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Short Communication

Antioxidant Potentialities of 4-Acyl isochroman-1,3-Diones

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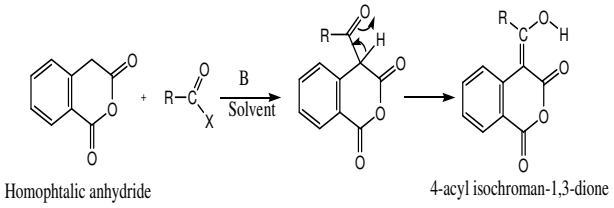
Abstract

A new family of compounds (4-acyl isochroman-1,3-diones), demonstrating antioxidant properties, have been synthesized and described. Their antioxidant properties are studied herein. These antioxidant characters increased with the electronic withdrawing character of the acyl substituent. So, 4-p-Cyanobenzoyl isochroman-1,3-dione and 4-p-Nitrobenzoyl isochroman-1,3-dione have been found to exhibit a reducing power and to scavenge the DPPH• free radical using FRAP and DPPH assays..

Key words: Antioxidant activity, DPPH scavenging activity, Fe^{3+} reducing power, 4-acyl isochroman-1,3-diones, electro attracting character.

Introduction

The synthesis of 4-acyl isochroman-1,3-diones have been described for the first time in 1965 by J. Schnekenburger[1], followed in 1978 by R. N. Usgaonkar and al.[2] Only three models of 4-acyl isochroman-1,3-diones had been obtained and described. Since a multitude of difficulties have been encountered in synthesizing 4-acyl isochroman-1,3-diones, no more investigations have been reported until 1996, when A. Saba[3] evidenced best conditions for the preparation of these compounds. Then, some of these compounds have been synthesized in our laboratories according to scheme 1 to study their properties.



Scheme 1
Reaction scheme for the formation of 4-acyl isochroman-1,3-diones
X = Cl or OCOR ; B = Pyridine or Triethylamine ;
Solvent = diethyl ether or THF

1: R = CH_3; **2**: R = C_2H_5; **3**: R= C_6H_5; **4**: R = *p*-FC_6H_4 ;

5: R = *p*-$CH_3OC_6H_4$ **6** : R = *p*-CNC_6H_4 : **7**: R = *p*-$NO_2C_6H_4$.

These compounds (**1**-**7**) have been identified by their melting points (mp), IR, ^1H, ^{13}C + DEPT 135 and ^{17}O NMR data[3-5] and their structure studied by crystallography[6-8]. Recently, they have been found to be fluorescents[5].

As the difficulties to obtain 4-acyl isochroman-1,3-diones have been overcome, we are now focusing on their chemical and biological potentialities. Enolic proton of 4-acyl isochroman-1,3-diones is susceptible to interfere with oxido- reduction. So these compounds could be antioxidants. Antioxidants have been widely used in different fields of industry and medicine as substances, which interrupt radical-chain oxidation processes, improve general health, help cell rejuvenation and prevent cancer[9]. As a part of our continuing investigations about 4-acyl isochroman-1,3-diones, we report in this paper, for the very first time, their antioxidant potentialities, using *in vitro* evaluation models.

Material and Methods

Synthesis of 4-acyl isochroman-1,3-diones: 4-acyl isochroman-1,3-diones were synthesized as previously described and characterised[3,5]. The general scheme of synthesis is shown by figure 1. In brief, homophtalic anhydride and the selected R acid chloride (or R acid anhydride) with pyridine (when R is an aliphatic moiety), or triethylamine (for aromatic one) are stirred at room temperature in THF (or diethyl ether) for 2 to 3 hours to give the acylated compound in good yield. The crude product is recrystallized in dichloromethane or chloroform. When R is an aromatic moiety, it is necessary to reflux the mixture for 2 hours before purification.

DPPH• radical scavenging activity: DPPH• radical scavenging activity was measured as described elsewhere[11]. Briefly, 1.5 mL of a freshly prepared DPPH solution (20 mg/mL in methanol) was added to 0.75 mL of 4-acyl isochroman-1,3-diones (1.562 – 100 µg/mL final concentrations). After shaking, the mixture was incubated for 15 min in darkness at room temperature and then absorbance was measured at 517 nm against a blank (without 4-acyl isochroman-1,3-dione). Inhibition

percentage of free DPPH radicals (I %) was calculated following the formula: I (%) = (1 - A_{Sample}/A_{Blank}) x 100. A_{blank} and A_{sample} are the absorbance of the blank and sample reactions. IC_{50} (Concentration inhibiting 50% of free DPPH$^{\bullet}$ radicals) was calculated from the plotting of inhibition percentage versus sample concentrations. Gallic acid (0.156 - 10 µg/mL) was used as positive control.

