

Coumarin-Chalcone Hybrids as new scaffolds in drug discovery

Saleta Vázquez Rodríguez^{a*}, Silvia Serra^a, Lourdes Santana^a and Eugenio Uriarte^a.

^a *Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782, Spain.*

* *E-mail: svre77@hotmail.com*

Abstract: The first hydroxylated series of coumarin-chalcone derivatives has been synthesized starting from the corresponding salicyl aldehyde and β -ketoester precursors by a Knoevenagel reaction in order to obtain the methoxy derivatives which have been further hydrolyzed with a Lewis acid.

Keywords: Coumarin, Chalcone, Knoevenagel

Introduction

Coumarins and chalcone are a family of natural and synthetic compounds that have raised an enormous interest for a long time due to its biological applications. One of the biggest applications of coumarins resides on the wide range of pharmacological activities such as antimicrobial, antiviral, antioxidant, antiplatelet, vasorelaxant or enzymatic inhibitors^{1,2,3,4} so this coumarin scaffold give us a hint in the discovery and development of new drugs. Besides coumarins, chalcones share a wide range of this biological properties like antiproliferative, cardioprotector, or anti-inflammatory activity^{5,6,7} and in the present year chalcones have been proposed as valid scaffolds for monoamino oxidases inhibitors⁸.

On the other hand, many studies suggest that polyphenols may be involved in neurotoxic or cyclooxygenase activity as well as they play a role as chemopreventive and tumor growth inhibition agents and their protective properties against oxidative stress.^{9,10,11} It is for these reasons that we have synthesized a novel series of hydroxylated coumarin-based compounds containing a chalcone moiety in order to make different biological essays and test their potential pharmacological activities.

Results and Discussion

The aim of this work has been to synthesize new hydroxy coumarin-chalcone hybrids which contain the hydroxyl substituents in the aromatic rings that can potentially be used as new lead compounds in drug discovery.

Compounds were synthesized using a two steps synthetic strategy that allows us to obtain methoxy derivatives which were further hydrolyzed using a Lewis acid.

(*Figure 1*)

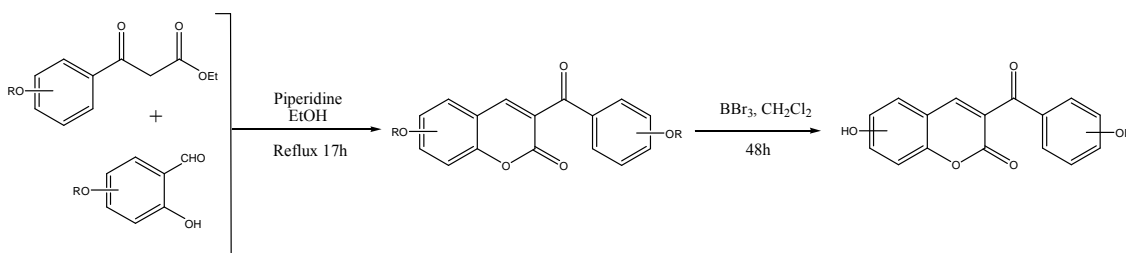
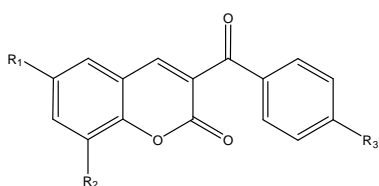


Figure 1. Synthetic route used to prepare hydroxy coumarin-chalcone hybrids.

The main scaffold with methoxy substituents was prepared by a Knoevenagel reaction in basic conditions in 82-93% yields. First synthesized derivatives have the methoxy substituents placed in positions 8 and 4', (*Table 1*)

Table 1. Coumarin-chalcone hybrids

Compound	1	2	3	4
R ₁	-H	-Br	-H	-Br



R₂	-H	-OMe	-H	-OH
R₃	-OMe	-H	-OH	-H

Hydroxy derivatives were further prepared from the ether precursors by catalysis with a Lewis acid, BBr₃ in CH₂Cl₂¹². Purification of compounds **1-2** was made by recrystallization in MeOH, while compounds **3-4** were purified by flash chromatography.

The followed methodologies to prepare compounds **1-2**, in a parallel synthesis way, bring the opportunity of synthesize structural related compounds with punctual modifications in the aromatic rings depending on the starting materials.

Biological assays as vasodilators, antioxidants and monoaminoxidase inhibitors are currently being carried out and results will be further presented.

