JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo401189x • Publication Date (Web): 10 Jul 2013

Multicomponent Synthesis of Antibacterial Dihydropyridin and Dihydropyran Embelin Derivatives

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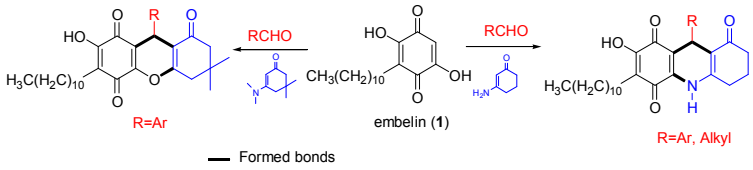


ABSTRACT

A series of dihydropyran and dihydropyridin embelin derivatives were synthesized through a novel and straightforward, one pot protocol based on a three component reaction with embelin, aldehydes and cyclic enaminones as synthetic imputs. The type of substituent on the nitrogen atom of the β-enaminone is key to obtain nitrogenated or oxygenated rings. The obtained compounds were active against Gram-positive bacteria, including multiresistant *Staphylococcus aureus* clinical isolates

INTRODUCTION

Quinones are a large class of compounds that show a wide range of applications in medicinal chemistry, photochemistry, and redox systems.[1] Benzoquinones are the simplest representatives of quinoid compounds. They are widely distributed in the natural world, being found in bacteria, plants and arthropods.[2] The 1,4-benzoquinone core is embedded in several natural products, including sesquiterpenes,[3] kinamycins,[4] and terpenylquinones.[5] Additionally, there are several drugs and therapeutic leads that contain the quinone subunit.[6] Embelin (2,5-dihydroxy-3-undecyl-[1,4]benzoquinone) (**1**), is found to be the active principle of the species *Embelia ribes* used in Indian and Chinese traditional medicine.[7] **1** displays many biological activities, including antibacterial,[8] antihelmintic,[9] antifertility,[10] analgesic,[11] anti-inflammatory[12] and antitumor effects.[13c] All these bioactivities make embelin an interesting scaffold for medicinal chemists. Most of the embelin derivatives have been synthesized attending to the replacement of the C-11 alkyl chain for other alkyl, benzyl, or aryl groups.[13] Thus, Dessolin *et al* synthesized a library of embelin derivatives bearing a long hydrophilic amino acid chain.[13a] Grée *et al* prepared new derivatives by changing the nature of the hydrophobic chain by incorporation of aromatic groups through Suzuki-Miyaura coupling reactions,[13b] and Wang afforded new embelin derivatives with hydrocarbon tails of different sizes from the reaction of the corresponding alkyl triphenylphosphonium bromides with 5,6-dimethoxy-benzo[1,3]dioxole-4-carbaldehyde, followed by hydrogenation, oxidation with CAN and treatment with $HClO_4$/HCl.[13c]

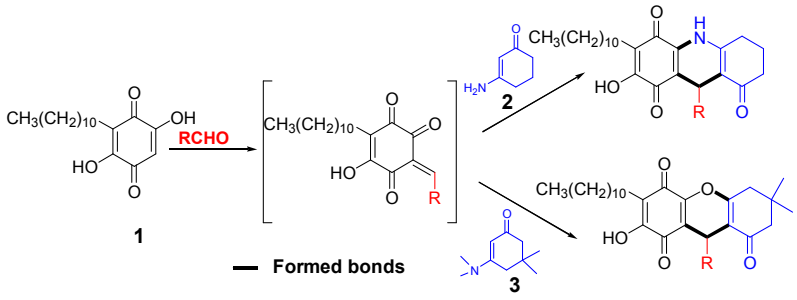
Our research group is especially interested in antitumoral and antibacterial compounds based on quinone core fused to heterocyclic rings.[14] With the aim of obtaining new bioactive embelin analogues, we decided the preparation of

dihydropyridin and dihydropyran derivatives, since these heterocyclic rings are present in a vast number of natural products and bioactive substances.[15] Herein, we present our results in this area, and disclose a novel and straightforward, one pot protocol based on a three component reaction with embelin (**1**), aldehydes and cyclic enaminones as synthetic imputs. Furthermore most of the synthesized compounds displayed antibacterial activity against Gram-positive bacteria, including multiresistant *Staphylococcus aureus* clinical isolates.[14g]

