Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

*Article*
**Volume 11, Issue 1, 2021, 8009 - 8017**
https://doi.org/10.33263/BRIAC111.80098017

# Synthesis of Some $C^5$ Substituted 4-Phenylimino-Thiazolidin-2-Ones as Possible Anti-Inflammatory Agents

**Zoriana Chulovska [1], Taras Chaban [1], Iryna Drapak [1], Vasyl Matiychuk [2], Ihor Chaban [1,*], Ihor Nektegaev [1]**

[1] Danylo Halytsky Lviv National Medical University, Pekarska 69, Zip Code: 79010, Lviv, Ukraine
[2] Ivan Franko National University of Lviv, 6 Kyryla and Mefodia, Zip Code: 79005, Lviv, Ukraine
* Correspondence: chabanihor@ukr.net;

Scopus Author ID 7003601284
**Received: 7.06.2020; Revised: 2.07.2020; Accepted: 4.07.2020; Published: 9.07.2020**

**Abstract:** Based on the Knoevenagel condensation, nitrosation, and azo coupling reactions, the synthesis of some $C^5$ substituted 4-phenylimino-thiazolidin-2-ones was carried out. The chemical structures of the synthesized products have been determined by $^1$H NMR spectroscopy and elemental analysis. Evaluation of novel compounds over the carrageenan-summoned rat paw edema revealed a powerful anti-inflammatory effect of some substances which exceeds the activity of the comparative drug Ibuprofen.

**Keywords:** organic synthesis; 4-phenylimino-thiazolidin-2-ones; analytical and spectral methods; anti-inflammatory activity.



## 1. Introduction

Inflammation in one form or another is at the cause of the majority of the common diseases. It is the protection mechanism to self-healing after a spread of diseases beginning from traumatic disorder or pyrexia related to the infection to major life dangerous ailments like a brain hemorrhage or myocardial infarction [1]. Non-steroidal anti-inflammatory drugs are the best extensively used medicinal agents for the therapy of pain and inflammation and of tremendous therapeutic benefit in the management of varying types of the inflammatory process [2]. However, at the present time NSAIDS can have essential, serious side effects. In particular of the observed gastrointestinal damage, hemorrhage, ulceration, and their related sequela [3]. To surmount these limitations, the search is ongoing throughout the world to develop more effective anti-inflammatory agents.

Organic heterocyclic compounds currently account for about 70 % of all clinically used drugs [4]. Thiazolidinones are one of the most intensively investigated classes in non-condensed heterocyclic systems. They are biologically important five-membered compounds possessing practically all types of pharmacological activities [5-11].

4-Iminothiazolidones, in simile with isomeric 2-imino derivatives, are have been deficient studied [12-15]. It is worth noting that the use of iminoazolidinones with an unsubstituted vicinal carbon atom opens up access to various types of condensed heterocyclic systems [16-25]. 4-Iminothiazolidinones in have also been also used as sensitive analytical reagents [26-33].

In this article, which is the portion of our exploring biologically active heterocycles [34-53] we synthesized a series of $C^5$ substituted 4-phenylimino-thiazolidin-2-ones for pharmacological screening of anti-inflammatory activity.

## 2. Materials and Methods

### *2.1. Materials.*

The reagents used in the synthesis were commercially available and of analytical grade. All solvents and reagents were used without further purification. Ibuprofen was purchased from a medical store.

### *2.2. Chemistry.*

All melting points were determined in an open capillary. $^1$H- spectra were recorded on a Varian Mercury 400 (400 MHz for $^1$H) instrument with TMS or deuterated solvent as an internal reference. Chemical shifts are reported as δ (ppm). Elemental analysis was performed on a Vario MICRO cube automatic CHNS analyzer. This experimental analysis data on contents of Carbon, Hydrogen, and Nitrogen were within ±0.3% of the theoretical values.

***General procedure for the synthesis of 5-arylidene-4-phenylimino-thiazolidin-2-ones (1-10)***: To 40ml of acetate acid was added 0.01 mol of 4-phenylimino-thiazolidin-2-one, 0.01 mol of the corresponding aromatic aldehyde and a few drops of monoaminoethanol were added. Then the specified mixture was heated for 30 min. The crystalline precipitated after cooling is filtered off, washed with water, and dried. The obtained compounds are recrystallized from acetate acid.

***5-(2-Nitro-benzylidene)-4-phenylimino-thiazolidin-2-one* (1).** Yield 60%, mp >260°C. $^1$H NMR (400 MHz, DMSO) δ 10.97 (s, 1H, NH), 8.33 (s, 1H, CH), 8.20 (dd, *J* = 8.2 Hz, 1H, $C_6H_4$), 7.93-7.71 (m, 5H, $C_6H_4$+N-phenyl), 7.47 (t, *J* = 7.9 Hz, 2H, N-phenyl), 7.28 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92. Found: C, 59.15; H, 3.51; N, 12.79.

***5-(3-Nitro-benzylidene)-4-phenylimino-thiazolidin-2-one* (2).** Yield 65%, mp 249°C. $^1$H NMR (400 MHz, DMSO) δ 10.85 (s, 1H, NH), 8.38 (s, 1H, CH), 8.28 (dd, *J* = 8.2 Hz, 1H, $C_6H_4$), 8.25 (s, 1H, $C_6H_4$), 8.00 (d, *J* = 7.8 Hz, 1H, $C_6H_4$), 7.86-7.80 (m, 3H, $C_6H_4$+N-phenyl), 7.47 (t, *J* = 7.9 Hz, 2H, N-phenyl), 7.27 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92. Found: C, 59.11; H, 3.38; N, 12.99.

