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Synthesis and Anti-Inflammatory Activity Evaluation of Novel Chroman Derivatives

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In an effort to develop potent anti-inflammatory agents, a series of novel chroman derivatives including acyclic amidochromans, chromanyl esters and chromanyl acrylates have been designed, synthesized and fully characterized. These chroman analogues were screened for their anti-inflammatory activities through inhibition of the TNF-α-induced ICAM-1 expression on human endothelial cells. A structure–activity relationship was also established and it has been found that in case of carboxy chromans and amidochromans, the chain length of the amide moiety, branching of the side chain and the presence of the substituents on the phenyl ring have significant effects on their inhibitory activities, while in chromanyl acrylates, the number of methoxy groups, their relative positions on the phenyl ring, presence of functional groups in the α,β–unsaturated ester moiety played a critical role on their activities. The compound **14** (*N*-hexyl-7-hydroxy-2,2-dimethylchromane-6-carboxamide) was found to be the most potent compound in inhibiting the TNF-α-induced expression of ICAM-1 on endothelial cells.

Introduction

To treat the deleterious inflammatory responses in several human diseases, anti-inflammatory agents are extensively used clinically. However, anti-inflammatory compounds such as NSAIDs (Non-Steroidal Anti-inflammatory Drugs), corticosteroids and chemotherapeutic agents have severe side effects. Therefore, there is an unmet therapeutic need to develop more selective potent drugs for clinically important diseases, such as asthma, COPD, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, allergies and atherosclerosis, etc.[1,2]

Various inflammatory mediators including cytokines like TNF-α, IL-1β and bacterial lipopolysaccharides induce the expression of endothelial cell adhesion molecules, *viz.* intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin on the vascular endothelium.[3] The indiscriminate infiltration of the leukocytes across the blood vessels causes inflammation which is a direct consequence of the increased expression of cell adhesion molecules on the endothelial cells that alter the adhesive property of the vasculature.[4,5]

Inhibition of cell adhesion molecules has shown to be a useful therapeutic approach to regulate inflammatory responses. Various strategies including monoclonal antibodies (mAbs), specific to cell adhesion molecules and small molecules from natural and synthetic sources have been used successfully to down-regulate the induced expression of the cell adhesion molecules, hence preventing inflammation.[6] The practical use of mAbs is limited due to the problems associated with them like endotoxin contamination, secondary antibody formation, cellular activation, and other complications (like sensitization) leading to serum sickness and anaphylaxis.[7,8] In order to develop safe and active anti-inflammatory drugs, many groups have synthesized a number of small molecules which abrogate TNF-α induced expression of E-selectin, VCAM-1 and ICAM-1 on endothelial cells. Among these cell adhesion molecules, however, ICAM-1 is considered to be the most critical as it is most widely expressed on cells of both hematopoietic and non-hematopoietic tissues. Also, it's expression on vascular endothelium is a key step in initiating leukocyte adhesion and migration of cells into tissue sites of inflammation by extravasation.[6]

Chroman nucleus constitutes the core of numerous natural products and they have proven to have various biological activities in several therapeutic areas including cardiovascular diseases,[9,10] diabetes,[11] hypertension,[12] cancer,[13] central nervous system,[14]

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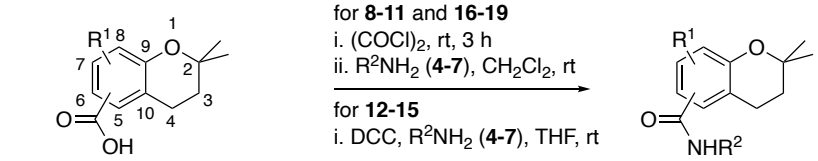
endocrine disorders,[15] and infectious diseases.[16,17] But their effect on cytokine induced cell adhesion molecule expression has not been explored much.

In the present study, we report the design, synthesis, and inhibitory activity of chroman derivatives as inhibitors of TNF-α induced expression of ICAM-1. Also the structure-activity relationship of various chromans has been studied. Herein, an exploration of the inhibition of the cell adhesion molecules by various analogues of chromans *viz.* acyclic amidochromans, chromanyl esters and chromanyl acrylates has been discussed in detail.

Results and discussion

The synthesis of novel classes of amidochromans **8-19** was achieved by the direct amidation of the corresponding carboxychromans **1**, **2** and **3** with the appropriate amine **4**, **5**, **6** or **7** (Scheme 1). Starting from carboxychroman **1** and **3** having carboxylic group at C6 and C7, respectively the use of oxalyl chloride to produce the corresponding acyl chloride and then the aliphatic amine furnished the target **8-11** and **16-19** in good yields (>78 % yield). Starting from carboxychroman **2** having a β-hydroxy carboxylic acid the corresponding amides **12-15** was obtained directly by addition of the aliphatic amine in the presence of DCC in similar yields (>74 % yield).

The synthesis of different chromanyl acrylate analogues **31**-**37** and **58**-**69** employing different synthetic approaches were described (Schemes 2 and 3). The intermediate **22** was obtained in 30 % yield by the reaction of 4-hydroxybenzaldehyde (**20**) with isoprene (**21**) in the presence of orthophosphoric acid, its reaction with malonic acid in the presence of piperidine afforded the compound **23** which on conventional esterification with appropriate alcohols **24**-**30** produced the chromanyl esters **31**-**37** in good yields. Ester **31** was synthesized using thionyl chloride and methanol in a one-pot reaction by Method A while the synthesis of esters **32-34** and **37** was achieved only with a two-steps procedure (Method B). For the synthesis of esters **35** and **36** having phenyl and 4-*t*-butylphenyl core, triphenylphosphine, CCl_4 and triethylamine were necessary (Method C). Due to different reactivities of various alcohols used in the reaction, three different methods (Methods A, B and C) were adopted for the synthesis of esters **31-37**. The esters were synthesized in good yields with nominal reaction times and less side product formation.



1, R^1 = H and COOH at C-6
2, R^1 = OH at C-7 and COOH at C-6
3, R^1 = OH at C-5 and COOH at C-7

8-11, R^1 = H and $CONHR^2$ at C-6
12-15, R^1 = OH at C-7 and $CONHR^2$ at C-6
16-19, R^1 = OH at C-5 and $CONHR^2$ at C-7

Compound No.	R^2
4, **8**, **12** and **16**	*n*-C_4H_9
5, **9**, **13** and **17**	*n*-C_5H_{11}
6, **10**, **14** and **18**	*n*-C_6H_{13}
7, **11**, **15** and **19**	$CH_2CH(CH_2CH_3)CH_2CH_2CH_2CH_3$

Scheme 1. Synthesis of amidochromans.

Similarly, the intermediates **41**-**43** were obtained in 45-50 % yields by the reaction of diene **21** with the appropriate phenol **38**-**40** and orthophosphoric acid, these were further methylated using dimethylsulphate to the methoxy substituted 2,2-dimethylchromans **44**-**46** in 70-53 % yields. The chromans **44**-**46** were selectively formylated by the well-known Vilsmeier-Haack reaction in the presence of $POCl_3$ and DMF to afford the compounds **47**-**49** in 70-75 % yields. Further, the chromanyl esters **58**-**69** were synthesized by a two-step reaction of the compounds **47**-**49** with malonic acid to form the compounds **51**-**53,** which on classic esterification with the alcohols **54**-**57** yielded the desired products.

All the compounds were fully characterized from their physical data, and ^{1}H and ^{13}C NMR spectral data and HRMS. The data of the known compounds compared well those of the corresponding compounds reported in literature, and the structures of the new compounds were compatible with their ^{1}H and ^{13}C NMR spectral data and HRMS.

The effects of chroman analogues (Table 1 and Table 2) on the TNF-α–induced expression of ICAM-1 was examined on endothelial cells. It was found that different chroman derivatives inhibit the TNF-α-induced expression of ICAM-1 to different extents. The levels of inhibition (%) were presented at the maximum tolerable dose (MTD), where cell viability and morphology was not affected. The cell viability and morphology were determined by MTT (methylthiazolyldiphenyltetrazolium bromide) assay. The IC_{50} values (the concentration at which 50 % inhibition of ICAM-1 expression was obtained) and the percentage inhibition at the maximum tolerable dose (MTD) have been summarized in Table 1 and Table 2. The anti-inflammatory activity data of the three classes of chromans, namely acyclic amidochromans, chromanyl esters and chromanyl acrylates indicated that several structural factors have significant effects on the inhibition of TNF-α–induced expression of ICAM-1 on endothelial cells. Further, the inhibitory activity of acyclic amidochromans and chromanyl esters was compared, the former exhibited higher activity in comparison to their ester analogues.

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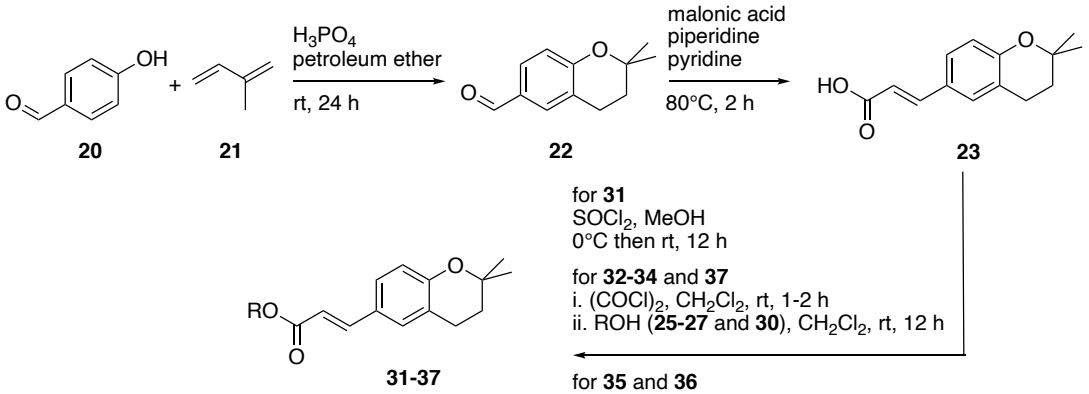


Compound No.	R
24, **31**	CH_3
25, **32**	*n*-C_3H_7
26, **33**	*n*-C_4H_9
27, **34**	$CH_2(C_6H_5)$
28, **35**	C_6H_5
29, **36**	(C_6H_4)-4-(*t*-C_4H_9)
30, **37**	(C_6H_4)-4-NO_2

Scheme 2. Synthesis of chromanyl acrylates **31**-**37**.

Table 1. IC_{50} values and the percentage inhibition values of compounds **1-2** and **8-19**

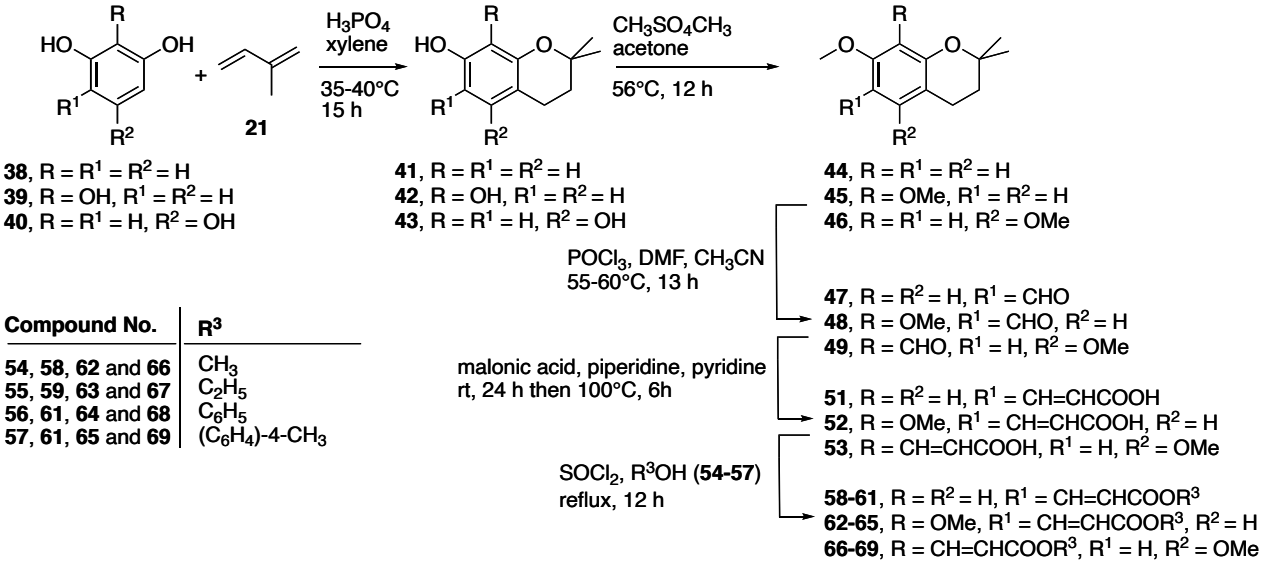
Compound No.	IC_{50} (μM)	% Inhibition at MTD
1	NR	41.5
2	100	71.6
8	125	62.7
9	68	75.18
10	22	90.6
11	25	91.7
12	83.6	76.8
13	45.2	85.7
14	15	97.2
15	38	86.8
3	105	68.2
16	85	80.4
17	56	86.8
18	22	93.2
19	88	71.9

NR: not reachable.

