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A new microwave-assisted hydrolysis, a catalytic acylation and an efficient synthesis of derivatives of flavanones with hydroxylamine and phenylhydrazines

Omar FANDOUGOUMA[1,2,3*], Nasser BELBOUKHARI [3], Naoual CHEIKH [4], Didier VILLEMIN [5]

[1] University African Ahmed Draya, 01000 Adrar, Algeria
[2] University Kasdi Merbah, 30000 Ouargla, Algeria
[3] Laboratory of Chiral Separation of Bioactive Molecules (LCSBM), University of Bechar, 08000 Bechar, Algeria.
[4] Laboratory of Catalysis & Synthesis on Organic Chemistry (LCSOC), University of Abou Bekr Belkaid, 13000 Tlemcen, Algeria
[5] Laboratory of molecular chemistry & thioorganic (LMCT), UMR CNRS 6507, ENSICAEN, 14050 Caen, France

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Corresponding author Email: fandougouma@yahoo.fr

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Abstract. *For the first time, acidic hydrolysis of flavanone-7-O-glycosides was demonstrated under Microwave irradiation. This new economical procedure allowed us to obtain the flavanones in very good yields ~90% better than of hydrolysis in reflux. Secondly, we describe for the first time, a profitable synthesis of Hesperidin-octa-acetate, Naringin-octa-acetate, Hesperetin-triacetate and Naringenin-triacetate from the flavanones with 4-(N,N-Dimethylamino)-pyridine. We synthetized a series, of oxime derivatives of 2-phenylchroman-4-one; by coupling hydroxylamine with flavanones. We have also able to synthetized and characterized a new products flavanone-4-one hydrazones by standard analytical methods, according to a new reaction between the flavanones and phenylhydrazines derivatives.*

***Key Words*:** *Flavanone-7-O-glycosides, Microwave, Oxime, Phenylhydrazines*

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1. Introduction

Flavonoids are a group of naturally occurring polyphenolic compounds ubiquitously found in fruits and vegetables.[1] They are widely distributed in the leaves, flowers and fruits of plants as secondary metabolites and constitute a natural part of our diet.[2] Citrus fruits such as *Citrus sinensis, Citrus paradise, Citrus reticulata, Citrus aurantium* are the major sources of flavonoids for humans.[3-6] In the last two decades, the biological activities of flavonoids have attracted many studies, which have shown that flavonoids possess a number of important properties. In addition, flavonoids are a compound having a C6–C3–C6 structural pattern, they present two benzene ring (A- and B-ring) are linked through a heterocyclic pyran or pyrone ring (C-ring) in the middle. The B-ring is located at the 2-position and the C-ring contains a C2–C3 double[7-8] (Figure 1a). Flavonoids are classified into flavones; flavanones and flavanols based on their structure and these occur as aglycones glycosides.[9-11] In particular, flavanones (2, 3-dihydro-2-phenyl-4H-1-benzopyran-4-one 1 (Figure 1b) derivatives) are a class of flavonoids mainly present in citrus fruits such as orange, grapefruit and lemon; called citroflavonoids. They are present in solid wastes and residues obtained during their industrial processing. They are usually found as flavanone-7-*O*-glycosides.[12-15]

Hesperidin **2** (3', 5, 7-trihydroxy-4'-methoxyflavanone-7-α-L-rhamnopyranosyl-(1→6)-β-*D*-glucoside) (Figure 1c) and Naringin **3** (4',5,7-trihydroxyflavanone-7-α-*L*-rhamnopyranosyl-(1→2)-β-D-glucoside) (Figure 1d) are inexpensive products which occur almost exclusively in argumes. A number of pharmacological properties of Hesperidin **2** and Naringin **3** have been reported until now. Hesperidin **2** has been reported to have anti-cholesterol inhibition, antioxidant,[16] anti-mutagenic, anti-hypertensive,[17] diuretic,[18] antidiabetic,[19] anti-carcinogenic[20] and; diminution loss of bone density.[21-22] The content of Hesperidin **2** in orange juice extends from 200 to 600 mg/l.[23] Naringin **3** is responsible for the characteristic sour flavor of the fruits, and has been empirically proven to have no side effects, as humans have been ingesting grapes and citrus fruits for a long time, it was proven to have hypocholesterolaemic effects,[24] hypoglycemic,[25] and anti-inflammatory.[26-27]

Therefore, Hesperidin **2** and Naringin **3** are chiral glycosides flavonoids; contains two parts; Rutinoside and Neohesperidose (Figure.1 g-h); which determines their bitterness, while Hesperetin **4** (3',5,7-trihydroxy-4'-methoxyflavanone) and Naringenin **5** (4',5,7-trihydroxyflavanone) aglycones (Figure.1e-f) determine their own hydrogen-donating ability, respectively.[28] A cohort study found that the intake of Hesperetin **4** and Naringenin **5** reduces the risk of chronic diseases such as cerebrovascular disease and asthma.[29] Hesperidin **2** and Naringin **3** are hydrolyzed in the gastrointestinal tract by the enzymes of intestinal bacteria followed by absorption and conjugation of their aglycones.[30]

View to; the importance of bioactive flavonoids; researchers have thought of replacing the oxygen atom of the flavonoid carbonyl group with a sulphur atom or an amine group substituted; to verify their effect and the effect of various substituents on the biological activities of flavonoids. In 2006, the group

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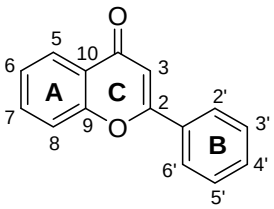
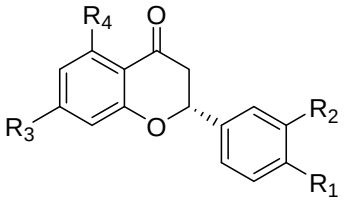
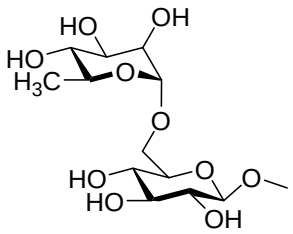
of Ullah Mughal described a new synthetic of 4-iminoflavones;[31] from flavones and 2,4-dinitrophenylhydrazine in the presence of H_2SO_4 in ethanol. Three years later, Li et al, were synthesized and characterized hesperetin-4-one-(benzoyl) hydrazone to give a deep search the ramifications of Hesperetin. Hesperetin-4-one-(benzoyl) hydrazone was synthesized by refluxing Hesperetin in the presence of acetic acid with benzoyl hydrazine.[32-33]



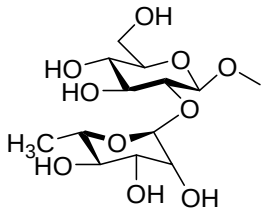
a



b: **1** : R_1= R_2= R_3= R_4= H.
c: **2** : R_1= OCH_3, R_2= R_4= OH, R_3= *O*-Rutinoside.
d: **3** : R_1= R_4= OH, R_2= H, R_3= *O*-néohesperidose.
e: **4** : R_1= OCH_3, R_2= R_3= R_4= OH.
f: **5** : R_1= R_3= R_4= OH, R_2= H



g: Rutinoside



h: Neohesperidose

Figure 1: Structures of Flavanone **1**, Hesperidin **2**, Naringin **3**, Hesperetin **4** and Naringenin **5**

2. Material and Methods

2.1. Instrumentations:

All reagents were obtained from commercial suppliers unless otherwise stated. Hesperidin was extracted and purified from *Citrus sinensis* peels. Naringin was purchased by Alfa Aesar. Hydroxylamine sulfate and phenylhydrazines were purchased by Sigma-Aldrich. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker DPX apparatus of 400. The products were analyzed in deuterated chloroform ($CDCl_3$), deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts δ are given in ppm relative to TMS and coupling constants *J* in Hz multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, split; m, multiplet. ^{13}C NMR spectra were recorded at 100.6

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MHz using a Bruker DPX unit of 400 and 125.7 MHZ on a Bruker AC 500 device. Chemical shifts δ are given in ppm relative to TMS. Infrared absorption spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. The absorption bands are expressed in cm^{-1}. Analysis LC/MS were performed on a QTOF Micro unit (Waters) with the following characteristics: ionization positive electrospray mode (ESI+) or negative (ESI-) lock spray PEG introduction (5 mL/min), the source of temperature 800 °C, desolation temperature 120 °C. The thin layer chromatography was carried out on silica plates Merck 60 F254. Melting points were determined using a Gallenkamp apparatus. The microwave irradiation was performed in a Microwave oven types Antony Paar® (600W, 30 bars).

