPSI Complex

The newly synthesized compounds were characterized by ^{1}H NMR, and ^{13}C{^{1}H} NMR spectroscopies.

As seen in the ^{1}H NMR spectra (Figure 4), the NHC salt has an acidic NC*H*N proton which came at 11.24 ppm as a characteristic sharp singlet. When NHC salts formed to Pd-PEPPSI complex, they lost the acidic proton. At the ^{1}H NMR spectrum Pd-PEPPSI complex, the disappearance of the acidic proton is evidence of complex formation complex from NHC salt. N*C*HN carbon on NHC salt was observed at 141.1 ppm in the ^{13}C{^{1}H} NMR spectrum (Figure 5). After complexation, N*C*N carbon resonance on the Pd-PEPPSI complex shifted much downfield region compared to the NHC salt to 160.2 ppm. These results are in agreement with reported data for similar compounds (Doğan et al., 2011).

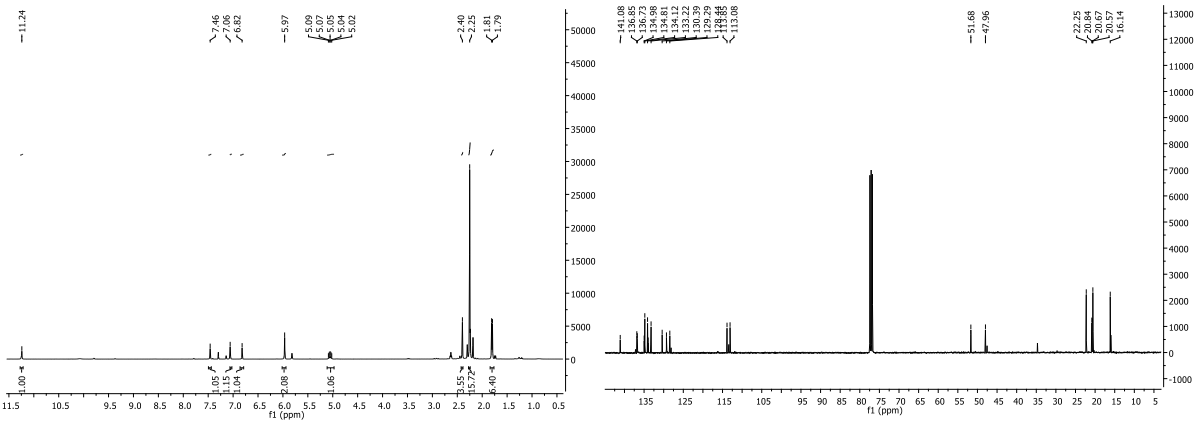

Figure 4. ^{1}H and ^{13}C{^{1}H} NMR Spectrums of NHC Salt

