Synthesis of Novel Flavonoid Derivatives as Potential HIV- Integrase Inhibitors

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Eighteen novel flavonoid derivatives – substituted chalcones and flavones were synthesized and characterized by using NMR, IR, UV/Vis spectroscopy and elemental analysis. The target compounds were achieved by using a sequence of simple and effective reactions starting from phloroglucinol. The initial hydroxyl groups were protected by methylation and in the final flavones the 5-OH group was selectively demethylated by means of $AlBr_3$. 5-methoxy flavones exhibit a strong fluorescence, which was quenched after the removal of the methyl group.

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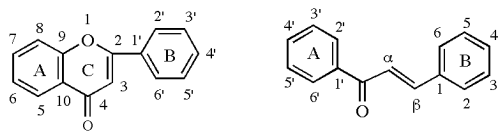
Introduction.

The current HIV-1 chemotherapy is based mainly on two of the enzymes that are important for the viral replication – HIV-1 reverse transcriptase and HIV-1 protease. Although very effective, the available medications cause significant adverse effects. The observed constant mutation of the virus is another reason to look for other potential targets for blocking the viral life cycle. HIV-1 integrase can be a promising candidate for this purpose. This enzyme is required for the function of the virus but it does not have an analog in the host cells. The integration of the virus into the host DNA is a two-step process. First, a 3' processing of the viral DNA occurs where the two terminal nucleotides are removed from the 3' end of the viral DNA followed by a transesterification reaction connecting the viral DNA to the 5' ends of the target DNA [1,2]. After the amino acid sequence and the structure of the catalytic domain of the HIV-1 integrase were revealed [3,4], there was an excellent basis for structure-activity relationship studies as well as for more successful design of potential inhibitors. Together with the nucleotide and peptide-based inhibitors there is a number of natural products, such as caffeic acid phenethyl ester (CAPE) [5,6], flavones and flavonoids [7-9] and s.o., showing promising anti-viral activity.

Scheme 1



Structure and numbering of flavones and chalcones.

The basic structure and numbering of flavones and chalcones is shown on Scheme 1. The synthetic, biochemical and theoretical studies on flavonoids, conducted so far, show a clear activity trend based on the substitution pattern, charge distribution and sterical characteristics. Polyhydroxylated flavones, such as quercetine, show significant activity, especially those with two neighboring hydroxyl groups [5,10,11]. Other compounds, such as Baicalein and its derivative Baicalin, have been found to inhibit HIV-replication by inhibiting the activity of the HIV-reverse transcriptase (RT) [12-14]. The presence of a methoxy substituent in position 6 reduces the activity [5]. Flavonoids are known to inhibit protein kinases by mimicking the adenine moiety of ATP where the 5-OH plays a critical role [15,16]. Very successful combination is the presence of a substituent in position 8 and a hydroxyl group in position 5 in the flavone moiety. The rationale for the presumed biological activity of the chalcones is based mainly on steric factors – the syn mutual disposition of the C=O and C=C groups is considered favorable for HIV-1 integrase binding. However, the substitution pattern may also play a role, especially the presence of hydroxyl groups [17].

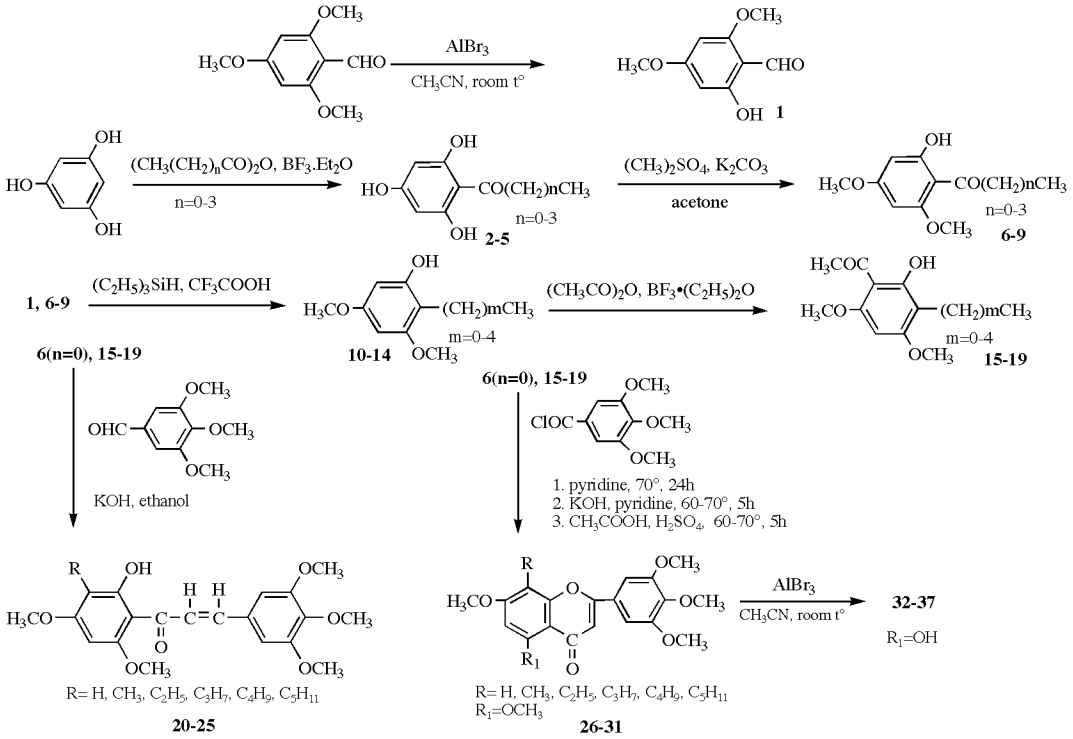
The substituted chalcones and flavones reported in this paper were designed following the current most promising trends in structure-activity relationship. We discuss the synthesis and the structural characteristics of the compounds as well as their absorption and emission properties.

Results and Discussion.

Phloroglucinol was selected as a starting material for the synthesis of both chalcones and flavones (Scheme 2). It was acylated with the corresponding acidic anhydrides in presence of BF_3•Et_2O [18] to achieve compounds **2-5**. The corresponding alkyl aryl ketone was obtained as a main product, however, some amount of a diketone, as well as *O*-alkylated compounds were present in the reaction mixture that required separation of the products by column chromatography. Methylation of the ketones **2-5** [19] with excess of dimethyl sulfate resulted in di- or trimethoxy compounds depending on the reaction time. Usually, the dimethoxy compounds **6-9** were obtained as a single product after 30-40 minutes reflux.

