Bioorganic & Medicinal Chemistry 16 (2008) 10319–10325

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and antimicrobial activity of 2-alkenylchroman-4-ones, 2-alkenylthiochroman-4-ones and 2-alkenylquinol-4-ones

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ARTICLE INFO

Article history:
Received 18 August 2008
Revised 11 October 2008
Accepted 17 October 2008
Available online 22 October 2008

Keywords:
Antimicrobial activity
Chromanones
Heterocycles

ABSTRACT

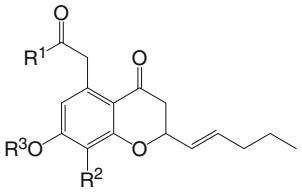
2-Alkenylchroman-4-ones, 2-alkenylthiochroman-4-ones, and 2-alkenylquinol-4-ones were prepared with very good regioselectivity by Me_3SiOTf-mediated conjugate addition of alkenylmagnesium bromides and alkenyllithium compounds to chromones thiochromones, and quinol-4-ones. A number of products exhibit a considerable antimicrobial activity. The best activity, with respect to the spectrum of antimicrobial activity, was observed for 2-vinylchroman-4-ones containing an unsubstituted vinyl group and a chloride group located at the chromanone moiety.

1. Introduction

We are witnessing today a dramatic world-wide increase of serious infections by resistant and multi-resistant microbes.[1,2] Infectious diseases are nowadays the second major cause of death worldwide and the third leading cause of death in developed countries.[3] Multiresistant strains of *Staphylococcus aureus*, such as MRSA (Methicillin resistant *S. aureus*) are often a source for severe and life-threatening infections in patients during their stay in hospitals or in immunosuppressed persons. Therefore, the search for new lead structures and new chemical entities (NCEs) for the development of antimicrobial agents is an increasingly important problem in medicinal chemistry. Unfortunately, pharmaceutical companies are more and more leaving this area, due to economic reasons.[4] Despite much technological advances in the field of genomics, combinatorial synthesis, and high throughput screening (HTS), chemical companies have been unable to identify new and valid antimicrobial agents by random screening of compound libraries.[4] For several decades no innovative antibiotics were launched on the market. In 2000 and 2003, the oxazolidinone linezolid[5] and the lipopeptide daptomycin[6] were the first new chemical entities which appeared on the market after a long period of time, respectively.

Noteworthy, new and structurally unusual lead structures for the development of antibiotics are often found based on the screening of natural products and their analogues.[4]

The natural products aposphaerin A and B, containing a rare 2-vinylchroman-4-one system, were isolated from extracts of the endophytic fungus *Aposphaeria spec* (Fig. 1).[7] Only a few related natural products, such as cavoxinone, are known to date.[8–10] Syntheses of 2-vinyl-chroman-4-ones have only scarcely been reported so far.[11] In 2002, a qualitative study showed that synthetic 2-(prop-1-en-1-yl)chroman-4-ones exhibit some antimicrobial activity.[12] Recently, we have reported the first synthesis of 2-vinylchroman-4-ones containing a non-substituted vinyl group. The syntheses were carried out by regioselective trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf)-mediated reaction of chromones with vinylmagnesium bromide.[13–15] These compounds show a remarkable activity against several human-pathogenic bacteria and yeast.[13,14] The minimum inhibitory con-



Aposphaerin A:
$R^1 = R^2 = OH$, $R^3 = Me$
Aposphaerin B:
$R^1 = OEt$, $R^2 = R^3 = H$

Figure 1. Naturally occuring 2-vinylchroman-4-ones.

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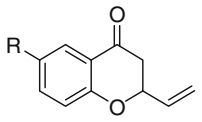
doi:10.1016/j.bmc.2008.10.043



6-Chloro-2-vinylchroman-4-one (R = Cl)
6-Bromo-2-vinylchroman-4-one (R = Br)

Figure 2. Synthetic 2-vinylchroman-4-ones active against Gram-positive bacteria and MRSA.

centrations of the most active derivative, 6-chloro-2-vinylchroman-4-one (Fig. 2), was shown to be 4.17 μg/mL (against *Bacillus subtilis* ATCC 6051), 4.17 μg/mL (against *Escherichia coli* ATCC 11229) and 7.30 μg/mL (against *Staphylococcus aureus* ATCC 6538) (Fig. 2). The minimum inhibitory concentration of 6-bromo-2-vinylchroman-4-one against *Staphylococcus aureus* ATCC 6538 was even better (5.62 μg/mL). 6-Chloro- and 6-bromo-2-vinylchroman-4-one proved to be highly active also against isolates of MRSA (obtained from the Universitätsklinikum Greifswald). Structure activity relationship experiments (SAR) showed that the presence of a vinyl group at carbon C-2 is mandatory for the biological activity. In fact, the corresponding ethyl-substituted derivatives showed no activity. The presence of a chlorine or bromine atom resulted in an increase of the antimicrobial activity.

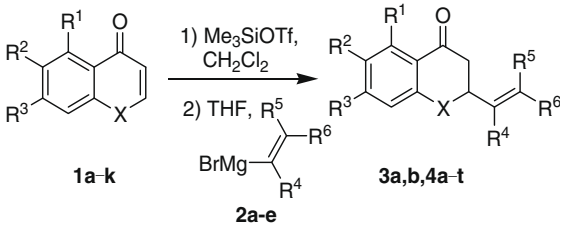
Recently, the response of *B. subtilis* to 6-bromo-2-vinylchroman-4-one using proteome and transcriptome analyses was studied.[16] Induction of the HrcA, CtsR and Spx regulons indicated that the 6-bromo-2-vinylchroman-4-one resulted predominantly in protein damage in *B. subtilis*. The nitroreductase encoding yodC gene is induced in response to the drug which depends on the MarR-type repressor YodB; the ycnDE operon was most strongly induced. In summary, the studies showed that 6-bromo-2-vinylchroman-4-one effects a common induction of protein damage in *B. subtilis* as revealed by the upregulation of the HrcA, CtsR and Spx stress regulons.

Herein, we report a detailed study related to the structure-activity-relationship of 2-vinylchroman-4-ones and related compounds. This includes, for the first time, 2-vinylchroman-4-ones containing a substituted vinyl group, 2-vinylquinol-4-ones, and 2-vinylthiochroman-4-ones.

2. Results and discussion

2.1. Chemistry and synthesis

The direct reaction of chromone (**1a**) with vinylmagnesium bromide (**2a**) results in the formation of complex mixtures, due to competing attack of the Grignard reagent onto the carbonyl group and onto the double bond (conjugate addition). We have previously reported[11] the successful synthesis of 2-vinylchroman-4-ones **3a**,**b** by reaction of **2a** with chromones **1a**,**b** in the presence of Me_3SiOTf (Scheme 1). The reaction of Me_3SiOTf with the chromones resulted in the formation of the corresponding 4-silyloxybenzopyrylium triflates. The addition of **2a** onto the latter and subsequent addition of an aqueous solution of ammonium chloride (1 M) resulted in regioselective formation of **3a**,**b**. In the present study, this protocol was applied to the synthesis of a variety of new 2-vinylchroman-4-ones in order to study their antimicrobial activities. Since the best pharmacological activity was observed for chloro-substituted derivative **3b**, we mainly studied the synthesis of chloro- and bromo-substituted 2-vinylchroman-4-ones.



Scheme 1. Synthesis of 2-alkenylchroman-4-ones and their derivatives.

The Me_3SiOTf-mediated reaction of 6-chlorochromone (**1b**) and 6-bromochromone (**1c**) with (prop-1-en-yl)magnesium bromide (**2b**) afforded the 2-(propen-1-yl)chroman-4-ones **4a** and **4b** as mixtures of *cis*/*trans*-isomers, respectively (Table 1). The reaction of 2-(*iso*propenyl)magnesium bromide (**2c**) with **1a**–**c** gave the 2-(isopropenyl)chroman-4-ones **4c**–**e**. The 2-(1-methylprop-1-en-1-yl)chroman-4-ones **4f** and **4g** were prepared by reaction of chromones **1b** and **1c** with (1-methyl-1-prop-1-en-1-yl)magnesium bromide (**2d**). The reaction of **1b**,**c** with (2-methyl-1-propen-1-yl)magnesium bromide (**2e**) afforded the 2-(2-methylprop-1-en-1-yl)chroman-4-ones **4h** and **4i**. The 2-(isopropenyl) and 2-vinyl-1-thiochroman-4-ones **4j**–**m** were prepared by Me_3SiOTf-mediated reaction of thiochromone (**1d**) and 6-chlorothiochromone (**1e**) with **2a** and **2c**. The Me_3SiOTf-mediated reaction of **2a**,**c** with quinol-4-ones **1f**–**k** afforded the 2-alkenyl-2,3-dihydroquinol-4-ones **4n**–**t**.