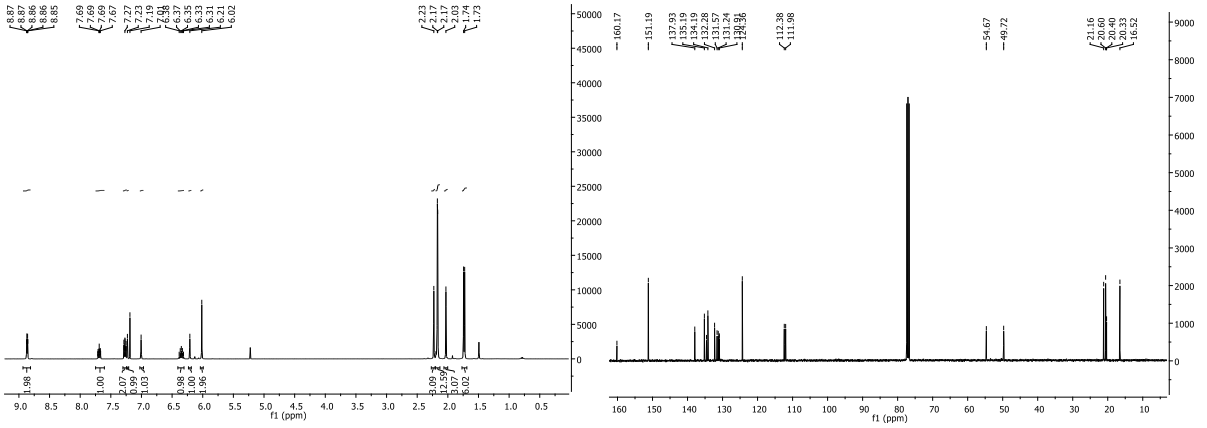

Figure 5. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectrums of Pd-PEPPSI Complex

The FT-IR spectra of the compounds contain some characteristic bands of the stretching vibrations of the C=N, C-N, C-H and C=C groups. Benzimidazole ring C=N vibrations of NHC salt was assigned at 1551 cm^{-1}. This vibration was seen with a shift in the Pd-PEPPSI complex at 1404 cm^{-1}. This negative shift is because of the electropositive metal center which pulls electron density towards itself and as a result of C=N vibrations shifts to the lesser energy region in the complex. And also, this shifting is an other evidence of formation Pd-PEPPSI complex.

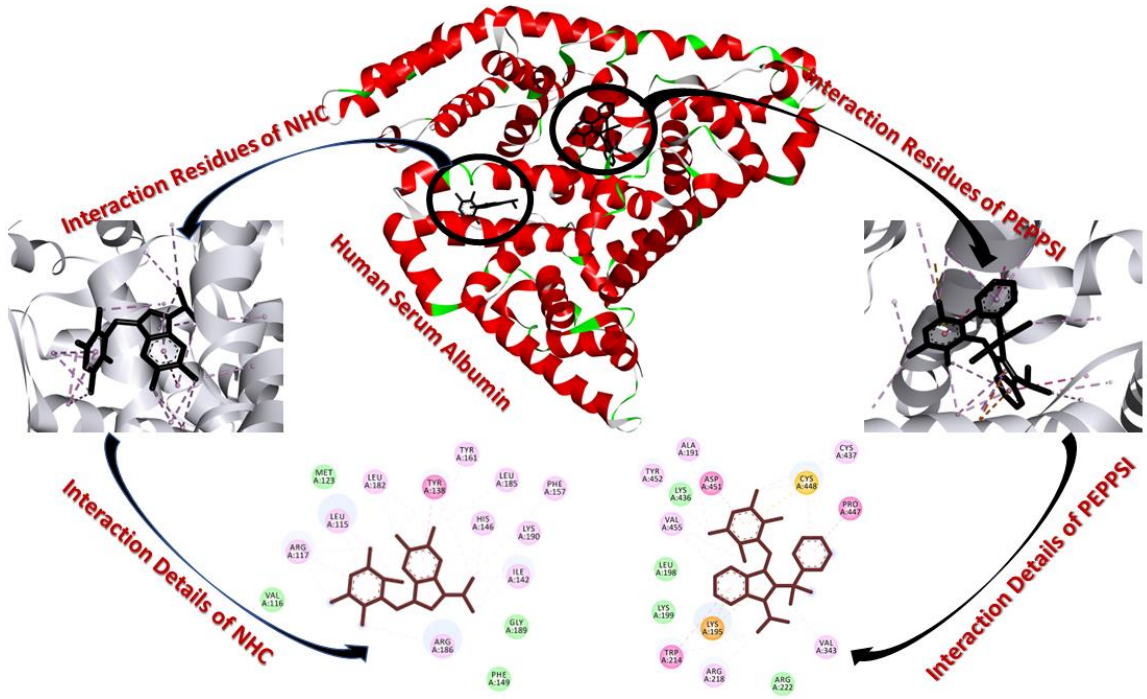

Figure 6. Interaction Residues and the Interaction Details of NHC Salt (left side) and PEPPSI Complex (right side) Against HSA