2.2. Extraction of Hesperidin:

Hesperidin **2** was extracted and purified from *Citrus sinensis* peels were air-dried at room temperature. Extracts of *Citrus sinensis* (40 g) were extracted using Soxhlet extractor with 500 ml of petroleum ether (40-60°C) until the siphoned material become colorless for 2 hours. After, the extraction was continued in 2^{nd} time by adding 300 ml of methanol over a period of 2 hours. The methanol extract was dried *in vacuum* at 65°C, and recrystallized with aqueous acetic acid. The flavanone glycoside, Hesperidin **1**, was separated as beige needles, **mp** 261-262°C; the total yield quantity was 8.52 g (21.3%). **M. M**. 610.57 $g.mol^{-1}$ $C_{28}H_{34}O_{15}$. **^{1}H RMN** (400MHz, DMSO) δ (ppm) 12.02 (s, 1H, 5-OH), 9.11 (s, 1H, 3′-OH), 6.94-6.93 (m, 3H, H-2′, H5′ & H-6′), 6.14 (d, *J* = 2.4 Hz, 1H, H-6), 6.12 (d, *J* = 2.0 Hz, 1H, H-8), 5.50 (dd, *J* = 12.8 Hz & 3.2 Hz, 1H, H-2), 5.42 (d, *J* = 4.8 Hz, 1H, H-1^{Glu}), 5.21-5.18 (m, 2H, H-1^{Rhm}, 6^{Glu}-OH), 5.00-4.97 (m, 1H, 4^{Rhm}-OH), 4.72-4.49 (m, 4H, 3^{Glu}-OH, 4^{Glu}-OH, 2^{Rhm}-OH & 3^{Rhm}-OH), 3.89-3.81 (m, 1H, H-3^{a}), 3.77 (s, 3H, 4′-OCH_3), 3.63-3.12 (m, 10H, H-2^{Glu}, H-3^{Glu}, H-4^{Glu}, H-5^{Glu}, H-$6^{Glu,a}$, H-$6^{Glu,b}$, H-2^{Rhm}, H-3^{Rhm}, H-4^{Rhm}, H-5^{Rhm}) ,2.77 (dd, *J* = 3.2 Hz, 1H, H-3^{b}), 1.09 (d, *J* = 6.4 Hz, 3H, H-6^{Rhm}). **^{13}C RMN** (100.6 MHz, DMSO) δ (ppm) 196.8 (C-4), 164.8 (C-7), 162.8 (C-5), 162.2 (C-9), 147.7 (C-4′), 146.2 (C-3′), 130.6 (C-1′), 113.9 (C-6′), 111.7 (C-2′), 103.0 (C-5′), 100.3 (C-10), 98.0 (C-6), 96.1 (C-8), 78.1 (C-2), 75.9-68.0 (11 Carbons of the saccharide portion), 55.4 (4′-OCH_3), 42.0 (C-3), 17.6 (C-6^{Rhm}).

*2.3. Microwave-assisted hydrolysis of Hesperidin **2** and Naringin **3***

Hesperetin **4** and Naringenin **5** were prepared by hydrolysis of 1 g of Hesperidin **2** and Naringin **3** in 10 ml of water; with 0.5 mL of H_2SO_4 heated to 120 °C; using a microwave oven Paar® for 10 minutes. The yellow solution was filtered, crystallized with ethanol to give a desired product Hesperetin **4** and Naringenin **5**, respectively.

*2.4. Hydrolysis at reflux of Hesperidin **2** and Naringin **3***

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Hesperetin **4** was prepared from the hydrolysis of Hesperidin **2** (3 g) in 60 mL of ethylene glycol with 3 mL H_2SO_4 at reflux (100 °C) for 40 minutes. The solution is followed by 150 mL of water and the precipitate **4** was filtered and crystallized with ethanol to give a brown product **4**.
Naringenin **5** prepared by hydrolysis of 2 g (3.4 mmol) of Naringin **3** in 30 mL of water with 1 mL of H_2SO_4 heated at reflux for 5 hours. 15 mL of ethyl acetate was added; and the mixture was decanted. The organic portion was dried over $MgSO_4$ and concentrated in vacuum and the solid obtained was recrystallized from ethanol to give a yellow product **5**.

*2.5. Catalytic acylation of Flavanones **2-5***

The products **7-10** were prepared from the acylation of flavanones **2-5**. In a 50 mL flask, was brought to reflux of flavanones **2-5** dissolved in 25 mL of acetic anhydride with 4-dimethylamino-pyridine **6** as catalyst for 24 hours. The yellow organic solution was added to a solution of water/ethyl acetate (10 mL/10 mL). The organic portion was washed with sodium carbonate Na_2CO_3 (4 x 50 mL) until all traces of acetic anhydride was removed. The organic portion was dried over $MgSO_4$ and concentrated in vacuum and the solids obtained were recrystallized from ethanol.

*2.6. Synthesis of Flavanone oximes **12-16***

In a round-bottomed flask equipped with a condenser. A mixture of flavanones **1-5**, and hydroxylamine sulfate **11** was dissolved in 10 ml of ethanol and 0.5 ml of pyridine for 1-2 hours at reflux. After removal of ethanol, 5 ml of water was added to the residue, the mixture was cooled in an ice bath until the oxime crystallizes. The solid was filtered and washed with a little water. The product **12-16** was recrystallized with ethanol/water 2:8 v/v.

*2.7. Synthesis of Flavanone-4-hydrazones **19-28***

In a round-bottomed flask equipped with a condenser. A reflux mixture; of flavanones **1-5**, and phenylhydrazines **17-18** was dissolved in 25 ml of ethanol containing 1 ml of hydrochloric acid HCl for 1-4 hours. The reaction medium is concentrated under vacuum and the resulting solid is crystallized with an aqueous ethanol solution.

3. Results and Discussion

In the last decade, microwave irradiation has proved to be an efficient tool to perform the organic reactions at shorter reaction time with high yields and higher selectivity. In the first, we make the ordinary hydrolysis of flavanone-7-*O*-glycosides **2-3** to achieve their flavanone aglycones **4-5**. A mixture of **2-3** in ethylene glycol or water, in the presence of acid H_2SO_4; for 5 hours furnished Hesperetin **4** and Naringenin **5** (Scheme 1).

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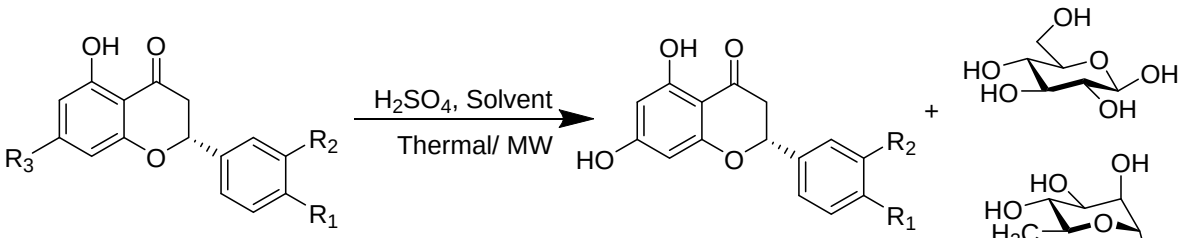

2- R_1= OCH_3; R_2= OH; R_3= O-Rutinoside
3- R_1= OH; R_2= H; R_3= O-Neohesperidose

4- R_1= OCH_3; R_2= OH.
5- R_1= OH; R_2= H.

Scheme 1: Hydrolysis of Hesperidin **2** and Naringin **3**

After having the aglycones **4-5**; they were purified and identified by analysis methods. The ^{1}H NMR spectrum for **4** and **5** offered two redouble and one multiple characteristics from the C-ring at δ 5.42 (dd, 1H, H-2), δ 3.29-3.15 (m, 1H, H-3^a) and δ 2.67 or 2.69 (dd, 1H, H-3^b) respectively, it also showed one characteristic aromatic at δ 5.88 (2H, H-6 & H-8), with the novel signal at δ 12.10 (s, 1H, 5-OH) for the aromatic A-ring. The ^{13}C NMR showed no signals for the saccharides portions. Our objective to perform the ordinary hydrolysis of **2-3** in presence of H_2SO_4 to **4-5** respectively which gives average yields (Entry 1 and 2, Table 1). Thereafter this work, to improve the yields of the aglycones was obtained when we performed the reaction in water H_2O. Then, we looked at the utilization of microwave (MW) irradiation (600W, 120°C, and 6.6 bars); on the reaction of hydrolysis of 2 and 3 in H_2O. Fortunately, under this condition a significant increase in yield of **4** and **5** to 90 % was observed in a very short reaction time (entry 3 and 4, Table 1).

Table 1: Hydrolysis of Hesperidin **2** and Naringin **3**

Entry	Reagent	Solvent	Thermal/ MW	Time	Product	Yield %
1	**2**	Ethylene glycol	Reflux, 100 °C	2H	**4**	70.7
2	**3**	H_2O	Reflux, 100 °C	5H	**5**	67.4
3	**2**	H_2O	MW, 120 °C	10 min	**4**	90.8
4	**3**	H_2O	MW, 120 °C	10 min	**5**	89.5

Reaction conditions: **2-3** (5 mmol/ Thermal, 1.6 mmol/ MW), H_2SO_4 (60 mmol/Thermal, 10 mmol/MW), Solvent (60 mL/Thermal, 10 mL/MW).

