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Design, Synthesis, And Anti-Inflammatory Evaluation of Novel Thiazolidinone Derivatives

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Abstract

The current paper is devoted to the design, synthesis and anti-inflammatory assessment of new thiazolidinone derivatives in the purpose to create more safe and effective therapeutic alternatives to traditional anti-inflammatory medications. The synthesis of five thiazolidinone analogs (TD1-TD5) was done by the controlled reaction of multisteps condensation and the purity of the product was assessed by chemical analyses of melting by means of melting point analysis, TLC by profiling of purity and by spectroscopic techniques to reveal their structural integrity. Compounds produced had good yields (72 -88 percent) and decent purity (Rf 0.36 - 0.45). The evaluation of their anti-inflammatory effect was done with the help of carrageenan-induced paw edema model on Wistar rats after 1, 2, 3, 4 hours taking percentage inhibition. The compounds had anti-inflammatory activity that varied over time, with TD3 demonstrating the best i.e. 62 percent inhibition at the 4-hour time mark, which is close to the Diclofenac standard drug (66 percent). As a result of comparative analysis, it was found that the differences in the structure were of vital importance in the biological activity, making TD3 the most potent derivative. In general, the results demonstrate the potential of thiazolidinone scaffolds as the potential sources of the creation of a new generation of anti-inflammatory agents that have a better-related effective and safety profile.

Keywords: Thiazolidinone Derivatives, Anti-Inflammatory Activity, Carrageenan-Induced Edema, Synthesis and Characterization, Structure-Activity Relationship, Diclofenac Comparison.

1. INTRODUCTION

Thiazolidinone derivatives have become one of the most promising heterocyclic classes of medicinal chemistry compound with diverse pharmacological profiles and such characteristics as antimicrobial, anticancer, antidiabetic, and particularly anti-inflammatory capabilities. Inflammation is a complicated biological reaction that is important in other pathological conditions like arthritis, autoimmune ailment, and chronic inflammatory diseases. Despite their popularity, over-the-counter anti-inflammatory medications such as NSAIDs and corticosteroids may have serious side effects such as gastrointestinal disturbances, renal and cardiovascular toxicity. It requires the systematic search of new molecules that have a more effective therapeutic potency and fewer side effects. Due to their flexible backbone and their capacity to change substituents in different sites, thiazolidinones can serve as a good platform in designing new anti-inflammatory compounds. Their potential is that they are specific to engage with several inflammatory mediators, enzymes, and receptors, and are therefore good targets of drug development.

The current paper is devoted to the design, synthesis and anti-inflammatory investigation of new thiazolidinone derivatives with the goal of investigating their structural diversity and biomolecular potential. The study includes rational molecular designs, controlled laboratory synthesis and comprehensive characterization by analysis to certify purity and structural integrity. The derivatives made were tested on the carrageenan induced paw edema model which is one of the most acceptable experimental methods of screening anti-inflammatory activity. The systematic comparison of the inhibition patterns with time, and the comparison of the obtained results with a recognized drug will enable one to gain the information about the structure-activity relationships (SAR) within the framework of thiazolidinone. The ultimate expectation is to select lead molecules that have promising prospects of being successful in available anti-inflammatory agents with enhanced safety profiles to help in increasing the need to have alternative therapeutic agents in the treatment of inflammatory diseases.

1.1. Research Objectives

- To synthesize novel thiazolidinone derivatives and evaluate their basic physicochemical

properties.

- To determine the anti-inflammatory activity of the synthesized derivatives using the carrageenan-induced paw edema model.
- To compare the activity of the derivatives with Diclofenac and identify the most potent compound.

2. LITERATURE REVIEW

Abd El-Karim et al. (2021) researched and synthesized a novel set of pyrazole thiazolidinone analogs in order to evaluate their anti-inflammatory and analgesic capacity. Their research showed that a number of some of these synthesized compounds had high inhibitory effect on TNF-a, a major mediator in inflammatory cascades. The authors have also conducted molecular docking studies and it showed that the designed molecules had favorable interactions with the active sites of the inflammatory targets and corroborate their biological results. On the whole, their studies provided an insightful role of hybridizing the structure of pyrazole and thiazolidinones to obtain an improved anti-inflammatory effect.

