Journal of Medicinal and Chemical Sciences 6 (2023) 346-354

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

*Original Article*

# Synthesis, Characterization, and Computational Study of Novel Thiazolidinone Derivatives Containing the Indole

**Auhood Kadhim Zaid***

*Department of Chemistry, College of Science, University of Thi-Qar, Iraq*

**ARTICLE INFO**

**Article history**

Receive: 2022-05-02
Received in revised: 2022-06-15
Accepted: 2022-08-26
Manuscript ID: JMCS-2208-1612
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Gholamabbas Chehardoli

**DOI:10.26655/JMCHEMSCI.2023.2.15**

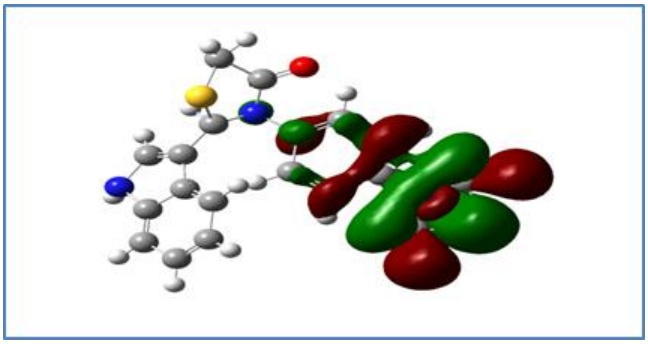
**KEYWORDS**

*Thiazolidinone*
*Heterocyclic derivatives*
*Indole*
*Gaussian program*

**ABSTRACT**

The present study includes the synthesis and characterization of thiazolidinedion containing indole ring. Two compounds were prepared: (4-fluorophenyl)-2-(1*H*-indol-3-yl)thiazolidin-4-one (I) and(4-(dimethylamino)phenyl)-2-(1*H*-indol-3-yl)thiazolidin-4-one(II), the prepared compounds diagnosed by using infrared spectra, NMR spectra ($^1$H-NMR), and the results were identical to what is expected in practice. The Gaussian program was used for the computational study of thiazolidinedion and the theoretical calculations of the thermodynamic variables showed that compound (I) is the more softness with the lowest hardness. Meanwhile, compound (II) the more hardness with less softness.

**GRAPHICAL ABSTRACT**



* Corresponding author: Auhood Kadhim Zaid
✉ E-mail: Email: ohoud.k_mschem@sci.utq.edu.iq

## Introduction

Thiazolidinones are considered the saturated form of a thiazole, 1,3-thiazolidin-4-one. Thiazolidinones consist of a five-membered ring containing a sulfur, nitrogen, and carbonyl group [1,2] (Figure 1). Sulfur occupies position 1 in the five-membered ring, while nitrogen is in position 3, and the carbonyl group is in position 4 [3-5].

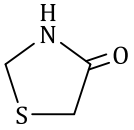
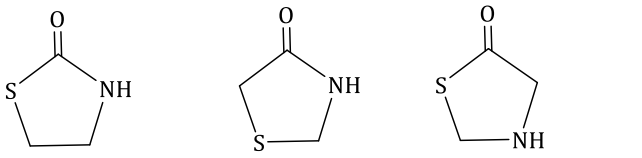


**Figure 1:** Thiazolidinone ring

Thiazolidinones have three isomeric [6], and they have the following structures:



thiazolidin-2-one thiazolidin-4-one thiazolidin-5-one

**Figure 2:** Isomeric structures of thiazolidines

The thiazolidinedione ring is of great importance because it is a structure in many naturalproducts and medicines, for example thiazolidine-4-one derivatives (Figure 3). It indicates the activity against inflammatory, analgesic, and anti-ulcer [7].

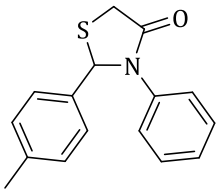


**Figure 3:**3-phenyl-2-(ρ-toyl)thiazolidin-4-one

Also, the prepared compound 2-aryl-4-oxothiazoilidin-3-ylamides showed the activity against prostate cancer cells (Figure 4) [8].

