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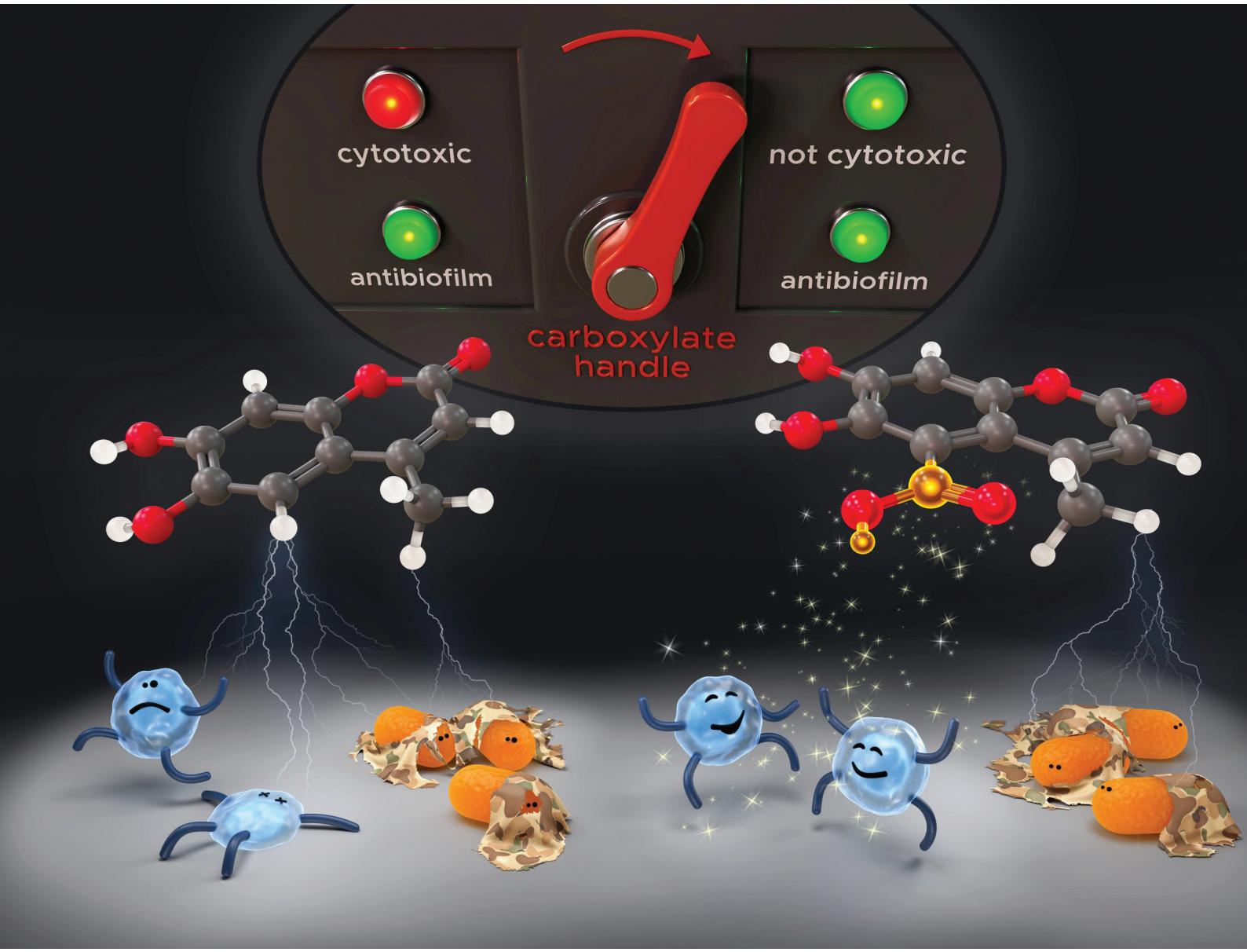

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Design of non-cytotoxic 6,7-dihydroxycoumarin-5-carboxylates with antibiofilm activity against *Staphylococcus aureus* and *Candida albicans*†

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The 6,7-dihydroxycoumarin-5-carboxylates DHCou and 4-Me-DHCou have been synthesized *via* five-step route including a propargyl-Claisen rearrangement as key step. The compounds show antibiofilm activity against *Stapylococcus aureus* and *Candida albicans* but lack the cytotoxic activity of parent 6,7-dihydroxycoumarines such as esculetin and 4-methylesculetin.

The occurrence of resistance of microbial pathogens against market antimicrobial drugs has been continuously rising since 1970s and nowadays we see ourselves confronted with multi-drug-resistant microbial pathogens causing a strong need for new drugs and concepts to counter act this threat for public health.[1–7] In addition, microbial biofilms provide challenges for the development of antimicrobials as bacterial[8–13] and fungal pathogens[14–16] tend to hide in biofilms preventing drug penetration and leading to recurring and persistent infections.[15] Beyond planktonic cells, biofilms are a principal form of microbial growth on surfaces in which microbes embed themselves in sugar, peptide and lipid containing hydrogels. Biofilms are often critical to development of clinical infections in human host[14] and can be found for many microbial pathogens such as Methicillin-resistant *Staphylococcus aureus* (MRSA),[10,17] *Pseudomonas aeruginosa*[8,18–21] and *Candida albicans*[15,22,23] causing severe infections.

