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Professional paper

DESIGN AND SYNTHESIS OF SOME NOVEL COMPOUNDS DERIVED FROM HYBDRID COUMARIN-THIAZOLE STRUCTURES

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Abstract

Coumarins are molecules that belong to a special family of compounds which, due to the conjugated double bond become interesting molecules for many fields of study. Their structure and physical properties make them a privileged scaffold in medicinal chemistry. Also, they exhibit a wide range of biological activity including free radical scavenging. Recent research has focused attention on the anticancer activity of coumarin and coumarin-derived compounds due to their high level of cytotoxicity. Thiazole rings, on the other hand, also showed remarkable anticancer activity on various cancer cells. Based on this, the idea was to combine those two heterocyclic units in one hybrid unique molecular structure with high anticancer potential. The synthetic strategy was simple, applying the reaction of diazotation of 2-aminothizoles and using the corresponding diazonium salts as good electrophiles to attack the 4-hydoxycoumarin core at position 3. Furthermore, it was revealed by previous investigation that the alkyl substituent at the thiazole ring plays playing key role. Namely, by increasing of the nonpolar tail at that part of the molecule, the biological activity is also increased. Based on this, some 4-substituated-2-aminothiazoles were synthesized by optimization of the Hantzsch reaction, before diazotation and coupling with the coumarin core. All of the newly synthesized compounds were purified by crystallization and the melting point was determined. Finally, the obtained compounds were characterized by spectroscopic means.

Keywords: synthesis, coumarin, thiazole, Hantzsch reaction, anticancer activity.

1. Introduction

Carbazoles and coumarins are major compounds found in roots, root bark, stem bark, twigs, and fruit of *C. harmandiana* and some identified essential oils as α-pinene and copaene [1]. Coumarin (1,2-benzopyrone or 2*H*-1-benzopyran-2-one) and coumarin derivatives are a widespread class of natural phenolic compounds, which contain a benzene ring fused with an α-pyrone ring, and exhibit a wide range of biological activity including free radical scavenging [2]. Indeed, coumarins have been reported to affect the formation and scavenging of reactive oxygen species (ROS) and influence free-radical-mediated oxidative damage, thus the development of new synthetic coumarins is promising [3]. Recent research has focused attention on the anticancer activity of coumarin and coumarin-derived compounds due to their high level of biological activity and low toxicity [4]. Different mechanisms are thought to be responsible for the anticancer activity of coumarins, including the blocking of the cell cycle, the induction of cell apoptosis, the modulation of the estrogen receptor, or the inhibition of DNA-associated enzymes such as telomerase and topoisomerase (TOP). Topoisomerase enzymes play an important role in DNA metabolism, and the search for novel enzyme inhibitors is an important target in the development of new anticancer drugs [4-6].
From the topography of 4-hydroxycoumarin (**1**) the possibility of, both electrophilic and nucleophilic properties is evident. The most significant reactivity is the nucleophilicity of the carbon atom at position 3. This has been noted for more than a hundred years. Thus, reactions

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such as the Mannich reaction and aromatic electrophilic substitution as halogenation, sulfonation, nitration, and acylation are taking place readily at this carbon. It seemed that hard nucleophiles attack preferentially the carbon atom at position 4, while soft ones, attack preferentially the carbon atom at position 3.

To find new coumarin structure-based drugs with anticancer activity, there have been promising developments in the synthesis of compounds that combine the coumarin core and five-membered heterocycles like isoxazoles and thiazoles [7]. Isoxazole and thiazole rings are important pharmacophores. Their anticancer effects were demonstrated *in vivo* and *in vitro* using various cancer cell lines, including breast cancer cells [8]. Thiazole is a good pharmacophore nucleus due to its various pharmaceutical applications. Its derivatives have a wide range of biological activities such as antioxidant, analgesic, antibacterial, anticancer, antiallergic, antihypertensive, anti-inflammatory, antimalarial, antifungal, and antipsychotic [9, 10]. The thiazole scaffold is present in more than 18 FDA-approved drugs. Among them are cefiderocol, which was the first siderophore antibiotic approved by the FDA in 2019 under the brand name Fetroja®. This thiazole derivative, which is based on penicillin, was found to be active against a wide range of multi-drug resistant Gram-negative bacteria, including *Pseudomonas aeruginosa*, and used to treat complicated urinary tract infections in cases when no other treatment is available [11, 12]. Another thiazole-based drug is alpelisib with the brand name Pigray®, which was approved again in 2019 for the treatment of certain types of breast cancer. Worldwide, breast cancer is one of the most common severe diseases and the second leading cause of cancer death mostly in less developed countries [13]. Based on those facts the goal of the present work was to develop the idea of combining those two heterocyclic compounds (the thiazole ring and the coumarin ring) in a one-hybrid molecule *via* hydrazinylidene bridge.

