HETEROCYCLES 43. SYNTHESIS, CHARACTERIZATION AND ANTIOXIDANT ACTIVITY OF SOME THIAZOLE HYDROXYCHALCONES AND THEIR FLAVONOIDIC DERIVATIVES

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Abstract

Natural and synthetic chalcones are biologically active molecules, as well as precursors for the preparation of several pharmacologically useful compounds, belonging to the class of the epoxides, flavanones, flavones and aurones. The thiazole ring is present in the structure of many compounds with therapeutic potential. Starting from these premises, the aim of this study was the synthesis and characterization of new thiazole chalcones, flavanones and flavones and the evaluation of their antioxidant potential. Chalcones were obtained by applying the Claisen-Schmidt condensation of thiazole aldehydes with acetophenones substituted in *ortho* or *para* with a hydroxyl group. The *ortho* hydroxychalcones were used as precursors for the synthesis of thiazole flavanones and flavones, in different reaction conditions: flavanones were obtained by cyclization in acidic/basic catalysis and flavones were obtained by oxidative cyclization with iodine in dimethylsulfoxide (DMSO). The structures were confirmed by ¹H NMR, ¹³C NMR, IR and MS analysis. The antioxidant activity was determined by 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging method. The synthesized compounds have a low antioxidant activity.

Rezumat

Calcone naturale și de sinteză sunt molecule biologice active și precursori pentru sinteza unor compuși din clasele epoxizilor, flavanonelor, flavonelor și auronelor. Nucleul tiazolic este prezent în numeroși compuși cu proprietăți terapeutice. Pornind de la aceste premize, au fost sintetizate și caracterizate o serie de calcone, flavanone și flavone tiazolice și s-a evaluat potențialul lor antioxidant. Calcone au fost obținute prin reacția de condensare Claisen-Schmidt a unor aldehide tiazolice cu acetofenone substituie în *orto* sau *para* cu o grupă hidroxil. *Orto* hidroxicalconele au fost utilizate ca precursori pentru sinteza flavanonelor și flavonelor tiazolice, în diferite condiții de reacție: flavanonele s-au obținut prin ciclizare în cataliză acidă/bazică, iar flavonele s-au obținut prin ciclizare oxidativă cu iod în dimetilsulfoxid (DMSO). Structurile au fost confirmate prin analiză ¹H RMN, ¹³C RMN, IR și MS. Activitatea antioxidantă a compușilor sintetizați a fost determinată prin metoda neutralizării radicalul liber 2,2-difenil-1-picrilhidrazil (DPPH). Compușii sintetizați au o activitate antioxidantă redusă.

Keywords: Chalcone, Flavone, Flavanone, Thiazole, Spectral analysis

Introduction

Flavonoids are a group of natural and synthetic compounds exhibiting C₆-C₃-C₆ frame [16]. Depending on the chemical structure, flavonoids are classified in: flavanones, flavones, chalcones, anthocyanidins, flavonols, flavanonols (dihydroflavonols), isoflavones and flavanols (flavan-3-ols /catechins) [10].

Chalcones, 1,3-diphenyl-2-propen-1-ones, are available in many conjugate forms in nature. The two aromatic moieties are joined by an α,β-unsaturated carbonyl

bridge of three carbon atoms. The most common method for the synthesis of chalcones is the Claisen-Schmidt condensation reaction of benzaldehydes and acetophenones. The reaction takes place in basic or acidic catalysis [15]. Butein, a natural tetrahydroxy-chalcone, is known to inhibit lipid peroxidation. Also, its ability to reduce DPPH stable radical is similar with α-tocopherol [9].

Chalcones and their derivatives are known for their diverse applications, because of the antioxidant, anti-

inflammatory, analgesic, anti-platelet, anti-ulcer, anti-bacterial, anticancer, antiviral, antihyperglycemic, anti-HIV properties and so forth [17]. Due to the presence of vinyl keto reactive group, chalcones show antioxidant properties. In eukaryotic cells, Michael type additions are responsible for specific effects of the chalcones [24]. The antioxidant activity of chalcones is influenced by the aryl groups and their substitution patterns [25].

Flavanones are generally obtained by the cyclization of chalcones substituted in *ortho* position with a hydroxyl group. The reaction is carried out in acidic or basic catalysis, thermal, photochemical or electrochemical processes. Hesperidin is a natural flavanone with outstanding therapeutic properties [12, 13]. Hesperidin derivatives have been reported for their anti-inflammatory, antimicrobial, antioxidant, anticancer, cardioprotective, hepatoprotective, nephroprotective, neuroprotective and antiarthritic effects [1]. Flavones may be synthesized by oxidative cyclization of *ortho* hydroxychalcones with iodine in DMSO [7]. Among natural flavones, quercetin is known for its antioxidant activity, being able to neutralize highly reactive species, such as hydroxyl and peroxy radicals [6].

The thiazole ring is present in the structure of a large number of compounds with antioxidant properties, antimicrobial, anti-inflammatory and antitumor activities. This heterocycle is present in both natural compounds (vitamin B₁, bleomycins) and synthetic compounds (sulfathiazole, cefotaxime and so forth) recognized for their pharmacological value. Recently, it was reported that a series of 3,4,5-trimethoxyphenylazetidin-1,3-thiazole-2,4-diamine derivatives presented antioxidant activity comparable with ascorbic acid [11]. The antioxidant properties of thiazole compounds are accomplished in two ways: by neutralizing free radicals and by inhibiting lipid peroxidation [11, 13, 20, 24]. Antioxidants are molecules capable of inhibiting the oxidation of other molecules, in this way preventing cell death and other several pathologies determined by the presence of free radicals. The free radicals (superoxide, hydroxyl radicals), hydrogen peroxide and lipid peroxidation are known to cause various pathologies, such as asthma, cancer, cardiovascular diseases, diabetes, inflammatory processes and periodontology. The antioxidant activity of natural flavonoids, including chalcones, is exercised through different mechanisms, such as free radicals neutralization, hydrogen transfer and chelating metal ions. The antioxidant properties of chalcones are influenced by the volume of the two subunits and the nature of the substituents grafted on the aromatic rings. The hydroxyl group has a key-role in the antioxidant activity due to its easy conversion to the phenoxyl radical by a hydrogen transfer mechanism [21].

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay is currently used in order to evaluate

the antioxidant activity of various synthetic compounds and natural products [8]. The method is based on the measurement of the capacity of antioxidants to neutralize the DPPH radicals. DPPH is a stable free radical, which can be reduced by accepting an electron/hydrogen atom, becoming a stable molecule, diamagnetic. DPPH radical has a strong absorption band at 517 nm, while the reduced form does not absorb at 517 nm. When DPPH accepts an electron/hydrogen atom from the antioxidants, the odd electron of the nitrogen atom becomes paired off and the initial deep violet solution is discoloured to yellow and becoming a stable molecule, depending on the number of electrons uptaken [5].

The aim of this study is the synthesis and physico-chemical characterization of *ortho* and *para* hydroxychalcones containing the 2-arylthiazole moiety and flavonoid derivatives obtained by cyclization and oxidative cyclization, in order to evaluate *in vitro* their antioxidant potential.

Materials and Methods

Chemistry

The necessary reagents for the synthesis of the compounds were purchased from Sigma Aldrich (Germany) and the solvents were purchased from Chemical Company (Romania).

The ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ or DMSO-D₆ solution on a Bruker Avance DPX-300 spectrometer operating at 600 MHz and respectively 150 MHz. Chemical shifts on the δ scale are expressed in ppm values from TMS as internal standard. The following abbreviations are used in order to indicate the peak patterns: s-singlet, d-doublet, dd-double doublet, br s-broad singlet.