In biofilms these pathogens can even co-occur during infection.[24] Compounds which are able to disrupt biofilms or inhibit their formation are of vast importance to make these pathogens susceptible again against antimicrobial drugs.[25] The inhibition of biofilm formation can be achieved *via* different modes of action of compounds: while targeting of efflux pumps by efflux pump inhibitors disables the secretion of building blocks for the biofilms,[26] the inhibition of cell–cell communication by quorum sensing inhibitors is another successful strategy to avoid biofilm formation and impair virulence of the pathogens.[25]

For several coumarins antibiofilm properties have been demonstrated,[27–30] such as coumarin (**1**), esculetin (**2**), dephnetin (**3**), umbelliferone (**4**), 4-hydroxycoumarine (**5**), and scopoletin (**6**) (Fig. 1).[31–36] The biofilm inhibitory effect of dihydroxycoumarins such as umbelliferone (**4**) and esculetin (**2**) has been reported to be mediated by both, efflux pump inhibition as well as impairment of quorum sensing,[31,33] making them interesting lead structures for the development of novel biofilm inhibitors. However, both compounds show

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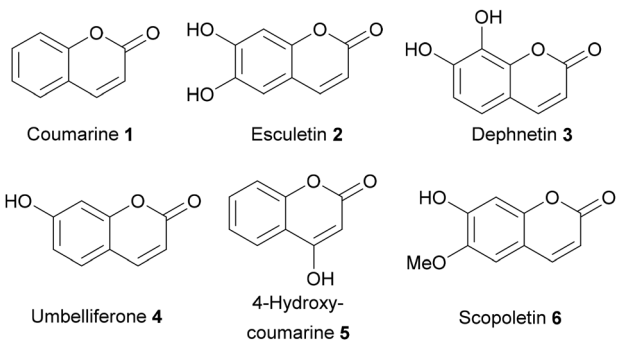

Fig. 1 Structures of selected coumarin derivatives showing antibiofilm activities.

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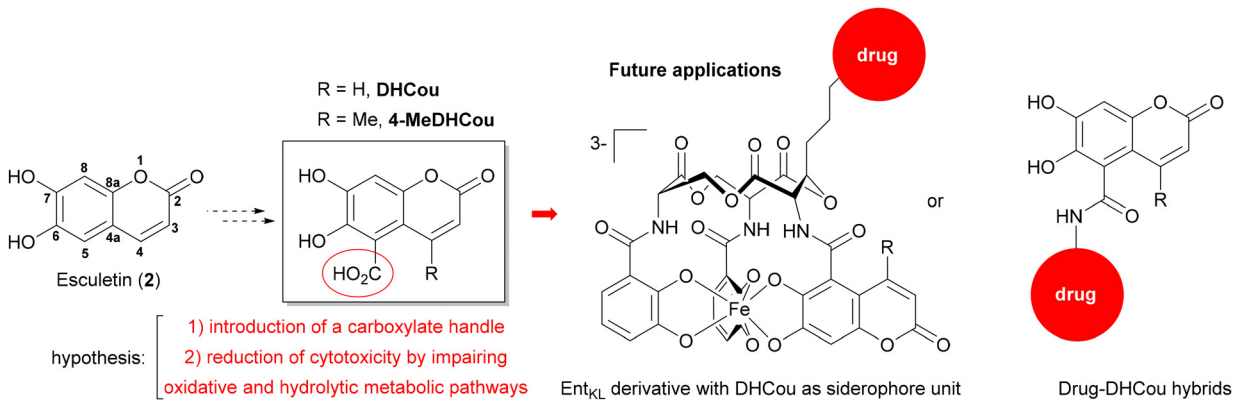
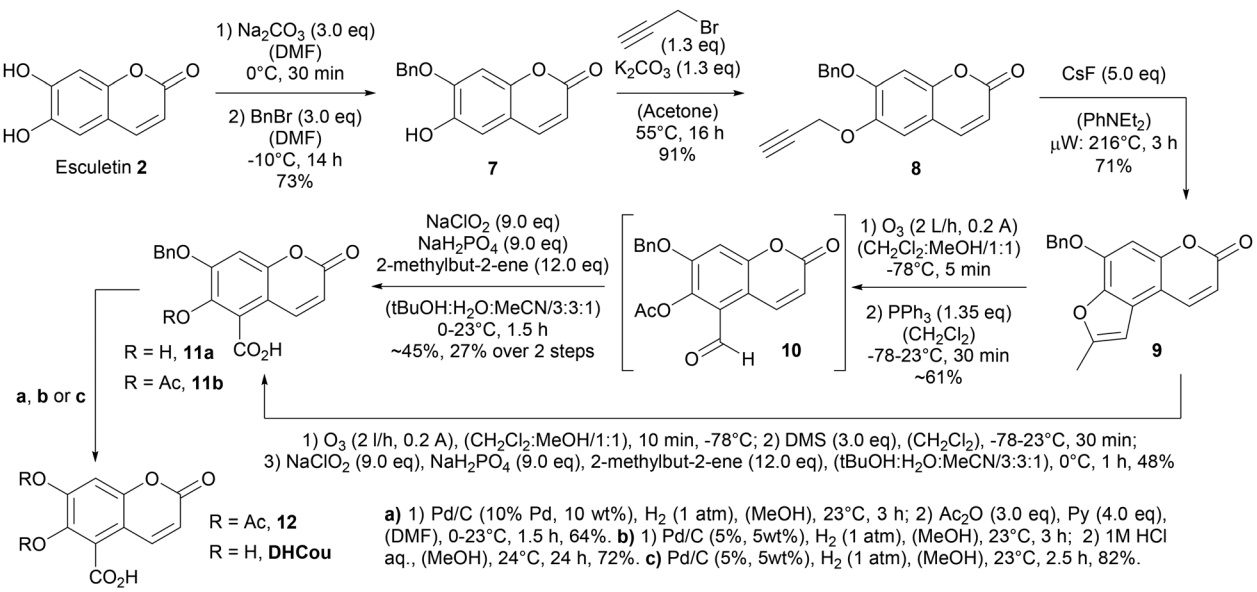
distinct antiproliferative activities against human cells limiting their potential application.[37–40]