General Experimental Procedure

All reactions were carried out under dry and deoxygenated argon atmosphere. Solvents were used as anhydrous by reflux of each solvent over an appropriate dryer agent and further distillate under argon atmosphere.

Qualitative identification of the compounds and course of the reactions were visualized using TLC plates (Merck, silica gel 60F₂₅₄) under UV light (254-366 nm). Melting points were determined using a Reichert Kofler thermopan or in capillary tubes on a Büchi 510 apparatus and are uncorrected. ¹H NMR spectra were recorded on a Bruker WM-250 at 250 MHz using TMS as internal standard (chemical shifts in δ values, *J* in Hz).

General procedure for the preparation of 3-benzoylcoumarins: In a round bottom flask the appropriated salicylaldehyde (1 equiv.unless otherwise noted) and ethyl benzoylacetate (1 eq. unless otherwise indicated) were dissolved in dry EtOH. Were then added 5 drops of piperidine, and the reaction was subjected to reflux. The reaction was monitored by TLC and after the end of it, the solution was cooled on ice and the precipitate was filtered and washed with ether. The solid obtained was purified by recrystallization in MeOH: CH₂Cl₂ and / or column chromatography.

General procedure for the preparation of hydroxy 3-benzoylcoumarins:

Ether derivatives of 3-benzoylcoumarins (1 eq.) were dissolved in dry DCM and BBr₃ (20 eq.) was added dropwise at room temperature in a sealed tube. Mixture was stirred and heated at 80°C for 48h. After cooling to room temperature, the crude reaction mixture was quenched carefully with ice, water and 1 N HCl. The aqueous layer was extracted with AcOEt (3 × 50 cm³) and the combined organic extracts were washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄) and concentrated to dryness.

3-(*p*-methoxybenzoyl)coumarin (1): Yield: 93%. ¹H-NMR (250 MHz, DMSO-*d*₆) δ ppm 8.34 (s, 1H, H-4), 7.92 (d, *J* = 8.8 Hz, 2H, H-2', H-6'), 7.83 (d, *J* = 8.6 Hz, 1H, H-5), 7.70 (d, *J* = 7.26 Hz, 1H, H-8), 7.55-7.33 (m, 2H, H-6, H-7), 7.05 (d, *J* = 8.8 Hz, 2H, H-3', H-5'), 3.85 (s, 3H, -CH₃). MS *m/z* (%): 281 ([M+1]⁺, 19), 280 ([M]⁺, 82), 135 (100), 77 (20).

3-benzoyl-5-bromo-8-methoxycoumarin (2): Yield: 82%. ¹H-NMR (250 MHz, CDCl₃) δ ppm 7.78 (s, 1H, H-4), 7.69 (d, *J* = 7.3, 2H, H-2', H-6'), 7.51-7.24 (m, 3H, H-3', H-4', H-5'), 7.14 (s, 1H, H-5), 7.09 (s, 1H, H-7), 3.82 (s, 3H, -CH₃) MS *m/z* (%): 360 ([M+1]⁺, 18), 359 ([M]⁺, 58), 358 (18), 357 (58), 105 (100), 77 (70).

3-(*p*-hydroxybenzoyl)coumarin (3): Yield: 67%. ¹H NMR: (250 MHz, DMSO-*d*₆) δ ppm 10.6 (s, 1H, -OH), 8.3 (s, 1H, -H4), 7.8 (d, *J* = 8.5 Hz, 4H, -H2', -H3', -H5', -H6'), 7.7 (t, *J* = 7.50 Hz, 1H, -H5), 7.5-7.3 (m, 2H, H6, H7), 6.9 (d, *J* = 8.5 Hz, 1H, -H8). MS *m/z* 267 ([M+1]⁺, 12), 266 ([M]⁺, 57), 249 (22)

3-benzoyl-5-bromo-8-hydroxycoumarin (4): Yield: 52%. ¹H NMR: (250 MHz, DMSO-*d*₆) δ ppm 10.8 (s, 1H, -OH), 7.8 (d, *J* = 7.9 Hz, 2H, H2', H6') 7.6-7.3 (m, 3H, -H3', -H4', -H5'), 7.0 (s, 1H, -H5), 6.8 (s, 1H, H7). MS *m/z* 346 ([M+1]⁺, 18), 345 ([M]⁺, 62), 344 (18), 343 (53), 105 (100).

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