Following these successful hydrolysis under Microwave irradiation, we have expanded our search to an acylation reaction of compounds **2-5**. In this study, we describe for the first time, a profitable synthesis

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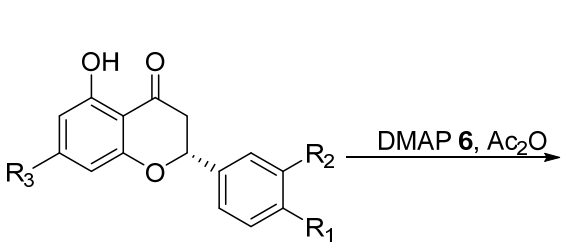
of Hesperidin-octa-acetate **7**, Naringin-octa-acetate **8**, Hesperetin-triacetate **9** and Naringenin-triacetate **10** from the flavanones **2-5** respectively with 4-(*N*,*N*-Dimethylamino)-pyridine DMAP **6**, under ordinary conditions using acetic anhydride as solvent and acyl donor (Scheme 2).

Furthermore the reaction of flavanone **2-5** and DMAP **6** in presence of acetic anhydride were performed under microwave irradiation to afford their poly-acetates **7-10**. For thermal reactions (Entry 1-4, Table 2), the products **7-10** were obtained after 24 hours by mixing 5 mmol of flavanones **2-5** in 60 mL acetic anhydride with average yields. In contrast, as shown the table 2, the acylation reaction gives good yield using the microwave better than in reflux which increases the yield of 60- 75% to about 90- 95% (Entry 5-8, Table 2). Using microwave (600W, 180 °C, 6.6 bars), The best conditions for synthetized the products **7-10** was determined with 1.6 mmol flavanones **2-5** with 10 mL of Ac_2O in the presence of DMAP **6** as catalyst. The reactions were finished in 5 min (monitored by TLC).The structures of products **7-10** were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS spectral data.



2- R_1= OCH_3, R_2= OH, R_3= *O*-Rutinoside;
3- R_1= OH, R_2= H, R_3=*O*-Néohesperidose;
4- R_1= OCH_3, R_2= R_3= OH.
5- R_1= R_3= OH, R_2= H.

7- R_1= OCH_3, R_2= OAc, R_3= *O*-Rutinoside-Acetyl.
8- R_1= OAc, R_2= H, R_3=*O*-Neohesperidose-Acetyl.
9- R_1= OCH_3, R_2= R_3= OAc.
10- R_1= R_3= OAc, R_2= H.

Scheme 2: Acylation of flavanones **2-5**

Table 2: Acylation of flavanones **2-5**

Entry	Reagent	Thermal/ MW	Time	Product	Yield, %
1	**2**	Reflux, 90 °C	24H	**7**	74
2	**3**	Reflux, 90 °C	24H	**8**	70
3	**4**	Reflux, 90 °C	24H	**9**	65
4	**5**	Reflux, 90 °C	24H	**10**	75
5	**2**	MW, 150 °C	5 min	**7**	89
6	**3**	MW, 150 °C	5 min	**8**	91
7	**4**	MW, 150 °C	5 min	**9**	94

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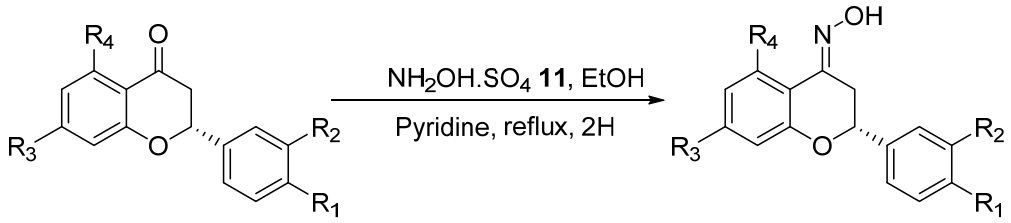
8	**5**	MW, 150 °C	5 min	**10**	92

Reaction conditions: **2-5** (5 mmol/ Thermal, 1.6/ MW), solvent (60 mL/ Thermal, 10 mL/MW).

In this study, we present the synthesis, characterization and spectroscopic properties of flavanone oxime compounds **12-16** via a simple and cost effective method. The key step of synthesis of these derivatives is based on hydroxylamine **11** condensation reactions with an electrophilic site. We tried to access flavanone oximes to synthesize the products **12-16**, starting from 2-phenylchroman-4-one **1**, flavanone glycosides **2-3** and their aglycones **4-5**. Indeed, in function with reaction conditions. We saw earlier that it was possible to use bases such as KOH, AcONa, etc ... to form oximes. It was therefore possible to make such reaction in the presence of pyridine and their derivatives (Scheme 3).



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4 : R_1= OCH_3, R_2= R_3= R_4= OH.
5 : R_1= R_3= R_4= OH, R_2= H

12 : 95.4 %
13 : No reaction
14 : 74.2 %
15 : 85.1 %
16 : 80.2 %

Scheme 3: Synthesis of flavanone oximes **12-16**

According to the scheme 3, we observe that the condensation reaction of Hesperidin **2** with hydroxylamine **11** does not give any result because of the difficulty of solubility of Hesperidin **2** in ethanol and organic solvents. By against, we note that after two hours of reflux reaction; of flavanone **1**, Naringin **3**, Hesperetin **4** and Naringenin **5** with Hydroxylamine **11** gives the corresponding Oximes **12-16** with good yields between 74-95%.

Moreover; we wondered about the possible access to flavanone-4- hydrazones through a new and easy reaction; from flavanones **1-5** with phenylhydrazines **17-18**. These molecules could be easily obtained from a reaction between flavanones **1-5** and the phenylhydrazines **17-18**, followed in the same pot by dehydration provides flavanones hydrazones **19-28**. These are prepared by using this time one equivalent of flavanones **1-5** with one equivalent of various phenylhydrazines **17-18**. Products **19-28** are obtained after reflux 2H in ethanol containing hydrochloric acid, in good yields varied from 68 to 95% (Scheme 4).

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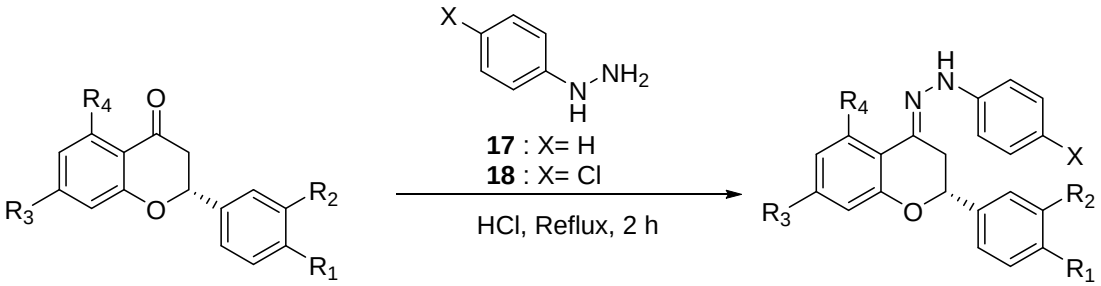

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4 : R_1= OCH_3, R_2= R_3= R_4= OH.
5 : R_1= R_3= R_4= OH, R_2= H.

Scheme 4: Synthesis of flavanone-4-hydrazones **19-28**

According to table 3, we still observe that the reaction of Hesperidin **2** with phenylhydrazines **17-18** is impractical because of the difficulty of solubility of Hesperidin **2** (Entry 2 & 7, Table 3).

Table 3: Synthesis of flavanone-4-hydrazones **19-28**

Entry	Reagents		Product	Yield, %
	Flavanone	Phenylhydrazine		
1	**1**	**17**	**19**	95
2	**2**	**17**	**20**	NR
3	**3**	**17**	**21**	86
4	**4**	**17**	**22**	89
5	**5**	**17**	**23**	92
6	**1**	**18**	**24**	85
7	**2**	**18**	**25**	NR
8	**3**	**18**	**26**	68
9	**4**	**18**	**27**	85
10	**5**	**18**	**28**	70

NR: No Reaction.

4. Conclusions

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In conclusion, a new original method, efficient and economical use of acid hydrolysis of Hesperidin and Naringin to provide their aglycones in presence of water as a solvent has been described under Microwave. The utilization of the latter was also examined in the acylation of the flavanone-7-*O*-glycoside, Hesperidin, Naringin and their aglycones Hesperetin and Naringenin. 2-phenylchroman-4-one oxime derivatives have been synthetized from corresponding hydroxylamine with carbonyl in C-4 of flavanones. Likewise, a series of flavanones was used for coupling with some phenylhydrazines to output new flavanone-4-hydrazones.

