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Synthesis and structure–activity relationships of 2-vinylchroman-4-ones as potent antibiotic agents

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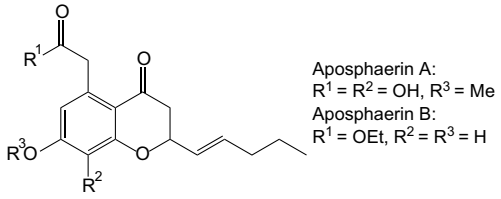
Abstract—A series of novel 2-vinylchroman-4-ones, analogues of the natural products Aposphaerin A and B, were identified as potent antibiotics. Derivatives exhibit a significant activity against multiresistant strains of *S. aureus*, such as MRSA (methicillin resistant *S. aureus*). The 2-vinylchroman-4-ones were efficiently prepared by Lewis acid mediated conjugate addition of vinylmagnesium bromide to chromones.

1. Introduction

The development of new antimicrobial agents represents an important field in medicinal chemistry, due to the increasing problem of the formation of resistant strains of bacterial pathogenes. Natural products often represent important lead structures for the development of new antibiotics. For example, chroman-4-ones are widely distributed among pharmacologically relevant natural products.[1] Recently, the natural products Aposphaerin A and B were isolated from extracts of the endophytic fungus *Aposphaeria* spec.[2] These compounds contain a rare 2-vinylchroman-4-one system.[3,4] Herein, we wish to report a convenient synthesis of 2-vinylchroman-4-ones by Lewis acid mediated conjugate addition of vinylmagnesium bromide to chromones. The products exhibit a remarkable activity against several humanpathogenic bacteria and yeast. Derivatives have been identified which exhibit a significant activity against multiresistant strains of *S. aureus*, such as MRSA (methicillin resistant *S. aureus*).[5] These bacteria are often a source for severe infections in patients during their stay in hospitals or in immunosuppressed persons.



2. Chemistry

The direct reaction of parent chromone (**1a**) with vinyllithium or vinyl magnesium bromide gave complex mixtures, due to competing 1,2- and 1,4-additions and decomposition. The reaction of vinyl magnesisum bromide (**2**) with benzopyrylium triflate **A**, generated in situ by treatment of **1a** with Me_3SiOTf,[6] resulted in regioselective conjugate addition to give the desired 2-vinylchroman-4-one **3a** (Scheme 1). The best yields (up to 86%) were obtained when the reaction was carried out (a) at −78 °C (reaction time: 30 min, no warming) and (b) in the absence of base. To completely hydrolyze the silyl enol ether moiety of intermediate **B**, an aqueous solution of ammonium chloride (1 M) was used for the work-up. The use of hydrochloric acid resulted in a significant decrease of the yield, due to decomposition.

The Me_3SiOTf mediated reaction of chromones **1a**–**g** with vinyl magnesium bromide (**2**) afforded the 2-vinylchroman-4-ones **3a**–**g** (Scheme 2, Table 1). The reaction

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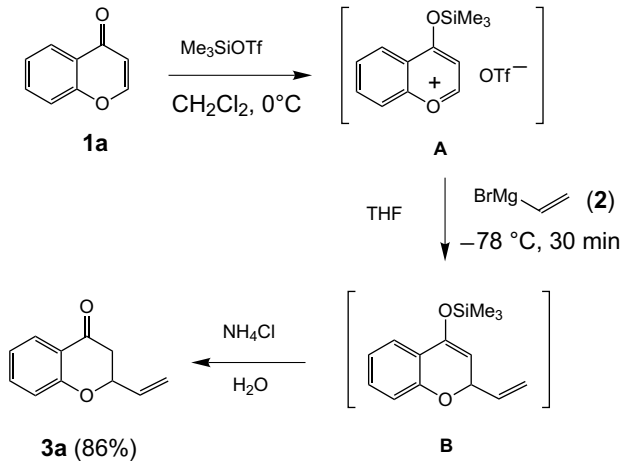


Scheme 1. Synthesis of 2-vinylchroman-4-one (**3a**).

Scheme 2. Synthesis of chroman-4-ones **3a**–**j**.

