DEVELOPMENT AND OPTIMIZATION OF THE SYNTHESIS OF NEW THIAZOLIDIN-4-ONE DERIVATIVES OF IBUPROFEN

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DEVELOPMENT AND OPTIMIZATION OF THE SYNTHESIS OF NEW THIAZOLIDIN-4-ONE DERIVATIVES OF IBUPROFEN (Abstract): Ibuprofen, an important nonsteroidal anti-inflammatory agent, is one of the most prescribed drugs for the treatment of pain and inflammation from various rheumatic diseases, but some side effects can occur on long-term use. Aim: The method for synthesis optimization of new derivatives of Ibuprofen with thiazolidin-4-one moiety, with improved pharmacological and toxicological profile. Material and methods: To optimize the derivatization method of free carboxyl group of Ibuprofen (2-(4-isobutylphenyl)propionic acid) the reaction conditions were varied (reagent ratio, catalyst, reaction medium). Results: The most favorable method was proved to be the reaction between ibuprofen hydrazone and mercaptoacetic acid, in excess, at 80-85°C, for 6 h with 96% conversion rate. Conclusions: The synthesis of 2-phenyl-3-[2-(4-isobutyl)phenyl]-2-methylacetamido-thiazolidin-4-one derivative was optimized in view of applying it as a general procedure for the synthesis of other derivatives with related structure. The chemical structure and molecular weight of the synthesized compound were confirmed by spectral methods (IR, ¹H NMR, ¹³C NMR, HR-MS). Keywords: IBUPROFEN, THIAZOLIDIN-4-ONE, SYNTHESIS, OPTIMIZATION.

Development of new nonsteroidal anti-inflammatory drugs (NSAIDs) is the major concern of researchers in the field because of the impact of inflammatory and rheumatic diseases on patient health status. NSAIDs are some of the oldest classes of drugs, the humanity having being related to pain, fever and inflammation from its beginnings. From Hippocrates who used a willow bark extract to treat fever and inflammation to the discovery of salicin and then the synthesis of salicylic acid, the researches have evolved and at the end of 19th century, Hoffman synthesized the acetylsalicylic acid, which was introduced in therapy under the name Aspirin by Bayer Company (1).

Researches on the discovery of new active drugs, safer than classical therapeutic agents had continued and so Ibuprofen was patented as a new analgesic and anti-inflammatory drug in 1961 by Dr. Stewart Adams (Boots Company) and his collaborators. Even if Ibuprofen was proved to be an efficient therapeutic alternative to treat
inflammatory and rheumatic diseases, its long-term use was associated with gastrointestinal and renal side effects. Today, it is known that the toxicological potential of Ibuprofen is related to the lack of the cyclooxygenase (COX) selectivity, an enzyme responsible for prostaglandin synthesis. Ibuprofen is a nonselective COX inhibitor that inhibits COX-2 isoform at the site of inflammation but also COX-1 isoform responsible for the gastric cytoprotective prostaglandin synthesis (2).

To increase the analgesic and anti-inflammatory activity and reduce the side effects, the recent researches were focused on derivatization of carboxyl group of classical NSAIDs with various heterocyclic systems (oxazole, isoxazole, pyrazole, oxadiazole, thiazole, thiadiazole, triazole etc.) (2, 3).

On the other hand, thiazolidin-4-one derivatives are an important class of heterocyclic organic compounds because of their various biological properties: anti-inflammatory and analgesic activity (4), antimicrobial, antifungal (5) and antymycobacterial effects, antioxidant potential (6), antiviral and anti-HIV activity, anticonvulsant effect (7), hypoglycemic or antitumor activity (6).

In order to develop potential new therapeutic agents with anti-inflammatory properties, a general procedure for the synthesis of thiazolidin-4-one derivatives by structural modulation of carboxyl free group of ibuprofen has been optimized.

**MATERIAL AND METHODS**

Ibuprofen sodium salt, thionyl chloride, hydrazine hydrate, benzaldehyde, mercaptoacetic acid, organic solvents (p.a. quality) were purchased from Sigma Aldrich Company.

