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

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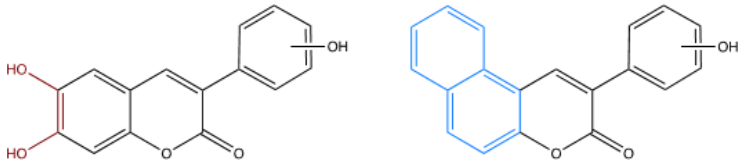
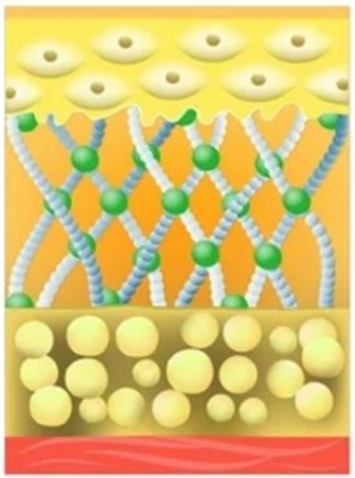
Improvement of synthetic 3-arylcoumarins as skin aging-related enzymes inhibitors



3-arylcoumarins

YOUNGER SKIN

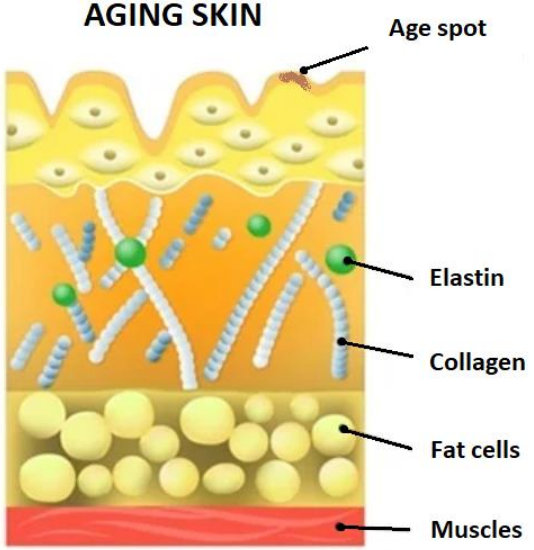


Tyrosinase

Elastase

Collagenase

AGING SKIN

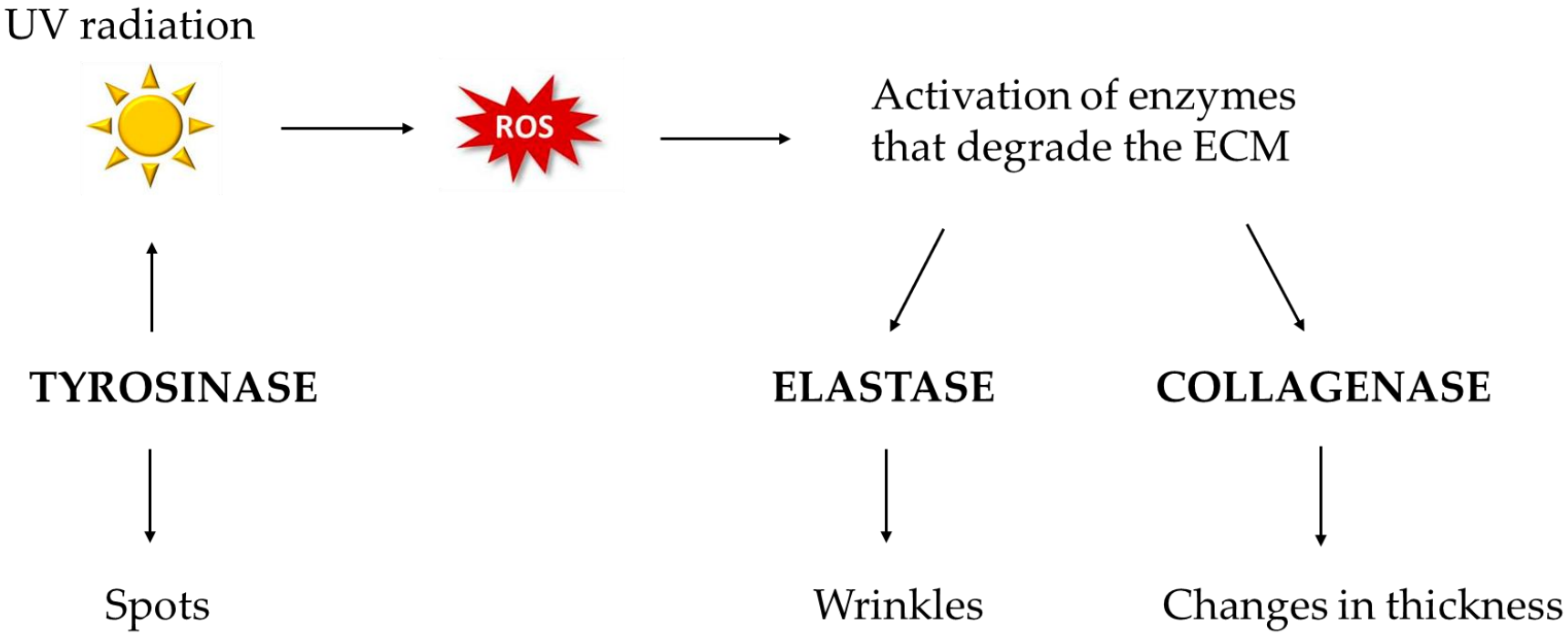


Abstract

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.

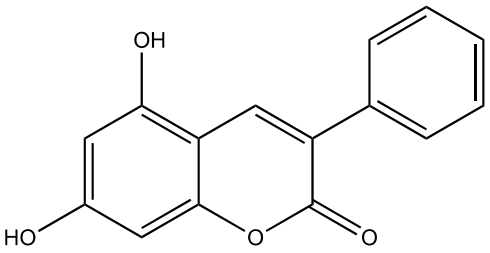
Keywords: collagenase; coumarin ring; elastase; tyrosinase.