***5-(4-Nitro-benzylidene)-4-phenylimino-thiazolidin-2-one* (3).** Yield 84%, mp 257°C. $^1$H NMR (400 MHz, DMSO) δ 10.96 (s, 1H, NH), 8.39 (d, *J* = 8.9 Hz, 2H, $C_6H_4$), 8.25 (s, 1H, CH), 7.86 (d, *J* = 8.9 Hz, 2H, $C_6H_4$), 7.80 (d, *J* = 8.0 Hz, 2H, N-phenyl),7.48 (t, *J* = 7.6 Hz, 2H, N-phenyl), 7.28 (t, *J* = 6.7 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92. Found: C, 58.96; H, 3.45; N, 12.88.

***5-(4-Dimethylamino-benzylidene)-4-phenylimino-thiazolidin-2-one* (4).** Yield 55%, mp >260°C. $^1$H NMR (400 MHz, DMSO) δ 10.90 (s, 1H, NH), 8.28 (s, 1H, CH), 7.96 (d, *J* = 7.9 Hz, 2H, N-phenyl), 7.47 (t, *J* = 7.7 Hz, 2H, N-phenyl), 7.40 (d, *J* = 9.0 Hz, 2H, $C_6H_4$), 7.27 (t, *J* = 7.4 Hz, 1H, N-phenyl), 6.87 (d, *J* = 9.0 Hz, 2H, $C_6H_4$), 3.00 (s, 6H, 2*$CH_3$). Anal. Calcd. for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.77; H, 5.33; N, 12.85.

***5-(4-Diethylamino-benzylidene)-4-phenylimino-thiazolidin-2-one* (5).** Yield 58%, mp >260°C. $^1$H NMR (400 MHz, DMSO) δ 10.46 (s, 1H, NH), 8.03 (s, 1H, CH), 7.79 (d, *J* = 8.1 Hz, 2H, N-phenyl), 7.47 (d, *J* = 9.1 Hz, 2H, $C_6H_4$), 7.41 (t, *J* = 7.8 Hz, 2H, N-phenyl), 7.27 (t,

*J* = 7.4 Hz, 1H, N-phenyl), 6.82 (d, *J* = 9.1 Hz, 2H, $C_6H_4$), 3.45-3.40 (m, 4H, 2*$CH_2$), 1.13 (t, *J* = 7.0 Hz, 6H, 2*$CH_3$). Anal. Calcd. for $C_{20}H_{21}N_3OS$: C, 68.35; H, 6.02; N, 11.96. Found: C, 68.39; H, 5.97; N, 11.88.

***5-(4-Bromo-benzylidene)-4-phenylimino-thiazolidin-2-one* (6).** Yield 88%, mp >260°C. $^1$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H, NH), 8.11 (s, 1H, CH), 7.80-7.76 (m, 4H, $C_6H_4$+N-phenyl), 7.56 (d, *J* = 8.5 Hz, 2H, $C_6H_4$), 7.46 (t, *J* = 8.0 Hz, 2H, N-phenyl), 7.26 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{16}H_{11}BrN_2OS$: C, 53.49; H, 3.09; N, 7.80. Found: C, 53.55; H, 3.12; N, 7.90.

***5-(4-Hydroxy-3-methoxy-benzylidene)-4-phenylimino-thiazolidin-2-one* (7).** Yield 72%, mp 259-260°C. $^1$H NMR (400 MHz, DMSO) δ 10.65 (s, 1H, NH), 9.98 (s, 1H, OH), 8.08 (s, 1H, CH), 7.79 (d, *J* = 7.7 Hz, 2H, N-phenyl), 7.45 (t, *J* = 8.3 Hz, 2H, N-phenyl), 7.23 (t, *J* = 7.4 Hz, 1H, N-phenyl), 7.13 (d, *J* = 8.3 Hz, 2H, $C_6H_3$), 6.97 (d, *J* = 8.0 Hz, 1H, $C_6H_3$), 3.85 (s, 3H, $CH_3$). Anal. Calcd. for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58. Found: C, 62.43; H, 4.41; N, 8.66.

***5-(3-Chloro-benzylidene)-4-phenylimino-thiazolidin-2-one* (8).** Yield 85%, mp 242-243°C. $^1$H NMR (400 MHz, DMSO) δ 10.82 (s, 1H, NH), 8.11 (s, 1H, CH), 7.79 (d, *J* = 8.0 Hz, 2H, N-phenyl), 7.59-7.52 (m, 4H, $C_6H_4$), 7.46 (t, *J* = 7.8 Hz, 2H, N-phenyl), 7.26 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{16}H_{11}ClN_2OS$: C, 61.05; H, 3.52; N, 8.90. Found: C, 61.18; H, 3.60; N, 8.82.

***5-(4-Chloro-benzylidene)-4-phenylimino-thiazolidin-2-one* (9).** Yield 88%, mp 260-261°C. $^1$H NMR (400 MHz, DMSO) δ 10.80 (s, 1H, NH), 8.14 (s, 1H, CH), 7.80 (d, *J* = 7.4 Hz, 2H, N-phenyl), 7.65-7.59 (m, 4H, $C_6H_4$), 7.46 (t, *J* = 7.7 Hz, 2H, N-phenyl), 7.26 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{16}H_{11}ClN_2OS$: C, 61.05; H, 3.52; N, 8.90. Found: C, 61.25; H, 3.48; N, 8.96.

***5-(3,4-Dimethoxy-benzylidene)-4-phenylimino-thiazolidin-2-one* (10).** Yield 80%, mp 254-256°C. $^1$H NMR (400 MHz, DMSO) δ 10.64 (s, 1H, NH), 8.09 (s, 1H, CH), 7.80 (d, *J* = 8.0 Hz, 2H, N-phenyl), 7.44 (t, *J* = 7.7 Hz, 2H, N-phenyl), 7.25-7.22 (m, 2H, N-phenyl+$C_6H_3$), 7.15 (d, *J* = 8.3 Hz, 2H, $C_6H_3$), Anal. Calcd. for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.12; H, 4.85; N, 8.11.

