Open Journal of Nano
ISSN: 2147-0081
(2023) 8–1
Research Article

Molecular Docking Study of Midostaurin, an Effective Drug in the Treatment of Myeloid Leukemia

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Submission Date: 12.04.2022 Acceptation Date: 14.07.2022

Abstract - Midostaurin ($C_{35}H_{30}N_4O_4$) is a multi-target kinase inhibitor used to treat some types of acute myeloid leukemia in combination with other chemotherapy agents. Firstly, the structural preferences of the Midostaurin were evaluated due to the importance to determine the most stable conformer of a bioactive molecule to elucidate its bioactivity. The conformational analysis of the Midostaurin molecule was performed using the PM3, a semi-experimental method. The three most stable conformers and their relative energies were determined. The Epidermal Growth Factor receptor (EGFR) is an integral membrane protein, and its over-expression is associated with the development of a wide variety of tumors. For this reason, EGFR inhibitors can act as anticancer drugs as preventing the growth of EGFR-expressing tumors and increasing the survival rates of patients. On the other hand, DNA is an important target for anticancer drugs. To elucidate the anticancer properties of Midostaurin, the molecular docking simulations were performed against EGFR and DNA targets. The binding modes and binding affinities of the ligand-target receptor complexes were determined. Midostaurin showed strong binding affinity to DNA (ΔG = -8.6 kcal/mol) and EGFR (ΔG = - 9.6 kcal/mol). The results revealed the significant anti-tumor effect of Midostaurin.

Keywords: Conformational analysis, DNA, EGFR, Midostaurin, Molecular docking

1. Introduction

Acute myeloid leukemia (AML) causes healthy hematopoietic cells to become mutated [1]. AML is defined as a malignant clonal disease that occurs as a result of incomplete maturation of blast cells and accumulation of abnormal immature cells first in the bone marrow and then rapidly in the blood [1-2]. It is known that AML disease has a genetic origin due to the transfer of mutated genes [1]. Whole genome sequencing, RNA sequencing and whole exome sequencing studies of AML disease have been important for a better understanding of its molecular structure. Genetic mutations, signaling, transcriptional regulation, nucleocytoplasmic shuttle, and chromatin modification have all been shown to produce genetic abnormalities in patients with AML [3].

Since AML is a heterogeneous disease, the response to treatment may vary depending on the risk factors of the patient. Treatment of AML disease is applied as chemotherapy and/or hematopoietic stem cell transplantation [4]. Nucleoside analogs and topoisomerase II inhibitors are two therapeutic chemotherapeutic agents used in the treatment of AML [5].

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DOI: **10.56171/ ojn.1102513**

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Fms-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase and is expressed almost exclusively in the hematopoietic compartment. Mutations of the Fms-like tyrosine kinase 3 gene (FTL3) are seen in 30% of adults with newly diagnosed AML . Midostaurin is a versatile small molecule kinase inhibitor that is used to treat adult patients with AML who have AML FLT3 mutations [6-7]. In investigations employing animal models, midostaurin has been identified as an FTL3 inhibitor [8].

GI (gastrointestinal) toxicities such as vomiting, nausea, and diarrhea are the Midostaurin side effects [9]. Patients in the Phase I study of midostaurin reported nausea and vomiting as adverse effects. In another study, it was stated that no hematological toxicity and cardiac conduction abnormality were encountered if Midostaurin was not used together with a different agent [10]. In some studies, skin rash, gastrointestinal and hepatic toxicity were observed in midostaurin treatment [11].

Anticancer drugs are divided into several classes as antitumor antibiotics, which reduce DNA/RNA synthesis and hence slow cancer cell growth and division [12], mitotic inhibitors, which interfere with the mitosis phase of cells [13], and topoisomerase inhibitors, which impede DNA transcription [14].

