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Clarification of the Structure of 1,4-Bis(2-Chloro-4-Nitrophenyl)Piperazine Molecule and Its Molecular Docking Analysis with DNA

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Piperazine, Anticancer, DNA, Molecular Docking, Conformational analysis

Abstract

Piperazine-derived molecules have important anticancer activities. In this study, conformational analysis was performed using the Spartan06 program to elucidate the structure of 1,4-Bis(2-chloro-4-nitrophenyl)piperazine ($C_{16}H_{14}Cl_2N_4O_4$). Among the conformations determined as a result of the conformation analysis, the molecular structure with the lowest energy was determined. DNA is an important target for anticancer molecules. For this reason, the interaction of 1,4-Bis(2-chloro-4-nitrophenyl)piperazine with DNA (PDB ID: 1BNA) was investigated through docking simulations. The obtained lowest energy conformer of the title molecule was taken as the starting geometry of the ligand for docking simulations with target DNA. As a result, the binding affinity and the binding mode of the title molecule with DNA were evaluated. 1,4-Bis(2-chloro-4-nitrophenyl)piperazine has -7.5 and -7.4 kcal/mol binding affinities to DNA, in two different sites. Depending on the molecular docking studies, the1,4-Bis(2-chloro-4-nitrophenyl)piperazine was predicted to possess strong anti-tumor effects.

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1 INTRODUCTION

Cancer is described as the fast division of cells as a result of DNA damage in cells, resulting in the formation of new cells and their spread throughout the body. The reason why cancers are fatal is due to their metastasis feature [1]. According to the reports of the World Health Organization, 19.3 million new cancer cases were encountered in 2020 and 10.0 million deaths were reported [2]. Various cancer treatments known as surgery, radiation and chemotherapy are insufficient to eradicate the disease and make patients' lives better. Therefore, many researchers have worked to find selective, less side-effective treatment options that provide more effective treatment against cancer cells, and studies are still ongoing. [3].

Piperazine and pyrazole derivatives play an important role in anticancer activity. Piperazine skeleton and its analogs have a heterocyclic ring included in anticancer, antifungal, antibacterial, antimalarial, antipsychotic, HIV protease inhibitors and antidepressant effective compound structures. In medicinal chemistry, the piperazine ring has importance due to its flexible binding properties and its ability to be a potent and selective ligand for various biological targets [4]. Piperazine analogs are known to show antiproliferative (inhibiting cell growth) activity against colon, prostate, breast, lung and leukemia tumors. Some piperazines have been shown to inhibit the synthesis of microtubules (which are the structures that form the cytoskeleton, they hold or release the receptors), cell cycle and angiogenesis, which are necessary for tumor cell growth and metastasis. Piperazine-derived compounds arrested cell growth in myeloid leukemia and human erythroleukemia cells [5]. For instance, Yarm et al. produced piperazine-derived compounds and tested their efficiency in liver, breast, colon, stomach, and endometrial cancer cells in a research. These chemicals have been proven to have a strong cytotoxic impact on the proliferation of malignant cells as a result of study [6].

Çalışkan et al. reported the anti-inflammatory and anticancer activity of 1,5- and 1,3-diaryl pyrazole derivative molecules [7]. Cancer and inflammation have been associated in epidemiological research, and patients with chronic inflammatory illnesses are more likely to develop cancers such as bladder, cervical, gastric, skin, intestinal, and pancreatic cancers [7]. Xia et al. synthesized 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide and hydrazone derivatives and evaluated their inhibitory activity on A549 lung cancer cells. As a result of their studies, they determined that these derivatives showed anticancer activity by inducing apoptosis in A549 cells depending on the dose and time [8,9]. Williams et al., in their study on piperazine-derived molecules, developed compounds that inhibit FGFR2 activity. Fibroblast growth factors (FGF 1-10 and 16-23) are mitogenic signaling molecules with roles such as angiogenesis, wound healing, cell migration, embryonic development and neuronal overgrowth. FGFRs are transmembrane catalytic receptors with intracellular tyrosine kinase activity. Alterations in FGFR2 gene activity have been associated with many cancers. Increase in altered gene expression increases many cancer-related events such as proliferation, cell movements, and angiogenesis. Overexpression of FGFR2 has been detected in gastric, prostate, ovarian, cervical, pancreatic, head and neck cancers [10].