All products were isolated in moderate to very good yields, except for **4h**,**i**. The low yields of these products seems to depend on the use of Grignard reagent **2e.**

2.2. Antimicrobial screening

The compounds **4** were investigated towards their antimicrobial activity. The results of the test against the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* as well as the Gram negative *Escherichia coli* and the yeast *Candida maltosa* are summarised in Table 2. The test results show a weak activity of some derivatives. Noteworthy is the inhibition of the growth of *S. aureus* by 2-vinylchroman-4-ones **4d** and **4e**. The halogenation of the aro-

Table 1
Products and yields.

1	2	3,4	R^1	R^2	R^3	R^4	R^5	R^6	X	%[a]	*cis*:*trans*[b]
a	**a**	**3a**	H	H	H	H	H	H	O	86	—
b	**a**	**3b**	H	Cl	H	H	H	H	O	56	—
b	**b**	**4a**	H	Cl	H	H	H	Me	O	48	2:1
c	**b**	**4b**	H	Br	H	H	H	Me	O	68	3:2
a	**c**	**4c**	H	H	H	Me	H	H	O	63	—
b	**c**	**4d**	H	Cl	H	Me	H	H	O	38	—
c	**c**	**4e**	H	Br	H	Me	H	H	O	40	—
b	**d**	**4f**	H	Cl	H	Me	H	Me	O	30	2:1
c	**d**	**4g**	H	Br	H	Me	H	Me	O	51	3:2
b	**e**	**4h**	H	Cl	H	H	Me	Me	O	9	—
c	**e**	**4i**	H	Br	H	H	Me	Me	O	6	—
d	**c**	**4j**	H	H	H	Me	H	H	S	80	—
e	**c**	**4k**	H	Cl	H	Me	H	H	S	56	—
d	**a**	**4l**	H	H	H	H	H	H	S	66	—
e	**a**	**4m**	H	Cl	H	H	H	H	S	42	—
f	**a**	**4n**	H	Cl	H	H	H	H	NCO_2Me	85	—
g	**a**	**4o**	H	Br	H	H	H	H	NCO_2Me	84	—
h	**a**	**4p**	H	F	H	H	H	H	NCO_2Me	53	—
i	**a**	**4q**	Cl	H	Cl	H	H	H	NCO_2Me	46	—
j	**a**	**4r**	Me	H	H	H	H	H	NCO_2Allyl	42	—
f	**c**	**4s**	H	Cl	H	Me	H	H	NCO_2Me	71	—
k	**c**	**4t**	H	Br	H	Me	H	H	NCO_2Et	74	—

[a] Isolated yields.
[b] By ^1H NMR.

Table 2
Results of the antimicrobial screening.[a]

Compound	Gram positive		Gram negative	Yeast
	S. aureus	*B. subtilis*	*E. coli*	*C. maltosa*
4a	r	r	10	r
4b	r	r	9	r
4c	r	r	10	r
4d	17	r	9	r
4e	16	r	8	r
4f	r	r	r	r
4g	r	r	r	r
4h	n.t.	n.t.	n.t.	n.t.
4i	n.t.	n.t.	n.t.	n.t.
4j	r	r	r	r
4k	r	r	r	r
4l	r	r	r	6
4m	r	r	r	6
4n	r	r	r	r
4o	r	r	r	r
4p	r	r	r	r
4q	r	r	r	r
4r	r	r	r	r
4s	r	r	r	r
3a	r	r	r	r
3b[14]	40	29	17	40
Ampicillin	27	25	19	n.t.
Nystatin	n.t.	n.t.	n.t.	28

[a] Inhibition zones are stated in diameter [mm] without the diameter of the paper disc [6 mm], r = resistant, n.t. = not tested.

matic ring seems to be important for the antimicrobial activity. This is shown by the inhibition properties of compounds **4a**–**e**. It is worth to be noted that the presence of a methyl group located at the vinyl group (derivatives **4a–e**) results in a decrease of the activity compared to unsubstituted derivative **3b**. In addition, the spectrum of antimicrobial activity is affected. The selectivity against *E. coli* and/or *S. aureus* is increased. Dimethylation (derivatives **4f,g**) results in a complete loss of the antimicrobial activity, even though a chlorine or bromine atom is present at the benzene moiety.

The substitution of oxygen by sulfur or nitrogen in the heterocyclic ring system did not result in an increase of the biological activity. The compounds tested in this study did not show activities similar to those observed for 6-chloro-2-vinylchroman-4-one **3b** or the standards ampicillin and nystatin. A considerable lower activity was observed for derivatives containing a substituted vinyl group (as present, for example, in the natural products).[11,12] Noteworthy, 2-vinylthiochroman-4-ones and 2-vinylquinol-4-ones proved to be pharmacologically inactive.[12] Whereas vinylchroman-4-one **4c** shows some activity against *E. coli*, the corresponding thia-analogue **4j** proved to be unactive.

In conclusion, the best antimicrobial activities are observed for 2-vinylchroman-4-ones containing an unsubstituted vinyl group and a halogen atom attached to the benzene moiety. The activity decreases for 2-vinylthiochroman-4-ones and 2-vinylquinol-4-ones and for 2-vinylchroman-4-ones containing a substituted vinyl group.

3. Experimental

3.1. General

^{1}H NMR spectra (250.13 MHz, 300.13 MHz and 500.13 MHz) and ^{13}C NMR spectra (62.9 MHz, 75.5 MHz and 125.8 MHz) were recorded on Bruker spectrometers AV II 250, AV III 300 and AV 500 in $CDCl_3$, DMSO-d_6 and C_6D_6 as solvents. The calibration of spectra was carried out on solvent signals ($CDCl_3$: $\delta(^1H) = 7.25$, $\delta(^{13}C) = 77.0$; DMSO-d_6: $\delta(^1H) = 2.50$, $\delta(^{13}C) = 39.7$; C_6D_6: $\delta(^1H) = 7.16$, $\delta(^{13}C) = 128.0$). Infrared spectra were recorded on a FTIR spectrometer. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). Melting points are uncorrected. Analytical thin layer chromatography was performed on 0.20 mm 60 A silica gel plates. Column chromatography was performed on 60 A silica gel (60–200 mesh). Abbreviations: s = singlet, d = doublet, dd = doublet of doublet, dddd = doublet of doublet of doublet of doublet, t = triplet, q = quartet, m = multiplet.

3.2. General procedure for the synthesis of 2-alkenylchroman-4-ones 4a–k,s,t

To a CH_2Cl_2 solution of **1** was added TMSOTf at 0 °C. After stirring for 1 h at 0 °C, the mixture was cooled to −78 °C and THF and the alkenylmagnesium bromide **2** (1 M solution in THF) was added. After stirring for 30 min at −78 °C and aqueous solution of NH_4Cl (10 mL, 1 M) was added. The mixture was allowed to warm to ambient temperature and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3× 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc/heptanes).

3.2.1. 6-Chloro-2-(prop-1-enyl)-chroman-4-one (4a)