5. Experimental Section

Hesperetin (4): *MW (0.449 g 90.8%). and at reflux (1.05 g, 70.69 %). M. M. 302.27 g.mol^{-1} $C_{16}H_{14}O_6$. m_p: 225-226 °C. IR ν (cm^{-1}): 3500, 3117, 3035-2623, 2160, 2011, 1635, 1580, 1504, 1441, 1359, 1262, 1240, 1180. ^{1}H NMR (400MHz, DMSO) δ (ppm) 12.12 (s, 1H, 5-OH), 10.80 (s, 1H, 7-OH), 9.10 (s, 1H, 3′-OH), 6.93-6.85 (m, 3H, H-2′, H-5′ & H-6′), 5.87 (d, J = 3.6 Hz, 2H, H-6 & H-8), 5.42 (dd, J = 12.4 & 2.8 Hz, 1H, H-2), 3.76 (s, 3H, 4′-OC$\underline{H_3}$), 3.19 (dd, J = 17.2 & 12.4 Hz, 1H, H-3^a), 2.69 (dd, J = 17.2 & 2.8 Hz, 1H, H-3^b). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 196.1 (C-4), 166.5 (C-7), 163.4 (C-5), 162.7 (C-9), 147.8 (C-4′), 146.3 (C-3′), 131.0 (C-1′), 117.6 (C-6′), 113.9 (C-2′), 111.8 (C-5′), 101.7 (C-10), 95.7 (C-6), 94.9 (C-8), 78.1 (C-2), 55.6 (4′-O$\underline{C}$H$_3$), 41.9 (C-3). MS (ESI-, m/z): 301.1 [(M-H)$^-$, 100%]. HRMS-ESI m/z for $C_{16}H_{13}O_6$ [M-H]$^-$ calculated 301.0712 found 301.0719. R_f = 0.755 (Ethyl acetate / Cyclohexane; 5/5).*

Naringenin (5): *MW (0.371 g, 89.5%) and at reflux (0.632 g, 67.4%). M. M. 272.25 g.mol^{-1} $C_{15}H_{12}O_5$. m_p: 252-253 °C. IR ν (cm^{-1}): 3255, 3108, 3035, 2913-2622, 1627, 1600, 1519, 1497, 1460, 1310, 1247, 1156. ^{1}H NMR (400MHz, DMSO) δ (ppm) 12.15 (s, 1H, 5-OH), 10.80 (s, 1H, 7-OH), 9.60 (s, 1H, 4′-OH), 7.31 (d, J = 8.8 Hz, 2H, H-2′ & H-6′), 6.79 (d, J = 8.8 Hz, 2H, H-3′ & H-5′), 5.88 (s, 2H, H-6 & H-8), 5.42 (dd, J = 12.8 & 2.8 Hz, 1H, H-2), 3.25 (dd, J = 17.2 & 12.8 Hz, 1H, H-3^a), 2.67 (dd, J = 17.2 Hz et 2.8 Hz, 1H, H-3^b). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 196.3 (C-4), 166.5 (C-7), 163.4 (C-5), 162.8 (C-9), 157.6 (C-4′), 128.7 (C-1′), 128.2 (C-2′ & C-6′), 115.1 (C-3′ & C-5′), 101.7 (C-10), 95.7 (C-6), 94.9 (C-8), 78.3 (C-2), 41.9 (C-3). MS (ESI-, m/z): 271.1 [(M-H)$^-$, 100%]. HRMS-ESI m/z for $C_{15}H_{11}O_5$ [M-H]$^-$ calculated 271.0606 found 271.0614. R_f = 0.620 (Ethyl acetate / Cyclohexane; 5/5).*

(*2S,3R,4S,5R,6R*)-2-(((*S*)-5-acetoxy-2-(3-acetoxy-4-methoxyphenyl)-4-oxochroman-7-yl)oxy)-6-((((*2R,3R,4R,5S,6S*)-3,4,5-triacetoxy-6-methyltetrahydro-*2H*-pyran-2-yl)oxy)methyl)tetrahydro-*2H*-pyran-3,4,5-triyl triacetate (7): *The compound **7** was synthesized according to the general*

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*procedure in Section 2.5. Hesperidin **2** (1g, 1.64 mmol) was treated with 30 mg of 4-dimethylamino-pyridine. **7** was isolated as a white crystal (1.15 g, 74.2%). M. M. 946.27 g.mol^{-1} $C_{44}H_{50}O_{23}$. m_p: 168-169 °C. IR ν (cm^{-1}): 2942, 2107, 1752, 1694, 1619, 1571, 1517, 1429, 1368, 1242, 1210, 1048, 1032. ^{1}H NMR (400MHz, DMSO) δ (ppm) 7.39 (d, J = 8.0 Hz, 1H, H-6′), 7.29 (s, 1H, H-2′), 7.17 (d, J = 8.0 Hz, 1H, H-5′), 6.67 (s, 1H, H-6), 6.45 (s, 1H, H-8), 5.77 (d, J = 7.6 Hz, 1H, H-2), 5.56 (d, J = 12.4 Hz, 1H, H-1^{Glu}), 5.10 (t, J = 9.6 Hz, 1H, H-2^{Glu}), 5.08-5.01 (m, 3H, H-3^{Glu}, H-1^{Rhm} & H-3^{Rhm}), 4.85 (t, J = 10.0 Hz, 1H, H-2^{Rhm}), 4.74 (s, 1H, H-4^{Glu}), 4.26 (m, 1H, H-4^{Rhm}), 3.79 (s, 3H, 4′-OC$\underline{H}_3$), 3.76-3.71 (m, 2H, H-5^{Glu}, H-5^{Rhm}), 3.61-3.58 (m, 1H, H-3^a), 3.45-3.41 (m, 1H, H-6^{Glu,a}), 3.26-3.18 (m, 1H, H-6^{Glu,b}), 2.68-2.64 (m, 1H, H-3^b), 2.27 (s, 6H, 2×CO-C$\underline{H}_3$), 2.06 (s, 3H, CO-C$\underline{H}_3$), 2.02 (s, 3H, CO-C$\underline{H}_3$), 2.00 (s, 6H, 2×CO-C$\underline{H}_3$), 1.97 (s, 3H, CO-C$\underline{H}_3$), 1.91 (s, 3H, CO-C$\underline{H}_3$), 1.07-1.00 (m, 3H, H-6^{Rhm}). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 198.0 (C-4), 172.1 (O-$\underline{C}$O), 169.63 (O-$\underline{C}$O), 169.57 (O-$\underline{C}$O), 169.5 (O-$\underline{C}$O), 169.4 (O-$\underline{C}$O), 169.2 (O-$\underline{C}$O), 169.0 (O-$\underline{C}$O), 168.4 (O-$\underline{C}$O), 164.2 (C-7), 163.0 (C-5), 162.6 (C-9), 151.1 (C-4′), 139.1 (C-3′), 130.6 (C-1′), 125.6 (C-6′), 121.5 (C-2′), 121.4 (C-5′), 112.6 (C-1^{Glu}), 103.7 (C-10), 98.0 (C-1^{Rhm}), 96.9 (C-6), 95.3 (C-8), 78.0 (C-2), 71.8.0 (C-5^{Glu}), 70.4 (C-2^{Glu}), 69.9 (C-3^{Rhm}), 68.6 (C-4^{Rhm}), 68.5 (C-2^{Rhm}), 68.1 (C-3^{Glu}), 68.9 (C-4^{Glu}), 68.0 (C-5^{Rhm}), 60.5 (C-6^{Glu}), 55.9 (4′-O$\underline{C}$H$_3$), 40.1 (C-3), 21.0 (CO-$\underline{C}$H$_3$), 20.5 (2× CO-$\underline{C}$H$_3$), 20.4 (2× CO-$\underline{C}$H$_3$), 20.35 (CO-$\underline{C}$H$_3$), 20.32 (CO-$\underline{C}$H$_3$), 20.2 (CO-$\underline{C}$H$_3$), 16.9 (C-6^{Rhm}). MS (ESI+, m/z): 969.7 [(M+Na)$^+$, 100%]. HRMS-ESI m/z for $C_{44}H_{50}O_{23}Na$ [M+Na]$^+$ calculated 969.2641 found 969.2651. R_f = 0.474 (Ethyl acetate / Cyclohexane; 5/5).*