In this work, we aimed to design novel 6,7-dihydroxycoumarin-5-carboxylate derivatives with reduced cytotoxic activity bearing a molecular handle for attachment and hybridization with further antimicrobial drugs or siderophores moieties to enable future transfer of the antibiofilm activity of 6,7-hydroxycoumarins onto these entities as outlined in Scheme 1. We hypothesized that the 5-position of the coumarin core might be suitable for the incorporation of a carboxylate handle allowing for the conjugation of such compounds to artificial siderophores such as the recently published enterobactin derivative $\mathbf{Ent_{KL}}$ [41–43] or additional antimicrobial drug moieties[3] while retaining the antibiofilm properties. Furthermore, a main metabolic pathway of coumarins mediated by cytochrome P450 monooxygenases.[44,45] Leading to cytotoxic intermediates and additionally to depletion of cellular glutathione levels is the 3,4-epoxidation of the core. We expected substituents in 5-position to impair this oxidative metabolization leading to a reduced cytotoxicity of the respective 6,7-dihydroxycoumarines.

Therefore, we followed a semi-synthetic strategy to generate the 6,7-dihydroxycoumarin-5-carboxylate (**DHCou**) starting from the natural product esculetin (**2**) in 5 steps. First, the selective alkylation of the 7-hydroxy function[46] with benzyl bromide at −15 °C gave access to the 7-benzyloxy coumarin derivative **7** in 73% yield, which could be further *O*-alkylated at the 6-hydroxy function in presence of propargyl bromide obtaining the *O*,*O*-dialkylated coumarin **8** in 91% yield. Compound **8** was submitted to a cascade-reaction consisting of a thermal [3.3]sigmatropic propargyl-Claisen rearrangement and subsequent CsF-mediated nucleophilic 5-*exo-dig* cyclization of the intermediate allenylphenolate forming the 2-methylbenzo[*d*]furan **9** in 71% yield upon heating to 216 °C



Scheme 1 Concept of 6,7-dihydroxcoumarin-5-carboxylates as potential antibiofilm compounds bearing a handle for conjugation to siderophores and antimicrobial drug moieties.



Scheme 2 Synthesis of **DHCou** from esculetin (**2**).

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in the microwave over 3 h. This methodology had been invented by Ishii and co-workers[47] and was used earlier for the conversion of *O*-alkyl derivatives of scopoletin (**6**) (Scheme 2).[48] In order, to enable oxidative cleavage of the furan ring forming the 5-formyl coumarin derivative **10** we explored different oxidative reactions conditions. Most 2-step procedures forming first the corresponding 3,4-epoxide and subsequently furnishing the oxidative cleavage in the presence of sodium periodate or lead tetraacetate failed to give access to the product.

