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Chromone derivatives which bind to human hair

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Abstract—Chromone derivatives bearing a quaternary ammonium functionality which bind to human hair were synthesised. The radical scavenging activity, according to the DPPH assay, of the chromone derivatives is considerably lower compared with flavonoids. The compounds show interesting UV absorption properties that depend on the position of a methoxy substituent. A bathochromic shift of 29 nm was observed when the methoxy group on the ammonium salts were shifted from position 7 to position 6.

1. Introduction

Chromones are a group of naturally occurring compounds that are ubiquitous in nature especially in plants.[1] They are oxygen-containing heterocyclic compounds with a benzoannelated γ-pyrone ring, with the parent compound being chromone (4*H*-chromen-4-one, 4*H*-1-benzopyran-4-one).[2] Molecules containing the chromone structure (for example chromones and flavonoids) have a wide range of biological activities including tyrosine and protein kinase C inhibitors, antifungal, antiallergenic, antiviral, antitublin, antihypertensive and anticancer agents, as well being active at benzoazepine receptors, lipoxygenase, cyclooxygenase and modulating P-glycoprotein-mediated multidrug resistance (MDR).[2–5] Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans (Fig. 1).[6]

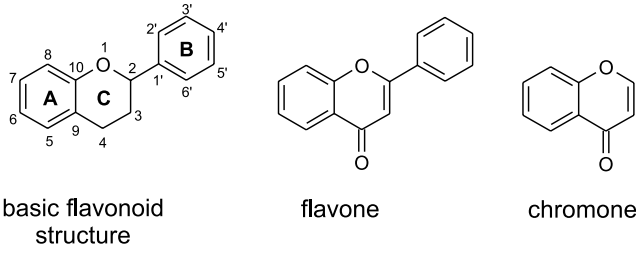

Figure 1. Basic structure of flavonoids, flavones and chromones.

Many of these biological actions are attributed to the ability of flavonoids to transfer electrons, chelate metal catalysts,[7] activate antioxidant enzymes,[8] reduce α-tocopherol radicals,[9] inhibit oxidases[10] as well as through their possible influences on the intracellular redox status, however, the precise mechanisms remain unclear.[11] Recent studies have speculated that the classical hydrogen-donating antioxidant activity of flavonoids[12] is unlikely to be the sole explanation for cellular effects.[13]

The antioxidant characteristics of flavonoids in combination with their favourable UV absorption properties are also exploited by plants to protect them from the suns UV radiation and scavenge UV-generated reactive oxygen species (ROS).[14] For example, there is evidence that flavonoids in leaves, deposited in either the epidermal cells or in the waxy upper leaf surface provide protection from the potential damage of UVB radiation.[15] This use could also be utilised in the protection of human hair from UV-radiation. It is well known that exposure to UV-radiation can damage hair fibres. UVB radiation is the principal radiation responsible for hair protein loss (causing dryness, reduced strength, rough surface texture, decreased luster, stiffness and brittleness), while UVA radiation is responsible for colour changes regardless of hair type.[16] Hair melanins provide some photochemical protection to hair proteins, especially at lower wavelengths where both the hair pigments and proteins absorb radiation.[17] These melanins also immobilise many of the free radicals generated by UV-radiation, however, in the process they are often degraded or bleached.[18] Here we reported the synthesis of new chromone derivatives, bearing a cationic functionality which bind to human hair.

Keywords: Chromone; Hair substantivity; UV activity; Antioxidant; Binding.
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2. Results and discussion

Quaternary ammonium compounds (cationic surfactants, cationic polyelectrolytes and cationic quaternary derivatives of hydrolyzed proteins) have been widely used as hair conditioning agents.[19] The deposition (substantivity) of such compounds can effect the hair fibre friction, stiffness, gloss, anti-static qualities and strength of hair.[17] By synthesising a chromone derivative with quaternary ammonium functionality it was hoped that this compound would show not only activity of cosmetic interest but also hair substantivity.

The synthetic strategy chosen for the preparation of the 2-amido-chromone required the preparation of 2-ethylester-chromone **2**. Condensation of **1** with diethyl oxalate in the presence of sodium ethanoxide in ethanol and followed by acidic cyclisation afforded the ester **2**.[5,20] By reacting different amines with **2**, a variety of chromone amides were synthesised (Scheme 1).