Starting with 6-chlorochromone (**1a**) (0.270 g, 1.50 mmol), TMSOTf (0.433 g, 1.95 mmol), dissolved in CH_2Cl_2 (0.6 mL), THF (7.0 mL) and 1-propenylmagnesium bromide (**2a**) (3.9 mL, 0.5 M in THF), **4a** was isolated as a *cis*/*trans*-mixture ($cis_{(I)}/trans_{(II)} = 2{:}1$) as a yellow solid (0.161 g, 48%), mp 31–32 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 1.73$ (dd, $^3J_{2',Me} = 7.0$ Hz, $^4J_{1',Me} = 1.8$ Hz, 3H, $Me_{(I)}$), 1.76 (ddd, $^3J_{2',Me} = 6.5$ Hz, $^4J_{1',Me} = 2.5$ Hz, $^5J_{2,Me} = 1.0$ Hz, 3H, $Me_{(II)}$), 2.66 (dd, $^2J_{3a,3b} = 17.0$ Hz, $^3J_{2,3a} = 3.2$ Hz, 1H, H-3a$_{(I)}$), 2.72 (dd, $^2J_{3a,3b} = 17.0$ Hz, $^3J_{2,3a} = 4.3$ Hz, 1H, H-3a$_{(II)}$), 2.76 (dd, $^2J_{3a,3b} = 17.0$ Hz, $^3J_{2,3b} = 6.8$ Hz, 1H, H-3b$_{(II)}$), 2.77 (dd, $^2J_{3a,3b} = 17.0$ Hz, $^3J_{2,3b} = 12.5$ Hz, 1H, H-3b$_{(I)}$), 4.88 (ddd't', $^3J_{2,1'} = 11.0$ Hz, $^3J_{2,3b} = 6.8$ Hz, $^3J_{2,3a} = 4.3$ Hz, $^4J_{2,2'} = {}^5J_{2,Me} = 1.0$ Hz, 1H, H-2$_{(II)}$), 5.26 (dddd, $^3J_{2,3b} = 12.5$ Hz, $^3J_{2,1'} = 8.2$ Hz, $^3J_{2,3a} = 3.2$ Hz, $^4J_{2,2'} = 1.2$ Hz, 1H, H-2$_{(I)}$), 5.62–5.70 (m, 1H$_{(I)}$, 1H$_{(II)}$, H-1'$_{(I)}$, H-1'$_{(II)}$), 5.80 (ddq, $^3J_{1',2'} = 10.8$ Hz, $^3J_{2',Me} = 7.0$ Hz, $^4J_{2,2'} = 1.2$ Hz, 1H, H-2'$_{(I)}$), 5.89 (ddq, $^3J_{1',2'} = 15.4$ Hz, $^3J_{2',Me} = 6.5$ Hz, $^4J_{2,2'} = 1.0$ Hz, 1H, H-2'$_{(II)}$), 6.93 (d, $^3J_{7,8} = 8.8$ Hz, 1H, H-8$_{(II)}$), 6.93 (d, $^3J_{7,8} = 8.8$ Hz, 1H, H-8$_{(I)}$), 7.38 (dd, $^3J_{7,8} = 8.8$ Hz, $^4J_{5,7} = 2.7$ Hz, 1H, H-7$_{(II)}$), 7.39 (dd, $^3J_{7,8} = 8.8$ Hz, $^4J_{5,7} = 2.7$ Hz, 1H, H-7$_{(I)}$), 7.80 (d, $^4J_{5,7} = 2.7$ Hz, 1H, H-5$_{(II)}$), 7.82 (d, $^4J_{5,7} = 2.7$ Hz, 1H, H-5$_{(I)}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 13.5$ ($Me_{(I)}$), 17.8 ($Me_{(II)}$), 42.68 (C-3$_{(II)}$), 42.74 (C-3$_{(I)}$), 74.1 (C-2$_{(I)}$), 78.5 (C-2$_{(II)}$), 119.7 (C-8$_{(II)}$), 120.0 (C-8$_{(I)}$), 121.7 (C-4a$_{(II)}$), 121.7 (C-4a$_{(I)}$), 126.2 (C-5$_{(II)}$), 126.3 (C-5$_{(I)}$), 126.4 (C-6$_{(II)}$), 126.9 (C-6$_{(I)}$), 127.3 (C-1'$_{(I)}$), 128.0 (C-1'$_{(II)}$), 130.2 (C-2'$_{(I)}$), 131.1 (C-2'$_{(II)}$), 135.8 (C-7$_{(II)}$), 135.8 (C-7$_{(I)}$), 159.8 (C-8a$_{(II)}$), 160.0 (C-8a$_{(I)}$), 190.8 (C-4$_{(I)}$), 190.8 (C-4$_{(II)}$). IR (Nujol, cm^{-1}): ν~ = 1703 (w), 1603 (m), 1572 (s), 1271 (s), 1215 (m), 1176 (w), 1132 (w), 1058 (w), 982 (w), 901 (w). MS (EI, 70 eV): *m/z* (%) = 224 (M^+, ^{37}Cl, 7), 222 (M^+, ^{35}Cl, 21), 209 (36), 207 (100), 156 (29), 154 (82), 128 (28), 126 (74), 100 (9), 98 (25). Anal. Calcd for $C_{12}H_{11}ClO_2$ (222.04): C 64.73, H 4.98; found: C 64.86, H 5.05.

3.2.2. 6-Bromo-2-(prop-1'-enyl)-chroman-4-one (4b)

Starting with 6-bromochromone (**1b**) (0.338 g, 1.50 mmol), TMSOTf (0.433 g, 1.95 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (7.0 mL) and 1-propenylmagnesium bromide (**2a**) (3.9 mL, 0.5 M in THF), **4b** was isolated as *cis*/*trans*-mixture ($cis_{(I)}/trans_{(II)} = 3{:}2$) as a yel-

low solid (0.276 g, 69%), mp 35–36 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.73 (dd, $^3J_{2',Me}$ = 6.9 Hz, $^4J_{1',Me}$ = 1.8 Hz, 3H, $Me_{(I)}$), 1.76 (br, dd, $^3J_{2',Me}$ = 6.6 Hz, $^4J_{1',Me}$ = 2.2 Hz, 3H, $Me_{(II)}$), 2.66 (dd, $^2J_{3a,3b}$ = 17.0 Hz, $^3J_{2,3a}$ = 3.2 Hz, 1H, H-3a$_{(I)}$), 2.72 (dd, $^2J_{3a,3b}$ = 16.8 Hz, $^3J_{2,3a}$ = 4.2 Hz, 1H, H-3a$_{(II)}$), 2.76 (dd, $J_{3a,\ 3b}$ = 16.8 Hz, $^3J_{2,3b}$ = 6.5 Hz, 1H, H-3b$_{(II)}$), 2.77 (dd, $^2J_{3a,3b}$ = 17.0 Hz, $^3J_{2,3b}$ = 12.3 Hz, 1H, H-3b$_{(I)}$), 4.88 (ddd't', $^3J_{2,1'}$ = 11.0 Hz, $^3J_{2,3b}$ = 6.8 Hz, $^3J_{2,3a}$ = 4.3 Hz, $^4J_{2,2'}$ = $^5J_{2,Me}$ = 1.0 Hz, 1H, H-2$_{(II)}$), 5.26 (dddd, $^3J_{2,3b}$ = 12.5 Hz, $^3J_{2,1'}$ = 8.2 Hz, $^3J_{2,3a}$ = 3.2 Hz, $^4J_{2,2'}$ = 1.3 Hz, 1H, H-2$_{(I)}$), 5.62–5.70 (m, 1H$_{(I)}$, 1H$_{(II)}$, H-1'$_{(I)}$, H-1'$_{(II)}$), 5.80 (ddq, $^3J_{1,2'}$ = 11.0 Hz, $^3J_{2',Me}$ = 7.0 Hz, $^4J_{2,2'}$ = 1.2 Hz, 1H, H-2'$_{(I)}$), 5.89 (ddq, $^3J_{1',2'}$ = 15.4 Hz, $^3J_{2',Me}$ = 6.5 Hz, $^4J_{2,2'}$ = 1.0 Hz, 1H, H-2'$_{(II)}$), 6.88 (d, $^3J_{7,8}$ = 8.8 Hz, 1H, H-8$_{(I)}$), 6.87 (d, $^3J_{7,8}$ = 8.8 Hz, 1H, H-8$_{(II)}$), 7.51 (dd, $^3J_{7,8}$ = 8.8 Hz, $^4J_{5,7}$ = 2.5 Hz, 1H, H-7$_{(II)}$), 7.5 (dd, $^3J_{7,8}$ = 8.8 Hz, $^4J_{5,7}$ = 2.5 Hz, 1H, H-7$_{(I)}$), 7.95 (d, $^4J_{5,7}$ = 2.5 Hz, 1H, H-5$_{(II)}$), 7.97 (d, $^4J_{5,7}$ = 2.5 Hz, 1H, H-5$_{(I)}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.5 ($Me_{(I)}$), 17.8 ($Me_{(II)}$), 42.6 (C-3$_{(II)}$), 42.7 (C-3$_{(I)}$), 74.0 (C-2$_{(I)}$), 78.4 (C-2$_{(II)}$), 113.9 (C-6$_{(II)}$), 114.0 (C-6$_{(I)}$), 120.1 (C-8$_{(II)}$), 120.2 (C-8$_{(I)}$), 122.2 (C-4a$_{(II)}$), 122.2 (C-4a$_{(I)}$), 127.3 (C-1'$_{(I)}$), 128.0 (C-1'$_{(II)}$), 129.3 (C-5$_{(II)}$), 129.4 (C-5$_{(I)}$), 130.3 (C-2'$_{(I)}$), 131.2 (C-2'$_{(II)}$), 138.6 (C-7$_{(II)}$), 138.6 (C-7$_{(I)}$), 160.2 (C-8a$_{(II)}$), 160.4 (C-8a$_{(I)}$), 190.7 (C-4$_{(II)}$), 190.7 (C-4$_{(I)}$). IR (Nujol, cm^{-1}): ν~ = 1702 (s), 1600 (s), 1570 (w), 1270 (s), 1215 (s), 1173 (w), 1135 (m), 1059 (w), 980 (w), 968 (w). MS (EI, 70 eV): *m/z* (%) = 268 (M^+, ^{81}Br, 13), 266 (M^+, ^{79}Br, 14), 253 (64), 251 (67), 200 (49), 198 (53), 172 (43), 170 (44), 144 (18), 142 (11). Anal. Calcd for $C_{12}H_{11}BrO_2$ (265.99): C 53.96, H 4.15; found: C 53.80, H 4.16.