2,4-Dimethoxy-6-hydroxybenzaldehyde **1** was selected as a starting material for the synthesis of 8-methyl flavones and 3'-methyl chalcones correspondingly. Compound **1** was obtained by demethylation of 2,4,6-trihydroxybenzaldehyde in presence of $AlBr_3$ in acetonitrile.

Scheme 2



Synthesis of substituted chalcones and flavones

The aldehyde **1** and the ketones **6-9** were reduced by means of $(C_2H_5)_3SiH$ in CF_3COOH to give the corresponding 2-alkyl-3,5-dimethoxyphenoles **10-14** [20]. 1-(2,4,6-Trimethoxyphenyl)alkanones, used by us in additional studies [21] were reduced within 2-5 hours at room temperature whereas the dimethoxy analogues **1**, **6-9** with an 2-OH group require more time. The possible reason for this might be the hydrogen bond between the hydroxyl hydrogen and the carbonyl group. Increasing the reaction temperature resulted in formation of side products, probably alkylated compounds, which significantly reduces the reaction yield. Acylation of **10-14** with acetic anhydride gave the appropriately substituted precursors **15-19** both for chalcone and flavone formation.

The increased interest to the biologically active flavones lead to development of many different approaches to their synthesis [22-31]. In our case best results in terms of reaction yield, isolation and purification were achieved by applying the classical Baker-Venkataraman synthesis [11] using the already synthesized substituted ketones **15-19** and 3,4,5–trimethoxy benzoyl chloride. The simple 3-step procedure resulted in 8-alkyl substituted flavones **26-31**.

5-OH Flavones **32-37** were achieved by treating **26-31** with aluminum bromide in acetonitrile at room temperature which demethylates selectively the 5-methoxy group.

The corresponding chalcones were synthesized by Claisen condensation between the substituted acetophenone and 3,4,5–trimethoxybenzaldehyde in presence of KOH in ethanol with average yields [25].

For comparison of the biological activity, two non-alkylated compounds (**20, 26**) were synthesized as well.

The ^{1}H-NMR signals for the methoxy groups in the flavones **26-31** appeared as four singlets in the area 3.90 – 3.99 ppm with total integral corresponding to 15 hydrogen atoms. In the ^{1}H-NMR spectra of 5-OH flavones **32-37** three singlets for methoxy protons were observed with total integral corresponding to 12 hydrogen atoms. The 3-H signals appeared in fairly strong field at ~6.55 ppm. Chalcones **20-25** exhibited two sharp and one broad singlet for 15 methoxy protons at 3.82-3.90 ppm. The two vicinal ethylene protons gave a double doublet in the area 7.60-7.80 ppm.

In the IR spectra of all compounds there are several characteristic bands that can be identified. The carbonyl stretching vibrations of the chalcones and 5-methoxyflavones exhibit an intensive peak at 1628-1638 cm^{-1}. The removal of the 5-methoxy group causes shifting of this signal to ~1600 cm^{-1}. The double bond stretching vibrations appear as a low intensity signal next to the band owing to the aromatic stretching vibrations at 1580-1590 cm^{-1}. The C-O stretching vibrations owing to the presence of the ether groups can be observed between 1120-1130 cm^{-1}.

The absorption and emission properties of the flavones and chalcones are of interest for the spectroscopists for

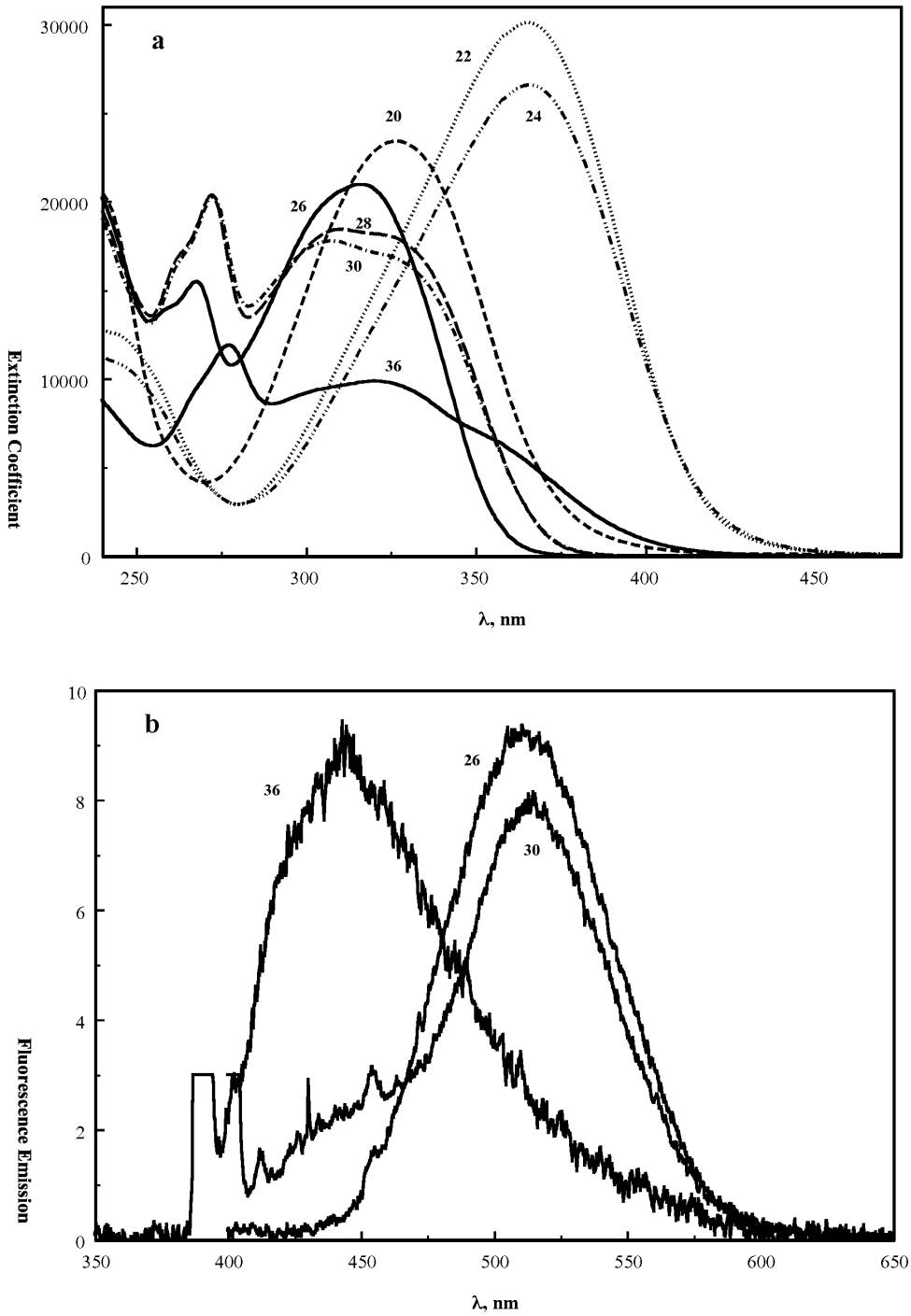


Figure 1. a) Absorption spectra of selected chalcones and flavones. b) Emission spectra of representative flavones.