(*2S,3R,4R,6S*)-2-(((*2S,3R,4S,5R,6R*)-4,5-diacetoxy-2-(((*S*)-5-acetoxy-2-(4-acetoxyphenyl)-4-oxochroman-7-yl)oxy)-6-(acetoxymethyl)tetrahydro-*2H*-pyran-3-yl)oxy)-6-methyltetrahydro-*2H*-pyran-3,4,5-triyl triacetate (8): *The compound **8** was synthesized according to the general procedure in Section 2.5. Naringin **3** (1g, 1.7 mmol) was treated with 30 mg of 4-dimethylamino-pyridine. **8** was isolated as a solid pure white yellowish (1.04 g, 70%). M. M. 916.79 g.mol^{-1} $C_{43}H_{48}O_{22}$. m_p: 127-128 °C. IR ν (cm^{-1}): 2161, 2031, 1743, 1689, 1618, 1437, 1367, 1217, 1138, 1035. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 7.55 (dd, J = 2.0, 2H, H-2′ & H-6′), 7.25 (dd, J = 2.0, 2H, H-3′ & H-5′), 6.24-6.22 (m, 2H, H-6 & H-8), 5.56-5.51 (m, 1H, H-2), 5.45-5.40 (m, 1H, H-1^{Glu}), 5.27-5.24 (m, 1H, H-1^{Rhm}), 5.20-5.16 (m, 2H, H-2^{Glu}, 3^{Glu}), 5.13-5.07 (m, 3H, H-4^{Glu}, H-5^{Glu}, H-6^{Glu,a}), 4.33-4.32 (m, 1H, H-6^{Glu,b}), 4.24-4.18 (m, 3H, H-2^{Rhm}, H-3^{Rhm}, H-4^{Rhm}), 3.97-3.96 (m, 1H, H-5^{Rhm}), 3.20-3.15 (m, 1H, H-3^a), 2.97-2.91 (m, 1H, H-3^b), 2.41 (s, 3H, CO-C$\underline{H}_3$), 2.23 (s, 3H, CO-C$\underline{H}_3$), 2.18 (s, 3H, CO-C$\underline{H}_3$), 2.15 (s, 3H, CO-C$\underline{H}_3$), 2.11 (s, 3H, CO-C$\underline{H}_3$), 2.02 (s, 3H, CO-C$\underline{H}_3$), 1.51 (s, 6H, 2×CO-C$\underline{H}_3$), 1.34 (s, 3H, H-6^{Rhm}). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 195.9 (C-4), 170.5 (O-$\underline{C}$O), 170.0 (O-$\underline{C}$O), 169.9 (O-$\underline{C}$O), 169.8 (O-$\underline{C}$O), 169.7 (O-$\underline{C}$O), 169.5 (O-$\underline{C}$O), 169.2 (O-$\underline{C}$O), 168.3 (O-$\underline{C}$O), 164.2 (C-7), 163.8 (C-5), 162.7 (C-9),150.9 (C-4′), 135.5 (C-1′), 127.4 (C-2′), 127.3 (C-6′), 122.03 (C-3′), 122.01 (C-5′), 104.3 (C-1^{Glu}), 97.9 (C-10), 97.8 (C-1^{Rhm}), 97.7 (C-6), 95.7 (C-8), 78.7 (C-2), 74.2 (C-5^{Glu}), 72.2 (C-2^{Glu}), 70.8*

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(C-3^{Rhm}), 69.9 (C-4^{Rhm}), 68.3 (C-2^{Rhm}), 68.2 (C-3^{Glu}), 66.7 (C-4^{Glu}), 61.7 (C-5^{Rhm}), 60.3 (C-6^{Glu}), 43.3 (C-3), 26.8 (CO-CH$_3$), 21.0 (CO-CH$_3$), 20.7 (CO-CH$_3$), 20.65 (CO-CH$_3$), 20.6 (CO-CH$_3$), 20.5 (CO-CH$_3$), 20.48 (CO-CH$_3$), 20.3 (CO-CH$_3$), 17.4 (C-6^{Man}). MS (ESI+, m/z): 939.3 [(M+Na)$^+$, 100%]. HRMS-ESI m/z for $C_{43}H_{48}O_{22}Na$ [M+Na]$^+$ calculated 939.2535 found 939.2534. R_f = 0.408 (Ethyl acetate / Cyclohexane; 6/4).

(*S*)-2-(3-acetoxy-4-methoxyphenyl)-4-oxochromane-5,7-diyl diacetate (9): *The compound **9** was synthesized according to the general procedure in Section 2.5. Hesperetin **4** (1g, 3.3 mmol) was treated with 25 mg of 4-dimethylamino-pyridine. **9** was isolated as a white product (0.7572 g, 53.4 %). M. M. 428.27 g.mol^{-1} $C_{22}H_{20}O_9$. m_p: 143-144 °C. IR ν (cm^{-1}): 3113, 2844-2636, 1769, 1693, 1617, 1560, 1519, 1439, 1372, 1265, 1126. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 7.26 (dd, J = 8.4 Hz & 2.0 Hz, 1H, H-6′), 7.15 (d, J = 2.0 Hz, 1H, H-2′), 7.01 (d, J = 8.4 Hz, 1H, H-5′), 6.77 (d, J = 2.0 Hz, 1H, H-6), 6.53 (d, J = 2.4 Hz, 1H, H-8), 5.42 (dd, J = 12.8 Hz et 2.4 Hz, 1H, H-2), 3.86 (s, 3H, 4′-OCH$_3$), 3.02 (m, 1H, H-3^a), 2.76 (dd, J = 17.4 & 2.4 Hz, 1H, H-3^b), 2.38 (s, 3H, CO-CH$_3$), 2.33 (s, 3H, CO-CH$_3$), 2.30 (s, 3H, CO-CH$_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 189.2 (C-4), 172.9 (O-CO), 169.4 (O-CO), 168.9 (O-CO), 168.1 (C -7), 163.4 (C-5), 156.0 (C-9), 151.2 (C-4′),151.3 (C-3′),140.2 (C-1′), 130.6 (C-6′), 124.9 (C-2′), 121.2 (C-5′), 112.6 (C-10), 110.6 (C-6), 109.2 (C-8), 78.9 (C-2), 56.1 (4′-OCH$_3$), 45.0 (C-3), 21.3 (CO-CH$_3$), 21.1 (CO-CH$_3$), 20.7 (CO-CH$_3$). MS (ESI+, m/z): 451.1 [(M+Na)$^+$, 100 %], 429.117 [(M+H)$^+$, 45 %]. HRMS-ESI m/z for $C_{22}H_{21}O_9$ [M+H]$^+$ calculated 429.1186 found 429.1176. R_f = 0.796 (Ethyl acetate / Cyclohexane; 5/5).*

(*S*)-2-(4-acetoxyphenyl)-4-oxochromane-5,7-diyl diacetate (10): *The compound **10** was synthesized according to the general procedure in Section 2.5. Naringenin **5** (1g, 3.67 mmol) was treated with 25 mg of 4-dimethylamino-pyridine. **10** was isolated as a white product (0.366 g, 75 %). M. M. 398.25 g.mol^{-1} $C_{21}H_{18}O_8$. m_p: 83-84 °C. ^{1}H NMR (400MHz, DMSO) δ (ppm) 7.59 (d, J = 8.4 Hz, 2H, H-2′ & H-6′), 7.19 (d, J = 8.0 Hz, 2H, H-3′ & H-5′), 6.88 (s, 1H, H-6), 6.70 (s, 1H, H-8), 5.70 (dd, J = 11.6 & 2.8 Hz, 1H, H-2), 3.45-3.40 (m, 1H, H-3^a), 2.74 (dd, J = 17.2 & 2.8 Hz, 1H, H-3^b), 2.29 (s, 3H, CO-CH$_3$), 2.27 (s, 6H, 2× CO-CH$_3$). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 190.2 (C-4), 175.2 (O-CO), 169.4 (O-CO), 169.0 (O-CO), 168.3 (C-7), 168.1 (C-5), 153.5 (C-9), 151.6 (C-4′), 148.6 (C-1′), 131.6 (C-2′ & C-6′), 123.7 (C-3′ & C-5′), 114.3 (C-10, C-6), 108.0 (C-8), 78.1 (C-2), 44.2 (C-3), 21.3 (2× CO-CH$_3$), 20.7 (CO-CH$_3$). EIMS m/z (% relative abundance): 421 (M+Na, 100). HRMS-ESI m/z for $C_{21}H_{18}O_8Na$ [M+Na]$^+$ calculated 421.1973 Found 421.1954. R_f = 0.654 (Ethyl acetate / Cyclohexane; 5/5).*

2-phenylchroman-4-one oxime (12): *The compound **12** was synthesized according to the general procedure in Section 2.6. Flavanone **1** (0.224 g, 1 mmol) was treated with hydroxylamine sulfate **11***