3.2.3. 2-(*iso*Propenyl)chroman-4-one (4c)

Starting with chromone (**6a**) (0.292 g, 1.95 mmol), TMSOTf (0.578 g, 2.60 mmol) dissolved in CH_2Cl_2 (1.0 mL), THF (9.0 mL) und *iso*propenylmagnesium bromide (**2b**) (5.2 mL, 0.5 M in THF), **4c** was isolated as a yellow solid (0.236 g, 63%), mp 49–50 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87 (s, 3H, CH_3), 2.72 (dd, ^2J = 16.8 Hz, $^3J_{syn}$ = 3.3 Hz, 1H, $COCH_2$), 2.88 (dd, ^2J = 16.8 Hz, $^3J_{anti}$ = 12.2 Hz, 1H, $COCH_2$), 4.86 (dd, $^3J_{syn}$ = 3.3 Hz, $^3J_{anti}$ = 12.2 Hz, 1H, OCH), 5.05 (d, ^2J = 0.9 Hz, 1H, C=CH_2), 5.14 (d, ^2J = 0.9 Hz, 1H, C=CH_2), 6.97–7.03 (m, 2H, CH), 7.47 (ddd, ^4J = 1.8 Hz, ^3J = 6.5 Hz, ^3J = 7.1 Hz, 1H, Ar), 7.87 (dd, ^4J = 1.8 Hz, ^3J = 8.2 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3 (CH_3), 41.7 ($COCH_2$), 80.5 (CH), 114.0 (C=CH_2), 118.0 (CH_{Ar}) 126.8 (C), 121.3, 126.9, 135.0 (CH_{Ar}), 142.1, 161.3 (C), 192.2 (C=O). IR (neat, cm^{-1}): ν~ = 3438 (br, w), 3078 (w), 3065 (w), 2976 (w), 2921 (w), 1693 (s), 1653 (w), 1603 (m), 1462 (s), 1379 (w). MS (EI, 70 eV): *m/z* (%) = 188 (M^+, 17), 173 (18), 147 (55), 131 (9), 120 (100). Anal. Calcd for $C_{12}H_{12}O_2$ (188.04): C 76.57, H 6.43; found: C 76.72, H 6.50.

3.2.4. 6-Chloro-2-(*iso*propenyl)-chroman-4-one (4d)

Starting with 6-chlorochromone (**1b**) (0.27 g, 1.50 mmol), TMSOTf (0.43 g, 1.95 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (7.0 mL) and *iso*propenylmagnesium bromide (**2b**) (3.9 mL, 0.5 M in THF), **4d** was isolated as a yellow solid (0.13 g, 38%), mp 46–47 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.86 (s, 3H, CH_3), 2.75 (dd, ^2J = 16.8 Hz, $^3J_{syn}$ = 3.7 Hz, 1H, $COCH_2$), 2.88 (dd, ^2J = 16.8 Hz, $^3J_{anti}$ = 11.9 Hz, 1H, $COCH_2$), 4.86 (dd, $^3J_{syn}$ = 3.7 Hz, $^3J_{anti}$ = 11.9 Hz, 1H, OCH), 5.07 (d, ^2J = 0.9 Hz, 1H, C=CH_2), 5.14 (d, ^2J = 0.9 Hz, 1H, C=CH_2), 6.97 (d, ^3J = 7.0 Hz, 1H, H-8), 7.41 (dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz, 1H, H-7), 7.82 (d, ^4J = 2.7 Hz, 1H, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.3 (CH_3), 41.3 ($COCH_2$), 80.7 (OCH), 114.4 (C=CH_2), 119.7 (CH_{Ar}), 121.6 (C), 126.2 (CH_{Ar}), 126.9 (C), 135.8 (CH_{Ar}), 141.7, 159.7 (C), 191.0 (C=O). IR (Nujol, cm^{-1}): ν~ = 1704 (m), 1650 (w), 1602 (m), 1572 (w), 1272 (s), 1218 (m), 1172 (w), 1130 (w), 1064 (w), 1001 (w). MS (EI, 70 eV): *m/z* (%) = 224 (M^+, ^{37}Cl, 14), 222 (M^+, ^{35}Cl, 43), 209 (9), 207 (28), 183 (25), 181 (89), 156 (29), 154 (100), 128 (17), 126 (49). Anal. Calcd for $C_{12}H_{11}ClO_2$ (222.04): C 64.73, H 4.98; found: C 64.77, H 5.12.

3.2.5. 6-Bromo-2-(*iso*propenyl)-chroman-4-one (4e)

Starting with 6-bromochromone (**1c**) (0.338 g, 1.50 mmol), TMSOTf (0.433 g, 1.95 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (7.0 mL) and *iso*propenylmagnesium bromide (**2b**) (3.9 mL, 0.5 M in THF), **4e** was isolated as a yellow solid (0.224 g, 40%), mp 28–29 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87 (s, 3H, CH_3), 2.78 (dd, ^2J = 16.8 Hz, $^3J_{syn}$ = 3.7 Hz, 1H, $COCH_2$), 2.91 (dd, ^2J = 16.8 Hz, $^3J_{anti}$ = 11.6 Hz, 1H, $COCH_2$), 4.86 (dd, $^3J_{anti}$ = 11.6 Hz, $^3J_{syn}$ = 3.7 Hz, 1H, OCH), 5.06 (s, 1H, C=CH_2), 5.11 (s, 1H, C=CH_2), 6.90 (d, ^3J = 8.9 Hz, 1H, H-8), 7.55 (dd, ^4J = 2.8 Hz, ^3J = 8.9 Hz, 1H, H-7), 7.98 (d, ^4J = 2.8 Hz, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2 (CH_3), 41.3 ($COCH_2$), 80.7 (OCH), 114.0 (C), 114.4 (C=CH_2), 120.1 (CH_{Ar}), 122.2 (C), 129.3, 138.6 (CH_{Ar}), 141.7, 160.2 (C), 190.9 (C=O). IR (neat, cm^{-1}): ν~ = 3358 (s), 3094 (s), 3065 (s), 2971 (m), 2915 (m), 2883 (s), 2857 (s), 1696 (w), 1653 (m), 1598 (w), 1569 (m), 1467 (w), 1419 (w). MS (EI, 70 eV): *m/z* (%) = 268 (M^+, ^{81}Br, 61), 266 (M^+, ^{79}Br, 63), 253 (33), 251 (34), 227 (91), 225 (100), 200 (92), 198 (95), 172 (48), 170 (46). HRMS (EI, 70 eV) Calcd for $C_{12}H_{11}BrO_2$ (M^+, ^{79}Br): 265.9937, found: 265.9935.

3.2.6. 2-(1'-Methylprop-1'-enyl)-6-chlorochroman-4-one (4f)