The ErbB family of receptor tyrosine kinases has four members. EGFR is one of them. Many malignancies have overexpressed or mutated the receptor, underlining its potential as a therapeutic cancer diagnostic. EGFR has a role in a variety of biological activities, including proliferation, angiogenesis, and cell death suppression. It is a transmembrane protein that transmits important signals from the epithelial cell surface to the intracellular domain for cell proliferation, motility, and adhesion regulation. Overexpressed EGFR sends various signals to cells, causing them to grow faster and live longer [15-18]. It also plays a role in cancer carcinogenesis. A better understanding of molecular signal transduction has led to the development of new cancer therapy tactics and approaches. As a result, turning off EGFR's signal transduction is expected to stop cancer cells from growing and surviving. Because EGFR plays such a significant role in cancer, it is being investigated as a possible therapeutic target for cancer treatment [15-19].

To enlighten the anticancer activity of Midostaurin, conformational preferences of the molecule were searched in this work the energetically favorable conformer was determined. Afterwards, by using the most stable conformer of Midostaurin, molecular docking analysis into B-DNA and EGFR tyrosine kinase domains were performed. The binding modes, and binding affinities were determined.

2. Materials and Methods

The conformational analysis of the Midostaurin was performed with Spartan06, a molecular modelling and computational chemistry program [20]. The semiempirical PM3 method [21-24], which provides a reasonably accurate, rapid estimation of the probable conformations of a molecule, was used. The obtained most stable conformation of the Midostaurin was used as the initial conformation of the ligand molecule for docking studies. For docking studies, the crystal structure of DNA (PDB ID: 1BNA) and EGFR tyrosine kinase domain (PDB ID: 2GS2) were obtained from the protein data bank (http://www.rcsb.org/pdb). The CAVER program [25] was used to determine the possible binding sites on the receptor surface. On the obtained active sites, molecular docking was performed using AutoDock-Vina software [26]. For docking simulations, a semi-flexible docking protocol was applied, where the target receptors (DNA or EGFR) were kept rigid while the ligand was kept flexible for being docked upon.

DOI: **10.56171/ ojn.1102513**

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3. Results and Discussions

3.1. Structure

Midostaurin has the five lowest energy conformers, as revealed by a conformational study. Table 1 lists the relative energies of the most stable three conformers, and Figure 1 depicts their molecular geometries.

Table 1. The energies of the most stable three conformations of Midostaurin.

Conformers	Total energy (kJ/mol)	Relative energy (kJ/mol)
Conformer I	-62.46	0
Conformer II	-62.45	0.01
Conformer III	-61.64	0.82

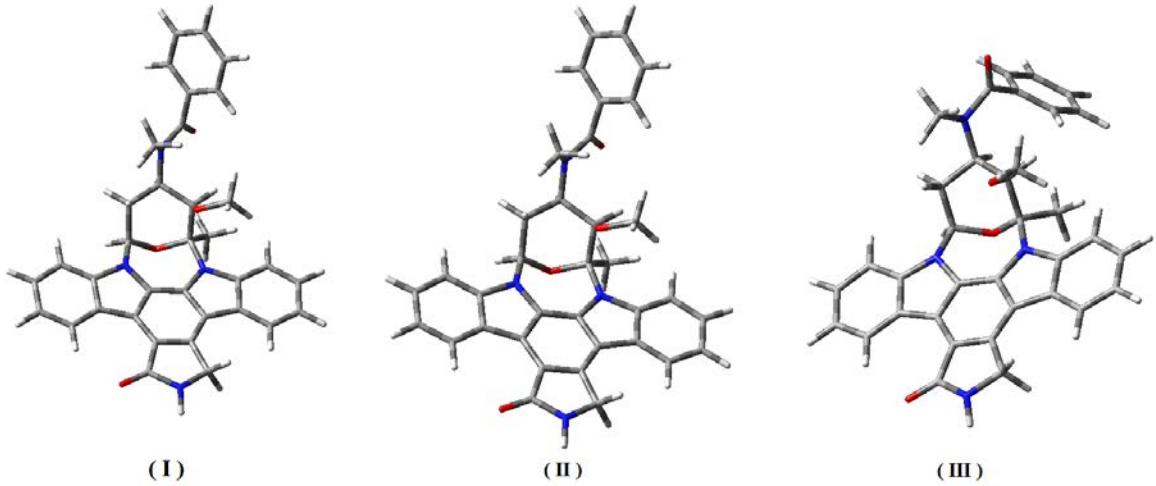

Figure 1. The obtained three lowest energy conformers of Midostaurin by conformational analysis.