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*(0.164 g, 1 mmol). **12** was isolated as a yellowish-white (95.4%). M. M. 239.09 g. mol^{-1} $C_{15}H_{13}NO_2$. m_p: 166-167 °C. IR ν (cm^{-1}): 3210, 2910, 2800, 1603, 1573, 1453, 1222. ^{1}H NMR (400MHz, DMSO) δ (ppm) 11.36 (s, 1H, N-OH), 7.81 (d, J = 7.7 Hz, 1H, H-5), 7.50 (d, J = 7.2 Hz, 2H, H-2′ & H-6′), 7.42-7.33 (m, 3H, H-7, H-3′ & H-5′), 7.28 (dd, J = 7.8 & 7.4 Hz, 1H, H-6), 6.99-6.94 (m, 2H, H-8 & H-4′), 5.17 (dd, J = 11.6 & 3.2 Hz, 1H, H-2), 3.33 (dd, J = 17.4 & 11.6 Hz, 1H, H-3^a), 2.73 (dd, J = 17.4 & 3.2 Hz, 1H, H-3^b), ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 155.6 (C-9), 147.3 (C-4), 139.9 (C-1′), 130.6 (C-8), 128.5 (C-3′ & C-5′), 128.2 (C-6), 126.4 (C-2′ & C-6′), 123.3 (C-4′), 121.4 (C-7), 118.9 (C-10), 117.7 (C-5), 76.3 (C-2), 43.8 (C-3). MS (ESI+, m/z): 240.1 [(M+H)$^+$, 50%]. HRMS-ESI m/z for $C_{15}H_{14}NO_2$ [M+H]$^+$ calculated 240.1025 found 240.1035.*

(2*S*,*E*)-7-(((2*S*,3*R*,5*S*,6*R*)-4,5-dihydroxy-6-(hydroxymethyl)-3-(((2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)oxy)-5-hydroxy-2-(4-hydroxyphenyl)chroman-4-one oxime (14): *The compound **14** was synthesized according to the general procedure in Section 2.6. Naringin **3** (0.580 g, 1 mmol) was treated with hydroxylamine sulfate **11** (0.164 g, 1 mmol). **14** was isolated as a beige product (0.213 g, 74.2%). M. M. 595.19 g.mol^{-1} $C_{27}H_{33}NO_{14}$. m_p: 66-68 °C. IR ν (cm^{-1}): 3415, 3277, 2920-2890, 1637, 1620, 1548, 1420, 1338, 1262, 1173. ^{1}H NMR (400MHz, DMSO) δ (ppm) 11.44 (s, 1H, 5-OH), 8.14 (s, 1H, N-OH), 7.56-7.28 (m, 2H, H-2′ & H-6′), 6.78 (s, 2H, H-3′ & H-5′), 6.06 (s, 1H, H-8), 5.72 (s, 1H, H-6), 5.18 (dd, J = 12.4 & 2.5 Hz, 1H, H-2), 3.25 (dd, J = 12.4 & 13.8 Hz, 1H, H-3^a), 2.72 (dd, J = 13.8 & 2.5 Hz, 1H, H-3^b), 1.14 (s, 3H, 6^{Rhm}-CH_3). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 174.2 (C-5 & C-7), 164.4 (C-9), 158.5 (C-4′), 157.9 (C-4), 128.2 (C-1′), 127.8 (C-2′ & C-6′), 115.0 (C-3′ & C-5′), 100.1 (C-1^{Rhm}), 99.0 (C-1^{Glu}), 97.0 (C-10), 96.5 (C-6), 96.1 (C-8) 76.9 (C-2), 76.6 (C-2^{Glu}) 75.9 (C-5^{Glu}), 71.6 (C-3^{Glu}), 70.2 (C-5^{Rhm}), 70.1 (C-2^{Rhm}), 69.4 (C-4^{Rhm}), 69.3 (C-3^{Rhm}),67.9 (C-4^{Glu}), 60.1 (C-6^{Glu}), 40,9 (C-3), 17.8 (C-6^{Rhm}). MS (ESI-, m/z): 594.2 [(M-H)$^-$, 100%]; 595.2 [25%]. **HRMS-ESI** m/z for $C_{27}H_{33}NO_{14}Na$ [M+Na]$^+$ calculated 618.1799 found 618.1797.*

(*S*,*E*)-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one oxime (15): *The compound **15** was synthesized according to the general procedure in Section 2.6. Hesperetin **4** (0.302 g, 1 mmol) was treated with hydroxylamine sulfate **11** (0.164 g, 1 mmol). **15** was isolated as a yellowish-white (85.1%). M. M. 317.09 g.mol^{-1} $C_{16}H_{15}NO_6$. m_p: 196-198 °C. IR ν (cm^{-1}): 3520, 3290, 1623, 1605, 1587, 1513, 1275. ^{1}H NMR (400MHz, DMSO) δ (ppm) 12.12 (s, 1H, 5-OH), 11.21 (s, 1H, 3′-OH), 10.78 (s, 1H, 7-OH), 9.09 (s, 1H, N-OH), 6.93-6.84 (m, 3H, H-2′, H-5′ & H-6′), 5.88-5.85 (m, 2H, H-6 & H-8), 5.42 (dd, J = 12.3 & 2.9 Hz, 1H, H-2), 3.76 (s, 3H, 4′-OC$\underline{H_3}$), 3.18 (dd, J = 17.6 & 12.3 Hz, 1H, H-3^a), 2.71-2.66 (m, 1H, H-3^b). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 167.1 (C-5), 163.9 (C-7), 163.3 (C-9), 150.1 (C-4), 148.3 (C-4′), 146.9 (C-3′), 131.6 (C-1′), 118.1 (C-6′), 114.5 (C-2′), 112.4 (C-5′), 102.3 (C-*

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10), 96.2 (C-6), 95.4 (C-8), 78.7 (C-2), 56.1 (4′-O<u>C</u>H$_3$), 42.5 (C-3). MS (ESI+, m/z): 340.1 [(M+Na)$^+$, 100 %]. HRMS-ESI m/z for $C_{16}H_{15}NO_6Na$ [M+Na]$^+$ calculated 340.0861 found 415.0852

(*S*,*E*)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one oxime (16): *The compound **16** was synthesized according to the general procedure in Section 2.6. Naringenin **5** (0.272 g, 1 mmol) was treated with hydroxylamine sulfate **11** (0.164 g, 1 mmol). **16** was isolated as a beige product (80.2%). M. M. 287.08 g.mol^{-1} $C_{15}H_{13}NO_5$. m_p: 232-233 °C. IR ν (cm^{-1}): 3535, 3310, 3107, 2832, 1626, 1601, 1520. ^{1}H NMR (400MHz, DMSO) δ (ppm) 12.14 (s, 1H, 5-OH), 11.23 (s, 1H, N-OH), 9.85 (s, 1H, 7-OH), 9.62 (s, 1H, 4′), 7.29 (dd, J = 12.4 & 8.4 Hz, 2H, H-2′ & H-6′), 6.79-6.76 (m, 2H, H-3′ & H-5′), 5.89-5.84 (m, 2H, H-6 & H-8), 5.43 (dd, J = 12.8 & 2.8 Hz, 1H, H-2), 3.25 (dd, J = 17.6 & 12.8 Hz, 1H, H-3^a), 2.80-2.65 (m, 1H, H-3^b). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 166.5 (C-5), 164.8 (C-7), 163.0 (C-9), 153.4 (C-4), 152.5 (C-4′), 129.6 (C-1′), 129.2 (C-2′ & C-6′), 116.3 (C-3′ & C-5′), 100.9 (C-10), 95.5 (C-6), 94.4 (C-8), 78.8 (C-2), 42.2 (C-3). MS (ESI+, m/z): 288.1 [(M+H)$^+$, 100%]. HRMS-ESI m/z for $C_{15}H_{14}NO_5$ [M+H]$^+$ calculated 288.1157 found 288.1043.*

(*S*,*E*)-1-phenyl-2-(2-phenylchroman-4-ylidene)hydrazine (19): *The compound **19** was synthesized according to the general procedure in Section 2.7. Flavanone **1** (0.224 g, 1 mmol) was treated with phenylhydrazine **17** (0.108 g, 1 mmol). **19** was isolated as a yellowish white product (95 %). M. M. 314.38 g.mol^{-1} $C_{21}H_{18}N_2O$. m_p: 188-190 °C. IR ν (cm^{-1}): 3207, 3032, 2938-2654, 1604, 1588, 1574, 1495, 1301, 1227. ^{1}H NMR (400MHz, DMSO) δ (ppm) 10.16 (s, 1H, N-H), 7.76 (d, J = 7.8 Hz, 1H, H-7), 7.59-7.50 (m, 1H, H-6), 7.42-7.35 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.28-7.24 (m, 2H, H-2′ & H-6′), 7.10-7.06 (m, 4H, H-8, H-3′, H-4′ & H-5′), 6.95-6.91 (m, 2H, H-4″ & H-5), 5.63 (dd, J = 12.7 & 2.7 Hz , 1H, H-2), 3.25-3.17 (m, 1H, H-3^a), 2.81 (dd, J = 16.8 & 2.7 Hz, 1H, H-3^b). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 161.0 (C-9), 145.3 (C-4), 138.8 (C-1″), 136.5 (C-1′), 129.0 (C-3″ & -5″), 128.6 (C-7), 128.5 (C-5), 126.6 (C-3′), 126.5 (C-5′), 126.3 (C-4′), 121.6 (C-2′), 121.5 (C-6′), 120.6 (C-4″), 118.0 (C-6), 114.4 (C-2″ & -6″), 112.6 (C-10), 111.9 (C-8), 78.8 (C-2), 43.4 (C-3). MS (ESI-, m/z): 313.4 [(M-H)$^-$, 100%]. HRMS-ESI m/z for $C_{21}H_{19}N_2O$ [M+H]$^+$ calculated 315.4534 found 315.4524.*