In a study on the anticancer activity of pyrazole derivatives, it was observed that some compounds bearing the pyrazole ring showed anticancer activity by inhibiting the cyclin-dependent kinase-1 (CDK-1) enzyme involved in cell division [3]. In another study, it was concluded that pyrazole-5-carboxylate, pyrazole-5-carboxamide and pyrazole 5-carbohydrazide derivative compounds exhibited anticancer activity against A549 lung cancer cells by inducing apoptosis or autophagy [8,11]. Lee et al. have determined that the piperazine derivative molecule they synthesized inhibits the proliferation of cancerous cells by conducting 11 different cell culture studies. In the molecule G2/M phase, it induced cell death and apoptosis by decreasing the Bcl-2 protein level. With its high bioavailability, half-life and suitable plasma level, the molecule is a suitable drug candidate [12]. Nassar et al. found that 1- [1- [3-methylphenyl] -5-phenyl-4- (phenylsulfonyl) -1H-pyrazol-3-yl] ethanone is the most active molecule in the series they synthesized, with higher anti-inflammatory activity and fewer gastrointestinal side effects when compared to the reference substance indomethacin [13].

4,5-dihydro-1,5-diaryl-1H-pyrazole 3-substituted heteroazole derivatives were also produced by Dekhane et al. In the carrageenan-induced paw edema test, the product, a tetrazole derivative from the molecules, demonstrated superior anti-inflammatory action than diclofenac sodium [14]. TNF-α is a cytokine produced in activated monocytes and macrophages, and its excessive and uncontrolled production has been observed in viral diseases such as rheumatoid arthritis, inflammation, inflammatory bowel diseases, multiple sclerosis, asthma, HIV, herpes simplex, cytomegalovirus and Epstein-Barr. IL-1 and IL-8 are other pro-inflammatory cytokines observed in all conditions involving inflammation. Inhibition of these cytokines by inhibition of p38 kinase is important in the control and regression of these diseases [15]. Bandgar et al. synthesized 3,5-diarylpyrazole derivative compounds and evaluated their anticancer and anti-inflammatory activities. Inhibitory activity has been observed in derivatives of serine substituted with chlorine and bromine halogens in breast, lung, leukemia, prostate and colon cancer cells and in the generation of TNF-α and IL-6 cytokines [16]. ENR is a promising target for narrow-spectrum

antimalarial drug research since FAS differs from Plasmadium falciparum and humans. The major enzyme of the type II fatty acid synthesis system (FAS) is enoyl-acyl carrier protein reductase (ENR) [17]. Kumar et al. found that a 1,5-disubstituted pyrazole derivative chemical had strong inhibitory efficacy in their investigation [18].

A molecule may have several spatial arrangements, with the same molecular formula, that are called conformational isomers that can be obtained by rotating around its single bonds. The most stable conformer of a molecule is determined by energy minimization procedure [19]. Since in bioactive molecules, presence of structure-activity relationship, the obtaining the most stable conformer of a molecule is important.

DNA has become the target for the prediction of novel potent anticancer agents [20,21]. DNA, the deoxyribonucleic acid molecule, contains the instructions an organism needs to develop, live, and reproduce. It controls all the chemical changes in cells. For this reason, to interfere with transcription and DNA replication, a major step in cell growth and division, DNA is a major target for anticancer drug interaction.

The molecule we examined is a piperazine derivative with anticancer activities. In the literature, detailed studies on the elucidation of the structure of the 1,4-Bis(2-chloro-4-nitrophenyl) piperazine molecule and the analysis of molecular docking with DNA have not been encountered. In this study, firstly, the most stable conformation of the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule was determined. Afterwards, the molecular docking simulations were performed to identify its interaction with the target DNA. The binding affinity and the interacting sites were determined.

2 MATERIALS AND METHODS

The conformational analysis was carried out with the Spartan06 software [22], which employed the AM1 semiempirical quantum mechanical approach [23],and the possible conformations of the investigated molecule were evaluated, and the most stable conformation was determined. The molecular docking simulations were performed by using AutoDock Vina program [24]. AutoDock Vina is a well known an open-source program for molecular docking and virtual screening. In this study, for molecular docking, a semi-flexible docking protocol, where the ligand (1,4-Bis(2-chloro-4-nitrophenyl)piperazine) is flexible and target DNA is rigid, was applied.