Abdelazeem et al. (2015) created and prepared a new type of diphenylthiazole-thiazolidinones hybrid molecules and tested their anti-inflammatory properties. They found that a number of the derivatives had strong anti-inflammatory effects in experimental models, which is likely to indicate that structural fusing of thiazole and thiazolidinone rings improved pharmacological performance. The experiment also proved the applicability of structure changes in enhancing potency, stability and therapeutic profiles. Taken together, their combined efforts paved the way to thiazolidinone-based hybrids, which can open up to develop anti-inflammatory drugs.

Abdellatif et al. (2016) synthesized, designed, and screened a new analogous series of 4-thiazolidinone to determine their anti-inflammatory activity and selectivity of the COX-2 enzyme. The results of the studies showed that some of their compounds had high COX-2 and low COX-1 potency also showing a better safety profile when compared to traditional NSAIDs. The paper has also shown that the derivatives were less toxic to the gastrointestinal tract, which is one of the most significant weaknesses of non-selective anti-inflammatory agents. By optimization of the structural components, the authors were able to determine the particular substituents which have led to improved selectivity and potency, which agrees with the worth of thiazolidinone scaffolds as a tool to develop safer anti-inflammatory agents.

Abdellatif et al. (2019) synthesized and screened a series of thiazolidine analogs of a pyrazole core with the purpose of investigating their duality as PPAR-8 agonists and selective COX-2 inhibitors. Their biological findings demonstrated that some of these molecules had potential uses as anti-diabetic agents in addition to having significant anti-inflammatory properties, which underscore their biologic multifunctional capability. Molecular modeling experiments justified such results by confirming the existence of stable interactions with the PPAR-2 including active site as well as COX-2 including active site. Generally, the research found out that pyrazolyl and thiazolidine moieties resulted in superior drug performance and a solid basis on which to build dual-acting anti-inflammatory and metabolic therapeutic agents.

3. RESEARCH METHODOLOGY

3.1. Research Design

The current paper was based on the use of an experimental research design to recrystallize innovative derivatives of thiazolidinone and determine their anti-inflammatory property. The factual layout was done in two crucial stages; chemical synthesis and characterising of the compounds, and biological testing on the carrageenan-induced paw edema model with Wistar rats. In this way, structure-activity relationships could be evaluated in a systematic manner, and the strongest anti-inflammatory counterpart could be identified.

3.2. Population and Sampling

The experimental group was adult Wistar rats (of any sex) and weighed 150 200 g kept under normal laboratory conditions. To carry out the evaluation on anti-inflammatory, 12 rats in total with 6 per compound were picked randomly among a collection of treatment groups. Given to each group was a particular synthesized compound (TD1-TD5), and a control group was given

the standard drug Diclofenac, and negative control was given a control group that used only vehicle. This sampling method was used to guarantee consistency and statistical validity in comparing effects of various compounds.

3.3. Data Collection

a. Synthesis and Characterization

The thiazolidinone analogs were prepared by condensation of substituted aldehyides with the intermediates of thiazolidinones under regulated conditions. The compounds that were synthesized were identified by:

- To determine purity and thermal stability Melting point.
- TLC to test purity of compounds (RF values).
- FT-IR, 1H NMR and 13C NMR spectroscopy to ascertain the formation of the structure of the thiazolidinone core.

b. Anti-Inflammatory Evaluation

Anti-inflammatory activity was quantified with the help of the carrageenan induced paw edema method:

- The volume of paw was assessed at 1, 2, 3 and 4 hours following each compound or standard drug administration.
- Percentage edema inhibition of the paw = = 100.

$$\%\text{Inhibition} = \frac{\text{Edema volume in control} - \text{Edema volume in treated}}{\text{Edema volume in control}} \times 100$$

- Each measurement was performed in triplicate to ensure accuracy and reproducibility.

