World of Science: Journal on Modern Research Technologies

Volume 3 Issue 2, Year 2024

ISSN:2835-3072

https://univerpubl.com/index.php/woscience

Article

Preparation, Characterization and Evaluation of Biological Activity and Study of Molecular Docking of Some New Thiazolidine Derivatives

Abdul Wahed Abdul Sattar Talluh[1], Jamil Nadhem Saleh[2], Mohammed Jwher Saleh[2]

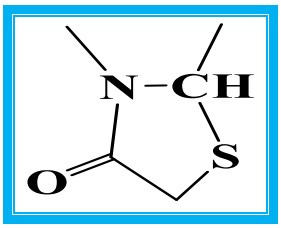
1. Tikrit University, College of Basic Education, Shirqat, Tikrit, Iraq
* Correspondence: altlwhbdalwahd@gmail.com
2. Salah Al-Din Education Directorate, Iraq

Abstract: In this work, equal moles of hydrazone base derivatives and thioglycolic acid react to form pentacyclic thiazolidine derivatives with zinc chloride as a catalyst and using dioxane as a solvent. Proton nuclear magnetic resonance spectroscopy, infrared spectroscopy, and physical and spectroscopic techniques have confirmed the complex structures. Furthermore, the purity and melting points were determined, and thin-layer chromatography (TLC) was used to track the reaction development. The researchers examined how several chemicals produced affected the development of two bacterial isolates: Escherichia coli, gram-negative, and Staphylococcus aureus, gram-positive. Using MOE software (2009), molecular docking probes of compounds (AB20, AB21) against E. coli were performed. The most stable form of these molecules (lowest energy barrier) was achieved using an energy minimization procedure.

Keywords: hydrazone, thiazolidinone, biological activity, molecular docking

1. Introduction

One class of derivatives of thiazolidines is thiazolidinone compounds. These are heterocyclic compounds with nitrogen and sulfur; they are called thiazolidine-4-one when they have a carbonyl group at position -4. Compared to thiophene, which is stable against acid at moderate temperatures, these systems seem more stable [1].



Thiazolidinedione compounds are biologically active. It is essential because it contains a sulfur and nitrogen atom. It has developed a series of antidiabetic agents for type 2 diabetes and mainly studied the blood sugar level and the extent to which the cell genetically reduces its activities in resisting obesity. This means that cells sometimes become resistant to insulin, as it has caused a significant breakthrough in Antidiabetic treatment by increasing insulin secretion, so it is also called "insulin sensitizers" [2]. Both compounds are used to treat diarrhoea [3]. It also showed high effectiveness as an anti-cancer [4], antibacterial [5], anti-fungal agent [6], in addition to being an anti-inflammatory [7].

Citation: Talluh, A. W. A. S., Saleh, J. N., & Saleh, M, J. Preparation, Characterization and Evaluation of Biological Activity and Study of Molecular Docking of Some New Thiazolidine Derivatives. World of Science: Journal of Modern Research Technologies 2024, 3(2), 49-57.

Received: 8th March 2024
Revised: 13th March 2024
Accepted: 20th March 2024
Published: 27th March 2024

2. Materials and Methods

2.1. Material

Without any additional purification, all of the compounds utilized in this investigation were acquired from BDH, Fluka, and Aldrich.

2.2. Devices used

A thermoelectric melter 9300 was used to determine melting points. Using KBr disk at a scale of (400–4000) cm^{-1}, Shimadzu FT-IR 8400S spectrophotometer; 1H-NMR and 13C-NMR spectra using Bruker apparatus operating at 400 MHz. Thicknessed at 0.2 mm, Fluka silica gel plates were employed in thin-layer chromatography (TLC). The plates were activated with fluorescent silica gel G, and visibility was achieved by UV light.

2.3. Preparation of thiazolidinone [8], [9]

A mixture was raised in 40 milliliters of dry gasoline in a water bath with continuous stirring. The ingredients were prepared hydrazone derivatives [AB2-AB6] (0.01 mol), anhydrous zinc chloride (0.01 mol), and thioglycolic acid (0.01 mol, 0.7 g). After confirming that the reaction had finished using thin-layer chromatography, the solution was left to cool for seven hours. Remote heating was used to extract the solvent during this time. It was filtered and recrystallized with ethanol to give a precipitate, and Table 1 shows some physical properties of thiazolidinone derivatives [AB17-AB21].