3.2. Molecular Docking

As Midostaurin is known to have anticancer properties [27-28] we performed molecular docking studies with DNA and EGFR. Since DNA is the genetic information carrier, and the ability of anticancer agents to interfere the transcription and DNA replication has importance. On the other hand, EGFR is the target for anticancer agents, due to its role of signaling in proliferation, angiogenesis and suppression of cell death causing cancer.

AutoDockVina [26] was used to perform docking analyses. From the protein database [29], the crystal structure of DNA (PDB ID: 1BNA) was obtained and prepared for docking analysis. Water molecules were deleted, polar hydrogens were added, and Kollman's DNA charges were determined. The partial charges of the Midostaurin were computed using the Geistenger approach, and the active region of DNA was identified using a grid size of 40x40x40. The Midostaurin was found to interact with the nucleic acids DT8, DC9, DG10, DC13, and DC15 of DNA, through pi-alkyl, pi-pi-T shaped and pi-donor hydrogen bond interactions (Figure 2). The molecular docking simulations revealed the binding affinity (ΔG) of Midostaurin to DNA as -8.6 kcal/mol. The interactions between Midostaurin and DNA's nucleic acids are: Pi-alkyl interaction between DT8 and Midostaurin with a length of 5.28 Å; pi-pi-T shaped interactions between DC9 and Midostaurin with 5.23 and 5.28 Å lenths; pi-pi-T shaped and pi-donor hydrogen bond interactions between DG10 and Midostaurin with a length of 5.22 and 3.04 Å, respectively; pi-donor hydrogen bond interaction between DC13 and Midostaurin with a length of 3.15 Å; pi-donor hydrogen bond interactions between DC15 and Midostaurin with 2.57 and 3.24 Å lengths.

In the molecular docking study of 5-chlorouracil (5-FU) into DNA, 5-FU was found to interact with DG10, DC15 and DG16 nucleic acids, through hydrogen bond interactions [30]. In the molecular

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docking simulations, the docked cyclic dipeptide, cyclo(Ala-His), into DNA, it was found that the peptide interacted with nucleic acids DC9, DG10, DC11, DG16 and DA17 of DNA through hydrogen bonding interactions with 3.1, 2.39, 2.96, 2.53, 2.39 and 2.99 Å lengths, respectively [31]. In the molecular docking studies of Acalabrutinib, an anticancer drug, and DNA, Acalabrutinib was found to interact DG10 (2.11 and 2.14 A) and DG16 (2.06 and 2.47 A) by hydrogen bond interactions [32]. In another study, the N4-tetradentate thiosemicarbazone docked into DNA was found to interact with the DT8, DC9, DG12, DG16, DA17 and DA18 residues [33]. The results indicated that Midostaurin was docked in a similar active region of DNA as described in the literature [30-33].

For docking study of Midostaurin into EGFR, the crystal structure of EGFR tyrosine kinase domain (PDB ID: 2GS2) was obtained from the protein database [34] and prepared for docking analysis. Water molecules were deleted, polar hydrogens were added, and EGFR tyrosine kinase domain charges of Kollman were determined. The partial charges of the Midostaurin were computed using the Geistenger approach, and the active region of the EGFR tyrosine kinase domain was identified using a grid size of 40Å×40Å×40Å.

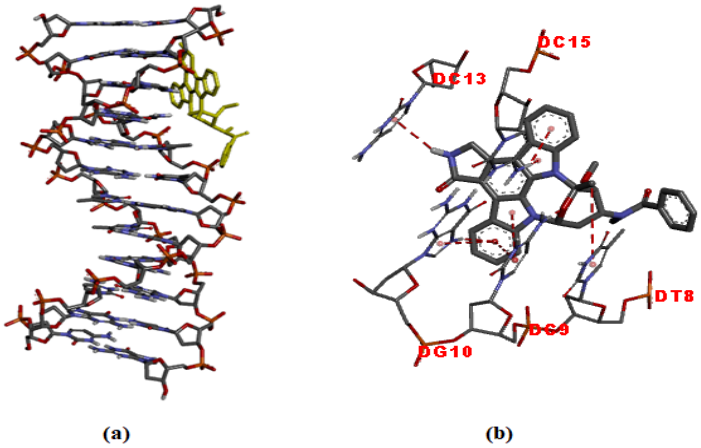

Figure 2. Molecular docked model of Midostaurin with DNA (a), The interactions between the Midostaurin and DNA are labeled using colored dashed lines (b) (ΔG = -8.6 kcal/mol).