Starting with 6-chlorochromone (**1b**) (0.270 g, 1.50 mmol), TMSOTf (0.433 g, 1.95 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (7.0 mL) and 1-methyl-1-propenylmagnesium bromide (**2c**) (3.9 mL, 0.5 M in THF), **4f** was isolated as a *cis*/*trans*-mixture (*cis*$_{(I)}$/*trans*$_{(II)}$ = 2:1) as a yellow solid (0.110 g, 30%), mp 64–65 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ = 1.65 (d'q', $^3J_{2',3'}$ = 7.2 Hz, 3H, 3'$_{(I)}$), 1.68 (br, d, $^3J_{2',3'}$ = 7.0 Hz, 3H, 3'$_{(II)}$), 1.76 (br, d, $^4J_{3',Me}$ = 1.2 Hz, 3H, $Me_{(II)}$), 1.85 (m, 3H, $Me_{(I)}$), 2.47 (dd, $^2J_{3a,3b}$ = 16.7 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-3a$_{(I)}$), 2.63 (dd, $^2J_{3a,3b}$ = 16.7 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-3a$_{(II)}$), 2.91 (dd, $^2J_{3a,3b}$ = 16.7 Hz, $^3J_{2,3b}$ = 13.0 Hz, 1H, H-3b$_{(II)}$), 2.96 (dd, $^2J_{3a,3b}$ = 16.7 Hz, $^3J_{2,3b}$ = 14.2 Hz, 1H, H-3b$_{(I)}$), 4.79 (dd, $^3J_{2,3b}$ = 13.0 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-2$_{(II)}$), 5.33 (dd, $^3J_{2,3b}$ = 14.2 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-2$_{(I)}$), 5.68 (m, 1H, H-2'$_{(II)}$), 5.53 (m, 1H, H-2'$_{(I)}$), 6.93 (d, $^3J_{7,8}$ = 8.8 Hz, 1H, H-8$_{(II)}$), 6.94 (d, $^3J_{7,8}$ = 8.8 Hz, 1H, H-8$_{(I)}$), 7.39 (dd, $^3J_{7,8}$ = 8.8 Hz, $^4J_{5,7}$ = 2.8 Hz, 1H, H-7$_{(II)}$), 7.40 (dd, $^3J_{7,8}$ = 8.8 Hz, $^4J_{5,7}$ = 2.8 Hz, 1H, H-7$_{(I)}$), 7.81 (d, $^4J_{5,7}$ = 2.8 Hz, 1H, H-5$_{(II)}$), 7.84 (d, $^4J_{5,7}$ = 2.8 Hz, 1H, H-5$_{(I)}$). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 11.8 ($Me_{(II)}$), 13.1 (3'$_{(I)}$), 13.3 (3'$_{(II)}$), 18.0 ($Me_{(I)}$), 40.8 (C-3$_{(I)}$), 41.4 (C-3$_{(II)}$), 76.0 (C-2$_{(I)}$), 83.1 (C-2$_{(II)}$), 119.7 (C-8$_{(II)}$), 119.8 (C-8$_{(I)}$), 121.6 (C-4a$_{(I)}$), 121.6 (C-4a$_{(II)}$), 124.8 (C-2'$_{(II)}$), 125.0 (C-2'$_{(I)}$), 126.2 (C-5$_{(II)}$), 126.3 (C-5$_{(I)}$), 126.7 (C-6$_{(II)}$), 126.8 (C-6$_{(I)}$), 132.3 (C-1'$_{(I)}$), 132.7 (C-1'$_{(II)}$), 135.8 (C-7$_{(I)}$), 135.8 (C-7$_{(II)}$), 160.1 (C-8a$_{(II)}$), 160.5 (C-8a$_{(I)}$), 191.6 (C-4$_{(I)}$), 191.6 (C-4$_{(II)}$). IR (Nujol, cm^{-1}): ν~ = 1704 (m), 1682 (m), 1602 (m), 1572 (w), 1272 (s), 1218 (w), 1129 (w), 978 (w), 899 (w), 822 (w). MS (EI, 70 eV): *m/z* (%) = 238 (M^+, ^{37}Cl, 8), 236 (M^+, ^{35}Cl, 26), 223 (29), 221 (100), 183 (9), 181 (28), 156 (11), 154 (27), 128 (9), 126 (20). HRMS (EI, 70 eV) Calcd for $C_{13}H_{13}ClO_2$ (M^+, ^{37}Cl): 236.05986, found: 236.0599.

3.2.7. 2-(1'-Methylprop-1'-enyl)-6-bromochroman-4-one (4g)

Starting with 6-bromochromone (**1c**) (0.338 g, 1.50 mmol), TMSOTf (0.433 g, 1.95 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (7.0 mL) and 1-methyl-1-propenylmagnesium bromide (**2c**) (3.9 mL, 0.5 M in THF), **4g** was isolated as a *cis*/*trans*-mixture (*cis*$_{(I)}$/*trans*$_{(II)}$ = 3:2) as a yellow solid (0.165 g, 51%), mp 51–52 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ = 1.65 (d'q', $^3J_{2',3'}$ = 7.3 Hz, 3H, 3'$_{(I)}$), 1.68 (br, d, $^3J_{2',3'}$ = 6.8 Hz, 3H, 3'$_{(II)}$), 1.76 (m, 3H, $Me_{(II)}$), 1.85 (m, 3H, $Me_{(I)}$), 2.47 (dd, $^2J_{3a,3b}$ = 16.8 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-3a$_{(I)}$), 2.63 (dd, $^2J_{3a,3b}$ = 16.7 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-3a$_{(II)}$), 2.91 (dd, $^2J_{3a,3b}$ = 16.7 Hz, $^3J_{2,3b}$ = 13.0 Hz, 1H, H-3b$_{(II)}$), 2.96 (dd, $^2J_{3a,3b}$ = 16.8 Hz, $^3J_{2,3b}$ = 14.2 Hz, 1H, H-3b$_{(I)}$), 4.79 (dd, $^3J_{2,3b}$ = 13.0 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-2$_{(II)}$), 5.33 (dd, $^3J_{2,3b}$ = 14.2 Hz, $^3J_{2,3a}$ = 2.5 Hz, 1H, H-2$_{(I)}$), 5.54 (m, 1H, H-2'$_{(I)}$), 5.68 (m, 1H, H-

2′$_{(II)}$), 6.88 (d, $^3J_{7,8}$ = 8.8 Hz, 1H, H-8$_{(II)}$), 6.89 (d, $^3J_{7,8}$ = 8.8 Hz, 1H, H-8$_{(I)}$), 7.53 (dd, $^3J_{7,8}$ = 8.8 Hz, $^4J_{5,7}$ = 2.5 Hz, 1H, H-7$_{(II)}$), 7.54 (dd, $^3J_{7,8}$ = 8.8 Hz, $^4J_{5,7}$ = 2.5 Hz, 1H, H-7$_{(I)}$), 7.97 (d, $^4J_{5,7}$ = 2.5 Hz, 1H, H-5$_{(II)}$), 8.00 (d, $^4J_{5,7}$ = 2.5 Hz, 1H, H-5$_{(I)}$). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 11.8 (Me$_{(II)}$), 13.1 (Me$_{(I)}$), 13.3 (3′$_{(II)}$), 18.0 (3′$_{(I)}$), 40.7 (C-3$_{(I)}$), 41.4 (C-3$_{(II)}$), 76.0 (C-2$_{(I)}$), 83.1 (C-2$_{(II)}$), 113.9 (C-6$_{(I)}$), 113.9 (C-6$_{(II)}$), 120.1 (C-8$_{(II)}$), 120.2 (C-8$_{(I)}$), 122.1 (C-4a$_{(I)}$), 122.1 (C-4a$_{(II)}$), 124.9 (C-2′$_{(II)}$), 125.1 (C-2′$_{(I)}$), 129.3 (C-5$_{(II)}$), 129.4 (C-5$_{(I)}$), 132.3 (C-1′$_{(I)}$), 132.7 (C-1′$_{(II)}$), 138.6 (C-7$_{(I)}$), 138.6 (C-7$_{(II)}$), 160.6 (C-8a$_{(II)}$), 161.0 (C-8a$_{(I)}$), 191.5 (C-4$_{(I)}$), 191.5 (C-4$_{(II)}$). IR (Nujol, cm^{-1}): ν~ = 1696 (m), 1682 (w), 1598 (m), 1272 (s), 1218 (m), 1181 (w), 1131 (w), 1070 (w), 979 (w), 898 (w). MS (EI, 70 eV): *m/z* (%) = 282 (M$^+$, ^{81}Br, 30), 280 (M$^+$, ^{79}Br, 31), 267 (98), 265 (100), 227 (20), 225 (22), 200 (20), 198 (20), 172 (9), 170 (9). HRMS (EI, 70 eV) Calcd for $C_{13}H_{13}BrO_2$ (M$^+$, ^{79}Br): 280.0093, found: 282.0060.