Introduction



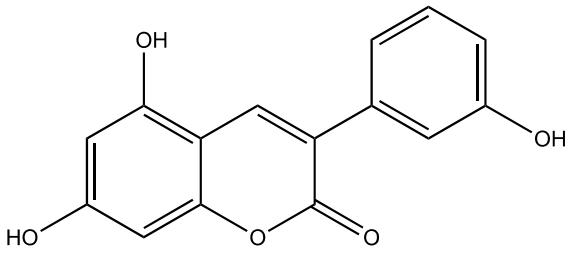
Introduction

1. Previously synthetized compounds



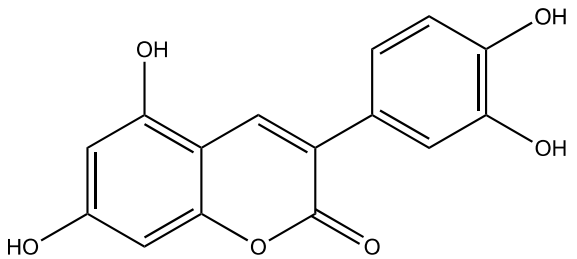
Compound 1

Tyrosinase inhibition IC_{50} = 440 μM



Compound 2

Tyrosinase inhibition IC_{50} = 730 μM



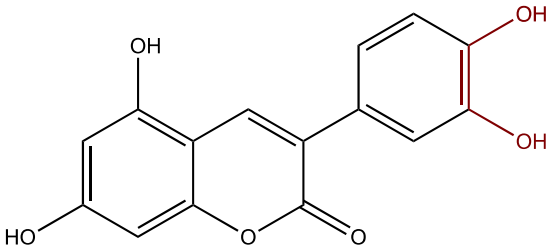
Compound 3

Tyrosinase inhibition IC_{50} = 376 μM

M. J. Matos, C. Varela, S. Vilar, G. Hripcsak, F. Borges, L. Santana, E. Uriarte, A. Fais, A. Di Petrillo, F. Pintus and B. Era. Design and discovery of tyrosinase inhibitors based on a coumarin scaffold., RSC Adv., 2015, 5, 94227.