In recent years, the high agreement between theoretical and experimental results is remarkable. It is possible to have an idea about the stability of the molecules with DFT-based calculation methods (Serdaroğlu, 2002). In addition, it is also possible to acquire knowledge in several topics such as the bioactivities and inhibition capacities of molecules by using calculation methods such as molecular docking (Ata et al., 2022; Türker et al., 2022; Üstün & Şahin, 2022). These docking data provide foresight about the synthesis of more active molecules as well as provide data about the activity mechanisms of the molecules (Umare et al., 2022; Zhou et al., 2022). For this purpose, the interactions of molecules with a well-known biomacromolecule (enzymes, proteins...) which is

effective in pertinent bioactivity have been investigated in detail. One of the most important pharmacokinetic investigations of a molecule is the analysis of transport and release mechanisms (Matin et al., 2022). The drug molecules are frequently bound to HSA and delivered to the target tissue. The strength of the binding is very important in these transports. Strong binding is advantage safe transportation to the target tissue during transport, but it is trouble in the effective releasing in the target tissue (Molaei et al., 2022). Esfahlan and Azar (2016) analyzed the interactions between Glutathione and Serum Albumin, and they recorded that Glutathione formed many hydrogen bonds with −8.99 kcal/mol binding affinity, could bind serum albumins effectively, and transfer in the blood stream. Also, interactions between Serum Albumin and NHC molecules and their silver complexes were evaluated with the molecular docking method by Çelik et al. (2022). They recorded binding constants as ≈5 kcal/mol for NHCs and ≈7.5 kcal/mol for their silver complexes.

In this study, the NHC salt and its PEPPSI complex interacted with HSA by using molecular docking methods. According to the interaction of NHC with HSA, binding affinity of -8.04 kcal/mol and inhibition constant of 1.29 µM were determined. Alkyl interactions with Leu115, Arg117, Ile142, His146, Phe157, Tyr161, Leu182, Leu185, Arg186, and Lys190 as well as pi-pi T-shaped interaction with Tyr138 are effective in these obtained values. In addition, van der Waals interactions with Val116, Met123, Phe149, and Gly189 were also noted. The interactions of the Pd-PEPPSI complex with HSA are more multifarious. The interactions of pi-cation with Lys195, pi-sulfur with Cys448, pi-sigma and pi-amide with Trp214, Pro447, and Asp451 are also remarkable. Furthermore, alkylic interactions with Ala191, Arg218, Val343, Cys437, Tr452, and Tyr452 and van der Waals interactions with Leu198, Lys199, Arg222, and Lys436 were also recorded. As a result of these interactions, the binding affinity was calculated as -7.04 kcal/mol and the inhibition constant as 6.92 µM. Acquired results show that NHC molecule would bind more strongly than the PEPPSI complex (Figure 6).

Conclusions

The promising results that obtained in research on the bioactivity of PEPPSI-type palladium complexes provide motivation for new studies. Therefore, a new PEPPSI complex in which novel NHC salt was used was synthesized and characterized. The interaction of possible bioactive molecules with HSA is important in terms of analyzing the transportation of molecules and the interactions with proteins. In this study, the NHC salt and PEPPSI complex interact with different regions of HSA. it was determined that the total NHC salt had stronger interactions than PEPPSI. In future studies, it is planned to synthesize new complexes containing different NHC salt and to examine the interactions of these new ones.

Author Contribution

Neslihan Şahin, performed the experimental process. *Elvan Üstün*, performed the data collection and theoretical analysis. The authors read and approved the article.