2.4. Evaluation of biological activity [10]

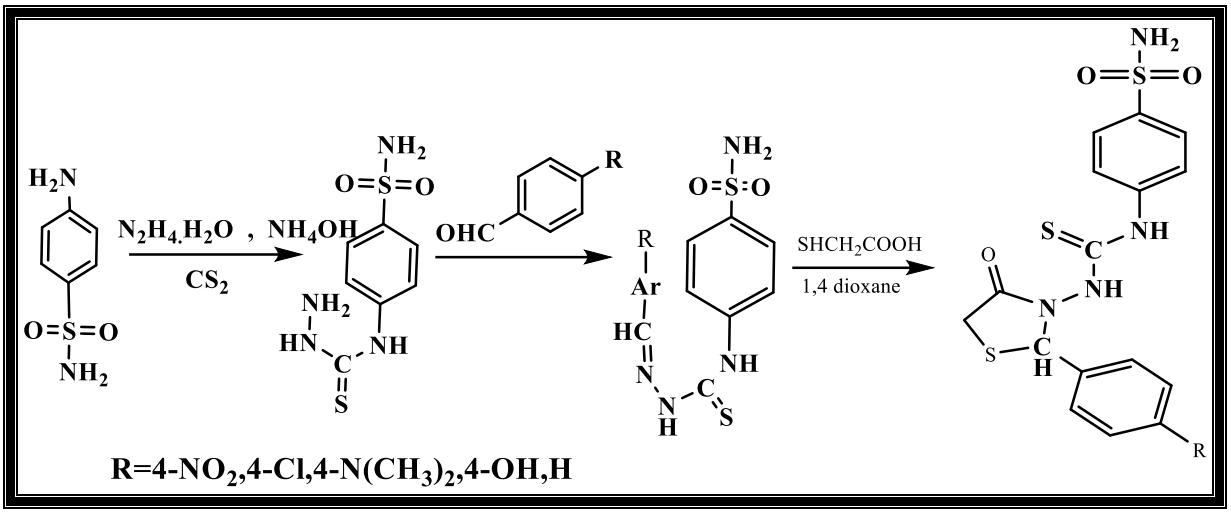
Bacteria species stock cultures were overnight activated in nutrient broth; inoculum was prepared by diluting activated bacteria with 0.8 % normal saline to obtain cell concentration of about 1.5×108 cell/ml, the turbidity of bacteria solution adjusted visually to 0.5 McFarland standard via Twickenham card then the obtained inoculum was streaked directly on agar plates (MHA) by using sterile cotton swabs, wells (holes) with a diameter of 6 mm was made subsequently on the surface of these plates where the solution will be loaded [11]. The negative control plates were maintained with autoclaved plate loaded with DMSO. In contrast, positive control was standard antibiotic disk [12].

2.5. Molecular docking study of some prepared compounds [13], [14]

Using the MOE program (2009), molecular docking investigations were carried out for a few produced compounds (AB12, AB13) against a common bacterial strain, Escherichia coli. The goal was to reduce the energy of the compounds under study to achieve the lowest energy barrier or the most stable conformation. The *Escherichia coli* protein structure was obtained from the International Protein Bank. High-performance computing resources were utilized because these programs are very demanding and require sophisticated, multi-core processors for quick and effective computational operations, especially when working with giant molecules and complex atom configurations, among other things.

3. Results and Discussion

This study included the preparation of thiazolidinone derivatives belonging to the class of pentacyclic rings from the reaction of hydrazones prepared with thioglycolic acid in the presence of zinc chloride as a catalyst, using dioxane as a solvent, as in Scheme 1.



Scheme 1. Path of the ready compounds (AB17-AB21)

3.1. Characterization of thiazolidinone

Absorption bands at the D range (1243-1281) and in the range (1685-1701) cm-1 were identified in the infrared spectrum and were attributed to the thiazolidines' (C=O) group. Two bands at (1456-1506) cm^{-1} and (1568-1595) cm-1 are attributed to the group (C=C), bands at (3035-3078) cm^{-1} are attributed to (Ar-C-H), and absorption bands at (2928-2988) cm^{-1} are attributed to (C-H) affinity [15]. The absorption bands are caused by the (C-N) group in the same ring as in Table 2 and Figure 1 and 2.

Upon analyzing the 1H-NMR spectrum, several signals were detected within the 7.16–7.64 ppm range, and a signal associated with the protons of the (NH) group was detected at the 8.24–10.94 ppm range. The proton (CH2) of the thiazolidine ring was found to be the source of a signal at position (3.94) ppm, while the protonation of the thiazolidine ring connected to the aromatic ring (CH) was responsible for a signal at location (5.11) ppm [16] as in Figure 3.