Mass spectra were recorded on Agilent 1100 Ion Trap mass spectrometer operating at 70 eV.

The FT-IR analysis was performed on a Jasco FT/IR 470 Plus spectrometer by using the Spectra Manager software. The solid sample was introduced in the ATR (attenuated total reflection) device's slot and the IR spectra were recorded between 4000 and 400 cm⁻¹ wavelengths at 4 cm⁻¹ resolution.

Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60F254 sheets. Spots were visualized in UV light. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 Å (63 - 200 μ m).

Melting points were determined on open glass capillaries using an Electrothermal IA 9000 digital apparatus (Bibby Scientific Limited, Staffordshire, UK).

Synthesis of thiazole hydroxychalcones 3a-h

2-Arylthiazole-4-carbaldehyde **1a-h** (1 mmol) was dissolved in ethanol (2.5 mL). The acetophenone was added in an equimolar amount (1 mmol, 0.150 g *ortho/para* hydroxyacetophenone). The obtained solution was cooled and treated with an aqueous solution of 50% KOH (0.2 mL, 0.179 mmols KOH). The reaction

mixture was stirred at room temperature for 23 hours. After the completion of reaction (monitored by TLC, eluent petroleum ether:ethyl acetate or dichloromethane:acetone, as indicated for each individual compound, in the Results and Discussions section), the reaction mixture was poured into ice and acidified with glacial acetic acid. The formed precipitate was filtered, dried and purified by recrystallization or column chromatography, using as eluent different solvent mixtures, as indicated for each individual compound, in the Results and Discussions section.

Synthesis of thiazole flavanones **4a-d**

Method 1: an ethanolic solution of *ortho* hydroxychalcone **3e-h** (1 mmol chalcone and 5 mL of ethanol) was treated with 0.8 mL concentrated H_2SO_4 and refluxed at 100°C . The reaction was monitored by TLC using as eluent a mixture of petroleum ether:ethyl acetate 9/1 or 6/1 v/v. After completion of the reaction (checked by TLC after 6 hours, 12 hours and 18 hours), the solvent was evaporated under reduced pressure. The obtained flavanone was purified by column chromatography using as eluent a mixture of petroleum ether:ethyl acetate 9/1 or 6/1 v/v.

Method 2: a mixture of *ortho* hydroxychalcone **3e-h** (1 mmol) with sodium acetate (6 mmols, 500 mg) in ethanol (5 mL) and three drops of water was refluxed at 100°C , for 48 hours. The reaction was monitored by TLC after every 8 hours. The obtained flavanone was extracted with ethyl acetate and purified by column chromatography using as eluent a mixture of petroleum ether - ethyl acetate.

Method 3: a solution of *ortho* hydroxychalcone **3e-h** (1 mmol) in glacial acetic acid (5 mL) was refluxed for 72 hours. The reaction was monitored by TLC after every 8 hours, using as eluent a mixture of petroleum ether:ethyl acetate 9/1 v/v. The obtained reaction mixture was poured into ice. The formed precipitate was filtered, dried and purified by column chromatography using as eluent a mixture of petroleum ether:ethyl acetate 9/1 v/v.

Synthesis of thiazole flavones **5a-d**

To a solution of *ortho* hydroxychalcone **3e-h** (1 mmol) dissolved in dimethyl sulfoxide (5 mL) I_2 was added (1 mmol, 254 mg). The reaction mixture was refluxed at 160°C for 3 - 4 hours. The reaction was monitored

by TLC using a mixture of petroleum ether and ethyl acetate in different volume ratios, as indicated for each individual compound. After completion of the reaction, the excess of iodine was quenched with 20% $\text{Na}_2\text{S}_2\text{O}_3$ aqueous solution for 30 minutes. The obtained flavone was extracted with ethyl acetate and purified by column chromatography using as eluent a mixture of petroleum ether - ethyl acetate in different volume ratios, as indicated for each individual compound, in the Results and discussions section.

Evaluation of the antioxidant activity

The spectrophotometric measurements of the antioxidant activity were performed using a V-530 Jasco spectrophotometer, at 517 nm, in methanol or dichloromethane as solvent.

The obtained thiazole chalcones **3a-h**, flavanones **4a-d** and flavones **5a-d** were evaluated for their antioxidant activity *in vitro*, by applying the DPPH free radical scavenging method. The solutions were prepared in methanol ($0.085 \mu\text{mol/mL}$ for compounds **3a-d**) or in dichloromethane ($0.06 \mu\text{mol/mL}$ for compounds **3e-h**, **4a-d**, **5a-d**). An amount of 4 mL of the total reaction mixture (compound + 2 mL methanol/2 mL dichloromethane + 2 mL DPPH solution 10 mg/100 mL solvent) were allowed to react at 40°C for 30 minutes. The absorbance values were spectrophotometrically measured at 517 nm for three times, for each compound, and the average value of the three determinations was converted into a percentage of antioxidant activity. For every compound we determined two percentage values of the antioxidant activity. The standards used in the antioxidant activity were ascorbic acid and quercetin.

Results and Discussion

Synthesis of thiazole aldehydes

Thiazole aldehydes **1a-d** were synthesized as previously described in the literature [22]. The four thiazole aldehydes obtained were purified by column chromatography, using as eluent a mixture of petroleum ether:ethyl acetate = 4/1 v/v (Figure 1). The global yields of the thiazole aldehydes synthesis ranged from 47% to 54%.

Figure 1.

Synthesis of thiazole aldehydes **1a-d**; reaction conditions: **I.** ethanol, triethylamine, room temperature (r.t.), 48 h; **II.** acetone, r.t., 24 h; **III.** 1. urotropine, chloroform, water bath, 1.5 h, 2. urotropine, 50% acetic acid, reflux, 1 h.

Synthesis and characterization of new thiazole hydroxy-chalcones

The synthesis of thiazole hydroxychalcones **3a-h** (Table I) was performed by Claisen-Schmidt condensation [14, 18], starting from equimolar amounts of the previously obtained thiazole aldehydes **1a-d** and the acetophenones substituted with a hydroxyl group in *ortho* or *para* position (Figure 2). The reaction was catalysed by potassium hydroxide [14]. The influence of the nature of the substituents in the two units (aldehyde

and acetophenone) were studied for the reaction course. It was found that the reaction rate is neither influenced by the nature of the substituents grafted on the thiazole aldehyde, nor by the position of the hydroxyl group of the acetophenone. For the eight chalcones synthesized, the reaction time was about 23 hours. Chalcones substituted with a hydroxyl group in the *ortho* position of acetophenone were used for the synthesis of flavones and flavanones.

Figure 2.

Synthesis of thiazole *ortho/para* hydroxychalcones; reaction conditions: 50% KOH/ethanol, r.t., 23 h

Table I

The reaction yields and chemical structures of the synthesized thiazole hydroxychalcones **3a-h**

3a-d	R ₁	R ₂	R ₃	Yield %	3e-h	R ₁	R ₂	R ₃	Yield %
3a	H	H	OH	69	3e	H	OH	H	52
3b	CH ₃	H	OH	61	3f	CH ₃	OH	H	52
3c	Cl	H	OH	35	3g	Cl	OH	H	37
3d	OCH ₃	H	OH	66	3h	OCH ₃	OH	H	36

The synthesized thiazole chalcones were purified by recrystallization or column chromatography and characterized by ¹H NMR, ¹³C NMR, IR and MS methods. The mass spectra revealed the corresponding molecular peaks.