Fourier transform infrared (FTIR) spectra were recorded on a FT-IR Bomem MB-104 spectrometer (Canada), with a resolution of 4 cm\(^{-1}\) after 32 scans between 4000 and 600 cm\(^{-1}\). NMR spectra (\(^1\)H-NMR, \(^13\)C-NMR) were determined using NMR Bruker 400 MHz spectrometer (Germany), and molecular weight was determined by using Maxis Bruker high resolution mass spectrometer.

**Chemistry**

The synthesis of thiazolidin-4-one derivative of Ibuprofen (9) was realized through two methods (fig. 1).

*Method A* is based on “one step” reaction between Ibuprofen hydrazide (5), benzaldehyde (6) and mercaptoacetic acid (7) using different ratios between reagents, reaction medium, catalyst, time and reaction temperature.

*Method B* is a two-step reaction that firstly involves the condensation of hydrazide (5) and benzaldehyde (6) resulting Ibuprofen hydrazone (8), which in the next step is cyclized with mercaptoacetic acid (7) using various ratios between reagents, reaction medium, catalyst, time and reaction temperature.

Ibuprofen hydrazide was obtained from ibuprofen (2-(4-(isobutyl)phenyl)propionic acid) (2) that was formed by treating the sodium salt (1) with hydrochloric acid. After several steps that include the synthesis of acid chloride (3), its conversion to corresponding ethyl ester (4) and then the reaction with excess hydrazine hydrate, the Ibuprofen hydrazide (5) was obtained (8).

**General procedure for synthesis of thiazolidin-4-one derivatives of Ibuprofen**

*Method A.* In a corresponding flask were introduced 2-(4-isobutylphenyl) pro-
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Propionyl hydrazine (MW = 220.31 g/mol), benzaldehyde (MW = 106.12 g/mol, d = 1.0415 g/cm³) and mercaptoacetic acid (MW = 92.12 g/mol, d = 1.32 g/cm³) were used in a flask. The reaction conditions were modified: reagents ratio (1.5:1:1.3; 1:2:3), reaction medium (anhydrous toluene, dichloromethane = DCM), reaction temperature (120°C, 22°C), time (24h, 45h), in the presence or absence of catalyst (N,N'-dicyclohexyl-carbodiimide, DCC). The reaction mixture was evaporated and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with sodium bicarbonate, sodium chloride (saturated solutions) and water, after which it was dried under anhydrous MgSO₄, filtered and concentrated under reduced pressure.

Method B. N'-benzylidene-2-(4-isobutylphenyl)propionyl hydrazine (MW = 308.42 g/mol) and mercaptoacetic acid (MW = 92.12 g/mol, d = 1.32 g/cm³) were introduced in a flask. The reaction conditions were modified: reagents ratio (1:1.3; 1:1.5; 1:4.5), reaction medium (anhydrous toluene, anhydrous dioxane, acetic acid), reaction temperature (80–85°C, 105°C, 120°C), time (6h, 12h, 24h, 30h, 38h), catalyst (zinc chloride, sodium acetate). The reaction mixture was dissolved in

Fig. 1. Scheme of the synthesis of Ibuprofen derivative with thiazolidin-4-one structure
ethyl acetate and the organic layer was extracted and washed with sodium bicarbonate, sodium chloride (saturated solutions) and water. The organic layer was collected, dried under anhydrous MgSO₄ and filtered. After evaporation under reduced pressure, the residue was purified by flash chromatography on silica gel column (dichloromethane:methanol = 9.8:0.2) resulting a colorless residue that was precipitated with diethyl ether to afford a white powder (reaction condition - reagents ratio 1:4.5, reaction temperature 80-85°C, time reaction 6h).