The carbon of the (C=O) group in the thiazolidine ring was found to be the source of a signal at (165.79) ppm in the 13C-NMR spectrum. The carbon of the (CH2) group was identified as the source of a signal at (18.24) ppm, and the carbon of the (CH) group was identified as the source at (59.66) ppm. It has a multiple signal at (122.99-152.65) ppm attributed to the aromatic ring's carbons in addition to the same ring linked to the aromatic ring [17] as in Figure 4.

3.2. Evaluation of biological activity of (AB17, AB18, AB19, AB20)

Some generated compounds (AB17, AB18, AB19, and AB20) were tested against various bacterial strains using the cup plate agar diffusion technique, including gram-positive bacteria Staph. Aureus, as well as gram-negative E. Coli [18] 0.8% sterile saline was added to the microbial cultures after incubating them for eight hours at 37 °C [19]. The concentration of the drug solution in DMSO was maintained at 100μg/mL. Ciprofloxacin was employed as a negative control. The biological activity was determined by measuring the inhibition diameter of bacterial growth surrounding the in-use disk [20], [21] as seen in Table 3.

3.3. Results of molecular docking study for some prepared compounds [22]

The molecular docking of some of the prepared compounds (AB20, AB21) was studied on one line: *Pseudomonas aeruginosa* bacteria. The values of the binding energies of the prepared compounds were calculated using the MOE program (2009). As shown in Table

4, the study showed that the compound (AB20) interacts with amino acid residues, which are present in the active site, by forming one type of bond, three hydrogen bonds. The first connects the residue of the amino acid CYS 1 present in the active site with the electronic pair of the oxygen atom of the hydroxyl group, and two hydrogen bonds connect the amino acid residues ASP192, GLN193 is located in the enzyme's active site with the electron pair of the sulfur atom, the thiocarbamide group. When studying the compound (AB21), a single hydrogen bond was formed linking the amino acid residue GLN193 located in the active site with the electronic pair of the oxygen atom of the carbonyl group in the thiazolidine ring as in Figure 5 and 6.

Table 1. The produced chemicals' physical attributes (AB17-AB21)

Comp. No.	R	Molecular formula	m.p. °C	Yield%	Color
AB17	4-NO_2	$C_{16}H_{15}N_5O_5S_3$	191-193	65	White
AB18	4-Cl	$C_{16}H_{15}ClN_4O_3S_3$	216-218	71	Brown
AB19	4-$N(CH_3)_2$	$C_{18}H_{21}N_5O_3S_3$	286-288	63	Blue
AB20	4-OH	$C_{16}H_{16}N_4O_4S_3$	223-225	81	Yellow
AB21	4-H	$C_{16}H_{16}N_4O_3S_3$	254-256	69	Orange

Table 2. The synthesized compounds' FT-IR data (AB17-AB21) cm^{-1}

Comp. No.	R	IR (KBr) cm^{-1}						
		ν(C-H) Arom.	ν(C-H) Aliph.	ν C=O)	ν(N-H)	ν(C=C) Arom.	ν(C=N)	Others
AB17	4-NO_2	3053	2960	1699	3174	1467,1595	1276	ν (N-O) 1332
AB18	4-Cl	3078	2967	1685	3216	1447,1557	1254	ν (C-Cl) 741
AB19	4- $N(CH_3)_2$	3035	2925	1701	3180	1506,1591	1244	--
AB20	4-OH	3037	2988	1691	3165	1481,1568	1281	ν (OH)3381
AB21	4-H	3058	2628	1687	3171	1456,1592	1243	---

Table 3. Antibiotics and other generated chemicals (AB17, AB18, AB19, AB20) have the ability to prevent the growth

Comp. No.	E. Coil Conc. mg/ml			Staph. Aureus Conc. mg/ml		
	0.01	0.001	0.0001	0.01	0.001	0.0001
AB17	18	14	10	15	10	10
AB18	15	15	10	10	5	--
AB19	10	5	5	5	5	-
AB20	15	12	8	18	15	10
Amoxicillin	12	10	10	21	20	10