many years [32-36]. Figure 1 illustrates some spectroscopic characteristics of the newly synthesized compounds described in this paper. Flavones exhibit a broad absorption band at ~ 310 nm with molar absorptivity ~ 20000. Addition of a substituent in position 8 broadens additionally the shape of the absorption band and causes slight bathochromic shift and lower molar absorptivity. Increasing the number of the methylene groups in the substituent obviously does not affect much the absorption properties – there is only a slight difference between 8-ethyl and 8- butyl compounds. 5-hydroxyflavone 36 exhibits significantly lower molar absorptivity compared with its methoxy analog 28. The 3'-H chalcone shows a broad symmetrical absorption band with maximum at

325 nm. The absorption spectra of 3'– alkyl substituted chalcones are bathochromicaly shifted (~ 50 nm) with respect to the 3'-H chalcones and flavones and again the number of the methylene groups in position 3' does not affect significantly the shape and intensity of the absorption band.

5-methoxyflavones exhibited intense fluorescence at 520 nm (λ_{ex} 370 nm). Removal of the methoxy group caused a hypsochromic shift of the fluorescence maximum that appeares at 450 nm.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer FTIR 1430 spectrophotometer, using KBr pellets. ^{1}H nmr and ^{13}C nmr spectra were obtained with a Brucker HX-300 spectrometer and the chemical shifts were reported as parts per million (ppm) downfield. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Column chromatography and a Chromatotrom 8924 (Harrison Research) instrument were used for purification of the compounds. Davisil Chromatographic Silicagel (200-425 mesh) was used for column chromatographic separations and Silicagel Merck, TLC grade 7749 with gypsum binder and fluorescent indicator was used for preparation of the Chromatotron rotors. All reactions and purification procedures were monitored using Whatman TLC plates with fluorescent indicator. All solvents and chemicals were purchased from Fisher Scientific Company and Aldrich Chemical Company.

General Acylation Procedure [18].

The compound to be acylated was dissolved in equimolar amount of the corresponding acidic anhydride. BF_3•Et_2O was added dropwise in 2.5 times molar excess. The reaction mixture warms up to 50-60 °C, after which it cools down to room temperature. It was stirred at room temperature for 24-48 hours. Then water was added and the reaction mixture was extracted with ethyl acetate. After evaporation of the solvent the raw material was purified by column chromatography on silicagel using hexane:ethyl acetate 3:2 as an eluent. Using this procedure, compounds **2-5** were obtained in 70-80% yield. The corresponding diketone was isolated as a minor product in 5-10% yield.

Compounds **15-19** were synthesized using the same procedure and were isolated as follows: The raw material was dissolved in hot ethanol and water was added to the hot solution until turbidity appears. Then it was cooled slowly to room temperature and the precipitated material was collected and dried in the air. The yield of the pure compounds was 60-70%.

General Methylation Procedure [19].

Anhydrous K_2CO_3 (2 times excess for each hydroxyl group) was suspended in acetone. Ketones **2-5** were dissolved in the mixture and $(CH_3)_2SO_4$ was added (2 times excess for each hydroxyl group). The reaction mixture was heated to 50-60 °C for 30 minutes. After that time, the starting material is completely consumed and the corresponding 1-(2-hydroxy-4,6-dimethoxyphenyl)alkanone **6-9** was formed as a single product. The acetone was filtered, the solid residue washed with hot acetone and the solvent evaporated. The crude product was recrystallyzed from ethanol. Yield 80-90%.

General Reduction Procedure [20].

Compounds **1, 6-9** were dissolved in 20 times molar excess of CF_3COOH and 2.5 times excess of $(C_2H_5)_3SiH$ were added. The reaction mixture was stirred 24-48 hours at room temperature. The reaction was followed by TLC on silicagel with hexane:ethyl acetate 3:1 as a mobile phase and was carried out until the starting material was completely consumed. After that water was added and the reaction mixture was extracted with diethyl ether. The solvent was evaporated under vacuum and the crude product was acylated using the General Acylation Procedure described above without further purification.

Synthesis of the Chalcones **20-25** [25].

The corresponding ketone was mixed with an eqimolar amount of 3,4,5 – trimethoxybenzaldehyde in ethanol. Water KOH (5 mL 50%) was added and the reaction mixture was heated at 50-60 °C for 5 hours. The product precipitated after cooling as yellow crystals which were collected, recrystallized from ethanol and finally purified on Chromatotron using hexane:ethyl acetate 3:2 as an eluent. Yield 60-70%.

Synthesis of Flavones **26-31** [11].

Compounds **6, 15-19** were mixed with 1.2 times excess of 3,4,5–trimethoxy benzoyl chloride in pyridine. The reaction mixture was heated at 70-75 °C for 12 hours, then poured on ice containing 10% HCl. The precipitate formed was collected, dried in the air and dissolved in pyridine in presence of powdered KOH. The reaction was carried out for 5 hours at 60-70 °C, then the mixture poured into ice-5%HCl, the yellow precipitate was collected filtration and dried in air. Then the crude product was dissolved in acetic acid containing 0.5 ml concentrated H_2SO_4 and was heated at 60-70 °C, then pored into ice -$NaHCO_3$ mixture. The product was collected by filtration and recystallized from ethanol. The pure flavone was obtained by purification on Chromatotrone with CH_2Cl_2:MeOH 8:1 as eluent.

General Demethylation Procedure [11].

This procedure was used to obtain the starting 2-hydroxy-4,6-dimethoxybenzaldehyde **1** as well as hydroxyflavones **32-37**. The corresponding compound was suspended in acetonitrile and 3 times molar excess of $AlBr_3$ was added. The mixture was stirred at room temperature for 5 hours. Water was added and the reaction mixture was extracted with CH_2Cl_2, the solvent evaporated under vacuum to yield an oily substance that crystallized after several hours in the air. The hydroxyflavones **32-37** were purified on a Chromatotrone using hexane:ethyl acetate 3:2 as an eluent. All 5-OH flavones exhibit very poor solubility in most common organic solvents. The average yield of the demethylated flavones was 20%. Compound **1** was recrystallized from ethanol and used in the next reaction step.