RESULTS AND DISCUSSION

In our approach 2-hydroxy-1,4-quinone moiety is employed as an adequate synthetic equivalent to a 1,3-dicarbonyl compound. In this case the Knoevenagel condensation with aldehydes leads to a reactive intermediate quinone methide[16] which is susceptible to be trapped by diverse electron rich alkenes as dienophiles *via* hetero Diels-Alder reactions[14a-d] or reacts with diverse nucleophiles *via* Michael addition.[14e-g] On the other hand, enaminones have two electron-rich centres (C-2 and amino group) and the reaction with polydentate reagents usually affords heterocycles.[17] The preparation of azapodophyllotoxin derivatives[18] and the recent synhesis of pyrrolo [2,3.4-*kl*]acridin-1-one[19] and diverse fused naphthyridines[20] are good examples of the use of β-enaminones as 1,3-bidonors to construct nitrogen containing heterocycles. Taking into account all above mentioned, we decide to study the preparation of dihydropyridin embelin derivatives from a three component reaction using the hydroxybenzoquinone **1**, aldehydes, and commercial cyclic enaminones such as 3-amino-cyclohex-2-enone (**2**) or 3-dimethylamino-5,5-dimethyl-cyclohex-2-enone (**3**). We found that dihydropyridin and dihydropyran rings could be obtained depending on the type of substituents on the nitrogen atom of the enaminone (See Scheme 1).

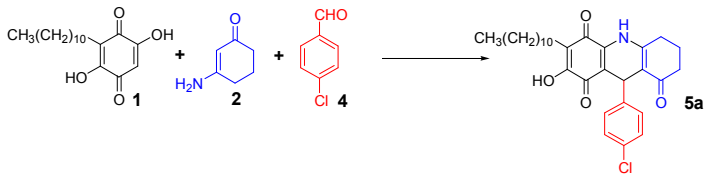
Scheme 1. Synthesis of dihydropyridin and dihydropyran embelin derivatives



Attending to the structural diversity, the synthetic sequence is very attractive because nitrogenated or oxygenated adducts are generated in one-pot reaction, allowing after biological evaluation the direct comparison between both isosters in the Structure-Activity relationship study. With both enaminones good yields were obtained with aromatic aldehydes, and only with the primary enaminone **2**, the reaction also worked with aliphatic aldehydes.

In the case of 3-amino-cyclohex-2-enone (**2**), we selected 4-chlorobenzaldehyde to search for the best reaction conditions (Table 1). The best yield was obtained using 2 equiv of aldehyde, 2 equiv of enaminone **2**, EtOH as solvent under MW irradiation at 150 ºC (entry 7).

Table 1. Optimization of the reaction conditions for the formation of 5a from 1, 2 and 4

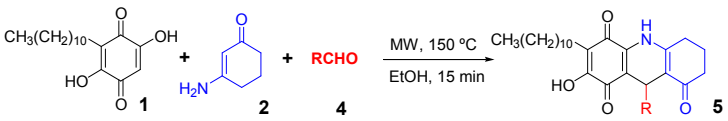


entry	1/2/4	conditions	Yield (%)[a]
1	1.0/1.0/1.0	EtOH, reflux, 5h	19
2	1.0/1.5/1.5	EtOH, reflux, 5h	61
3	1.0/1.0/1.0	EtOH, MW,[b] 150 ºC, 20 min	24
4	1.0/1.5/1.5	EtOH, MW, 150 ºC, 20 min	55
5	1.0/1.5/1.5	EtOH, MW, 170 ºC, 10 min	48
6	1.0/2.0/2.0	EtOH, reflux, 5h	78
7	1.0/2.0/2.0	EtOH, MW, 150 ºC, 15 min	80
8	1.0/2.0/2.0	DCE, MW, 150 ºC, 15 min	17
9	1.0/2.0/2.0	CH_3CN, MW, 150 ºC, 15 min	12
10	1.0/2.0/2.0	EtOH, MW, 150 ºC, 20 min	71
11	1.0/3.0/3.0	EtOH, MW, 150 ºC, 15 min	74

[a]Isolated yields. [b]A CEM-Discover monomode MW reactor was used

We chose the best conditions to generate compound **5a** (Table 1, entry 7) in order to examine the scope of the reaction, regarding the aldehyde used in the condensation. Good yields (72-98%) were obtained using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents (Table 2). The use of heteroaromatic aldehyde such as 2-furyl also afforded a good result (Table 2, entry 9). When the reaction was carried out with the aliphatic aldehydes heptanal or propionaldehyde the corresponding dihydropyridin adducts were also obtained in high yield (entries 11 and 12).