While no conversion to the intermediate 3,4-epoxide was observed in the presence of *m*CPBA, decomposition occurred when DMDO was applied for epoxide formation. A first success was achieved forming the 3,4-epoxide in the presence of trifluoroacetic acid anhydride (TFAA) and hydrogen peroxide at 0 °C over 5 h and subsequently cleaving the epoxide with sodium periodate in a 1 : 1-mixture of MeOH and water. However, compound **10** was only obtained impure in roughly 26% yield as the reaction occurred with several side reactions. Similarly, **10** was obtained impure in roughly 25% yield, when 2-methylbenzofurane **9** was ozonolyzed at 78 °C in CH_2Cl_2 followed by reductive workup with dimethyl sulfide. Ozonolysis at 78 °C in a 1 : 1-mixture of CH_2Cl_2 : MeOH/1 : 1 and reductive workup with triphenylphosphine gave access to impure 5-formyl coumarin derivative **10** in roughly 61% yield. Subsequent Pinnick oxidation of the impure aldehyde **10** delivered the *O*-protected 6,7-dihydroxycoumarin-5-carboxylate **11b** in roughly 45% and 27% over two steps from furane **9**. We then found that a similar procedure for the direct conversion of compound **9** into compound **11a** lacking the acetate was also possible in a one-pot fashion giving 48% yield. The hydrogenolytic cleavage of the *O*-benzyl moiety in the presence of palladium on charcoal and subsequent *O*-acetylation with acetic acid anhydride and pyridine gave access to the *O*,*O*-diacetate **12** in 64% yield. Furthermore, **DHCou** was obtained in 72% yield and an overall yield of 16% over 5 steps after hydrogenolytic cleavage of the *O*-benzyl moiety and subsequent acidic deacetylation in the presence of aqueous HCl.

When **DHCou** was evaluated by crystal violet staining assay for its effects against formation of *S. aureus* biofilms no inhibitory activity was observed at the highest concentration of 250 μg mL^{-1}, while esculetin (**2**) showed inhibition effects of 93% on the formation of *S. aureus* biofilms at the concentration of 250 μg mL^{-1} and of 33% at 125 μg mL^{-1} (Table 1). However, inhibitory effects of 62% could be observed against *C. albicans* biofilms when **DHCou** was applied at 250 μg mL^{-1} in the early stage of biofilm formation (Table 1). Esculetin (**2**) showed a slightly higher biofilm inhibition against *C. albicans* of 77% at the same concentration but was not active against preformed biofilms of *S. aureus*.

However, due to its cytotoxic effects, these values must be taken with care (Table 2) and a conclusion on the single standing influence of the C5 substitution is not possible. Although, a clear loss in antibiofilm activity against *S. aureus* was observed, a significant portion of the initial antibiofilm activity against *C. albicans* could be retained by C5 substitution. Beyond that, validating our initial hypothesis, **DHCou** showed neither cytotoxicity nor antiproliferative activity against the tested mammalian cell lines (L929 and KB3.1) at the highest concentration tested (1 mg mL^{-1} = 4.5 mM). Nevertheless, to increase the overall biofilm inhibitory activity of the compounds, we planned to increase the lipophilicity by incorporation of a methyl substituent in the 4-position of the coumarin

Table 1 Inhibition of biofilm formation on *S. aureus* and *C. albicans* biofilms[49–51]

	Biofilm inhibition [% ± SD]	
Compound	*S. aureus* (DSM 1104)	*C. albicans* (DSM 11225)
Esculetin (**2**)	93 ± 2 (250 μg mL^{-1})[a] 33 ± 6 (125 μg mL^{-1})[a]	77 ± 7 (250 μg mL^{-1})[c] 58 ± 17 (125 μg mL^{-1})[c]
4-Methylesculetin (**14**)	94 ± 1 (250 μg mL^{-1})[a] 48 ± 8 (125 μg mL^{-1})[a]	76 ± 7 (250 μg mL^{-1})[c] 48 ± 14 (125 μg mL^{-1})[c]
DHCou	—[b]	62 ± 9 (250 μg mL^{-1})[d]
4-MeDHCou	75 ± 5 (250 μg mL^{-1})[b] 43 ± 11 (125 μg mL^{-1})[b] 31 ± 15 (62.5 μg mL^{-1})[b]	60 ± 2 (250 μg mL^{-1})[d]

(–): no activity, SD: standard deviation, references [%]. [a] Microporenic acid A (MAA): 93 ± 0.3 (250 μg mL^{-1}), 93 ± 1 (62.5 μg mL^{-1}), 62 ± 6 (7.8 μg mL^{-1}). [b] MMA: 82 ± 6 (250 μg mL^{-1}), 81 ± 8 (62.5 μg mL^{-1}), 73 ± 17 (7.8 μg mL^{-1}). [c] Farnesol: 87 ± 3 (250 μg mL^{-1}), 79 ± 14 (31.3 μg mL^{-1}), 67 ± 11 (15.6 μg mL^{-1}). [d] Farnesol: 75 ± 6 (250 μg mL^{-1}), 58 ± 15 (31.3 μg mL^{-1}), 46 ± 14 (15.6 μg mL^{-1}).