1-(2'-Hydroxy-4',6'-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**20**).

This compound was obtained as pale yellow needles after recrystallization from ethanol with 70% yield, mp 181-182 °C; ^{1}H nmr (deuteriochloroform): δ 3.82, 3.88, 3.89 (s, 15H, CH_3O), 5.94-5.95 (d, J=2.4 Hz, 1H, Ar), 6.09-6.10 (d, J=2.4Hz, 1H, Ar), 6.82(s, 2H, Ar), 7.65-7.81(dd, J=15.6 Hz, 2H, CH=CH-), 14.25

(s, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 55.5 (*C*H$_3$O at C-4'), 55.7 (*C*H$_3$O at C-6'), 56.0 (*C*H$_3$O at C-3 and C-5), 60.9 (CH$_3$O at C-4), 91.1 (C-5'), 93.8 (C-3'), 105.4 (C-2 and C-6), 106.2 (C-1'), 126.8 (α-*C*H=), 131.0 (C-1), 140.0 (C-4), 142.3 (β-*C*H=), 153.3 (C-3 and C-5), 162.3 (C-6'), 166.1 (C-2'), 168.3 (C-4'), 192.2 (-*C*=O). ir (potassium bromide): 1638 (C=O), 1579 (C=C ar), 1575 (C=C), 1122 (C-O) cm^{-1}.

Anal. Calcd. for $C_{20}H_{22}O_7$ (374.38): C, 64.16; H, 5.92. Found: C, 64.28, H, 6.15.

1-(2'-Hydroxy-4',6'-dimethoxy-3'-methylphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**21**).

This compound crystallized from the reaction mixture as pale yellow crystals. It was recrystallized from ethanol and finally purified on a Chromatotron instrument thus giving 60% product; mp 188-189 °C; ^{1}H nmr (deuteriochloroform): δ 2.03 (s, 3H, -CH$_3$), 3.88, 3.89, 3.90, 3.93 (s, 15H, CH$_3$O), 5.99 (s, 1H, Ar), 6.82 (s, 2H, Ar), 7.64-7.80 (dd, J= 15.6 Hz, 2H), 14.04 (s, 1H, OH). ^{13}C nmr (deuteriochloroform): δ 7.2 (*C*H$_3$ at C-3'), 55.4 (*C*H$_3$O at C-4'), 55.7 (*C*H$_3$O at C-6'), 56.1 (*C*H$_3$O at C-3 and C-5), 60.9 (*C*H$_3$O at C-4), 86.3 (C-5'), 105.4 (C-2 and C-6), 106.0 (C-1'), 106.2 (C-3'), 127.2 (α-*C*H=), 131.2 (C-1), 139.9 (C-4), 141.9 (β-*C*H=), 153.3 (C-3 and C-5), 160.9 (C-6'), 163.5 (C-2'), 164.2 (C-4'), 192.7 (-*C*=O). ir (potassium bromide): 1631 (C=O), 1580 (C=C ar), 1572 (C=C), 1125 (C-O) cm^{-1}.

Anal. Calcd. for $C_{21}H_{24}O_7$ (388.15): C, 64.94; H, 6.23. Found: C, 64.85, H, 6.33.

1-(3'-Ethyl-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**22**).

The compound was obtained after concentrating the reaction mixture under vacuum and addition of water as yellow oil, which crystallized from ethanol; yield 60%. mp 172-173 °C; ^{1}H nmr (deuteriochloroform): δ 1.04-1.10 (t, J=7.3 Hz, 3H, -CH$_2$CH$_3$), 2.58-2.65 (q, J=7.3 Hz, 2H, -CH$_2$CH$_3$), 3.89, 3.90, 3.91, 3.94 (s, 15H, CH$_3$O), 6.00 (s, 1H, Ar), 6.84 (s, 2H, Ar), 7.66-7.80 (dd, J=15.0 Hz, 2H, -CH=CH-), 9.80 (s, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 13.4 (CH$_3$CH$_2$ at C-3'), 15.5 (CH$_3$*C*H$_2$ at C-3'), 55.4 (*C*H$_3$O at C-4'), 55.7 (*C*H$_3$O at C-6'), 56.0 (*C*H$_3$O at C-3 and C-5), 60.9 (*C*H$_3$O at C-4), 86.4 (C-5'), 105.4 (C-2 and C-6), 106.3 (C-1'), 112.4 (C-3'), 127.3 (α-*C*H=), 131.2 (C-1), 139.9 (C-4), 141.9 (β-*C*H=), 153.3 (C-3 and C-5), 161.0 (C-6'), 163.3 (C-2'), 164.0 (C-4'), 192.7 (-*C*=O). ir (potassium bromide): 1635 (C=O), 1582 (C=C), 1559 (C=C ar), 1128 (C-O) cm^{-1}.

Anal. Calcd. for $C_{22}H_{26}O_7$ (402.17): C, 65.66; H, 6.51. Found: C,65.58, H, 6.60.

1-(2'-Hydroxy-4',6'-dimethoxy-3'-propylphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**23**).

The compound was obtained as yellow oil after addition of water and concentration of the reaction mixture under vacuum. The oil was dissolved in ethanol and the yellow precipitate was collected; yield 65%. mp 171-172 °C; ^{1}H nmr (deuteriochloroform): δ 0.87- 0.92 (t, J=7.3 Hz, 3H, -CH$_2$CH$_2$CH$_3$), 1.45-1.54 (m, 2H, CH$_2$CH$_2$CH$_3$), 2.52-2.58 (t, J=7.3 Hz, 2H, CH$_2$CH$_2$CH$_3$), 3.85, 3.86, 3.90 (s, 15H, CH$_3$O), 5.98 (s, 1H, Ar), 6.82 (s, 2H, Ar), 7.61-7.76 (dd, J=15.6 Hz, 2H, -CH=CH-), 13.93 (s, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 14.1 (CH$_3$CH$_2$CH$_2$ at C-3'), 22.1 (CH$_3$CH$_2$*C*H$_2$ at C-3'), 24.2 (CH$_3$*C*H$_2$CH$_2$ at C-3'), 55.4 (*C*H$_3$O at C-4'), 55.7 (*C*H$_3$O at C-6'), 56.1 (*C*H$_3$O at C-3 and C-5), 60.9 (*C*H$_3$O at C-4), 86.3 (C-5'), 105.4 (C-2 and C-6), 106.2 (C-1'), 110.9 (C-3'), 127.3 (α-*C*H=), 131.2 (C-1), 139.9 (C-4), 141.8 (β-*C*H=), 153.3 (C-3 and C-5), 161.0 (C-6'), 163.6 (C-2'), 164.2 (C-4'), 192.7 (-*C*=O).ir (potassium bromide): 1628 (C=O), 1579 (C=C ar), 1555 (C=C), 1131 (C-O) cm^{-1}.