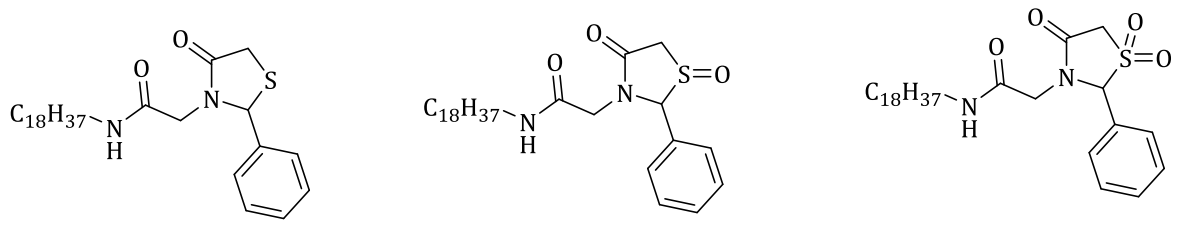


**Figure 4:** Prepared thiazolidine compounds as against prostate cancer cells

## Materials and methods

*Synthesis of imines [9,10]*

*(E)-N-(4-fluorophenyl)-1-(1H-indol-34-yl)methanimine (a)*

It was prepared by the reaction of indol-3-carboxyaldehyde (1 g, 6.89 mmol) with 4-fluroanline (0.77 g, 6.89 mmol) and (10 drops) of ($CH_3COOH$) glacial acetic acid was added, and then they were refluxed in water bath for 16 hours. The product was precipitated and recrystallized with the addition of methanol droplets, (M.p=223-225°C), ($R_f$ = 0.8), IR (KBr disk): (1632.62) $cm^{-1}$ (C=N), yield = 74% (Figure 5).

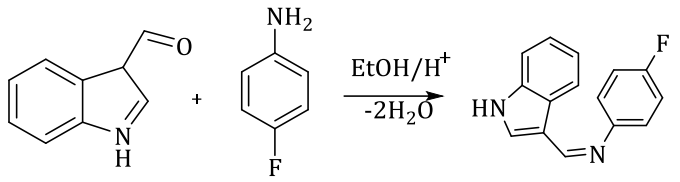



**Figure 5:** Preparation of (*E*)-*N*-(4-fluorophenyl)-1-(1H-indol-34-yl)methanimine

*(E)-4-(((1H–indol-3-yl) methylene)amino)–N,N-dimethylaniline (b)*

It was prepared by the reaction of Indol-3-carboxyaldehyde (1 g, 6.9 mmol) with N, N-dimethylbenzen-1,4-diamine (0.93 g,6.9 mmol) and (10 drops) of ($CH_3COOH$) glacial acetic acid was added, and then they were refluxed in water bath for 20 hours. The product was precipitated and recrystallized with the addition of methanol droplets, (M.p = 220-222°C), ($R_f$ = 0.9), IR (KBr disk): (1603.65) $cm^{-1}$ (C=N), yield = 80% (Figure 6).

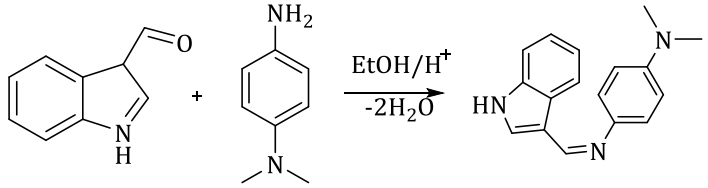



**Figure 6:** Preparation of (*E*)-4-(((1H–indol-3-yl) methylene)amino)–*N,N*-dimethylaniline

*Synthesis of thiazoledinones [11,12]*

*3-(4-fluorophenyl)-2-(1H-indol-3-yl)thiazolidin-4-one(I)*

It was prepared by the reactant (1 g, 4.2 mmol) (*E*)-N-(4-fluorophenyl)-1-(1H-indol-3-yl)methanimine with (0.39 g, 4.2 mmol) thioglycolic acid acid in (15 ml) chloroform, and then it was refluxed for 18 hours with stirring. The product was precipitated and recrystallized with the addition of ethanol $R_f$ =0.7, yield=70%, M.p=229-231 °C (Figure 7).