Ferric-reducing power: The FRAP assay[12] was used to evaluate the Fe(III) to Fe(II) reducing power. Briefly, 1 mL of sample (500µg/mL or 31.25 µg/mL in methanol) was mixed with 2.5 mL of phosphate buffer (0.2 mol, pH 6.6) and 2.5 mL of potassium hexacyanoferrate (1% in water). After 30 min incubation at 50 °C, 2.5 mL of trichloroacetic acid (10% in water) was added, and the mixture centrifuged at 3000 rpm for 10 min. The supernatant (2.5 mL) was mixed with water (2.5 mL) and 0.5 mL of $FeCl_3$ (0.1 % in water), then absorbance was read at 700 nm against a calibration curve (100 - 1.562 µg/mL) of ascorbic acid. The reducing power was expressed as mg ascorbic acid equivalent g^{-1} of compound (mg AAE/g). Gallic acid (10 µg/mL) was used as positive control.

Statistical analysis: Assays were run in triplicate and data given as mean value ± standard deviation. The software Graphpad Prism® 5.03 for window was used to analyse the statistical significance of data by conducting Student's *t* tests and a *p* value ≤ 0.01 was considered as being significant.

Results and Discussion

Antioxidant activity is a complex process that can occur through several mechanisms. Due to its complexity, more than one test must be carried out when evaluating the antioxidant activity of pure compounds or extracts[10]. Then, the antioxidant potentiality of 4-acyl isochroman-1,3-diones (scheme 1) was evaluated using both DPPH and FRAP essays. The DPPH test intends to measure the ability of antioxidant compounds to scavenge the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$) by donation of hydrogen atom while the FRAP essay was used to estimate their Fe^{3+} to Fe^{2+} reducing power, resulting from their electron-donating capacity. Results are summarized in table 1.

Table-1
Antioxidant activities of 4-acyl isochroman-1,3-diones

Compounds	DPPH$^{\bullet}$ Scavenging Activity IC_5 (µg mL^{-1})	Fe^{3+} Reducing Power (mmol AAE g^{-1})
1 R = CH_3	n.a.	0.05 ± 0.01 [a]
2 R = C_2H_5	na	0.01 ± 0.01 [a]
3 R = C_6H_5	n.a.	0.01 ± 0.01 [a]
4 R = *p*-FC_6H_4	n.a.	0.05 ± 0.01 [a]
5 R = *p*-$MeOC_6H_4$	n.a.	0.05 ± 0.01 [a]
6 R = *p*-CNC_6H_4	9.00 ± 00 [b]	0.58 ± 0.01 [c]
7 R = *p*-$NO_2C_6H_4$	20.40 ± 0.50 [a]	1.95 ± 0.03 [d]
Gallic acid	0.57 ± 0.01 [c]	18.73 ± 0.21 [e]

Expressed as mean values ± SD of three replicates; n.a. Not active (IC_{50} > 100 µg/ml). In each column, data with different letters in superscript are statistically different by Student's *t* tests (*p* value ≤ 0.01). Reducing power was given as mmol of Ascorbic Acid Equivalent/ g of 4-acyl isochroman-1,3-diones (mmol AAE g^{-1}).

DPPH$^{\bullet}$ scavenging activity (IC_{50}) was given as concentration (µg/mL) of 4-acyl isochroman-1,3-diones inhibiting/ scavenging 50% of free DPPH$^{\bullet}$ radicals.

The best antioxidant potentiality was recorded for the 4-*p*-Cyanobenzoyl-isochroman-1,3-dione **6** and 4-*p*-Nitrobenzoyl- isochroman-1,3-dione **7**, **6** being the strongest DPPH$^{\bullet}$ radical scavenger (IC_{50} = 9.00 µg/ml) while **7** exhibit the best reducing power (1.95 mmole AAE g^{-1}). The compounds substituted with a methyl, ethyl, benzoyl, *p*-Fluorobenzoyl or *p*-Methoxybenzoyl group did not show any significant Fe^{3+} reducing nor DPPH$^{\bullet}$ scavenging activity. The difference observed in the antioxidant profile of **1**, **2**, **3**, **4**, **5**, **6**, and **7** could be related to the electro attracting character of substituted groups. The nitro (NO_2) and cyano (CN) functions in position para of the phenyl ring render the *p*-Nitrobenzoyl and *p*-Cyanobenzoyl groups more electro attractant than the other groups. Consequently, the enolic proton of **6** and **7** is comparatively, more available than those of **1**, **2**, **3**, **4**, and **5** for the oxido-reduction reaction conferring to both molecules **6** and **7**, their antioxidant properties. Compared to gallic acid used as positive control, **6** and **7** demonstrate a weak to moderate antioxidant activities. However, taking in consideration our hypothesis, it might be possible to synthesize promising antioxidant 4-acyl isochroman-1,3-diones using more electro attracting acyl groups.

Conclusion

Antioxidant potentialities of 4-acyl isochroman-1,3-diones (**1** – **7**) have been evaluated in this work. Compounds **6** and **7** have been found to be the most active in both DPPH and FRAP assays. The electro attracting character of the substituent R of these compounds was found to be responsible of the antioxidant activities. Hence, 4-acyl isochroman-1,3-diones with high electronic withdrawing character should be promising antioxidant compounds.

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