In the ¹H NMR spectra of thiazole chalcones, all signals corresponding to the aromatic protons are appearing in the aromatic region at chemical shifts between 6.91 and 8.09 ppm. The proton located in the 5th position of the thiazole ring appears as a singlet at chemical shifts between 7.23 and 8.27 ppm. The vinylic protons from the propenone chain are appearing as a doublet (d) or doublet of doublets (dd) at chemical shifts between 7.67 and 8.14 ppm. In all cases, the vinylic protons located in the 3rd position of the propenone chain are more deshielded (7.69 - 7.84 ppm). The high coupling constants (*J* = 14.9 - 15.2 Hz) for the vinylic protons are indicating that the chalcones **3a-h** were obtained with *E* configuration [26].

In the ¹³C NMR spectra of thiazole chalcones, all signals corresponding to the aromatic carbons are present in the spectra (115.55 - 167.85 ppm). The characteristic carbonylic signal appears at chemical shifts of 187.22 - 194.42 ppm. The vinylic carbon from the 3rd position of the propenone chain appear at 130.06 - 133.21 ppm, being more deshielded than the

vinylic carbon from the 2nd position of the propenone chain, the latter having chemical shifts between 120.24 and 123.73 ppm. In the thiazole ring, the most deshielded carbon is located in the 2nd position, appearing at chemical shifts between 163.7 and 168.0 ppm. The carbon located in the 5th position of the thiazole ring appears at 123.49 - 125.40 ppm.

In the IR spectra of thiazole chalcones **3a-h**, the range of wave numbers for aromatic C–H stretching band is 3097 - 3092 cm⁻¹, and for carbonyl bands (ketone type) is 1655 - 1646 cm⁻¹, excepting compound **3g** (1579 cm⁻¹) and compound **3h** (1576 cm⁻¹).

Synthesis and characterization of new thiazole flavanones

The synthesis of thiazole flavanones (**4a-d**, Table II) was performed by the cyclization of *ortho* hydroxy-chalcones. Different reaction conditions were tested for the efficient production of the target compounds: in ethanol as solvent, with concentrated sulfuric acid at reflux [4], in ethanol with sodium acetate at reflux [19] and in glacial acetic acid, at reflux [7]. The reaction time and yield for each cyclization method are mentioned in Table II.

It was found that the cyclization of *ortho* hydroxy-chalcones in ethanol in the presence of concentrated sulfuric acid at 100°C is the most beneficial for the

reaction course, in terms of efficiency and reaction rate (Table II). It has been observed that a rise in temperature favours some secondary reactions, which results in a significant decrease of the yield.

The cyclization of *ortho* hydroxychalcones in glacial acetic acid at reflux proved to be unfavourable for the synthesis of flavanones, because the reaction occurred

with low rate and the product was obtained with low yield (22%).

The use of sodium acetate in ethanol at reflux afforded the desired product with moderate yield (41%), but the reaction rate was low. Based on these results, the synthesis of the thiazole flavanones was performed by the most efficient method – treatment with concentrated sulfuric acid, in ethanol, at 100°C.

Table II

Synthesis, reaction time and yields of the thiazole flavanones **4a-d**

Compound	Compound	R ₁	Reaction conditions	Reaction time (hours)	Yield (%)
3e	4a	H	CH ₃ COOH, reflux	72	22
3e	4a	H	CH ₃ COONa/ethanol, reflux	46	41
3e	4a	H	H ₂ SO ₄ conc/ethanol, reflux	18	45
3f	4b	CH ₃	H ₂ SO ₄ conc/ethanol, reflux	27	55
3g	4c	Cl	H ₂ SO ₄ conc/ethanol, reflux	18	40
3h	4d	OCH ₃	H ₂ SO ₄ conc/ethanol, reflux	22	48

The obtained thiazole flavanones were purified by column chromatography and characterized by ¹H NMR, ¹³C NMR, IR and MS analysis. In the mass spectra of thiazole flavanones **4a-d**, the molecular peaks confirm that the desired products were formed. The cyclization of chalcones to flavanones determined characteristic spectral changes. In the ¹H NMR spectra of flavanones **4a-d**, two characteristic signals corresponding to the protons located in the 2nd and 3rd positions of the chroman-4-one ring are present in the aliphatic area. The protons located in the 2nd position of the chroman-4-one are appearing as doublet of doublets (dd) at chemical shifts between 3.18 and 3.32 ppm. The two aliphatic protons from the 3rd position of the chroman-4-one ring are appearing as two distinct dd at 5.71 - 5.73 ppm. The signals of the vinylic protons are not present in the ¹H NMR spectra, indicating that the cyclisation of chalcones occurred. In the ¹³C NMR spectra, the formation of the chroman-4-one ring was confirmed by the presence of two signals in the aliphatic area corresponding to the sp³ carbons from the 2nd (75.98 - 76.10 ppm) and 3rd (42.66 - 42.87 ppm) positions of the chroman-4-one. A characteristic carbonylic signal at 191.60 - 191.77 ppm indicates the presence of the chroman-4-one C=O group.

In the IR spectra of the thiazole flavanones **4a-d**, the wave number for aliphatic C–H stretching is exactly 2918.73 cm⁻¹ for all flavanones, the wavenumber for aromatic C–H stretching is in the range 3100.97 - 3100.01 cm⁻¹. The carbonyl group of chroman-4-one has the stretching wave number between 1686.44 - 1686.37 cm⁻¹.

Synthesis and characterization of new thiazole flavones

Thiazole flavones **5a-d** were obtained by oxidative cyclization of *ortho* hydroxychalcones, using iodine in dimethylsulfoxide (Table III). Chimenti and collaborators performed the oxidative cyclization at 130°C [10]. In our case, it was found that the oxidative cyclisation with iodine in dimethylsulfoxide occurred at 160°C with higher reaction rate. Therefore, this temperature was used for the synthesis of all thiazole derived flavones **5a-d**. The obtained products were purified by column chromatography and characterized by ¹H NMR, ¹³C NMR, IR and MS spectral methods.

In the mass spectra of flavones **5a-d**, the presence of the molecular peaks are revealing the formation of the desired products. In the ¹H NMR spectra, the vinylic signals are absent, thus confirming that the cyclization of chalcones occurred. A characteristic singlet (s) at 7.31 - 7.40 ppm, corresponding to the proton from the 3rd position, indicates the formation of the chromen-4-one moiety.

In the ¹³C NMR spectra, the formation of the chromen-4-one ring system was confirmed by the presence of two signals corresponding to the carbon atoms from the 2nd (156.19 - 156.21 ppm) and 3rd (108.40 - 108.75 ppm) position of the chromen-4-one moiety. In the IR spectra of the thiazole derived flavones **5a-d**, the wave number for aliphatic C–H stretching is in the range 2923.56 - 2920.66 cm⁻¹, the wavenumber for aromatic C–H stretching is in the range 3142.44 - 3063.37 cm⁻¹. The carbonyl group of chromen-4-one has the stretching wavenumber between 1607.38 and 1606.41 cm⁻¹.