Table 4. Values of the produced compounds' binding energies

Comp. No.	RMSD	Docking Score
AB20	2.24	-6.51
AB21	2.08	-7.074

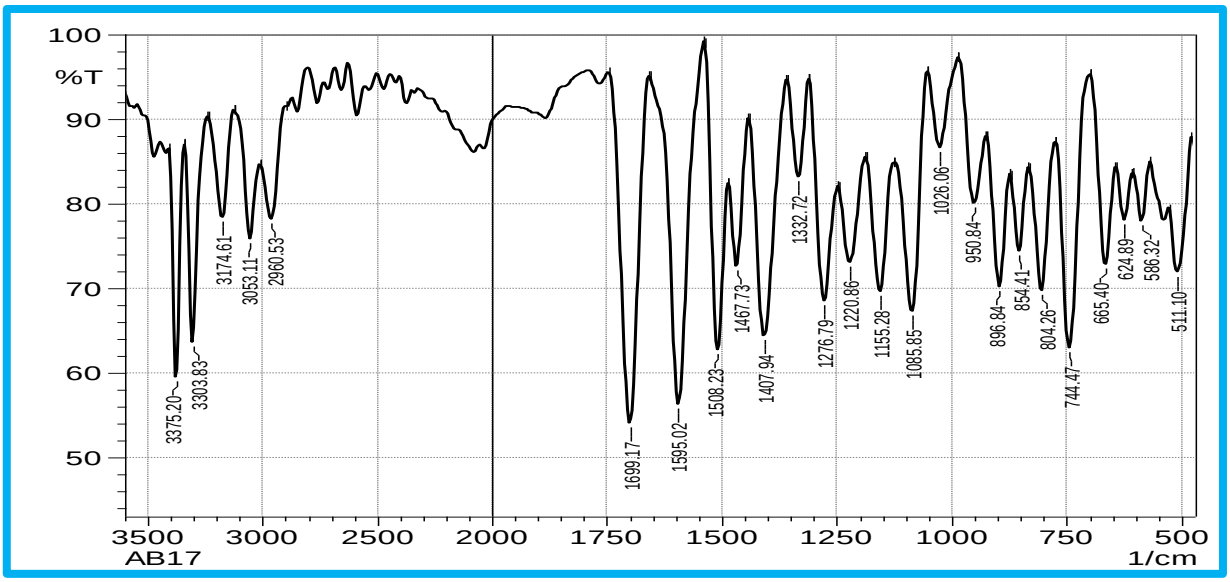


Figure 1. The compound's infrared spectrum (AB17)

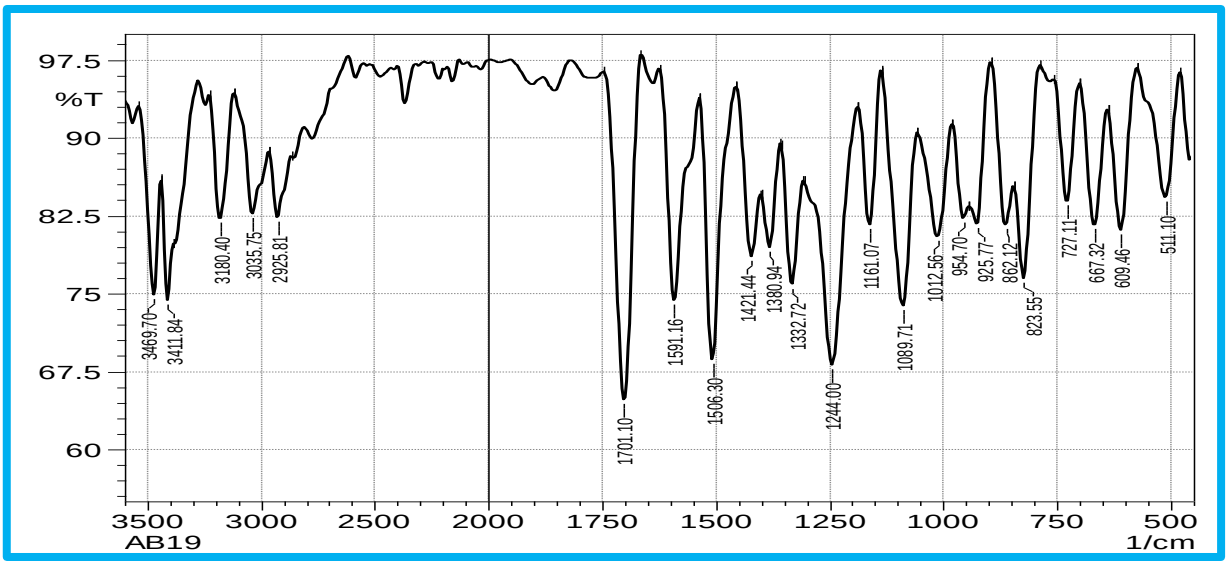


Figure 2. The compound's infrared spectrum (AB19)