(*2S,3R,4R,5R,6S*)-2-(((*2S,3R,5S,6R*)-4,5-dihydroxy-2-(((*E*)-5-hydroxy-2-(4-hydroxyphenyl)-4-(2-phenylhydrazono)chroman-7-yl)oxy)-6-(hydroxymethyl)tetrahydro-*2H*-pyran-3-yl)oxy)-6-methyltetrahydro-*2H*-pyran-3,4,5-triol (21): *The compound **21** was synthesized according to the general procedure in Section 2.7. Naringin **3** (0.508 g, 1 mmol) was treated with phenylhydrazine **17** (0.108 g, 1 mmol). **21** was isolated as a brown product (86 %). M. M. 670.67 g.mol^{-1} $C_{33}H_{38}N_2O_{13}$. m_p: 92-93 °C. IR ν (cm^{-1}) 3470, 3273, 2960, 2863, 2400, 1635, 1614, 1519, 1497, 1446, 1373, 1251, 1167. ^{1}H NMR (400MHz, DMSO) δ (ppm) 12.01 (s, 1H, 5-OH), 10.23 (s, 2H, 4′-OH, N-H), 7.48-7.16 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.12-6.84 (m, 3H, H-4″, H-2′ & H-6′), 6.79-6.62 (m, 2H, H-3′ & H-5′), 6.11-*

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6.05 (m, 1H, H-8), 5.88 (s, 1H, H-6), 5.49-5.38 (m, 1H, H-2), 3.24-3.11 (m, 1H, H-3^{a}), 2.67 (dd, J = 17.7 & 2.8 Hz, 1H, H-3^{b}), 1.09-1.02 (m, 3H, 6^{Rhm}-CH$_3$). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 166.6 (C-7), 162.7 (C-5), 157.7 (C-9), 157.6 (C-4′), 145.4 (C-4 & C-1″), 128.8 (C-1′), 128.6 (C-3″ & C-5″), 128.1 (C-2′ & C-6′), 121.2 (C-4″), 115.0 (C-3′ & C-5′), 114.3 (C-2″ & C-6″), 103.1 (C-1^{Rhm}), 101.6 (C-1^{Glu}), 96.3 (C-10), 95.7 (C-6), 95.3 (C-8), 78.5 (C-2), 76.9 (C-2^{Glu}), 76.2 (C-5^{Glu}), 73.3 (C-3^{Glu}), 71.9 (C-5^{Rhm}), 70.6 (C-2^{Rhm}), 70.2 (C-4^{Rhm}), 69.3 (C-3^{Rhm}), 68.1 (C-4^{Glu}), 61.6 (C-6^{Glu}), 41.9 (C-3), 17.9 (C-6^{Rhm}). MS (ESI-, m/z): 669.2 [(M-H)$^-$, 100%]. HRMS-ESI m/z for $C_{33}H_{38}N_2O_{13}Na$ [M+Na]$^+$ calculated 693.1802 found 693.1804.

(*S*,*E*)-2-(3-hydroxy-4-methoxyphenyl)-4-(2-phenylhydrazono)chromane-5,7-diol (22): *The compound **22** was synthesized according to the general procedure in Section 2.7. Hesperetin **4** (0.302 g, 1 mmol) was treated with phenylhydrazine **17** (0.108 g, 1 mmol). **22** was isolated as a dark yellow product (89 %). M. M. 392.137 g.mol^{-1} $C_{22}H_{20}N_2O_5$. m$_p$: 194-196 °C. IR ν (cm^{-1}): 3450, 3204, 3002, 2939-2650, 1635, 1586, 1520, 1494, 1445, 1166. ^{1}H NMR (400MHz, DMSO) δ (ppm). 12.24 (s, 1H, 5-OH), 10.45 (s, 1H, 7-OH), 9.08 (s, 1H, 3′-OH), 8.96 (s, 1H, N-H), 7.28-7.24 (m, 5H, H-2″, H-3″, H-4″, H-5″ & H-6″), 6.94-6.89 (m, 3H, H-2′, H-5′ & H-6′), 5.88 (d, J = 2.6 Hz, 2H, H-6 & H-8), 5.37 (dd, J = 12.4 Hz & 3.2 Hz, 1H, H-2), 3.73 (s, 3H, 4′-OC<u>H</u>$_3$), 3.44-3.10 (m, 1H, H-3^{a}), 2.33 (dd, J = 16.7 Hz & 3.2 Hz, 1H, H-3^{b}). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 167.0 (C-5), 163.7 (C-7), 163.1 (C-9), 148.2 (C-4′), 146.7 (C-3′), 145.6 (C-4), 133.0 (C-1″), 131.3 (C-1′), 129.4 (C-3″ & C-5″), 122.0 (C-4″), 118.2 (C-6′), 114.7 (C-2″ & C-6″), 114.3 (C-2′), 112.3 (C-5′), 102.1 (C-10), 96.2 (C-6), 95.4 (C-8), 78.5 (C-2), 55.9 (4′-OCH$_3$), 42.3 (C-3). MS (ESI+, m/z): 415.1 [(M+Na)$^+$, 100 %]. HRMS-ESI m/z for $C_{22}H_{21}N_2O_5Na$ [M+Na]$^+$ calculated 415.0852 found 415.0845.*

(*S*,*E*)-2-(4-hydroxyphenyl)-4-(2-phenylhydrazono)chromane-5,7-diol (23): *The compound **23** was synthesized according to the general procedure in Section 2.7. Naringenin **5** (0.272 g, 1 mmol) was treated with phenylhydrazine **17** (0.108 g, 1 mmol). **23** was isolated as a dark yellow product (92 %). M. M. 362.38 g.mol^{-1} $C_{21}H_{18}N_2O_4$. m$_p$: 190-192 °C. IR ν (cm^{-1}) 3364, 3206, 3031, 3003-2655, 1627, 1599, 1587, 1495, 1235, 1156. ^{1}H NMR (400MHz, DMSO) δ (ppm) 12.12 (s, 1H, 5-OH), 10.24 (s, 3H, N-H, 7-OH, 4′-OH), 7.31-7.25 (m, 4H, H-2″, H-3″, H-5″ & H-6″), 6.98-6.92 (m, 3H, H-2′, H-6′ & H-4″), 6.79-6.78 (m, 2H, H-3′ & H-5′), 5.89 (s, 2H, H-6 & H-8), 5.42 (dd, J = 12.3 & 2.8 Hz, 1H, H-2), 3.29-3.25 (m,1H, H-3^{a}), 2.66 (dd, J = 16.8 & 2.8 Hz, 1H, H-3^{b}). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 166.5 (C-5), 163,2 (C-7), 162.6 (C-9), 157.5 (C-4′), 145.3 (C-4 & C-1″), 128.7 (C-1′), 128.5 (C-3″ & C-5″), 128.0 (C-2′ & C-6′), 121.1 (C-4″), 114.9 (C-3′ & C-5′), 114.2 (C-2″ & C-6″), 101.4 (C-10), 95.5 (C-6), 94.7 (C-8), 78.1 (C-2), 41.7 (C-3). MS (ESI-, m/z): 361.1 [(M-H)$^-$, 100%]. HRMS-ESI* m/z for $C_{21}H_{19}N_2O_4$ [M+H]$^+$ calculated 363.1345 found 363.1345.

