Improvement of synthetic 3-arylcoumarins as skin aging-related enzymes inhibitors

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Improvement of synthetic 3-arylcoumarins as skin aging-related enzymes inhibitors

3-arylcoumarins

YOUNGER SKIN

AGING SKIN

Tyrosinase

Elastase

Collagenase

Age spot

Elastin

Collagen

Fat cells

Muscles
Abstract

Coumarin and its derivatives possess interesting biological, pharmacological, biochemical, therapeutic, and photochemical properties. Previously reported studies have demonstrated the properties of coumarins in the inhibition of skin aging-related enzymes as tyrosinase, elastase and collagenase. Skin aging process depends on several intrinsic and extrinsic phenomena, and degradation of proteins of extracellular matrix represents one of the main causes of alteration of the skin integrity, as well as the appearance of hyperpigmented spots due to the tyrosinase activity. Our previous studies have proved that both simple hydroxycoumarins and hydroxy-3-arylcoumarins are interesting scaffolds to modulate the tyrosinase inhibitory activity. According to these considerations, we have modulated the 3-arylcoumarin scaffold to improve the inhibitory potency against tyrosinase, as well as elastase and collagenase. We have also selected for this study, benzo[f]coumarins, with an extra phenyl ring on the coumarin scaffold. In the present study a screening of hydroxy substituted 3-arylcoumarins and 3-arylbenzo[f]coumarins has been performed, with the aim of identifying compounds with potential inhibitory activity against key target enzymes for the prevention and treatment of skin photoaging. This preliminary study gives some insights into the synthesis and biological activity of these molecules against these important targets.

Keywords: collagenase; coumarin ring; elastase; tyrosinase.
Introduction

UV radiation → ROS → Activation of enzymes that degrade the ECM

TYROSINASE

Spots

ELASTASE

Wrinkles

COLLAGENASE

Changes in thickness
Introduction

1. Previously synthesized compounds

![Compound 1](image1)
Tyrosinase inhibition IC$_{50}$ = 440 µM

![Compound 2](image2)
Tyrosinase inhibition IC$_{50}$ = 730 µM

![Compound 3](image3)
Tyrosinase inhibition IC$_{50}$ = 376 µM

Introduction

2. Design of new compounds

Compounds and their properties:

- **Compound 3**
  - Tyrosinase inhibition IC₅₀ = 376 µM

- Change the position of the hydroxyl groups on the coumarin scaffold: catechol groups
- Condensation of a new ring at 5 and 6 positions of the coumarin ring: naphthalene derivatives
Introduction

3. Synthetic route for obtaining the new compounds

When R = OCH₃

= possibility of including an extra phenyl ring

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Introduction

4. New synthetized compounds

MJM555*  MJM556*  T09

T10  T11

T12  T14

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## Results and discussion

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tyrosinase (50 μM)</th>
<th>Elastase (50 μM)</th>
<th>Collagenase (100 μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MJM555*</td>
<td>22.7</td>
<td>24.5</td>
<td>39.3</td>
</tr>
<tr>
<td>MJM556*</td>
<td>8.6</td>
<td>29.6</td>
<td>35.7</td>
</tr>
<tr>
<td>T9</td>
<td>23.2</td>
<td>20.7</td>
<td>51.5</td>
</tr>
<tr>
<td>T10</td>
<td>22.3</td>
<td>35.3</td>
<td>21.2</td>
</tr>
<tr>
<td>T11</td>
<td>N.I.</td>
<td>N.I.</td>
<td>N.I.</td>
</tr>
<tr>
<td>T12</td>
<td>N.I.</td>
<td>22.8</td>
<td>7.9</td>
</tr>
<tr>
<td>T14</td>
<td>10.0</td>
<td>22.4</td>
<td>15.6</td>
</tr>
</tbody>
</table>

N.I. = No Inhibition
Conclusions

• Among the three skin aging-related enzyme, the new synthetized compounds showed the best inhibitory activity against collagenase.

• Compound T9 reveals to possess the higher inhibitory potential against collagenase with a percentage of inhibition even better than that of the standard inhibitor epigallocatechin gallate at the same concentration (51.5% and 37.2% respectively).

\[
\text{\includegraphics[width=0.5\textwidth]{image.png}}
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• This study reveals new insights into the synthesis and biological activity of 3-arylcoumarins against skin aging-related enzymes.
Acknowledgments