3 RESULTS AND DISCUSSION

3.1 Structure

Table 1 compares the relative energies of the four lowest energy conformers of 1,4-Bis(2-chloro-4-nitrophenyl) piperazine (Figure 1) that were obtained by conformational analysis.

Table 1. The relative energies of the four most stable conformers.

Conformers	Relative energy (kj/mol)
(I)	0
(II)	0.01
(III)	3.52
(IV)	7.3

3.2 Molecular Docking

The 1,4-Bis(2-chloro-4-nitrophenyl)piperazine has known to have anticancer properties [25]. In this study, a molecular docking simulation was performed to reveal its interaction with DNA.

The crystal structure of DNA (PDB ID: 1BNA) was acquired with reference to the protein database [26] and the docking analysis of the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule was carried out using AutoDockVina [24]. DNA was modified for the docking study by removing water molecules and adding polar hydrogens, and the DNA charges of Kollman were calculated before the docking study. The Geistenger method was used to compute the partial charges of the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule, and the active area of DNA was identified as 40Å × 40Å × 40Å. The following are the calculation findings for the two most stable dockings discovered after molecular docking.

The docking simulations of the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule within the DNA revealed two possible binding sites. The most stable binding of the ligand to target DNA revealed ΔG = -7.5 kcal/mol binding affinity. The 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule interacted with the nucleic acids of DG4 and

DA6 by pi-alkyl interactions and hydrogen bond (See Figure 2). The active site of DNA that was obtained in this study was consistent with the literature [27,28]. The revealed interacting sites and distances are as follows: DG4 and 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule have a pi-alkyl interaction with lengths of 4.89 Å; DA6 and 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule have a hydrogen bond interaction with lengths of 1.92 Å. The 3D interaction scheme of the ligand and target DNA is shown in Fig 2. In previous studies on cationic pentapeptide (Glu-Gln-Arg-Pro-Arg) and DNA interaction [29] and on vanillin-derived imine compound and DNA interactions [30], ligands were found to interact with DNA through DG4 nucleic acid. In the case of the molecular docking study between Val-Met dipeptide and DNA by Celik et al., [28] it was also found that the ligand made hydrogen bonds with DG4. These results indicate that 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule docked into DNA, in the same active site where previous ligands were docked.

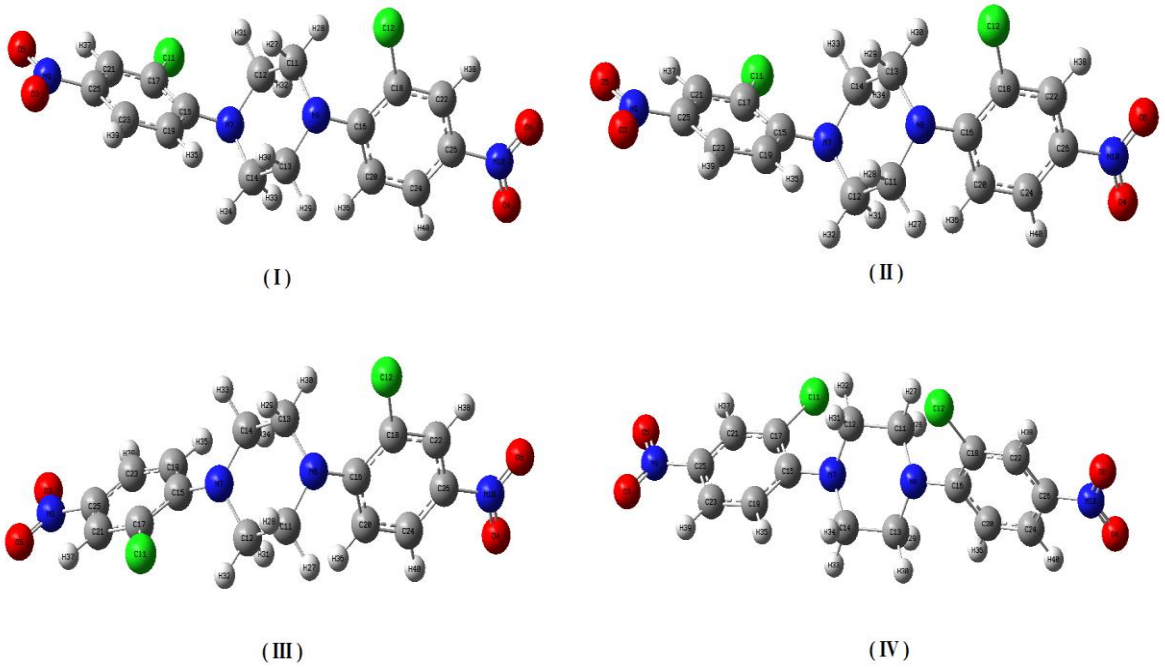


Figure 1. The four lowest energy conformers of the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule, obtained by conformational analysis.