Many studies have reported a beneficial effect of coumarins on cancer types including malignant melanoma, leukemia, renal cell carcinoma, and prostate and breast cancer cell progression [14-16]. Jashari, A., *et al.* [17] 2014 synthetized some compounds based on coumarin core and revealed three novel coumarin derivatives (**2**, **3**, and **4**) with hydrazinylidene-chromandione structures (*Figure 1*). Studies showed that those three compounds, containing thiazole ring exert more potent anti-proliferative and pro-apoptotic effects on various cancer cell lines than the reference compound 4-hydroxycoumarin (**1**). Furthermore, a study was reported by Ballazhi, L., *et al*. [18] in 2015 where those derivatives were evaluated for their inhibitory activity against human lung and bone cancer cell lines derived from breast cancer. Of all the evaluated compounds, three of them (again the same three compounds as shown in *Figure 1*) showed a stronger effect on the viability of both cell lines during the whole study period than **1** as the control substance. The most potent molecules have a thiazole moiety attached to the coumarin ring via hydrazinylidene linker at position 3, with or without additional methyl group(s) attached to the carbon at position(s) 5 and/or 4 on the thiazole ring. Those three compounds have shown that they can effectively inhibit the proliferation of cancer cells, inhibit cell migration induce chromatin condensation, DNA damage, and caspase-dependent apoptosis, and arrest the cell cycle at the G2/M stage. The synergy with Tamoxifen and Doxorubicin (commercial chemotherapeutic agents) showed that they exhibit even higher cytotoxic activity and increased apoptosis. The major conclusion of those investigations is that there is a correlation between the structure and the activity. So, there is the regularity of increasing the activity with the presence of more nonpolar groups at the thiazole ring, which means that the hydrophobicity in that part is increasing). The molecular docking revealed that the hydrophilic part of the molecule (the lactone from the coumarin part) fits into the hydrophilic pocket of the active side and the hydrophobic part of the molecule (the thiazole part) fits into the hydrophobic part of the active side of the specific enzyme (*Figure 2*).

2. Results and Discussion

To synthetize novel similar structures but with bulky alkyl groups as substituent on the thiazole part, the Hantzsch reaction (*Scheme 1*) was optimized and some (non-commercial) 2-aminothiazoles (**7**) with larger alkyl groups were synthetized. Afterwards, novel thiazolylhydrazinylidene-chroman-2,4-diones (**8**) were synthesized (*Scheme 2*), by coupling of diazonium salts (derived from those 2-aminothiazoles (**7**) with larger alkyl groups) and **1**.