***4-Phenylimino-thiazolidine-2,5-dione 5-oxime* (11).** 0.01 Mol of 4-phenylimino-thiazolidin-2-one are added in 10 ml of 10 % HCl, chilled to 0 °C. The solution of 2.1 g sodium nitrite in 5 ml of water is appended to the suspension by dropping during mixing and cooling for 1 h. The resulting mixture is left at a temperature of 20-25 °C for 10-12 hours. The precipitate is filtered off, washed with water and dried at 60 °C. Yield 52%, mp 196°C. $^1$H NMR (400 MHz, DMSO) δ 13.27 (s, 1H, NH), 11.15 (s, 1H, OH), 7.83 (d, *J* = 7.8 Hz, 2H, N-phenyl), 7.42 (t, *J* = 7.5 Hz, 2H, N-phenyl), 7.24 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99. Found: C, 48.74; H, 3.07; N, 19.08.

**General procedure for the synthesis of 5-aryl-hydrazono]-4-phenylimino-thiazolidin-2-ones (12-14).** 0.01 mol of the corresponding amine is dissolved in 3 ml of concentrated hydrochloric acid, after which 5 ml of water is added. The solution obtained at this stage, with cooling, is diazotized with 0.72 g of sodium nitrite dissolved in 3 ml of water. The resulting diazonium salt is added over 30 minutes to a solution of 0.01 mol of 4-phenylimino-thiazolidin-2-one previously diluted in 80 ml of glacial acetate acid containing 4 g of anhydrous sodium acetate (pH = 4.5-5.0) with stirring and cooling. The mixture is left at 12:00, after which it is poured into 200 ml of water. The precipitate is filtered, washed on the filter with water and dried at 100 C.

***5-[(4-Nitro-phenyl)-hydrazono]-4-phenylimino-thiazolidin-2-one* (12).** Yield 90%, mp 252-254°C. $^1$H NMR (400 MHz, DMSO) δ 10.90 (s, 1H, NH), 10.67 (s, 1H, NH), 8.20 (d, *J* = 8.7 Hz, 2H, $C_6H_4$), 7.82 (d, *J* = 7.7 Hz, 2H, N-phenyl), 7.71 (d, *J* = 8.8 Hz, 2H, $C_6H_4$), 7.47 (t, *J* = 7.9 Hz, 2H, N-phenyl), 7.26 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{15}H_{11}N_5O_3S$: C, 52.78; H, 3.25; N, 20.52. Found: C, 52.84; H, 3.20; N, 20.44.

***5-[(4-Chloro-phenyl)-hydrazono]-4-phenylimino-thiazolidin-2-one* (13).** Yield 75%, mp 243-244°C. $^1$H NMR (400 MHz, DMSO) δ 10.83 (s, 1H, NH), 10.47 (s, 1H, NH), 8.05 (d, *J* = 7.9 Hz, 2H, $C_6H_4$), 7.78 (d, *J* = 8.0 Hz, 2H, N-phenyl), 7.65 (d, *J* = 8.0 Hz, 2H, $C_6H_4$), 7.48 (t, *J* = 7.8 Hz, 2H, N-phenyl), 7.27 (t, *J* = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for $C_{15}H_{11}ClN_4OS$: C, 54.46; H, 3.35; N, 16.94. Found: C, 54.55; H, 3.41; N, 16.88.

***5-{[4-(5-Ethyl-[1,3,4]thiadiazol-2-ylamino)-phenyl]-hydrazono}-4-phenylimino-thiazolidin-2-one* (14).** Yield 60%, mp >260°C. $^1$H NMR (400 MHz, DMSO) δ 13.89 (s, 1H, NH), 10.81 (s, 1H, NH), 10.71 (s, 1H, NH), 7.80 (d, *J* = 7.8 Hz, 2H, N-phenyl), 7.73-7.66 (m, 4H, $C_6H_4$), 7.46 (t, *J* = 7.7 Hz, 2H, N-phenyl), 7.27 (t, *J* = 7.4 Hz, 1H, N-phenyl), 2.85-2.79 (m, 2H, $CH_2$), 1.21 (t, *J* = 7.5 Hz, 3H, $CH_3$). Anal. Calcd. for $C_{19}H_{17}N_7OS_2$: C, 53.88; H, 4.05; N, 23.15. Found: C, 53.78; H, 3.99; N, 23.28.

*2.3. Pharmacology.*

Anti-inflammatory activity was assessed by using the functional model of carrageenan-induced rat paw edema. The experiment was carried out in correspondence with the demand of the European Convention for the Protection of Vertebrate Animals utilized for Experimental and other scientific purposes.

The laboratory animals were separated into 16 groups. Every group consisted of 5 animals. To analysis the anti-inflammatory activity of 14 synthesized compounds and Ibuprofen, 15 test groups were utilized, and the 16th experimental group was a control group. Rats were comprised of the standard conditions and temperature on a standard diet prior to the experiment. Tested substances and standard drug Ibuprofen were dissolved in dimethylsulfoxide and entered intraperitoneally. Dimethylsulfoxide was entered into the animals from the control group.

After 30 minutes later, 0.1 mL of a 2% carrageenan solution was aseptic injected the sub-plantar region of the sole of the rat's hind limb. The inflammatory reaction was established at 4 h after the carrageenan injection by the oncometric method. Inhibition of the inflammatory reaction was expressed as a percent reduction in paw volume and calculated applying the next formula:

$$\%\ \text{Inhibition} = \frac{V_{\text{control}} - V}{V_{\text{control}}} \cdot 100\,\%$$

where $V_{\text{control}}$ is the increase in paw volume in the control group of animals;
V is the increase in paw volume in animals injected with the test substances.