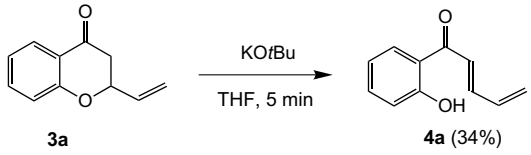
Table 1. Products and yields

3	R^1	R^2	R^3	R^4	Yield (%)[a]
a	H	H	H	–CH=CH_2	86
b	Cl	H	H	–CH=CH_2	56
c	CH_3	H	H	–CH=CH_2	55
d	OCH_3	H	H	–CH=CH_2	25
e	H	H	Br	–CH=CH_2	51[b]
f	Br	H	H	–CH=CH_2	50
g	Cl	CH_3	H	–CH=CH_2	50
h	H	OH	H	–CH=CH_2	60
i	H	H	H	–C≡CPh	50
j	H	H	H	–CH_2CH_3	58

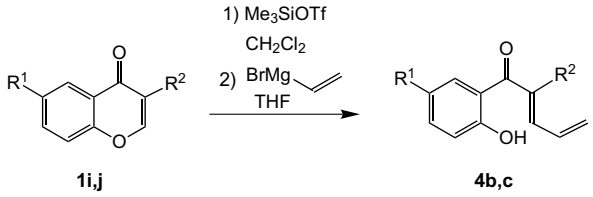
[a] Yields of isolated products.
[b] *trans*/*cis* = 2:1.

of **2** with 7-trimethylsilyloxychromone (**1h**) resulted in formation of 7-hydroxy-2-vinylchroman-4-one (**3h**). Phenylalkynyl-substituted chroman-4-one **3i** was prepared from **1a** and lithium phenylacetylide. The reaction of **1a** with ethyl magnesium bromide afforded 2-ethylchroman-4-one **3j**.

It was expected, that the pharmacological activity of 2-vinylchroman-4-ones involves a ring-opening reaction of the labile arylallyl-ether moiety to give 1-(2-hydroxyphenyl)-penta-2,4-dien-1-ones. Therefore, the synthesis of these compounds and their pharmacological activity were studied. Treatment of 2-vinylchroman-4-one (**3a**) with KO*t*Bu (THF, 5 min) afforded 1-(2-hydroxyphenyl)-penta-2,4-dien-1-one (**4a**) by a retro-Michael reaction (Scheme 3). Extension of the reaction time



Scheme 3. Base mediated retro-Michael reaction of **3a**.



Scheme 4. Reaction of **1i**, **j** with vinyl magnesium bromide, **4b** (R^1 = OBn, R^2 = H, 36%); **4c** (R^1 = H, R^2 = Me, 35%).

resulted in a decreasement of the yield, due to decomposition.

The reaction of chromones **1i** and **1j** with vinyl magnesium bromide resulted in the direct formation of the open-chained products **4b** and **4c**, respectively (Scheme 4). The formation of 2-vinylchroman-4-ones was not observed.

3. Pharmacological screening

All compounds were tested against several humanpathogenic bacteria to elucidate their potential as antibiotics. The compounds **3a** and **b** and **3d**–**j** were subjected to an antimicrobial screening using the paper disc diffusion method (Table 2).[7,8] Derivatives **3b**, **e** and **f** showed a remarkable antimicrobial activity. The 1-(2-hydroxyphenyl)-penta-2,4-dien-1-ones **4a**–**c** proved to be non active.

The activity of 2-vinylchroman-4-ones against multiresistant bacteria was next studied (Table 3). Derivatives **3b** and **3d**–**g** show a significant inhibitory effect on the

Table 2. Results of the antimicrobial screening[a]

3/4	*Bacillus subtilis* ATCC 6051	*Escherichia coli* ATCC 11229	*C. maltosa* ATCC 200
3a	r	r	r
3b	29	17	40
3d	r	r	r
3e	20	15	20
3f	24	14	r
3g	r	r	r
3h	r	r	r
3i	r	r	r
3j	r	r	r
4a	r	r	r
4b	r	r	r
4c	r	r	r

[a] Inhibition zones are stated in diameter (cm) without the diameter of the paper disc (6 mm), r = resistant.

Table 3. Results of antimicrobial screening against MRSA[a]

3	MRSA (North-German hospital strain)	*S. aureus* ATCC 6538	*S. epidermis* 125	*S. aureus* 36881	*S. aureus* 38418	*S. aureus* 315	*S. aureus* 520
b	40	40	>40	38	38	38	38
d	8	8	8	8	8	8	8
e	20	20	18	20	20	18	18
f	32	32	40	30	30	30	30
g	10	14	20	10	10	10	12

[a] Inhibition zones are stated in diameter (cm) without the diameter of the paper disc (6 mm).

Table 4. Determination of the minimum inhibitory concentration (MIC) using the microdilution method[a]

3	*B. subtilis* ATCC 6051	*E. coli* ATCC 11229	*Staphylococcus aureus* ATCC 6538
a	17.42	60.44	34.84
b	4.17	4.17	7.30
d	61.27	30.63	61.27
e	10.12	2.53	12.65
f	10.12	25.31	5.62
g	24.49	44.53	33.40

[a] (μg/mL).

growth of MRSA (methicillin resistant *S. aureus*) and of other multiresistant strains of *S. aureus*.