Ethic

There are no ethical issues with the publication of this article.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ORCID

Elvan Üstün https://orcid.org/0000-0002-0587-7261

Neslihan Şahin https://orcid.org/0000-0003-1498-4170

References

Akkoc, S., Ilhan, I. Ö., Gök, Y., Upadhyay, P. J., & Kayser, V. (2016). In vitro cytotoxic activities of new silver and PEPPSI palladium N-heterocyclic carbene complexes derived from benzimidazolium salts. *Inorganica Chimica Acta, 449*, 75-81. https://doi.org/10.1016/j.ica.2016.05.001

Akkoç, S., Kayser, V., İlhan, İ. Ö., Hibbs, D. E., Gök, Y., Williams, P. A., Hawkins, B., & Lai, F. (2017). New compounds based on a benzimidazole nucleus: Synthesis, characterization and cytotoxic activity against breast and colon cancer cell lines. *Journal of Organometallic Chemistry, 839*, 98-107. https://doi.org/10.1016/j.jorganchem.2017.03.037

Al-Harthi, S., Lachowicz, J. I., Nowakowski, M. E., Jaremko, M., & Jaremko, Ł. (2019). Towards the functional high-resolution coordination chemistry of blood plasma human serum albumin. *Journal of Inorganic Biochemistry, 198*, 110716. https://doi.org/10.1016/j.jinorgbio.2019.110716

Ata, A. Ç., Tanrıverdi, A. A., Yıldıko, Ü., & Çakmak, İ. (2022). A heterocyclic compound hispidulin: Theoretical investigation by DFT/TD-DFT öethods and öolecular docking studies. *Süleyman Demirel Üniversitesi Fen Bilimleri Enstitüsü Dergisi, 26*(3), 515-522. https://doi.org/10.19113/sdufenbed.1126132

Becke, A. D. (1988). Density-functional exchange-energy approximation with correct asymptotic behavior. *Physical Review A, 38*(6), 3098. https://doi.org/10.1103/PhysRevA.38.3098

Bucur, P., Fülöp, I., & Sipos, E. (2022). Insulin complexation with cyclodextrins—A molecular modeling approach. *Molecules, 27*(2), 465. https://doi.org/10.3390/molecules27020465

Carter, D. C., & Ho, J. X. (1994). Structure of serum albumin. *Advances in Protein Chemistry, 45*, 153-203. https://doi.org/10.1016/S0065-3233(08)60640-3

Çelik, C., Üstün, E., Şahin, N., & Tutar, U. Antimicrobial and antibiofilm activity, and bovine serum albumin binding properties of benzimidazolium type NHC salts and their Ag (I)-NHC complexes. *Applied Organometallic Chemistry*, *36*(12) *e6891*. https://doi.org/10.1002/aoc.6891

Daşgın, S., Gök, Y., Celepci, D. B., Taslimi, P., Izmirli, M., Aktaş, A., & Gülçin, İ. (2021). Synthesis, characterization, crystal structure and bioactivity properties of the benzimidazole-functionalized PEPPSI type of Pd (II) NHC complexes. *Journal of Molecular Structure, 1228*, 129442. https://doi.org/10.1016/j.molstruc.2020.129442

Doğan, Ö., Demir, S., Özdemir, İ., & Cetinkaya, B. (2011) Palladium (II)-NHC complexes containing benzimidazole ligand as a catalyst for C-N bond formation, *Appl. Organomet. Chem. 25*, 163-167. https://doi.org/10.1002/aoc.1731

Fowler, J. M., Britton, E., Pask, C. M., Willans, C. E., & Hardie, M. J. (2019). Cyclotriveratrylene-tethered trinuclear palladium (ii)–NHC complexes; reversal of site selectivity in Suzuki–Miyaura reactions. *Dalton Transactions, 48*(39), 14687-14695. https://doi.org/10.1039/C9DT03400E

Hussaini, S. Y., Haque, R. A., & Razali, M. R. (2019). Recent progress in silver (I)-, gold (I)/(III)-and palladium (II)-N-heterocyclic carbene complexes: A review towards biological perspectives. *Journal of Organometallic Chemistry, 882*, 96-111. https://doi.org/10.1016/j.jorganchem.2019.01.003