Table III

Synthesis, reaction time and yields of thiazole flavones **5a-d**

Compound	Compound	R ₁	Reaction time (hours)	Yield (%)
3e	5a	H	3	45
3f	5b	CH ₃	3.5	55
3g	5c	Cl	4	39
3h	5d	OCH ₃	4	32

(*E*)-1-(4-Hydroxyphenyl)-3-(2-phenylthiazol-4-yl)prop-2-en-1-one (**3a**) [3]: Pale-yellow powder; purified by recrystallization from dimethyl formamide; yield: 69%; mp: 211 - 214.7°C; R_f = 0.42 (eluent: petroleum ether:ethyl acetate = 9:1 v/v). IR: $\bar{\nu}$ (cm⁻¹): 3092.3 (C-H arom), 1595.81 (C=O); ¹H NMR (600 MHz, DMSO) δ 10.47 (br s, OH), 8.25 (s, 1H, CH-5 thiazole), 8.10 - 8.04 (m, 2H, CH-2', CH-6' Phe), 8.02 (d, J = 8.7 Hz, 2H, CH-2, CH-6), 7.98 (d, J = 15.2 Hz, 1H, CH-3 vinyl), 7.71 (d, J = 15.1 Hz, 1H, CH-2 vinyl), 7.58 - 7.52 (m, 3H, CH-3', CH-4', CH-5' Phe), 6.93 (d, J = 8.7 Hz, 2H, CH-3, CH-5); ¹³C NMR (151 MHz, DMSO) δ 187.26 (C, C=O), 167.76 (C, C-2 thiazole), 162.32 (C, C-4-OH), 152.71 (C, C-4 thiazole), 134.97 (C, C-1' Phe), 132.59 (CH, C-3 vinyl), 131.07 (CH, C-4' Phe), 130.81 (CH, C-2, C-6), 129.32 (C, C-1), 128.99 (C, C-3', C-5' Phe), 126.56 (CH, C-2', C-6' Phe), 124.25 (CH, C-5 thiazole), 123.59 (CH, C-2 vinyl), 115.55 (CH, C-3, C-5); MS: m/z 308.8 [M+H⁺] (calculated for C₁₈H₁₄NO₂S⁺: 308.07).

(*E*)-1-(4-Hydroxyphenyl)-3-(2-(*p*-tolyl)thiazol-4-yl)prop-2-en-1-one (**3b**) [3]: White powder; purified by recrystallization from ethanol and water; yield: 61%; mp: 192.2 - 194.5°C; R_f = 0.43 (eluent: petroleum ether:ethyl acetate = 7:3 v/v). IR: $\bar{\nu}$ (cm⁻¹): 3095.19 (C-H arom), 1577.49 (C=O); ¹H NMR (600 MHz, DMSO) δ 10.51 (br s, OH), 8.19 (s, 1H, CH-5 thiazole), 8.01 (d, J = 8.7 Hz, 2H, CH-2, CH-6), 7.95 (d, J = 15.0 Hz, 1H, CH-3 vinyl, overlapped with 7.95 (d, J = 8.2 Hz, 2H, CH-2', CH-6'), 7.69 (d, J = 15.1 Hz, 1H, CH-2 vinyl), 7.35 (d, J = 8.0 Hz, 2H, CH-3', CH-5'), 6.92 (d, J = 8.7 Hz, 2H, CH-3, CH-5), 2.38 (s, 3H, CH₃); ¹³C NMR (151 MHz, DMSO) δ 187.41 (C, C=O), 168.00 (C, C-2 thiazole), 162.37 (C, C-4-OH), 152.65 (C, C-4 thiazole), 140.86 (C, C-4'), 135.12 (C, C-1'), 131.15 (CH, C-2, C-6), 130.06 (CH, C-3 vinyl), 129.93 (CH, C-3', C-5'), 129.08 (C, C-1), 126.57 (CH, C-2', C-6'), 123.96 (CH, C-5 thiazole), 123.53 (CH, C-2 vinyl), 115.64 (CH, C-3, C-5), 21.08 (CH₃); MS: m/z 322.6 [M+H⁺] (calculated for C₁₉H₁₆NO₂S⁺: 322.09).

(*E*)-3-(2-(4-Chlorophenyl)thiazol-4-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one (**3c**) [3]: Pale-yellow powder; purified by recrystallization from dimethyl formamide;

yield: 35%; mp: 201.7 - 204.9°C; R_f = 0.55 (eluent: dichloromethane:acetone = 9:1 v/v). IR: $\bar{\nu}$ (cm⁻¹): 3093.26 (C-H arom), 1589.06 (C=O); ¹H NMR (600 MHz, DMSO) δ 10.48 (s, 1H, OH), 8.27 (s, 1H, CH-5 thiazole), 8.09 (d, J = 8.5 Hz, 2H, CH-2', CH-6'), 8.02 (d, J = 8.7 Hz, 2H, CH-2, CH-6), 7.97 (d, J = 15.2 Hz, 1H, CH-3 vinyl), 7.71 (d, J = 15.2 Hz, 1H, CH-2 vinyl), 7.61 (d, J = 8.5 Hz, 2H, CH-3', CH-5'), 6.93 (d, J = 8.7 Hz, 2H, CH-3, CH-5); ¹³C NMR (151 MHz, DMSO) δ 187.22 (C, C=O), 166.42 (C, C-2 thiazole), 162.33 (C, C-4-OH), 152.79 (C, C-4 thiazole), 135.35 (C, C-4'), 134.82 (C, C-1'), 131.43 (CH, C-3 vinyl), 131.07 (CH, C-2, C-6), 129.37 (CH, C-3', C-5'), 128.97 (C, C-1), 128.26 (CH, C-2', C-6'), 124.61 (CH, C-5 thiazole), 123.73 (CH, C-2 vinyl), 115.55 (CH, C-3, C-5); MS: m/z 342.4 [M+H⁺] (calculated for C₁₈H₁₃ClNO₂S⁺: 342.04).

(*E*)-1-(4-Hydroxyphenyl)-3-(2-(4-methoxyphenyl)thiazol-4-yl)prop-2-en-1-one (**3d**): Pale-yellow powder; purified by recrystallization from dimethyl formamide; yield: 66%; mp: 117.4 - 121.3°C; R_f = 0.45 (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm⁻¹): 3092.3 (CH arom), 1588.09 (C=O); ¹H NMR (600 MHz, DMSO) δ 10.41 (s, 1H, OH), 8.12 (s, 1H, CH-5 thiazole), 8.03 - 7.96 (m, 4H, CH-2', CH-6', CH-2, CH-6), 7.93 (d, J = 15.1 Hz, 1H, CH-3 vinyl), 7.67 (d, J = 15.1 Hz, 1H, CH-2 vinyl), 7.08 (d, J = 8.5 Hz, 2H, CH-3', CH-5'), 6.91 (d, J = 6.9 Hz, 2H, CH-3, CH-5), 3.84 (s, 3H, OCH₃); ¹³C NMR (151 MHz, DMSO) δ 187.26 (C, C=O), 167.61 (C, C-2 thiazole), 162.25 (C, C-4 OH), 161.25 (C, C-4'), 152.50 (C, C-4 thiazole), 135.01 (C, C-1'), 130.95 (CH, C-2, C-6), 130.91 (CH, C-3 vinyl), 129.01 (C, C-1), 128.14 (CH, C-2', C-6'), 125.40 (CH, C-5 thiazole), 123.32 (CH, C-2 vinyl), 115.48 (CH, C-3, C-5), 114.55 (CH, C-3', C-5'), 55.40 (CH₃, OCH₃); MS: m/z 338.4 [M+H⁺] (calculated for C₁₉H₁₆NO₃S⁺: 337.08).