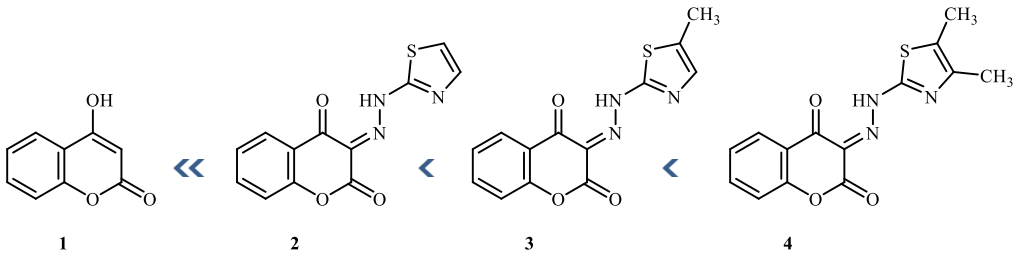


Figure 1. Correlation of the activity and structure

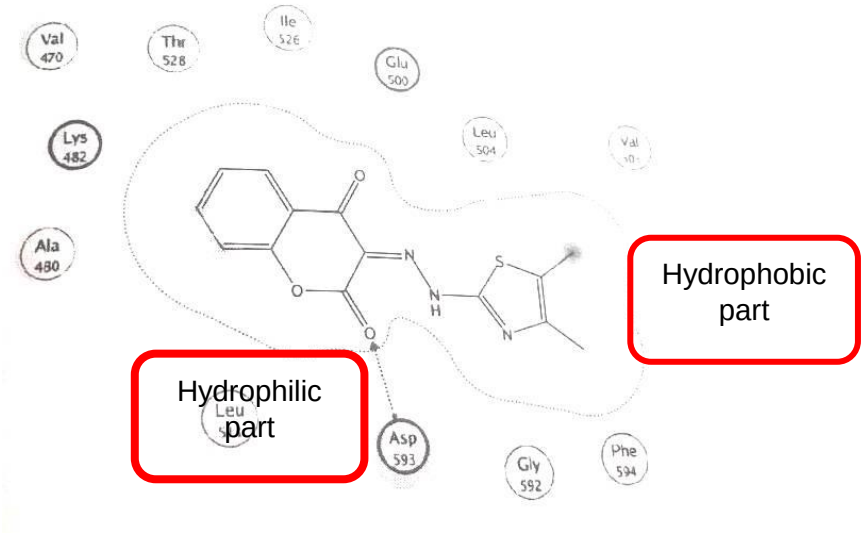
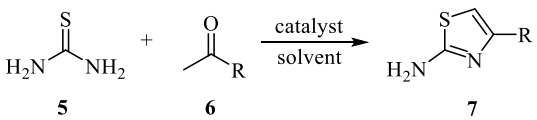
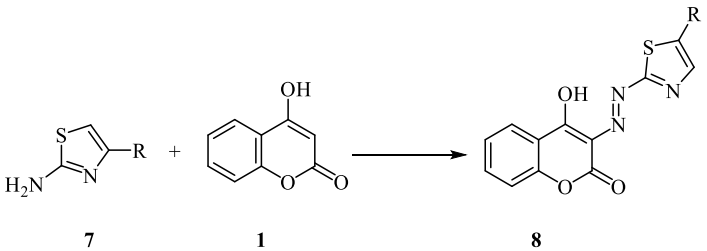


Figure 2. Hydrophilic and Hydrophobic part of the synthetized molecule fitting in to the active side of the enzyme

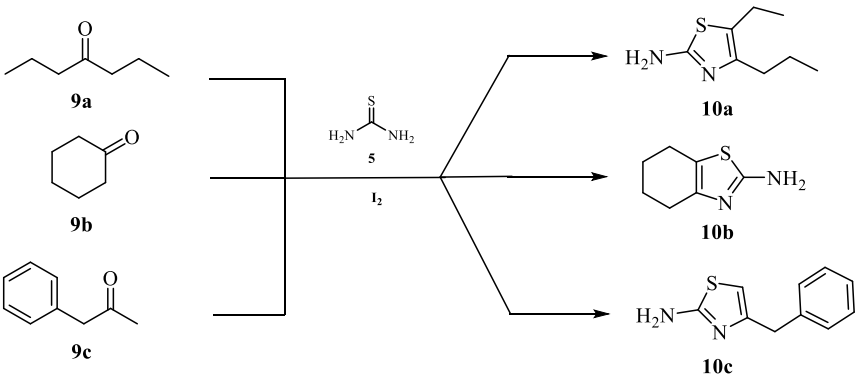


Scheme 1. General scheme of the Hantzsch Reaction



Scheme 2. General scheme of coupling of novels 2-aminothiazoles (**7**) with 4-hydoroxycoumarin (**1**)

Based on this, heptan-4-one (**9a**) cyclohexanone (**9b**) and benzyl methyl ketone (**9c**), were used in the Hantzsch reaction with thiourea (**5**) and elemental iodine (*Scheme 3*).