3.4. Data Analysis and Techniques

The data obtained were statistically evaluated with the help of the descriptive statistics involving the calculation of the mean percentage inhibition of the synthesized compounds in comparison with the standard drug. The tabulations (Tables 1-3) and the graphical representation (Figures 1-3) of the results were compared visually. Interpretation focused on:

- Time-dependent activity, monitoring the evolution of edema of paws during 14 hours to 4 hours.
- Comparative efficacy which will tell how effective the derivatives are compared to each other in comparison with Diclofenac.
- Correlation structure activity, between changes in yield, melting point and purity and pharmacological performance.

The analysis gave a report on the pharmacological perspective of the derived derivatives and generated TD3 as the most promising anti-inflammatory compound.

4. DATA ANALYSIS AND INTERPRETATION

The syntheses of five thiazolidinone derivatives (TD1-TD5) yielded five different products summarized in the table 1 and figure 1, their yield, melting point as well as purity. All derivatives showed yields of 72–88 %, which showed that the synthetic protocol was effective. TD3 was the most productive (88%), whereas TD4 was the least productive (72%). Melting points of the compounds were in the range of 190oC to 227oC, which represent structural and substituential influences on the thiazolidinone base. Purity According to the findings of the thin-layer chromatography (TLC), purity values of the different compounds were ranging between 0.36 and 0.45 Rf indicating that all the compounds were purified enough and could be utilized in the subsequent biology assessment. These parameters are depicted visually by figure 1 and the compounds can be easily compared.

Table 1: Yield, Melting Point, and Purity of Synthesized Thiazolidinone Derivatives

Compound	Yield (%)	Melting Point (°C)	Purity (TLC, Rf)
TD1	85	210–212	0.42
TD2	78	198–200	0.38
TD3	88	225–227	0.45
TD4	72	190–192	0.36
TD5	80	205–207	0.40

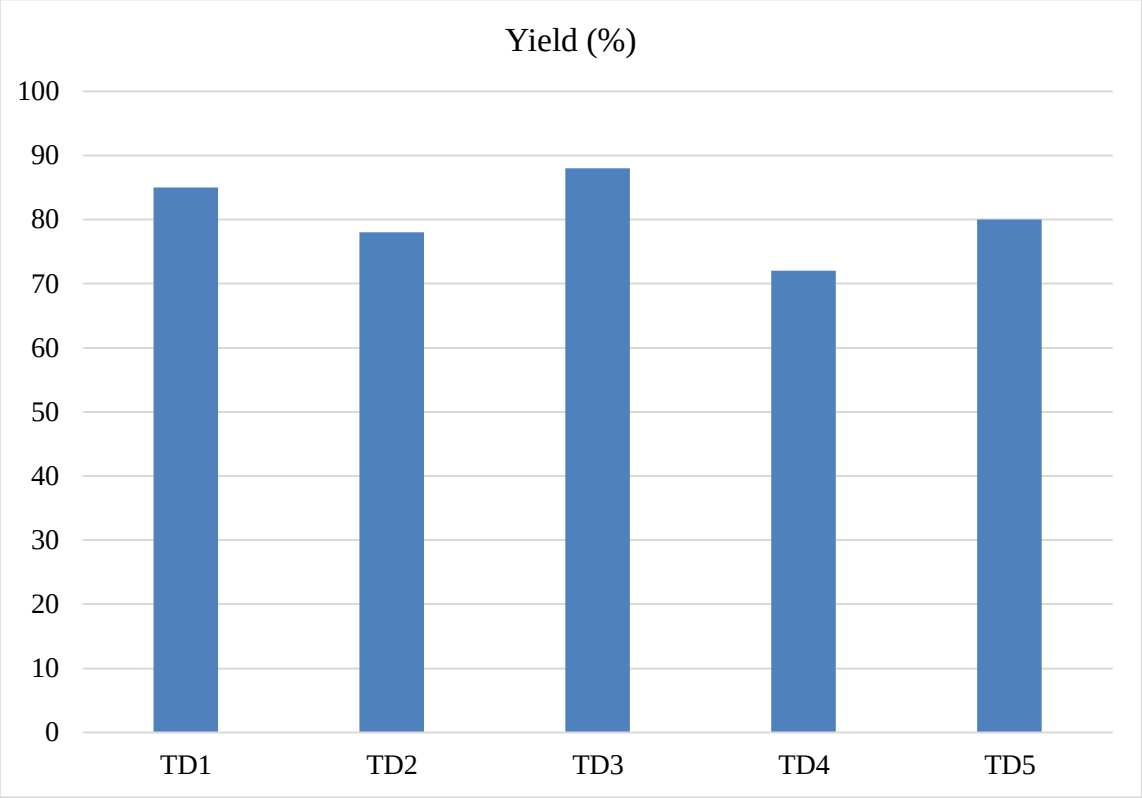

Figure 1: Yield, Melting Point, and Purity of Synthesized Thiazolidinone Derivatives