(*E*)-1-(2-Hydroxyphenyl)-3-(2-phenylthiazol-4-yl)prop-2-en-1-one (**3e**) [3]: Yellow powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 9/1 v/v); yield: 52%; mp: 139.3 - 141.4°C; R_f = 0.48 (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm⁻¹): 3097.12 (CH arom), 1576.52 (C=O); ¹H NMR (600 MHz, CDCl₃) δ 12.87 (s, 1H, OH),

8.13 (d, $J = 14.9$ Hz, 1H, CH-3 vinyl), 8.07 - 8.03 (m, 3H, CH-2', CH-6', CH-6), 7.84 (dd, $J = 14.9$, 1.7 Hz, 1H, CH-2 vinyl), 7.57 (s, 1H, CH-5 thiazole), 7.54 - 7.48 (m, 4H, CH-4, CH-3', CH-4', CH-5'), 7.04 (dd, $J = 8.3$, 0.8 Hz, 1H, CH-3), 7.00 - 6.96 (m, 1H, CH-5); ^{13}C NMR (151 MHz, CDCl_3) δ 194.39 (C, C=O), 169.24 (C, C-2 thiazole), 163.74 (C, C-2), 153.12 (C, C-4 thiazole), 136.65 (CH, C-4), 136.60 (C, C-1'), 133.21 (CH, C-3 vinyl), 130.89 (CH, C-4'), 130.28 (CH, C-6), 129.22 (CH, C-3', C-5'), 127.07 (CH, C-2', C-6'), 123.77 (CH, C-5 thiazole), 122.88 (C, C-1), 120.28 (CH, C-2 vinyl), 119.10 (CH, C-5), 118.65 (CH, C-3); MS: m/z 308.2 $[\text{M}+\text{H}^+]$ (calculated for $\text{C}_{18}\text{H}_{14}\text{NO}_2\text{S}^+$: 308.07).

(*E*)-1-(2-Hydroxyphenyl)-3-(2-(*p*-tolyl)thiazol-4-yl)-prop-2-en-1-one (**3f**) [3]: Yellow powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 9/1 v/v); yield: 52%; mp: 101.7 - 103.9°C; $R_f = 0.52$ (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3100.01 (CH arom), 2930.31 (C-H aliphatic), 1577.49 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 12.88 (br s, 1H, OH), 8.11 (d, $J = 14.9$ Hz, 1H, CH-3 vinyl), 8.05 (d, $J = 8.0$ Hz, 1H, CH-6), 7.93 (d, $J = 8.1$ Hz, 2H, CH-2', CH-6'), 7.82 (dd, $J = 14.9$, 1.6 Hz, 1H, CH-2 vinyl), 7.53 (s, 1H, CH-5 thiazole) overlapped with 7.53 - 7.50 (m, 1H, CH-4), 7.29 (d, $J = 7.9$ Hz, 2H, CH-3', CH-5'), 7.03 (dd, $J = 8.3$, 0.7 Hz, 1H, CH-3), 7.00 - 6.95 (m, 1H, CH-5), 2.43 (s, 3H, CH_3); ^{13}C NMR (151 MHz, CDCl_3) δ 194.42 (C, C=O), 169.40 (C, C-2 thiazole), 163.73 (C, C-2), 153.00 (C, C-4 thiazole), 141.28 (C, C-4'), 136.77 (CH, C-4), 136.60 (C, C-1'), 130.58 (CH, C-3 vinyl), 130.27 (CH, C-6), 129.88 (CH, C-3', C-5'), 126.98 (CH, C-2', C-6'), 123.49 (CH, C-5 thiazole), 122.71 (C, C-1), 120.29 (CH, C-2 vinyl), 119.04 (CH, C-5), 118.63 (CH, C-3), 21.65 (CH_3); MS: m/z 322.4 $[\text{M}+\text{H}^+]$ (calculated for $\text{C}_{19}\text{H}_{16}\text{NO}_2\text{S}^+$: 322.09).

(*E*)-3-(2-(4-Chlorophenyl)thiazol-4-yl)-1-(3-hydroxyphenyl)prop-2-en-1-one (**3g**) [3]: Yellow powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 9/1 v/v); yield: 37%; mp: 157.8 - 159.9°C; $R_f = 0.45$ (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3101.94 (CH arom), 1579.41 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 12.84 (s, 1H, OH), 8.10 (d, $J = 14.9$ Hz, 1H, CH-3 vinyl), 8.03 (d, $J = 8.4$ Hz, 1H, CH-6), 8.00 - 7.96 (m, 2H, CH-2', CH-6'), 7.82 (dd, $J = 14.9$, 1.6 Hz, 1H, CH-2 vinyl), 7.57 (s, 1H, CH-5 thiazole), 7.52 (ddd, $J = 8.5$, 7.3, 1.6 Hz, 1H, CH-4), 7.48 - 7.45 (m, 2H, CH-3', CH-5'), 7.04 (dd, $J = 8.4$, 0.9 Hz, 1H, CH-3), 7.00 - 6.95 (m, 1H, CH-5); ^{13}C NMR (151 MHz, CDCl_3) δ 194.30 (C, C=O), 167.85 (C, C-2 thiazole), 163.75 (C, C-2), 153.25 (C, C-4 thiazole), 136.91 (C, C-4'), 136.70 (C, C-1'), 136.44 (CH, C-4), 131.69 (CH, C-3 vinyl), 130.24 (CH, C-6), 129.46 (CH, C-3', C-5'), 128.25 (CH, C-2', C-6'), 123.81 (CH, C-5 thiazole), 123.06 (C, C-1), 120.24 (CH, C-2 vinyl), 119.07 (CH,

C-5), 118.69 (CH, C-3); MS: m/z 342.07 $[\text{M}+\text{H}^+]$ (calculated for $\text{C}_{18}\text{H}_{13}\text{ClNO}_2\text{S}^+$: 342.04).

(*E*)-1-(3-Hydroxyphenyl)-3-(2-phenylthiazol-4-yl)-prop-2-en-1-one (**3h**): Yellow powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 9/1 v/v); yield: 36%; mp: 123.4 - 126.6°C; $R_f = 0.37$ (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3091.33 (CH arom), 2931.27 (C-H aliphatic), 1575.56 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 12.83 (s, 1H, OH), 8.14 (d, $J = 14.9$ Hz, 1H, CH-3 vinyl), 8.05 (d, $J = 8.0$ Hz, 1H, CH-6), 8.00 (d, $J = 8.4$ Hz, 2H, CH-2', CH-6'), 7.82 (d, $J = 14.9$ Hz, 1H, CH-2 vinyl), 7.58 (s, 1H, CH-5 thiazole), 7.52 (tt, $J = 10.9$, 5.4 Hz, 1H, CH-4), 7.46 (d, $J = 8.5$ Hz, 2H, CH-3', CH-5'), 7.04 (d, $J = 9.1$ Hz, 1H, CH-3), 6.98 (t, $J = 7.6$ Hz, 1H, CH-5), 3.90 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, CDCl_3) δ 194.28 (C, C=O), 167.99 (C, C-2 thiazole), 163.76 (C, C-4'), 163.44 (C, C-2), 153.13 (C, C-4 thiazole), 136.72 (CH, C-4), 136.25 (C, C-1'), 131.53 (CH, C-3 vinyl), 130.26 (CH, C-6), 129.50 (CH, C-2', C-6'), 128.32 (CH, C-3', C-5'), 123.77 (CH, C-5 thiazole), 123.26 (C, C-1), 120.25 (CH, C-2 vinyl), 119.09 (CH, C-5), 118.69 (CH, C-3), 55.79 (CH_3 , OCH_3); MS: m/z 338.2 $[\text{M}+\text{H}^+]$ (calculated for $\text{C}_{19}\text{H}_{16}\text{NO}_3\text{S}^+$: 338.09).