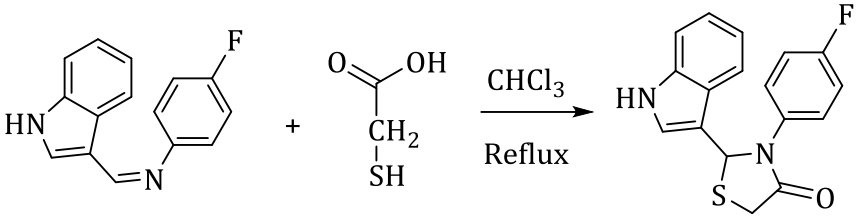



**Figure 7:** Preparation of 3-(4-fluorophenyl)-2-(1H-indol- 3-yl)thiazolidin-4- one

*3- (4- (dimethylamino)phenyl)-2-(1H-indol-3-yl)thiazolidin-4-one(II)*

It was prepared by reactant (1g, 3.8 mmol) (*E*)-4-(((1H-indol-3-yl) methylene)amino)-*N,N*-dimethylaniline with (0.36 g, 3.8 mmol) thioglycolic acid acid in 15 ml chloroform, and then it was refluxed for 18 hours with stirring. The product was precipitated and recrystallized with the addition of ethanol $R_f$ =0.8, yield = 75%, M.p=230-232 °C (Figure 8).

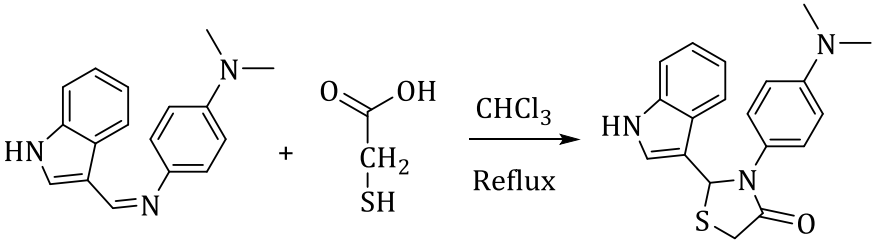



**Figure 8:** Preparation of 3-(4-(dimethylamino)phenyl)-2-(1H-indol-3-yl)thiazolidin-4-one

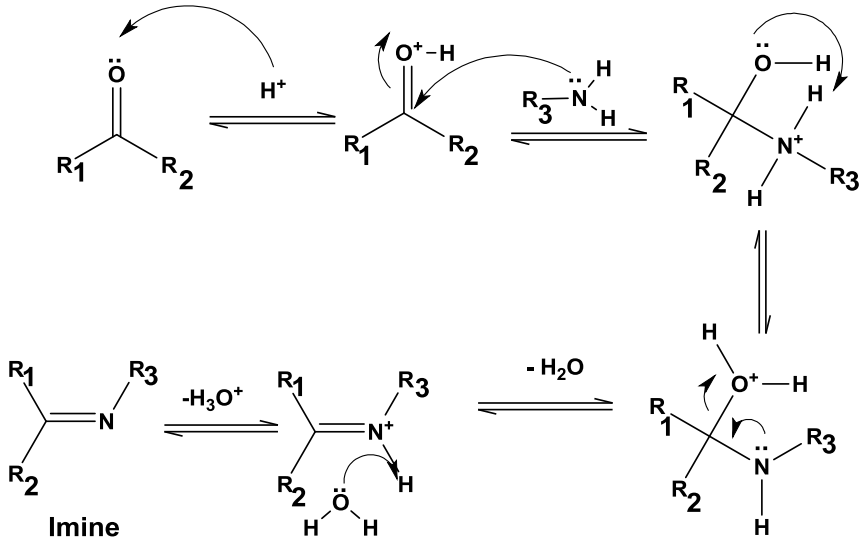
*Quantum chemical calculations*

Gaussian 09 W program was used to calculate EHOMO, ELUMO, energy gap (ΔE), and other parameters of the prepared compounds by implementing density function theory (DFT).

## Results and discussion

*The mechanism of preparing imines*

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. De-protonation of nitrogen gives the final imine product, as displayed in Scheme 1.




**Scheme 1:** Mechanism of imines formation

Table 1 shows the melting point measurement for the prepared compounds (a and b) diagnosed by (FT-IR) (Table 2), whose bands correspond to the vibration bands aliphatic (C-H), (aromatic C-H), (C=C)), and (azomethine band C=N). These bands occur (2925, 2923), (3037, 3042, 3097), (1591, 1567), and (1603, 1632), respectively.