To evaluate the inhibitory effects of the test compounds in solution, the minimum inhibitory concentrations (MIC) were determined using the microdilution method.[8] The results are summarized in Table 4.

In conclusion, 2-vinylchroman-4-ones are strong inhibitors of the growth of pathogenic and non-pathogenic microbes. The halogenated derivatives **3b**, **e** and **f** show remarkable activities. The structure–activity relationship experiments (SAR) revealed that the presence of a vinyl group at carbon C-2, the arylallyl-ether subunit, is mandatory for biological activity. The ethyl-substituted derivative **3j** and the 1-(2-hydroxyphenyl)-penta-2,4-dien-1-ones **4a**–**c** showed no activity against the test strains. The presence of a chlorine or bromine atom represents an important feature for a high antimicrobial activity.

4. Experimental

4.1. General procedure for the preparation of 2-vinylchroman-4-ones (3a–h)

To a CH_2Cl_2 solution of the chromone **1** was added TMSOTf at 20 °C. After stirring for 1 h at 20 °C the reaction was cooled to −78 °C and THF and vinyl magnesium bromide (1 M solution in THF, Aldrich) was added. After stirring for 30 min at −78 °C an aqueous solution of NH_4Cl (10 mL, 1 M) was added. The solution was warmed to room temperature. The organic and the aqueous layer were separated and the latter was extracted with ether (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1:50) to give the 2-vinylchroman-4-one **3**.

4.2. 2-Vinylchroman-4-one (3a)

Starting with **1a** (0.73 g, 5.0 mmol), dissolved in 1 mL of CH_2Cl_2, TMSOTf (1.44 g, 6.5 mmol), 20 mL of THF and vinyl magnesium bromide (6.5 mL, 1 M), **3a** was obtained as a colourless oil (0.75 g, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.80 (d, ^3J = 7 Hz, 2H, CH_2), 4.98 (dt, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 5.34 (dd, ^2J = 1 Hz, $^3J_{cis}$ = 11 Hz, 1H, CH_2), 5.45 (dd, ^2J = 1 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH_2), 6.01 (ddt, ^3J = 7 Hz, $^3J_{cis}$ = 11 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH), 7.01 (m, 2H, CH), 7.47 (t, ^3J = 7 Hz, 1H, CH), 7.88 (d, ^3J = 7 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 42.46 (CH_2), 77.79 (CH), 117.89 (CH_2), 117.95 (CH), 120.88 (C), 121.28, 126.77, 135.13, 135.96 (CH), 160.99 (C), 191.50 (CO). MS (70 eV): *m*/*z* (%) = 174 (M^+, 13), 154 (16), 120 (18), 92 (12), 28 (100). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3082 (w), 1693 (s), 1651 (w), 1607 (s), 1578 (s), 1472 (s), 1464 (s), 1428 (m), 1403 (m). Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79; found: C, 75.68; H, 5.59.

4.3. 6-Chloro-2-vinylchroman-4-one (3b)

Starting with **1b** (0.18 g, 1.0 mmol), dissolved in 0.3 mL of CH_2Cl_2, TMSOTf (0.29 g, 1.3 mmol), 4 mL of THF and vinyl magnesium bromide (1.3 mL, 1 M), **3b** was obtained as white solid (0.12 g, 56%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.79 (d, ^3J = 7 Hz, 2H, CH_2), 4.97 (dt, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 5.38 (dd, ^2J = 1 Hz, $^3J_{cis}$ = 11 Hz, 1H, CH_2), 5.44 (dd, ^2J = 1 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH_2), 6.04 (ddt, ^3J = 7 Hz, $^3J_{cis}$ = 11 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH), 6.97 (d, ^3J = 8 Hz, 1H, Ar-H), 7.42 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar-H), 7.84 (d, ^4J = 2 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 42.24 (CH_2), 78.13 (CH), 118.47 (CH), 119.78 (C), 126.26 (CH), 126.98 (C), 134.79, 135.93 (CH), 159.55 (C), 190.56 (CO). MS (70 eV): *m*/*z* (%) = 208 (100, M^+), 181 (33), 165 (12), 154 (90), 126 (47). IR (KBr, cm^1): $\tilde{\nu}$ = 1695 (s), 1604 (s), 1470 (s), 1422 (s), 1407 (w). Anal. Calcd for $C_{11}H_9ClO_2$: C, 63.32; H, 4.35; found: C, 63.09; H 4.59.