After preparing the EGFR tyrosine kinase domain and the ligand for molecular docking analysis, docking simulations were conducted on the active site of the target protein. The binding affinity of the investigated ligand was found to be -9.6 kcal/mol. Figure 3 shows a 3D view and interactions of docked Midostaurin in the active region of the EGFR tyrosine kinase domain.

The interactions between Midostaurin and the EGFR target receptor are as follows:

A 4.74 Å length pi-alkyl interaction with Leu694; 4.51 Å length pi-alkyl interaction with Ala698; 4.58 and 4.87 Å lengths pi-alkyl and 5.38 Å length alkyl interactions with Val702; 4.73 Å length pi-alkyl interaction with Ala719; 4.63 Å length alkyl interaction with Lys721; 5.49 Å length pi-sulfur interaction with Met742; 5.06 and 5.42 Å lengths pi-alkyl interactions with Leu820.

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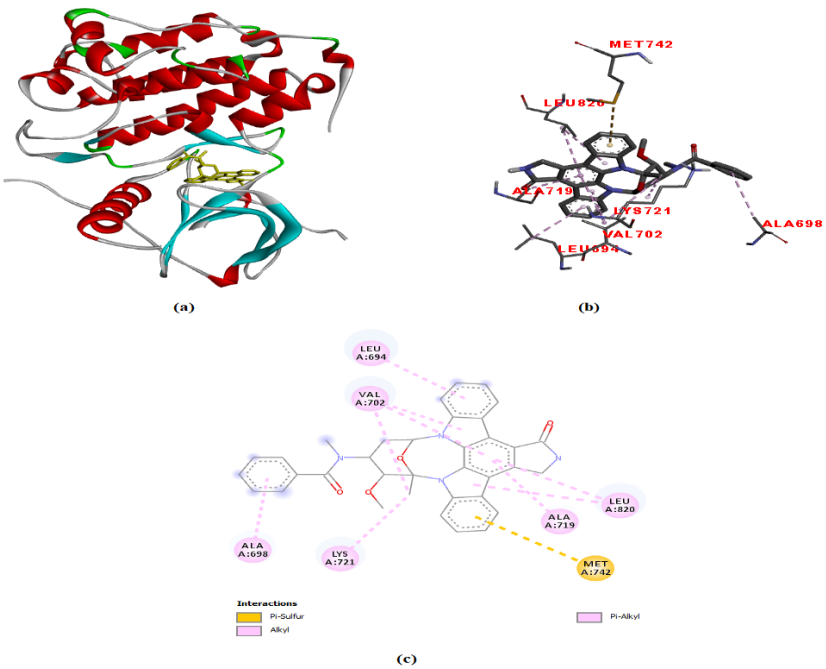

Figure 3. Molecular docked model of Midostaurin with EGFR tyrosine kinase domain (-9.6 kcal/mol) (a), 3D and 2D representations describing bindings of Midostaurin with the active site of EGFR tyrosine kinase domain (b-c).