**Table 1:** physical properties of imines

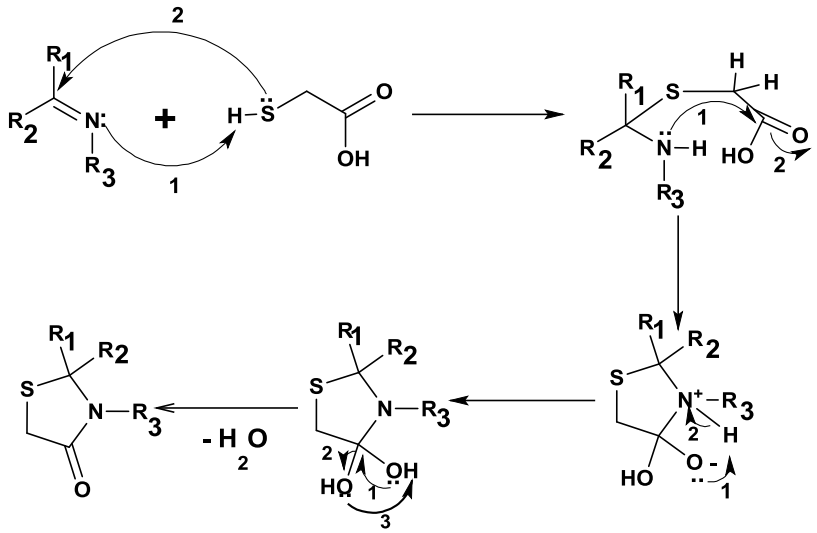
| Yield% | Reaction time | Rf | Color | Melting point | Compound |
|---|---|---|---|---|---|
| 74 | 16h | 0.8 | Yellow | 223-225 | **a** |
| 80 | 20h | 0.9 | Yellow | 220-222 | **b** |

**Table 2:** IR spectra of imines

| Compound | Aromatic (CH) stretching ($cm^{-1}$) | Aliphatic (CH) stretching ($cm^{-1}$) | Azomethine (C=N) Stretching ($cm^{-1}$) | Aromatic (C=C) stretching ($cm^{-1}$) |
|---|---|---|---|---|
| a | 3042<br>3104 | 2925 | 1632 | 1591 |
| b | 3037<br>3097 | 2923 | 1603 | 1567 |

*Synthesis of Thiazolidinones*

The mechanism of preparing thiazolidinediones includes the reaction of the prepared Schiff bases with thioglycolic acid. The following scheme shows the reaction mechanism involving cycloaddition to form thiazolidinediones [13].



**Scheme 2:** Mechanism of thiazoldinone formation

*FT-IR data*

The prepared compounds (I,II) melting point and physical properties for prepared compounds are represented in Table 3. Compounds diagnosed specifying (FT-IR) listed in Table 4, demonstrated the featured packages most notably, C-H aromatic, aromatic C=C, aliphatic C-H, and carbonyl amide group which occur within (3041.48, 3104.91), (1574.91, 1576.47), (2976.37, 2811.03), (1686.24, 1646.81), respectively.

**Table 3:** Physical properties of thiazoledinones

| Compound | Melting point | Color | RF | Reaction time | Yield% |
|---|---|---|---|---|---|
| I | 229-231 | White | 0.7 | 18 h | 70 |
| II | 230-232 | Yellow | o.8 | 18 h | 75 |

**Table 4:** FTIR spectral data of thiazolidinones

| Compound | Aromatic (C- H) stretching $cm^{-1}$ | Aromatic (C= C) stretching $cm^{-1}$ | Aliphatic (C- H) stretching $cm^{-1}$ | Amide (C= O) stretching $cm^{-1}$ (thia-) | (C-N) stretching | (C-S) Bending $cm^{-1}$ |
|---|---|---|---|---|---|---|
| I | 3041. 48<br>3104.91 | 1576.47 | 2976.37 | 1686.24 | 1334.15 | 787.97 |
| II | 3033.01<br>3089.35 | 1574.91 | 2972.70 | 1646.81 | 1355.51 | 884.82 |

*$^1$H NMR spectral*

$^1$H-NMR data of thiazoledinones are indicated in Table 5.