Table 2 Cytotoxic activity on different mammalian cell lines[a] [52,53]

	Cytotoxicity IC_{50} [μM]			
Cell line	**DHCou**	**4-MeDHCou**	Esculetin (**2**)	4-Methylesculatin (**14**)
KB3.1 (ACC158)	—	—	29.8	30.2
L929 (ACC2)	—	—	41.5	33.8
A549 (ACC107)	n.t.	n.t.	18.5	21.9
A431 (ACC91)	n.t.	n.t.	41.5	38.5
PC-3 (ACC465)	n.t.	n.t.	46.0	38.0
SKOV-3 (ATCC HTB 77)	n.t.	n.t.	45.5	42.7
MCF-7 (A115)	n.t.	n.t.	19.6	27.1

[a] For control references epothilon B see Table S4 in the ESI;† (–): no cytotoxicity or changed cells observed (max. concentration 1 mg mL^{-1} = 4.5 mM for **4-MeDHCou** and 4.2 mM for **DHCou**), n.t.: not tested.

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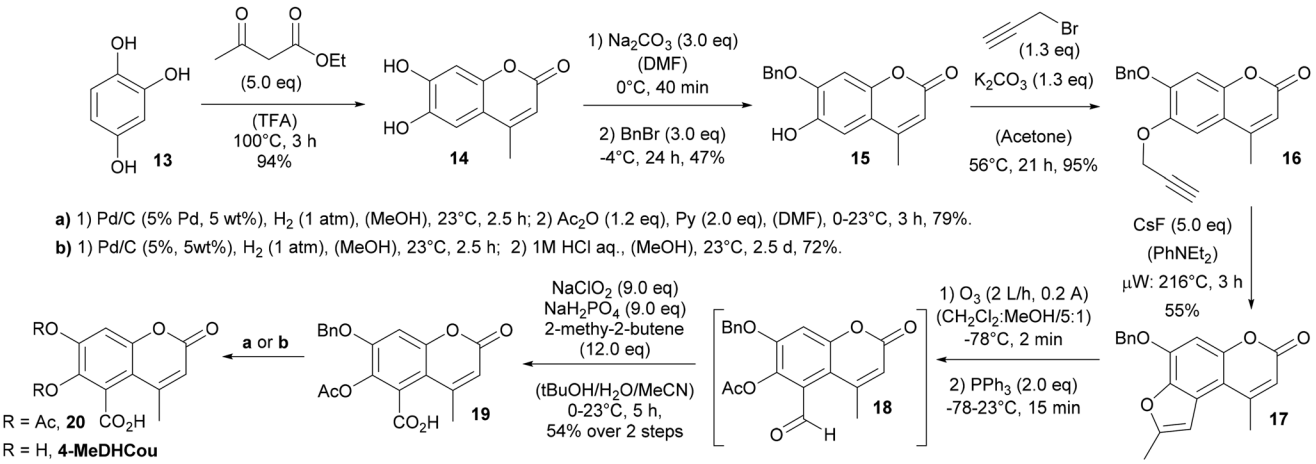

Scheme 3 Synthesis of **4-MeDHCou** from 4-methylesculetin (**2**).

core. Therefore, we generated 4-methylesculetin (**14**) *via* a Pechmann condensation of 1,2,4-trihydroxybenzene (**13**) with ethylacetoacetate in TFA at 100 °C (Scheme 3). Following the earlier strategy, selective *O*-benzylation of the 7-hydoxy position and subsequent *O*-propargylation of the 6-hydroxy position gave access to the *O*,*O*-dialkylated precursor for the cascade rearrangement.

The thermal [3.3]sigmatropic propargyl-Claisen rearrangement and subsequent CsF-mediated nucleophilic 5-*exo-dig* cyclization proceeded with 55% yield and gave access to the 2-methylbenzofurane **17** (Scheme 3). Ozonolysis, followed by reductive workup in the presence of triphenylphosphine and subsequent Pinnick oxidation led to formation of the *O*-protected 6,7-dihydroxycoumarin-5-carboxylate **19** in 54%. Again, it turned out difficult to isolate the intermediate aldehyde **18**, which could only be obtained in small amounts and with certain impurities when the oxidative cleavage was done *via* a sequence of oxidation with trifluoroperoxoacetic acid and subsequent cleavage in the presence of sodium periodate (see ESI†). From **19** the *O*,*O*-diacetate **20** and **4-MeDHCou** were obtained following the procedure established before.

Similar to **DHCou**, **4-MeDHCou** showed no cytotoxic activity against the mammalian cervic carcinoma cell line KB3.1 and the mouse fibroblasts cell line L929 when applied at the highest concentration of 1 mg mL^{-1} (4.2 mM).

In contrast to that and in accordance with the observed cytotoxicity of esculetin (**2**), 4-methylesculetin (**14**) exhibited cytotoxic activity against all tested mammalian cell lines (Table 2). Furthermore, while the inhibitory effects against *C. albicans* biofilms were comparable to that of **DHCou**, **4-MeDHCou** inhibited the formation by 60% at 250 μg mL^{-1} (Table 1), we could also observe activity against *S. aureus* biofilms. Thus, **4–MeDHCou** showed inhibition effects of 75% on the formation of *S. aureus* biofilms at the concentration of 250 μg mL^{-1} and of 43% at 125 μg mL^{-1}. The antibiofilm activity of 4-methylesculetin (**14**) was observed to be higher compared to **4-MeDHCou** with 76% inhibition at 250 μg mL^{-1} and 48% at 125 μg mL^{-1} against *C. albicans* and 94% inhibition at 250 μg mL^{-1} and 48% at 125 μg mL^{-1} against *S. aureus*. Furthermore, no dispersal effects against preformed biofilms of *S. aureus* were observed for **4-MeDHCou** and 4-methylesculetin (**14**).

