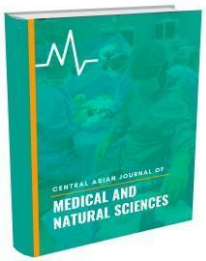


CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
https://cajmns.centralasianstudies.org/index.php/CAJMNS
Volume: 06 Issue: 01 | January 2025 ISSN: 2660-4159

Article

Synthesis, Characterization, and DFT cucalutions, Biological Study of Five-membered Cyclic Containing the sulfur and nitrogen

Zina Saleh Hassan[1], Auhood Kadhim Zaid[2], Ahmed. M.I. Alsanafi[3]

1,2 Department of Chemistry, College of Science, University of Thi-Qar, Thi-Qar, 64001, Iraq
3. Ast-teacher-Nasiriyah Education department, Directorate of Education, Ministry of Education,64001 Nasiriya City Iraq
* Correspondence: 1zina.sa.ch@sci.utq.edu.iq

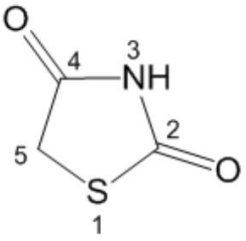
Abstract: Thiazolidinediones have biological activity in the pharmaceutical industry. N-3 and C-5 positions in the TZD core scaffold make it a versatile and flexible piece that exhibits its biological activities. Therefore, two thiazolidinedione derivatives were prepared and their antimicrobial activity was studied. The antibacterial activity was measured, and the synthesised derivatives' computational study was performed using a Gaussian program to calculate some important thermodynamic parameters.

Keywords: Thiazolidine-2,4-dione, thermodynamic parameters, biological activities, Gaussian program.

1. Introduction

Thiazolidine-2,4-dione derivatives are of major interest to chemists and pharmacists due to their biological activity in Pharmaceutical industry as they are able to deal with diseases such as type 2 diabetes, antioxidant, anti-inflammatory و anti-HIV1 and respression for inflammatory molecules2.Their pharmacological and biological activity is because of the responsibility of these compounds in regulating blood sugar and genes associated with fat metabolism3 .Thiazolidinediones are used in industry as corrosion inhibitors for metals and sensitive metal detectors in chemistry and analysis, and also inhibit some enzymes such as aldose reductase, phosphoinositide-3-kinase, PEM kinase, cyclooxygenase, D-glutamate ligase, and thion deacetylase, and some of their derivatives have shown good potential for inhibiting lipoxygenase9,10.

These compounds (TZD) were first prepared in the 19th century by Liebermann et al.1 By 1972 TZD was the first compound to make the characterization of the thiazole cycle (Figure 1).

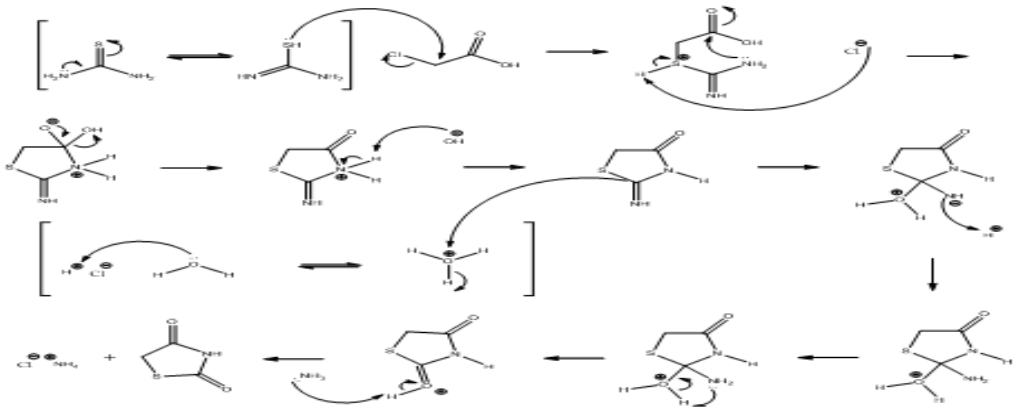


Citation: Hassan S. Z., Zaid A. K., Alsanafi A. M. I. Synthesis, Characterization, and DFT cucalutions, Biological Study of Five-membered Cyclic Containing the sulfur and nitrogen. Central Asian Journal of Medical and Natural Science 2025, 6(1), 300-306.