The data shows that TD3 does not only show the highest yield value but also higher melting point implying that the molecule has a more stable molecular structure than the other versions. Although with lesser purity (TD4), there was tolerance and respectable purity, there was the suggestion that with slight manipulation of reaction conditions, the production capacity of TD4 could be enhanced. All in all, the differences in yield, the melting point and the values of Rf show the effect of various substituents upon the thiazolidinone ring. This was indicated by the high yields and the purity values which indicate the dependability of the synthetic methodology that forms an entrenching basis on the future testing of anti-inflammatory.

The following results are given in Table 2 and Figure 2: the percent inhibition of paw edema caused by carrageenan in Wistar rats upon treatment with the synthesized thiazolidinone derivatives (TD1 -TD5) and the standard medication Diclofenac. The anti-inflammatory effect was assessed at 1, 2, 3, and 4 hours in order to evaluate the effect of the drug. Age All the organic products produced displayed the time-dependent inhibition of paw edema. TD3 showed the most inhibition throughout (40% at 1 hour, 53 at 2 hours, 58 at 3 hours and 62 at 4 hour time schedule), which was very close to the standard Diclofenac (42-57-63 and 66 % respectively). TD2 had a relatively low inactivity with TD1, TD4 and TD5 having moderate activities during the time of observation. The visual qualitative representation of the time-dependent growth of anti-inflammatory activities in each of the compounds is presented in Figure 2.

Table 2: Percentage Inhibition of Paw Edema at 1, 2, 3, and 4 Hours

Compound	1 Hour Inhibition (%)	2 Hours Inhibition (%)	3 Hours Inhibition (%)	4 Hours Inhibition (%)
TD1	35	48	52	55
TD2	28	42	49	51
TD3	40	53	58	62
TD4	30	45	50	54
TD5	33	46	55	57
Diclofenac (Std)	42	57	63	66