Anal. Calcd. for $C_{23}H_{28}O_7$ (416.18) C, 66.33; H, 6.78. Found: C, 66.06; H,6.87.

1-(3'-Butyl-2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**24**).

Compound partially crystallized after cooling the reaction mixture to room temperature. The rest of it was recovered after partial evaporation of the liquid. Crystallized from ethanol giving yellow crystals; yield 62%; mp 149-150 °C; ^{1}H nmr (deuteriochloroform): δ 0.84-0.95 (t, J=7.3 Hz, 3H, CH$_2$CH$_2$CH$_2$CH$_3$), 1.30-1.5 (m, 4H, CH$_2$CH$_2$CH$_2$CH$_3$), 3.82, 3.86, 3.87, 3.88, 3.92 (s, 15H, CH$_3$O), 5.97 (s, 1H, Ar), 6.81 (s, 2H, Ar), 7.63-7.78 (dd, J=15.6 Hz, 2H,-CH=CH-), 13.9 (s, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 14.1 (*C*H$_3$CH$_2$CH$_2$CH$_2$ at C-3'), 22.7 (CH$_3$CH$_2$*C*H$_2$CH$_2$ at C-3'), 23.0 (CH$_3$*C*H$_2$CH$_2$CH$_2$ at C-3'), 31.7 (CH$_3$CH$_2$CH$_2$*C*H$_2$ at C-3'), 55.5 (*C*H$_3$O at C-4'), 55.7 (*C*H$_3$O at C-6'), 56.0 (*C*H$_3$O at C-3 and C-5), 60.9 (*C*H$_3$O at C-4), 86.4 (C-5'), 105.4 (C-2 and C-6), 106.3 (C-1'), 109.8 (C-3'), 127.4 (α-*C*H=), 131.2 (C-1), 139.9 (C-4), 141.8 (β-*C*H=), 153.3 (C-3 and C-5), 161.0 (C-6'), 163.5 (C-2'), 164.2 (C-4'), 192.7 (-*C*=O). ir (potassium bromide): 1628 (C=O), 1578 (C=C ar), 1570 (C=C), 1132 (C-O) cm^{-1}.

Anal. Calcd. for $C_{24}H_{30}O_7$(430.20): C, 66.96; H, 7.02. Found: C,66.56; H,7.10.

1-(2'-Hydroxy-4',6'-dimethoxy-3'-pentylphenyl)- 3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**25**).

After evaporation of the reaction mixture, yellow oil was collected and dissolved in ethanol. Yellow crystals with 65% yield; mp 145-146 °C; ^{1}H nmr (deuteriochloroform): δ 0.85-0.90 (t, J=6.7 Hz, 3H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.29-1.49 (m, 6H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.54-2.59 (t, J= 7.3 Hz, 2H, CH$_2$CH$_2$-CH$_2$CH$_2$CH$_3$), 3.88, 3.89, 3.92 (s, 15H, CH$_3$O), 7.63-7.79 (dd, J=15.3, 2H, CH=CH-), 13.9 (s, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 14.1 (*C*H$_3$CH$_2$CH$_2$CH$_2$CH$_2$ at C-3'), 22.2 (CH$_3$CH$_2$-*C*H$_2$CH$_2$CH$_2$ at C-3'), 22.6 (CH$_3$*C*H$_2$CH$_2$CH$_2$CH$_2$ at C-3'), 28.7 (CH$_3$CH$_2$CH$_2$CH$_2$*C*H$_2$ at C-3'), 31.9 (CH$_3$*C*H$_2$CH$_2$*C*H$_2$CH$_2$ at C-3'), 55.5 (*C*H$_3$O at C-4'), 55.7 (*C*H$_3$O at C-6'), 56.1 (*C*H$_3$O at C-3 and C-5), 60.9 (*C*H$_3$O at C-4), 86.4 (C-5'), 105.4 (C-2 and C-6), 106.4 (C-1'), 111.3 (C-3'), 127.4 (α-*C*H=), 131.2 (C-1), 139.9 (C-4), 141.9 (β-*C*H=), 153.4 (C-3 and C-5), 161.0 (C-6'), 163.5 (C-2'), 164.2 (C-4'), 192.8 (-*C*=O). ir (potassium bromide): 1629 (C=O), 1578 (C=C ar), 1570 (C=C), 1132 (C-O) cm^{-1}.

Anal. Calcd. for $C_{25}H_{32}O_7$ (444.21): C, 67.55; H, 7.26. Found: C, 67.57, H, 7.42.

5,7-Dimethoxy-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**26**).

The dark brown precipitate obtained from the mother liquid was first recrystallized from ethanol to give 50% yield of a pale brownish solid. mp198-199 °C; ^{1}H nmr (deuteriochloroform): δ 3.90, 3.91, 3.93, 3.94 (s, 15 H, -CH$_3$O), 6.36-6.37 (d, J=2.4 Hz, 1H, Ar), 6.55-6.56 (d, J=2.4 Hz, 1H, Ar), 6.66 (s, 1H, O=C-CH=), 7.06 (s, 2H, Ar); ^{13}C nmr (deuteriochloroform): δ 55.7 (*C*H$_3$O at C-7), 56.2 (*C*H$_3$O at C-3'+C5'), 56.3 (*C*H$_3$O at C-5), 60.9 (*C*H$_3$O at C-4'), 92.8 (C-8), 96.1 (C-6), 103.2 (C2'+C6'), 108.6 (C-3), 109.0 (C-10), 126.6 (C-1'), 140.7 (C-4'), 153.4

(C-3'+C-5'), 159.7 (C-9), 164.0 (C-7), 160.4 (C-2), 160.7 (C-5), 177.5 (C-4). ir (potassium bromide): 1638 (C=O), 1604 (C=C ar), 1590 (C=C), 1127 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{20}H_{20}O_7$ (372.12): C, 64.51; H, 5.41. Found: C, 64.19; H, 5.54.

5,7-Dimethoxy-8-methyl-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**27**).