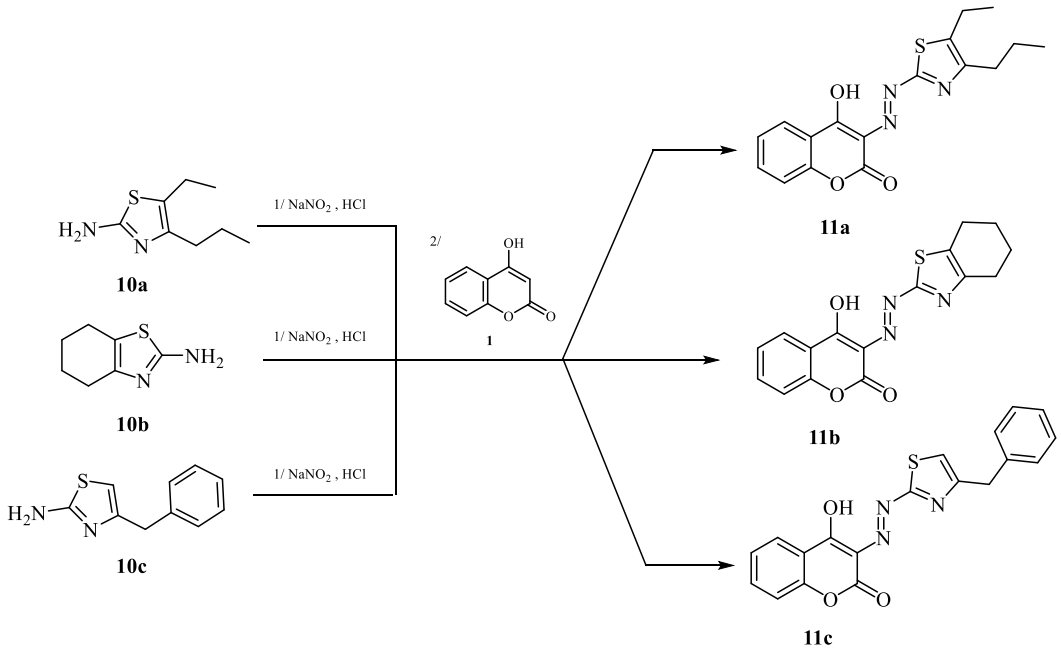


Scheme 3. Synthesis of 2-aminothiazoles (**10a-c**)

The reaction was heated overnight at 100 °C and, after the workup, the corresponding 2-aminothiazoles (**10a-c**) were obtained in good yields. Two 2-aminothiazoles **10b** and **10c** were characterized by their IR spectrums while the 2-amino-4-ethyl-5-propylthiazole (**10a**) was characterized by its ^{1}H-NMR spectrum. On the ^{1}H-NMR spectrum of **10a** it can be clearly noticed that there are three triplets, from which two appear in the upfield of the spectrum, three protons of CH_3 (from the ethyl group) at 1.17 ppm and the other is from the other three protons of CH_3 (form the propyl group) in the region from 0.9-1.09 ppm. The other triplet comes from CH_2 (propyl group) and appears in the downfield at 2.4 ppm. Two protons of NH_2 group which are singlet appear in the region from 4.50-4.75 ppm. The ^{1}H-NMR spectrum also revealed that in the region 2.6 ppm are two protons which are quartet and come from the CH_2 group (ethyl group), and the other CH_2 protons (propyl group) give a multiplet and appear at 1.6 ppm. Thus, the ^{1}H-NMR spectrum completely corresponds to the proposed structure of **10a**. On the other hand, on the IR spectrum of **10b** one band in the region 3430-3250 cm^{-1} can be observed which probably corresponds to stretching vibrations of NH_2 group (asymmetric and symmetric) and a characteristic peak for CH_2 symmetric stretching in the region 2950-2850 cm^{-1}. Characteristic peaks from C=C (deformations of the benzene ring in the plane) can be observed at 1610-1510 cm^{-1}. Afterwards**, 10c** was synthetized and IR spectrum was measured. It can be observed one band on the region 3450-3430 cm^{-1} which probably corresponds to asymmetric stretching vibrations of NH_2 group while symmetric stretching vibrations of this group can be observed at 3250 cm^{-1}. A characteristic peak for CH_2 symmetric stretching vibrations is observed in a region from 3000-2800 cm^{-1} while three peaks in 3150, 3100 and 3050 cm^{-1} probably come from the stretching vibrations of the aromatic -CH groups. Furthermore, for this compound (**10c**) MS spectrum was also measured. Since the measurements were done via MS/EI it should be expected a signal from $M^{+\bullet}$ ion. The molecular weight for this compound is 190, and the same value was also recorded by MS, which proves that the proposed structure fits with the spectroscopic results. That spectral characterization showed that the Hantzsch reactions were successfully developed obtaining the desired 2-aminothiazoles (**10a-c)**.