Reacting the ester **2** with either an *n*-alkyl amine (butylamine, octylamine, dodecylamine) or 3-dimethylaminopropylamine gave the amides **3** and **4**, respectively. Treatment of the latter with methyl iodide gave the trimethyl ammonium salt **5**.

Although numerous other methods exist for introducing a new functionality at the C-2 position of chromone,[3,4,21] the chosen synthetic route is short, has two possibilities for introducing diversity (variation of acetophenone and variation of amine) needed to generate a small library and utilises cheap reagents which is an important factor for industrial applications.

In order to increase the radical scavenging activity of **3** and **5**, the 7-hydroxy-4-oxo-4*H*-chromene-2-carboxylic acid ethyl ester was synthesised. Due to the formation of a zwitterion in compound **9** this synthetic route was not expanded for other hydroxy-4-oxo-4*H*-chromene-2-carboxylic acid ethyl esters with other substitution patterns (Scheme 2).

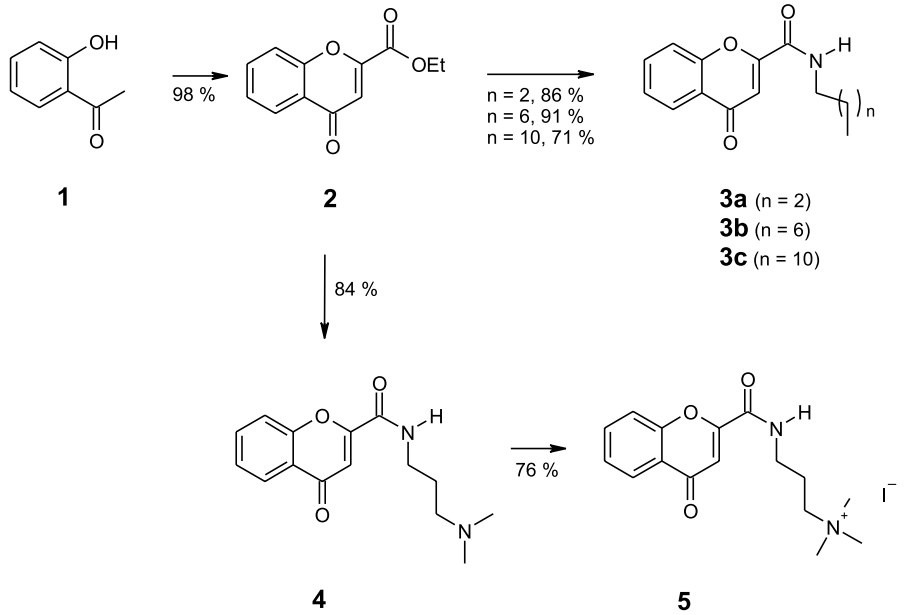
Alternatively, the methoxy derivatives **12** were synthesized (Scheme 3). Although in general hydroxyl groups give a better radical scavenging activity,[22] there are some examples where a hydroxyl group is deleterious and methoxy group beneficial to such activity.[4,23,24] Compound **12** was prepared from the commercially available **11**. The methoxy derivatives **14** could now be easily synthesised and purified without fear of zwitterion formation.

Numerous attempts with various conditions at *O*-demethylating **14a–c** failed.[25] Alternative protecting groups that can withstand the reaction conditions and are industrially feasible in order to readily synthesise hydroxyl derivatives are currently being investigated.

2.1. Hair substantivity

Compounds **2**, **3**, and **5** served as models for hair binding assay. Although there are various methods to measure the substantivity of cationic species to hair,[19,26] many are complicated, require specialized instrumentation and are time-consuming. As many compounds contained in cosmetic products including cationic surfactants[27] and dyes[28] can penetrate into hair fibres, it is important to choose an analytical method which can quantitatively recover the analyte.

Although a number of methods for hair substantivity were tested,[29] only two (MALDI MS[30] and hair digestion followed by HPLC analysis) could confirm the presence of compound bound to hair. The practicality of HPLC analysis and the large number of samples made the HPLC method very feasible. The compound was dissolved in a 70:30 ethanol/water mixture, to which then sterile, washed hair was added and allowed to stir for 1 h. The hair was then



Scheme 1. General synthesis of unsubstituted 2-amido chromones.