## 3. Results and Discussion

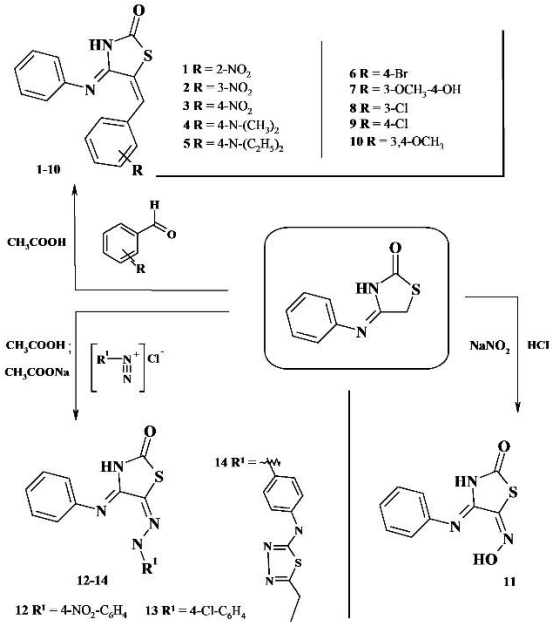
*3.1. Synthesis of some 4-phenylimino-thiazolidin-2-ones.*

The interesting pharmacological activities of 4-iminothiazolidin-2-ones prompted us to synthesize some $C^5$ substituted 4-phenylimino-thiazolidin-2-ones and test them for anti-inflammatory activity. Literature survey data showed that the interaction of 4-iminothiazolidin-2-one with aniline allows to obtained 4-phenylimino-thiazolidin-2-one [54]. The specified

scaffold represents a comfy intermediate in order to give $C^5$ substituted 4-phenylimino-thiazolidin-2-ones.

The active methylene group presence in $C^5$ position of the basic scaffold provides an entry for its utilization in Knoevenagel condensation, nitrosation and azo coupling reactions leading to appropriate 5-arylidene, 5-oxime and 5-aryl-hydrazono derivatives of 4-phenylimino-thiazolidin-2-one generation.

We studied for the Knoevenagel condensation the behavior of 4-phenylimino-thiazolidin-2-one with aromatic aldehydes. One of the conditions for this transformation is the use of basic catalysts. Acetic acid was discovered to be the most suited medium. It was found that the most optimal conditions for the Knoevenagel condensation imply interaction of equimolar amounts of 4-phenylimino-thiazolidin-2-one with corresponding aromatic aldehyde and a few drops of monoaminoethanol. The specified transformation allowed us to obtained 5-arylidene-4-phenylimino-thiazolidin-2-ones (1-10) (Scheme 1).




**Scheme 1.** Synthesis of $C^5$ substituted 4-phenylimino-thiazolidin-2-ones (1-14).

It is known that the hydroxylamine moiety belongs to the pharmacophore groups and the compounds that contain it show a variety of biological activity. Therefore, the functionalization of 4-phenylimino-thiazolidin-2-one in position $C^5$ was performed *via* the reaction of nitrosation. It has been detected that the basic scaffold reacts with nitric acid formed by the interaction of sodium nitrite with hydrochloric acid. This transformation allowed obtaining the corresponding 4-phenylimino-thiazolidine-2,5-dione 5-oxime (11) (Scheme 1).

The subsequent strategy included the core heterocycle structural modification at $C^5$ position in the azo coupling reaction. This transformation confirms the high activity of the methylene group 4-phenylimino-thiazolidin-2-one. According to the picked conditions the 5-aryl-hydrazono]-4-phenylimino-thiazolidin-2-ones (12-14) were received in good yields (Scheme 1).

The structures of the obtained compounds have been determined by $^1$H NMR spectroscopy and elemental analysis. The spectroscopic data of all compounds correspond to the proposed structures.

*3.2. Pharmacology.*

Exudative inflammation is considered a classic sample of sharp inflammation. *In vivo* studies of the exudative phase, inflammation was executed based on the functional model of carrageenan-induced rat paw edema [55]. For comparison, the anti-inflammatory activity of a famous anti-inflammatory drug – Ibuprofen in average therapeutic doses was studied in similar conditions. The anti-inflammatory activity results for tested compounds and Ibuprofen are shown in table 1.

**Table 1.** Anti-inflammatory effect of 4-phenylimino-thiazolidin-2-ones on carrageenan-induced rat paw edema (ml) *in vivo* evaluation, % protection from inflammation.

| Compound ID | Paw edema volume (mL) ± SEM* | % Inhibition | Activity relative to Ibuprofen, % |
|---|---|---|---|
| **Control** | 2.20 ± 0.050 | - | |
| **1** | 1.57± 0.040 | **28.6** | 71.2 |
| **2** | 1.59 ± 0.040 | **27.9** | 69.4 |
| **3** | 1.62 ± 0.040 | **26.5** | 65.9 |
| **4** | 1.78 ± 0.045 | **19.3** | 48.0 |
| **5** | 1.83 ± 0.045 | **16.8** | 41.8 |
| **6** | 1.37± 0.035 | **37.7** | 93.8 |
| **7** | 1.69± 0.040 | **23.2** | 57.7 |
| **8** | 1.29± 0.035 | **41.5** | 103.2 |
| **9** | 1.40± 0.035 | **40.3** | 100.3 |
| **10** | 1.31± 0.035 | **24.6** | 61.2 |
| **11** | 1.87 ± 0.045 | **15.0** | 37.3 |
| **12** | 1.72 ± 0.045 | **21.7** | 54.0 |
| **13** | 1.66 ± 0.040 | **24.8** | 61.7 |
| **14** | 1.53 ± 0.040 | **30.4** | 75.6 |
| **Ibuprofen** | 1.32 ± 0.035 | **40.2** | 100 |