Afterward, those 2-amionthizoles (**10a-c**) were used in the reaction of diazotation by aqueous solution of sodium nitrite and the obtained corresponding diazonium salts were use immediately (*in situ*) as electrophilic attacking agents on 4-hydroxycoumarin core (*Scheme 4*). As a result, voluminous and very intensively colored precipitates of the novel coupling derivatives (**11a-c**) were obtained. The yields were moderate to good and the purification was successfully applied by recrystallization, using isopropanol as a convenient solvent. The reactions and the purity of the products were checked by TLC using hexane:acetone or benzene:acetonitrile as eluents. Next, IR spectrums of those products were measured. In the IR spectrum of **11a** a characteristic

peak for a keto group was observed at 1780 cm^{-1}, also antisymmetric and symmetric stretching vibrations respectively, of CH_3 groups were observed at region 2985 and 2872 cm^{-1} as well as picks at 2942 and 2828 cm^{-1} probably from the antisymmetric and symmetric stretching vibrations respectively, from the CH_2 groups. In the region from 1600-1500 cm^{-1} were observed the deformations of benzene ring in the plane, while the vibrations out of plane of the benzene ring appears at 780 cm^{-1} and 650 cm^{-1} as two very intensive picks. Afterwards, the IR Spectrum of **11b** was measured and a band for a keto group was observed at practically the same value at 1785 cm^{-1}. Also, stretching vibrations of CH_2 group were observed in a region from 2950-2850 cm^{-1} in the IR spectrum, but in this case only two picks that correspond with the proposed structure because there are no methyl groups now. Finally, in the IR spectrum of 11c can also be observed two weak picks (much weaker than the previous two compounds) in the region of 2950-2850 cm^{-1} from the one methylene group present in the structure, while other picks are practically the same the others. In addition, mass spectra were measured using the ESI in positive mode. Thus, in the MS/ESI+ of **11a** can be observed two main picks at 344 and 366 *m/z*, corresponding to the $[M+H]^+$ and $[M+Na]^+$ species, in the spectrum of **11b** be observed two main picks at 328 and 350 *m/z*, corresponding to the $[M+H]^+$ and $[M+Na]^+$ species, and in the spectrum of **11c** be observed also two main picks at 364 and 386 *m/z*, corresponding to the $[M+H]^+$ and $[M+Na]^+$ species, respectively. The spectral characteristics are practically identical with the previously reported compounds [17], which of course is expected because of the identical *structural skeleton* where the only difference is in the alkyl substituents at the thiazole part of the molecule. Based on those spectral characterizations was concluded that the coupling reactions were successfully developed and the novel hybrid molecules **11a-c** were isolated.



Scheme 4. Synthesis of novel coupled derivatives (**11a-c**)

5. Experimental Section

Materials and Instrumentation

All reagents and chemicals were purchased from commercial sources and used as received. TLC monitoring was performed by using silica gel 60 F_{254} on aluminum sheets (Merck®), and visualization was achieved under UV at λ = 254 nm; I_2 bath or ninhydrin spray). NMR spectra were recorded on Bruker® AM 600 instruments operating at 600 MHz. All chemical shifts (δ

value) are given in ppm with internal standard (TMS added). Melting points were measured on an ELECTROTHERMAL® instrument and were not corrected. Mass spectra were carried out on a LTQ ORBITRAP® XL (Thermo Scientific) instrument which was externally calibrated using the manufacturer's APCI or ESI(+) calibration mix. The samples were introduced into the spectrometer by direct infusion. The Infrared spectra were recorded on Perkin Elmer FT IR system 2000 using ATR module, and in some cases KBr pellet technique.

General procedure for synthesis of 10a-c

2.67 g (35.03 mmol) of thiourea (**5**) and 4.45 g (17.51 mmol) of Iodine were mixed in a small round bottom flask from 50 mL. Then, 17.51 mmol of the ketone **9a-c** was added to this mixture. The mixture was allowed to mix and reflux for 24 h at 100 °C. After 24 hours, the system was taken out of the oil bath and left to cool to room temperature, meanwhile 350 mL of distilled water was measured and heated to boiling, the boiling water was used in portions to dissolve the reaction mass and everything was transferred to a laboratory glass and left to cool to room temperature. After it settled, 3 extractions were made with 55 mL of diethyl ether to remove the unreacted ketone, I_2 and sulfur and other impurities. Then, 50 mL of NH_4OH (25% solution) was added to the aqueous solution, and three consequent extractions were made with diethyl ether, with aliquots of 55 mL each (the ethereal layers were combined, and dried over $MgSO_4$). After drying of the organic layer, filtration was done with cotton or paper directly, it was rinsed with diethyl ether, and evaporated in a rotavapor.

5.1 Synthesis of 2-amino-5-ethyl-4-propylthiazol (10a): The product **10a** was obtained as a yellow oil. Yield: 86.17%; mp/°C = 48-50; ^{1}H NMR ($CDCl_3$, δ/ppm, *J*/Hz): 4.5-4.75 (2H, *s*), 2.6 (2H, *q*), 1.6 (2H, *m*), 2.4 (2H, *t*), 0.9-1.09 (3H, *t*), 1.17 (3H, *t*).