In the case of carboxychromans and their amido derivatives, the comparison of different analogues (Table 1) indicated that the acid moiety, the chain length of the amide moiety, branching of the side chain and the presence of substituents on the phenyl ring have a significant effect on their inhibitory activities. The change in the acid moiety of compound **1** to amides **8**-**11** causes an increase in their inhibition activities. The conversion of the carboxychromans to their amide derivatives causes an increase in their ICAM-1 expression inhibition activities. The increase in the chain length of the alkyl group on the amido functionality causes a significant increase in the % inhibition (Table 1, entries 3-10) while the increase in the branching in the side chain decreases the % inhibition (Table 1, entries 9-10 and 14-15). Lastly, the compounds containing the phenolic hydroxyl groups (Table 1, entries 2 and 7-15) were found to be more active than their corresponding unsubstituted analogues (Table 1, entries 1 and 3-6).

The % inhibition of various anlogues of chromanyl acrylates (Table 2) revealed that the number of methoxy groups, their relative positions on the phenyl ring, presence of functional group in the α, β–unsaturated ester moiety played a crucial role on their activities. With an increase in the number of methoxy groups, an increase in % inhibition values and decrease in IC_{50} values were observed (Table 2, entries 1, 8, 12 and entries 5, 10, 14). Variation of alkyl group in the α, β–unsaturated ester moiety affected the % inhibition of the ICAM-1 expression. In the case of the methoxy substituted chromanyl acrylates, increase in the number of carbon atoms in alkyl chain increases the % inhibition. On the contrary, in unsubstituted chromanyl acrylates, increase in the number of carbon atoms in the alkyl chain decreases their inhibitory activity. Furthermore, substitution on the phenyl ring leads to an increase in

the activity of the chromanyl acrylates (Table 2, entries 1, 5, 12 and 14). But an exception was observed in the case of monomethoxy chromanyl acrylate, in this case a decrease in the inhibition activity was observed (Table 2, entries 8 and 10). The presence of electron releasing groups on the phenyl ring increases the inhibitory activity (Table 2, entries 6, 11, 15 and 19) and the presence of the electron withdrawing group on phenyl ring decreases its activity (Table 2, entry 7). Lastly, the change in the position of α, β–unsaturated ester and methoxy group decreases the inhibitory activity to a considerable extent (Table 2, entries 16-19).



Scheme 3. Synthesis of chromanyl acrylates **58-69**.

Table 2. IC_{50} values and the percentage inhibition values of compounds of **31-37** and **58-69**

Compound No.	IC_{50} (μM)	% Inhibition at MTD
31	NR	37
32	NR	21
33	NR	3
35	208	59
36	76	84
37	NR	32
58	65	62
59	78	65
60	67	60
61	53	70
62	68	65
63	60	72
64	55	78
65	40	85
66	80	55
67	70	65
68	60	73
69	54	78

NR: not reachable.

Conclusions

In summary, a large number of acyclic amidochromans, chromanyl esters and chromanyl acrylates have been synthesized and well characterized. These novel chroman analogues have shown ability to inhibit the TNF-∝-induced ICAM-1 expression on human endothelial cells. The compound 14 (*N*-hexyl-7-hydroxy-2,2-dimethylchromane-6-carboxamide) was found to be the most potent compound (IC_{50} = 15 μM) in inhibiting the TNF-∝-induced expression of ICAM-1 on endothelial cells. This concentration is lower than those of known anti inflammatory compounds, such as diclofenac, N-acetyl cysteine, pyrrolidone dithiocarbamate and others.[5] The results may motivate further research on using this molecule as a template for developing lead molecules towards the development of better anti-inflammatory agents.

Experimental

Materials

Anti-ICAM-1 antibody and TNF-α were purchased from Pharmingen, USA. M199, L-glutamine, penicillin, streptomycin, amphotericin B, endothelial cell growth factor, trypsin, Pucks saline, HEPES, DMSO, o-phenylenediamine dihydrochloride and anti-mouse IgG-HRP were purchased from Sigma Chemical Co., USA. Fetal calf serum was purchased from Biological Industries, Israel. All other chemicals and solvents used were of analytical grade or better and were obtained from one of the following suppliers and used without further purification: S.D. Fine Chemicals, Qualigens Chemicals and Aldrich, India.

Melting points were determined in a sulfuric acid bath and are uncorrected. The IR spectra were recorded on a Perkin Elmer model 2000 FT-IR spectrophotometer. The ^{1}H NMR and the ^{13}C NMR spectra

were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75.5 MHz, respectively using TMS as internal standard. The chemical shift values are on δ scale and the coupling constant values (*J*) are in Hz. The HRMS were recorded on a JMS-AX 505W instrument at 70 eV in FAB on positive ion mode. Analytical TLCs were performed on pre-coated Merck silica gel 60F254 plates with fluorescence indicator; the spots were detected by viewing under UV light. Column chromatography was carried out using silica gel (100-200 mesh).

Cell-ELISA for measurement of ICAM-1

Cell-ELISA was used for measuring the expression of ICAM-1 on surface of endothelial cells.[5] Endothelial cells were incubated with or without the derivatives at various concentrations for 2 h, followed by treatment with TNF-α (10 ng/mL) (BD, USA) for 16 h for ICAM-1 expression. The cells were fixed with 1.0 % glutaraldehyde (Sigma, USA). Non-specific binding of antibody was blocked by using skimmed milk (3.0 % in PBS). Cells were incubated overnight at 4 ºC with anti-ICAM-1mAb (BD, USA), diluted in blocking buffer, the cells were further washed with PBS and incubated with peroxidase-conjugated goat anti-mouse secondary antibody (Sigma, USA). After washings, cells were exposed to the peroxidase substrate (*o*-phenylenediamine dihydrochloride 40 mg/100 mL in citrate phosphate buffer, pH 4.5). Reaction was stopped by the addition of 2N sulfuric acid and absorbance at 490 nm was measured using microplate reader (Spectramax 190, Molecular Devices, USA).

General procedure for the synthesis of chroman derivatives 8-11 and 16-19

The appropriate carboxylic acid **1** or **3** (500 mg) was stirred with oxalyl chloride (3 mL, 34.9 mmol) for 3 h. The resulting solution was concentrated to dryness under reduced pressure and the residue was dispersed in dry toluene (10 mL). The solvent was eliminated under reduced pressure, the process was repeated twice. The residue was dispersed in anhydrous dichloromethane (3 mL) and a solution of the appropriate amine (2.4 mmol) in anhydrous dichloromethane were added with stirring. The progress of the reaction was followed by TLC. On completion, the reaction was stopped and extracted with water 2 times, the organic layer was dried over Na_2SO_4 and the crude products **8**-**11** and **16**-**19** were purified by column chromatography.

***N*-Butyl-2,2-dimethylchroman-6-carboxamide (8).** Following the general procedure, with carboxylic acid **1** (500 mg, 2.4 mmol), oxalyl chloride (3 mL, 34.9 mmol) and butyl amine (175.4 mg, 2.4 mmol), *N*-butyl-2,2-dimethylchroman-6-carboxamide **(8)** was obtained (572 mg, 78% yield) as a brown viscous oil. IR spectrum (KBr), cm^{-1}: 3299 (NH), 2960, 1633 (C=O), 1491, 1266. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* ppm: 0.90-0.97 (3H, m, C-4'H), 1.25-1.43 (8H, m, 2 x CH_3 and C-3'H), 1.53-1.62 (2H, m, C-2'H), 1.78-1.83 (2H, m, C-3H), 2.72-2.81 (2H, m, C-4H), 3.39-3.45 (2H, m, C-1'H), 6.13 (NH), 6.76 (1H, d, *J* = 8.4 Hz, C-8H), 7.45 (1H, d, *J* = 8.4 Hz, C-7H), 7.56 (1H, s, C-5H). ^{13}C NMR (75.5 MH_Z, $CDCl_3$) *δ* ppm: 13.81 (C-4'), 20.17 (C-3'), 22.36 (C-4), 26.84 (2 x CH_3), 31.85 (C-3), 32.54 (C-2'), 39.69 (C-1'), 75.84 (C-2), 117.10 (C-8), 120.90 (C-10), 125.77 (C-5), 128.21 (C-7), 129.05 (C-6), 156.86 (C-9), 167.36 (C=O). HRMS: found 262.1807 $[M+H]^+$; calculated 262.1802 for $C_{16}H_{24}NO_2$.

2,2-Dimethyl-*N*-pentylchroman-6-carboxamide (9). Following the general procedure, with carboxylic acid **1** (500 mg, 2.4 mmol), oxalyl chloride (3 mL, 34.9 mmol) and pentyl amine (209 mg, 2.4 mmol), 2,2-dimethyl-*N*-pentylchroman-6-carboxamide **(9)** was obtained (620 mg, 85% yield) as a brown viscous oil. IR spectrum (KBr), cm^{-1}: 3306 (NH), 2931, 1633 (C=O), 1490, 1265. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* ppm: 0.90 (3H, brs, C-5'H), 1.36-184 (10H, brs, 2 x CH_3, C-3'H and C-4'H), 1.60-1.62 (2H, m, C-2'H), 1.79 (2H, t, *J* = 6.5 Hz, C-3H), 2.76 (2H, t, *J* = 6.6 Hz, C-4H), 3.31-3.35 (2H, m, C-1'H), 6.13 (NH), 6.80 (1H, d, *J* = 8.4 Hz, C-8H), 7.52 (1H, d, *J* = 8.4 Hz, C-7H), 7.86 (1H, s, C-5H). ^{13}C NMR (75.5 MH_Z, $CDCl_3$) *δ* ppm: 13.79 (C-5'), δ 22.13 (C-4'), 22.25 (C-4), 26.89 (2 x CH_3), 28.80 (C-3'), 28.92 (C-2'), 32.43 (C-3), 39.68 (C-1'), 75.53 (C-2), 117.32 (C-8), 120.41 (C-10), 125.29 (C-5), 126.04 (C-7), 129.82 (C-6), 159.84 (C-9), 167.36 (C=O). HRMS: found 298.1813 ($[M+Na]^+$; calculated 298.1818 for $C_{17}H_{25}NO_2Na$.

***N*-Hexyl-2,2-dimethylchroman-6-carboxamide (10).** Following the general procedure, with carboxylic acid **1** (500 mg, 2.4 mmol), oxalyl chloride (3 mL, 34.9 mmol) and hexyl amine (242.6 mg, 2.8 mmol), *N*-hexyl-2,2-dimethylchroman-6-carboxamide **(10)** was obtained (600 mg, 78% yield) as a brown viscous oil. IR spectrum (KBr), cm^{-1}: 3306 (NH), 2931, 1633 (C=O), 1490, 1265. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* ppm: 0.89-0.94 (3H, brs, C-6'H), 1.26 (12H, brs, 2 x CH_3, C-3'H, C-4'H and C-5'H), 1.49-1.51 (2H, m, C-2'H), 1.79-1.83 (2H, m, C-3H), 2.78-2.82 (2H, m, C-4H), 3.32-3.35 (2H, m, C-1'H), 6.02 (NH), 6.69 (1H, d, *J* = 8.4 Hz, C-8H), 7.45 (1H, d, *J*=8.4 Hz, C-7H), 7.57 (1H, s, C-5H). ^{13}C NMR (75.5 MH_Z, $CDCl_3$) *δ* ppm: 13.98 (C-6'), δ 22.32 (C-4), 22.52 (C-5'), 26.44 (C-3') 26.79 (2 x CH_3), 29.68 (C-2'), 31.49 (C-4'), 32.49 (C-3), 40.00 (C-1'), 75.02 (C-2), 117.07 (C-8), 120.41 (C-10), 125.76 (C-5), 125.95 (C-7), 129.03 (C-6), 156.83 (C-9), 167.40 (C=O). HRMS: found 312.1935 $[M+Na]^+$; calculated 312.1934 for $C_{18}H_{27}NO_2Na$.