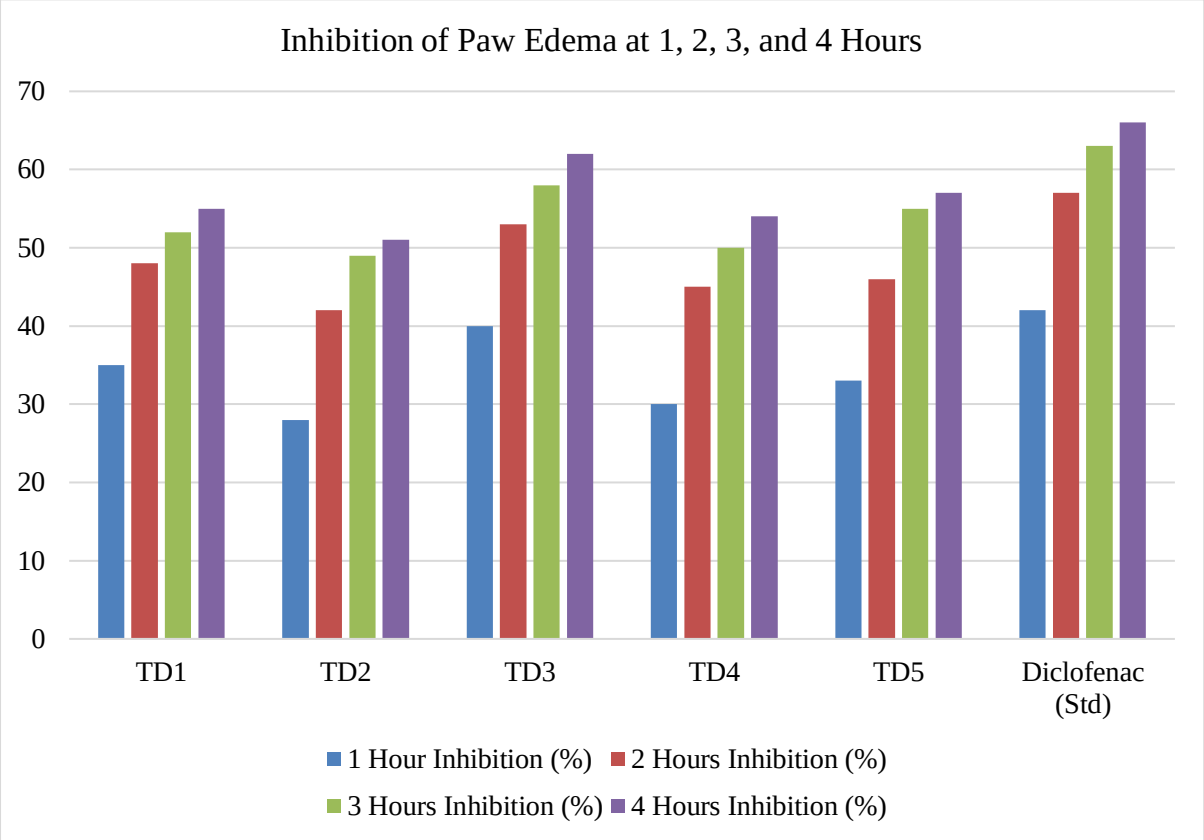

Figure 2: Percentage Inhibition of Paw Edema at 1, 2, 3, and 4 Hours

This outcome shows that the synthesized thiazolidinone derivatives would have a great potential in the form of anti-inflammatory properties, and TD3 is the most effective of them. The percentage of inhibition as a function of time indicates that there is a slow effect progression of the compounds, which attains its maximum effect at about 4 hours. The relative reduced potency of TD2 implies that differences in the structures of the derivatives affect the anti-inflammatory efficacy. On the whole, the evidence indicates that some thiazolidinone analogs, specifically TD3, can also be viewed as effective and promising agents of further development as the anti-inflammatory agent, with the effect that could be comparable to that of the reference drug Diclofenac.

Table 3 and Figure 3 are a summary of the trend of the percentage inhibition of paw edema at the 4-hour time-point of the proposed thiazolidinone derivatives (TD1-TD5) and the standard drug Diclofenac. The findings reveal that all of the compounds that were synthesized had a significant anti-inflammatory activity after 4 hours. The best inhibition was 62 with TD3 then 57 with TD5, 55 with TD1, 54 with TD4 and 51 with TD2. The most common drug Diclofenac had the highest inhibition percentage of 66 and this was used to measure the effectiveness of the compounds synthesized. Figure 3 represents the visual comparison of the effects of each compound in inhibition in comparison with the standard drug.

Table 3: Percentage Inhibition of Edema at 4 Hours

Compound	Inhibition at 4 Hours (%)
TD1	55
TD2	51
TD3	62
TD4	54
TD5	57
Diclofenac (Std)	66