Received: 2th Jan 2025
Revised: 3th Jan 2025
Accepted: 9th Jan 2025
Published: 16th Jan 2025

Figure 1: compound of thiazolidine-2, 4-dione

The mechanism for obtaining these compounds involves the attack of thiourea sulfide by the free electron pair on 2C in chloroacetic acid and then an intermolecular nucleophilic substitution that results in the cleavage to H2O of the nitrogen free electron pair above the carboxylic carbon and subsequent removal of hydrochloric acid. Finally, the imino group at position 2 is hydrolyzed, a step catalyzed by the subsequent formation of hydrochloric acid during the reaction to form thiazolidine-2,4-dione (Figure 2).

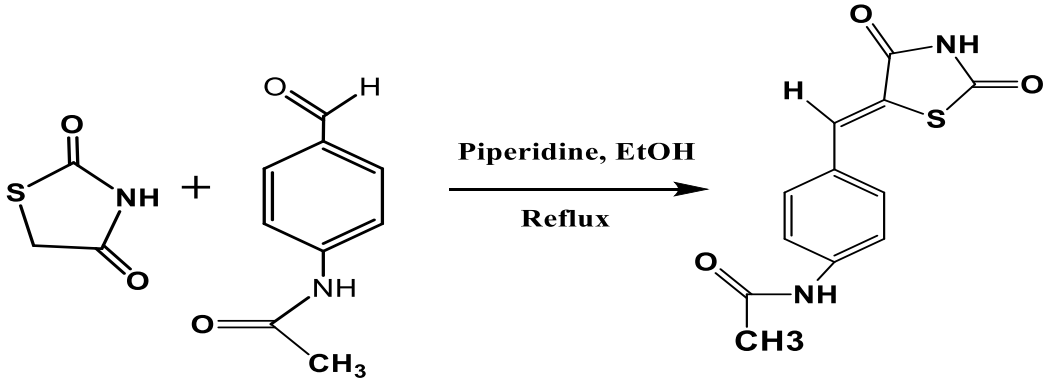


Figure(2) : Mechanism of interaction

2. Materials and Methods

Synthesis of (Z)-N-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)acetamide

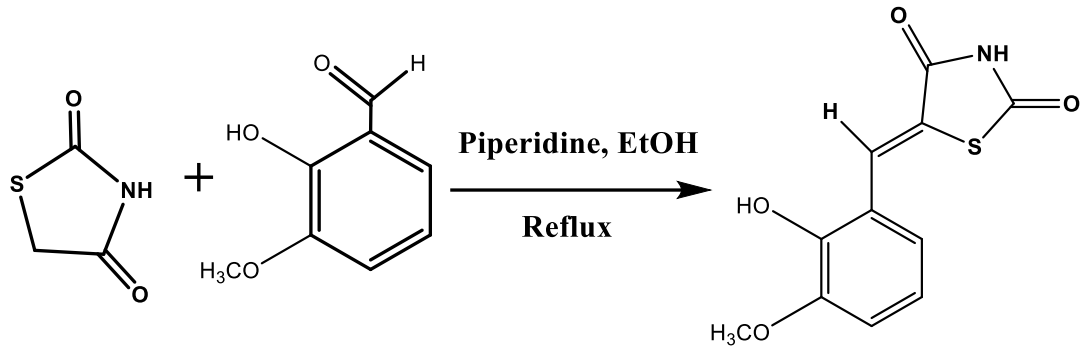
It was prepared by reacting thiazolidine-2,4-dioneone (0.5 g, 4 mmol) with 4-(dimethylamino)benzaldehyde (0.63 g, 4 mmol). Yield= 75%,m.p.= 254-256 ˚C. IR (ῡ, cm-1,KBr disk): 3218 (NH), 2921 (C-H) aliphatic, 1605(S-C=O) cyclic thio, 1580 (N-C=O) amide, 1494 cm-1 (C=C) endo, 1496 cm-1 (C=C) exo. 1H-NMR (400 MHz, DMSO-d6, δ, ppm):2.504(DMSO),8.641(s,1H,N-H),7.899(s,CH=),6.67-7.87(m,Ar-H).