Table 2. Scope of the reaction with aldehydes 4.

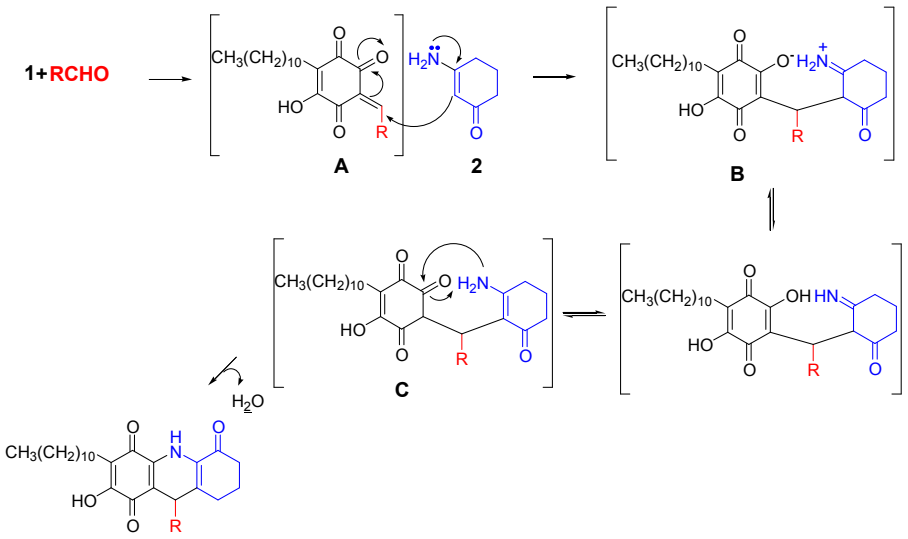


entry	compound	R	yield (%)[a, b]
1	**5a**	4-Cl-Ph	80
2	**5b**	4-Br-Ph	85
3	**5c**	4-F-Ph	83
4	**5d**	3-F-Ph	98
5	**5e**	4-NO_2-Ph	89
6	**5f**	3,4-dimethoxyphenyl	82
7	**5g**	3,4-methylenedioxiphenyl	72
8	**5h**	Ph	96
9	**5i**	2-furyl	78
10	**5j**	3-fluor-4-methoxyphenyl	76
11	**5k**	$CH_3(CH_2)_5$	93
12	**5l**	CH_3CH_2	83

[a]Isolated yields. [b]A CEM-Discover monomode MW reactor was used

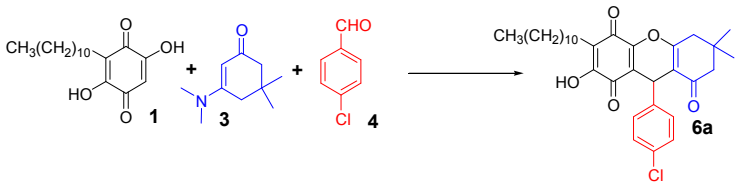
A plausible formation of the dihydropyridin embelin derivatives is shown in Scheme 2. The Knoevenagel condensation of embelin (**1**) with an aldehyde produces the quinone-methide reactive intermediate (A) which is attacked by the enaminone **2**. The reaction takes place through more electron deficient α,β-unsaturated carbonyl moiety (flanked by two carbonyl groups) to yield the intermediate (B) which experiments various intramolecular proton transfers to produce the intermediate C that evolutes via intramolecular cyclization and dehydration to yield the 1,4-dihydropyridin ring.

Scheme 2. Plausible formation of dihydropyridin embelin derivatives.