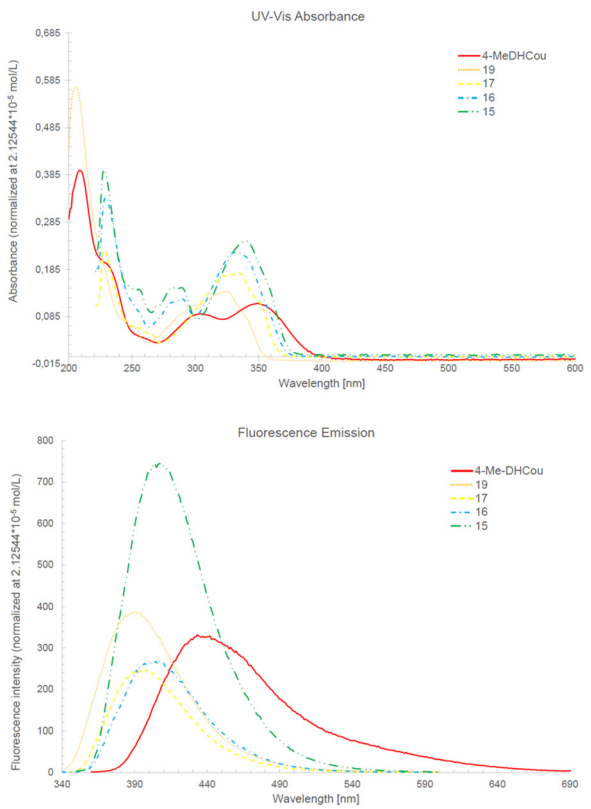

Fig. 2 UV/Vis absorption and fluorescence emission of **4-MeDHCou** and its precursors **15**, **16**, **17** and **19** at normalized concentration 2.125 × 10^{-5} mol L^{-1}.

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However, considering a potential contribution of the observed cytotoxicity of 4-methylesculetin (**14**) to its antibiofilm activity, a significant portion of the antibiofilm activity could be retained by C5 carboxylate substitution in **4-MeDHCou**.

In addition, none of the compounds (**DHCou**, **4-MeDHCou**, esculetin (**2**) or 4-methylesculetin (**14**)) showed antimicrobial activity (see Table S1 in the ESI†) against a panel of Gram-positive and Gram-negative bacteria (*B. subtilis*, *S. aureus*, *M. Smegmatis*, *A. baumanni*, *C. violaceum*, *E. coli*, and *P. aeruginosa*) and different fungi (*M. hiemalis*, *P. anomala*, *R. glutinis*, *C. albicans* and *S. pombe*) up to a concentration of 66.7 μg mL^{-1}.

Besides their antibiofilm activity, coumarins are known for their UV fluorescence and use as dyes in chemical biology. In line with that also **4-MeDHCou** and its coumarin precursors **15**, **16**, **17** and **19** showed fluorescence with maximal emission wavelengths between 400–450 nm (Fig. 2). Interestingly **4-MeDHCou** was the most bathochromic shifted compound of this series, although fluorescence intensity at normalized concentration decreased along the synthesis route.

Currently different approaches to further optimize the structure for higher antibiofilm activity and incorporate **4-MeDHCou** to artificial siderophores and antimicrobial drug hybrids are under investigation to explore its potential to serve as mediator for antibiofilm activity (as outlined in Scheme 1).

Conclusions

We synthesized two novel 6,7-dihydroxycoumarin-5-carboxylates, namely **DHCou** and **4-MeDHCou**. In contrast, to their non-carboxylated parent 6,7-dihydroxycoumarins esculetin (**2**) and 4-methylesculetin (**14**), these compounds lack any cytotoxic activity towards different mammalian cell lines, while retaining an antibiofilm activity. **DHCou** displayed inhibitory effects against the early stage of *C. albicans* biofilm formation but showed no activity against *S. aureus* biofilms. Furthermore, **4-MeDHCou** exhibited antibiofilm activity against both, the formation of *S. aureus* and *C. albicans* biofilms. Although the structure activity relationships need to be further investigated to fully understand the observed effects and improve the antibiofilm activity of the compounds, a proof-of-principle for the design of non-cytotoxic hydroxycoumarins retaining antibiofilm activity has been made, holding potential to overcome a major limitation for the application of coumarins as biofilm disruptors. In addition, these moieties might be able to transfer their antibiofilm activity by conjugation to other entities such as antimicrobials drugs or siderophores. Further investigations are ongoing to explore their potential.