Figure(3: Synthesis of (Z)-N-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)acetamide

Synthesis of (Z)-5-(2-hydroxy-3-methoxybenzylidene)thiazolidine-2,4-dione

It was prepared by reacting thiazolidine-2,4-dioneone (0.5 g, 4 mmol) with 2-hydroxy-3-methoxybenzylidene (0.63 g, 4 mmol). Yield= 75%,m.p.= 254-256 ˚C. IR (ῡ, cm-1,KBr disk): 3209 (NH), 2890 (C-H) aliphatic, 1620(S-C=O) cyclic thio, 1508 (N-C=O) amide, 1430 cm-1 (C=C) endo, 1496 cm-1 (C=C) exo. 1H-NMR (400 MHz, DMSO-d6, δ, ppm):2.505(DMSO),8.396(s,1H,N-H),3.02(3H,O-CH3),9.67(s,1H,OH) 6.76-7.74(m,Ar-H);7.76(s,1H.=CH).



Figure(4) : Synthesis of (Z)-5-(2-hydroxy-3-methoxybenzylidene)thiazolidine-2,4-dione

Antibacterial activity

The prepared compounds were measured to determine their biological activity against bacteria by agar diffusion technique using two types of bacteria (Staph. aureus and E. coli) and adding dimethyl sulfoxide as a control (0.1 ml) of the concentrations of the prepared compounds to the cups. After 48 hours of incubation at 37°C, the results appeared and by measuring the diameter of inhibition against bacteria, the antimicrobial activity was evaluated13.

Quantum Chemical Calculations

The Gaussian 09 W program, coupled with Gauss view 5.0, was used to implement density function theory (DFT) to calculate all the important parameters in this work.

3. Results and Discussion

Characterization

Compounds are studied with various analysis techniques.

Infrared spectral

All synthesis compounds are colored. The prepared product was characterized by 1-Infrared (IR) spectra: IR absorption bands were identified in the KBr tablet .The compounds were identified by their infrared spectrum and compared with the infrared spectrum of Schiff bases, where bands appeared and other bands disappeared. The most important feature of the spectrum of Schiff rules is the absorption band of the group (C=N), which appears at the wave number (1550) cm-1 . The infrared spectrum of the prepared compounds showed a double-headed band at wave numbers 3083-3354, belonging to the extension of the symmetrical and asymmetric N-H bond, respectively [14]. Likewise, the appearance of a band at (1665, 1620,) dating back to the extension of the bond (C=O) and the disappearance of the expansion band (C=N) at 1550 cm-1, as well as the appearance of a new band at wave number (1580 cm-1), (1508 cm-1) due to the expansion of the bond NC=O .

Table(1)FT-IR spectra for the prepared compounds

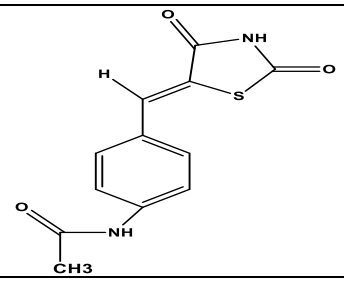
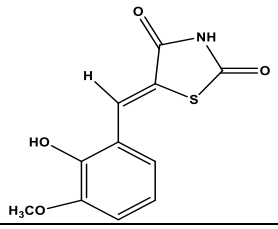
Compound	-NH-	C-H	C=C	NC=O	C=O	-SC=O
1	3218	2921	1494	1580	1665	1605
2	3209	2890	1430	1508	____	1620

1HNMRspectrum

1H-NMR spectrum of the newly formed compounds, revealed signals at rang δ=(8.165-7.763) ppm as singlet which attributed to of (-CH=, NHTZD) The aromatic protons displayed signals at δ=(6.679-7.846).