Characterization of 2-phenyl-3-[2-(4-(isobutyl)phenyl)-2-methyl]acetamido-thiazoli-din-4-one derivative (9). Mp = 125°C; yield (56.77%), IR (cm⁻¹) 3243 (-NH-), 2959 (CH₆), 1716 (C=O cyclic), 1666 (-CO-NH-), 1203 (C-N), 694 (C=S).¹H NMR (400 MHz, DMSO) – isomers mixture 60/40: δ 10.26 (d, J = 3.1 Hz, 1H, -NH-), 7.50 – 7.35 (m, 2H, Ar-H), 7.34 – 7.21 (m, 3H, Ar-H), 7.11 (d, J = 7.6 Hz, 1H, Ar-H), 7.01 (dd, J = 14.8, 7.6 Hz, 3H, Ar-H), 5.82 (5.67*, s, 1H, CH thiazolidin-4-one), 3.86 (t, J = 14.9 Hz, 1H de la CH₂ thiazolidin-4-one), 3.72 (dd, J = 14.9, 9.0 Hz, 1H de la CH₂ thiazolidin-4-one), 3.61 – 3.47 (m, 1H, -CH₂-CH₂), 2.39 (d, J = 6.7 Hz, 2H, -CH₂-CH(CH₃)₂), 1.79 (dt, J = 13.4, 6.7 Hz, 1H, -CH₂-CH(CH₃)₂), 1.25 (dd, J = 24.2, 7.0 Hz, 3H, -CH₂-CH(CH₃)₂), 0.85 (d, J = 6.7 Hz, 6H, -CH₂-CH(CH₃)₂).¹³C NMR (101 MHz, DMSO) – isomers mixture 60/40: δ 172.23 (d, J = 4.5 Hz, C₉), 168.77 (d, J = 17.4 Hz, C₉), 139.31 (d, J = 2.9 Hz, C₉), 138.15 (d, J = 6.0 Hz, C₉), 137.95 (d, J = 5.1 Hz, C₉), 128.93 (d, J = 10.2 Hz, CH₆), 128.69 (d, J = 6.0 Hz, CH₆), 128.47 (d, J = 15.2 Hz, CH₆), 127.80 (d, J = 3.4 Hz, CH₆), 126.87 (d, J = 28.3 Hz, CH₆), 61.43 (d, J = 16.1 Hz, CH thiazolidin-4-one), 44.22 (d, J = 2.8 Hz, -CH₂-CH-(CH₃)₂), 42.12 (d, J = 8.1 Hz, -CH-CH₃), 29.62 (d, J = 3.3 Hz, -CH₂-CH-(CH₃)₂), 29.27 (CH₂ thiazolidin-4-one), 22.13 (d, J = 3.3 Hz, -CH₂-CH-(CH₃)₂), 18.81 (17.90*, -CH-CH₃). HRMS (EI-MS): m/z calculated for C₂₂H₂₃N₂O₂S was 383,178776 and [M+H]⁺ found was 383,178716.

RESULTS AND DISCUSSION

The analysis of nuclear magnetic resonance spectra revealed that the application of method A for synthesis of 2-phenyl-3-[2-(4-(isobutyl)phenyl)-2-methyl]acetamido-thiazoli-din-4-one derivative was carried on conversion rate between 40% and 60%. The highest rate (60%) was obtained when anhydrous toluene was used as reaction medium at 120°C and during 24 hours (tab. I).

For method B it was observed that the reagent conversion rates in the final compound was between 34% and 96%, which varied according to the reaction conditions (reagents ratio, reaction medium, temperature, time, catalyst). The highest conversion rate was 96% when the mercaptoacetic acid was used in excess (1:4.5). At temperatures higher than 95°C (120°C) the synthesis of the final compound but also the presence of the mercaptoacetic dimmer that could not be removed by crystallization, precipitation, liquid-liquid extraction, flash chromatography on silica gel column were observed (tab. I).

The chemical structure of the thiazolidin-4-one derivative was confirmed by IR, NMR and HR-MS spectroscopy. In IR spectrum the characteristic absorption bands of the functional groups were identified. The characteristic absorption band of amidic group (CO-NH-) was observed at 1666 cm⁻¹ and the cyclic C=O group (thia-
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Thiazolidin-4-one derivative appeared at 1716 cm⁻¹. The characteristic band of C-S bond was identified at 694 cm⁻¹ and the NH group at 3243 cm⁻¹. The aromatic ring was observed by the characteristic absorption bands of C-H bond at 2959 cm⁻¹.