***N*-(2'-Ethylhexyl)-2,2-dimethylchroman-6-carboxamide (11).** Following the general procedure, with carboxylic acid **1** (500 mg, 2.4 mmol), oxalyl chloride (3 mL, 34.9 mmol) and 2-ethylhexyl amine (310 mg, 2.8 mmol), *N*-(2'-ethylhexyl)-2,2-dimethylchroman-6-carboxamide **(11)** was obtained (650 mg, 78% yield) as dark brown viscous oil. IR spectrum (KBr), cm^{-1}: 3306 (NH), 2931, 1633 (C=O), 1490, 1265. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* ppm: 0.89- 0.94 (6H, m, C-6'H and C-2''H), 1.31-1.54 (15H, m, C-2 x CH_3, C-3'H, C-4'H, C-5'H, and C-1''H), 1.79-1.83 (2H, m, C-3H), 2.80 (2H, t, *J* = 6.0 H_Z, C-4H), 3.37 (2H, brs, C-1'H), 6.09 (NH), 6.69 (1H, d, *J* = 8.4 Hz, C-8H), 7.38 (1H, d, *J* = 8.4 Hz, C-7H), 7.45 (1H, s, C-5H). ^{13}C NMR (75.5 MH_Z, $CDCl_3$) *δ* ppm: 10.89 (C-2''), 13.97 (C-6'), δ 22.34 (C-4), 22.99 (C-5'), 24.33 (C-1''), 26.81 (2 x CH_3), 28.90 (C-4'), 31.10 (C-3'), 32.51 (C-3), 39.53 (C-1'), 42.78 (C-2'), 75.03 (C-2), 117.09 (C-8), 120.93 (C-10), 125.65 (C-5), 126.11 (C-7), 129.02 (C-6), 156.83 (C-9), 167.41 (C=O). HRMS: found 318.2426 $[M+H]^+$; calculated 318.2428 for $C_{20}H_{32}NO_2$.

***N*-Butyl-5-hydroxy-2, 2-dimethylchroman-7-carboxamide (16).** Following the general procedure, with carboxylic acid **3** (500 mg, 2.2 mmol), oxalyl chloride (3 mL, 34.9 mmol) and butyl amine (160.8 mg, 2.2 mmol), *N*-butyl-5-hydroxy-2,2-dimethylchroman-7-carboxamide **(16)** was obtained (560 mg, 81%) as a white solid (mp: 223-225 ^oC). IR spectrum (nujol), cm^{-1}: 3327 (NH), 2933, 1658 (C=O), 1558, 1144. ^{1}H NMR (300 MHz, DMSO-d_6) *δ* ppm: 0.87-0.92 (3H, t, *J*=7.2 Hz, C-4'H), 1.17-1.28 (6H, brs, 2 x CH_3), 1.30-1.38 (2H, m, C-3'H), 1.41-1.48 (2H, m, C-2'H), 1.67 (2H, t, *J* = 6.6 Hz, C-3H), 2.59 (2H, t, *J* = 6.6 Hz, C-4H), 3.13-3.17 (2H, m, C-1'H), 6.13 (1H, d, *J* = 2.4 Hz, C-6H), 6.26 (1H, d, *J* = 2.4 Hz, C-8H), 8.15 (NH). ^{13}C NMR (75.5 MH_Z, DMSO-d_6) *δ* ppm:

13.70 (C-4'), 19.28 (C-4), 19.62 (C-3'), 26.49 (2 x CH_3), 31.21 (C-2'), 32.21 (C-3), 38.37 (C-1'), 73.72 (C-2), 104.01 (C-6), 106.47 (C-8), 108.93 (C-10), 138.71 (C-7), 154.46 (C-9), 155.93 (C-5), 168.49 (C=O). HRMS: found 278.1761 $[M+H]^+$; calculated 278.1751 for $C_{16}H_{24}NO_3$.

***N*-Pentyl-5-hydroxy-2,2-dimethylchroman-7-carboxamide (17).** Following the general procedure, with carboxylic acid **3** (500 mg, 2.2 mmol), oxalyl chloride (3 mL, 34.9 mmol) and pentyl amine (191.6 mg, 2.2 mmol), *N*-pentyl-5-hydroxy-2,2-dimethylchroman-7-carboxamide **(17)** was obtained (610 mg, 83% yield) as a yellow viscous oil. IR spectrum (nujol), cm^{-1}: 3327 (NH), 2933, 1658 (C=O), 1558, 1144. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 0.82-0.89 (3H, t, C-5'H), 1.16-1.33 (10H, brs, 2 x CH_3, C-3'H, and C-4'H), 1.41-1.48 (2H, m, C-2'H), 1.66 (2H, t, J = 6.6 Hz, C-3H), 2.59 (2H, t, J = 6.6 Hz, C-4H), 3.06-3.18 (2H, m, C-1'H), 6.13 (1H, d, J = 2.4 Hz, C-6H), 6.26 (1H, d, J = 2.4 Hz , C-8H); 8.13 (NH). ^{13}C NMR (75.5 $MH_{Z,}$ DMSO-$d_{6,}$) δ ppm: 13.86 (C-5'), 19.26 (C-3), 21.98 (C-4') 26.04 (2 x CH_3), 28.99 (C-3') 30.92 (C-2'), 32.16 (C-4), 38.63 (C-1'), 73-68 (C-2), 103.96 (C-6), 106.40 (C-8), 108.88 (C-10), 138.68 (C-7), 154.41 (C-9), 155.90 (C-5), 168.43 (C=O). HRMS: found 292.1907 $[M+H]^+$; calculated 292.1907 for $C_{17}H_{26}NO_3$.

***N*-Hexyl-5-hydroxy-2,2-dimethylchroman-7-carboxamide (18).** Following the general procedure, with carboxylic acid **3** (500 mg, 2.2 mmol), oxalyl chloride (3 mL, 34.9 mmol) and hexyl amine (222 mg, 2.2 mmol), *N*-hexyl-5-hydroxy-2,2-dimethylchroman-7-carboxamide **(18)** was obtained (570 mg, 81% yield) as a yellow viscous oil. IR spectrum (nujol), cm^{-1}: 3327 (NH), 2930, 1638 (C=O), 1582, 1141. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 0.85-0.90 (3H, m, C-6'H), 1.18-1.31 (12H, brs, 2 x CH_3, C-3'H, C-4'H and C-5'H), 1.45-1.49 (2H, m, C-2'H), 1.66 (2H, t, J = 6.6 Hz, C-3H), 2.60 (2H, t, J = 6.6 Hz, C-4H), 3.12-3.19 (2H, m, C-1'H), 6.13 (1H, d, J = 2.4 Hz, C-6H), 6.26 (1H, d, J = 2.4 Hz, C-8H), 8.13 (NH). ^{13}C NMR (75.5 $MH_{Z,}$ DMSO-$d_{6,}$) δ ppm: 13.97 (C-6'), δ 19.30 (C-3), 21.82 (C-5') 26.49 (2 x CH_3 and C-4'), 28.65 (C-3'), 28.74 (C-2'), 32.16 (C-4), 38.67 (C-1'), 73.73 (C-2), 104.01 (C-6), 106.46 (C-8), 108.94 (C-10), 138.71 (C-7), 154.46 (C-9), 155.94 (C-5), 168.49 (C=O). HRMS: found 306.2064 $[M+H]^+$; calculated 306.2064 for $C_{18}H_{28}NO_3$.

***N*-(2'-Ethylhexyl)-5-hydroxy-2,2-dimethylchroman-7-carboxamide (19).** Following the general procedure, with carboxylic acid **3** (500 mg, 2.2 mmol), oxalyl chloride (3 mL, 34.9 mmol) and 2-ethylhexyl amine (284.1 mg, 2.2 mmol), *N*-(2'-ethylhexyl)-5-hydroxy-2,2-dimethylchroman-7-carboxamide **(19)** was obtained (590 mg, 85% yield) as a white solid (mp: 195 ^{o}C). IR spectrum (nujol), cm^{-1}: 3327 (NH), 2930, 1638 (C=O), 1582, 1141. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 0.83-0.88 (6H, m, C-6'H and C-1''H), 1.18-1.68 (15H, brs, 2 x CH_3, C-2'H, C-3'H, C-4'H, C-5'H and C-1''H), 1.71 (2H, t, J = 6.6 Hz, C-3H), 2.59 (2H, t, J = 6.6Hz, C-4H), 3.08-3.12 (2H, m, C-1'H), 6.13 (1H, d, J = 2.4 Hz, C-6H), 6.26 (1H, d, J = 2.4 Hz, C-8H), 8.24 (NH). ^{13}C NMR (75.5 $MH_{Z,}$ DMSO-$d_{6,}$) δ ppm: 10.73 (C-2'') 13.96 (C-6'), 19.31 (C-3), 22.53 (C-5'), 23.74 (C-1''), 26.47 (2 x CH_3), 28.33 (C-4'), 30.40 (C-3'), 32.16 (C-4), 38.67 (C-1'), 41.69 (C-2'), 73.69 (C-2), 103.95 (C-6), 106.48 (C-8), 108.88 (C-10), 138.84 (C-7), 154.43 (C-9), 155.92 (C-5), 168.66 (C=O). HRMS: found 334.2375 $[M+H]^+$; calculated 334.2377 for $C_{20}H_{32}NO_3$.

General procedure for the synthesis of chroman derivatives 12-15

Compound **2** (500 mg, 2.2 mmol) was dissolved in THF and the aliphatic amines (2.4 mmol) and *N*,*N'*-dicyclohexylcarbodiimide (453.5 mg, 2.2 mmol) were added to the reaction mixture. The reaction mixture was stirred at 25-28 ºC in an incubator shaker and the progress of the reaction was followed by TLC. On completion, the reaction was stopped and extracted twice with water, the organic layer was dried over Na_2SO_4 and the crude products **12-15** were purified by column chromatography.

***N*-Butyl-7-hydroxy-2,2-dimethylchroman-6-carboxamide (12).** Following the general procedure, with carboxylic acid **2** (500 mg, 2.2 mmol), *N*,*N'*-dicyclohexylcarbodiimide (453.5 mg, 2.2 mmol) and butyl amine (160.8 mg, 2.2 mmol), *N*-butyl-7-hydroxy-2,2-dimethylchroman-6-carboxamide **(12)** was obtained (530 mg, 78% yield) as a light yellow viscous liquid. IR spectrum (nujol) cm^{-1}: 3277 (NH), 2928, 2856, 1678 (C=O), 1572, 1293. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.95 (3H, m, C-4'H), 1.32 (8H, brs, 2 x CH_3 and C-3'H), 1.59 (2H, m, C-2'H), 1.79 (2H, m, C-3H), 2.69 (2H, m, C-4H), 3.42 (2H, m, C-1'H), 6.15 (NH), 6.34 (1H, s, C-8H), 7.05 (1H, s, C-5H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 13.75 (C-4'), 20.11 (C-3'), 21.72 (C-4), 26.62 (2 x CH_3), 31.65 (C-2'), 32.74 (C-3), 39.24 (C-1'), 75.16 (C-2), 105.16 (C-8), 107.33 (C-10), 112.07 (C-6), 126.29 (C-5), 159.00 (C-9), 161.32 (C-7), 169.86 (C=O). HRMS: found 300.1565 $[M+Na]^+$; calculated 300.1570 for $C_{16}H_{23}NO_3Na$.