When we carried out the same reaction using the tertiary enaminone 3-dimehtyamino-5,5-dimethyl-cyclohex-2-enone (**3**), we obtained dihydropyran derivatives instead of nitrogenated derivatives. In this case, the microwave heating did not favor the desired reaction pathway, since the formation of many products was detected and the corresponding dihydropyran derivative was isolated in low yield (10%) (Table 3, entry 6). When a larger MW irradiation time was employed with less polar solvent (Table 3, entry 8), a complex mixture of compounds was formed and the compound **6a** could not be isolated. In order to improve this yield we carried out the reaction using different conditions as is shown in Table 3. The best result was obtained using the aprotic solvent toluene under reflux conditions (Table 3, entry 7).

Table 3. Optimization of the reaction conditions for the formation of 6a from 1, 3 and 4.

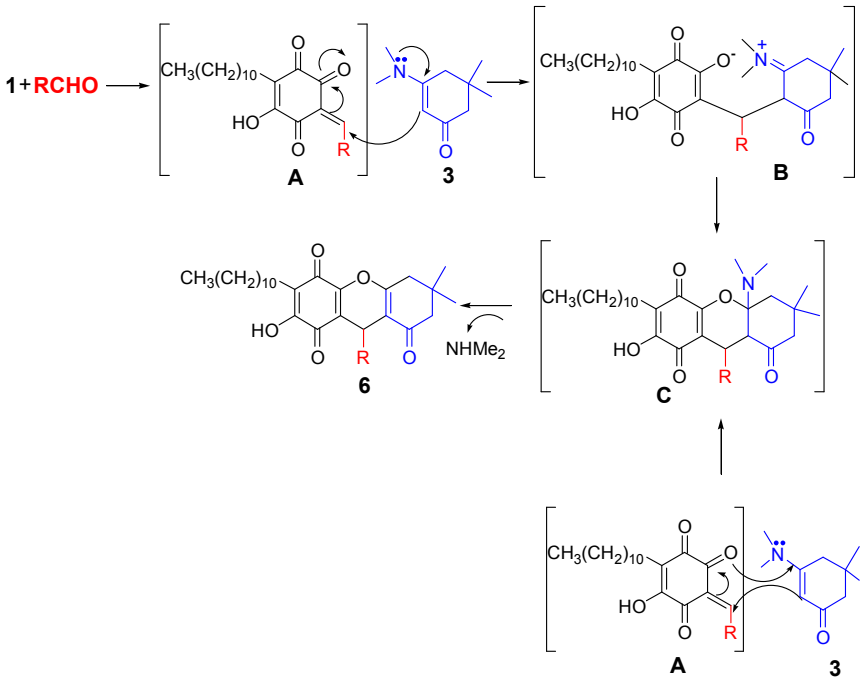


entry	1/3/4	conditions	yield (%)[a]
1	1.0/1.5/1.5	EtOH, reflux, overnight	4
2	1.0/1.5/1.5	C_7H_8, reflux, 8 h	72
3	1.0/1.0/1.0	C_7H_8, reflux, 8 h	27
4	1.0/1.5/1.5	DCE, reflux, 8 h	--
5	1.0/1.5/1.5	CH_3CN, reflux, 8 h	11
6	1.0/2.0/2.0	MW, EtOH, 150 ºC, 15 min	10
7	1.0/2.0/2.0	C_7H_8, reflux, 8 h	76
8	1.0/2.0/2.0	C_7H_8, MW, 150 ºC, 30 min	--

[a]Isolated yields.

The oxygenated bioisosters can be formed *via* two plausible routes (Scheme 3). One of them is based on the nucleophilic attack of the enaminone **3** on the quinonemethide intermediate A to produce the intermediate B followed by intramolecular cyclization to yield intermediate C which suffers a loss of $NHMe_2$ giving the desired compound **6**. On the other hand, **6** can be also formed considering a hetero Diels-Alder reaction between the quinonemethide intermediate A and the enaminone.

Scheme 3. Plausible formation of dihydropyran embelin derivatives.