The synthesized 4-phenylimino-thiazolidin-2-ones possess various anti-inflammatory activity. Evaluation shown that for some substances, the anti-inflammatory effect is below in comparison to the reference drug, the inflammatory reaction inhibition indicators for them are within the diapason of 15.0–30.4 %. Nevertheless, the anti-inflammatory effect of the other three compounds is approximately equivalent to that of the Ibuprofen, and total 37.7 % for compound 6, 41.5 % for compound 8 and 40.3 % for compound 9.

The results of the pharmacological tests were analyzed concerning the structure of the compounds. Structural modification of 4-phenylimino-thiazolidin-2-one allowed introducing a number of substituents in the $C^5$ position. Among the ten prepared by the Knoevenagel condensation reaction $C^5$-substituted 4-phenylimino-thiazolidin-2-ones, three compounds (6, 8, 9) possessed inflammation inhibition. Comparison of the substituents nature on the phenyl ring of test compounds specified that chlorine or bromine atom attendance conduce to the inflammation inhibition effectiveness. Others of substituents in the $C^5$ position did not influence distinguishably on the anti-inflammatory effect of 4-phenylimino-thiazolidin-2-one derivatives.

## 4. Conclusions

In summary, we presented an efficient synthetic approaches to a number of 4-phenylimino-thiazolidin-2-one derivatives for their anti-inflammatory activity evaluation. We have demonstrated that the proposed ways have given the opportunity to design 4-thiazolidinones diversity with a sizable chemical novelty. The obtained results of the performed anti-inflammatory activity evaluation have shown that synthesized compounds have expressive anti-inflammatory properties, and some of them approach or prevail the Ibuprofen in terms of activity.

## Funding

This research received no external funding.

## Acknowledgments

We are grateful Department of Pharmacology Danylo Halytsky Lviv National Medical University, Ukraine, for the *in vivo* evaluation of the anti-inflammatory activity.

## Conflicts of Interest

The authors declare no conflict of interest.

## References

1. Brenner, P.; Krakauer, T. Regulation of Inflammation: A review of recent advances in anti- inflammatory strategies. *Current Medicinal Chemistry* **2003**, *2*, 274-283, https://doi.org/10.2174/1568014033483752.
2. Pirlamarla, P.; Bond, R.M. FDA labeling of NSAIDs: Review of non-steroidal anti-inflammatory drugs in cardiovascular disease. *Trends Cardiovascular Medicine* **2016**, *26*, 675-680, https://doi.org/10.1016/j.tcm.2016.04.011.
3. Bacchi, S.; Palumbo, P.; Sponta, A.; Coppolino, M. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry* **2012**, *11*, 52–64, https://doi.org/10.2174/187152312803476255.
4. Taylor, A.; Robinson, R.; Fobian, Y.; Blakemore, D.; Jones, L.; Fadeyi, O. Modern advances in heterocyclic chemistry in drug discovery. *Organic & Biomolecular Chemistry* **2016**, *14*, 6611-6637, https://doi.org/10.1039/C6OB00936K.
5. Kaminskyy, D.; Kryshchyshyn, A.; Lesyk, R. 5-Ene-4-thiazolidinones–An efficient tool in medicinal chemistry. *European Journal of Medicinal Chemistry* **2017**, *140*, 542–594, https://doi.org/10.1016/j.ejmech.2017.09.031.
6. Kryshchyshyn, A.; Kaminskyy, D.; Karpenko, O.; Gzella, A.; Grellier P.; Lesyk, R. Thiazolidinone/thiazole based hybrids – New class of antitrypanosomal agents. *European Journal of Medicinal Chemistry* **2019**, *174*, 292-308, https://doi.org/10.1016/j.ejmech.2019.04.052.
7. Chaban, Z.; Harkov, S.; Chaban, T.; Klenina, O.; Ogurtsov, V.; Chaban, I. Recent advances in synthesis and biological activity evaluation of condensed thiazoloquinazolines: A review. *Pharmacia* **2017**, *64*, 52-66.
8. Holota, S.; Kryshchyshyn, A.; Derkach, H.; Gzella, A.; Trufin Y.; Demchuk I.; Grellier P.; Lesyk, R. Synthesis of 5-enamine-4-thiazolidinone derivatives with trypanocidal and anticancer activity. *Bioorganic Chemistry* **2019**, *86*, 126-136, https://doi.org/10.1016/j.bioorg.2019.01.045.
9. Horishny, V.; Chaban, T.; Matiychuk, V. Synthesis and Primary Antitumor Screening of 5-Ylidene Derivatives of 3-(Morpholin-4-yl)-2-sulfanylidene-1,3-thiazolidin-4-one. *Russian Journal of Organic Chemistry* **2020,** *56*, 454-457, https://doi.org/10.1134/S1070428020030148.
10. Holota, S.M.; Derkach, H.O.; Demchuk, I.L.; Vynnytska, R.B.; Antoniv, O. I.; Furdychko, L. O.; Slyvka, N.Y.; Nektegayev, I. O.; Lesyk, R. B. Synthesis and in vivo evaluation of pyrazoline-thiazolidin-4-one hybrid Les-5581 as a potential non-steroidal anti-inflammatory agent. *Biopolymers and Cell* **2019**, *35*, 437-447, http://dx.doi.org/10.7124/bc.000A17.
11. Chaban, T.; Klenina, O.; Chaban, I.; Ogurtsov, V.; Harkov, S.; Lelyukh, M. Thiazolo[5,4-*d*]pyrimidines and thiazolo[4,5-*d*] pyrimidines: A review on synthesis and Pharmacological importance of their derivatives. *Pharmacia* **2018**, *65*, 54-70.
12. Komaritsa, I.D. Studies on azolidones and their derivatives-I. Preparation and properties of 4-iminothiazolid-2-one. *Chemistry of Heterocyclic Compounds* **1968,** *4*, 324–325, https://doi.org/10.1007/BF00755270.
13. Komogortsev, A.N.; Lichitsky, B.V.; Krylov, K.S.; Dudinov, A.A.; Purygin, P.P.; Krayushkin, M.M. Recyclization of 1-aryl-4-iminoimidazolidin-2-ones on treatment with hydrazine: synthesis of 5-arylaminomethyl-2,4-dihydro[1,2,4]triazol-3-ones. *Mendeleev Communication* **2014**, *24*, 161-162, https://doi.org/10.1016/j.mencom.2014.04.012.
14. Kaminskyy, D.; Subtel'na, I.; Zimenkovsky, B.; Karpenko, O.; Gzella, A.; Lesyk, R. Synthesis and evaluation of anticancer activity of 5-ylidene-4-aminothiazol-2(5H)-one derivatives. *Journal of Medicinal Chemistry* **2015,** *11*, 517-530, https://doi.org/10.2174/1573406411666150211112049.
15. Chaban, T.; Ogurtsov, V.; Chaban, I.; Myrko, I.; Harkov, S.; Leluykh, M. Synthesis of some new 4-iminothiazolidine-2-ones as possible antioxidants agents. *Pharmacia* **2019**, *66*, 27-32, https://doi.org/10.3897/pharmacia.66.e35131.
16. Komaritsa, I.D. Reaction of 4-iminothiazolidinone-2 with acetoacetic ester. *Chemistry of Heterocyclic Compounds* **1989**, *25*, 1297-1299, https://doi.org/10.1007/BF00481527.