Jahanban-Esfahlan, A., & Panahi-Azar, V. (2016). Interaction of glutathione with bovine serum albumin: Spectroscopy and molecular docking. *Food Chemistry, 202*, 426-431. https://doi.org/10.1016/j.foodchem.2016.02.026

Kaloğlu, M., Kaloğlu, N., & Özdemir, İ. (2021). Palladium-PEPPSI-NHC complexes bearing imidazolidin-2-ylidene ligand: Efficient precatalysts for the direct C5-arylation of N-methylpyrrole-2-carboxaldehyde. *Catalysis Letters, 151*(11), 3197-3212. https://doi.org/10.1007/s10562-021-03561-4

Kaloğlu, N., & Özdemir, İ. (2019). PEPPSI-Pd-NHC catalyzed Suzuki-Miyaura cross-coupling reactions in aqueous media. *Tetrahedron, 75*(15), 2306-2313. https://doi.org/10.1016/j.tet.2019.02.062

Matin, M. M., Uzzaman, M., Chowdhury, S. A., & Bhuiyan, M. M. H. (2022). In vitro antimicrobial, physicochemical, pharmacokinetics and molecular docking studies of benzoyl uridine esters against SARS-CoV-2 main protease. *Journal of Biomolecular Structure and Dynamics, 40*(8), 3668-3680. https://doi.org/10.1080/07391102.2020.1850358

Meng, G., & Szostak, M. (2018). Palladium/NHC (NHC= N-heterocyclic carbene)-catalyzed B-alkyl suzuki cross-coupling of amides by selective N–C bond cleavage. *Organic Şetters, 20*(21), 6789-6793. https://doi.org/10.1021/acs.orglett.8b02911

Molaei, P., Mahaki, H., Manoochehri, H., & Tanzadehpanah, H. (2022). Binding sites of anticancer drugs on human serum albumin (HSA): A review. *Protein and Peptide Letters, 29*(8), 651-675 https://doi.org/10.2174/0929866529666220426124834

Morris, G. M., Huey, R., & Olson, A. J. (2008). Using autodock for ligand-receptor docking. *Current Protocols in Bioinformatics, 24*(1), 8-14. https://doi.org/10.1002/0471250953.bi0814s24

Neese, F. (2007). Calculation of the zero-field splitting tensor on the basis of hybrid density functional and Hartree-Fock theory. *The Journal of Chemical Physics, 127*(16), 164112. https://doi.org/10.1063/1.2772857

Neese, F. (2012). The ORCA program system. Wiley interdisciplinary reviews: *Computational Molecular Science, 2*(1), 73-78. https://doi.org/10.1002/wcms.81

Neese, F., Wennmohs, F., Becker, U., & Riplinger, C. (2020). The ORCA quantum chemistry program package. *The Journal of Chemical Physics, 152*(22), 224108. https://doi.org/10.1063/5.0004608

Netherton, M.R., & Fu, G.C. (2005). Palladium-catalyzed cross-coupling reactions of unactivated alkyl electrophiles with organometallic compounds. In Tsuji, J. (eds) *Palladium in Organic Synthesis. Topics in Organometallic Chemistry*. Springer. https://doi.org/10.1007/b104127

Perdew, J. P. (1986). Density-functional approximation for the correlation energy of the inhomogeneous electron gas. *Physical Review B, 33*(12), 8822. https://doi.org/10.1103/PhysRevB.33.8822

Peters Jr, T. (1985). Serum albumin. *Advances in Pprotein Chemistry, 37*, 161-245. https://doi.org/10.1016/S0065-3233(08)60065-0

Rabbani, G., & Ahn, S. N. (2019). Structure, enzymatic activities, glycation and therapeutic potential of human serum albumin: A natural cargo. *International Journal of Biological Macromolecules, 123*, 979-990. https://doi.org/10.1016/j.ijbiomac.2018.11.053