2-(2-Phenylthiazol-4-yl)chroman-4-one (**4a**): White powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 9/1 v/v); yield: 45%; mp: 108.2 - 111.8°C; $R_f = 0.35$ (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3100.97 (CH arom), 2918.73 (CH aliphatic), 1686.37 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 8.00 - 7.89 (m, 3H, CH-2', CH-6', CH-5 chroman-4-one), 7.52 (t, $J = 8.1$ Hz, 1H, CH-7 chroman-4-one), 7.46-7.43 (m, 3H, CH-3', CH-4', CH-5'), 7.40 (s, 1H, CH-5 thiazole), 7.09 - 7.05 (m, 2H, CH-6, CH-8 chroman-4-one), 5.73 (dd, $J = 11.8$, 3.3 Hz, 1H, CH-2 chroman-4-one), 3.32 (dd, $J = 16.9$, 11.8 Hz, 1H, CH-3 chroman-4-one), 3.20 (dd, $J = 17.0$, 3.4 Hz, 1H, CH-3 chroman-4-one); ^{13}C NMR (151 MHz, CDCl_3) δ 191.75 (C, C=O), 169.16 (C, C-2 thiazole), 161.11 (C, C-8a chroman-4-one), 154.73 (C, C-4 thiazole), 136.30 (CH, C-5 thiazole), 133.42 (C, C-1'), 130.48 (CH, C-7 chroman-4-one), 129.12 (CH, C-3', C-5'), 127.18 (C, C-4'), 126.78 (CH, C-2', C-6'), 121.87 (CH, C-5 chroman-4-one), 121.34 (CH, C-6 chroman-4-one), 118.25 (C, C-4a chroman-4-one), 116.30 (CH, C-8 chroman-4-one), 76.10 (CH, C-2 chroman-4-one), 42.87 (CH_2 , C-3 chroman-4-one); MS: m/z 308.3 $[\text{M}+\text{H}^+]$ (calculated for $\text{C}_{18}\text{H}_{14}\text{NO}_2\text{S}^+$: 308.07).

2-(2-(*p*-Tolyl)thiazol-4-yl)chroman-4-one (**4b**): White powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 6/1 v/v); yield: 55%; mp: 124.6 - 128.1°C; $R_f = 0.43$ (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3100.01 (CH arom), 2918.73 (CH aliphatic), 1686.44 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 7.94 (dd, $J = 7.8$, 1.6 Hz,

1H, CH-5 chroman-4-one), 7.85 (d, $J = 8.1$ Hz, 2H, CH-2', CH-6'), 7.57 - 7.47 (m, 1H, CH-7 chroman-4-one), 7.36 (s, 1H, CH-5 thiazole), 7.24 (d, $J = 8.0$ Hz, 2H, CH-3', CH-5'), 7.11 - 7.03 (m, 2H, CH-6, CH-8 chroman-4-one), 5.73 (dd, $J = 11.8, 3.4$ Hz, 1H, CH-2 chroman-4-one), 3.31 (dd, $J = 17.0, 11.8$ Hz, 1H, CH-3 chroman-4-one), 3.19 (dd, $J = 17.0, 3.5$ Hz, 1H, CH-3 chroman-4-one); ^{13}C NMR (151 MHz, CDCl_3) δ 191.70 (C, C=O), 169.39 (C, C-2 thiazole), 161.09 (C, C-8a chroman-4-one), 154.39 (C, C-4 thiazole), 140.88 (C, C-4'), 136.26 (CH, C-5 thiazole), 130.62 (CH, C-7 chroman-4-one), 129.78 (CH, C-3', C-5'), 127.15 (C, C-1'), 126.72 (CH, C-2', C-6'), 121.84 (CH, C-5 chroman-4-one), 121.32 (CH, C-6, chroman-4-one), 118.23 (C, C-4a, chroman-4-one), 115.82 (CH, C-8 chroman-4-one), 76.02 (CH, C-2 chroman-4-one), 42.66 (CH_2 , C-3 chroman-4-one), 21.57 (C, CH_3); MS: m/z 322.5 [$\text{M}+\text{H}^+$] (calculated for $\text{C}_{19}\text{H}_{15}\text{NO}_2\text{S}^+$: 322.09).

2-(2-(4-Chlorophenyl)thiazol-4-yl)chroman-4-one (4c): Pale-yellow powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 9/1 v/v); yield: 40%; mp: 157.3 - 161°C; $R_f = 0.28$ (eluent: petroleum ether:ethyl acetate = 9/1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3100.01 (CH arom), 2918.73 (CH aliphatic), 1686.44 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 7.94 (dd, $J = 7.8, 1.7$ Hz, 1H, CH-5 chroman-4-one), 7.88 (d, $J = 8.5$ Hz, 2H, CH-2', CH-6'), 7.52 (ddd, $J = 8.7, 7.3, 1.7$ Hz, 1H, CH-7 chroman-4-one), 7.41 (d, $J = 8.5$ Hz, 2H, CH-3', CH-5') overlapped with 7.41 (s, 1H, CH-5 thiazole), 7.09 - 7.05 (m, 2H, CH-6, CH-8 chroman-4-one), 5.72 (dd, $J = 11.7, 3.5$ Hz, 1H, CH-2 chroman-4-one), 3.30 (dd, $J = 16.9, 11.7$ Hz, 1H, CH-3 chroman-4-one), 3.18 (dd, $J = 16.9, 3.5$ Hz, 1H, CH-3 chroman-4-one); ^{13}C NMR (151 MHz, CDCl_3) δ 191.60 (C, C=O), 167.77 (C, C-2 thiazole), 161.00 (C, C-8a chroman-4-one), 154.88 (C, C-4 thiazole), 136.44 (C, C-4'), 136.33 (CH, C-5 thiazole), 131.87 (CH, C-7 chroman-4-one), 129.34 (CH, C-3', C-5'), 127.95 (CH, C-2', C-6'), 127.18 (C, C-1'), 121.92 (CH, C-5 chroman-4-one), 121.31 (CH, C-6 chroman-4-one), 118.21 (C, C-4a chroman-4-one), 116.60 (CH, C-8 chroman-4-one), 75.98 (CH, C-2 chroman-4-one), 42.81 (CH_2 , C-3 chroman-4-one); MS: m/z 342.2 [$\text{M}+\text{H}^+$] (calculated for $\text{C}_{18}\text{H}_{13}\text{ClN}_2\text{O}_3\text{S}^+$: 342.04).