Bahmani et al. investigated the pyrazolopyrimidine-based derivatives as EGFR inhibitors by molecular docking and multi-QSAR methods [35]. It was reported that the docked 1u compound of pyrazolopyrimidine-based derivative into EGFR, which showed the lowest binding energy to EGFR, was located in the locality of several hydrophobic amino acid residues including Phe699, Ala731, Ilu735, Val762, phe832, and Leu834. The result concluded that hydrophobic interactions play the most important role in the formation of the 1u-EGFR complex. In addition, it was reported that 1u compound interacted with Lys721, Glu722, Glu734, Asp737, Glu738 and Lys836 residues by electrostatic interactions and formed a hydrogen bond with Gly833 [35]. In the molecular docking study of the cyclic octopeptide CVRACGAD into EGFR, cyclic octopeptide was found to interact with Lys721, Thr766 andAla719, Asp831, Gly695, Gly772, Leu694, Leu768 residues of target receptor [36]. *In silico* docking studies of a series of 6, 7-dialkoxy-4-anilinoquinazolines against EGFR showed that compound 33 interacted with the Ser696, Gly700, Val702, Val704, Ala719, Lys721, Thr766, Met769, Glu738 and Asn818 residues of the target receptor, that were the same residues that the well-known anticancer drug Gefitinib interacted [37]. The comparison of the literature results with the molecular docking results of Midostaurin into EGFR revealed that investigated ligand was docked in a similar active region of EGFR as described in the literature [35-37].

To determine the binding free energy of small ligands to biological macromolecules, molecular mechanics Poisson-Boltzmann Surface Area (MM/PBSA) and molecular mechanics generalized born surface area (MM/GBSA) techniques are often used [38-43]. Since both the MM/PBSA and MM/GBSA techniques are important, Wang et al. (2019) [42] created a software that combines the two as the MM/PB(GB)SA approach.

The binding free energies of Midostaurin with DNA and the EGFR tyrosine kinase domain were computed in this investigation using Wang's program [42], which is based on the MM/PB(GB)SA approach. Using the MM/PB(GB)SA methods with the GAFF2 and ff14SB force field combinations and the GB6 process [42], the predicted binding free energies of Midostaurin with DNA and with the EGFR tyrosine kinase domain were -14.63 and -30.42 kcal/mol, respectively.

DOI: **10.56171/ ojn.1102513**

4. Conclusions

The conformational preferences of the Midostaurin were investigated using PM3 which is semi-experimental approach. The docking simulations were used to enlighten the biological activity of the title molecule in its most stable conformation. Because DNA and the EGFR tyrosine kinase domain are both prominent targets for anticancer medicines, docking simulations of Midostaurin with DNA and the EGFR protein were done to predict anticancer efficacy. Based on the binding affinity of -8.6 and -9.6 kcal/mol to DNA and EGFR, respectively, and their interactions with targets, molecular docking simulations suggest that Midostaurin ligand will have a significant anti-tumor effect.

Peer-review: Externally peer - reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by the Research funds of Istanbul University (ÖNAP-2423).

References (Please use for reference management programs like Mendeley or Zatero)

[1] Prada-Arismendy, J., Arroyave, J. C., Röthlisberger, S. 2017. Molecular biomarkers in acute myeloid leukemia, Blood reviews 31(1), 63-76.

[2] Kumar, C. C. 2011. Genetic abnormalities and challenges in the treatment of acute myeloid leukemia, Genes & cancer 2(2), 95-107.

[3] Rubnitz, J. E., Gibson, B., & Smith, F. O. 2008. Acute myeloid leukemia, Pediatric clinics of North America 55(1), 21-51.

[4] Schiller, G. J. 2014. Evolving treatment strategies in patients with high-risk acute myeloid leukemia, Leukemia & lymphoma 55(11), 2438-2448.

[5] Absalon, M. J., Smith, F. O. 2009. Treatment strategies for pediatric acute myeloid leukemia, Expert opinion on pharmacotherapy 10(1), 57-79.

[6] Stone, R. M., Mandrekar, S. J., Sanford, B. L., Laumann, K., Geyer, S., Bloomfield, C. D., Thiede, C., Prior, T.W., Döhner, K., Marcucci, G., Lo-Coco, F., Klisovic, R.B., Wei, A., Sierra, J., Sanz, M.A., Brandwein, J.M., de Witte, T., Niederwieser, D., Appelbaum, F.R., Medeiros, B.C., Tallman, M.S., Krauter, J., Schlenk, R.F., Ganser, A., Serve, H., Ehninger, G., Amadori, S., Larson, R.A., Döhner, H. 2017. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation, New England Journal of Medicine 377(5), 454-464.