7-Hydroxy-2, 2-dimethyl-*N*-pentylchroman-6-carboxamide (13). Following the general procedure, with carboxylic acid **2** (500 mg, 2.2 mmol), *N*,*N'*-dicyclohexylcarbodiimide (453.5 mg, 2.2 mmol) and pentyl amine (191.6 mg, 2.2 mmol), 7-hydroxy-2, 2-dimethyl-*N*-pentylchroman-6-carboxamide **(13)** was obtained (568 mg, 79% yield) as a light yellow viscous liquid. IR spectrum (nujol), cm^{-1}: 3277 (NH), 2928, 2856, 1677 (C=O), 1572, 1293. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.91 (3H, t, J = 6.0 Hz, C-5'H), 1.25-1.37 (10 H, brs, 2 x CH_3, C-3'H and C-4'H), 1.41-1.63 (2H, m, C-2'H), 1.79 (2H, t, J = 6.0 Hz, C-3H,), 2.69 (2H, t, J = 6.0 Hz, C-4H), 3.37-3.43 (2H, m, C-1'H), 6.15 (NH), 6.35 (1H, s, C-8H), 7.05 (1H, s, C-5H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 13.90 (C-5'), 21.73 (C-4'), 22.25, (C-4), 26.62 (2 x CH_3), 28.90 (C-2'), 29.30 (C-3'), 32.74 (C-3), 39.52 (C-1'), 75.16 (C-2), 105.16 (C-8), 107.33 (C-10), 112.07 (C-6), 126.29 (C-5), 159.00 (C-9), 161.32 (C-7), 169.86 (C=O). HRMS: found 314.1730 $[M+Na]^+$; calculated 314.1527 for $C_{17}H_{25}NO_3Na$.

***N*-Hexyl-7-hydroxy-2,2-dimethylchroman-6-carboxamide (14).** Following the general procedure, with carboxylic acid **2** (500 mg, 2.2 mmol), *N*,*N'*-dicyclohexylcarbodiimide (453.5 mg, 2.2 mmol) and hexyl amine (222 mg, 2.2 mmol), *N*-hexyl-7-hydroxy-2,2-dimethylchroman-6-carboxamide **(14)** was obtained (550 mg, 77% yield) as a light yellow viscous liquid. IR spectrum (nujol), cm^{-1}: 3277 (NH), 2928, 2856, 1677 (C=O), 1572, 1293. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.89 (3H, t, J = 6.0 Hz, C-6'H), 1.25-1.36 (12H, brs, 2 x CH_3, C-5'H, C-4'H and C-3'H), 1.53-1.62 (2H, m, C-2'H), 1.79 (2H, t, J = 6.0 Hz, C-3H), 2.69 (2H, t, J = 6.0 Hz, C-4H), 3.37-3.43 (2H, m, C-1'H), 6.15 (NH), 6.35 (1H, s, C-8H), 7.05 (1H, s, C-5H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 14.00 (C-6'), 21.73 (C-5'), 22.53 (C-4), 26.62 (2 x CH_3), 29.12 (C-3'), 29.57 (C-2'), 31.65 (C-4'), 32.74 (C-3), 39.71 (C-1'), 75.15 (C-2), 105.16 (C-8), 107.33 (C-10), 112.06 (C-6), 126.29 (C-5), 158.99 (C-9), 161.32 (C-7), 169.86 (C=O). HRMS: found 328.1883 $[M+Na]^+$; calculated 328.1872 for $C_{18}H_{27}NO_3Na$.

***N*-(2'-Ethylhexyl)-7-hydroxy-2,2-dimethylchroman-6-carboxamide (15).** Following the general procedure, with carboxylic

acid **2** (500 mg, 2.2 mmol), *N*,*N'*-dicyclohexylcarbodiimide (453.5 mg, 2.2 mmol) and 2-ethylhexyl amine (284.1 mg, 2.2 mmol), *N*-(2'-ethylhexyl)-7-hydroxy-2,2-dimethylchroman-6-carboxamide **(15)** was obtained (610 mg, 74% yield) as a light yellow semi-liquid. IR spectrum (nujol) cm^{-1}: 3277 (NH), 2928, 2856, 1679 (C=O), 1572, 1293. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.90-0.95 (6H, m, C-2''H, C-6'H), 1.25-1.56 (15H, brs, 2xCH_3, C-1''H, C-3'H, C-4'H and C-5'H), 1.79 (2H, t, *J* = 6.0 Hz, C-3H), 2.70 (2H, t, *J* = 6.0 Hz, C-4H), 3.35 (2H, t, *J* = 7.2 Hz, C-1'H), 6.14 (NH), 6.35 (1H, s, C-8H), 7.05 (1H, s, C-5H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 10.84 (C-2''), 14.05 (C-6'), 21.74 (C-5'), 22.54 (C-4), 24.91 (C-1''), 26.84 (2 x CH_3), 29.12 (C-3'), 31.65 (C-4'), 32.74 (C-3), 39.41(C-1'), 42.34 (C-2'), 75.00 (C-2), 105.19 (C-8), 107.42 (C-10), 112.05 (C-6), 126.21 (C-5), 158.98 (C-9) 161.31 (C-7), 169.90 (C=O). HRMS: found 356.2195 ([M+Na]$^+$; calculated 356.2196 for $C_{20}H_{31}NO_3Na$.

6-Formyl-2,2-dimethyl-3,4-dihydro-(2*H*)-benzopyran (22)[18]

4-Hydroxybenzaldehyde (**20**, 500 mg, 4.1 mmol) was converted into 6-formyl-2,2-dimethyl-3,4-dihydro-(2*H*)-benzopyran **(22)** (234 mg, 30% yield) as a gummy mass by following the procedure described by Koul *et al*.[18] The structure of **22** was confirmed by comparing its spectral data with those reported in the literature.[18]

3-[2,2-Dimethyl-3,4-dihydro-(2*H*)-benzopyran-6yl]-2E-propenoic acid (23)[18, 19]

The benzaldehyde **22** (500 mg, 2.6 mmol) was converted into 3-[2,2-Dimethyl-3,4-dihydro-(2*H*)-benzopyran-6yl]-2E-propenoic acid **(23)** (181 mg, 30% yield) by following the procedure described by Koul *et al*.[18] The structure of **23** was confirmed by comparing its spectral data with those reported in the literature.[18]

General procedure for the synthesis of the ester 31 (Method A)

To a stirred suspension of compound **23** (2.0 mmol) in anhydrous methanol (5 mL) at 0 °C, thionyl chloride (5.0 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight, the solvent was removed on a rotary evaporator. The crude syrup was washed with dilute aqueous $NaHCO_3$ and dried to give its methyl ester (as white needles) in quantitative yield.[20]

Methyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate (31). Following the general procedure, with compound **23,** the ester **31** was obtained (443 mg, 90% yield) as white solid. IR spectrum (nujol) cm^{-1}: 1717, 1632, 1606, 1578, 1495, 1436, 1369, 1318, 1264, 1233, 1170, 1152, 1122, 1040, 1018, 983, 948, 893, 857, 822. 1H NMR (300 MHz, CDCl3) δ ppm: δ 1.34 (6H, s, C-2-(CH3)2), 1.81 (2H, t, J = 6.6 Hz, C- 3'H), 2.78 (2H, t, J = 6.6 Hz, C-4'H), 3.78 (3H, s, C-1-OCH3), 6.28 (1H, t, J = 15.9 Hz, C- 2H), 6.77 (1H, t, J = 8.7 Hz, C- 8'H), 7.24 (1H, s, C- 5'H), 7.29 (1H, dd, J = 8.7, 2.0 Hz, C- 7'H), 7.62 (1H, d, J = 15.9 Hz, C- 3H). 13C NMR (75.5 MHZ, CDCl3) δ ppm: 167.94, 156.34, 145.00, 130.03, 127.37, 126.11, 121.25, 117.88, 114.52, 75.09, 51.53, 32.56, 26.90, 22.35. HRMS: found 269.1142; calculated for $C_{15}H_{18}O_3Na$ [M+H]$^+$: 269.1148.

General procedure for the synthesis of the esters 32-34 and 37 (Method B)

The cinnamic acid **23** (464.2 mg, 2 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and oxalyl chloride (304.6 mg, 2.4 mmol) was added dropwise under nitrogen over 15 minutes. After stirring for an additional 1-2 hours, the solvent was evaporated and the residue was redissolved in dry CH_2Cl_2 (10 mL) and to the crude acid chloride, appropriate alcohol (propanol, butan-1-ol, benzyl alcohol or 4-nitrophenol, 2 mmol) was added. The mixture was stirred overnight and the solvent was removed on a rotary evaporator. Further purification by column chromatography afforded the corresponding ester.[21]

***n*-Propyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate (32).** Following the general procedure, with cinnamic acid **23** (464.2 mg, 2.0 mmol), oxalyl chloride (304.6 mg, 2.4 mmol) and n-propanol (121.8 mg, 2 mmol), *n*-propyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate **(32)** was obtained (438.6 mg, 80% yield) as a white solid (mp: 46–48 °C). IR spectrum (film), cm^{-1}: 1708, 1630, 1607, 1492, 1370, 1316, 1264, 1233, 1151, 1121, 1063, 1042, 983, 948, 821. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.99 (3H, t, *J* = 7.2 Hz, -CH_2-CH_2-CH_3), 1.34 (6H, s, C-2'-(CH_3)$_2$), 1.72 (2H, m, *J* = 7.2, 6.9 Hz, -CH_2-CH_2-CH_3), 1.81 (2H, t, *J* = 6.6 Hz, C-3'H), 2.78 (2H, t, *J* = 6.6 Hz, C-4'H), 4.14 (2H, t, *J* = 6.9 Hz, -OCH_2-CH_2-CH_3), 6.28 (1H, d, *J* = 15.9 Hz, C-2H), 6.77 (1H, d, *J* = 8.7 Hz, C-8'H), 7.25 (1H, s, C-5'H), 7.29 (1H, dd, *J* = 8.7, 2.0 Hz, C-7'H), 7.61 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 10.49 (-CH_2-CH_2-CH_3), 22.14 (-CH_2-CH_2-CH_3), 22.35 (C-4'), 26.90 (C-2-(CH_3)$_2$), 32.57 (C-3'), 65.90 (-OCH_2-CH_2-CH_3), 75.06 (C-2'), 115.03 (C-2), 117.85 (C-8'), 121.22 (C-10'), 126.21 (C-6'), 127.34 (C-7'), 129.97 (C-5'), 144.68 (C-3), 156.26 (C-9'), 167.60 (C=O). HRMS: found 297.1464 [M+Na]$^+$; calculated 297.1461 for $C_{17}H_{22}O_3Na$.

***n*-Butyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate (33).** Following the general procedure, with cinnamic acid **23** (464.2 mg, 2.0 mmol), oxalyl chloride (304.6 mg, 2.4 mmol) and n-butanol (148.2 mg, 2 mmol), *n*-butyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate **(33)** was obtained (432.5 mg, 75% yield) as a colorless viscous oil. IR spectrum (film) cm^{-1}: 1709, 1633, 1607, 1578, 1494, 1451, 1423, 1384, 1370, 1316, 1266, 1233, 1170, 1151, 1121, 1065, 1026, 982, 948, 897, 857, 821, 771. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.96 (3H, t, *J* = 7.0 Hz, -CH_2-CH_2-CH_2-CH_3), 1.34 (6H, s, C-2-(CH_3)$_2$), 1.39-1.47 (2H, m, -CH_2-CH_2-CH_2-CH_3), 1.63-1.73 (2H, m, -CH_2-CH_2-CH_2-CH_3), 1.81 (2H, t, *J* = 6.6 Hz, C-3'H), 2.78 (2H, t, *J* = 6.6 Hz, C-4'H), 4.19 (2H, t, *J* = 7.0 Hz, -OCH_2-CH_2-CH_2-CH_3), 6.28 (1H, d, *J* = 15.9 Hz, C-2H), 6.77 (1H, d, *J* = 8.4 Hz, C-8'H), 7.25 (1H, s, C-5'H), 7.29 (1H, d, *J* = 8.4 Hz, C-7'H), 7.60 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 13.72 (-CH_2-CH_2-CH_2-CH_3), 19.16 (-CH_2-CH_2-CH_2-CH_3), 22.27 (C-4'), 26.82 (C-2-(CH_3)$_2$), 30.76 (-CH_2-CH_2-CH_2-CH_3), 32.49 (C-3'), 64.10 (-OCH_2-CH_2-CH_2-CH_3), 74.98 (C-2'), 114.96 (C-2), 117.77 (C-8'), 121.14 (C-10'), 126.12 (C-6'), 127.26 (C-7'), 129.90 (C-5'), 144.59 (C-3), 156.18 (C-9'), 167.53 (C=O). HRMS: found 311.1611 [M+Na]$^+$; calculated 311.1618 for $C_{18}H_{24}O_3Na$.

Benzyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate (34). Following the general procedure, with cinnamic acid **23** (464.2 mg, 2.0 mmol), oxalyl chloride (304.6 mg, 2.4 mmol) and benzylic alcohol (216.3 mg, 2 mmol), benzyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate **(34)** was obtained (451 mg, 70% yield) as a solid (mp: 75–77 °C). IR spectrum (film), cm^{-1}: 1707, 1628, 1606, 1578, 1496, 1458, 1370, 1315, 1263, 1234, 1149, 1121, 983, 948, 897, 822, 751, 697. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (*J*, Hz): 1.33 (6H, s, C-2'-(CH_3)$_2$), 1.80 (2H, t, *J* = 6.8 Hz, C-3'H),

2.76 2H, (t, *J* = 6.8 Hz, C-4'H), 5.23 (2H, s, -OCH_2-Ph), 6.32 (1H, d, *J* = 16.0 Hz, C-2H), 6.76 (1H, d, *J* = 8.7 Hz, C-8'H), 7.23 (1H, s, C-5'H), 7.28 (1H, dd, *J* = 8.7, 2.0 Hz, C-7'H), 7.32-7.43 (5H, m, C-2", 3", 4", 5" & 6"H), 7.65 (1H, d, *J* = 16.0 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 22.35 (C-4'), 26.92 (C-2'-(CH_3)$_2$), 32.57 (C-3'), 66.13 (-OCH_2-Ph), 75.12 (C-2'), 114.60 (C-2), 117.91 (C-8'), 121.27 (C-10'), 126.12 (C-6'), 127.44 (C-7'), 128.17 (C-4"), 128.23 (C-3" & C-5"), 128.59 (C-2" & C-6"), 130.10 (C-5'), 136.33 (C-1"), 145.34 (C-3), 156.42 (C-9'), 167.31 (C=O). HRMS: found 345.1457 $[M+Na]^+$; calculated 345.1461 for $C_{21}H_{22}O_3Na$.

***p*-Nitrophenyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate (37).** Following the general procedure, with cinnamic acid **23** (464.2 mg, 2.0 mmol), oxalyl chloride (304.6 mg, 2.4 mmol) and 4-nitrophenol (278.2 mg, 2 mmol), *p*-nitrophenyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate **(37)** was obtained (460 mg, 65% yield) as a white powder (mp: 110–112 °C). IR spectrum (film), cm^{-1}: 1736, 1602, 1593, 1524, 1491, 1347, 1269, 1209, 1158, 1113, 983, 946, 860, 823, 748. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.37 (6H, s, C-2'-(CH_3)$_2$), 1.84 (2H, t, *J* = 6.6 Hz, C-3'H), 2.81 (2H, t, *J* = 6.6 Hz, C-4'H), 6.44 (1H, d, *J* = 15.9 Hz, C-2H), 6.82 (1H, d, *J* = 8.4 Hz, C-8'H), 7.33 (1H, s, C-5'H), 7.34 (1H, dd, *J* = 8.4, 2.0 Hz, C-7'H), 7.36 (dd, 2H, *J* = 9.0, 2.1 Hz, C-2"H & C-6"H), 7.83 (1H, d, *J* = 15.9 Hz, C-3H), 8.29 (d, 2H, *J* = 9.0, 2.1 Hz, C-3"H & C-5"H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 22.34 (C-4'), 26.93 (C-2'-(CH_3)$_2$), 32.50 (C-3'), 75.42 (C-2'), 112.59 (C-2), 118.15 (C-8'), 121.53 (C-10'), 122.52 (C-3" & C-5"), 125.18 (C-2" & C-6"), 125.55 (C-6'), 127.87 (C-7'), 130.68 (C-5'), 145.11 (C-4"), 148.26 (C-3), 155.89 (C-1"), 157.23 (C-9'), 164.85 (C=O). HRMS: found 376.1155 $[M+Na]^+$; calculated 376.1155 for $C_{20}H_{19}NO_5Na$.

General procedure for the synthesis of the esters 35 and 36 (Method C)

A mixture of the cinnamic acid **23** (464.2 mg, 2.0 mmol), phenol derivative (2 mmol), triphenylphosphine (629.5 mg, 2.4 mmol), CCl_4 (0.23 mL, 2.4 mmol) and triethylamine (242.9 mg, 2.4 mmol) was dissolved in acetonitrile (20 mL); after stirring at room temperature for 2-4 hours, the mixture was refluxed overnight and the solvent was removed on a rotary evaporator. Further purification was performed by column chromatography to afford the corresponding ester, poor yields for compounds containing nitro group were obtained due to the simultaneous formation of a colored matter from phosphine and nitro group.[22]

Phenyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate (35). Following the general procedure, with cinnamic acid **23** (464.2 mg, 2.0 mmol), phenol (188.2 mg, 2 mmol), triphenylphosphine (629.5 mg, 2.4 mmol), CCl_4 (0.23 mL, 2.4 mmol) and triethylamine (242.9 mg, 2.4 mmol), phenyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate **(35)** was obtained (431.7 mg, 70% yield) as a white powder (mp: 93–95 °C). IR spectrum (film), cm^{-1}: 1726, 1630, 1605, 1577, 1492, 1423, 1318, 1268, 1234, 1196, 1160, 1135, 1119, 982, 947, 820, 748, 688. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.35 (6H, s, C-2'-(CH_3)$_2$), 1.83 (2H, t, *J* = 6.9 Hz, C-3'H), 2.79 (2H, t, *J* = 6.9 Hz, C-4'H), 6.46 (1H, d, *J* = 16.0 Hz, C-2H), 6.80 (1H, d, *J* = 8.4 Hz, C-8'H), 7.30 (1H, s, C-5'H), 7.32 (1H, dd, *J* = 8.4, 2.0 Hz, C-7'H), 7.16 (2H, d, *J* = 7.8 Hz, C-2"H & C-6"H), 7.20-7.25 (1H, m, C-4"H), 7.39 (2H, t, *J* = 7.8 Hz, C-3"H & C-5"H), 7.79 (1H, d, *J* = 16.0 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 22.37 (C-4'), 26.95 (C-2'-(CH_3)$_2$), 32.56 (C-3'), 75.25 (C-2'), 113.91 (C-2), 118.03 (C-8'), 121.39 (C-10'), 121.75 (C-2" & C-6"), 125.63 (C-4"), 125.95 (C-6'), 127.67 (C-7'), 129.41 (C-3" & C-5"), 130.39 (C-5'), 146.77 (C-3), 150.98 (C-1"), 156.76 (C-9'), 165.92 (C=O). HRMS: found 331.1299 $[M+Na]^+$; calculated 331.1305 for $C_{20}H_{20}O_3Na$.

***p*-*t*-Butylphenyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate (36).** Following the general procedure, with cinnamic acid **23** (464.2 mg, 2.0 mmol), 4-*t*-butylphenol (300.2 mg, 2 mmol), triphenylphosphine (629.5 mg, 2.4 mmol), CCl_4 (0.23 mL, 2.4 mmol) and triethylamine (242.9 mg, 2.4 mmol), *p*-*t*-butylphenyl 3-[2,2-dimethyl-3,4-dihydro-(*2H*)-benzopyran-6yl]-*2E*-prop-2-enoate **(36)** was obtained (546.7 mg, 75% yield) as a white poder (mp: 134–136 °C). IR spectrum (film), cm^{-1}: 1726, 1710, 1634, 1605, 1578, 1506, 1493, 1453, 1320, 1267, 1229, 1197, 1123, 1034, 985, 945, 854, 822, 753, 702. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.33 (9H, s, -C(CH_3)$_3$), 1.35 (6H, s, C-2'-(CH_3)$_2$), 1.83 (2H, t, *J* = 6.6 Hz, C-3'H), 2.80 (2H, t, *J* = 6.6 Hz, C-4'H), 6.46 (1H, d, *J* = 15.9 Hz, C-2H), 6.80 (1H, d, *J* = 8.4 Hz, C-8'H), 7.08 (d, 2H, *J* = 8.7 Hz, C-2"H & C-6"H), 7.31 (1H, s, C-5'H), 7.35 (1H, dd, *J* = 8.4, 2.0 Hz, C-7'H), 7.40 (2H, d, *J* = 8.7 Hz, C-3"H & C-5"H), 7.78 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 22.37 (C-4'), 26.94 (C-2'-(CH_3)$_2$), 31.46 (-C(CH_3)$_3$), 32.58 (C-3'), 34.49 (-C(CH_3)$_3$), 75.22 (C-2'), 114.10 (C-2), 118.0 (C-8'), 121.00 (C-2" & C-6"), 121.36 (C-10'), 126.01 (C-6'), 126.29 (C-3" & C-5"), 127.64 (C-7'), 130.33 (C-5'), 146.57 (C-3), 148.38 (C-4"), 148.60 (C-1"), 156.70 (C-9'), 166.09 (C=O). HRMS: found 387.1928 $[M+Na]^+$; calculated 387.1931 for $C_{24}H_{28}O_3Na$.

General procedure for the synthesis of 2,2-dimethylchroman 41-43

2-Methyl-buta-1,3-diene was bubbled into a mixture of phenol derivative **38-40** (500 mg, 4.5 mmol), orthophosphoric acid (85%, 0.6 mL) and xylene (3.5 mL) with constant stirring at 35-40 °C for 1-2 h. Stirring was continued for 15 h more and then the mixture neutralised with sodium hydrogen carbonate solution (5%, 35 mL). It was extracted with ether, the organic phase washed with water, dried (Na_2S0_4) and the solvent distilled off.

7-Hydroxy-2,2-dimethylchroman (41). Following the general procedure, with phenol derivative **38** (500 mg, 4.5 mmol), diene **21** and orthophosphoric acid, 7-hydroxy-2,2-dimethylchroman (**41**) was obtained (360.9 mg, 45 % yield) as a white solid. The structure of **41** was confirmed by comparing its spectral data with those reported in the literature.[32]

7,8-Dihydroxy-2,2-dimethylchroman (42). Following the general procedure, with phenol derivative **39** (572 mg, 4.5 mmol), diene **21** and orthophosphoric acid, 7,8-dihydroxy-2,2-dimethylchroman (**42**) was obtained (437 mg, 50 % yield) as a white solid. The structure of **42** was confirmed by comparing its spectral data with those reported in the literature.[32]

5,7-Dihydroxy-2,2-dimethylchroman (43). Following the general procedure, with phenol derivative **40** (572 mg, 4.5 mmol), buta-1,3-diene **21** and orthophosphoric acid, 5,7-dihydroxy-2,2-dimethylchroman (**43**) was obtained (437 mg, 50 % yield) as a white solid. The structure of **43** was confirmed by comparing its spectral data with those reported in the literature.[32]

General procedure of methylation of 2,2-dimethylchromans 44-46

A solution of dimethyl sulfate (1 mL, 10.5 mmol) in anhydrous acetone (10 mL) was added to a solution of 2,2-dimethylchroman (**41**-**43**, 2.80 mmol) in anhydrous acetone (40 mL) and the reaction mixture was refluxed for 12 h. After completion of the reaction as followed by TLC, the solvent was removed under reduced pressure and water was added to it, and the contents were extracted with ethyl acetate (2 x 30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure, the residue was subjected to column chromatography on silica using gradient ethyl acetate-petroleum ether.