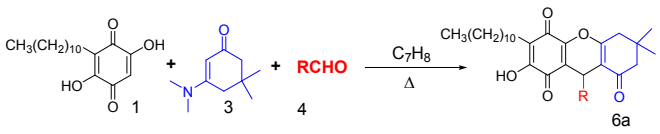


Using the best conditions shown in Table 3 (entry 7), we carried out the reaction of **1**, **3** and several aromatic aldehydes. The corresponding results are given in Table 4. In this case, slightly lower yields (57-76%) were obtained compared to the enaminone **2**, and when aliphatic aldehydes were employed we did not detect the formation of dihydropyran derivatives. This fact could be explained on the basis of a possible competitive condensation between the nucleophilic tertiary enaminone **3** and the more reactive aliphatic aldehydes.[21]

Furthermore, in order to analyze the type of derivative obtained when the reaction is carried out with secondary enaminones, we synthesized 3-benzylamino-cyclohex-2-enone from cyclohexane-1,3-dione and benzylamine in the presence of ceric ammonium nitrate as a catalyst.[22] Thus when embelin (**1**) was treated with 1.8 equiv of 3-benzylamino-cyclohex-2-enone and 1.8 equiv of 4-chlorobenzaldehyde in toluene under

reflux the N-benzyldihydropyridin derivative (**7**) was obtained in 29% yield (Scheme 4), via the plausible route shown in Scheme 2. No traces of the dihydropyran derivative was detected, but the reaction resulted be less clean as when enaminones (**2**) and (**3**) were used. Therefore only with the tertiary enaminone (**3**) the dihydropyran derivatives were obtained. The loss of dimethylamine in the corresponding intermediate favors the cyclization via the formation of the oxygenated ring instead of the alternative 1,1-dimethyl-1,4-dihydro-pyridinium ring.

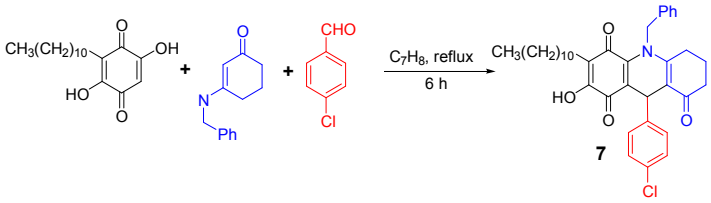
Table 4. Scope of the reaction with aldehydes 4



entry	compound	R	yield (%)
1	**6a**	4-Cl-Ph	76
2	**6b**	4-Br-Ph	75
3	**6c**	4-F-Ph	70
4	**6d**	3-F-Ph	69
5	**6e**	4-NO_2-Ph	62
6	**6f**	3,4-dimethoxyphenyl	57
7	**6g**	3,4-methylenedioxyphenyl	74
8	**6h**	Ph	75
9	**6i**	3-fluoro-4-methoxyphenyl	68

[a]Isolated yields.

Scheme 4. Reaction with 3-benzylamino-cyclohex-2-enone.



We tested our dihydropyridin and dihydropyran derivatives for antibacterial activity due to the antecedents of embelin, and they showed antibacterial activities against a set of reference and clinically relevant Gram-positive strains. The compounds had no effect on the growth of the two assayed Gram-negative bacteria: *Escherichia coli* and *Pseudomonas aeruginosa* and on the growth of the yeast *Saccharomyces cereviciae* (GI_{50} > 100 μM). Most of compounds were selectively active against the three Gram-positive bacteria tested: methicillin-sensitive *Staphylococcus aureus* ATCC25923 (MSSA); methicillin-resistant *S. aureus* NRS402, which is also intermediate resistant to vancomycin (VISA); and *Enterococcus faecalis* ATCC29212 (Table 5) and they were more active than embelin (**1**). This constitutes a very interesting result since *S. aureus* is the causal agent of most staphylococcal infections and serious complications occur because of multiple-antibiotic-resistant *S. aureus*.[23] Thus, it is urgent the finding of new molecules that could become new active antibiotics against multiresistant *S. aureus*. In the case of vancomycin resistant *S. aureus* (NRS402), the dihydropyran derivatives (**6a**-**6j**) displayed highest values, while in the other two strains the best results were achieved with the dihydropyridin derivatives (**5a-5j**). In both series the fluoro derivatives produced the best antibiotic activities.

Table 5. Concentration (in μM)[a] that inhibited growth of the three selected Gram-positive bacterial strains by 50% (GI_{50}) for compounds 1, 5a-5j and 6a-6i.