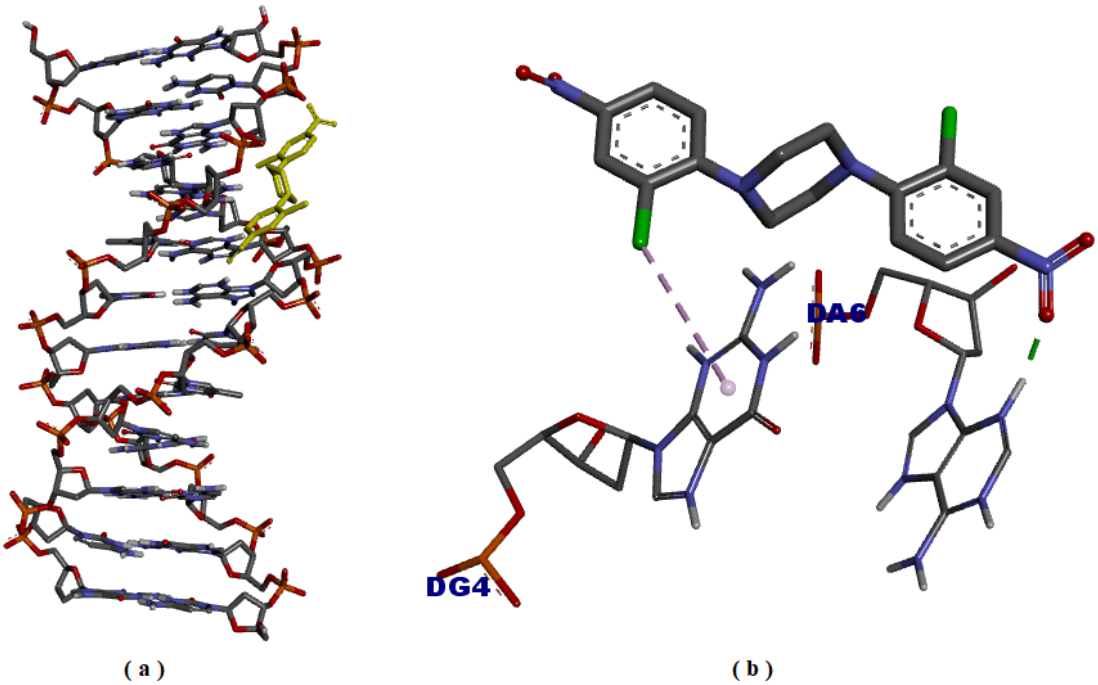
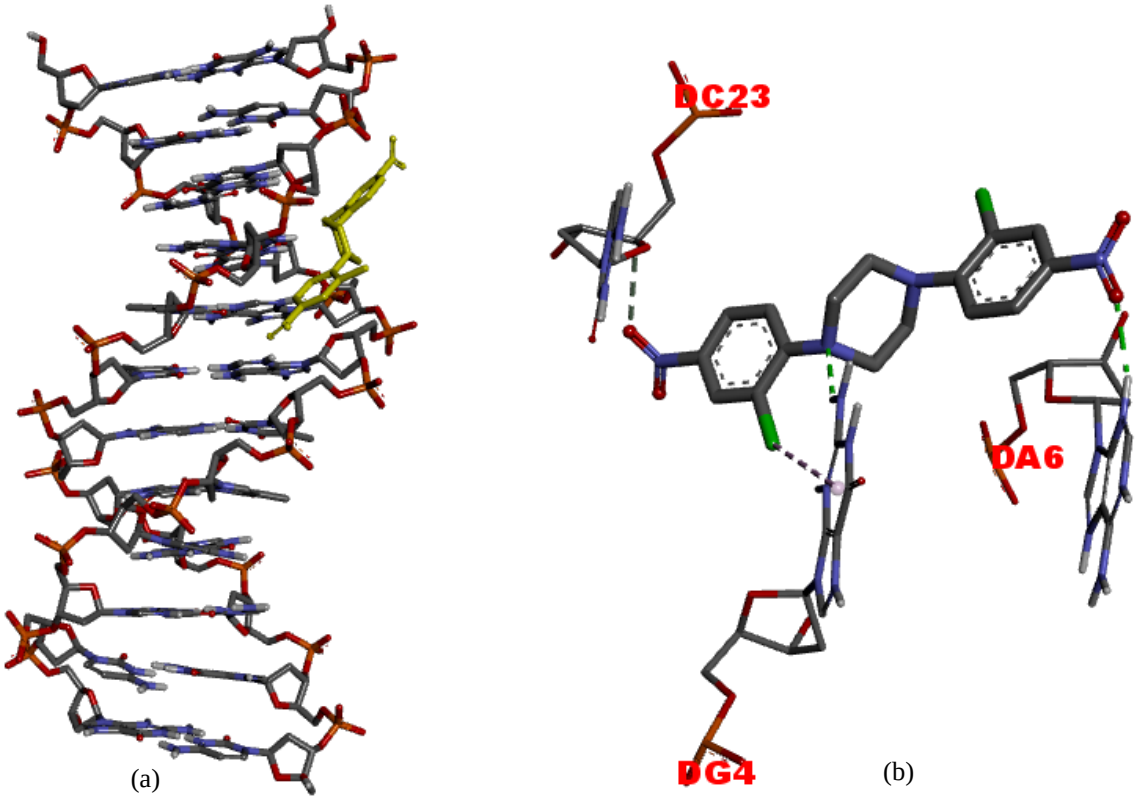