7-Methoxy-2,2-dimethylchroman (**44**). Following the general procedure, with 2,2-dimethylchroman **41** (500 mg, 2.80 mmol) and dimethyl sulfate (1.9 mL, 5.6 mmol), 7-methoxy-2,2-dimethylchroman (**44**) is obtained (376.5 mg, 70% yield) as a viscous oil. The structure of **44** was confirmed by comparing its spectral data with those reported in the literature.[24-26]

7,8-Dimethoxy-2,2-dimethylchroman (45). Following the general procedure, with 2,2-dimethylchroman **42** (543.4 mg, 2.80 mmol) and dimethyl sulfate (1.9 mL, 5.6 mmol), 7-methoxy-2,2-dimethylchroman (**45**) is obtained (447.8 mg, 72% yield) as a viscous oil. The structure of **45** was confirmed by comparing its spectral data with those reported in the literature.[24-26]

5,7-Dimethoxy-2,2-dimethylchroman (46). Following the general procedure, with 2,2-dimethylchroman **43** (543.4 mg, 2.80 mmol) and dimethyl sulfate (1.9 mL, 5.6 mmol), 7-methoxy-2,2-dimethylchroman (**46**) is obtained (454 mg, 73% yield) as a viscous oil. The structure of **46** was confirmed by comparing its spectral data with those reported in the literature.[24-26]

General procedure for the synthesis of 2,2-dimethylchroman carbaldehydes 47-49

To a stirred solution of **44**-**46** (0.184 mol) in acetonitrile (200 mL), dry DMF (80 mL) and $POCl_3$ (80 mL) were added drop wise at room temperature over 30 minutes and the reaction mixture was stirred at 55-60 ºC for 13 h. The reaction was quenched by adding ice water and the aq. solution was extracted with ethyl acetate (2 x 30 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using gradient of ethyl acetate-petroleum ether (1:9).

7-Methoxy-2,2-dimethylchroman-6-carbaldehyde (47). Following the general procedure, with 2,2-dimethylchroman **44** (192 mg, 1.184 mol), 7-methoxy-2,2-dimethylchroman-6-carbaldehyde **(47)** is obtained (182.5 mg, 70% yield). The structure of **47** was confirmed by comparing its spectral data with those reported in the literature.[27]

7,8-Dimethoxy-2,2-dimethylchroman-6-carbaldehyde (48). Following the general procedure, with 2,2-dimethylchroman **45** (227.4 mg, 1.184 mol), 7,8-dimethoxy-2,2-dimethylchroman-6-carbaldehyde **(48)** is obtained (222.2 mg, 75% yield) as a viscous oil. IR spectrum (film), cm^{-1}: 2976, 2935, 1679 (C=O), 1601, 1474, 1338, 1307. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.34 (6H, s, 2 x CH_3), 1.83 (2H, t, J = 6.6 Hz, C-3H), 2.77 (2H, t, J = 6.6 Hz, C-4H), 3.84 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 7.35 (1H, s, C-5H), 10.20 (1H, s, CHO). ^{13}C NMR (75.5 MH_Z, DMSO-d_6,) δ ppm: 21.80 (C-4), 26.49 and 29.16 (2 x CH_3), 32.35 (C-3), 60.49 and 62.15 (2 x OCH_3), 74.75 (C-2), 117.41 (C-10), 121.01 (C-6), 121.93 (C-5), 140.92 (C-8), 154.27 (C-7), 155.06 (C-9), 188.76 (C=O). HRMS: found 273.1092 $[M+Na]^+$; calculated 273.1097 for $C_{14}H_{18}O_4Na$.

5,7-Dimethoxy-2,2-dimethylchroman-8-carbaldehyde (49): Following the general procedure, with **2,2-dimethylchroman** 45 (263 mg, **1.184** mol), 5,7-dimethoxy-2,2-dimethylchroman-8-carbaldehyde **(49)** was obtained (222.2 mg, 75% yield) as a yellow solid (mp: 97 ^{o}C). IR spectrum (film), cm^{-1}: 2929, 1671 (C=O), 1601, 1466, 1396, 1346, 1244. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.35 (6H, s, 2 x CH_3), 1.77 (2H, t, J = 6.6 Hz, C-3H), 2.56 (2H, t, J = 6.6 Hz, C-4H), 3.83 & 3.89 (6H, 2s, 2 x OCH_3), 6.06 (1H, s, C-6H), 10.35 (1H, s, CHO). ^{13}C NMR (75.5 MH_Z, DMSO-d_6) δ ppm: 16.22 (C-4), 26.49 and 29.16 (2 x CH_3), 31.72 (C-3), 55.35 and 55.66 (2 x OCH_3), 75.31 (C-2), 86.22 (C-6), 102.06 (C-10), 108.21 (C-8), 158.35 (C-9), 161.33 (C-7), 163.00 (C-5), 188.14 (C=O). HRMS: found 273.1093 $[M+Na]^+$; calculated 273.1097 for $C_{14}H_{18}O_4Na$.

General procedure of the synthesis of chromanyl acrylic acids 51-53

To the aldehydes **47-49** (2.2 mmol) in pyridine (2.5 mL) and piperidine (0.1 mL) was added malonic acid (2.6 mmol) and contents stirred for 24 h, followed by heating on water bath for 6 h. The contents were cooled, poured in ice-cold water, acidifed with 2N HCl. The resulting precipitate was filtered, washed with water and air dried to give final products **51-53**.

3-(7'-Methoxy-2', 2'-dimethylchroman-6'-yl) acrylic acid (51). Following the general procedure, with aldehyde **47** (500 mg, 2.2 mmol), malonic acid **50** (274.7 mg, 2.6 mmol) and piperidine (0.1 mL), 3-(7'-methoxy-2', 2'-dimethylchroman-6'-yl) acrylic acid **(51)** was obtained (461.3 mg, 80% yield) as a white solid (mp: 158 ^{o}C). IR spectrum (film), cm^{-1}: 3401, 2939, 1713 (C=O), 1600, 1510, 1464, 1350, 1297. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.37 (6H, s, 2 x CH_3), 1.82 (2H, t, J = 6.0 Hz, C-3'H), 2.74 (t, 2H, J = 6.0 Hz, C-4'H) , 3.84 (s, 3H, OCH_3), 6.36 (s, 1H, C-8'H), 6.44 (1H, d, J = 15.9 Hz, C-2H), 7.26 (1H, s, C-5'H), 8.01 (1H, d, J = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MH_Z, $CDCl_3$) δ ppm: 21.50 (C-4'), 26.75 & 26.88 (2 x CH_3), 32.75 (C-3'), 55.47 (OCH_3), 75.38 (C-2'), 100.11 (C-8'), 113.18 (C-10'), 114.40 (C-6'), 115.47 (C-2) 130.75 (C-5'), 142.61 (C-3), 157.59 (C-7'), 158.63 (C-9'), 173.63 (C=O). HRMS: found 285.1092 $[M+Na]^+$; calculated 285.1097 for $C_{15}H_{18}O_4Na$.

3-(7',8'-Dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylic acid (52). Following the general procedure, with aldehyde **48** (550 mg, 2.2 mmol), malonic acid **50** (274.7 mg, 2.6 mmol) and piperidine (0.1 mL), 3-(7',8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylic acid **(52)** was obtained (514 mg, 80% yield) as a light brown solid (mp: 124 ^{o}C). IR spectrum (KBr), cm^{-1}: 3431, 2933, 1685 (C=O), 1598, 1474, 1259. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.38 (6H, s, 2 x CH_3), 1.83 (2H, t, J = 6.6 Hz, C-3'H), 2.77 (2H, t, J = 6.6 Hz, C-4'H) , 3.88 (6H, s, 2 x OCH_3), 6.39 (1H, d, J =15.9 Hz, C-2H), 7.07 (1H, s, C-5'H), 7.98 (1H, d, J = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MH_Z, $CDCl_3$) δ ppm: 22.13 (C-4'), 26.91 (2 x CH_3), 32.54 (C-3'), 60.69 & 61.58 (2 x OMe), 75.50 (C-2'), 115.25 (C-6'), 117.93 (C-10'), 119.35 (C-2), 123.33 (C-5') 141.84 (C-8'), 142.25 (C-9'), 150.83 (C-3), 151.77 (C-7'), 173.00 (C=O). HRMS: found 315.1192 $[M+Na]^+$; calculated 315.1203 for $C_{16}H_{20}O_5Na$.

3-(5',7'-Dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylic acid (53). Following the general procedure, with aldehyde **49** (550 mg, 2.2

mmol), malonic acid **50** (274.7 mg, 2.6 mmol) and piperidine (0.1 mL), 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylic acid **(53)** was obtained (515 mg, 80% yield) as a light brown solid (mp: 130 ^{o}C). IR spectrum (KBr), cm^{-1}: 3420, 2928, 1678 (C=O), 1601, 1465, 1353, 1305, 1252. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.37 (6H, s, 2 x CH_3), 1.76 (2H, t, *J* = 6.6 Hz, C-3'H), 2.57 (2H, t, *J* = 6.6 Hz, C-4'H) , 3.86 (6H, s, 2 x OCH_3), 6.04 (1H, s, C-6'H), 6.80 (1H, d, *J* = 15.9 Hz, C-2H), 8.22 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 16.67 (C-4'), 26.62 & 26.72 (2 x CH_3), 31.78 (C-3'), 55.35 & 55.66 (2 x OCH_3), 75.38 (C-2'), 86.59 (C-6'), 102.51 (C-10'), 105.30 (C-8'), 115.89 (C-2), 127.06 (C-3), 155.47 (C-9'), 159.76 (C-7'), 160.16 (C-5'), 174.65 (C=O). HRMS: found 315.1196 $[M+Na]^+$; calculated 315.1203 for $C_{16}H_{20}O_5$ Na.

General procedure of the synthesis of chromanyl acrylates 58-69

To a stirred suspension of carboxylic acid **51-53** (2 mmol) in the required alcohol **54-57 (10 mmol)** at 0 °C under nitrogen was added dropwise thionyl chloride (285.5 mg, 2.4 mmol). The reaction mixture was allowed to reflux overnight then cooled to room temperature and the solvent was removed to give the desired products **58-69**.

(*E*)-Methyl 3-(7'- methoxy-2', 2'-dimethylchroman-6'-yl) acrylate (58). Following the general procedure, with carboxylic acid **51** (524.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and methanol **54** (320 mg, 10 mmol), (*E*)-methyl 3-(7'- methoxy-2',2'-dimethylchroman-6'-yl)acrylate **(58)** was obtained (425.2 mg, 77% yield) as a white solid (mp: 104 ^{o}C). IR spectrum (KBr), cm^{-1}: 2965, 2932, 1722 (C=O), 1611, 1491, 1322, 1201. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.34 (6H, s, 2 x CH_3), 1.79 (2H, t, *J* = 6.6 Hz, C-3'H), 2.71 (2H, t, *J* = 6.6 Hz, C-4'H) , 3.77 (3H, s, C-1''H), 3.81 (3H, s, OCH_3), 6.32 (1H, s, C-8'H), 6.40 (1H, d, *J* =15.9 Hz, C-2H), 7.20 (1H, s, C-5'H), 7.88 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 21.55 (C-4'), 26.89 (2 x CH_3), 32.82 (C-3'), 51.39 (OCH_3), 55.47 (C-1''), 75.25 (C-2'), 100.15 (C-8'), 113.11 (C-10'), 115.07 (C-2), 115.78 (C-6'), 130.36 (C-5'), 140.49 (C-3), 157.16 (C-9'), 158.40 (C-7'), 168.46 (C=O). HRMS: found 277.1431 $[M+H]^+$; calculated 277.1434 for $C_{16}H_{21}O_4$.

(*E*)-Ethyl 3-(7'-methoxy-2', 2'-dimethylchroman-6'-yl) acrylate (59). Following the general procedure, with carboxylic acid **51** (524.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and ethanol **55** (460 mg, 10 mmol), (*E*)-ethyl 3-(7'-methoxy-2', 2'-dimethylchroman-6'-yl) acrylate **(59)** was obtained (464.2 mg, 80% yield) as a viscous oil. IR spectrum (film), cm^{-1}: 2976, 2936, 1706 (C=O), 1613, 1491, 1448, 1320, 1257, 1160. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.29 (3H, t, *J* = 7.2 Hz, C-2''H), 1.32 (6H, s, 2 x CH_3), 1.79 (2H, t, *J* = 6.6 Hz, C-3'H), 2.70 (2H, t, *J* = 6.6 Hz, C-4'H), 3.81 (3H, s, OCH_3), 4.23 (2H, q, *J* = 7.2 Hz, C-1''H), 6.33 (1H, s, C-8'H), 6.40 (1H, d, *J* = 15.9 Hz, C-2H), 7.20 (1H, s, C-5'H), 7.88 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 14.41 (C-2''), 21.53 (C-4'), 26.87 (2 x CH_3), 32.81 (C-3'), 55.49 (C-1''), 59.86 (OCH_3), 74.78 (C-2'), 100.12 (C-8'), 101.60 (C-10'), 110.13 (C-6'), 113.06 (C-5'), 127.79 (C-2), 138.47 (C-3), 154.11 (C-9'), 157.07 (C-7') and 168.03 (C=O). HRMS: found 291.1594 $[M+H]^+$; calculated 291.1591 for $C_{17}H_{23}O_4$.