Author contributions

Conceptualization, funding acquisition, project administration and writing of original draft: PK; supervision: PK, HS; writing – review and editing: PK, RZ, AC, APL, HS and HZ. Investigation: RZ, AC, APL, HS, HZ and WC. Methodology: PK, RZ, AC and APL; resources: PK, AC, RZ, and APL; visualization: PK, HS and APL.

Conflicts of interest

There are no conflicts to declare.

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References

1 D. J. Krysan, *Virulence*, 2017, **8**, 135–137.
2 E. Ksiezopolska and T. Gabaldón, *Genes*, 2018, **9**, 461.
3 P. Klahn and M. Brönstrup, *Nat. Prod. Rep.*, 2017, **34**, 832–885.
4 P. Klahn and M. Brönstrup, *Curr. Top. Microbiol. Immunol.*, 2016, **389**, 365–417.
5 M. A. Cook and G. D. Wright, *Sci. Transl. Med.*, 2022, **14**, eabo7793.
6 N. Mobarki, B. Almerabi and A. Hattan, *Int. J. Med. Dev. Countries*, 2019, **40**, 561–564.
7 T. M. Privalsky, A. M. Soohoo, J. Wang, C. T. Walsh, G. D. Wright, E. M. Gordon, N. S. Gray and C. Khosla, *J. Am. Chem. Soc.*, 2021, **143**, 21127–21142.
8 A. Vetrivel, M. Ramasamy, P. Vetrivel, S. Natchimuthu, S. Arunachalam, G.-S. Kim and R. Murugesan, *Biologics*, 2021, **1**, 312–336.
9 N. Høiby, T. Bjarnsholt, M. Givskov, S. Molin and O. Ciofu, *Int. J. Antimicrob. Agents*, 2010, **35**, 322–332.
10 V. Silva, L. Almeida, V. Gaio, N. Cerca, V. Manageiro, M. Caniça, J. L. Capelo, G. Igrejas and P. Poeta, *Pathogens*, 2021, **10**, 970.
11 M. H. Muhammad, A. L. Idris, X. Fan, Y. Guo, Y. Yu, X. Jin, J. Qiu, X. Guan and T. Huang, *Front. Microbiol.*, 2020, **11**, 1–20.