Figure 2. 1,4-Bis(2-chloro-4-nitrophenyl)piperazine docked with DNA in a molecular docking model (a), Coloured dashed lines(b) (-7.5 kcal/mol) are used to indicate the interactions between 1,4-Bis(2-chloro-4-nitrophenyl)piperazine and DNA.

In the second possible binding site, the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule was found to attach to the nucleic acids DG4,DA6, and DC23 via pi-alkyl interactions, hydrogen, and carbon hydrogen bonds (See Figure 3.). The binding affinity was found to be ΔG = -7.4 kcal/mol. The revealed interacting sites and distances are as follows:

Pi-alkyl interaction (4.91 Å) and hydrogen bond (2.51 Å) between DG4 and 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule; Hydrogen bond interaction with lengths of 2.18 Å between DA6 and 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule; Carbon hydrogen bond interaction with lengths of 3.76 Å between DC23 and 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule.



(a) (b)

Figure 3. Molecular docked models of 1,4-Bis(2-chloro-4-nitrophenyl)piperazine with DNA (a),The interactions between the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine and DNA are labeled using coloured dashed lines(b) (-7.4 kcal/mol).

4 CONCLUSION

A semi-experimental method AM1 was used to analyze the conformation of the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule. Because the protein-ligand interactions are important in drug design, docking simulations were performed to assess the biological activity of the title molecule in its most stable conformer. The docking of the 1,4-Bis(2-chloro-4-nitrophenyl)piperazine molecule with DNA was investigated to reveal its inhibitory action. As a result of docking studies, it was found that 1,4-Bis(2-chloro-4-nitrophenyl)piperazine has -7.5 and -7.4 kcal/mol binding affinities to DNA, in two different sites. The 1,4-Bis(2-chloro-4-nitrophenyl)piperazine predicted to possess strong anti-tumor effects, according to molecular docking studies.

Note

Initial version of this paper was selected from the proceedings of International Online Conference on Engineering and Natural Sciences (IOCENS'21) which was held on July 05-07, 2021, and was subjected to peer-review process before its publication.

Author Contributions

A. Demet DEMİRAG: Conceptualization, Methodology, Software, Investigation, Writing - Original Draft, Writing - Review & Editing
Sefa CELİK: Conceptualization, Methodology, Software, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision
Berkant ILGIN: Investigation, Writing - Original Draft
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Sevim AKYUZ: Conceptualization, Methodology, Software, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision
All authors read and approved the final manuscript.

Conflict of interest

No conflict of interest was declared by the authors.

References

[1] C. S. Potten, G. Owen, D. Booth, "Intestinal stem cells protect their genome by selective segregation of template DNA strands," *Journal of cell science*, vol. 115, no. 11, pp. 2381-2388, 2002.