(*E*)-Phenyl 3-(7'-methoxy-2', 2'-dimethylchroman-6'-yl) acrylate (60). Following the general procedure, with carboxylic acid **51** (524.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and phenol **56** (941.1 mg, 10 mmol), (*E*)-phenyl 3-(7'-methoxy-2', 2'-dimethylchroman-6'-yl) acrylate **(60)** was obtained (514.4 mg, 76% yield) as a white solid (mp: 155 ^{o}C. IR spectrum (KBr), cm^{-1}: 2969, 2932, 1701 (C=O), 1624, 1570, 1444, 1320, 1235, 1160. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.38 (6H, s, 2 x CH_3), 1.81 (2H, t, *J* = 6.6 Hz, C-3'H), 2.73 (2H, t, *J* = 6.6 Hz, C-4'H), 3.84 (3H, s, OCH_3), 6.36 (1H, s, C-8'H), 6.60 (1H, d, *J* = 15.9 Hz, C-2H), 7.14-7.26 (4H, m, C-5', C-4'', C-3'' & C-5''), 7.39-7.41 (2H, m, C-2'' & C-6''), 8.05 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 21.53 (C-4'), 26.91 (2 x CH_3), 32.78 (C-3'), 55.51 (OCH_3), 75.40 (C-2'), 100.18 (C-8'), 113.24 (C-10'), 114.43 (C-2), 115.62 (C-6'), 121.80 (C-3'' & C-5''), 125.46 (C-4''), 128.51 (C-2'' & C-6''), 130.91 (C-5'), 142.34 (C-3), 151.12 (C-1''), 157.58 (C-9'), 158.68 (C-7'), 166.46 (C=O). HRMS: found 339.1591 $[M+H]^+$; calculated 339.1591 for $C_{21}H_{23}O_4$.

(*E*)-4-Methoxyphenyl 3-(7'- methoxy-2', 2'-dimethylchroman-6'-yl) acrylate (61). Following the general procedure, with carboxylic acid **51** (524.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and 4-methoxyphenol **57** (1.2 g, 10 mmol), (*E*)-4-methoxyphenyl 3-(7'- methoxy-2', 2'-dimethylchroman-6'-yl) acrylate **(61)** was obtained (575.2 mg, 78% yield) as a white solid (mp: 143 ^{o}C). IR spectrum (film), cm^{-1}: 2974, 2936, 1724 (C=O), 1612, 1505, 1447, 1322, 1243, 1160. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.38 (6H, s, 2 x CH_3), 1.77 (2H, t, *J* = 6.6 Hz, C-3'H), 2.73 (2H, t, *J* = 6.6 Hz, C-4'H), 3.80 & 3.83 (6H, 2s, 2 x OCH_3), 6.35 (1H, s, C-8'H), 6.44 (1H, d, *J* = 15.9 Hz, C-2H), 7.26 (1H, s, C-5'H), 6.90 (2H, d, *J* = 8.4 Hz, C-3'' & C-5''), 7.07 (2H, d, *J* = 8.4 Hz, C-2''H & C-6''H), 8.29 (1H, d, *J* =15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 21.51 (C-4'), 26.88 (2 x CH_3), 32.76 (C-3'), 55.47 & 55.57 (2 x OCH_3), 75.36 (C-2'), 100.15 (C-8'), 113.20 (C-10'), 114.37 (C-2), 114.47 (C-3'' & C-5''), 115.62 (C-6'), 122.50 (C-2''& C-6''), 130.85 (C-5'), 142.13 (C-3), 144.58 (C-1''), 157.00 (C-4''), 157.50 (C-9'), 158.63 (C-7'), 166.82 (C=O). HRMS: found 369.1697 $[M+H]^+$; calculated 369.1697 for $C_{22}H_{25}O_5$.

(*E*)-Methyl 3-(7',8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate (62). Following the general procedure, with carboxylic acid **52** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and methanol **54** (320 mg, 10 mmol), (*E*)-methyl 3-(7',8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate **(62)** was obtained (496.1 mg, 81% yield) as a viscous oil. IR spectrum (film), cm^{-1}: 2975, 2933, 1715 (C=O), 1628, 1568, 1464, 1320, 1254, 1166. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.39 (6H, s, 2 x CH_3), 1.82 (2H, t, *J* = 6.6 Hz, C-3'H), 2.75 (2H, t, *J* = 6.6 Hz, C-4'H) , 3.78 (3H, s, C-1''H), 3.89 (6H, s, 2 x OCH_3), 6.38 (1H, d, *J* = 15.9 Hz, C-2H), 7.02 (1H, s, C-5'H), 7.87 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 $MH_{Z,}$ $CDCl_3$) δ ppm: 22.12 (C-4'), 26.89 (2 x CH_3), 32.51 (C-3'), 51.51 (C-1''), 60.69 & 61.53 (2 x OCH_3), 75.38 (C-2'), 115.81 (C-2), 117.85 (C-6'), 119.53 (C-10'), 123.00 (C-5'), 140.09 (C-3), 141.81 (C-8'), 150.37 (C-9'), 151.49 (C-7'), 168.12 (C=O). HRMS: found, *m/z*: 307.1689 $[M+H]^+$; calculated *m/z*: 307.1697 for $C_{17}H_{23}O_5$.

(*E*)-Ethyl 3-(7',8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate (63). Following the general procedure, with carboxylic acid **52** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and ethanol **55** (460 mg, 10 mmol), (*E*)-ethyl 3-(7',8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate **(63)** was obtained (505.5 mg, 79% yield) as a viscous oil. IR spectrum (film), cm^{-1}: 2975, 2932, 1714 (C=O), 1628, 1568, 1466, 1350, 1254, 1166. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.32 (3H, t, *J* = 7.2 Hz, C-2''H), 1.39 (6H, s, 2 x CH_3), 1.81 (2H, t, *J* = 6.6 Hz, C-3'H), 2.75 (2H, t, *J* = 6.6 Hz, C-4'H), 3.89 (6H, s, 2 x OCH_3), 4.23 (2H, q, *J* = 7.2 Hz, C-1''H), , 6.37 (1H, d, *J* = 15.9 Hz, C-2H),

7.03 (1H, s, C-5'H), 7.86 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 14.39 (C-2''), 22.15 (C-4'), 26.91 (2 x CH_3), 32.58 (C-3'), 60.19 (C-1''), 60.68 & 61.52 (2 x OCH_3), 75.35 (C-2'), 116.38 (C-6'), 117.82 (C-10'), 119.71 (C-5'), 122.99 (C-2), 139.83 (C-3), 141.85 (C-8'), 150.30 (C-9'), 151.51 (C-7'), 167.69 (C=O). HRMS: found: 321.1683 $[M+H]^+$; calculated 321.1697 for $C_{18}H_{25}O_5$.

(*E*)-Phenyl 3-(7', 8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate (64). Following the general procedure, with carboxylic acid **52** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and phenol **56** (941.1 mg, 10 mmol), (*E*)-phenyl 3-(7', 8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate **(64)** was obtained (589.4 mg, 80% yield) as a viscous oil. IR spectrum (film), cm^{-1}: 2924, 2853, 1725 (C=O), 1600, 1459, 1349, 1194. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.36 (6H, s, 2 x CH_3), 1.83 (2H, t, *J* = 6.6 Hz, C-3'H), 2.77 (2H, t, *J* = 6.6 Hz, C-4'H), 3.85 & 3.92 (6H, 2s, 2 x OCH_3), 6.57 (1H, d, *J* = 15.9 Hz, C-2H), 7.09 (1H, s, C-5'H), 7.15-7.18 (2H, m, C-3'' & C-5''), 7.23 (2H, d, *J* = 7.5 Hz, C-4''), 7.36-7.42 (2H, m, C-2''& C-6''), 8.04 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 21.13 (C-4'), 26.91 (2 x CH_3), 32.52 (C-3'), 60.70, & 61.57 (2 x OCH_3), 75.51 (C-2'), 114.08 (C-2), δ 117.93 (C-6'), 119.41 (C-10'), 120.48 (C-3'' & C-5''), 123.42 (C-5'), 122.55 (C-4''), 129.35 (C-2'' & C-6''), 141.86 (C-3), 141.93 (C-8'), 150.81 (C-9'), 151.03 (C-1''), 151.76 (C-7'), 166.10 (C=O). HRMS: found 369.1697 $[M+H]^+$; calculated 369.1697 for $C_{22}H_{25}O_5$.

(*E*)-4-Methoxyphenyl 3-(7', 8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate (65). Following the general procedure, with carboxylic acid **52** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and 4-methoxyphenol **57** (1.2 g, 10 mmol), (*E*)-4-methoxyphenyl 3-(7', 8'-dimethoxy-2', 2'-dimethylchroman-6'-yl) acrylate **(65)** was obtained (598.7 mg, 75% yield) as a viscous oil. IR spectrum (KBr), cm^{-1}: 2973, 2574, 1678 (C=O), 1596, 1490, 1306, 1269. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.40 (6H, s, 2 x CH_3), 1.83 (2H, t, *J* = 6.6 Hz, C-3'H), 2.77 (2H, t, *J* = 6.6 Hz, C-4'H), 3.81 (3H, s, OCH_3), 3.85 & 3.92 (6H, 2s, 2 x OCH_3), 6.55 (1H, d, *J* = 15.9 Hz, C-2H), 6.90 (2H, d, *J* = 8.7 Hz, C-2''& C-6''H), 7.06-7.09 (3H, m, C-5', C-3'' & C-5''), 8.02 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 22.14 (C-4'), 26.91 (2 x CH_3), 32.55 (C-3'), 55.60, 60.68 & 61.52 (3 x OCH_3), 75.48 (C-2'), 114.42 (C-3'' & C-5''), 115.30 (C-2), 117.91 (C-6'), 119.47 (C-10'), 122.47 (C-2''& C-6''), 123.38 (C-5'), 141.75 (C-3), 141.87 (C-8'), 144.56 (C-1''), 150.75 (C-9'), 151.74 (C-7'), 157.10 (C-4''), 166.44 (C=O). HRMS: found 399.1802 $[M+H]^+$; calculated 399.1804 for $C_{23}H_{27}O_6$.

(*E*)-Methyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate (66). Following the general procedure, with carboxylic acid **53** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and methanol **54** (320 mg, 10 mmol), (*E*)-methyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate **(66)** was obtained (477.5 mg, 78% yield) as a light brown solid (mp: 94 ^{o}C). IR spectrum (KBr), cm^{-1}: 2975, 2949, 1702 (C=O), 1602, 1464, 1353, 1292, 1162. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.36 (6H, s, 2 x CH_3), 1.75 (2H, t, *J* = 6.6 Hz, C-3'H), 2.57 (2H, t, *J* = 6.6 Hz, C-4'H), 3.77 (3H, s, C-1''H), 3.86 (6H, s, 2 x OCH_3), 6.04 (1H, s, C-6'H), 6.79 (1H, d, *J* = 15.9 Hz, C-2H), 8.12 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 16.69 (C-4'), 26.74 (2 x CH_3), 31.82 (C-3'), 51.24 (C-1''), 55.39 and 55.63 (2 x OCH_3), 75.27 (C-2'), 86.63 (C-6'), 102.54 (C-10'), 105.44 (C-8'), 116.51 (C-2), 136.29 (C-3), 155.26 (C-7'), 159.47 (C-9'), 159.74 (C-5'), 169.72 (C=O). HRMS: found 329.1352 $[M+Na]^+$; calculated 329.1359 for $C_{17}H_{22}O_5Na$.