**Table 5:** $^1$H-NMR data of thiazolidinones

| Compound | Thiazolidinone ring | | Aromatic proton | Aliphatic proton | $C_2H$ Indol | NH Indol |
|---|---|---|---|---|---|---|
| | (C-H) ring | (C-$H_2$) ring | | | | |
| I | 3.18- 3.41 ppm | 5.58 ppm | 6.72-8.69 ppm | --- | 11.12 ppm | 11.61 ppm |
| II | 3.40- 3.44 ppm | 5.21 ppm | 7.01-8.70 ppm | 3.66 ppm | 11.17 ppm | 12.6 ppm |

*Quantum chemical calculations*

In computational study of the prepared compounds, Table 6 indicates the calculation of the most important chemical parameters of the prepared compounds.

Whether a molecule is hard or soft, the HOMO-LUMO energy gap represents the chemical reaction of that molecule. Compound 2 is characterized by a small energy gap (ΔE gap=1.17 eV), while compound 1 has a slightly higher energy gap (ΔE gap=1.8 eV). Therefore, compound 2 has a large susceptibility to polarization because its excitation energy is small, so compound 2 is soft [14].

In addition, compound 2 has a low ionization potential IP=4.23 and this indicates a high reactivity of the molecules [15,16].

Low electron affinity values enhanced the electron-donating property of the molecule. Thus, the most donating molecule is compound 2 (EA = 3.06 eV) and the most acceptable molecule is compound 1 (EA = 3.12 eV) [17,18].

The stability and reactivity of the molecule can be known by the factors of hardness (ɳ) and chemical softness (ς) [19-22]. Hence, compound 1(ς =1.11 eV) is the more softness with the lowest hardness. Meanwhile, compound 2 (ς =1.71 eV) is the more hardness and less softness molecule (Figure 10-13).

**Table 6:** Quantum chemical parameters of the prepared compounds

| Compound | HOMO | LUMO | Energy gap (Eg) | Ionization potential (IP) | Electron affinity (EA) | Hardness (ɳ) | Electronegativity (χ) | Ductility (ς) | Chemical potential (μ) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | -4.92 | -3.12 | 1.8 | 4.92 | 3.12 | 0.9 | 4.02 | 1.11 | -4.02 |
| 2 | -4.23 | -3.06 | 1.17 | 4.23 | 3.06 | 0.585 | 3.65 | 1.71 | -3.65 |