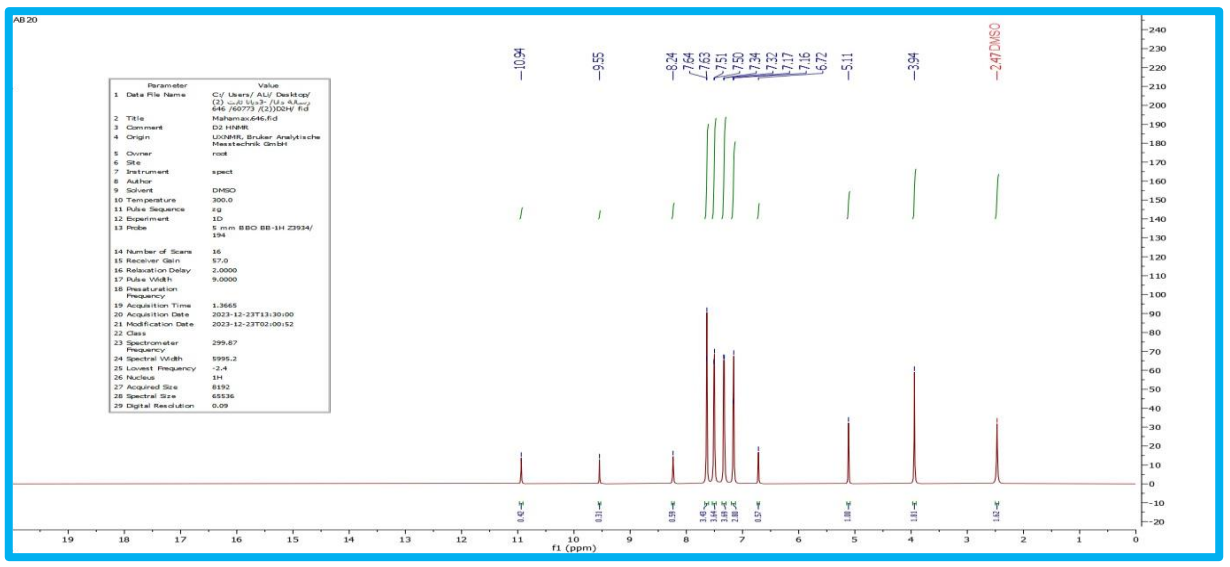


Figure 3. The chemical's 1H-NMR spectra (AB20)

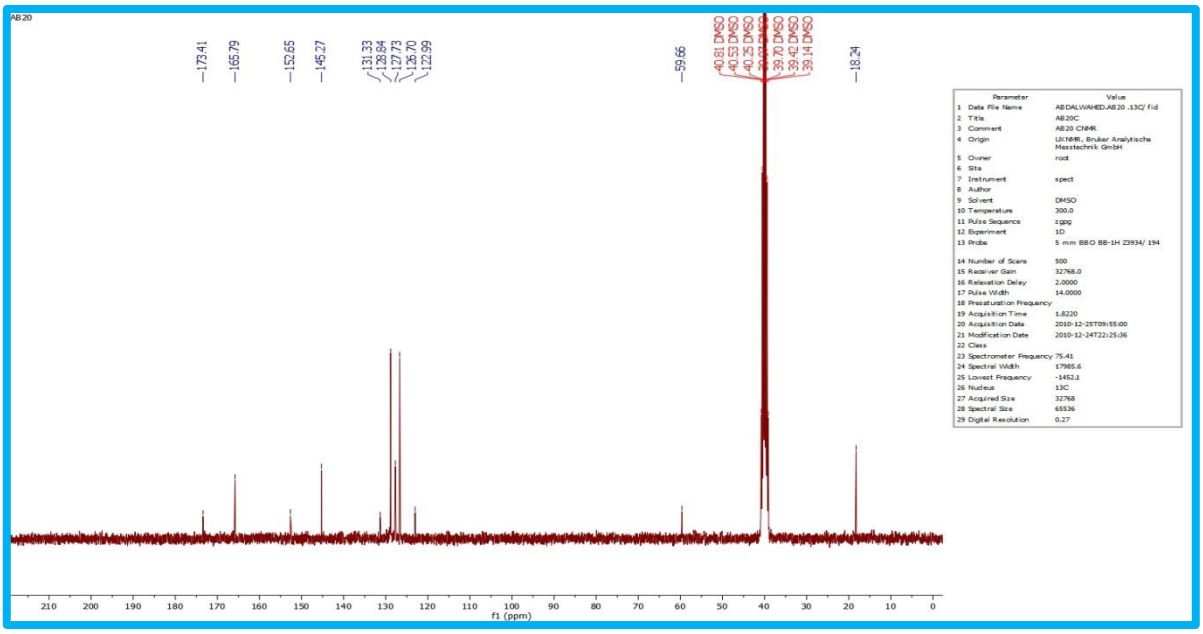


Figure 4. 13C-NMR spectra of the substance (AB20)