Table(2)1H-NMR spectral data(ppm) of compound

Compound		^{1}H-NMRspectraldata(ppm)

1		2.504(DMSO)8.641(s,1H,N-H(7.899(s,CH=);6.67-7.87 (m,AR-H)
2		2.505(DMSO)8.396(s,1H, N-H(3.02(3H,O-CH3);9.67(s,1H, OH)6.76-7.74(m,Ar-H);7.76(s,1H.=CH);

Biological activity

The prepared compounds (1,2,) showed different biological activity against two types of Gram-negative bacteria (E.coli) and Gram-positive bacteria (Staphylococcus aureus). The results showed that compound (1 and 2) were effective against Staphylococcus aureus. Compounds (1 and 2) showed moderate activity against Escherichia coli. All of these results are shown in the table below.

Table 3.Biological activities for Thiazolidine-2,4-dione

NO.	Gram positive bacteria *staph.aureas*	Gram negative bacteria *E.coli*
1	15	10
2	16	11

Quantum chemical calculations

Density functional theory (DFT) can allow us to determine and study molecular geometry, properties of the electronic structure in the ground, and the electronic excited states of molecules in both gaseous and aqueous phases and calculate molecular properties14,15.To study compounds and develop them as drugs, this theory was used to discuss chemical interaction16 as well as to link physical and chemical parameters17.

The results of calculating the global parameters of the chemical reaction from the energies of LUMO and HOMO shown in the table showed that the large energy gap (LUMO – HOMO) corresponds to a low chemical reaction and high kinetic stability. Compound 2 is characterized by a small energy gap (gap ΔE = 3.6227eV). This compound is known as The “soft” molecule has high polarizability because its excitation energy is small while sample 1 has the highest energy gap (gap ΔE = 3.7695eV). Therefore, it is known as a solid molecule, and thus affects the activity of the molecule from a biological standpoint. Figure 5 shows the boundary molecule orbital density distributions for the investigated compounds.

Ionization potential, electron affinity (EA), chemical softness (ς) and hardness (η) are important parameters for the chemical reaction of molecules because they show the ability of molecules to interact more through their ability to donate electrons to the molecule and their lack of stability. Therefore, in our results, we can expect Compound 2)IP5.881ev, EA2.147eV,ς0.265 eV,η 1.811eV) is the most reactive compound, the least stable, the most electron-accepting, the least rigid, and the softest, while Compound 1)IP5.916ev,

EA2.259eV,ς0.276eV,η1.884eV)has high stability, less ability to interact, as well as the property of donating an electron to the molecule, and is more rigid. As shown in Table 4, the geometry of the molecules has been completely improved, and the improved structures are shown in figures.

Table 4. Selected quantum chemical parameters for compounds.

Com.	HOMO(ev)	LUMO(ev)	Eg(ev)	IP(ev)	EA (ev)	χ (ev)	η (ev)	ω (ev)	ς (ev)	μ (ev)
1	-5.916	-2.147	3.7695	5.916	2.259	4.032	1.884	15.320	0.276	-4.070
2	-5.881	-2.259	3.6227	5.881	2.147	4.070	1.811	15.005	0.265	-4.032

Hint: energy gap (Eg), ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), softness (S), and chemical potential (μ).