17. Chaban, T.I.; Zimenkovskii, B.S.; Komaritsa, I.D.; Chaban, I.G. Reaction of 4-iminothiazolidin-2-one with acetylacetone. *Russian Journal of Organic Chemistry* **2012**, *48*, 268-270, https://doi.org/10.1134/S1070428012020170.
18. Chaban, T.I.; Panchuk, R.R.; Klenina, O.V.; Skorokhyd, N.R.; Ogurtsov, V.V.; Chaban, I.G. Synthesis and evaluation of antitumor activity of some thiazolo[4,5-*b*]pyridines. *Biopolymers and Cell* **2012**, *25*, 389-396, https://doi.org/10.7124/bc.000075.
19. Chaban, T.I.; Ogurtsov, V.V.; Chaban, I.G.; Klenina, O.V.; Komarytsia, J.D. Synthesis and antioxidant activity evaluation of novel 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridines. *Phosphorus, Sulfur Silicon Relat. Elem.* **2013**, *188*, 1611-1620, https://doi.org/10.1080/10426507.2013.777723.
20. Lozynskyi, A.; Zimenkovsky, B.; Radko, L.; Trebas, S.; Roman, O.; Gzella, A.K., Lesyk, R. Synthesis and cytotoxicity of new thiazolo[4,5-*b*]pyridine-2(3H)-one derivatives based on α,β-unsaturated ketones and α-ketoacids. *Chemical Papers* **2018**, *72*, 669-681, https://doi.org/10.1007/s11696-017-0318-1.
21. Chaban, T.; Klenina, O.; Harkov, S.; Ogurtsov, V.; Chaban, I.; Nektegaev I. Synthesis of some new $N^3$ substituted 6-phenylazo-3*H*-thiazolo[4,5-*b*]pyridin-2-ones as possible anti-inflammatory agents. *Pharmacia* **2017**, *64*, 16-30.
22. Chaban, T.; Matiychuk, V.; Ogurtsov, V.; Chaban, I.; Harkov, S.; Nektegaev, I. Synthesis and biological activity of some novel derivatives 5,7-dimethyl-6-phenylazo-3*H*-thiazolo[4,5-*b*]pyridine-2-one. *Pharmacia* **2018**, *65*, 51-62.
23. Krylov, C.S.; Komogortsev, A.N.; Lichitsky, B.V.; Fakhrutdinov, A.N.; Dudinov, A.A.; Krayushkin, M.M. Three-component condensation of 4-imino-1-phenylimidazolidin-2-one with aldehydesand Meldrum's acid: synthesis of imidazo[4,5-*b*]pyridine-2,5(4H,6H)-diones and 5-substituted 1-phenylhydantoins. *Chemistry of Heterocyclic Compounds* **2019**, *55*, 851–855, https://doi.org/10.1007/s10593-019-02548-9.
24. Chaban, T.I.; Ogurtsov, V.V.; Matiychuk, V.S.; Chaban, I.G.; Demchuk, I.L.; Nektegayev, I.A. Synthesis, anti-inflammatory and antioxidant activities of novel 3*H*-thiazolo[4,5-*b*]pyridines. *Acta Chimica Slovenica* **2019**, *66*, 103–111, https://doi.org/10.17344/acsi.2018.4570.
25. Chaban, T.; Matiychuk, V.; Mahlovanyy, A.; Chaban, I.; Ogurtsov, V.; Lelyukh, M. Antitumor properties of thiazolo[4,5-*b*]pyridin-2-one derivatives. *Biointerface Research in Applied Chemistry* **2020**, *10*, 5944-5950, https://doi.org/10.33263/BRIAC104.944950.
26. Lozynska, L.; Tymoshuk, O.; Chaban, T. Spectrophotometric studies of 4-[n'-(4-imino-2-oxo-thiazolidin-5-ylidene)-hydrazino]-benzenesulfonic acid as a reagent for the determination of Palladium. *Acta Chimica Slovenica* **2015**, *62*, 159-167, https://doi.org/10.17344/acsi.2014.866.