Scattolin, T., Voloshkin, V. A., Visentin, F., & Nolan, S. P. (2021). A critical review of palladium organometallic anticancer agents. *Cell Reports Physical Science, 2*(6), 100446. https://doi.org/10.1016/j.xcrp.2021.100446

Serdaroglu, G. (2022). Experimental and theoretical spectroscopic studies of the electronic structure of 2-Ethyl-2-phenylmalonamide. *Physical Chemistry Research, 10*(3), 333-344. https://doi.org/10.22036/PCR.2021.304087.1966

Serdaroğlu, G., Şahin, N., Üstün, E., Tahir, M. N., Arıcı, C., Gürbüz, N., & Özdemir, İ. (2021). PEPPSI type complexes: Synthesis, x-ray structures, spectral studies, molecular docking and theoretical investigations. *Polyhedron, 204*, 115281. https://doi.org/10.1016/j.poly.2021.115281

Slimani, I., Mansour, L., Özdemir, I., Gürbüz, N., & Hamdi, N. (2021). Synthesis, characterization and catalytic activity of PEPPSI-type palladium–NHC complexes. *Inorganica Chimica Acta, 515*, 120043. https://doi.org/10.1016/j.ica.2020.120043

Sugio, S., Kashima, A., Mochizuki, S., Noda, M., & Kobayashi, K. (1999). Crystal structure of human serum albumin at 2.5 Å resolution. *Protein Engineering, 12*(6), 439-446. https://doi.org/10.1093/protein/12.6.439

Tayyab, S., & Feroz, S. R. (2021). Serum albumin: Clinical significance of drug binding and development as drug delivery vehicle. *Advances in Protein Chemistry and Structural Biology, 123*, 193-218. https://doi.org/10.1016/bs.apcsb.2020.08.003

Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry, 31*(2), 455-461. https://doi.org/10.1002/jcc.21334

Türker, D., Üstün, E., Günal, S., Yıldız, H., D. Düşünceli, S., & Özdemir, İ. (2022). Cyanopropyl functionalized benzimidazolium salts and their silver N-heterocyclic carbene complexes: Synthesis, antimicrobial activity, and theoretical analysis. *Archiv der Pharmazie, 355*(6), e2200041. https://doi.org/10.1002/ardp.202200041

Umare, M., Alkathiri, F. A., & Chikhale, R. (2022). Development of nucleic acid targeting molecules: Molecular docking approaches and recent advances. In Erman Salih Istifli (Eds.), *Molecular Docking*. Intech. https://doi.org/10.5772/intechopen.107349

Üstün, E., Şakar, D., Ayvaz, M. Ç., Çelebi, M. S., & Ertürk, Ö. (2022). CO-Releasing, antioxidant, antibacterial, zeta potential,t, and electrochemical analysis of [Mn (CO) 3 (bpy) L] OTf type complexes. *Polyhedron, 224*, 115997. https://doi.org/10.1016/j.poly.2022.115997

Üstün, E., Şahin, N. (2022). Synthesis, and characterization and in-silico analysis against SARS CoV-2 of novel benzimidazolium salts*. Orbital: The Electronic Journal of Chemistry, 14*(4), 205-211. http://dx.doi.org/10.17807/orbital.v14i4.16834

Wani, T. A., Bakheit, A. H., Zargar, S., Alanazi, Z. S., & Al-Majed, A. A. (2021). Influence of antioxidant flavonoids quercetin and rutin on the in-vitro binding of neratinib to human serum albumin. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 246*, 118977. https://doi.org/10.1016/j.saa.2020.118977

Zhou, Y., Jiang, Y., & Chen, S. J. (2022). RNA–ligand molecular docking: Advances and challenges. *Wiley Interdisciplinary Reviews: Computational Molecular Science, 12*(3), e1571. https://doi.org/10.1002/wcms.1571