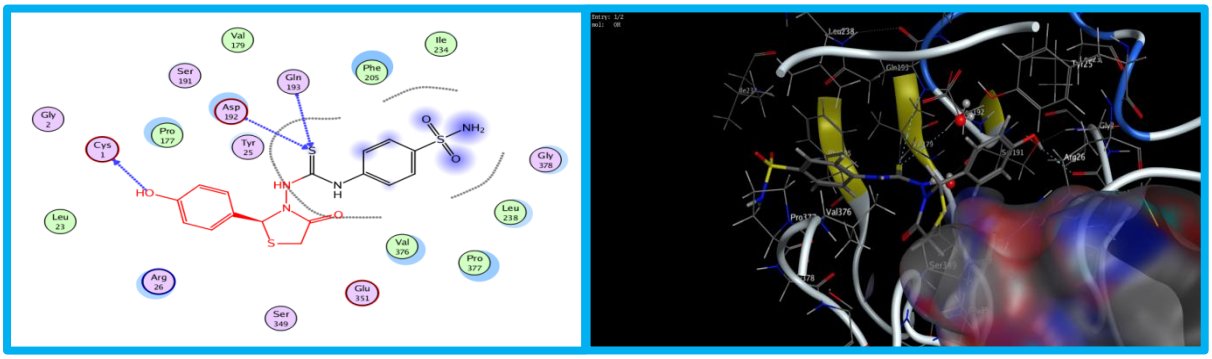


Figure 5. Compound (AB20) interactions in two and three dimensions

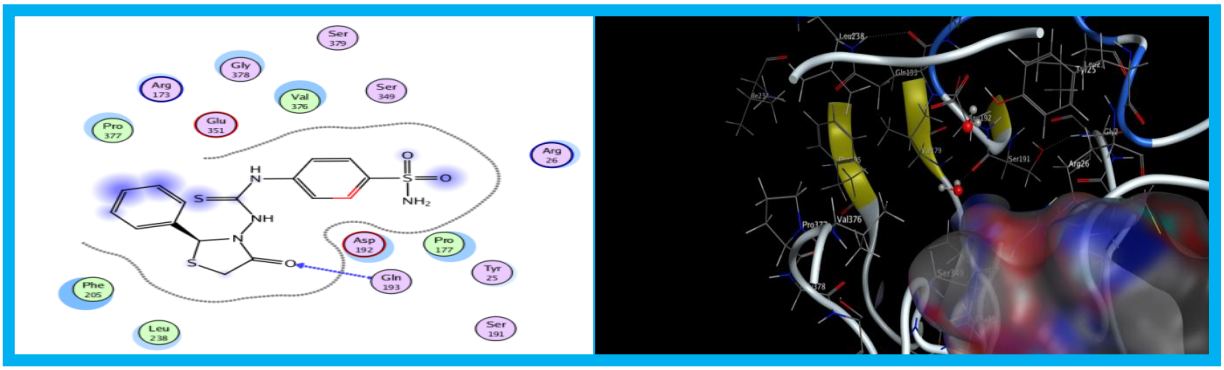


Figure 6. Compound (AB21) interactions in two and three dimensions

4. Conclusion

The reaction of hydrazone derivatives with compounds containing appropriate functional groups often gives rise to heterocyclic pentacyclic rings. Bioanalysis results indicate that most prepared compounds showed antibacterial activity and could inhibit bacterial growth. Some of these compounds showed higher biological activity than the antibiotics used as control samples. Physical and spectroscopic measurements showed the prepared compounds' composition accuracy, as the measurements showed that the prepared compounds were of high purity.

REFERENCES

[1] M. Abhinit, M. Ghodke, and N. A. Pratima, "Exploring potential of 4-thiazolidinone: a brief review," *Int J Pharm Pharm Sci*, 2009, [Online]. Available: https://www.researchgate.net/profile/Anna-Nikalje/publication/250535504_ChemInform_Abstract_Exploring_Potential_of_4-Thiazolidinone/links/5d01299f299bf13a3850dec7/ChemInform-Abstract-Exploring-Potential-of-4-Thiazolidinone.pdf

[2] G. Bansal, P. V Thanikachalam, R. K. Maurya, and ..., "An overview on medicinal perspective of thiazolidine-2, 4-dione: A remarkable scaffold in the treatment of type 2 diabetes," *Journal of advanced …*, 2020, [Online]. Available: https://www.sciencedirect.com/science/article/pii/S2090123220300084

[3] D. A. Molina, G. A. Ramos, A. Zamora-Vélez, and ..., "In vitro evaluation of new 4-thiazolidinones on invasion and growth of Toxoplasma gondii," *International Journal for …*, 2021, [Online]. Available: https://www.sciencedirect.com/science/article/pii/S2211320721000233