3.2.8. 6-Chloro-2-(2′-methylprop-1′-enyl)-chroman-4-one (4h)

Starting with 6-chlorochromone (**1b**) (0.270 g, 1.50 mmol), TMSOTf (0.433 g, 1.95 mmol) dissolved in CH_2Cl, (0.8 mL), THF (7.0 mL) and 2-methyl-1-propenylmagnesium bromide (**2d**) (3.9 mL, 0.5 M in THF), **4h** was isolated as a yellow oil (0.030 g, 9%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.81 (d, ^4J = 1.5 Hz, 3H, CH_3), 1.74 (d, ^4J = 1.6 Hz, 3H, CH_3), 2.77 (dd, $^3J_{anti}$ = 11.9 Hz, ^2J = 17.0 Hz, 1H, CH_2), 2.64 (dd, $^3J_{syn}$ = 3.6 Hz, ^2J = 17.0 Hz, 1H, CH_2), 5.15 (ddd, $^3J_{syn}$ = 3.6 Hz, ^3J = 8.6 Hz, $^3J_{anti}$ = 11.9 Hz, 1H, OCH), 5.42 (dqq, ^3J = 8.6 Hz, ^4J = 1.5 Hz, ^4J = 1.6 Hz, 1H, C=CH), 6.93 (d, ^3J = 8.5 Hz, 1H, H-8), 7.41 (dd, ^3J = 8.5 Hz, ^4J = 2.7 Hz, 1H, H-7), 7.83 (d, ^4J = 2.7 Hz, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 25.8 (CH_3), 43.1 (CH_2), 75.2 (CH), 119.8 (CH_{Ar}), 121.9 (CH), 126.2 (CH_{Ar}), 126.3, 126.8 (C), 135.8 (CH_{Ar}), 140.1, 160.1 (C), 191.3 (C=O). IR (neat, cm^{-1}): ν~ = 3428 (br, w), 3377 (br, w), 3072 (w), 2971 (m), 2917 (s), 2850 (m), 1694 (s), 1641 (m), 1603 (s), 1571 (m). MS (EI, 70 eV): *m/z* (%) = 238 (M$^+$, ^{37}Cl, 3), 236 (M$^+$, ^{35}Cl, 9), 221 (100). 155 (22), 126 (17), 82 (22). HRMS (EI, 70 eV): Calcd for $C_{13}H_{13}ClO_2$ (M$^+$, ^{37}Cl): 236.05986, found: 236.05996.

3.2.9. 6-Bromo-2-(2′-methylprop-1′-enyl)-chroman-4-one (4i)

Starting with 6-bromochromone (**1c**) (0.338 g, 1.50 mmol), TMSOTf (0.433 g, 1.95 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (7.0 mL) and 2-methyl-1-propenylmagnesium bromide (**2d**) (3.9 mL, 0.5 M in THF), **4i** was isolated as a yellow solid (0.025 g, 6%), mp 70–71 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.74 (d, ^4J = 1.3 Hz, 3H, CH_3), 1.81 (d, ^4J = 1.3 Hz, 3H, CH_3), 2.65 (dd, $^3J_{syn}$ = 3.7 Hz, ^2J = 17.1 Hz, 1H, $COCH_2$), 2.77 (dd, $^3J_{anti}$ = 11.9 Hz, ^2J = 17.1 Hz, 1H, $COCH_2$), 5.15 (ddd, ^3J = 8.6 Hz, $^3J_{syn}$ = 3.7 Hz, $^3J_{anti}$ = 11.9 Hz, 1H, OCH), 5.42 (dqq, ^3J = 8.6 Hz, ^4J = 1.3 Hz, ^4J = 1.3 Hz, 1H, C=CH), 6.87 (d, ^3J = 8.9 Hz, 1H, H-8), 7.52 (dd, ^4J = 2.5 Hz, ^3J = 8.9 Hz, 1H, H-7), 7.98 (d, ^4J = 2.5 Hz, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (CH_3), 22.8 (CH_3), 43.0 (CH_2), 75.2 (CH), 113.9 (C), 120.2 (CH_{Ar}), 121.9 (CH), 122.2 (C), 129.4 (CH_{Ar}), 138.6 (CH_{Ar}), 140.2 (C), 160.5 (C), 191.2 (C=O). IR (Nujol, cm^{-1}): ν~ = 3437 (br, w), 2967 (w), 2924 (w), 2853 (w), 1690 (s), 1602 (m), 1468 (s), 1420 (m), 1381 (w), 1280 (s). MS (EI, 70 eV): *m/z* (%) = 282 (M$^+$, ^{81}Br, 13), 280 (M$^+$, ^{79}Br, 13), 267 (99), 265 (100), 227 (3), 225 (3), 201 (12), 199 (12), 172 (6), 170 (5). HRMS (EI) Calcd for $C_{13}H_{13}BrO_2$ (M$^+$, ^{79}Br): 280.0093, found: 280.0085.

3.2.10. 2-*iso*Propenylthiochroman-4-one (4j)

Starting with thiochromone (**1d**) (0.163 g, 1.00 mmol), TMSOTf (0.289 g, 1.30 mmol) dissolved in CH_2Cl_2 (0.4 mL), THF (4.5 mL) und *iso*propenylmagnesium bromide (**2b**) (2.6 mL, 0.5 M in THF), **4j** was isolated as a yellow oil (0.163 g, 80%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.88 (s, 3H, CH_3), 3.04 (d, ^3J = 7.9 Hz, 1H, $COCH_2$), 3.05 (d, ^3J = 6.4 Hz, 1H, $COCH_2$), 4.10 (dd, ^3J = 7.9 Hz, ^3J = 6.4 Hz, 1H, OCH), 4.99 (d, ^2J = 1.2 Hz, 1H, C=CH_2), 5.03 (d, ^2J = 1.2 Hz, 1H, C=CH_2), 7.16 (ddd, ^3J = 7.0 Hz, ^3J = 7.3 Hz, ^4J = 1.2 Hz, 1H, Ar), 7.26 (dd, ^3J = 7.9 Hz, ^2J = 1.2 Hz, 1H, Ar), 7.38 (ddd, ^3J = 7.0 Hz, ^3J = 7.3 Hz, ^4J = 1.5 Hz, 1H, Ar), 8.08 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.4 (CH_3), 44.7 ($COCH_2$), 47.0 (CH), 114.7 (C=CH_2), 125.0, 127.5, 128.9 (CH_{Ar}), 130.4 (C), 133.5 (CH_{Ar}), 141.6, 142.1 (C), 194.5 (C=O). IR (neat, cm^{-1}): ν~ = 3448 (br, w), 3340 (w), 3079 (w), 3060 (w), 2973 (m), 2942 (m), 2914 (m), 2855 (w), 1679 (s), 1646 (s), 1591 (s), 1560 (m), 1458 (s), 1437 (s), 1402 (m). MS (EI, 70 eV): *m/z* (%) = 204 (M$^+$, 16), 176 (9), 162 (22), 136 (100), 108 (32). HRMS (EI, 70 eV): Calcd for $C_{12}H_{12}OS$ (M$^+$): 204.06034, found: 204.06025.

3.2.11. 6-Chloro-2-*iso*propenylthiochroman-4-one (4k)

Starting with 6-thiochlorochromone (**1e**) (0.150 g, 0.77 mmol), TMSOTf (0.223 g, 1.00 mmol) dissolved in CH_2Cl_2 (0.5 mL), THF (3.0 mL) and *iso*propenylmagnesium bromide (**2b**) (2.0 mL, 0.5 M in THF), **4k** was isolated as a yellow oil solid (0.097 g, 56%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87 (s, 3H, CH_3), 3.02–3.06 (m, 2H, $COCH_2$), 4.07 (dd, ^3J = 8.5 Hz, ^3J = 5.9 Hz, 1H, CH), 5.04 (s, 1H, C=CH_2), 5.06 (s, 1H, C=CH_2), 7.19 (d, ^3J = 8.4 Hz, 1H, H-8), 7.33 (dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, 1H, H-7), 8.04 (d, ^4J = 2.4 Hz, 1H, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.4 (CH_3), 44.3 ($COCH_2$), 47.0 (CH), 115.0 (C=CH_2), 128.5, 128.9 (CH_{Ar}), 131.2, 131.4 (C), 133.4 (CH_{Ar}), 139.8, 141.7 (C), 193.3 (C=O). IR (neat, cm^{-1}): ν~ = 3428 (br, w), 2423 (br, w), 3350 (w), 3081 (w), 2974 (m), 2942 (m), 2916 (m), 2855 (w), 1682 (s), 1622 (w). MS (EI, 70 eV): *m/z* (%) = 240 (M$^+$, ^{37}Cl, 17), 138 (M$^+$, ^{35}Cl, 51), 212 (5), 210 (15), 199 (12), 197 (41), 172 (53), 170 (100), 144 (13), 142 (37). HRMS (EI, 70 eV): Calcd for $C_{12}H_{11}OClS$ (M$^+$): 238.02136, found: 238.02161.