<table>
<thead>
<tr>
<th>Method</th>
<th>Reagents (eq.)</th>
<th>Catalyst (eq.)</th>
<th>Solvent</th>
<th>t°C</th>
<th>Time (h)</th>
<th>C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 1.⁹</td>
<td>5 (1.5 eq.)</td>
<td>6 (1 eq.) 7 (1.3 eq.)</td>
<td>-</td>
<td>anh. toluene</td>
<td>120</td>
<td>24</td>
</tr>
<tr>
<td>A 2.</td>
<td>5 (1 eq.)</td>
<td>6 (2 eq.) 7 (3 eq.)</td>
<td>-</td>
<td>anh. toluene</td>
<td>120</td>
<td>45</td>
</tr>
<tr>
<td>A 3.</td>
<td>5 (1 eq.)</td>
<td>6 (2 eq.) 7 (3 eq.)</td>
<td>DCC (1.5 eq.)</td>
<td>DCM</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>A 4.¹⁰</td>
<td>8 (1 eq.)</td>
<td>7 (1.5 eq.)</td>
<td>ZnCl₂ (some crystals)</td>
<td>anh. dioxane</td>
<td>105</td>
<td>38</td>
</tr>
<tr>
<td>A 5.¹¹</td>
<td>8 (1 eq.)</td>
<td>7 (1.5 eq.)</td>
<td>sodium acetate (2.1 eq.)</td>
<td>acetic acid</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td>A 6.¹²</td>
<td>8 (1 eq.)</td>
<td>7 (3 eq.)</td>
<td>-</td>
<td>anh. toluene</td>
<td>120</td>
<td>24</td>
</tr>
<tr>
<td>A 7.</td>
<td>8 (1 eq.)</td>
<td>7 (4.5 eq.)</td>
<td>-</td>
<td>-</td>
<td>105</td>
<td>12</td>
</tr>
<tr>
<td>A 8.¹³</td>
<td>8 (1 eq.)</td>
<td>7 (4.5 eq.)</td>
<td>-</td>
<td>-</td>
<td>80-85</td>
<td>6</td>
</tr>
</tbody>
</table>

C (%) = conversion percentage in the final compound

The aromatic ring protons were identified on ¹H-NMR spectrum as multiplet and doublet signals at 7.50-7.01 ppm, and the NH proton appeared at 10.26 ppm. The proton of CH from thiazolidin-4-one appeared as singlet at 5.82 ppm and the characteristic protons of the two aliphatic CH groups were identified as multiplet or doublet signals at 3.61-3.47 ppm or 1.79 ppm. The characteristic protons of CH₂ from thiazolidin-4-one were observed as triplet or doublet signals at 3.86 ppm and 3.72 ppm. The protons of aliphatic CH₂ were identified in ¹H-NMR spectrum as doublet signal at 2.39 ppm and the protons of the three CH₃ appeared as doublet of doublet or doublet at 1.25 ppm or 0.85 ppm.

In the ¹³C-NMR spectrum the aromatic carbons were identified at 128.69-126.87 ppm, the carbon of the thiazolidin-4-one cyclic CH appeared at 61.43 ppm and for the aliphatic CH at 42.12 or 29.62 ppm. The CH₂ carbons were observed at 29.27 ppm for the thiazolidin-4-one cycle and at 44.22 ppm for the aliphatic moiety. The two methyl group (-CH₂CH-(CH₃)₂) resonances were superimposed in one peak at 22.13 ppm and the third one (-CH-CH₃)
appeared as two peaks at different values 18.81 ppm and 17.90 ppm because the E/Z isomerism.

High Resolution Mass Spectroscopy confirmed the molecular weight of the synthesized compound.

CONCLUSIONS
Two synthesis methods of new thiazolidin-4-one derivative of Ibuprofen were developed in order to be used as general procedure for synthesis of new ibuprofen derivatives. The most efficient conversion rate was obtained when the Ibuprofen hydrazone was reacted with mercaptoacetic acid, at 80-85°C for 6 h. The structure of the synthesized derivative of Ibuprofen was confirmed by Infrared spectroscopy (IR), Nuclear Magnetic Resonance spectroscopy (1H-NMR, 13C-NMR) and High Resolution Mass Spectroscopy (HR-MS).

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