The compound was obtained as brown oil which hardened after drying in the air, mp 218-220 °C. It was recrystallized from in ethanol to give pale brownish crystals with 40% yield; ^{1}H nmr (deuteriochloroform): δ 2.31 (s, 3H, -CH_3), 3.91, 3.93, 3.96, 3.99 (s, 15 H, -CH_3O), 6.42 (s, 1H, Ar), 6.77 (s, 1H, O=C-CH=), 7.13 (s, 2H, Ar; ^{13}C nmr (deuteriochloroform): δ 7.9 (CH_3 at C-8), 55.7 (*C*H_3O at C-7), 56.1 (*C*H_3O at C-3'+C5'), 56.2 (*C*H_3O at C-5), 60.9 (*C*H_3O at C-4'), 91.3 (C-6), 103.2 (C2'+C6'), 105.7 (C-8), 107.8 (C-3), 108.5 (C-10), 127.0 (C-1'), 140.6 (C-4'), 153.4 (C-3'+C-5'), 156.4 (C-9), 158.9 (C-7), 160.0 (C-2), 161.3 (C-5), 178.1 (C-4).ir (potassium bromide): 1638 (C=O), 1601 (C=C ar), 1590 (C=C), 1125 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{21}H_{22}O_7$ (386.14): C, 65.28; H, 5.74. Found: C, 64.99, H, 5.82.

8-eEhyl-5,7-dimethoxy-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**28**).

The dark brown precipitate obtained from the mother solution was collected and recrystallized from ethanol; yield 55%; mp 228-229 °C; ^{1}H nmr (deuteriochloroform): δ 1.19-1.24 (t, J= 7.3 Hz, 3H -CH_2CH_3), 2.84-2.91 (q, J=7.3 Hz, 2H, -CH_2CH_3), 3.90, 3.92, 3.95, 3.99) (s, 15H, -CH_3O).6.42 (s, 1H, Ar), 6.80 (s, 1H, O=C-CH=), 7.13 (s, 2H, Ar); ^{13}C nmr (deuteriochloroform): δ 13.7 (*C*H_3CH_2 at C-8), 16.4 (CH_3*C*H_2 at C-8), 55.8 (*C*H_3O at C-7), 56.2 (*C*H_3O at C-3'+C5'), 56.3 (*C*H_3O at C-5), 60.9 (*C*H_3O at C-4'), 91.5 (C-6), 103.0 (C2'+C6'), 107.7 (C-3), 108.6 (C-10), 112.0 (C-8), 127.0 (C-1'), 140.6 (C-4'), 153.4 (C-3'+C-5'), 156.3 (C-9), 159.0 (C-7), 160.0 (C-2), 161.0 (C-5), 178.2 (C-4). ir (potassium bromide): 1638 (C=O), 1600 (C=C ar), 1580 (C=C), 1126 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{22}H_{24}O_7$ (400.15): C, 65.99; H, 6.04. Found: C, 65.54, H, 6.27.

5,7-Dimethoxy-2-(3',4',5'-trimethoxyphenyl)-8-propyl-4*H*-chromen-4-one (**29**).

The compound precipitated from the reaction solution and it was collected and recrystallized from ethanol to give light yellow solid, mp 180-181 °C; ^{1}H nmr (deuteriochloroform): δ 0.98-1.04 (t, J=7.3 Hz, 3H, -$CH_2CH_2CH_3$), 1.62-1.71 (m, 2H, -$CH_2CH_2CH_3$), 2.83-2.88 (t, J=7.3 Hz, 2H, -$CH_2CH_2CH_3$), 3.92, 3.94, 3.96, 4.01 (s, 15H, -CH_3O), 6.43 (s, 1H, Ar), 6.63 (s, 1H, , O=C-CH=), 7.13 (s, 2H, Ar); ^{13}C nmr (deuteriochloroform): δ 14.3 (*C*$H_3CH_2CH_2$ at C-8), 22.5 (CH_3CH_2*C*H_2 at C-8), 25.0 (CH_3*C*H_2CH_2 at C-8), 55.7 (*C*H_3O at C-7), 56.2 (*C*H_3O at C-5), 56.3 (*C*H_3O at C-3'+C5'), 60.9 (*C*H_3O at C-4'), 91.4 (C-6), 102.9 (C2'+C6'), 107.7 (C-8), 108.5 (C-10), 110.5 (C-3), 126.9 (C-1'), 140.5 (C-4'), 153.4 (C-3'+C-5'), 156.4 (C-9), 159.0 (C-7), 160.0 (C-2), 161.3 (C-5), 178.2 (C-4). ir (potassium bromide): 1639 (C=O), 1599 (C=C ar), 1580 (C=C), 1130 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{23}H_{26}O_7$ (414.17): C, 66.65; H, 6.32. Found: 66.38, H, 6.50.

8-Butyl-5,7-dimethoxy-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**30**).

Dark brown oil was isolated from the reaction mixture which hardened after drying in the air. It was recrystallized from ethanol; yield 60%; mp 216-217 °C; ^{1}H nmr (deuteriochloroform): δ 0.90-0.95 (t, J=7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.36-1.47 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.54-1.67 (m, 2H, CH_2CH_2-CH_2CH_3), 2.83-2.88 (t, J= 7.3 Hz, 2H, $CH_2CH_2CH_2CH_3$), 3.90, 3.92, 3.94, 3.98 (s, 15H, - CH_3O), 6.41 (s, 1H, Ar), 6.61 (s, 1H, O=C-CH=), 7.11 (s, 2H, Ar); ^{13}C nmr (deuteriochloroform): δ 14.0 (*C*$H_3CH_2CH_2CH_2$), 22.7 (CH_3CH_2*C*H_2CH_2), 23.0 (CH_3*C*$H_2CH_2CH_2$), 31.6 ($CH_3CH_2CH_2$*C*H_2), 55.7 (*C*H_3O at C-7), 56.0 (*C*H_3O at C-3' and C-5'), 56.3 (*C*H_3O at C-5), 60.9 (*C*H_3O at C-4'), 91.5 (C-6), 103.0 (C-2' and C-6'), 107.8 (C-8), 108.6 (C-10), 110.8 (C-3), 127.0 (C-1'), 140.6 (C-4'), 153.4 (C-3' and C-5'), 156.4(C-9), 159.0 (C-7), 160.1 (C-2), 161.3 (C-5), 178.2 (C-4). ir (potassium bromide): 1639 (C=O), 1598 (C=C ar), 1570 (C=C), 1129 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{24}H_{28}O_7$ (428.18): C, 67.28; H, 6.59. Found: C, 66.91, H, 6.83.