3.2.12. 6-Chloro-1-methoxycarbonyl-2-*iso*propenyl-2,3-dihydroquinolone (4s)

Starting with 6-chloro-1-methoxycarbonyl-4-quinolone (**1f**) (0.150 g, 0.6 mmol), TMSOTf (0.183 g, 0.8 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (3.0 mL) and *iso*propenylmagnesium bromide (**2b**) (1.7 mL, 0.5 M in THF), **4l** was isolated as a colourless solid (0.120 g, 71%), mp 68–69 °C. H NMR (250 MHz, $CDCl_3$): δ = 1.65 (s, 3H, CH_3), 3.03–3.04 (m, 2H, $COCH_2$), 3.87 (s, 3H, OCH_3), 4.71 (d, ^2J = 1.5 Hz, 1H, C=CH_2), 4.90 (d, ^2J = 1.5 Hz, 1H, C=CH_2), 5.42–5.43 (m, 1H, C=CH), 7.44 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H, H-7), 7.70 (d, ^3J = 8.9 Hz, 1H, H-8), 7.88 (d, ^4J = 2.5 Hz, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5 (CH_3), 41.0 ($COCH_2$), 53.7 (NCH), 57.4 (OCH_3), 115.0 (C=CH_2), 125.8 (CH_{Ar}), 126.1 (C), 126.3 (CH_{Ar}), 130.0 (C), 134.0 (CH_{Ar}), 139.4, 141.2 (C), 154.5 (NCO), 191.1 (C=O). IR (KBr, cm^{-1}): ν~ = 3429 (br, w), 3121 (w), 3087 (w), 1075 (w), 2971 (w), 2922 (w), 2857 (w), 1520 (s), 1694 (s), 1651 (w). S (EI, 70 eV): *m/z* (%) = 281 (M$^+$, ^{81}Br, 31), 279, (M$^+$, ^{79}Br, 100), 239 (31), 237 (94), 222 (40), 220 (67), 196 (14), 194 (45), 182 (24), 180 (85). HRMS (EI, 70 eV): Calcd for $C_{14}H_{14}O_3ClN$ (M$^+$): 279.06567, found: 279.06599. Anal. Calcd for $C_{14}H_{14}ClNO_3$ (279.07): C 60.11, H 5.04, N 5.01; found: C 59.87, H 5.11, N 4.80.

3.2.13. 6-Bromo-1-ethoxycarbonyl-2-*iso*propenyl-2,3-dihydroquinolone (4t)

Starting with 6-bromo-1-ethoxycarbonyl-4-quinolone (**1g**) (0.120 g, 0.41 mmol), TMSOTf (0.117 g, 0.53 mmol) dissolved in CH_2Cl_2 (0.6 mL), THF (2.0 mL) and *iso*propenylmagnesium bromide (**2b**) (1.1 mL, 0.5 M in THF), **4t** was isolated as a colourless solid (0.074 g, 74%), mp 87–88 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, ^3J = 7.0 Hz, 3H, CH_3), 1.65 (s, 3H, CH_3), 3.00–3.05 (m, 2H, $COCH_2$), 4.32 (q, ^3J = 7.0 Hz, 2H, OCH_2), 4.71 (dd, ^2J = 1.2 Hz, 1H, C=CH_2), 4.91 (dd, ^2J = 1.2 Hz, 1H, C=CH_2), 5.41–5.47 (m, 1H, CH), 7.57 (dd, ^3J = 8.8 Hz, ^4J = 2.4 Hz, 1H, H-7), 7.66 (d, ^3J = 8.8 Hz, 1H, H-8), 8.03 (d, ^4J = 2.4 Hz, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 20.5 (CH_3), 41.0 ($COCH_2$), 57.2 (NCH), 63.0 (OCH_2CH_3), 114.9 (C=CH_2), 117.4 (C), 126.0 (CH_{Ar}), 126.3 (C), 129.4, 136.8 (CH_{Ar}), 140.0, 141.3 (C), 153.9(NCO), 191.9 (C=O). IR (neat, cm^{-1}): ν~ = 3437

(br, w), 1089 (w), 2972 (w), 2947 (w), 1709 (s), 1687.1 (s), 1590 (w), 1474 (s), 1399 (m), 1379 (s). MS (EI, 70 eV): *m/z* (%) = 339 (M^+, ^{81}Br, 61), 337 (M^+, ^{79}Br, 61), 297 (45), 295 (46), 266 (100), 264 (96), 252 (19), 250 (11), 226 (51), 224 (76). HRMS (EI, 70 eV): Calcd for $C_{15}H_{16}BrNO_3$ (M^+, ^{79}Br): 337.0308, found: 337.0305.

3.3. General procedure for the synthesis of 2-alkenylchroman-4-ones 4l–r

To **1** (1.0 equiv) was added TMSOTf (1.3 equiv) at 0 °C. After stirring for 1 h at 0 °C, the mixture was cooled to −78 °C and THF (15 mL/mmol **1**) and vinylmagnesium bromide **2** (1.3 equiv, 1 M solution in THF) was added. After stirring for 30 min at −78 °C and aqueous solution of NH_4Cl (1 M, 10 mL/mmol **1**) was added. The mixture was allowed to warm to ambient temperature and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3× 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc/heptanes).

3.3.1. 2-Vinylthiochroman-4-one (4l)

Starting with thiochromone (0.166 g, 1.00 mmol), TMSOTf (0.24 mL, 1.30 mmol), THF (20.0 mL) and vinylmagnesium bromide (1.30 mL, 1.30 mmol, 1 M in THF), **4l** was isolated as a colourless oil (126 mg, 66%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.93–3.14 (m, 2H, $COCH_2$), 4.12 (m, 1H, SCH), 5.22 (m, 1H, CH=CH_2), 5.31 (m, 1H, CH=CH_2), 5.93 (m, 1H, CH=CH_2), 7.14–7.42 (m, 3H, Ar), 8.10 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.4 (CH_2), 45.0 (CH), 118.3 (=CH_2), 125.2, 127.6, 129.0 (CH), 130.6 (C), 133.6, 135.2 (CH), 141.0 (C), 194.0 (CO). IR (KBr, cm^{-1}): ν~ = 3061 (br, w), 2926 (w), 1681 (s), 1591 (m), 1437 (s), 1289 (br, m), 929 (br, w), 763 (br, m). MS (EI, 70 eV): *m/z* (%) = 190 ($[M]^+$, 40), 162 (7), 148 (8), 136 (100), 108 (31), 69 (11). HRMS (EI): Calcd for $C_{11}H_{10}OS$ ($[M]^+$): 190.04469, found: 190.04424.

3.3.2. 6-Chloro-2-vinylthiochroman-4-one (4m)

Starting with 6-chlorothiochromone (0.246 g, 1.25 mmol), TMSOTf (0.30 mL, 1.63 mmol), THF (20.0 mL) and vinylmagnesium bromide (1.63 mL, 1.63 mmol, 1 M in THF), **4m** was isolated as a colourless oil (119 mg, 42%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.94–3.15 (m, 2H, $COCH_2$), 4.12 (m, 1H, SCH), 5.24 (m, 1H, CH=CH_2), 5.33 (m, 1H, CH=CH_2), 5.92 (m, 1H, CH=CH_2), 7.24 (d, 1H, ^3J = 8.5 Hz, Ar), 7.35 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.4 Hz, Ar), 8.07 (d, 1H, ^4J = 2.4 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.3 (CH_2), 44.5 (CH), 118.6 (=CH_2), 128.6, 129.0 (CH), 131.4, 131.5 (C), 133.6, 134.8 (CH), 139.3 (C), 192.8 (CO). IR (KBr, cm^{-1}): ν~ = 3084 (br, w), 2955 (br, w), 1685 (br, s), 1582 (m), 1454 (s), 1392 (s), 1255 (s), 1096 (s), 930 (br, m), 818 (br, m). MS (EI, 70 eV): *m/z* (%) = 224 ($[M]^+$, 51), 197 (13), 170 (100), 142 (24), 107 (9), 97 (4). HRMS (EI): Calcd for $C_{11}H_9ClOS$ ($[M]^+$): 224.00571, found: 224.00568.

3.3.3. 6-Chloro-1-methoxycarbonyl-2-vinyl-2,3-dihydroquinolone (4n)

Starting with 6-chloro-1-methoxycarbonyl-4-quinolone (0.297 g, 1.25 mmol), TMSOTf (0.30 mL, 1.63 mmol), THF (20.0 mL) and vinylmagnesium bromide (1.63 mL, 1.63 mmol, 1 M in THF), **4n** was isolated as a colourless oil (282 mg, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.85–3.13 (m, 2H, $COCH_2$), 3.93 (s, 3H, OCH_3), 5.08 (m, 1H, CH=CH_2), 5.17 (m, 1H, CH=CH_2), 5.55 (m, 1H, NCH), 5.70–5.81 (m, 1H, CH=CH_2), 7.46 (dd, 1H, ^3J = 9.0 Hz, ^4J = 2.6 Hz, Ar), 7.83 (d, 1H, ^3J = 9.0 Hz, Ar), 7.91 (d, 1H, ^4J = 2.6 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.8 (CH_2), 53.8, 55.2 (CH, OCH_3), 118.4 (=CH_2), 125.6 (CH), 125.7 (C), 126.5 (CH), 129.7 (C), 134.3, 134.5 (CH), 139.9 (C), 154.2 (NCO), 191.5 (CO). IR (KBr, cm^{-1}): ν~ = 3078 (w), 2953 (w), 1712 (s), 1691 (br, s), 1596 (m), 1470 (m), 1440 (m), 1323 (br, m), 1290 (m), 762 (m). MS (EI, 70 eV): *m/z* (%) = 265 ($[M]^+$, ^{37}Cl, 100), 223 (26), 206 (39), 180 (74), 164 (10), 143 (6), 124 (11). Anal. Calcd for $C_{13}H_{12}ClNO_3$ (265.69): C 58.77, H 4.55, N 5.27; found: C 59.14, H 4.72, N 4.99.