4.4. 6-Methyl-2-vinylchroman-4-one (3c)

Starting with **1c** (0.48 g, 3.0 mmol), dissolved in 0.5 mL of CH_2Cl_2, TMSOTf (0.67 g, 3.9 mmol), 15 mL of THF and vinyl magnesium bromide (3.9 mL, 1 M), **3c** was

obtained as a colourless oil (0.32 g, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 3H, CH_3), 2.78 (d, ^3J = 7 Hz, 2H, CH_2), 4.95 (dt, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 5.34 (dd, ^2J = 1 Hz, $^3J_{cis}$ = 11 Hz, 1H, CH_2), 5.46 (dd, ^2J = 1 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH_2), 6.05 (ddt, ^3J = 7 Hz, $^3J_{cis}$ = 11 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH), 6.91 (d, ^3J = 8 Hz, 1H, Ar-H), 7.30 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar-H), 7.67 (d, ^4J = 2 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 20.38 (CH_3), 42.64 (CH_2), 77.90 (CH), 117.79 (CH_2), 118.00 (CH), 120.59 (C), 126.47 (CH), 130.86 (C), 135.35, 137.18 (CH), 159.20 (C), 191.98 (CO). MS (70 eV): *m/z* (%) = 188 (80, M^+), 161 (16), 134 (100), 106 (20), 78 (18). The exact molecular mass for $C_{12}H_{12}O_2$ *m/z* = 188.0837 ± 2 ppm [M^+] was determined by HRMS (EI, 70 eV). IR (KBr): $\tilde{\nu}$ = 2923 (w), 1692 (s), 1650 (w), 1618 (s), 1578 (w), 1489 (s), 1421 (m).

4.5. 6-Methoxy-2-vinylchroman-4-one (3d)

Starting with **1d** (0.53 g, 3.0 mmol), dissolved in 0.5 mL of CH_2Cl_2, TMSOTf (0.67 g, 3.9 mmol), 15 mL of THF and vinyl magnesium bromide (3.9 mL, 1 M), **3d** was obtained as a colourless oil (0.15 g, 25%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.79 (d, ^3J = 7 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.93 (dt, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 5.34 (dd, ^2J = 1 Hz, $^3J_{cis}$ = 11 Hz, 1H, CH_2), 5.45 (dd, ^2J = 1 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH_2), 6.04 (ddt, ^3J = 7 Hz, $^3J_{cis}$ = 11 Hz, $^3J_{trans}$ = 16 Hz, 1H, CH), 6.95 (d, ^3J = 8 Hz, 1H, Ar-H), 7.10 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar-H), 7.31 (d, ^4J = 2 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ_C 42.54 (CH_2), 55.73 (CH_3), 77.96 (CH), 107.49 (CH), 117.77 (CH_2), 119.22 (CH), 120.88 (C), 125.11, 135.45 (CH), 154.14, 155.81 (C), 191.50 (CO). MS (70 eV): *m/z* (%) = 204 (76, M^+), 177 (16), 161 (8), 150 (100), 107 (24). The exact molecular mass for $C_{12}H_{12}O_3$ *m/z* = 204.0786 ± 2 ppm [M^+] was determined by HRMS (EI, 70 eV). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3435 (s), 1685 (s), 1618 (m), 1486 (s), 1461 (m), 1442 (w), 1428 (s), 1413 (w).

4.6. 3-Bromo-2-vinylchroman-4-one (3e)

Starting with **1e** (0.22 g, 1.0 mmol), dissolved in 0.5 mL of CH_2Cl_2, TMSOTf (0.29 g, 1.3 mmol), 5 mL of THF and vinyl magnesium bromide (1.3 mL, 1 M), **3e** was obtained (130 mg, 51%) as a colourless solid (*trans*/*cis* = 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.40 (d, $^3J_{anti}$ = 2 Hz, 1H, CH), 4.56 (d, $^3J_{syn}$ = 6 Hz, 1H, CH), 4.80 (dd, $^3J_{anti}$ = 2 Hz, ^3J = 6 Hz, 1H, CH), 5.11 (dd, $^3J_{syn}$ = 6 Hz, ^3J = 6 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 48.88, 50.02, 78.89, 81.91 (CH), 118.02 (CH), 118.17, 118.80 (C), 120.44, 121.25 (CH_2), 122.16, 122.40, 127.95, 128.29, 132.06, 132.53, 136.74, 136.92 (CH), 159.18, 160.14 (C), 185.84, 184.99 (CO). MS (70 eV): *m/z* (%) = 254 (24, M^+), 173 (64), 145 (8), 129 (4), 120 (100). The exact molecular mass for $C_{11}H_9BrO_2$ *m/z* = 251.9786 ± 2 ppm [M^+] was determined by HRMS (EI, 70 eV). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1693 (s), 1607 (s), 1579 (m), 1473 (s), 1463 (s), 1426 (w).