5,7-Dimethoxy-2-(3',4',5'-trimethoxyphenyl)-8-pentyl-4*H*-chromen-4-one (**31**).

A brown precipitate was formed from the reaction mixture which was collected and recrystallized from ethanol; yield 40%; mp 223-224 °C; ^{1}H nmr (deuteriochloroform): δ 0.29- 0.34 (t, peak width 13.43 Hz, 3H, $CH_2CH_2CH_2CH_2CH_3$), 0.77-0.80 (m, 2H, $CH_2CH_2CH_2CH_2CH_3$), 1.06 (m, 2H, $CH_2CH_2CH_2$-CH_2CH_3), 1.39 (m, 2H, $CH_2CH_2CH_2CH_2CH_3$), 2.27-2.33 (t, 2H, $CH_2CH_2CH_2CH_2CH_3$), 3.88, 3.89, 3.92 (s, 15H, CH_3O), 5.95 (s, 1H, Ar), 6.09 (s, 1H, O=C-CH=), 6.61 (s, 2H, Ar); ^{13}C nmr (deuteriochloroform): δ 14.0 (*C*$H_3CH_2CH_2CH_2CH_2$), 22.6 (CH_3CH_2*C*$H_2CH_2CH_2$), 23.0 (CH_3*C*$H_2CH_2CH_2CH_2$), 29.1 ($CH_3CH_2CH_2CH_2$*C*H_2), 32.1 ($CH_3CH_2CH_2$*C*H_2CH_2), 55.7 (*C*H_3O at C-7), 56.0 (*C*H_3O at C-3' and C-5'), 56.2 (*C*H_3O at C-5), 60.9 (*C*H_3O at C-4'), 91.4 (C-6), 102.9 (C-2' and C-6'), 107.7 (C-3), 108.5 (C-10), 110.8 (C-8), 127.0 (C-1'), 140.5 (C-4'), 153.4 (C-3' and C-5'), 156.3(C-9), 159.0 (C-7), 160.0 (C-2), 161.2 (C-5), 178.2 (C-4). ir (potassium bromide): 1638 (C=O), 1598 (C=C ar), 1576 (C=C), 1130 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{25}H_{30}O_7$ (442.20): C, 67.86; H, 6.83. Found: C, 67.57, H, 7.42.

5-Hydroxy-7-methoxy-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**32**).

After addition of HCl to the reaction mixture a yellow precipitate was formed. The mother liquid was extracted with CH_2Cl_2 and the product obtained was combined with the precipitate. After purification on Chromatotrone a pale yellow solid was recovered with 20% yield; mp 188-189°; ^{1}H nmr (deuteriochloroform/DMSO-d_6): δ 3.87, 3.91, 3.94 (s, 12H, CH_3O), 6.01-6.2 (d, J= 2.4 Hz, 1H, Ar), 6.22-6.23 (d, J=2.4 Hz, 1H, Ar), 6.33 (s, 1H, O=C-CH=), 6.80 (s, 1H, Ar); ^{13}C nmr (DMSO-d_6): δ 56.0 (*C*H_3O at C-7), 56.3 (*C*H_3O at C-3' and C-5'), 60.1 (*C*H_3O at C-4'), 93.5 (C-8), 96.2 (C-6), 103.6 (C-2' and C-6'), 108.1 (C-3), 108.3 (C-10), 126.2 (C-1'), 140.2 (C-4'), 153.2 (C-3' and C-5'), 159.1(C-9), 159.3 (C-2), 160.2 (C-5), 163.7 (C-7), 175.7 (C-4). ir (potassium bromide): 1660 (C=O), 1619 (C=C ar), 1593 (C=C), 1129 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{19}H_{18}O_7$ (358.11): C, 63.68; H, 5.06. Found: C, 63.56, H, 5.22.

5-Hydroxy-7-methoxy-8-methyl-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**33**).

The crude product was collected after evaporation of CH_2Cl_2 and purified on Chromatotrone to give a pale yellow solid; Yield 25%. mp 244-245 °C; ^{1}H nmr (deuteriochloroform/ DMSO-d_6): 2.26 (s, 3H, CH_3) 3.90, 3.92, 3.94 (s, 12 H, CH_3O), 5.64-5.65 (d, J=2.2 Hz, 1H, Ar), 5.94-5.95 (d, J=2.2 Hz, 1H, Ar), 6.15 (s, 1H, O=C-CH=), 6.54 (s, 2H, Ar). ^{13}C nmr (DMSO-d_6): δ 7.4 (*C*H$_3$ at C-8), 56.1 (*C*H$_3$O at C-7), 56.3 (*C*H$_3$O at C-3' and C-5'), 60.2 (*C*H$_3$O at C-4'), 91.8 (C-6), 104.3 (C-8), 103.5 (C-2' and C-6'), 107.8 (C-3), 107.9 (C-10), 126.9 (C-1'), 140.1 (C-4'), 153.1 (C-3' and C-5'), 156.1 (C-9), 159.1 (C-2), 160.1 (C-5), 161.6 (C-7), 176.3 (C-4). ir (potassium bromide): 1655 (C=O), 1600 (C=C ar), 1592 (C=C), 1129 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{20}H_{20}O_7$ (372.12): C, 64.51; H, 5.41. Found: C, 64.22, H, 6.05.

8-Ethyl-5-hydroxy-7-methoxy-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**34**).

The crude product after evaporation of the CH_2Cl_2 was purified on Chomatotrone. A light yellow solid was collected and dried in the air; yield 25%; mp 238-239 °C; ^{1}H nmr (deuteriochloroform/DMSO-d_6): δ 1.10-1.16 (t, J=7.3 Hz, 3H, CH_2CH_3), 2.72-2.80 (q, J=7.3 Hz, 2H, CH_2CH_3), 3.82, 3.83, 3.86 (s, 12H, CH_3O), 6.31 (s, 1H, Ar), 6.55(s, 1H, O=C-CH=), 7.08 (s, 2H, Ar); ^{13}C nmr (DMSO-d_6): δ 13.5 (*C*H$_3$CH$_2$ at C-8), 16.0 (CH$_3$*C*H$_2$ at C-8), 56.1 (*C*H$_3$O at C-7), 56.4 (*C*H$_3$O at C-3' and C-5'), 60.2 (*C*H$_3$O at C-4'), 91.7 (C-6), 103.6 (C-2' and C-6'), 105.8 (C-8), 107.6 (C-3), 107.9 (C-10), 126.8 (C-1'), 140.0 (C-4'), 153.2 (C-3' and C-5'), 156.2(C-9), 159.2 (C-2), 160.3 (C-5), 161.5 (C-7), 176.2 (C-4). ir (potassium bromide): 1660 (C=O), 1610 (C=C ar), 1590 (C=C), 1129 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{21}H_{22}O_7$ (386.14): C, 65.28; H, 5.74. Found: C, 65.58, H, 6.16.