[7] Schlenk, R. F., Weber, D., Fiedler, W., Salih, H. R., Wulf, G., Salwender, H., Schroeder, T., Kindler, T., Lübbert, M., Wolf, D., Westermann, J., Kraemer, D., Götze, K.S., Horst, H.A., Krauter, J., Girschikofsky, M., Ringhoffer, M., Südhoff, T., Held, G., Derigs, H.G., Schroers, R., Greil, R., Grießhammer, M., Lange, E., Burchardt, A., Martens, U., Hertenstein, B., Marretta, L., Heuser, M., Thol, F., Gaidzik, V.I., Herr, W., Krzykalla, J., Benner, A., Döhner, K., Ganser, A., Paschka, P., Döhner, H. 2019. Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD, Blood 133(8), 840-851.

[8] Levis, M. 2017. Midostaurin approved for FLT3-mutated AML, Blood 129(26), 3403-3406.

[9] Stemler, J., Koehler, P., Maurer, C., Müller, C., Cornely, O. A. 2020. Antifungal prophylaxis and novel drugs in acute myeloid leukemia: the midostaurin and posaconazole dilemma, Annals of Hematology 99(7), 1429-1440.

[10] Gallogly, M. M., Lazarus, H. M. 2016. Midostaurin: an emerging treatment for acute myeloid leukemia patients, Journal of Blood Medicine 7, 73.

[11] Berger, T., Rozovski, U., Moshe, Y., Yaari, S., Frisch, A., Hellmann, I., Apel, A., Aviram, A., Koren-Michowitz, M., Yeshurun, M., Ram, R., Raanani, P., Ofran, Y., Wolach, O. 2019. Midostaurin in

combination with intensive chemotherapy is safe and associated with improved remission rates and higher transplantation rates in first remission-a multi-center historical control study, Annals of hematology 98(12), 2711-2717.

[12] Patil, Y., Amitay, Y., Ohana, P., Shmeeda, H., Gabizon, A. 2016. Targeting of pegylated liposomal mitomycin-C prodrug to the folate receptor of cancer cells: Intracellular activation and enhanced cytotoxicity, Journal of Controlled Release 225, 87-95.

[13] Michalska, M., Schultze-Seemann, S., Bogatyreva, L., Hauschke, D., Wetterauer, U., Wolf, P. 2016. In vitro and in vivo effects of a recombinant anti-PSMA immunotoxin in combination with docetaxel against prostate cancer, Oncotarget 7(16), 22531.

[14] Olsen, I. H., Knigge, U., Federspiel, B., Hansen, C. P., Skov, A., Kjær, A., Langer, S. W. 2014. Topotecan monotherapy in heavily pretreated patients with progressive advanced stage neuroendocrine carcinomas, Journal of Cancer 5(8), 628.

[15] Pomerantz, R. G., & Grandis, J. R. 2004. The epidermal growth factor receptor signaling network in head and neck carcinogenesis and implications for targeted therapy, In Seminars in oncology 31(6), 734-743.

[16] Shiomitsu, K., Johnson, C. L., Malarkey, D. E., Pruitt, A. F., Thrall, D. E. 2009. Expression of epidermal growth factor receptor and vascular endothelial growth factor in malignant canine epithelial nasal tumours, Veterinary and comparative oncology 7(2), 106-114.

[17] Higgins, R. J., Dickinson, P. J., LeCouteur, R. A., Bollen, A. W., Wang, H., Wang, H., Corely, L.J., Moore, L.M., Zang, W., Fuller, G. N. 2010. Spontaneous canine gliomas: overexpression of EGFR, PDGFRα and IGFBP2 demonstrated by tissue microarray immunophenotyping, Journal of neuro-oncology 98(1), 49-55.

[18] Lee, H. J., Xu, X., Choe, G., Chung, D. H., Seo, J. W., Lee, J. H., Lee, C.T., Jheon, S., Sung, S.W., Chung, J. H. 2010. Protein overexpression and gene amplification of epidermal growth factor receptor in nonsmall cell lung carcinomas: Comparison of four commercially available antibodies by immunohistochemistry and fluorescence in situ hybridization study, Lung Cancer 68(3), 375-382.