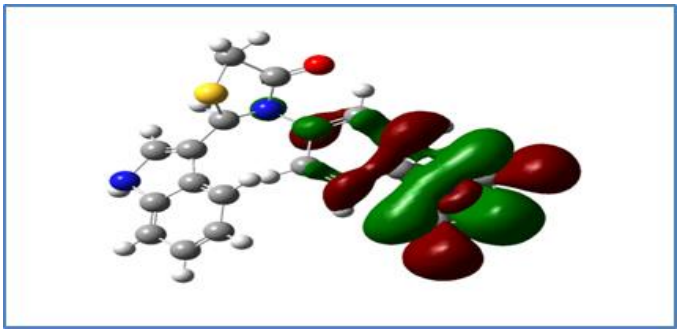


**Figure 10:** (HOMO) of compound 1

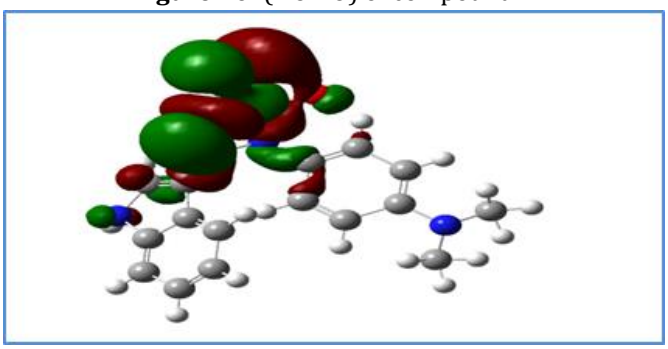


**Figure 11:** (LUMO) of compound 1

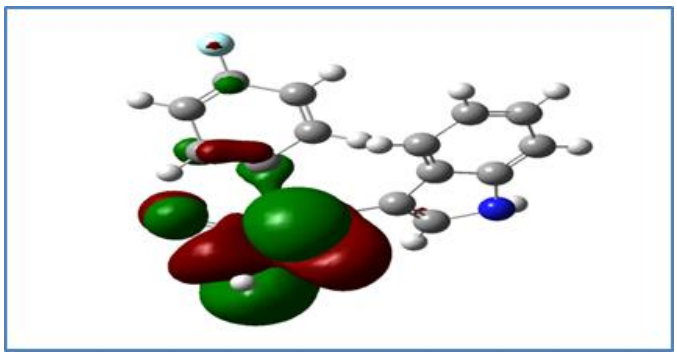


**Figure 12:** (HOMO) of compound 2

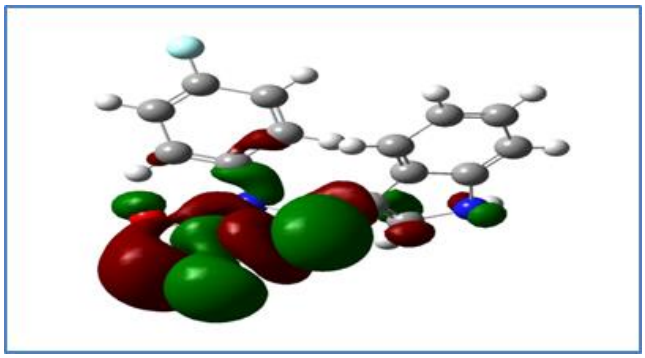


**Figure 13:** (LUMO) of compound 2

## Conclusion

The present study includes the synthesis and characterization of imine compounds, in addition to the synthesis of thiazolidinones from the reaction of the corresponding imine compounds with thioglycolic acid. These compounds were characterized with various spectral methods like (IR) and ($^1$H-NMR). Gaussian program was used to computational study thiazolidinones and the thermodynamic variables were calculated for these compounds.

## Acknowledgment

The author thanks the College of Science/ University of Thi-Qar.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

## Conflict of Interest

The author declared that they have no conflict of interest.

## ORCID:

*Auhood Kadhim Zaid*

*https://orcid.org/0000-0002-5912-5372*

## References

[1]. Nusrat S., Ayushi S., Jay S., Dinesh K.A., Shikha A., *Topics in current chem*., 2020, **378**:34 [Crossref], [Google Scholar], [Publisher]

[2]. Altowyan M.S., Khalil SMSM, Al-Wahaib D., Barakat A., Soliman S.M., Ali A.E., Elbadawy H.A., Molecules, 2022, 18;27(14):4583 [Crossref], [Google Scholar], [Publisher]

[3]. Zhang Q., Zhou H., Zhai S., Yan B., Natural product-inspired synthesis of thiazolidine and thiazolidinone compounds and their anticancer activities, *Current pharmaceutical design*, 2010, **16**:1826 [Crossref], [Google Scholar], [Publisher]

[4]. Gupta A., Singh R., Sonar P.K., Saraf S.K., Novel 4-thiazolidinone derivatives as anti-infective agents: synthesis, characterization, and antimicrobial evaluation, *Biochemistry research international*, 2016, **2016**:8086762 [Crossref], [Google Scholar], [Publisher]

[5]. Tabei A., Ejtemaei R., Mahboubi A., Saniee P., Foroumadi A., Dehdari A., Synthesis of new 2-(5-(5-nitrofuran-2-yl)-1, 3, 4-thiadiazol-2-ylimino) thiazolidin-4-one derivatives as anti-MRSA and anti-H. pylori agents, *BMC chemistry*, 2022, **16**:38 [Crossref], [Google Scholar], [Publisher]

[6]. Gowdra V.S., Mudgal J., Bansal P., Nayak P.G., Manohara Reddy S.A., Shenoy G.G., Valiathan M., Chamallamudi M.R., Nampurath G.K., Synthesis, characterization, and preclinical evaluation of new thiazolidin-4-ones substituted with p-chlorophenoxy acetic acid and clofibric acid against insulin resistance and metabolic disorder, *BioMed Research International*, 2014, **2014**:620434 [Crossref], [Google Scholar], [Publisher]

[7]. Avupati V.R., Yejella R.P., Akula A., Guntuku G.S., Doddi B.R., Vutla V.R., Anagani S.R., Adimulam L.S., Vyricharla A.K., Synthesis, characterization

and biological evaluation of some novel 2, 4-thiazolidinediones as potential cytotoxic, antimicrobial and antihyperglycemic agents, *Bioorganic & medicinal chemistry letters*, 2012, **22**:6442 [Crossref], [Google Scholar], [Publisher]