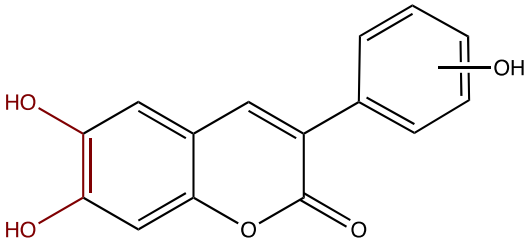
Introduction

2. Design of new compounds

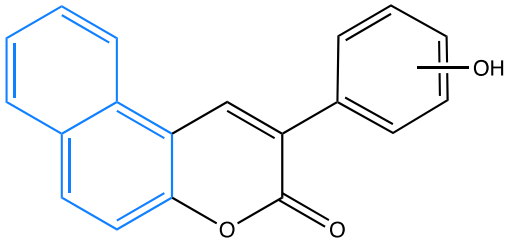


Compound 3

Tyrosinase inhibition IC_{50} = 376 μM



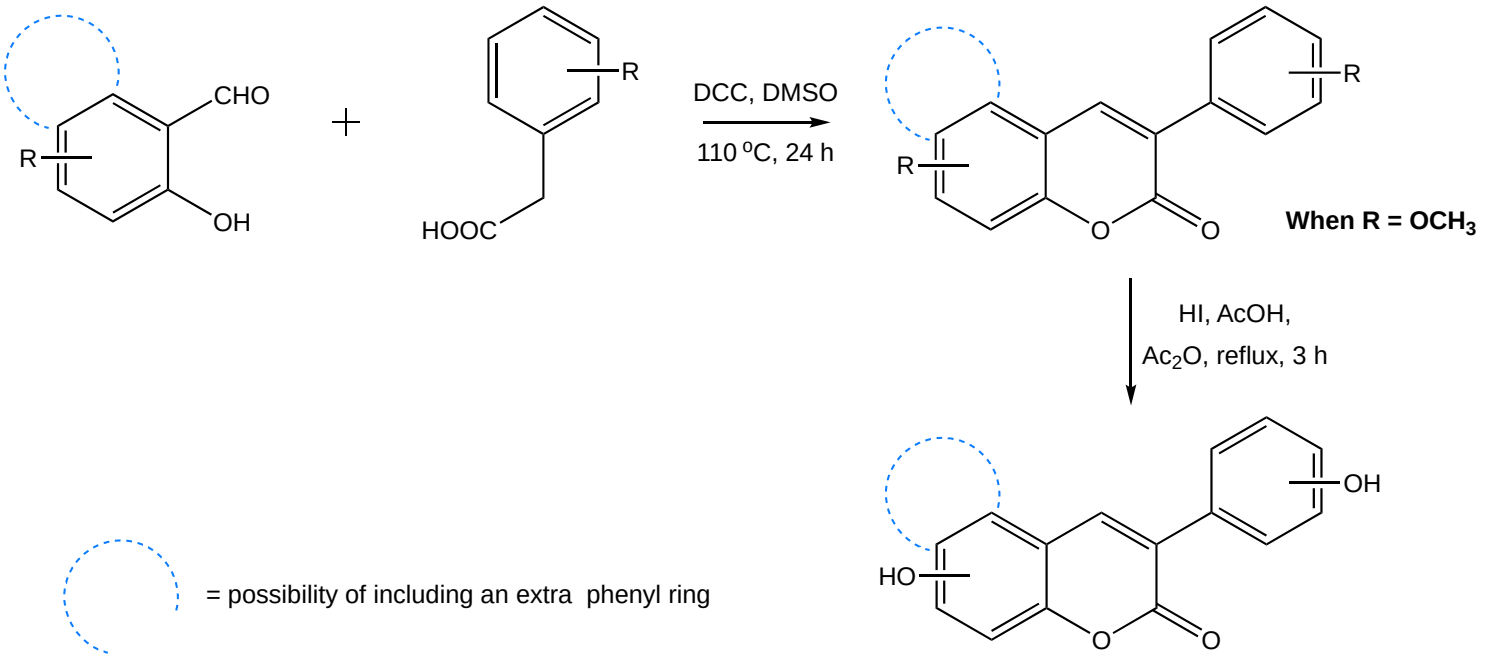
Change the position of the hydroxyl groups on the coumarin scaffold: catechol groups