[19] Duan, L., Wu, R., Ye, L., Wang, H., Yang, X., Zhang, Y., Chen, X., Zuo, G., Zhang, Y., Weng, Y., Luo, J., Tang, M., Shi, Q., He, T., Zhou, L. 2013. S100A8 and S100A9 are associated with colorectal carcinoma progression and contribute to colorectal carcinoma cell survival and migration via Wnt/β-catenin pathway, PloS one 8(4), e62092.

[20] Shao, Y., Molnar, L. F., Jung, Y., Kussmann, J., Ochsenfeld, C., Brown, S. T., Gilbert, A.T.B., Slipchenko, L.V., Levchenko, S.V., O'Neill, D.P., DiStasio Jr, R.A., Lochan, R.C., Wang, T., Beran, G.J.O, Besley, N.A., Herbert, J.M., Lin, C.Y., Voorhis, T.V., Chien, S.H., Sodt, A., Steele, R.P., Rassolov,V.A., Maslen, P.E., Korambath, P.P., Adamson, R. D., Austin, B., Baker, J., Byrd, E.F.C., Dachsel, H., Doerksen, R.J., Dreuw, A., Dunietz, B.D., Dutoi, A. D., Furlani,T. R., Gwaltney, S. R., Heyden, A., Hirata, S., Hsu, C.P., Kedziora, G., Khalliulin, R. Z., Klunzinger, P., Lee, A. M., Lee, M.S., Liang, W. Z., Lotan, I., Nair, N., Peters, B., Proynov, E. I., Pieniazek, P. A., Rhee, Y. M., Ritchie, J., Rosta, E., Sherrill, C. D., Simmonett, A. C., Subotnik, J. E., Woodcock, H. L., Zhang, W., Bell, A. T., Chakraborty, A. K., Chipman, D. M., Keil, F.J., Warshel, A., Hehre, W.J., Schaefer, H.F., Kong, J., Krylov, A.I., Gill, P.M.W., Head-Gordon, M. 2006. Advances in methods and algorithms in a modern quantum chemistry program package, Physical Chemistry Chemical Physics 8(27), 3172-3191.

[21] Stewart, J. J. 1989[a]. Optimization of parameters for semiempirical methods I. Method, Journal of computational chemistry 10(2), 209-220.

[22] Stewart, J. J.1989[b]. Optimization of parameters for semiempirical methods II. Applications, Journal of computational chemistry 10(2), 221-264.

[23] Stewart, J. J.1991. Optimization of parameters for semiempirical methods. III Extension of PM3 to Be, Mg, Zn, Ga, Ge, As, Se, Cd, In, Sn, Sb, Te, Hg, Tl, Pb, and Bi, Journal of computational chemistry 12(3), 320-341.

[24] Stewart, J. J. 2004. Optimization of parameters for semiempirical methods IV: extension of MNDO, AM1, and PM3 to more main group elements, Journal of Molecular Modeling 10(2), 155-164.

[25] Jurcik, A., Bednar, D., Byska, J., Marques, S. M., Furmanova, K., Daniel, L., Kokkonen, P., Brezovsky, J., Strnad, O., Stourac, J., Pavelka, A., Manak, M., Damborsky,J., Kozlikova, B. 2018. CAVER Analyst 2.0: analysis and visualization of channels and tunnels in protein structures and molecular dynamics trajectories, Bioinformatics 34(20), 3586-3588.

[26] 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.

[27] El Fitori, J., Su, Y., Büchler, P., Ludwig, R., Giese, N. A., Büchler, M. W., Quentmeier, H., Hines, O.J., Herr, I., Friess, H. 2007. PKC 412 small-molecule tyrosine kinase inhibitor: Single-compound therapy for pancreatic cancer, Cancer 110(7), 1457-1468.

[28] Stone, R. M., Fischer, T., Paquette, R., Schiller, G., Schiffer, C. A., Ehninger, G.,Cortes, j., Kantarjian, H.M., DeAngelo,D.J., Huntsman-Labed, A., Dutreix, C., del Corral, A., Giles, F. 2012. Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia, Leukemia 26(9), 2061-2068.