[2] H. Sung,, J. Ferlay,R. L. Siegel,M. Laversanne, I. Soerjomataram,A. Jemal, F. Bray, "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: a cancer journal for clinicians*, vol. 71, no. 3, pp. 209-249, 2021.

[3] I. M. El-Deeb, S. H. Lee, "Design and synthesis of new potent anticancer pyrazoles with high FLT3 kinase inhibitory selectivity," *Bioorganic & medicinal chemistry*, vol. 18, no. 11, pp. 3961-3973, 2010.

[4] R. Vardanyan, V. Hruby, "*Synthesis of best-seller drugs*," Academic press, 2016.

[5] N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, "Biomedical importance of indoles," *Molecules*, vol. 18, no. 6, pp. 6620-6662, 2013.

[6] M. Yarim, M. Koksal, I. Durmaz, R. Atalay, "Cancer cell cytotoxicities of 1-(4-substitutedbenzoyl)-4-(4-chlorobenzhydryl) piperazine derivatives," *International journal of molecular sciences*, vol. 13, no. 7, pp. 8071-8085, 2012.

[7] B. Çalışkan, A. Yılmaz, İ. Evren, S. Menevşe, O. Uludag, E. Banoglu, "Synthesis and evaluation of analgesic, anti-inflammatory, and anticancer activities of new pyrazole-3 (5)-carboxylic acid derivatives," *Medicinal Chemistry Research*,vol. 22, no. 2, pp. 782-793, 2013.

[8] Y. Xia, Z. W. Dong, B. X. Zhao, X. Ge, N. Meng, D. S. Shin, J. Y. Miao, "Synthesis and structure–activity relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide derivatives as potential agents against A549 lung cancer cells," *Bioorganic & medicinal chemistry*, vol. 15, no. 22, pp. 6893-6899, 2007.

[9] Y. Xia, C. D. Fan, B. X. Zhao, J. Zhao, D. S. Shin, J. Y. Miao, "Synthesis and structure–activity relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide hydrazone derivatives as potential agents against A549 lung cancer cells," *European journal of medicinal chemistry*, vol. 43, no. 11, pp. 2347-2353, 2008.

[10] Ş. C. Pirol, "Diarilpirazol Türevi Bileşiklerin Sentezi Ve Antikanser Etkilerinin Araştırılması Üzerinde Çalışmalar," *Gazi Üniversitesi (Doktora Tezi),* pp. 1-114, 2013.

[11] X. Li, X. Lu, M. Xing, X. H. Yang, T. T. Zhao,H. B. Gong, H. L. Zhu, "Synthesis, biological evaluation, and molecular docking studies of N, 1, 3-triphenyl-1H-pyrazole-4-carboxamide derivatives as anticancer agents," *Bioorganic & medicinal chemistry letters*, vol. 22, no. 11, pp. 3589-3593, 2012.

[12] Y. B. Lee, Y. D. Gong, D. J. Kim, C. H. Ahn, J. Y. Kong, N. S. Kang, "Synthesis, anticancer activity and pharmacokinetic analysis of 1-[(substituted 2-alkoxyquinoxalin-3-yl) aminocarbonyl]-4-(hetero) arylpiperazine derivatives," *Bioorganic & medicinal chemistry*, vol. 20, no. 3, pp. 1303-1309, 2012.

[13] E. Nassar, H. A. Abdel-Aziz, H. S. Ibrahim, A. M. Mansour, "Synthesis of diarylpyrazoles containing a phenylsulphone or carbonitrile moiety and their chalcones as possible anti-inflammatory agents," *Scientia pharmaceutica*, vol. 79, no. 3, pp. 507-524, 2011.

[14] D. V. Dekhane, S. S. Pawar, S. Gupta, M. S. Shingare, C. R. Patil, S. N. Thore, "Synthesis and anti-inflammatory activity of some new 4, 5-dihydro-1, 5-diaryl-1H-pyrazole-3-substituted-heteroazole derivatives," *Bioorganic & medicinal chemistry letters*, vol. 21, no. 21, pp. 6527-6532, 2011.

[15] R. M. Weier, J. Z. Crich, X. D. Xu, P. W. Collins, *U.S. Patent No. 6,509,361*. Washington, DC: U.S. Patent and Trademark Office, 2003.