5.2 Synthesis of 2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol (10b): The product **11b** was obtained as a light-yellow precipitate. Yield: 71.27%. mp/°C = 87-88. Recrystallization from Hexane. IR (ATR/cm^{-1}): 3430 (NH_2, antisymmetric stretching), 3250 (NH_2, symmetric stretching), 3150, 3100, 3050 (CH, aromatic stretching), 2950-2850 (CH_2, stretching), 1650 (NH_2, bending deformations).

5.3 Synthesis of 2-amino-4-benzylthiazol (10c): The product **11c** was obtained as a white precipitate. Yield: 73.58% mp/°C = 96-97; Recrystallization from benzene. IR (ATR/cm^{-1}): 3450 (NH_2, antisymmetric stretching), 3250 (NH_2, symmetric stretching), 2800 (CH_2, stretching), 3150, 3100, 3050 (CH, aromatic stretching), 1650 (NH_2, bending deformations). MS/EI (*m/z*): $M^{\bullet+}$ = 190, $C_{10}H_{10}N_2$, $[C_6H_5]^{\bullet+}$ = 77, $[C_{10}H_9N_2]^{\bullet+}$ = 157.

General procedure for synthesis of 11a-c

15 mmol of **10a-c** were weighed and placed in a conic flask in which 50 mL of HCl (6M) were added. After the complete dissolving of **11a-c**, salt-ice bath was formed and the conic flask was inserted in the bath. When the temperature drops at -5 °C to -10 °C, the aqueous solution of $NaNO_2$ (previously prepared by dissolving of 1.08 g (15.70 mmol) sodium nitrite in 12 mL water) was added dropwise in a time interval from 10-15 minutes. After this, the solution was left to mix for 45 minutes at the same temperature. After 45 minutes, 2.20 g (15 mmol) of **1** were weighed and dissolved in 50 mL NaOH (the solution was left in rt) and this was added with one portion to solution of the corresponding diazonium salt. As a result, a red and voluminous precipitate **11a-c** was formed immediately. The reaction system was left to stir for one hour on room temperature and finally the precipitate was vacuum filtrated. After washing

with small amounts of pure water the precipitate was left to dry in air. In the end, the products were recrystallized by isopropanol to obtain nice fine red crystalline products.

5.4 (E)-3-(2-(4-ethyl-5-propylthiazol-2-yl)hydrazineylidene)chromane-2,4-dione (11a): Red crystalline compounds; Yield: 78.10%. mp/°C > 200. IR (ATR/cm^{-1}): 3150, 3100 and 3050 (CH, aromatic stretching), 2985 (CH_3, antisymmetric stretching), 2872 (CH_3, symmetric stretching), 2942 (CH_2, antisymmetric stretching), 2850 (CH_2, symmetric stretching), 1780 (C=O, stretching), 1650, 1586 and 1492 (aromatic deformations in the plane), 780 and 650 (aromatic deformations out of plane). MS/ESI+ (*m/z*): 344 $[M+H]^+$, 366 $[M+Na]^+$.

5.5(E)-3-((4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)hydrazineylidene)chromane-2,4-dione (11b): Red crystalline compounds; Yield: 78.10%. mp/°C > 200. IR (ATR/cm^{-1}): 3150, 3100 and 3050 (CH, aromatic stretching), 2953 (CH_2, antisymmetric stretching), 2841 (CH_2, symmetric stretching), 1785 (C=O, stretching), 1650, 1586 and 1492 (aromatic deformations in the plane), 783 and 672 (aromatic deformations out of plane). MS/ESI+ (*m/z*): 328 $[M+H]^+$, 350 $[M+Na]^+$.

5.6 (E)-3-((5-benzylthiazol-2-yl) hydrazineylidene)chromane-2,4-dione (11c): Red crystalline compounds; Yield: 78.10%. mp/°C > 200. IR (ATR/cm^{-1}): 3150, 3100 and 3050 (CH, aromatic stretching), 2930 (CH_2, antisymmetric stretching), 2815 (CH_2, symmetric stretching), 1781 (C=O, stretching), 1650, 1586 and 1492 (aromatic deformations in the plane), 785 and 686 (aromatic deformations out of plane). MS/ESI+ (*m/z*): 364 $[M+H]^+$, 386 $[M+Na]^+$.

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