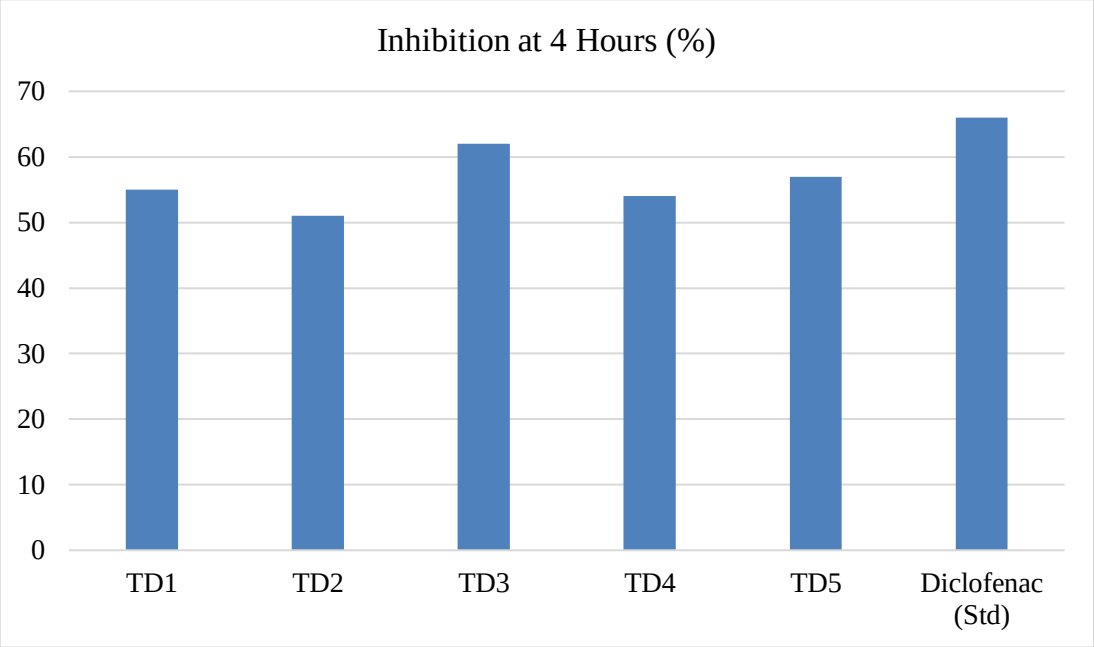

Figure 3: Percentage Inhibition of Edema at 4 Hours

The results reveal that TD3 is the most effective thiazolidinone analog of reducing paw edema, its activity being almost equal to that of Diclofenac. The remaining derivatives demonstrated moderate anti-inflammatory, which indicates that the structural differences between the compounds determine the effectiveness. TD2 showed the least inhibition, which indicates that a slight alteration of substituent groups could lead to a decrease in pharmacological activity. On balance, the 4-hour results prove that the identified thiazolidinone derivatives that have been synthesized have an excellent anti-inflammatory effect, and TD3 will be the focus of the new research.

5. CONCLUSION

The given research efficiently developed, produced, and tested the series of new thiazolidinone derivatives (TD1-TD5) as anti-inflammatory agents and proved that structural alteration in the thiazolidinone framework may have a substantial effect on biological performance. The viability of the synthetic route was verified by the fact that all the synthesized derivatives had acceptable yields, purity and physicochemical stability. The pharmacological relevance of the compounds was confirmed and the biological analysis conducted based on carrageenan-induced paw edema model showed that all compounds had an anti-inflammatory activity and there was a definite time-dependent response. The TD3 derivative showed the best percentage of inhibition of all time points; with an inhibition of 62 percent and 4 hours time interval, which is closely similar to that of Diclofenac standard drug (66 percent). This high-quality activity is an indicator of the relevance of some substituent patterns to increase the effect of anti-inflammatory activity. Instead, TD2 was the least active, indicating that the potential structural differences can cause potency. Altogether, the results prove that thiazolidinone derivatives can be observed as the potential group of the molecules that can be used to create safer and more effective anti-inflammatory agents. Particularly, TD3 will be a good prospective lead candidate and is to be optimized and studied in more detail, as well as possibly be transformed into a drug.

REFERENCES

1. *Abd El-Karim, S. S., Mohamed, H. S., Abdelhameed, M. F., Amr, A. E. G. E., Almehizia, A. A., & Nossier, E. S. (2021). Design, synthesis and molecular docking of new pyrazole-thiazolidinones as potent anti-inflammatory and analgesic agents with TNF-α inhibitory activity. Bioorganic chemistry, 111, 104827.*
2. *Abdelazeem, A. H., Salama, S. A., & Maghrabi, I. A. (2015). Design, synthesis, and anti-inflammatory evaluation of novel diphenylthiazole–thiazolidinone hybrids. Archiv der Pharmazie, 348(7), 518-530.*