[16] B. P. Bandgar, J. V. Totre, S. S. Gawande, C. N. Khobragade, S. C. Warangkar, P. D. Kadam, "Synthesis of novel 3, 5-diaryl pyrazole derivatives using combinatorial chemistry as inhibitors of tyrosinase as well as potent anticancer, anti-inflammatory agents," *Bioorganic & medicinal chemistry*, vol. 18, no. 16, pp. 6149-6155, 2010.

[17] M. R. Kuo, H. R. Morbidoni, D. Alland, S. F. Sneddon, B. B. Gourlie, M. M. Staveski, D. A. Fidock, "Targeting tuberculosis and malaria through inhibition of enoyl reductase: compound activity and structural data," *Journal of Biological Chemistry*, vol. 278, no. 23, pp. 20851-20859, 2003.

[18] S. Kumar, G. Kumar, M. Kapoor, A. Surolia, N. Surolia, "Synthesis and evaluation of substituted pyrazoles: Potential antimalarials targeting the enoyl-ACP reductase of plasmodium falciparum," *Synthetic communications*, vol. 36, no. 2, pp. 215-226, 2006.

[19] N. M. Godjayev, S. Akyüz, G. Akverdieva, "A molecular mechanics conformational study of peptide T," *Journal of molecular structure*, vol. 403, no. 1-2, pp. 95-110, 1997.

[20] Y. Gilad, H. Senderowitz, "Docking studies on DNA intercalators," *Journal of chemical information and modeling*, vol. 54, no. 1, pp. 96-107, 2014.

[21] M. Aminzadeh, M. Saeidifar, H. Mansouri-Torshizi, "Synthesis, characterization, DNA binding, cytotoxicity, and molecular docking approaches of Pd (II) complex with N, O-donor ligands as a novel potent anticancer agent," *Journal of Molecular Structure*, vol. 1215, pp. 128212, 2020.

[22] Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, R. A. DiStasio Jr, "Advances in methods and algorithms in a modern quantum chemistry program package," *Physical Chemistry Chemical Physics*, vol. 8, no. 27, pp. 3172-3191, 2006.

[23] M. J. S. Devar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, "AM1: A new General purposequantum mechanical molecular model," *J. Am. Chem. Soc.* Vol. 107, pp. 3902-3909, 1985.

[24] O. Trott, A. J. Olson, "AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading,". *J. Comput. Chem*. Vol. 31, pp. 455-461, 2010.

[25] K. Walayat, N. U. A. Mohsin, S. Aslam, M. Ahmad, "An insight into the therapeutic potential of piperazine-based anticancer agents," *Turkish Journal of Chemistry*, vol. 43, no. 1, pp. 1-23, 2019.

[26] H. R. Drew, R. M. Wing, T. Takano, C. Broka, S. Tanaka, K. Itakura, R. E. Dickerson, "Structure of a B-DNA dodecamer: conformation and dynamics," *Proceedings of the National Academy of Sciences*, vol. 78, no. 4, pp. 2179-2183, 1981.

[27] S. Celik, F. Ozkok, A. E. Ozel, Y. Müge Sahin, S. Akyuz, B. D. Sigirci, E. Karaoz, "Synthesis, FT-IR and NMR characterization, antimicrobial activity, cytotoxicity and DNA docking analysis of a new anthraquinone derivate compound," *Journal of Biomolecular Structure and Dynamics*, vol. 38, no. 3, pp. 756-770, 2020.

[28] S. E. Celik, A. Ozel, V. Durak, S. Akyuz, "Vibrational spectroscopic characterization, quantum chemical and molecular docking studies of Valyl-Methionine dipeptide," *Spectroscopy Letters*, vol. 53, no. 9, pp. 648-663, 2020.

[29] O. K. Gasymov, S. Celik, G. Agaeva, S. Akyuz, S. Kecel-Gunduz, N. M. Qocayev, J. A. Aliyev, "Evaluation of anti-cancer and anti-covid-19 properties of cationic pentapeptide Glu-Gln-Arg-Pro-Arg, from rice bran protein and its d-isomer analogs through molecular docking simulations," *Journal of Molecular Graphics and Modelling*, vol. 108, pp. 107999, 2021.

[30] S. Celik, F. Ozkok, A. E. Ozel, E. Cakir, S. Akyuz, "Synthesis, FT-IR and NMR Characterization, Antibacterial and Antioxidant Activities, and DNA Docking Analysis of a New Vanillin-Derived imine Compound," *Journal of Molecular Structure*, vol. 1236, pp. 130288, 2021.