Compound	*E.Faecalis* (ATCC29212)	*S. aureus* (ATCC25923)	*S. aureus* (NRS402)
1	55.0 ±13.6	31.8 ±9.6	16.6 ±3.7
5a	16.7 ± 1.0	17.5 ± 1.6	30.7 ± 2.5
5b	23.4 ± 4.9	35.1 ± 13.2	35.9 ± 5.0
5c	5.7 ± 1.2	9.1 ± 1.9	8.6 ± 1.9
5d	5.7 ± 0.9	9.3 ± 1.1	8.1 ± 3.3
5e	9.3 ± 1.0	11.4 ± 0.9	13.7 ± 0.1
5g	16.8 ± 7.5	10.3 ± 2.0	13.3 ± 3.8
5h	9.3 ± 3.3	3.9 ± 1.6	8.7 ± 3.2
5i	5.9 ± 1.3	3.9 ± 0.7	3.8 ± 1.8
5j	14.6 ± 0.6	15.2 ± 2.1	25.7 ± 8.4
6a	6.0 ± 2.7	5.2 ± 3.9	1.5 ± 0.0
6b	9.6 ± 8.0	6.2 ± 2.4	1.8 ± 0.3
6c	7.5 ± 1.8	1.8 ± 1.3	0.8 ± 0.5
6d	9.2 ± 7.1	3.8 ± 1.3	1.4 ± 1.0
6f	5.7 ± 3.1	4.1 ± 1.2	3.8 ± 0.2
6g	7.4 ± 5.1	6.7 ± 1.8	1.3 ± 0.6
6h	10.6 ± 6.4	5.8 ± 1.4	1.8 ± 0.4
6i	8.4 ± 6.6	6.3 ± 1.7	2.2 ± 0.1
ampilicin[b]	4.9±2.8 [1.8±1.0]	<2.7 [<1.0]	131±6.2 [48.7±2.3]

[a] Mean ± SD, n=3

[b] Concentration between square brackets is in the standard microbiological measurement of mg/L. Note that concentration range for ampicillin in this assay was 1-128 mg/L.

CONCLUSIONS

In summary, we have developed an efficient multicomponent reaction using embelin (**1**), aldehydes and cyclic enaminones giving dihydropyran or dihydropyridin derivatives depending on the type of substituent on the nitrogen atom of the β-enaminone. We optimized the reaction conditions and analyzed the scope regarding the type of aldehyde used in both domino reactions. Furthermore, the synthesized derivatives were tested for antibacterial activity and we were pleased to find how the introduction of the fused oxygenated or nitrogenated ring to the quinone core of embelin (**1**) enhanced the activity and selectivity against Gram-positive bacteria including the problematic methicillin-resistant vancomycin-intermidiate *Staphylococcus aureus* NRS402.

EXPERIMENTAL SECTION

General Methods

NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 400 MHz for ^1H NMR and 100 or 150 MHz for ^{13}C NMR. Chemical shifts are given in (δ) parts per million and coupling constants (*J*) in hertz (Hz). ^1H and ^{13}C spectra were referenced using the solvent signal as internal standard. Melting points were taken on a capillary melting point apparatus and are uncorrected. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor. HREIMS were recorded using a high resolution magnetic trisector (EBE) mass analyzer. Analytical thin-layer chromatography plates used were POLYGRAM-SIL G/UV254. Flash column chromatography was carried out with E. Merck silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes. All solvents and reagents were purified by Standard techniques reported[24] or used as supplied from commercial sources. The embelin (**1**) used in the reactions was obtained from *Oxalis*

erythrorhiza following the procedure described in reference 8. All compounds were named using ACD40 Name-Pro program, which is based on IUPAC rules. Antibacterial and antifungal activities were assayed by measuring the inferred concentration that gave 50% growth inhibition (GI_{50}) relative to a subculture with just the vehicle (1 % v/v DMSO). We followed the standard broth microdilution method described by the National Committee for Clinical Laboratory Standards as we have reported previously.[25] We determined bacterial GI_{50} by measuring growth after 24 h under the presence of 1:2 serial dilutions of each compound ranging from 1 to 128 μM. We also included 1 to 128 mg/L of the antibiotic ampicillin (Sigma Chemical Co.) as a control. The inoculum size was 1×10^5 CFU/ml for all bacteria.

General procedure for the preparation of dihydropyridin embelin derivatives (5a-5l).

A solution of embelin (30.0 mg, 0.1 mmol), 2.0 equiv of aldehyde, and 2.0 equiv of 3-amino-2-cyclohexen-1-one in EtOH (5 mL) was placed in a microwave-special closed vial and the solution was irradiated for 15 min in a single-mode microwave oven (150 ºC). The reaction mixture was then cooled to room temperature. After removing the solvent under reduced pressure the product was purified by flash chromatography.