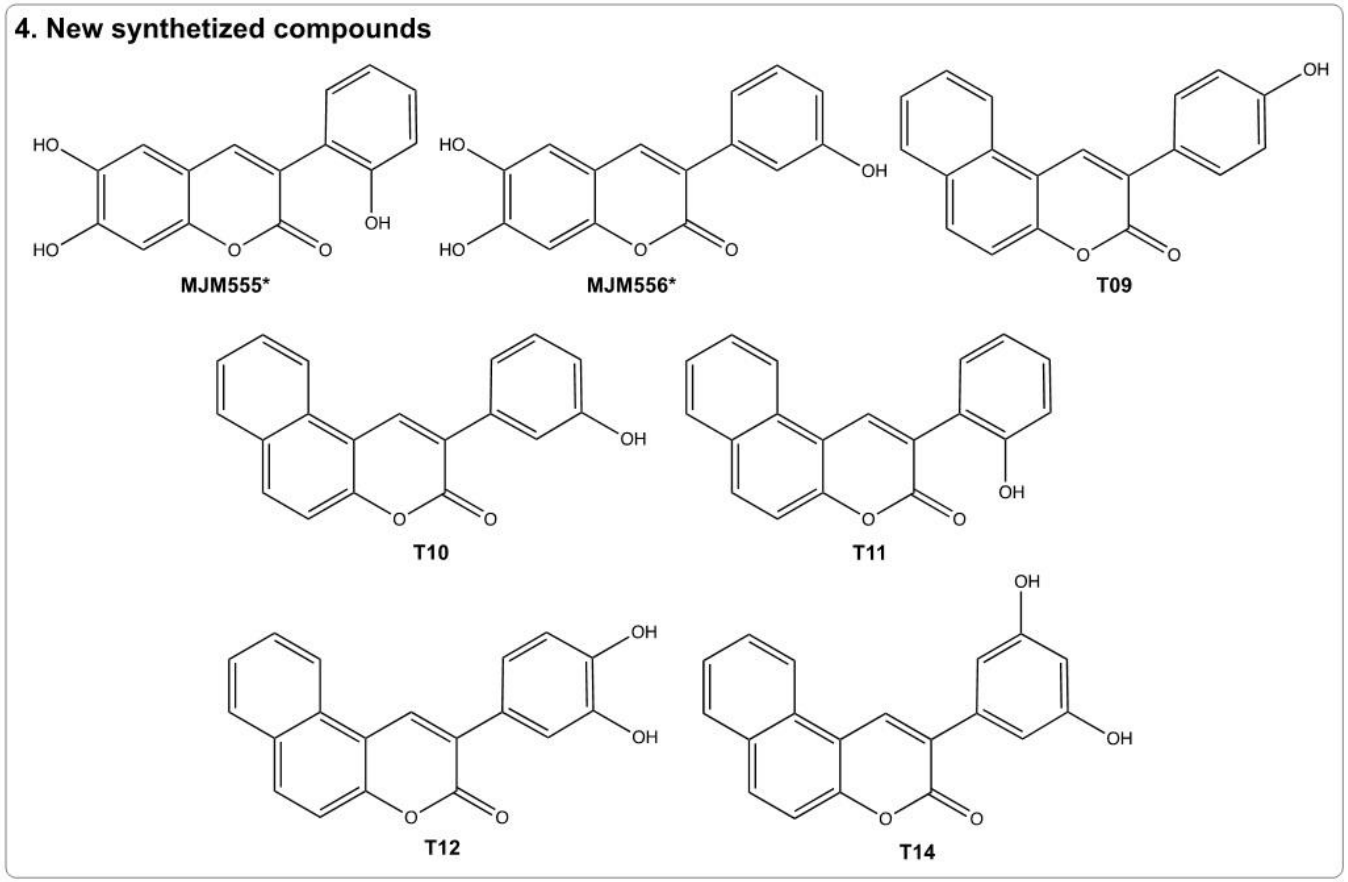
Condensation of a new ring at 5 and 6 positions of the coumarin ring: naphthalene derivatives

Introduction

3. Synthetic route for obtaining the new compounds



Introduction



Results and discussion

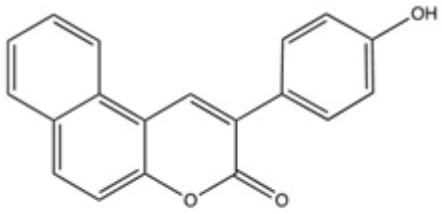
	Inhibition (%) [50 µM]		Inhibition (%) [100 µM]
Compound	**Tyrosinase**	**Elastase**	**Collagenase**
MJM555*	22.7	24.5	39.3
MJM556*	8.6	29.6	35.7
T9	23.2	20.7	51.5
T10	22.3	35.3	21.2
T11	N.I.	N.I.	N.I.
T12	N.I.	22.8	7.9
T14	10.0	22.4	15.6

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).



T09

- This study reveals new insights into the synthesis and biological activity of 3-arylcoumarins against skin aging-related enzymes.

Acknowledgments