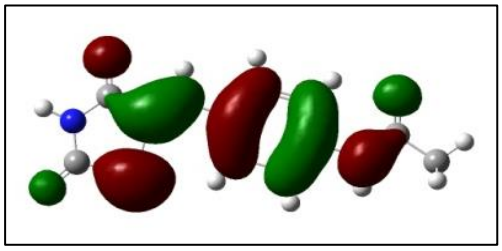


figure 2: HOMO molecular orbital of compound1

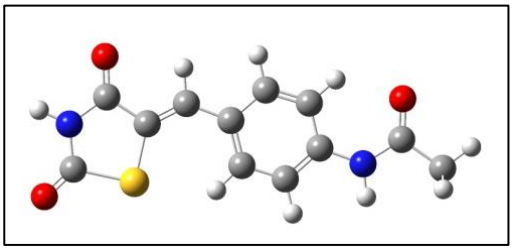


figure 1: Optimized structure of compound1

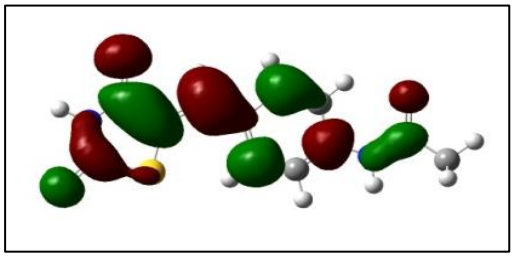


figure 2: LUMO molecular orbital of compound1

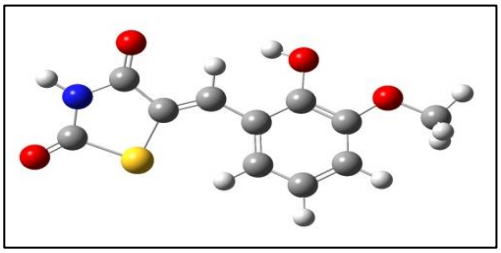


Figure 4: Optimized structure ofcompound2

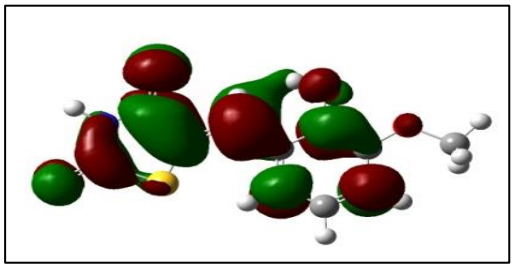


Figure 5: HOMO molecular orbital ofcompound2

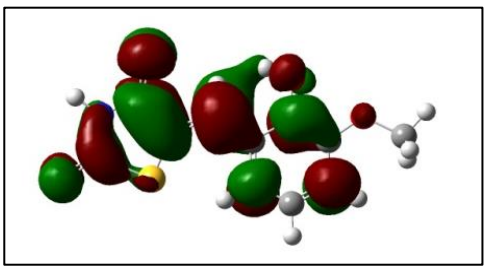


Figure 6: LUMO molecular orbital of compound2

4. Conclusion

Thiazolidinediones (TZDs) have proved to be a noteworthy core in the pharmaceutical industry because of their diverse biological activities arising from the reactivity of regions N-3 and C-5. In the present research work, two structures of TZD derivatives were prepared and tested for antimicrobial efficacy. Antibacterial assay results show promising activity against the tested strains, we therefore conclude that these derivatives can be considered as potential antimicrobial compounds.

As a supplementary to the experimental results, computational research employing the Gaussian program for the evaluation of essential thermodynamic characteristics was conducted. These calculations offered some additional insight into the stability and reactivity of the synthesized derivatives that would definitely be useful in the future. The integration of biological and computational analyses ensured that these compounds could be well assessed showing the need for a multimodal approach in drug discovery.

The findings show long-term potential of thiazolidinedione derivatives in dealing with microbial issues as resistance to antimicrobial agents persists. Even though this work dealt mainly with these two derivatives, more related compounds must be synthesized and tested in order to obtain still more potent and broader-spectrum inhibitors.

Further studies may focus on the alterations of the structural characteristics of TZD derivatives for enhancing its activity versus more numbers of microbial strains and determination of its activity. In addition, they can potentially call for better knowledge of their intramolecular structure using new computational approaches, which would be beneficial in the development of the newer generation of antimicrobial compounds. This work provides further support to the idea that TZDs are a very worthwhile workhorse for medicinal chemistry and emphasizes the possibility of their application in the treatment of modern diseases.