(*E*)-Ethyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate (67). Following the general procedure, with carboxylic acid **53** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and ethanol **55** (460 mg, 10 mmol), (*E*)-ethyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate **(67)** was obtained (518.7 mg, 81% yield) as a white solid (mp: 65 ^{o}C). IR spectrum (KBr), cm^{-1}: 2977, 2944, 1697 (C=O), 1602, 1467, 1353, 1291, 1168. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.32 (3H, t, *J* = 7.2 Hz, C-2''H), 1.34 (6H, s, 2 x CH_3), 1.75 (2H, t, *J* = 6.6 Hz, C-3'H), 2.57 (2H, t, *J* = 6.6 Hz, C-4'H), 3.87 (6H, s, 2 x OCH_3), 4.23 (2H, q, *J* = 7.2 Hz, C-1''H), 6.04 (1H, s, C-6'H), 6.78 (1H, d, *J* = 15.9 Hz, C-2H), 8.11 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 14.21 (C-2''), 16.72 (C-4'), 26.74 (2 x CH_3), 31.65 (C-3'), 55.39 & 55.64 (2 x OCH_3), 60.39 (C-1''), 75.24 (C-2'), 86.72 (C-6'), 102.57 (C-10'), 105.56 (C-8'), 117.04 (C-2), 136.05 (C-3), 155.21 (C-7'), 159.50 (C-9'), 159.69 (C-5'), 169.32 (C=O). HRMS: found 321.1691 $[M+H]^+$; calculated 321.1697 for $C_{18}H_{25}O_5$.

(*E*)-Phenyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate (68). Following the general procedure, with carboxylic acid **53** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and phenol **56** (941.1 mg, 10 mmol), (*E*)-phenyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate **(68)** was obtained (560 mg, 76% yield) as a white solid (mp: 170 ^{o}C). IR spectrum (KBr), cm^{-1}: 2969, 2925, 1731 (C=O), 1591, 1458, 1332, 1237, 1128. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.38 (6H, s, 2 x CH_3), 1.77 (2H, t, *J* = 6.6 Hz, C-3'H), 2.59 (2H, t, *J* = 6.6 Hz, C-4'H), 3.87 (6H, s, 2 x OCH_3), 6.06 (1H, s, C-6'H), 6.97 (1H,d, *J* = 15.9 Hz, C-2H), 7.15-7.25 (3H, m, C-4'', C-3'' & C-5''), 7.35-7.40 (2H, m, C-2'' & C-6'') and 8.30 (1H, d, *J* = 15.9 Hz, C-3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 16.71 (C-4'), 26.76 (2 x CH_3), 31.86 (C-3'), 55.43 & 55.69 (2 x OCH_3), 75.45 (C-2'), 86.69 (C-6'), 102.66 (C-10'), 105.51 (C-8'), 115.69 (C-2), 121.95 (C-2'' & C-6''), 125.22 (C-4''), 129.23 (C-3'' & C-5''), 138.11 (C-3), 151.45 (C-1''), 155.52 (C-7'), 159.81 (C-9'), 160.18 (C-5'), 167.70 (C=O). HRMS: found 369.1697 $[M+H]^+$; calculated 369.1697 for $C_{22}H_{25}O_5$.

(*E*)-4-Methoxyphenyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate (69). Following the general procedure, with carboxylic acid **53** (584.6 mg, 2.0 mmol), thionyl chloride (285.5 mg, 2.4 mmol) and 4-methoxyphenol **57** (1.2 g, 10 mmol), (*E*)-4-methoxyphenyl 3-(5',7'-dimethoxy-2', 2'-dimethylchroman-8'-yl) acrylate **(69)** was obtained (613.2 mg, 77% yield) as a light brown solid (mp: 184 ^{o}C). IR spectrum (KBr), cm^{-1}: 2969, 2936, 1723 (C=O), 1591, 1466, 1333, 1237, 1191. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.37 (6H, s, 2 x CH_3), 1.77 (2H, t, *J* = 6.6 Hz, C-3'H), 2.59 (2H, t, *J* = 6.6 Hz, C-4'H), 3.80 & 3.86 (9H, 2s, 2 x OCH_3), 6.06 (1H, s, C-6'H), 6.90 (1H, d, *J* = 15.9 Hz, C-2H), 6.91-7.10 (4H, m, C-2'', C-6'', C-3' '& C-5''), 8.29 (1H, d, *J* = 15.9 Hz, C-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 16.70 (C-4'), 26.75 (2 x CH_3), 31.84 (C-3'), 55.42 , 55.59 & 55.66 (3 x OCH_3), 75.43 (C-2'), 86.63 (C-6'), 102.61 (C-10'), 105.47 (C-8'), 114.31 (C-2), 115.71 (C-2'' & C-6''), 122.65 (C-3'' & C-5''), 137.94 (C-3), 144.90 (C-1''), 155.48 (C-4''), 156.87 (C-7'), 159.76 (C-9'), 160.12 (C-5'), 168.11 (C=O). HRMS: found 399.1802 $[M+H]^+$; calculated 399.1804 for $C_{23}H_{27}O_6$.

Conflicts of interest

There are no conflicts to declare.

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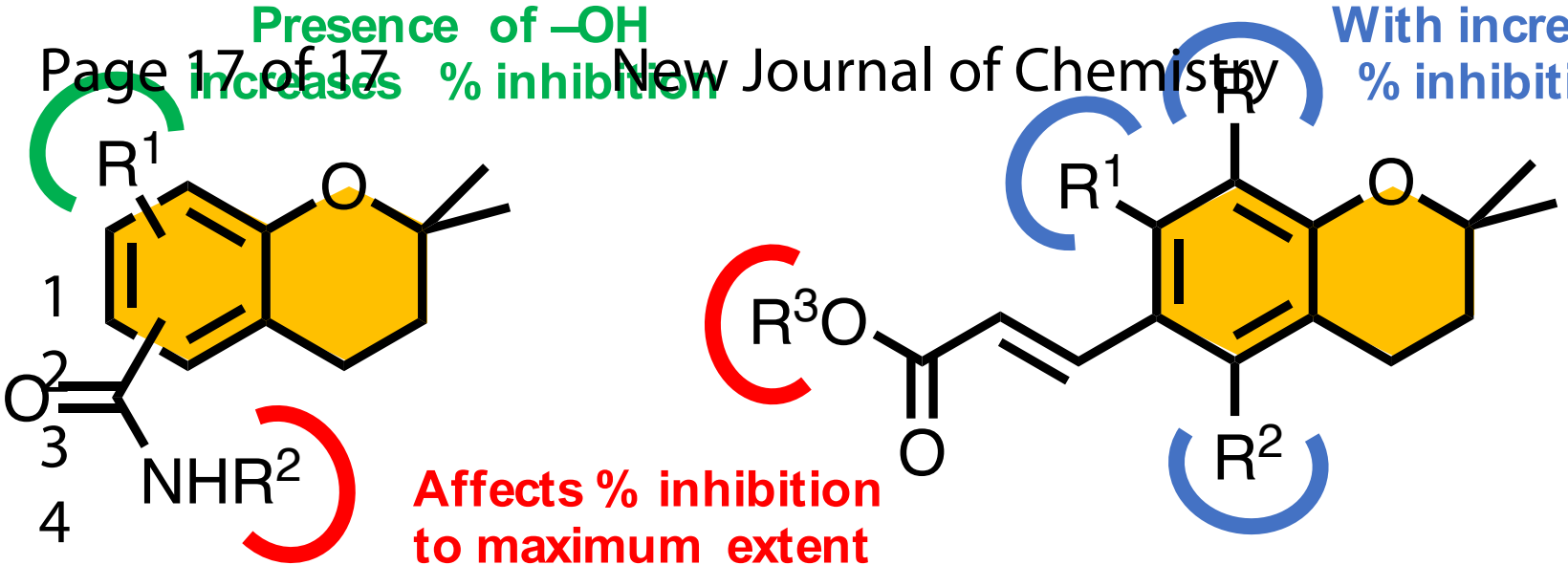
Notes and references

1 A. Gonzalez-Amaro and F. Sanchez-Madrid, *Expert Opin. Pharmacother.*, 2001, **2**, 3-17.
2 C. R. Mackay, *Nat. Immunol.*, 2008, **9**, 988-998.
3 A. Mantovani, F. Bussolino and M. Intona, *Immunol. Today*, 1997, **18**, 231-240.
4 C. F. Krieglstein and D. N. Granger, *Am. J. Hypertens*, 2001, **14**, 44S-54S.
5 B. Madan, S. Batra and B. Ghosh, *Mol. Pharmacol.*, 2000, **58**, 526-534.
6 A. Gorski, *Immunol. Today*, 1994, **15**, 251-255.
7 M.R. Weiser, S. A. L. Gibbs and H. B. Hechtman, In *Adhesion Molecules in Health and Disease*; Paul L C, Issekutz T B., Eds., Marcel Dekker: NewYork, 1997, pp 55.
8 S. Kumar, B. K. Singh, A. K. Pandey, A. Kumar, S. K. Sharma, H. G. Raj, A. K. Prasad, E. Van der Eycken, V. S. Parmar and B. Ghosh, *Bioorg. Med. Chem.*, 2007, **15**, 2952-2962.
9 K. Terao and E. Niki, *J. Free Radic. Biol. Med.*, 1986, **2**, 193-201.
10 J. M. Grisar, M. A. Petty, F. N. Bolkenius, J. Dow, J. Wagner, E. R. Wagner, K. D. Haegele and W. De Jong, *J. Med. Chem.*, 1991, **34**, 257-260.
11 G. Valsamakis and S. Kumar, *Expert Opin. Pharmacother.*, 2000, **1**, 1413-1421.
12 J. De Cree, H. Geukens, J. Leempoels and H. Verhaegen, *Drug Dev. Res.*, 1986, **8**, 109-117.
13 K. Morito, T. Hirose, J. Kinjo, T. Hirakawa, M. Okawa, T. Nohara, S. Ogawa, S. Inoue, M. Muramatsu and Y. Masamune, *Biol. Pharm. Bull.*, 2001, **24**, 351-356.
14 A. Ward and B. Holmes, *Drugs*, 1985, **30**, 127-144.
15 M. S. Sankaran and M. R. Prasad, *Contraception I*, 1974, **9**, 279-289.
16 K. Ishibashi, *J. Antibiot. Ser. A*, 1962, **15**, 161.
17 Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagishi, T. Fujioka, K. Mihashi, K. Mizuki, L. M. Cosentino, K. Fowke, S. L. Morris-Natschke and K. H. Lee, *Tetrahedron*, 2001, **57**, 1559-1563.
18 S. Koul, J. L. Koul, S. C. Taneja, K. L. Dhar, D. S. Jamwal, K. Singh, R. K. Reen and J. Singh, *Bioorg. Med. Chem.*, 2000, **8**, 251-268.
19 S. Venkateswarlu, M. S. Ramchandra, A. V. Krishnaraju, G. Trimurtulu and G. V. Subbaraju, *Indian J. Chem.*, 2006, **45B**, 252-257.
20 S. T. Marino, D. Stachurska-Buczek, D. A. Huggins, B. M. Krywult, C. S. Sheehan, T. Nguyen, N. Choi, J. G. Parsons, P.G. Griffiths, I. W. James, A. M. Bray, J. M. White and R. S. Boyce, *Molecules*, 2004, **9**, 405-426.
21 T. V. Hansen and Y. Stenstrom, *Synth. Commun.*, 2000, **30**, 2549-2557.
22 S. Hashimoto and I. Furukawa, *Bull. Chem. Soc., Japan*, 1981, **54**, 2839-2840.
23 V. K. Ahluwalia, C. Prakash and R. Gupta, *Tetrahedron*, 1982, **38**, 609-611.
24 H. Hamamoto, K. Hata, H. Nambu, Y. Shiozaki, H. Tohma and Y. Kita, *Tetrahedron Lett.*, 2004, **45**, 2293-2295.
25 M. Tsukayama, *Bull. Chem. Soc., Japan*, 1975, **48**, 80.
26 G. Sartori, G. Casiraghi, L. Bolzoni, and G. Casnati. J. Org. Chem. 1979, **44**, 803-805.
27 M. N. Kanvinde, S. A. Kulkarni and M. V. Paradkar, *Synth. Commun.*, 1990, **20**, 3259-3264.


Presence of –OH
increases % inhibition
With increase in –OMe
% inhibition increase
Affects % inhibition
to maximum extent