4.7. 6-Bromo-2-vinylchroman-4-one (3f)

Starting with **1f** (0.23 g, 1.0 mmol), dissolved in 0.3 mL of CH_2Cl_2, TMSOTf (0.29 g, 1.3 mmol), 4 mL of THF and vinyl magnesium bromide (1.3 mL, 1 M), **3f** was obtained as a colourless solid (0.13 g, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.80 (d, ^3J = 7 Hz, 2H, CH_2), 4.97 (dt, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 5.36 (dd, ^2J = 1 Hz, $^3J_{cis}$ = 11 Hz, 1H, CH_2), 5.45 (dd, ^2J = 1 Hz, $^3J_{trans}$ = 18 Hz, 1H, CH_2), 6.03 (ddt, ^3J = 7 Hz, $^3J_{cis}$ = 11 Hz, $^3J_{trans}$ = 18 Hz, 1H, CH), 6.92 (d, ^3J = 8 Hz, 1H, Ar-H), 7.55 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar-H), 7.98 (d, ^4J = 2 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 42.20 (CH_2), 78.12 (CH), 114.14 (C), 118.51 (CH_2), 120.14 (CH), 122.25 (C), 129.39, 134.77, 138.72 (CH), 159.99 (C), 190.43 (CO). MS (70 eV): *m/z* (%) = 252 (100, M^+), 227 (20), 225 (24), 200 (84), 198 (88), 170 (36). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (s), 1694 (s), 1599 (s), 1467 (s), 1418 (m), 1406 (w). Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; found: C, 52.48; H, 3.97.

4.8. 6-Chloro-7-methyl-2-vinylchroman-4-one (3g)

Starting with **1g** (0.20 g, 1.0 mmol), dissolved in 0.3 mL of CH_2Cl_2, TMSOTf (0.29 g, 1.3 mmol), 4 mL of THF and vinyl magnesium bromide (1.3 mL, 1 M), **3g** was obtained as a colourless solid (0.11 g, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (s, 3H, CH_3), 2.77 (d, ^3J = 7 Hz, 2H, CH_2), 4.95 (ddd, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 5.34 (dd, ^2J = 2 Hz, $^3J_{cis}$ = 10 Hz, 1H, CH_2), 5.44 (dd, ^2J = 2 Hz, $^3J_{trans}$ = 17 Hz, 1H, CH_2), 6.00 (ddd, ^3J = 7 Hz, $^3J_{cis}$ = 10 Hz, $^3J_{trans}$ = 17 Hz, 1H, CH), 6.91 (s, 1H, Ar-H), 7.82 (s, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 20.85 (CH_3), 42.27 (CH_2), 78.11 (CH), 118.31 (CH_2), 120.03 (C), 120.12 (CH), 126.62 (CH), 127.70 (C), 134.99 (CH), 145.19, 159.40 (C), 190.46 (CO). MS (70 eV): *m/z* (%) = 222 (94, M^+), 195 (28), 179 (12), 168 (100), 140 (28). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3436 (s), 1693 (s), 1613 (s), 1469 (m), 1452 (m), 1431 (w), 1406 (s). Anal. Calcd for $C_{12}H_{11}ClO_2$: C, 64.37; H, 4.98; found: C, 64.80; H, 5.39.

4.9. 7-Hydroxy-2-vinyl-chroman-4-one (3h)

Starting with 7-trimethylsilyloxychromone **1h** (0.47 g, 2.0 mmol), dissolved in 0.5 mL of CH_2Cl_2, TMSOTf (0.58 g, 2.6 mmol), 10 mL of THF and vinyl magnesium bromide (2.6 mL, 1 M), **3h** was obtained as a colourless solid (0.22 g, 60%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.76 (d, ^3J = 7 Hz, 2H, CH_2), 4.96 (ddd, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 5.34 (dd, ^2J = 2 Hz, $^3J_{cis}$ = 10 Hz, 1H, CH_2), 5.43 (dd, ^2J = 2 Hz, $^3J_{trans}$ = 17 Hz, 1H, CH_2), 6.01 (ddd, ^3J = 7 Hz, $^3J_{cis}$ = 10 Hz, $^3J_{trans}$ = 17 Hz, 1H, CH), 6.51 (dd, ^4J = 2 Hz, 1H, Ar-H), 6.52 (dd, ^3J = 8 Hz, 1H, Ar-H), 7.83 (d, ^3J = 8 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 41.48 (CH_2), 77.41, 102.43, 110.39 (CH), 113.56 (C), 117.33 (CH_2), 128.22, 135.90 (CH), 162.48, 164.53 (C), 189.22 (CO). MS (70 eV): *m/e* (%) = 190 (100, M^+), 163 (32), 148 (39), 136 (98), 108 (88). The exact molecular mass for $C_{11}H_{10}O_3$ *m/z* = 190.0630 ± 2 ppm [M^+] was determined by HRMS (EI, 70 eV). IR (KBr): $\tilde{\nu}$ = 3121 (s), 3062 (s),