[4] B. Skóra, A. Lewińska, A. Kryshchyshyn-Dylevych, and ..., "Evaluation of anticancer and antibacterial activity of four 4-thiazolidinone-based derivatives," *Molecules*, 2022, [Online]. Available: https://www.mdpi.com/1420-3049/27/3/894

[5] R. H. Saleh, W. M. Rashid, A. H. Dalaf, and ..., "Synthesis of some new thiazolidinone compounds derived from schiff bases compounds and evaluation of their laser and biological efficacy," *Ann Trop &Public …*, 2020, [Online]. Available: https://www.researchgate.net/profile/Adil-Dalaf/publication/342072595_SYNTHESIS_OF_SOME_NEW_THIAZOLIDINONE_COMPOUNDS_DERIVED_FROM_SCHIFF_BASES_COMPOUNDS_AND_EVALUATION_OF_THEIR_LASER_AND_BIOLOGICAL_EFFICACY/links/606d4bfa92851c4f26868cad/SYNTHESIS-OF-SOME-NEW-THIAZOLIDINONE-COMPOUNDS-DERIVED-FROM-SCHIFF-BASES-COMPOUNDS-AND-EVALUATION-OF-THEIR-LASER-AND-BIOLOGICAL-EFFICACY.pdf

[6] M. Shirke, M. Gangthade, P. Chaskar, and R. Somani, "Synthesis, characterization and pharmacological evaluation of bifenyl based 4-thiazolidinones," *Indian J. Pharm. Edu. Res*, 2021, [Online]. Available: https://ijper.org/sites/default/files/IndJPhaEdRes-55-2-363.pdf

[7] S. R. Atta-Allah, N. S. M. Ismail, and ..., "Synthesis, Design and Anti-inflammatory Activity of Novel 5-(Indol-3-yl) thiazolidinone Derivatives as COX-2 Inhibitors," *Letters in Drug Design & …*, 2021, [Online]. Available: https://www.ingentaconnect.com/content/ben/lddd/2021/00000018/00000006/art00003

[8] B. Rojin, K. Maher, and M. Shireen, "Synthesis of Some New Bis-4-Thiazolidinones Derived from 2-Hydroxy-1-naphthaldehyde," *Indian Journal of Heterocyclic …*, 2022, [Online]. Available: https://www.researchgate.net/profile/Shireen-Mohammed/publication/366425730_Synthesis_of_Some_New_Bis-4-Thiazolidinones_Derived_from_2-Hydroxy-1-naphthaldehyde/links/63a16694e42faa7e75d974a8/Synthesis-of-Some-New-Bis-4-Thiazolidinones-Derived-from-2-Hydroxy-1-naphthaldehyde.pdf

[9] B. Skóra, A. Lewińska, A. Kryshchyshyn-Dylevych, and ..., "Evaluation of anticancer and antibacterial activity of four 4-thiazolidinone-based derivatives," *Molecules*, 2022, [Online]. Available: https://www.mdpi.com/1420-3049/27/3/894

[10] M. G. González-Pedroza, A. R. T. Benítez, and ..., "Biogeneration of silver nanoparticles from Cuphea procumbens for biomedical and environmental applications," *Sci Rep*, 2023, [Online]. Available: https://www.nature.com/articles/s41598-022-26818-3

[11] J. N. Saleh and A. Khalid, "Synthesis, Characterization and Biological Activity Evaluation of Some New Pyrimidine Derivatives by Solid Base Catalyst AL2O3-OBa," *Central Asian Journal of …*, 2023, [Online]. Available: https://cajmns.centralasianstudies.org/index.php/CAJMNS/article/view/1692

[12] K. Kumar and B. K. Singh, "Synthesis, characterization and anti-microbial activity of some 4-thiazolidinone conjugatives," *Asian journal of pharmaceutical analysis*, 2020, [Online]. Available: https://www.indianjournals.com/ijor.aspx?target=ijor:ajpa&volume=10&issue=4&article=005

[13] A. Talluh, "Preparation, Characterization, Evaluation of Biological Activity, and Study of Molecular Docking of Azetidine Derivatives," *Central Asian Journal of Medical …*, 2024, [Online]. Available: https://cajmns.centralasianstudies.org/index.php/CAJMNS/article/download/2384/2403

[14] A. A. Khalaf, "Synthesis, Characterization and Study of the Molecular Docking With Biological Activity of Some Mannich Base Complexes Derived 4-Aminobenzoic Acid," *Central Asian Journal of Medical and …*, 2023, [Online]. Available: https://cajmns.centralasianstudies.org/index.php/CAJMNS/article/view/1910

[15] S. S. Ismaeel, M. F. Mahdi, and ..., "Design, synthesis and antibacterial study of new agents having 4-thiazolidinone pharmacophore," *Egyptian Journal of …*, 2020, [Online]. Available: https://ejchem.journals.ekb.eg/article_65393.html

