SYNTHESIS AND ANTI-INFLAMMATORY PROPERTIES OF C^5 SUBSTITUTED 4-PHENYLIMINO-THIAZOLIDIN-2-ONES

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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 infection to major life dangerous ailments like a brain hemorrhage or myocardial infarction. 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. 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. To surmount these limitations, the search is ongoing throughout the world to develop more effective anti-inflammatory agents.

Thiazolidinone derivatives are a traditionally known class of biologically active compounds. The results of recent studies of the chemistry and biological activity of the specified class of connections convincingly showed that they are promising as pharmacological agents with a broad spectrum of activity. In this work, which is the portion of our exploring biologically active heterocycles we synthesized a series of C^5 substituted 4-phenylimino-thiazolidin-2-ones for a pharmacological screening of anti-inflammatory activity.

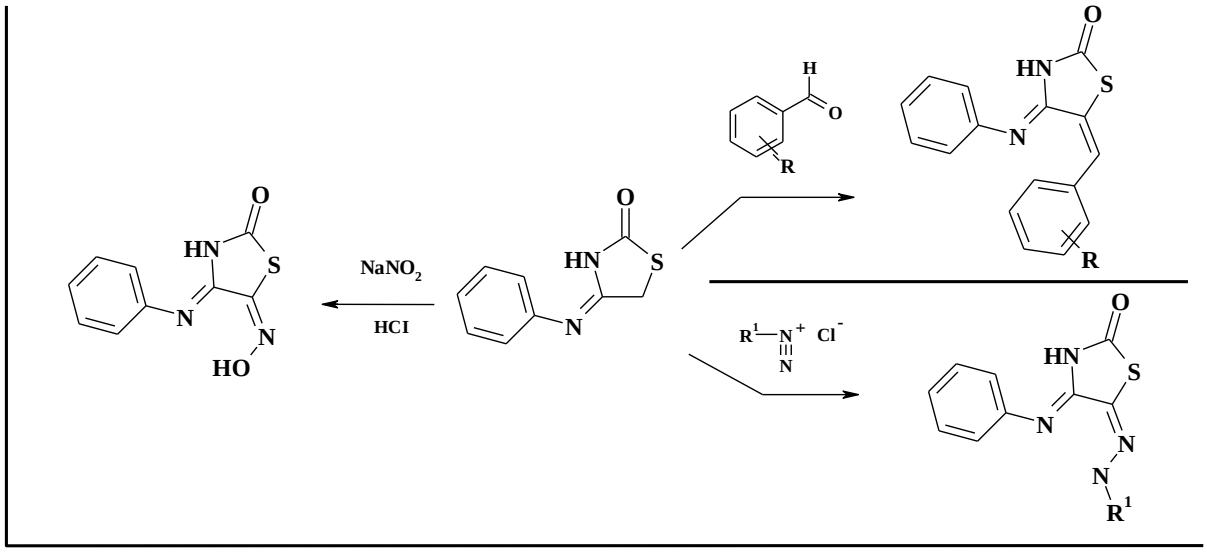
Literature survey data showed that the interaction of 4-iminothiazolidin-2-one with aniline allows to obtained 4-phenylimino-thiazolidin-2-one. The specified scaffold represents a comfy intermediate in order to give C^5 substituted 4-phenylimino-thiazolidin-2-ones.

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. 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.

It is known that the hydroxyimine 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 were 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.

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-oneswere received in good yields



The structures of the obtained compounds were confirmed by ^{1}H-NMR spectroscopy and elemental analysis. In ^{1}H-NMR spectra it was found that the signals for the protons of all the structural units were observed in their characteristic ranges.

In vivo studies of the exudative phase, inflammation was executed based on the functional model of carrageenan-induced rat paw edema. For comparison, the anti-inflammatory activity of a famous anti-inflammatory drug – Ibuprofen in average therapeutic doses was studied in similar conditions.

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. Further optimization of the structure to improve biological activity is currently in progress.