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(*S,E*)-1-(4-chlorophenyl)-2-(2-phenylchroman-4-ylidene)hydrazine (24): *The compound **24** was synthesized according to the general procedure in Section 2.7. Flavanone **1** (0.224 g, 1 mmol) was treated with p-chloro-phenylhydrazine, HCl **18** (0.178 g, 1 mmol). **24** was isolated as a brown product (85%). M. M. 348.10 g.mol^{-1} $C_{21}H_{17}ClN_2O$. m_p: 132-133 °C. IR ν (cm^{-1}) 3352, 3034, 2887, 1597, 1494, 1451. ^{1}H NMR (400MHz, DMSO) δ (ppm) 9.52 (s, 1H, N-H), 8.00 (dd, J = 1.5 Hz, 1H, H-7), 7.60-7.52 (m, 2H, H-6 & H-8), 7.45-7.35 (m, 3H, H-2′, H-4′, H-6′), 7.23-7.18 (m, 4H, H-2″, H-3″, H-5″ & H-6″), 7.09-7.06 (m, 1H, H-5), 7.01-6.91 (m, 2H, H-3′ & H-5′), 5.20 (dd, J = 12.0 & 2.7 Hz, 1H, H-2), 3.28-3.21 (m, 1H, H-3^a), 2.70 (dd, J = 17.0 & 2.7 Hz, 1H, H-3^b). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 158.9 (C-9), 146.6 (C-4), 141.2 (C-1″), 138.3 (C-1′), 131.6 (C-7), 131.2 (C-5), 129.6 (C-3″ & C-5″), 128.9 (C-3′ & C-5′), 127.7 (C-4″), 127.4 (C-4′), 127.1 (C-2′ & C-6′), 120.4 (C-6), 117.7 (C-2″ & C-6″), 117.3 (C-10), 114.1 (C-8), 78.8 (C-2), 43.4 (C-3). MS (ESI+, m/z): 349.1 [(M+H)$^+$, 50%]. HRMS-ESI m/z for $C_{21}H_{18}ClN_2O$ [M+H]$^+$ calculated 349.1108 found 349.1122.*

***(2S,3R,4R,5R,6S)*-2-(((2S,3R,5S,6R)-2-(((*E*)-4-(2-(4-chlorophenyl)hydrazono)-5-hydroxy-2-(4-hydroxyphenyl)chroman-7-yl)oxy)-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-*2H*-pyran-3-yl)oxy)-6-methyltetrahydro-*2H*-pyran-3,4,5-triol (26):** *The compound **26** was synthesized according to the general procedure in Section 2.7. Naringin **3** (0.508 g, 1 mmol) was treated with p-chloro-phenylhydrazine, HCl **18** (0.178 g, 1 mmol). **26** was isolated as a brown product (68 %). M. M. 704.19 g.mol^{-1} $C_{33}H_{37}ClN_2O_{13}$. m_p: 110-111 °C. IR ν (cm^{-1}) 3389, 3244, 2976-2870, 1613, 1518, 1491, 1339, 1248, 1158, 885, 830. ^{1}H NMR (400MHz, DMSO) δ (ppm) 10.43 (s, 1H, N-H), 7.53 (d, J = 8.8 Hz, 1H, H-2′), 7.39 (d, J = 8.8 Hz, 1H, H-6′), 7.30-6.91 (m, 4H, H-2″, H-3″, H-5″, H-6″), 6.76 (d, J = 8.8 Hz, 2H, H-3′ & H-5′), 5.87 (s, 2H, H-6 & H-8), 5.39 (dd, J = 12.6 & 2.8 Hz, 1H, H-2), 3.14-3.10 (m, 1H, H-3^a), 2.63 (dd, J = 17.2 & 2.9 Hz, 1H, H-3^b).1-12-1.09 (m, 3H, H-6^{Rhm}). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 167.8 (C-7), 165.3 (C-5), 160.4 (C-9), 157.3 (C-4′), 145.4 (C-4), 141.3 (C-1″), 128.8 (C-1′), 128.6 (C-3″ & C-5″), 127.9 (C-4″), 127.3 (C-2′ & C-6′), 116.1 (C-2″ & C-6″), 115.2 (C-3′ & C-5′), 102.3 (C-1^{Rhm}), 100.5 (C-1^{Glu}), 95.8 (C-10), 95.5 (C-6), 94.2 (C-8), 78.9 (C-2), 77.8 (C-2^{Glu}), 76.4 (C-5^{Glu}), 74.1 (C-3^{Glu}), 72.6 (C-5^{Rhm}), 71.5 (C-2^{Rhm}), 70.1 (C-4^{Rhm}), 69.9 (C-3^{Rhm}), 69.0 (C-4^{Glu}), 60.5 (C-6^{Glu}), 42.5 (C-3), 17.7 (C-6^{Rhm}). MS (ESI-, m/z): 703.1 [(M-H)$^-$, 100%]. HRMS-ESI m/z for $C_{33}H_{37}ClN_2O_{13}Na$ [M+Na]$^+$ calculated 727.0923 found 727.0918.*

(*S,E*)-4-(2-(4-chlorophenyl)hydrazono)-2-(3-hydroxy-4-methoxyphenyl) chromane-5,7-diol (27): *The compound **27** was synthesized according to the general procedure in Section 2.7. Hesperetin **4** (0.302 g, 1 mmol) was treated with p-chloro-phenylhydrazine, HCl **18** (0.178 g, 1 mmol). **27** was isolated as a brown product (85 %). M. M. 426.85 g.mol^{-1} $C_{22}H_{19}ClN_2O_5$. m_p: 202-204 °C. IR ν (cm^{-1}) 3374, 3208, 2938-2688, 1620, 1584, 1493, 1441, 1303, 1168, 1097, 865. ^{1}H NMR (400MHz, DMSO) δ (ppm) 12.08 (s, 1H, 5-OH), 10.39 (s, 2H, 7-OH, N-H), 7.31 (d, J = 8.7 Hz, 2H, H-3″ & H-5″), 7.00 (d,*

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J = 8.7 Hz, 2H, H-2″& H-6″), 6.92-6.84 (m, 3H, H-2′, H-5′& H-6′), 5.92 (d, J = 5.3 Hz, 2H, H-6 & H-8), 5.40 (dd, J = 12.4 & 2.8 Hz, 1H, H-2), 3.75 (s, 3H, 4′-OC$\underline{H}_3$), 3.16 (dd, J = 17.1 & 12.4 Hz, 1H, H-3^a), 2.68 (dd, J = 17.1 & 2.8 Hz, 1H, H-3^b). ^{13}C NMR (100.6 MHz, DMSO) δ (ppm) 166.5 (C-5), 163.1 (C-7), 162.4 (C-9), 147.5 (C-4′), 146.1 (C-3′), 144.2 (C-4), 130.8 (C-1″), 129.3 (C-1′), 128.3 (C-3″& C-5″), 124.7 (C-4″), 117.3 (C-6′), 115.8 (C-2″& C-6″), 113.7 (C-2′), 111.6 (C-5′), 101.4 (C-10), 95.5 (C-6), 94.7 (C-8), 77.82 (C-2), 55.32 (4′-O$\underline{C}$H$_3$), 41.71 (C-3). MS (ESI+, m/z): 427.1 [(M+H)$^+$, 20%]. HRMS-ESI m/z for $C_{22}H_{20}ClN_2O_5$ [M+H]$^+$ calculated 427.1028 found 427.1024.

(*S*,*E*)-4-(2-(4-chlorophenyl)hydrazono)-2-(4-hydroxyphenyl)chromane-5,7-diol (28): *The compound **28** was synthesized according to the general procedure in Section 2.7. Naringenin **5** (0.272 g, 1 mmol) was treated with p-chloro-phenylhydrazine, HCl **18** (0.178 g, 1 mmol). **28** was isolated as a yellowish white product (70 %). M. M. 396.83 g.mol^{-1} $C_{21}H_{17}ClN_2O_4$. **m$_p$**: 174-176 °C. **IR** ν (cm^{-1}): 3350, 3212, 3033, 2910-2697, 1626, 1598, 1494, 1461, 1309, 1161, 888. **^{1}H NMR** (400MHz, DMSO) δ (ppm) 12.18 (s, 1H, 5-OH), 10.83 (s, 1H, 7-OH), 10.16 (s, 1H, N-H), 9.62 (s, 1H, 4′-OH), 7.35-7.29 (m, 4H, H-2″, H-3″, H-5″& H-6″), 6.95 (d, J = 8.8 Hz, 2H, H-2′& H-6′), 6.78 (d, J = 8.8 Hz, 2H, H-3′& H-5′), 5.87 (s, 2H, H-6 & H-8), 5.42 (dd, J = 12.8 & 2.8 Hz, 1H, H-2), 3.25 (dd, J = 17.2 & 12.8 Hz, 1H, H-3^a), 2.66 (dd, J = 17.2 & 2.8 Hz, 1H, H-3^b). **^{13}C NMR** (100.6 MHz, DMSO) δ (ppm) 166.4 (C-5), 163.2 (C-7), 162.9 (C-9), 157.5 (C-4′), 144.2 (C-4), 132.8 (C-1″), 129.6 (C-1′), 128.5 (C-3″& C-5″), 128.3 (C-4″), 128.0 (C-2′& C-6′), 115.7 (C-2″& C-6″), 114.9 (C-3′& C-5′), 101.5 (C-10), 95.5 (C-6), 94.7 (C-8), 78.1 (C-2), 41.7 (C-3). **MS** (ESI+, m/z): 419.3 [(M+Na)$^+$, 100 %]. **HRMS-ESI** m/z for $C_{21}H_{17}ClN_2Na$ [M+Na]$^+$ calculated 419.3891 found 415.3901.*

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