2-(2-(4-Methoxyphenyl)thiazol-4-yl)chroman-4-one (4d): Pale-yellow powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 6/1 v/v); yield: 48%; mp: 141.2 - 144.6°C; $R_f = 0.43$ (eluent: petroleum ether:ethyl acetate = 4/1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3100.01 (CH arom), 2918.73 (CH aliphatic), 1686.44 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 7.93 (dd, $J = 7.9, 1.6$ Hz, 1H, CH-5 chroman-4-one), 7.89 (d, $J = 8.8$ Hz, 2H, CH-2', CH-6'), 7.53 - 7.48 (m, 1H, CH-7 chroman-4-one), 7.31 (s, 1H, CH-5 thiazole), 7.09 - 7.03 (m, 2H, CH-6, CH-8 chroman-

4-one), 6.94 (d, $J = 8.8$ Hz, 2H, CH-3', CH-5'), 5.71 (dd, $J = 11.8, 3.4$ Hz, 1H, CH-2 chroman-4-one), 3.85 (s, 3H, OCH_3), 3.30 (dd, $J = 17.0, 11.8$ Hz, 1H, CH-3 chroman-4-one), 3.18 (dd, $J = 17.0, 3.5$ Hz, 1H, CH-3 chroman-4-one); ^{13}C NMR (151 MHz, CDCl_3) δ 191.72 (C, C=O), 169.06 (C, C-2 thiazole), 161.53 (C, C-4'), 161.09 (C, C-8a chroman-4-one), 154.26 (C, C-4 thiazole), 136.24 (CH, C-5 thiazole), 128.63 (CH, C-7 chroman-4-one), 128.31 (CH, C-2', C-6'), 127.13 (C, C-1'), 121.81 (CH, C-5 chroman-4-one), 121.31 (CH, C-6 chroman-4-one), 118.23 (C, C-4a chroman-4-one), 115.37 (CH, C-8 chroman-4-one), 114.42 (CH, C-3', C-5'), 76.01 (CH, C-2 chroman-4-one), 55.53 (C, OCH_3), 42.83 (CH_2 , C-3 chroman-4-one); MS: m/z 338.6 [$\text{M}+\text{H}^+$] (calculated for $\text{C}_{19}\text{H}_{16}\text{NO}_3\text{S}^+$: 338.09).

2-(2-Phenylthiazol-4-yl)-4H-chromen-4-one (5a): White powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 7/1 v/v, after petroleum ether:ethyl acetate = 6:1 v/v or dichloromethane, after dichloromethane:acetone = 50:1 v/v); yield: 45%; mp: 188.7 - 191.2°C; $R_f = 0.24$ (eluent: petroleum ether:ethyl acetate = 6:1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3063.37 (CH arom), 2921.63 (C-H aliphatic), 1606.41 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 8.24 (dd, $J = 7.9, 1.2$ Hz, 1H, CH-5 chromen-4-one), 8.04 (s, 1H, CH-5 thiazole), 8.01 (dd, $J = 6.5, 2.9$ Hz, 2H, CH-2', CH-6'), 7.72 - 7.69 (m, 1H, CH-7), 7.55 (d, $J = 8.3$ Hz, 1H, CH-8 chromen-4-one), 7.50 - 7.47 (m, 3H, CH-3', CH-4', CH-5'), 7.42 (t, $J = 7.5$ Hz, 1H, CH-6 chromen-4-one), 7.39 (s, 1H, CH-3 chromen-4-one); ^{13}C NMR (151 MHz, CDCl_3) δ 178.82 (C, C=O), 169.42 (C, C-2 thiazole), 158.71 (C, C-8a chromen-4-one), 156.21 (C, C-2 chromen-4-one), 148.74 (C, C-4 thiazole), 134.09 (C, C-1'), 132.83 (CH, C-5 thiazole), 131.03 (CH, C-7 chromen-4-one), 129.26 (CH, C-3', C-5'), 126.91 (CH, C-2', C-6'), 126.01 (CH, C-4'), 125.48 (CH, C-5 chromen-4-one), 124.25 (CH, C-6 chromen-4-one), 120.41 (C, C-4a chromen-4-one), 118.11 (CH, C-8 chromen-4-one), 108.64 (CH, C-3 chromen-4-one); MS: m/z 306.4 [$\text{M}+\text{H}^+$] (calculated for $\text{C}_{18}\text{H}_{12}\text{NO}_2\text{S}^+$: 306.06).

2-(2-(p-Tolyl)thiazol-4-yl)-4H-chromen-4-one (5b): White powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 4/1 v/v); yield: 55%; mp: 157.8 - 161.1°C; $R_f = 0.34$ (eluent: petroleum ether:ethyl acetate = 4:1 v/v). IR: $\bar{\nu}$ (cm^{-1}): 3113.51 (CH arom), 2920.66 (C-H aliphatic), 1606.41 (C=O); ^1H NMR (600 MHz, CDCl_3) δ 8.25 - 8.21 (m, 1H, CH-5 chromen-4-one), 8.00 (s, 1H, CH-5 thiazole), 7.89 - 7.86 (m, 2H, CH-2', CH-6'), 7.72 - 7.68 (m, 1H, CH-7 chromen-4-one), 7.56 - 7.53 (m, 1H, CH-8 chromen-4-one), 7.44 - 7.38 (m, 2H, CH-6, CH-3 chromen-4-one), 7.28 - 7.24 (m, 2H, CH-3', CH-5'), 2.40 (s, 3H, CH_3); ^{13}C NMR (151 MHz, CDCl_3) δ 178.84 (C, C=O), 169.59 (C, C-2 thiazole), 158.92 (C, C-8a chromen-4-one), 156.20 (C, C-2 chromen-

4-one), 148.45 (C, C-4'), 141.46 (C, C-4 thiazole), 134.17 (CH, C-5 thiazole), 130.16 (C, C-1'), 129.90 (CH, C-3', C-5'), 126.81 (CH, C-2', C-6'), 125.97 (CH, C-7 chromen-4-one), 125.50 (CH, C-5 chromen-4-one), 124.04 (CH, C-6 chromen-4-one), 120.25 (C, C-4a chromen-4-one), 118.12 (CH, C-8 chromen-4-one), 108.40 (CH, C-3 chromen-4-one), 21.63 (CH₃); MS: m/z 320.5 [M+H⁺] (calculated for C₁₉H₁₄NO₂S⁺: 320.07).

2-(2-(4-Chlorophenyl)thiazol-4-yl)-4H-chromen-4-one (5c): White powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 6/1 v/v or dichloromethane, after dichloromethane:acetone = 50/1 v/v); yield: 39%; mp: 197.6 - 201.2°C; R_f = 0.27 (eluent: petroleum ether:ethyl acetate = 6/1 v/v). IR: $\bar{\nu}$ (cm⁻¹) 2922.59 (CH arom), 1606.41 (C=O); ¹H NMR (600 MHz, CDCl₃) δ 8.24 (dd, J = 7.9, 1.2 Hz, 1H, CH-5 chromen-4-one), 8.06 (s, 1H, CH-5 thiazole), 7.93 (d, J = 8.5 Hz, 2H, CH-2', CH-6'), 7.72 (t, J = 7.7 Hz, 1H, CH-7 chromen-4-one), 7.56 (d, J = 8.4 Hz, 1H, CH-8 chromen-4-one), 7.44 (d, J = 8.4 Hz, 2H, CH-3', CH-5'), 7.43 - 7.40 (m, 2H, CH-3, CH-6 chromen-4-one); ¹³C NMR (151 MHz, CDCl₃) δ 178.81 (C, C=O), 168.10 (C, C-2 thiazole), 158.73 (C, C-8a chromen-4-one), 156.20 (C, C-2 chromen-4-one), 148.77 (C, C-4 thiazole), 137.12 (C, C-4'), 134.32 (C, C-1'), 131.24 (CH, C-5 thiazole), 129.52 (CH, C-3', C-5'), 128.08 (CH, C-2', C-6'), 126.01 (CH, C-7 chromen-4-one), 125.65 (CH, C-5 chromen-4-one), 123.97 (CH, C-6 chromen-4-one), 120.85 (C, C-4a chromen-4-one), 118.13 (CH, C-8 chromen-4-one), 108.47 (CH, C-3 chromen-4-one); MS: m/z 340.6 [M+H⁺] (calculated for C₁₈H₁₁ClNO₂S⁺: 340.02).