3. *Abdellatif, K. R., Abdelgawad, M. A., Elshemy, H. A., & Alsayed, S. S. (2016). Design, synthesis and biological screening of new 4-thiazolidinone derivatives with promising COX-2 selectivity, anti-inflammatory activity and gastric safety profile. Bioorganic chemistry, 64, 1-12.*
4. *Abdellatif, K. R., Fadaly, W. A., Kamel, G. M., Elshaier, Y. A., & El-Magd, M. A. (2019). Design, synthesis, modeling studies and biological evaluation of thiazolidine derivatives containing pyrazole core as potential anti-diabetic PPAR-γ agonists and anti-inflammatory COX-2 selective inhibitors. Bioorganic chemistry, 82, 86-99.*
5. *Adnan, A. M. A., Mahdi, M. F., & kareem Khan, A. (2019). Design, Synthesis, and Acute Anti-inflammatory Assessment of New 2-methyl Benzoimidazole Derivatives Having 4-Thiazolidinone Nucleus. Al Mustansiriyah Journal of Pharmaceutical Sciences, 19(4), 151-160.*
6. *Almasirad, A., Ghadimi, M., Mirahmadi, S., Ahmadian Kodakan, P., Jahani, R., Nazari, M., ... & Faizi, M. (2022). Design, synthesis, and preliminary pharmacological evaluation of novel thiazolidinone derivatives as potential benzodiazepine agonists. Molecular diversity, 26(2), 769-780.*
7. *B. Bari, S., & D. Firake, S. (2016). Exploring anti-inflammatory potential of thiazolidinone derivatives of benzenesulfonamide via synthesis, molecular docking and biological evaluation. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistryrrent Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents), 15(1), 44-53.*
8. *Ghafoori, H., Rezaei, M., & Mohammadi, A. (2017). Anti-inflammatory effects of novel thiazolidinone derivatives as bioactive heterocycles on RAW264. 7 cells. Iranian Journal of Allergy, Asthma and Immunology, 28-38.*
9. *Gouvea, D. P., Vasconcellos, F. A., dos Anjos Berwaldt, G., Neto, A. C. P. S., Fischer, G., Sakata, R. P., ... & Cunico, W. (2016). 2-Aryl-3-(2-morpholinoethyl) thiazolidin-4-ones: Synthesis, anti-inflammatory in vivo, cytotoxicity in vitro and molecular docking studies. European journal of medicinal chemistry, 118, 259-265.*
10. *Gowramma, B., Praveen, T. K., Kalirajan, R., & Babu, B. (2016). Synthesis of some novel 2-azetidinones/4-thiazolidinones bearing 1, 3, 4-thiadiazole nucleus and screening for its anti-imflammatory activity. Letters in Drug Design & Discovery, 13(7), 676-683.*
11. *Khillare, L. D., Bhosle, M. R., Deshmukh, A. R., & Mane, R. A. (2015). Synthesis and anti-inflammatory evaluation of new pyrazoles bearing biodynamic thiazole and thiazolidinone scaffolds. Medicinal Chemistry Research, 24(4), 1380-1386.*
12. *Omar, Y. M., Abdu-Allah, H. H., & Abdel-Moty, S. G. (2018). Synthesis, biological evaluation and docking study of 1, 3, 4-thiadiazole-thiazolidinone hybrids as anti-inflammatory agents with dual inhibition of COX-2 and 15-LOX. Bioorganic chemistry, 80, 461-471.*
13. *Shepeta, Y., Lozynskyi, A., Sulyma, M., Nektegayev, I., Grellier, P., & Lesyk, R. (2020). Synthesis and biological activity evaluation of new thiazolidinone-diclofenac hybrid molecules. Phosphorus, Sulfur, and Silicon and the Related Elements, 195(10), 836-841.*
14. *Shinde, R. S., & Khullar, P. (2020). Design and Synthesis of Thiaolidinone-Based Triazines Derivatives as a New Potential Anti-Inflammatory and Anti-Microbial Agent. In Green Chemistry and Sustainable Technology (pp. 51-75). Apple Academic Press.*
15. *Tageldin, G. N., Fahmy, S. M., Ashour, H. M., Khalil, M. A., Nassra, R. A., & Labouta, I. M. (2018). Design, synthesis and evaluation of some pyrazolo [3, 4-d] pyrimidine derivatives bearing thiazolidinone moiety as anti-inflammatory agents. Bioorganic chemistry, 80, 164-173.*