3040 (s), 2954 (s), 2854 (s), 2831 (s), 2771 (m), 2772 (m), 2619 (m), 1647 (s), 1600 (s), 1570 (s), 1491 (s), 1425 (m), 1401 (m).

4.10. 7-Trimethylsilyloxychromone (1h)

Trimethylchlorosilane (1.96 g, 18 mmol) was added at 20 °C to a THF solution of 7-hydroxychromone (1.62 g, 10 mmol) and of NEt_3 (1.52 g, 15 mmol). After stirring for 36 h at 20 °C the solution was concentrated in vacuo, filtered and the solvent of the filtrate was removed in vacuo to give **1h** as a red solid (1.33 g, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.34 (s, 9H, $OSiMe_3$), 6.27 (d, ^3J = 6 Hz, 1H, Ar-H), 6.83 (d, ^4J = 2 Hz, Ar-H), 6.89 (dd, ^3J = 9 Hz, ^4J = 2 Hz, 1H, Ar-H), 7.77 (d, ^3J = 9 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 0.09 (CH_3), 107.51, 112.66, 118.88 (CH), 119.28 (C), 127.15, 154.93 (CH), 157.84, 160.20, 177.04 (C). MS (70 eV): *m/z* (%) = 234 (54, M^+), 219 (100). 201 (2), 189 (6), 163 (2). IR (KBr): $\tilde{\nu}$ = 3176 (m), 3170 (w), 1363 (m), 3099 (m), 3075 (m), 3045 (m), 2959 (m), 2823 (m), 2765 (m), 1642 (s), 1628 (s), 1594 (m), 1573 (s), 1505 (w), 1465 (w), 1454 (w), 1438 (m), 1409 (s). Anal. Calcd for $C_{12}H_{14}O_3Si$: C, 61.51; H, 6.02; found: C, 61.48; H, 5.88.

4.11. 2-Phenylethynylchroman-4-one (3i)

Starting with **1a** (0.29 g, 2.0 mmol), dissolved in 0.5 mL of CH_2Cl_2, TMSOTf (0.58 g, 2.6 mmol), 5 mL of THF and lithium phenylacetylenide, **3i** was obtained as white solid (0.24 g, 50%). The lithio reagent was prepared by addition of *n*BuLi (1.63 mL, 1.6 M) to a THF solution of phenylacetylene (0.29 g, 2.6 mmol) at −78 °C and stirring of the solution for 1 h at 78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.08 (d, ^3J = 7 Hz, 2H, CH_2), 5.50 (t, ^3J = 7 Hz, 1H), 7.06 (ddd, ^3J = 7 Hz, ^4J = 2 Hz, 2H, Ar-H), 7.30–7.34 (m, 3H, Ar-H), 7.40–7.44 (m, 2H, Ar-H), 7.51 (dt, ^3J = 7 Hz, ^4J = 2 Hz, 1H, Ar-H), 7.93 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 43.44 (CH_2), 68.02 (CH), 84.47, 87.36 (C), 118.23 (CH), 121.06, 121.45 (C), 121.96 (CH), 126.94, 128.28, 129.06, 131.95, 136.20 (CH), 160.14 (C), 190.42 (CO). MS (70 eV): *m/z* (%) = 248 (63, M^+), 222 (100), 209 (35), 193 (34), 129 (98). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3435 (s), 1693 (s), 1608 (s), 1576 (w), 1466 (s). Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87; found: C, 82.25; H, 5.36.