[8]. Liaras K., Fesatidou M., Geronikaki A., Thiazoles and thiazolidinones as COX/LOX inhibitors, *Molecules*, 2018, **23**:685 [Crossref], [Google Scholar], [Publisher]

[9]. Akbulut C., Öztürk B., Genc H., Zengin M., Yön N.D., Developmental Toxicity of (4S)-2-(4-hydroxy-3-methoxyphenyl) thiazolidine-4-carboxylic acid in Zebrafish (Danio rerio), *Brazilian Archives of Biology and Technology*, 2017, **60** [Crossref], [Google Scholar], [Publisher]

[10]. Rodriguez del Rey F.O., Floreancig P.E., Synthesis of Nitrogen-Containing Heterocycles through Catalytic Dehydrative Cyclization Reactions, *Organic Letters*, 2021, **23**:150 [Crossref], [Google Scholar], [Publisher]

[11]. Hayal M.Y., Magtoof M.S., Synthesis, Characterization of some New 4-Thiazolidinone of Acenaphthoquinone, *University of Thi-Qar Journal of Science*, 2021, **8**:76 [Google Scholar], [Publisher]

[12]. Alshibl H.M., Al-Abdullah E.S., Haiba M.E., Alkahtani H.M., Awad G.E.A., Mahmoud A.H., Ibrahim B.M.M., Bari A., Villinger A., Synthesis and evaluation of new coumarin derivatives as antioxidant, antimicrobial, and anti-inflammatory agents, *Molecules*, 2020, **25**:3251 [Crossref], [Google Scholar], [Publisher]

[13]. Zainab Amer Salla, *University of Thi-Qar journal of science*, 2020, **7**:87

[14]. Gupta A., Singh R., Sonar P.K., Saraf S.K., Novel 4-thiazolidinone derivatives as anti-infective agents: synthesis, characterization, and antimicrobial evaluation, *Biochemistry research international*, 2016,:8086762 [Crossref], [Google Scholar], [Publisher]

[15]. Kirishnamaline G., Magdaline J.D., Chithambarathanu T., Aruldhas D., Anuf A.R., Theoretical investigation of structure, anticancer activity and molecular docking of thiourea derivatives, *Journal of Molecular Structure*, 2021, **1225**:129118 [Crossref], [Google Scholar], [Publisher]

[16]. 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**:133758 [Crossref], [Google Scholar], [Publisher]

[17]. 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 [Crossref], [Google Scholar], [Publisher]

[18]. Huynh T.T., Pham H.Q., Nguyen A.V., Bach L.G., Ho V.T.T., Advanced nanoelectrocatalyst of Pt nanoparticles supported on robust Ti0. 7Ir0. 3O2 as a promising catalyst for fuel cells, *Industrial & Engineering Chemistry Research*, 2019, **58**:675 [Crossref], [Google Scholar], [Publisher]

[19]. Toghan A., Modwi A., Khairy M., Taha K.K., Influence of $TiO_2$ concentration on the characteristics of ZnO nanoparticles fabricated via sonication assisted with gelatin, *Chemical Physics*, 2021, **551**:111350 [Crossref], [Google Scholar], [Publisher]

[20]. Norma F. H., Juan Frau and Daniel G. M., Chemical-Reactivity Properties, Drug Likeness, and Bioactivity Scores of Seragamides A–F Anticancer Marine Peptides: Conceptual Density Functional Theory Viewpoint. *Computation* 2019, **7**:52 [Google Scholar], [Publisher]

[21]. Esselman B.J., Hill N.J., Integration of computational chemistry into the undergraduate organic chemistry laboratory curriculum, *Journal of Chemical Education*, 2016, **93**:932 [Crossref], [Google Scholar], [Publisher]

[22]. Wolf M.E., Norris J.W., Fynewever H., Turney J.M., Schaefer H.F., An Undergraduate Chemistry Lab Exploring Computational Cost and Accuracy: Methane Combustion Energy, *Journal of Chemical Education*, 2022, **99**:1479 [Crossref], [Google Scholar], [Publisher]

**HOW TO CITE THIS ARTICLE**
Auhood Kadhim Zaid. 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