2-(2-(4-Methoxyphenyl)thiazol-4-yl)-4H-chromen-4-one (5d): White powder; purified by column chromatography (eluent: petroleum ether:ethyl acetate = 4/1 v/v, after petroleum ether:ethyl acetate = 3/1 v/v); yield: 32%; mp: 183.6 - 186.4°C; R_f = 0.40 (eluent: petroleum ether:ethyl acetate = 4/1 v/v). IR: $\bar{\nu}$ (cm⁻¹): 3142.44 (CH arom), 2923.56 (CH aliphatic), 1607.38 (C=O); ¹H NMR (600 MHz, CDCl₃) δ 8.24 (dd,

J = 7.9, 1.5 Hz, 1H, CH-5 chromen-4-one), 7.95 (s, 1H, CH-5 thiazole) overlapped with 7.94 (d, J = 8.9 Hz, 2H, CH-2', CH-6'), 7.69 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H, CH-7 chromen-4-one), 7.54 (d, J = 8.2 Hz, 1H, CH-8 chromen-4-one), 7.45 - 7.37 (m, 1H, CH-6 chromen-4-one), 7.31 (s, 1H, CH-3 chromen-4-one), 6.98 (d, J = 8.8 Hz, 2H, CH-3', CH-5'), 3.88 (s, 3H, OCH₃); ¹³C NMR (151 MHz, CDCl₃) δ 178.81 (C, C=O), 169.17 (C, C-2 thiazole), 161.89 (C, C-4'), 158.51 (C, C-8a chromen-4-one), 156.19 (C, C-2 chromen-4-one), 148.58 (C, C-4 thiazole), 133.87 (CH, C-5 thiazole), 128.44 (CH, C-2', C-6'), 125.98 (CH, C-7 chromen-4-one), 125.82 (C, C-1'), 125.31 (CH, C-5 chromen-4-one), 124.48 (CH, C-6 chromen-4-one), 119.31 (C, C-4a chromen-4-one), 118.08 (CH, C-8 chromen-4-one), 114.56 (CH, C-3', C-5'), 108.75 (CH, C-3 chromen-4-one), 55.61 (C, OCH₃); MS: m/z 336.4 [M+H⁺] (calculated for C₁₉H₁₄NO₃S⁺: 336.07).

Evaluation of the antioxidant activity for the synthesized compounds

Among the methods used for testing the *in vitro* antioxidant activity, the best known is the neutralization of free DPPH radicals. DPPH molecule is a stable free radical that not dimerize due to the effect of free electron delocalization [2].

The antioxidant activities were calculated using the formula:

$$I\% = [(A_{\text{control}} - A_{\text{sample}})/A_{\text{control}}] * 100,$$

where: A_{control} = the absorbance measured for the mixture of DPPH and solvent (methanol/dichloromethane), and A_{sample} = the absorbance measured for the mixture of DPPH and compound and solvent (methanol/dichloromethane).

The determined antioxidant activities for standards, thiazole chalcones, flavanones and flavones are shown in Tables IV and V.

The obtained results were compared with the standards, ascorbic acid and quercetin, and the antioxidant activity was calculated with the formula:

$$\% \text{ Antioxidant activity} = (I_{\text{compound}}/I_{\text{standard}}) * 100.$$

Table IV

Antioxidant activity (I%) for chalcones, flavanones, flavones and standards

Compound	Solvent	Concentration ($\mu\text{mol/mL}$)	I% average
3a	Methanol	0.085	0.0497
3b	Methanol	0.085	0.0500
3c	Methanol	0.085	0.0462
3d	Methanol	0.060	0.0406
3e	Dichloromethane	0.060	0.0223
3f	Dichloromethane	0.060	0.0217
3g	Dichloromethane	0.060	0.0340
3h	Dichloromethane	0.060	0.0228
4a	Dichloromethane	0.060	0.0211
4b	Dichloromethane	0.060	0.0310
4c	Dichloromethane	0.060	0.0260
4d	Dichloromethane	0.060	0.0252
5a	Dichloromethane	0.060	0.0093
5b	Dichloromethane	0.060	0.0400

Compound	Solvent	Concentration ($\mu\text{mol/mL}$)	I% average
5c	Dichloromethane	0.060	0.0340
5d	Dichloromethane	0.060	0.0078
Ascorbic acid	Methanol	0.085	99.35
Ascorbic acid	Dichloromethane	0.060	90.48
Quercetin	Methanol	0.085	90.80
Quercetin	Dichloromethane	0.060	52.06

Table V

% Antioxidant activity of compounds related to ascorbic acid and quercetin

Compound	% Antioxidant activity related to ascorbic acid	% Antioxidant activity related to quercetin
3a	0.0498	0.0546
3b	0.0500	0.0548
3c	0.0465	0.0510
3d	0.0408	0.0446
3e	0.0247	0.0431
3f	0.0239	0.0416
3g	0.0376	0.0653
3h	0.0252	0.0438
4a	0.0233	0.0461
4b	0.0342	0.0595
4c	0.0287	0.0498
4d	0.0218	0.0378
5a	0.0103	0.0178
5b	0.0443	0.0768
5c	0.0038	0.0065
5d	0.0081	0.0140

For the synthesized thiazole hydroxychalcones, the antioxidant capacity varied between 0.0217% and 0.05%. The highest potential in the hydroxychalcone series has the compound **3b** with a *p*-tolyl group on the thiazole ring of the aldehyde and a hydroxyl group in the *para* position of acetophenone. For this compound, the antioxidant activity represents 0.05% of the ascorbic acid activity and 0.0548% of the quercetin activity.

In the thiazole flavanones series, the antioxidant activity ranged from 0.0211% to 0.031%. Flavanone **4b**, derived from *p*-tolyl thiazole, presented the highest antioxidant activity (0.0342% of the ascorbic acid antioxidant activity and 0.0595% of the quercetin activity).

The antioxidant activity of thiazole flavones varied between 0.0078% and 0.04%. The best antioxidant capacity was found for the flavone substituted with a *p*-tolyl group on the thiazole ring (compound **5b**). It has 0.0443% of the ascorbic acid antioxidant activity and 0.0768% of the quercetin activity.

Among the synthesized compounds, the highest activity has the chalcone **3b** containing a *p*-tolyl group on the thiazole ring and a hydroxyl group in the *para* position of the benzene ring coming from acetophenone. From the synthesized compounds, flavones have the weakest antioxidant activity.

Among the analysed series of compounds, thiazole chalcones are presenting the highest activity and thiazole flavones the less. It was found that the presence of the *para* tolyl group on the thiazole

moiety of chalcones determined a slight increase of the DPPH scavenging activity.

Thiazole chalcones, flavanones and flavones have a low antioxidant activity.

Conclusions

We have synthesized a series of hydroxychalcones and their corresponding flavanones and flavones derivatives to assess their antioxidant potential.

Ortho hydroxychalcones were cyclized in acidic or basic catalysis to the corresponding thiazole flavanones. The most effective method for obtaining flavanones is the cyclization with sulfuric acid in ethanol at 100°C. Thiazole flavones were synthesized by oxidative cyclization with iodine in dimethyl sulfoxide.

Spectral analysis ^1H NMR, ^{13}C NMR, IR and MS confirmed the structure of the synthesized compounds. It was determined the antioxidant activity of thiazole chalcones, flavanones and flavones by DPPH method. The synthesized compounds have a low antioxidant activity.

The synthesized compounds are currently evaluated for their anticancer and antimicrobial potential.

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