3.3.4. 6-Bromo-1-methoxycarbonyl-2-vinyl-2,3-dihydroquinolone (4o)

Starting with 6-bromo-1-methoxycarbonyl-4-quinolone (0.352 g, 1.25 mmol), TMSOTf (0.30 mL, 1.63 mmol), THF (20.0 mL) and vinylmagnesium bromide (1.63 mL, 1.63 mmol, 1 M in THF), **4o** was isolated as a colourless oil (327 mg, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.85–3.13 (m, 2H, $COCH_2$), 3.89 (s, 3H, OCH_3), 5.07 (m, 1H, CH=CH_2), 5.15 (m, 1H, CH=CH_2), 5.56 (m, 1H, NCH), 5.70–5.81 (m, 1H, CH=CH_2), 7.59 (dd, 1H, ^3J = 9.0 Hz, ^4J = 2.5 Hz, Ar), 7.78 (d, 1H, ^3J = 9.0 Hz, Ar), 8.05 (d, 1H, ^4J = 2.5 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.7 (CH_2), 53.8, 55.1 (CH, OCH_3), 117.3 (C), 118.4 (=CH_2), 125.8 (CH), 125.9 (C), 129.5, 134.5, 137.1 (CH), 140.4 (C), 154.2 (NCO), 191.4 (CO). IR (KBr, cm^{-1}): ν~ = 3074 (br, w), 2955 (m), 2908 (br, w), 1699 (br, s), 1593 (s), 1472 (br, s), 1317 (br, s), 1083 (s), 764 (br, m). MS (EI, 70 eV): *m/z* (%) = 311 ($[M]^+$, ^{81}Br, 99), 309 ($[M]^+$, ^{79}Br, 100), 267 (27), 252 (34), 224 (60), 170 (19), 143 (15), 115 (9), 89 (7). Anal. Calcd for $C_{13}H_{12}BrNO_3$ (310.14): C 50.34, H 3.90, N 4.52; found: C 50.42, H 3.90, N 4.06.

3.3.5. 6-Fluoro-1-methoxycarbonyl-2-vinyl-2,3-dihydroquinolone (4p)

Starting with 6-fluoro-1-methoxycarbonyl-4-quinolone (0.221 g, 1.00 mmol), TMSOTf (0.24 mL, 1.30 mmol), THF (20.0 mL) and vinylmagnesium bromide (1.30 mL, 1.30 mmol, 1 M in THF), **4p** was isolated as a colourless oil (165 mg, 53%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.78–3.05 (m, 2H, $COCH_2$), 3.80 (s, 3H, OCH_3), 4.99 (m, 1H, CH=CH_2), 5.08 (m, 1H, CH=CH_2), 5.49 (m, 1H, NCH), 5.62–5.73 (m, 1H, CH=CH_2), 7.14 (m, 1H, Ar), 7.51 (m, 1H, Ar), 7.74 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.8 (CH_2), 53.7, 55.2 (CH, OCH_3), 112.4 (d, $^2J_{C,F}$ = 23 Hz, CH_{Ar}), 118.3 (=CH_2), 121.7 (d, $^2J_{C,F}$ = 23 Hz, CH_{Ar}), 126.2 (d, $^3J_{C,F}$ = 6 Hz, CH_{Ar}), 126.3 (d, $^3J_{C,F}$ = 8 Hz, C_{Ar}), 134.7 (CH), 137.6 (d, $^4J_{C,F}$ = 2 Hz, C_{Ar}), 154.4 (NCO), 158.9 (d, $^1J_{C,F}$ = 245 Hz, C_{Ar}), 191.8 (d, $^4J_{C,F}$ = 2 Hz, CO). IR (KBr, cm^{-1}): ν~ = 3085 (br, m), 2957 (m), 2913 (br, m), 2853 (m), 1713 (br, s), 1490 (s), 1443 (s), 1302 (s), 1172 (s), 910 (s). MS (EI, 70 eV): *m/z* (%) = 249 ($[M]^+$, 100), 236 (22), 222 (11), 206 (20), 190 (30), 164 (61), 148 (13), 108(13). HRMS (EI): Calcd for $C_{13}H_{12}O_3NF$ ($[M]^+$) 249.07957, found: 249.07978.

3.3.6. 5,7-Dichloro-1-methoxycarbonyl-2-vinyl-2,3-dihydroquinolone (4q)

Starting with 5,7-dichloro-1-methoxycarbonyl-4-quinolone (0.340 g, 1.25 mmol), TMSOTf (0.30 mL, 1.63 mmol), THF (20.0 mL) and vinylmagnesium bromide (1.63 mL, 1.63 mmol, 1 M in THF), **4q** was isolated as a colourless oil (171 mg, 46%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.86–3.15 (m, 2H, $COCH_2$), 3.89 (s, 3H, OCH_3), 5.14 (m, 1H, CH=CH_2), 5.20 (m, 1H, CH=CH_2), 5.49 (m, 1H, NCH), 5.71–5.82 (m, 1H, CH=CH_2), 7.21 (d, 1H, ^4J = 2.0 Hz, Ar), 7.74 (d, 1H, ^4J = 2.0 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.3 (CH_2), 54.0, 54.6 (CH, OCH_3), 118.6 (=CH_2), 121.1 (C), 123.8, 128.0, 134.4 (CH), 135.2, 139.1, 144.0 (C), 154.1 (NCO), 190.2 (CO). IR (KBr, cm^{-1}): ν~ = 3086 (br, w), 2956 (m), 2924 (br, m), 1698 (br, s), 1580 (s), 1441 (s), 1418 (s), 1311 (br, s), 1113 (s), 855 (br, m). MS (EI, 70 eV): *m/z* (%) = 299 ($[M]^+$, 48), 256 (63), 242 (42), 214 (100), 198 (28), 177 (9), 158 (12), 123 (5). HRMS (EI): Calcd for $C_{13}H_{11}Cl_2NO_3$ ($[M]^+$): 299.01105, found: 299.01085.

3.3.7. 1-Allyloxycarbonyl-5,7-dimethyl-2-vinyl-2,3-dihydroquinolone (4r)

Starting with 1-allyloxycarbonyl-5,7-dimethyl-4-quinolone (0.321 g, 1.25 mmol), TMSOTf (0.30 mL, 1.63 mmol), THF (20.0 mL) and vinylmagnesium bromide (1.63 mL, 1.63 mmol, 1 M in THF), **4r** was isolated as a colourless oil (151 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.79 (m, 1H, $COCH_2$), 3.08 (m, 1H, $COCH_2$), 4.73 (m, 2H, OCH_2), 5.09–5.37 (m, 4H, 2× CH=CH_2), 5.48 (m, 1H, NCH), 5.72–5.83 (m, 1H, CH=CH_2), 5.91–6.02 (m, 1H, CH=CH_2), 6.79 (s, 1H, Ar), 7.37 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 23.3 (CH_3), 43.8 (CH_2), 54.8 (CH), 67.1, 117.9, 118.2 (CH_2), 122.0 (C), 123.7, 129.7, 132.1, 135.4 (CH), 141.5, 142.3, 143.8 (C), 154.0 (NCO), 194.2 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3086 (br, m), 297 (br, m), 2926 (m), 1707 (br, s), 1681 (br, s), 1609 (s), 1456 (br, s), 1380 (s), 1267 (br, s), 852 (m), 763 (m). MS (EI, 70 eV): *m/z* (%) = 285 ([M]$^+$, 80), 243 (36), 200 (100), 172 (27), 158 (57), 144 (6), 118 (7), 91(10). HRMS (EI): Calcd for $C_{17}H_{19}NO_3$ ([M]$^+$) 285.13594, found: 285.13548.

3.4. Antimicrobial screening

The biological investigations were performed according to the methods described in Ref. 14.

Acknowledgments

Financial support by the State of Mecklenburg-Vorpommern (Exzellenzförderprogramm UR 07 068) is gratefully acknowledged.

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