4.12. 2-Ethylchroman-4-one (3j)

Starting with **1a** (0.76 g, 3.0 mmol), dissolved in 0.5 mL of CH_2Cl_2, TMSOTf (0.87 g, 3.9 mmol), 15 mL of THF and ethyl magnesium bromide (3.9 mL, 1 M), **3j** was obtained as a yellow oil (306 mg, 58%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (t, ^3J = 7 Hz, 3H, CH_3), 1.79 (dt, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH_2), 1.88 (dt, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH_2), 2.69 (d, ^3J = 8 Hz, 2H, CH_2), 4.38 (ddd, ^3J = 8 Hz, ^3J = 7 Hz, ^3J = 7 Hz, 1H, CH), 6.99 (dt, ^4J = 2 Hz, ^3J = 7 Hz, 2H, CH), 7.47 (dt, ^4J = 2 Hz, ^3J = 7 Hz, 1H, CH), 7.87 (dd, ^4J = 2 Hz, ^3J = 7 Hz, 1H, CH). MS (70 eV): *m/z* (%) = 176 (M^+, 8), 146 (4), 121 (14), 92 (6), 28 (100). IR (KBr): $\tilde{\nu}$ = 2971 (m), 2934 (w), 2880 (w), 1693 (s), 1653 (w), 1609 (s), 1578 (m), 1467 (s), 1404 (w). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; found: C, 75.25; H, 6.76.

4.13. (*Z*)-1-(2-Hydroxyphenyl)-penta-2,4-dien-1-one (4a)

2-Vinylchroman-4-one(0.09 g, 0.5 mmol) was added at 20 °C to a THF solution (2 mL) of KO*t*Bu (0.07 g, 0.6 mmol). After stirring for 5 min an aqueous solution of NH_4Cl (20 mL, 1 M) and ether (20 mL) were added. The layers were separated, the aqueous layer was extracted with ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane = 1:50) to give **4a** as a yellow liquid (0.03 g, 34%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.65 (d, $^3J_{cis}$ = 10 Hz, 1H, CH_2), 5.77 (d, $^3J_{trans}$ = 17 Hz, 1H, CH_2), 6.61 (ddd, $^3J_{trans}$ = 17 Hz, $^3J_{cis}$ = 10 Hz, $^3J_{cis}$ = 8 Hz, 1H, CH), 6.91 (dd, $^3J_{trans}$ = 15 Hz, $^3J_{cis}$ = 8 Hz, 1H, CH), 7.00 (dd, ^4J = 2 Hz, ^3J = 7 Hz, 1H, CH), 7.12 (d, $^3J_{trans}$ = 15 Hz, 1H, CH), 7.48 (dt, ^4J = 2 Hz, ^3J = 7 Hz, 2H, CH), 7.80 (dd, ^4J = 2 Hz, ^3J = 7 Hz, 1H, CH), 12.74 (s, 1H, OH). MS (70 eV): *m/z* (%) = 174 (100, M^+), 147 (56), 131 (16), 121 (28), 93 (8). The exact molecular mass for $C_{11}H_{10}O_2$ *m/z* = 174.0681 ± 2 ppm [M^+] was determined by HRMS (EI, 70 eV). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2924 (w), 2342 (w), 1643 (s), 1620 (w), 1577 (s), 1487 (s), 1444 (m).

4.14. 1-(4-Benzyloxy-2-hydroxyphenyl)-penta-2,4-dien-1-one (4b)

Starting with **1i** (0.76 g, 3.0 mmol), dissolved in 0.5 mL of CH_2Cl_2, TMSOTf (0.87 g, 3.9 mmol), 15 mL of THF and vinyl magnesium bromide (3.9 mL, 1 M), **4b** was obtained as yellow solid (0.31 g, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.10 (s, 2H, CH_2), 5.60 (d, $^3J_{cis}$ = 10 Hz, 1H, CH_2), 5.73 ($^3J_{trans}$ = 17 Hz, 1H, CH_2), 6.51–6.66 (m, 3H, CH), 7.03 (d, $^3J_{trans}$ = 16 Hz, 1H, CH), 7.31–7.51 (m, 6H, CH), 7.72 (d, $^3J_{cis}$ = 10 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 70.20 (CH_2), 102.02, 108,16 (CH), 114.12 (C), 124.51 (CH), 127.12 (CH_2), 127.52, 128.29, 128.67, 131.25, 135.20, 144.36 (CH), 165.26, 166.51, 192.10 (C), 232.52 (CO). MS (70 eV): *m/e* (%) = 280 (32, M^+), 253 (4), 189 (4), 91 (100), 65 (6). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3438 (s), 1637 (s), 1617 (s), 1576 (s), 1504 (m). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; found: C, 77.43; H, 6.12.