[16] S. S. Ismaeel, M. F. Mahdi, and ..., "Design, synthesis and antibacterial study of new agents having 4-thiazolidinone pharmacophore," *Egyptian Journal of …*, 2020, [Online]. Available: https://ejchem.journals.ekb.eg/article_65393.html

[17] J. A. Abdullah, B. J. M. Aldahham, M. A. Rabeea, and ..., "Synthesis, characterization and in-silico assessment of novel thiazolidinone derivatives for cyclin-dependent kinases-2 inhibitors," *Journal of Molecular …*, 2021, [Online]. Available: https://www.sciencedirect.com/science/article/pii/S002228602031629X

[18] M. J. Saleh and K. A. Al-Badrany, "Preparation, Characterization of New 2-Oxo Pyran Derivatives by AL2O3-OK Solid Base Catalyst and Biological Activity Evaluation," *… Asian Journal of …*, 2023, [Online]. Available: https://cajmns.centralasianstudies.org/index.php/CAJMNS/article/view/1691

[19] W. M. Al-Joboury, K. A. Al-Badrany, and N. J. Asli, "N-alkylation of substituted 2-amino benzothiazoles by 1, 4-bis (bromo methyl) benzene on mixed oxides at room temperature and study their biological activity," *AIP Conf Proc*, 2022, [Online]. Available: https://pubs.aip.org/aip/acp/article-abstract/2394/1/040054/2821053

[20] S. A. Mohamed, K. A. Al-Badrany, and ..., "PREPARATION AND STUDY OF BIOLOGICAL ACTIVITY OF PYRIMIDINE COMPOUNDS DERIVED FROM 2-ACETYLPYRIDINE," *Vegueta. Anuario de la …*, 2022, [Online]. Available: https://vegueta.org/pdf/374.pdf

[21] K. A. Al-Badrany, A. S. Mohammed, and ..., "Synthesis of some new 1, 3, 4-oxadiazole compounds derived from 1H-imidazole and study their biological activity," *Eurasian Journal of …*, 2019, [Online]. Available: https://search.proquest.com/openview/c3d4c745ca2844c47c8c1a87743d022e/1?pq-origsite=gscholar&cbl=2042720

[22] E. Mohammed, *A Study of QSAR, Docking and Molecular Modeling of some Dihydropyrimidine Derivatives as Anticancer Agents*. Sudan University of Science and …, 2020.

[23] Y. Sharif, S. Irshad, M. H. Tariq, and M. N. Asghar, *Insilico identification of a ferroportin inhibitor for the management of iron-overload condition in Beta Thalassemia major patients.* researchsquare.com, 2021. [Online]. Available: https://www.researchsquare.com/article/rs-241407/latest

[24] J. K. Salim, "An efficient ultrasound-assisted CH<inf>3</inf>COONa catalyzed synthesis of thiazolidinone molecule: Theoretical and nonlinear optical evaluations of thiazolidinone-Schiff base derivative," *Opt Mater (Amst)*, vol. 133, 2022, doi: 10.1016/j.optmat.2022.112917.

[25] P. Roszczenko, "4-Thiazolidinone-Bearing Hybrid Molecules in Anticancer Drug Design," *Int J Mol Sci*, vol. 23, no. 21, 2022, doi: 10.3390/ijms232113135.

[26] J. Ceramella, "A Review on the Antimicrobial Activity of Schiff Bases: Data Collection and Recent Studies," *Antibiotics*, vol. 11, no. 2, 2022, doi: 10.3390/antibiotics11020191.

[27] H. Karimi-Maleh, "A green and sensitive guanine-based DNA biosensor for idarubicin anticancer monitoring in biological samples: A simple and fast strategy for control of health quality in chemotherapy procedure confirmed by docking investigation," *Chemosphere*, vol. 291, 2022, doi: 10.1016/j.chemosphere.2021.132928.

[28] L. Boike, "Advances in covalent drug discovery," *Nat Rev Drug Discov*, vol. 21, no. 12, pp. 881–898, 2022, doi: 10.1038/s41573-022-00542-z.

[29] Y. Liu, "CB-Dock2: improved protein-ligand blind docking by integrating cavity detection, docking and homologous template fitting," *Nucleic Acids Res*, vol. 50, 2022, doi: 10.1093/nar/gkac394.

[30] H. Karimi-Maleh, "Cyanazine herbicide monitoring as a hazardous substance by a DNA nanostructure biosensor," *J Hazard Mater*, vol. 423, 2022, doi: 10.1016/j.jhazmat.2021.127058.