27. Tupys, A.; Tymoshuk, O.; Rydchuk, P. Spectrophotometric investigation of Cu(ii) ions interaction with 1-(5-benzylthiazol-2-yl)azonaphthalen-2-ol. *Chemistry and Chemical Technology* **2016**, *10*, 19-26, https://doi.org/10.23939/chcht10.01.019.
28. Bazel, Y.; Tupys, A.,; Ostapiuk, Y.; Tymoshuk, O.; Imrich, J.; Sandrejova, J. A simple non-extractive green method for the spectrophotometric sequential injection determination of copper(ii) with novel thiazolylazo dyes. *RSC Advances* **2018**, *8*, 15940-15950, https://doi.org/10.1039/C8RA02039F.
29. Lozyns'ka, L.V.; Tymoshuk, O.S.; Vrublevs'ka, T.Y. Analysis of multicomponent systems for the contents of iridium and palladium. *Materials Science* **2015**, *50*, 870-876. https://doi.org/10.1007/s11003-015-9795-y.
30. Tymoshuk, O.; Oleksiv, L.; Khvalbota, L.; Chaban, T.; Patsay, I. Spectrophotometric determination of ru(iv) using 5-hydroxyimino-4-imino-1,3-thiazolidin-2-one as a novel analytical reagent. *Acta Chimica Slovenica* **2019**, *66*, 62–69, https://doi.org/10.17344/acsi.2018.4448.
31. Rydchuk, P.V.; Tymoshuk, O.S.; Oleksiv, L.V.; Chaban, T.I.; Matiychuk, V.S. Voltammetric determination of pt(Iv) using 5-hydroxyimino-4-imino-1,3-thiazolidine-2-one. *Methods and Objects of Chemical Analysis* **2019**, *14*, 130-139, https://doi.org/10.17721/moca.2019.130-139.
32. Lozynska, L.; Tymoshuk, O. Specrophotometric investigation of palladium(II) ions interaction with 5-hydroxyimino-4-imino-1,3-thiazolidin-2-one. *Chemistry and Chemical Technology* **2013**, *7*, 391-395, https://doi.org/10.23939/chcht07.04.391.
33. Tymoshuk, O.; Oleksiv, L.; Rydchuk, P.; Chaban, T.; Tymoshuk, S.; Matiychuk, V. Spectrophotometric Study of the Interaction of Platinum(IV) with New Derivatives of Azolidones. *Chemistry and Chemical Technology* **2020**, *14*, 139-145, https://doi.org/10.23939/chcht14.02.
34. Chaban, T.; Ogurtsov, V.; Mahlovanyy, A.; Sukhodolska, N.; Chaban, I.; Harkov, S.; Matiychuk, V. Antioxidant properties of some novel derivatives thiazolo[4,5-*b*]pyridine. *Pharmacia* **2019**, *66*, 171-180, https://doi.org/10.3897/pharmacia.66.e36764.
35. Pokhodylo, N.T.; Matiychuk, V.S. Synthesis of new 1,2,3-triazolo[1,5-a]quinazolinones. *Journal of Heterocyclic Chemistry* **2010,** *47*, 415-420, https://doi.org/10.1002/jhet.321.
36. Klenina, O.; Chaban, T.; Zimenkovsky, B.; Harkov, S.; Ogurtsov, V.; Chaban, I.; Myrko, I. Qsar modeling for antioxidant activity of novel $N^3$substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones. *Pharmacia* **2017**, *64*, 49-71.
37. Chaban, T.I.; Matiichuk, Y.E.; Horishny, V.Ya.; Chaban, I.G.; Matiychuk, V.S. Synthesis and Anticancer Activity of 2-aryl-3-methylbenzofuro[3,2-*B*]pyrazolo[4,3-*E*]azepine-4,11(2*H*,10*H*)-dione and 2-Aryl-3,7,9-