REFERENCES

1. LIMA JG. AlgunsAspectosQuímicos do Anel 2,4–tiazolidinadiona. Rev Uni Rural, SérCiêncExatas e da Terra. 1998;18/20(1/2):1–8.
2. Mohanty S, Reddy SG, Ramadevi B, et al. An assembly of structurally diverse small and simple 5–aminomethylene derivatives of 2,4–thiazolidinedione and studies of their biological activity. Med Chem Res. 2015;24(12):4037–4049.
3. Albrecht, U., Gördes, D., Schmidt, E., Thurow, K., Lalk, M., and Langer, P. (2005). Synthesis and Structure-Activity Relationships of 2-Alkylidenethiazolidine-4, 5-Diones as Antibiotic Agents. Bioorg. Med. Chem. 13 (14), 4402–4407. doi:10.1016/j.bmc.2005.04.046
4. 4-Jain, N., et al. (2013) A Generalized Approach for DG Planning and Viability Analysis under Market Scenario. IEEE Transactions on Industrial Electronics, 60, 5075-5085.https://doi.org/10.1109/TIE.2012.2219840
5. AuhoodKadhimZaid (2022). Synthesis, Characterization, and Computational, Biological Studies of Four-membered Cyclic Amides 2- azetinones. Journal of Chemical Health Risks. 12(4), 665-674 . DOI: 10.22034/jchr.2022.691252.
6. AuhoodKadhimZaid. Synthesis, Characterization, and Computational Study of Novel Thiazolidinone Derivatives Containing the Indole. J. Med. Chem. Sci., 2023, 6(2) 346-354 https://doi.org/10.26655/JMCHEMSCI.2023.2.15

   URL: http://www.jmchemsci.com/article_156196.html
7. Beharry-Borg, N., Hensher, D.A. and Scarpa, R. 2009. An Analytical Framework for Joint vs Separate Decisions by Couples in Choice Experiments: The Case of Coastal Water Quality in Tobago. Environmental Resource Economics 43, 95-117.
8. Kim S. H., Ha Y. M., Moon K. M., Choi Y. J., Park Y. J., Jeong H. O., et al. (2013). Anti-Melanogenic Effect of (Z)-5-(2, 4-Dihydroxybenzylidene) Thiazolidine-2,4-Dione, a Novel Tyrosinase Inhibitor. Arch. Pharm. Res. 36 (10), 1189–1197. 10.1007/s12272-013-0184-5
9. Bozdağ-Dündar O., Çoban T., Ceylan-Ünlüsoy M., Ertan R. (2009). Radical Scavenging Capacities of Some Thiazolylthiazolidine-2, 4-Dione Derivatives. Med. Chem. Res. 18 (1), 1–7. 10.1007/s00044-007-9081-0.
10. Avupati V. R., Rani Y., Singh A. (2018). Discovery of a Series of 5-Benzylidene-1, 3-Thiazolidine-2, 4-Dione-Linked Chalcone Hybrids as a Novel Class of 5-Lipoxygenase (5-LO) Inhibitors. J. Young Pharma 10 (2), 241–242. 10.5530/jyp.2018.10.53
11. Malik N. and Prasad D. N., Iranian Journal of Pharmaceutical Sciences, 8, 3,

    209-214, 2012.

12. Pattan S. R., Kerkare P., Nikalje A. and Hole M. B., Asian J Res Chem, 2, 123-6, 2009.
13. Ali R., 2011. Synthesis of New Schiff's Bases Derived from 4-Phthalimidyl Acetophenone. Journal of Al-Nahrain. 14(3), 1-8.
14. Medjahed, S.; Belaidi, S.; Djekhaba, S.; Tchouar, N.; Kerassa, A. Computational Study of Molecular Electrostatic Potential, Drug Likeness Screening and Structure-Activity/Property Relationships of Thiazolidine-2, 4-Dione Derivatives. J. Bionanoscience 2016, 10, 118–126.
15. Juma J.M., Vuai S.A., Computational studies of the thermodynamic properties, and global and reactivity descriptors of fluorescein dye derivatives in acetonitrile using density functional theory, Journal of Chemical Research, 2021, 45:800
16. Belaidi, S.; Melkemi, N.; Bouzidi, D. Molecular geometry and structure-property relationships for 1, 2-dithiole-3-thione derivatives. Int. J. Chem. Res.
17. Yeşilkaynak T., Özkömeç F.N., Çeşme M., Demirdöğen R.E., Kutlu E., Kutlu H.M., Emen F.M., Synthesis of new thiourea derivatives and metal complexes: Thermal behavior, biological evaluation, in silico ADMET profiling and molecular docking studies, Journal of Molecular Structure, 2022, 1269:133758Fortune DG, Main CJ, O'Sullivan TM, Griffiths CE, Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress, Br J Dermatol, 1997, 137:755-760.