5-Hydroxy-7-methoxy-2-(3',4',5'-trimethoxyphenyl)-8-propyl-4*H*-chromen-4-one (**35**).

The pale yellow solid was obtained after evaporation of CH_2Cl_2 and chromatographic purification; yield 18%; mp 176-177 °C; ^{1}H nmr (deuteriochloroform/DMSO-d_6): δ 0.88-0.93 (t, J=7.3 Hz, 3H, -$CH_2CH_2CH_3$), 1.51-1.60 (m, 2H, $CH_2CH_2CH_3$), 2.69-2.74 (t, J=7.3 Hz, 2H, $CH_2CH_2CH_3$), 3.82, 3.85, 3.87 (s, 12H, CH_3O), 6.31 (s, 1H, Ar), 6.57 (s, 1H, O=C-CH=), 7.08 (s, 2H, Ar); ^{13}C nmr (DMSO-d_6): δ 14.2 (*C*H$_3$CH$_2$CH$_2$ at C-8), 22.3 (CH$_3$CH$_2$*C*H$_2$ at C-8), 24.0 (CH$_3$*C*H$_2$CH$_2$ at C-8), 56.0 (*C*H$_3$O at C-7), 56.3 (*C*H$_3$O at C-3' and C-5'), 60.2 (*C*H$_3$O at C-4'), 91.7 (C-6), 103.5 (C-2' and C-6'), 104.9 (C-8), 107.8 (C-10), 108.2 (C-3), 126.9 (C-1'), 140.1 (C-4'), 153.2 (C-3' and C-5'), 156.1(C-9), 159.1 (C-2), 160.1 (C-5), 161.6 (C-7), 176.3 (C-4). ir (potassium bromide): 1652 (C=O), 1600(C=C ar), 1590 (C=C), 1130 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{22}H_{24}O_7$ (400.15): C, 65.99; H, 6.04. Found: C, 65.87, H, 6.17.

8-Butyl-5-hydroxy-7-methoxy-2-(3',4',5'-trimethoxyphenyl)-4*H*-chromen-4-one (**36**).

The product crystallized as pale yellow solid after chromatographic purification; yield 20%; mp 158-159°; ^{1}H nmr (deuteriochloroform/DMSO-d_6): δ 0.91-0.97 (t, J=7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.37-1.48 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.53-1.65 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.80-2.85 (t, J= 7.3 Hz, 2H, $CH_2CH_2CH_2CH_3$), 3.90, 3.94, 3.95 (s, 12H, CH_3O), 6.41 (s, 1H, Ar), 6.61 (s, 1H, O=C-CH=), 7.13 (s, 2H, Ar); ^{13}C nmr (DMSO-d_6): δ 14.2 (*C*H$_3$CH$_2$CH$_2$CH$_2$ at C-8), 22.6 (CH$_3$CH$_2$*C*H$_2$CH$_2$ at C-8), 23.1 (CH$_3$CH$_2$CH$_2$CH$_2$ at C-8), 31.6 (CH$_3$CH$_2$CH$_2$*C*H$_2$ at C-8), 56.0 (*C*H$_3$O at C-7), 56.4 (*C*H$_3$O at C-3' and C-5'), 60.2 (*C*H$_3$O at C-4'), 91.6 (C-6), 103.8 (C-2' and C-6'), 105.1 (C-8), 107.9 (C-10), 108.3 (C-3), 126.9 (C-1'), 140.1 (C-4'), 153.2 (C-3' and C-5'), 156.0 (C-9), 159.0 (C-2), 160.2 (C-5), 161.6 (C-7), 176.4 (C-4). ir (potassium bromide): 1656 (C=O), 1610 (C=C ar), 1592 (C=C), 1133 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{23}H_{26}O_7$(414.17): C, 66.65; H, 6.32. Found: C, 66.53, H, 6.60.

5-Hydroxy-7-methoxy-2-(3',4',5'-trimethoxyphenyl)-8-pentyl-4*H*-chromen-4-one (**37**).

The product was collected after the CH_2Cl_2 extract was evaporated to dryness. After chromatographic purification, pale yellow solid was collected; yield 25%; mp 154-155 °C; ^{1}H nmr (deuteriochloroform/DMSO-d_6): δ 0.76-0.81 (t, peak width 12.9 Hz, 3H, $CH_2CH_2CH_2CH_2CH_3$),1.16-1.33, 1.49-1.52 (m, 6H, CH_2CH_2-$CH_2CH_2CH_3$), 2.70-2.76 (t, peak width 15.04 Hz, 2H, $CH_2CH_2CH_2CH_2CH_3$),3.80, 3.83, 3.86 (s, 12H, CH_3O), 6.32 (s, 1H, Ar), 6.65 (s, 1H, O=C-CH=), 7.68 (s, 2H, Ar); ^{13}C nmr (DMSO-d_6): δ 14.2 (*C*H$_3$CH$_2$CH$_2$CH$_2$CH$_2$ at C-8), 22.7 (CH$_3$CH$_2$*C*H$_2$CH$_2$CH$_2$ at C-8), 22.9 (CH$_3$*C*H$_2$CH$_2$CH$_2$CH$_2$ at C-8), 28.9 (CH$_3$CH$_2$CH$_2$*C*H$_2$CH$_2$ at C-8), 32.1 (CH$_3$CH$_2$CH$_2$-CH$_2$*C*H$_2$ at C-8), 56.1 (*C*H$_3$O at C-7), 56.2 (*C*H$_3$O at C-3' and C-5'), 60.2 (*C*H$_3$O at C-4'), 91.6 (C-6), 103.7 (C-2' and C-6'), 106.1 (C-8), 107.8 (C-10), 108.3 (C-3), 126.8 (C-1'), 140.1 (C-4'), 153.2 (C-3' and C-5'), 156.1 (C-9), 159.0 (C-2), 160.3 (C-5), 161.5 (C-7), 176.3 (C-4). ir (potassium bromide): 1656 (C=O), 1605 (C=C ar), 1590 (C=C), 1134 (C-O) cm $^{-1}$.

Anal. Calcd. for $C_{24}H_{28}O_7$ (428.18): C, 67.28; H, 6.59. Found: C, 67.00, H, 6.87.

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