trimethylpyrido[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*E*]azepine-4,11(2*H*,10*H*)-diones. *Russian Journal of Organic Chemistry* **2020,** *56*, 813-818, https://doi.org/10.1134/S1070428020050139.
38. Drapak, I.; Zimenkovsky, B.; Perekhoda, L.; Kovalenko, S.; Logoyda, L. LC-MS/MS method development and validation for the determination of cardiazol in human plasma. *International Journal of Applied Pharmaceutics* **2019,** *11*, 380-385, https://doi.org/10.22159/ijap.2019v11i4.33482.
39. Chaban, T.I.; Matiychuk, V.S.; Ogurtsov, V.V.; Chaban, I.G.; Nektegayev, I.A. Development of effective anti-inflammatory drug candidates among novel thiazolopyridines. *Ukrainian Biochemical Journal* **2020**, *92*, 132-139, https://doi.org/10.15407/ubj92.02.132.
40. Matiichuk, V.S.; Potopnyk, M.A.; Obushak, N.D. Molecular design of pyrazolo[3,4-*d*]pyridazines. *Russian Journal of Organic Chemistry* **2008**, *44*, 1352-1361, https://doi.org/10.1134/S1070428008090182.
41. Finiuk, N.S.; Ivasechko, I.; Klyuchivska, O.; Ostapiuk, Y.V.; Hreniukh, V.P.; Shalai, Ya. R.; Matiychuk, V. S.; Obushak, M. D.; Stoika, R.S.; Babsky, A.M. Apoptosis induction in human leukemia cells by novel 2-amino-5-benzylthiazole derivatives. *Ukrainian Biochemical Journal* **2019**, *91*, 29-39, https://doi.org/10.15407/ubj91.02.029.
42. Matiichuk, Y.; Ogurtsov, V.; Ostapiuk, Y.; Chaban, T.; Matiychuk, V. Synthesis, anti-inflammatory activity and molecular docking of 2-methyl-3-furamides. *Biointerface Research in Applied Chemistry* **2020**, *10*, 5809-5814, https://doi.org/10.33263/BRIAC104.809814.
43. Shyyka, O.; Pokhodylo, N.; Finiuk, N.; Matiychuk, V.; Stoika, R.; Obushak, M. Anticancer activity evaluation of new thieno[2,3-*d*]pyrimidin-4(3*H*)-ones and thieno[3,2-*d*]pyrimidin-4(3H)-one derivatives. *Scientia Pharmaceutica* **2018**, *86*, 28-32, https://doi.org/10.3390/scipharm86030028.
44. Lelyukh, M.; Demchuk, I.; Harkov, S.; Chaban T.; Drapak, I.; Chaban I.; Shelepeten, L.; Matiychuk, V. A review on synthetic routes for obtaining of 2,5-disubstituted 1,3,4-oxadiazoles via cyclodehydration and oxidative cyclization reactions. *Biointerface Research in Applied Chemistry* **2020**, *10*, 5960-5971, https://doi.org/10.33263/BRIAC104.960971.
45. Matiichuk, Y.; Ostapiuk, Y.; Chaban, T.; Ogurtsov, V.; Matiychuk, V. Synthesis and anticancer properties of n-(5-r-benzyl-1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides. *Biopolymers and Cell* **2020**, *36*, 74-83, http://dx.doi.org/10.7124/bc.000A22.
46. Chaban, T.; Klenina, O.; Drapak, I.; Ogurtsov, V.; Chaban, I.; Novikov, V. Synthesis of some novel thiazolo[4,5-*b*]pyridines and their tuberculostatic activity evaluation. *Chemistry and Chemical Technology* **2014**, *89*, 287-292, https://doi.org/10.23939/chcht08.03.287.
47. Finiuk, N.; Klyuchivska, O.; Ivasechko, I.; Hreniukh, V.P.; Ostapiuk, Y.V.; Shalai, Ya. R.; Panchuk, R. R.; Matiychuk, V. S.; Obushak, M. D.; Stoika, R., Babsky, A. Proapoptotic Effects of Novel Thiazole Derivative on Human Glioma Cells. *Anticancer Drugs* **2019**, *30*, 27-37, https://doi.org/10.1097/CAD.0000000000000686.
48. Klenina, O.; Drapak, I.; Chaban, T.; Ogurtsov, V.; Chaban, I.; Golos, I. QSAR studies of some thiazolo[4,5-*b*]pyridines as novel antioxidant agents: enhancement of activity by some molecular structure parameters. *Chemistry and Chemical Technology* **2013**, *7*, 397-404, https://doi.org/10.23939/chcht07.04.397.
49. Lelyukh, M.; Adamchuk, S.; Harkov, S.; Chaban I.; Shelepeten, L., Chaban T. Synthetic approaches, chemical modification and biological activity of non-condensed 1,3,4-thiadiazole derivatives: A review. *Pharmacia* **2018**, *65*, 72-88.
50. Chaban, T.; Klenina, O.; Zimenkovsky, B.; Chaban, I.; Ogurtsov, V.; Shelepeten, L. Synthesis of novel thiazolo[4,5-*b*]pyridines as potential biologically active substances. *Der Pharma Chemica* **2016**, *8*, 534-542.
51. Ostapiuk, Y.V.; Frolov, D.A.; Vasylyschyn, R.Y.; Matiychuk, V.S. Synthesis and antitumor activities of new n-(5-benzylthiazol-2-yl)-2-(heteryl-5-ylsulfanyl)-acetamides. *Biopolymers and Cell* **2018**, *34*, 59-71, http://doi.org/10.7124/bc.000971.
52. Drapak, I.; Foliush, V.; Chaban, T.; Matiychuk, V. Synthesis antimicrobial and antitumor activities of 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones. *Biointerface Research in Applied Chemistry* **2020**, *10*, 5507-5511, https://doi.org/10.33263/BRIAC103.507511.
53. Matiichuk, V.S.; Frolov, D.A.; Pokhodylo, N.T.; Pavlyuk, V.V.; Obushak, M.D. Selective Formation of Products of Interrupted Feist-Benary Reaction under the Conditions of Hantzsch Pyrrole Synthesis. *Russian Journal of Organic Chemistry* **2018**, *54*, 799-801, https://doi.org/10.1134/S1070428018050238.
54. Grischuk, A.P.;, Komaritsa, I.D.;, Baranov, S.N. 4-Thionazolidones, derivatives and analogs - III. Synthesis and reactions of 4-thionthiazolid-2-one (isorhodanine). *Chemistry of Heterocyclic Compounds* **1966**, *2*, 541–543, https://doi.org/10.1007/BF00477515.
55. Pillai, A.D.; Rathod, P.D.; Franklin, P.X.; Padh, H.; Vasu K.K.; Sudarsanam, V. Design, synthesis, and SAR studies of some 5-aliphatic oximinoesters of thiophene as potential anti-inflammatory leads:comparative biological activity profile of aliphaticoximes vs aromatic oximes. *Biochemical and Biophysical Research Communications* **2004**, *317*, 1067-1074, https://doi.org/10.1016/j.bbrc.2004.03.148.