4.15. (*Z*)-1-(2-Hydroxyphenyl)-2-methylpenta-2,4-dien-1-one (4c)

Starting with **1j** (0.16 g, 1.0 mmol), dissolved in 0.3 mL of CH_2Cl_2, TMSOTf (0.29 g, 1.3 mmol), 4 mL of THF and vinyl magnesium bromide (1.3 mL, 1 M), **4c** was obtained as a yellow oil (0.06 g, 35%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 3H, CH_3), 5,51 (dd, $^3J_{trans}$ = 17 Hz, $^3J_{cis}$ = 9 Hz, 2H, CH_2), 6.54 (d, $^3J_{cis}$ = 11 Hz, 1H, CH), 6.75 (ddd, $^3J_{trans}$ = 17 Hz, $^3J_{cis}$ = 11 Hz, $^3J_{cis}$ = 9 Hz, 1H, CH), 6.87 (dt, ^4J = 1 Hz, ^3J = 7 Hz, 1H, CH), 7.02 (dd, ^4J = 1 Hz, ^3J = 7 Hz, 1H, CH), 7.47 (dt, ^4J = 1 Hz, ^3J = 7 Hz, 1H, CH), 7.63 (dd, ^4J = 1 Hz,

^3J = 7 Hz, 1H, CH), 11.74 (s, 1H, OH). MS (70 eV): *m/e* (%) = 188 (M^+, 97), 173 (35), 161 (100), 144 (23), 121 (82). IR (KBr): $\tilde{\nu}$ = 3427 (s), 2927 (w), 1721 (m), 1620 (s), 1482 (m), 1446 (w). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; found: C, 76.43; H, 6.02.

4.16. Pharmacological screening

The bacterial cultures were obtained from the ATCC. Isolates of MRSA (methicillin resistant *S. aureus*) were obtained from the Universitätsklinikum Greifswald.

4.17. Assay for antimicrobial and antifungal activity

A modified disc diffusion method[7,8] was used to determine the antimicrobial activity. A nutrient agar was used for bacteria and a malt agar was used for *Candida maltosa*. A sterile filter disc of 6 mm (B&D research) diameter impregnated with test compound was used for the assay. The paper disc was placed on the agar plate seeded with respective microorganisms. The plates were kept in the refrigerator at 4 °C for 4 h. Then the plates were turned over to incubate overnight at 37 °C in an inverted position. In contrast, *C. maltosa* was incubated at 28 °C for 72 h. At the end of the incubation period the clear zones of inhibition around the paper disc were measured. Negative control experiments were performed by using paper discs loaded with equivalent volume of solvent and positive control experiments were performed by use of an equivalent amount of OTC. The concentration of the compound tested during the experiments was 1000 nmol unless otherwise stated.

5. Determination of minimal inhibitory concentrations of compounds by dilution method

5.1. Sample preparation

The compound (1 mg) was dissolved in 1 mL of DMSO and serially diluted with nutrient agar medium to get the final concentrations.

5.2. Culture of micro-organisms

A column of 3 mL sterile broth was inoculated with about the pinhead size of respective bacteria and 100 μL of the bacterial suspension was further inoculated into 10 mL of sterile broth. The final inoculated bacterial suspension was placed on an orbital shaker (175 rpm) and incubated overnight at 25 °C. For the test, the bacterial suspension was diluted in the ratio of 1:100.

5.3. Antibacterial assay

The minimal inhibitory concentration (MIC) was measured by the 10-fold serial broth dilution method. The assay was carried out in a 96 well tray. The wells of the first row of the tray, A1 to H1, were filled with 150 μL diluted test substances in duplicate. From the second to 11th row, A2 H2 to A11 H11, the wells were first filled with 100 μL of PBS. Then 10 μL of the test substance from the first row was pipetted out in a stepwise manner from left to right up to the 11th row. Finally, 10 μL of the diluted substance was discarded from the 11th row. Each and every well from the row 1–11 was finally filled with 100 μL diluted bacterial suspension.

The wells 12A–12D were filled with 100 μL PBS and 100 mL bacterial suspension without test substance as control wells. The wells 12E–12G were filled with 100 μL PBS and 100 μL bacterial suspension without test substance as control wells. The well 12H was kept empty for photometric blank. The plate was shaken carefully and then incubated for 16 h at 35 °C. After incubation, the absorbance was measured at 620 nm in a plate reader (anthos). The MIC corresponds to the lowest concentration of the test compound that still produces bacterial growth inhibition. It was determined by spectrophotometry by measuring the turbidity of inoculated liquid broth in the presence and absence of the test compound. The highest concentration of the test substance for the assay was 500 μg/mL and lowest concentration was 0.0085 μg/mL unless otherwise specified.

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