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12 L. Hall-Stoodley, J. W. Costerton and P. Stoodley, *Nat. Rev. Microbiol.*, 2004, **2**, 95–108.
13 F. Hemmati, M. A. Rezaee, S. Ebrahimzadeh, L. Yousefi, R. Nouri, H. S. Kafil and P. Gholizadeh, *Mol. Biotechnol.*, 2021, **63**, 569–586.
14 S. Fanning and A. P. Mitchell, *PLoS Pathog.*, 2012, **8**, e1002585.
15 J. V. Desai, A. P. Mitchell and D. R. Andes, *Cold Spring Harbor Perspect. Med.*, 2014, **4**, a019729.
16 M. Gulati and C. J. Nobile, *Microbes Infect.*, 2016, **18**, 310–321.
17 A. Boudet, P. Sorlin, C. Pouget, R. Chiron, J.-P. Lavigne, C. Dunyach-Remy and H. Marchandin, *Front. Microbiol.*, 2021, **12**, 750489.
18 O. Ciofu and T. Tolker-Nielsen, *Front. Microbiol.*, 2019, **10**, 913.
19 M. T. T. Thi, D. Wibowo and B. H. A. Rehm, *Int. J. Mol. Sci.*, 2020, **21**, 8671.
20 F. F. Tuon, L. R. Dantas, P. H. Suss and V. S. Tasca Ribeiro, *Pathogens*, 2022, **11**, 300.
21 E. Banin, M. L. Vasil and E. P. Greenberg, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 11076–11081.
22 C. Tsui, E. F. Kong and M. A. Jabra-Rizk, *Pathog. Dis.*, 2016, **74**, ftw018.
23 T. Atriwal, K. Azeem, F. M. Husain, A. Hussain, M. N. Khan, M. F. Alajmi and M. Abid, *Front. Microbiol.*, 2021, **12**, 638309.
24 M. del M. Cendra and E. Torrents, *Biotechnol. Adv.*, 2021, **49**, 107734.
25 A. Ghosh, N. Jayaraman and D. Chatterji, *ACS Omega*, 2020, **5**, 3108–3115.
26 A. Reza, J. M. Sutton and K. M. Rahman, *Antibiotics*, 2019, **8**, 229.
27 M. G. da Cunha, J. de Cássia Orlandi Sardi, I. A. Freires, M. Franchin and P. L. Rosalen, *Microb. Pathog.*, 2020, **139**, 103855.
28 S. K. Roy, N. Kumari, S. Pahwa, U. C. Agrahari, K. K. Bhutani, S. M. Jachak and H. Nandanwar, *Fitoterapia*, 2013, **90**, 140–150.
29 J. H. Lee, J. H. Park, H. S. Cho, S. W. Joo, M. H. Cho and J. Lee, *Biofouling*, 2013, **29**, 491–499.
30 T. Das, M. C. Das, A. Das, S. Bhowmik, P. Sandhu, Y. Akhter, S. Bhattacharjee and U. C. De, *World J. Microbiol. Biotechnol.*, 2018, **34**, 170.
31 J.-H. J. H. Lee, Y. G. Kim, H. S. Cho, S. Y. Ryu, M. H. Cho and J.-H. J. H. Lee, *Phytomedicine*, 2014, **21**, 1037–1042.
32 Y. Zhang, A. Sass, H. Van Acker, J. Wille, B. Verhasselt, F. Van Nieuwerburgh, V. Kaever, A. Crabbé and T. Coenye, *Front. Microbiol.*, 2018, **9**, 1–10.
33 F. J. Reen, J. A. Gutiérrez-Barranquero, M. L. Parages and F. O'Gara, *Appl. Microbiol. Biotechnol.*, 2018, **102**, 2063–2073.
34 K. Xu, J. L. Wang, M. P. Chu and C. Jia, *J. Mycol. Med.*, 2019, **29**, 28–34.
35 F. A. Qais, M. S. Khan, I. Ahmad, F. M. Husain, R. A. Khan, I. Hassan, S. A. Shahzad and W. AlHarbi, *ACS Omega*, 2021, **6**, 18823–18835.
36 Z. He, W. Jiang, Y. Jiang, J. Dong, Z. Song, J. Xu and W. Zhou, *J. Oral Microbiol.*, 2022, **14**, 2055523.
37 S.-M. Yu, D.-H. Hu and J.-J. Zhang, *Mol. Med. Rep.*, 2015, **12**, 3869–3873.
38 L. Zhang, Q. Xie and X. Li, *Phytother. Res.*, 2022, **36**, 279–298.
39 J. Y. Yang, M. A. Della-Fera, D. L. Hartzell, C. Nelson-Dooley, D. B. Hausman and C. A. Baile, *Obesity*, 2006, **14**, 1691–1699.
40 C. Y. Chu, Y. Y. Tsai, C. J. Wang, W. L. Lin and T. H. Tseng, *Eur. J. Pharmacol.*, 2001, **416**, 25–32.
41 R. Zscherp, J. Coetzee, J. Vornweg, J. Grunenberg, J. Herrmann, R. Müller and P. Klahn, *Chem. Sci.*, 2021, **12**, 10179–10190.
42 P. Klahn, R. Zscherp and C. C. Jimidar, *Synthesis*, 2022, **54**, 3499–3557.
43 C. Rohrbacher, R. Zscherp, S. C. Weck, P. Klahn and C. Ducho, *Chem. – Eur. J.*, 2022, e202202408.
44 B. Lake, *Food Chem. Toxicol.*, 1999, **37**, 423–453.
45 A. Stefanachi, F. Leonetti, L. Pisani, M. Catto and A. Carotti, *Molecules*, 2018, **23**, 250.
46 M. Kawase, H. Sakagami, N. Motohashi, H. Hauer, S. S. Chatterjee, G. Spengler, A. V. Vigyikanne, A. Molnár and J. Molnár, *In Vivo*, 2005, **19**, 705–711.
47 H. Ishii, T. Ishikawa, S. Takeda, S. Ueki and M. Suzuki, *Chem. Pharm. Bull.*, 1992, **40**, 1148–1153.
48 H. Ishii, T. Ishikawa, H. Wada, H. Miyazaki, Y. Kaneko and T. Harayama, *Chem. Pharm. Bull.*, 1992, **40**, 2614–2619.
49 K. T. Yuyama, L. Wendt, F. Surup, R. Kretz, C. Chepkirui, K. Wittstein, C. Boonlarppradab, S. Wongkanoun, J. Luangsa-ard, M. Stadler and W.-R. Abraham, *Biomolecules*, 2018, **8**, 129.
50 K. T. Yuyama, C. Chepkirui, L. Wendt, D. Fortkamp, M. Stadler and W.-R. Abraham, *Microorganisms*, 2017, **5**, 80.
51 C. Chepkirui, K. T. Yuyama, L. A. Wanga, C. Decock, J. C. Matasyoh, W.-R. R. Abraham and M. Stadler, *J. Nat. Prod.*, 2018, **81**, 778–784.
52 K. Becker, A. Wessel, J. J. Luangsa-ard and M. Stadler, *Biomolecules*, 2020, **10**, 805.
53 P. Klahn, V. Fetz, A. Ritter, W. Collisi, B. Hinkelmann, T. Arnold, W. Tegge, K. Rox, S. Hüttel, K. I. Mohr, J. Wink, M. Stadler, J. Wissing, L. Jänsch and M. Brönstrup, *Chem. Sci.*, 2019, **10**, 5197–5210.