[29] Drew, H. R., Wing, R. M., Takano, T., Broka, C., Tanaka, S., Itakura, K., Dickerson, R. E. 1981. Structure of a B-DNA dodecamer:Conformation and Dynamics, Proceedings of the National Academy of Sciences 78(4), 2179–2183.

[30] Akalin, E., Celik, S., Akyuz, S. 2020. Molecular Modeling, Dimer Calculations, Vibrational Spectra, and Molecular Docking Studies of 5-Chlorouracil, Journal of Applied Spectroscopy 86(6), 975-985.

[31] Celik, S., Yilmaz, G., Ozel, A. E., Akyuz, S. 2022. Structural and spectral analysis of anticancer active cyclo (Ala–His) dipeptide, Journal of Biomolecular Structure and Dynamics 40(2), 660-672.

[32] Celik, S., Demirag, A.D., Arslan, S., Ozel, A.E.., Akyuz, S. 2022. Conformational, Toxic, Physicochemical and Molecular Docking Analysis of the Anticancer Acalabrutinib Molecule, Open Journal of Nano 7(1), 1-9.

[33] Eğlence-Bakır, S., Celik, S., Şahin, M., Ozel, A. E., Akyuz, S., & Ülküseven, B. 2021. Synthesis, molecular modelling, FT-IR, Raman and NMR characterization, molecular docking and ADMET study of new nickel (II) complex with an N4-tetradentate thiosemicarbazone, Journal of Biomolecular Structure and Dynamics 39(12), 4212-4224.

[34] Zhang, X., Gureasko, J., Shen, K., Cole, P. A., Kuriyan, J. 2006. An allosteric mechanism for activation of the kinase domain of epidermal growth factor receptor, Cell 125(6), 1137-1149.

[35] Bahmani, A., Tanzadehpanah, H., Hosseinpour Moghadam, N., & Saidijam, M. (2021). Introducing a pyrazolopyrimidine as a multi-tyrosine kinase inhibitor, using multi-QSAR and docking methods. Molecular Diversity, 25(2), 949-965.

[36] Mishra, A., & Dey, S. (2019). Molecular docking studies of a cyclic octapeptide-cyclosaplin from sandalwood. Biomolecules, 9(11), 740.

[37] Chandregowda, V., Kush, A. K., & Reddy, G. C. (2009). Synthesis and in vitro antitumor activities of novel 4-anilinoquinazoline derivatives. European journal of medicinal chemistry, 44(7), 3046-3055.

[38] Hao, G. F., Wang, F., Li, H., Zhu, X. L., Yang, W. C., Huang, L. S., Wu, J.W., Berry, E.A.., Yang, G. F. 2012. Computational discovery of picomolar Q o site inhibitors of cytochrome bc 1 complex, Journal of the American Chemical Society 134(27), 11168-11176.

[39] Cheron, N., Jasty, N., Shakhnovich, E. I. 2016. OpenGrowth: an automated and rational algorithm for finding new protein ligands, Journal of medicinal chemistry 59(9), 4171-4188.

[40] Hao, G. F., Jiang, W., Ye, Y. N., Wu, F. X., Zhu, X. L., Guo, F. B., Yang, G. F. 2016. ACFIS: a web server for fragment-based drug discovery, Nucleic acids research 44(W1), W550-W556.

[41] Yang, J. F., Wang, F., Jiang, W., Zhou, G. Y., Li, C. Z., Zhu, X. L., Hao, G.F., Yang, G. F. 2018.

PADFrag: a database built for the exploration of bioactive fragment space for drug discovery, Journal of chemical information and modeling 58(9), 1725-1730.

[42] Wang, Z., Wang, X., Li, Y., Lei, T., Wang, E., Li, D., Kang, Y.,Zhu, F., Hou, T. 2019. farPPI: a webserver for accurate prediction of protein-ligand binding structures for small-molecule PPI inhibitors by MM/PB (GB) SA methods, Bioinformatics 35(10), 1777-1779.

[43] Wang, E., Sun, H., Wang, J., Wang, Z., Liu, H., Zhang, J. Z., Hou, T. 2019. End-point binding free energy calculation with MM/PBSA and MM/GBSA: strategies and applications in drug design, Chemical reviews 119(16), 9478-9.