Synthesis of Some C$_5$ Substituted 4-Phenylimino-Thiazolidin-2-Ones as Possible Anti-Inflammatory Agents

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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 exceed the activity of the comparative drug Ibuprofen.

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

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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 C5 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. 1H- spectra were recorded on a Varian Mercury 400 (400 MHz for 1H) 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 acetic 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 monoaaninoethanol 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 acetic acid.

5-(2-Nitro-benzylidene)-4-phenylimino-thiazolidin-2-one (1). Yield 60%, mp >260°C. 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H, NH), 8.33 (s, 1H, CH), 8.20 (dd, J = 8.2 Hz, 1H, C6H4), 7.93-7.71 (m, 5H, C6H4+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 C15H11N3O3S: 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. 1H NMR (400 MHz, DMSO) δ 10.85 (s, 1H, NH), 8.38 (s, 1H, CH), 8.28 (dd, J = 8.2 Hz, 1H, C6H4), 8.25 (s, 1H, C6H4), 8.00 (d, J = 7.8 Hz, 1H, C6H4), 7.86-7.80 (m, 3H, C6H4+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 C16H11N3O3S: 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. 1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H, NH), 8.39 (d, J = 8.9 Hz, 2H, C6H4), 8.25 (s, 1H, CH), 7.86 (d, J = 8.9 Hz, 2H, C6H4), 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 C16H11N3O3S: 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. 1H 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, C6H4), 7.27 (t, J = 7.4 Hz, 1H, N-phenyl), 6.87 (d, J = 9.0 Hz, 2H, C6H4), 3.00 (s, 6H, 2°CH3). Anal. Calcd. for C18H17N3O3S: 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. 1H 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, C6H4), 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(6)H), 3.45-3.40 (m, 4H, 2*CH2), 1.13 (t, J = 7.0 Hz, 6H, 2*CH3). Anal. Calcd. for C20H21N3O: 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. 1H NMR (400 MHz, DMSO) δ 10.77 (s, 1H, NH), 8.11 (s, 1H, CH), 7.80-7.76 (m, 4H, C6H4+N-phenyl), 7.56 (d, J = 8.5 Hz, 2H, C(6)H), 7.46 (t, J = 8.0 Hz, 2H, N-phenyl), 7.26 (t, J = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for C18H11BrN2O2S: 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. 1H 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, C6H3), 6.97 (d, J = 8.0 Hz, 1H, C6H3), 3.85 (s, 3H, CH3). Anal. Calcd. for C17H14N2O3S: 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. 1H 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, C6H4), 7.46 (t, J = 7.8 Hz, 2H, N-phenyl), 7.26 (t, J = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for C16H11ClN2O2S: 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. 1H 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, C6H4), 7.46 (t, J = 7.7 Hz, 2H, N-phenyl), 7.26 (t, J = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for C16H11ClN2O2S: 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. 1H 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+C6H3), 7.15 (d, J = 8.3 Hz, 2H, C6H3), Anal. Calcd. for C18H16O3N2S: 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. 1H 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 C9H7N3O2S: 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-hydrazonoi-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 acetic 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. ¹H NMR (400 MHz, DMSO) δ 10.90 (s, 1H, NH), 10.67 (s, 1H, NH), 8.20 (d, J = 8.7 Hz, 2H, C₆H₄), 7.82 (d, J = 7.7 Hz, 2H, N-phenyl), 7.71 (d, J = 8.8 Hz, 2H, C₆H₄), 7.47 (t, J = 7.9 Hz, 2H, N-phenyl), 7.26 (t, J = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for C₁₅H₁₁N₅O₅S: 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. ¹H NMR (400 MHz, DMSO) δ 10.83 (s, 1H, NH), 10.47 (s, 1H, NH), 8.05 (d, J = 7.9 Hz, 2H, C₆H₄), 7.78 (d, J = 8.0 Hz, 2H, N-phenyl), 7.65 (d, J = 8.0 Hz, 2H, C₆H₄), 7.48 (t, J = 7.8 Hz, 2H, N-phenyl), 7.27 (t, J = 7.4 Hz, 1H, N-phenyl). Anal. Calcd. for C₁₅H₁₁ClN₅O₅S: 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. ¹H 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, C₆H₄), 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, CH₂), 1.21 (t, J = 7.5 Hz, 3H, CH₃). Anal. Calcd. for C₁₉H₁₇N₇O₂S₂: 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:

\[
\text{% Inhibition} = \frac{V_{\text{control}} - V}{V_{\text{control}}} \times 100 \%
\]

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 C⁵ 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

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scaffold represents a comfy intermediate in order to give C⁵ substituted 4-phenylimino-thiazolidin-2-ones.

The active methylene group presence in C⁵ 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](https://biointerfaceresearch.com/)

Scheme 1. Synthesis of C⁵ 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 C⁵ 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 C⁵ 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 ¹H 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 C5 position. Among the ten prepared by the Knoevenagel condensation reaction C5-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 C5 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.
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Conflicts of Interest

The authors declare no conflict of interest.

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