9-(4-Chloro-phenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5a). Following the general procedure described above 30.0 mg of embelin (0.1 mmol), 28.7 mg of 4-chlorobenzaldehyde (0.2 mmol), and 22.6 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were dissolved in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 70W). After removing the solvent, the crude was purified by flash chromatography with 40% Hex/EtOAc to provide 41.3 mg (80%) of **5a** as an amorphous purple solid; mp 152-153 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.68 (t, *J*=6.4 Hz, 3H), 1.06 (bs, 16H), 1.23 (m, 2H), 1.86 (m, 2H), 2.18 (m, 4H), 2.41 (m,

2H), 4.96 (s, 1H), 6.99 (d, *J*= 8.0 Hz, 2H), 7.05 (d, *J*= 9.2 Hz, 2H), 7.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 20.9 CH_2, 22.4 CH_2, 22.7 CH_2, 27.5 CH_2 , 28.0 CH_2, 29.3 CH_2, 29.4 CH_2, 29.6 CH_2 x 4, 31.9 CH_2, 33.7 CH, 36.9 CH_2, 112.7 C, 114.0 C, 117.1 C, 128.5 CH x 2, 129.6 CH x 2, 132.6 C, 136.9 C, 143.3 C, 148.8 C, 153.1, 180.2 C, 181.7 C, 195.5 C; EIMS *m/z* (%): 509 (M^+, 58), 398 (100), 368 (46), 258 (15); HREIMS: 509.2334 (calcd. for $C_{30}H_{36}NO_4Cl$ (M^+) 509.2333); IR ($CHCl_3$) ν_{max}: 1635, 1470, 1403, 1359, 1331, 1268, 1225, 1179, 1136, 743, 709, 604, 526 cm^{-1}.

9-(4-Bromo-phenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5b). Following the general procedure described above 30.0 mg of embelin (0.1 mmol), 30.0 mg of 4-bromobenzaldehyde (0.2 mmol), and 22.6 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 100W). The crude was purified by flash chromatography with 60% Hex/EtOAc to provide 47.9 mg (85%) of **5b** as an amorphous purple solid; mp 158-159 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.7 Hz, 3H), 1.26 (bs, 16H), 1.42 (m, 2H), 2.04 (m, 2H), 2.38 (m, 4H), 2.60 (m, 2H), 5.14 (s, 1H), 7.19 (d, *J*= 8.2 Hz, 2H), 7.35 (d, *J*= 8.2 Hz, 2H), 7.39 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 CH_3, 20.9 CH_2, 22.4 CH_2, 22.7 CH_2, 27.6 CH_2, 28.0 CH_2, 29.2 CH_2, 29.3 CH_2, 29.6 CH_2 x 4, 31.9 CH_2, 33.8 CH, 36.9 CH_2, 112.6 C, 113.9 C, 117.1 C, 120.8 C, 130.0 CH x 2, 131.5 CH x 2, 136.9 C, 143.8 C, 148.7 C, 153.1 C, 180.1 C, 181.7 C, 195.4 C; EIMS *m/z* (%): 555 (M^+, 45), 412 (22), 398 (100), 258 (11); HREIMS: 555.1811 (calcd. for $C_{30}H_{36}NO_4Br$ (M^+) 555.1807); IR ($CHCl_3$) ν_{max}: 1634, 1609, 1470, 1404, 1376, 1359, 1331, 1269, 1179, 1137, 743, 709, 604, 528 cm^{-1}.

9-(4-Fluoro-phenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5c). Following the general procedure described above 30.0 mg of embelin (0.1 mmol), 0.022 mL of 4-fluorobenzaldehyde (0.2 mmol), and 22.6 mg of 3-amino-2-

cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 60W). The crude was purified by flash chromatography with 40% Hex/EtOAc to provide 41.9 mg (83%) of **5c** as an amorphous purple solid; mp 146-148 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.6 Hz, 3H), 1.26 (bs, 16H), 1.43 (m, 2H), 2.05 (m, 2H), 2.38 (m, 4H), 2.60 (m, 2H), 5.18 (s, 1H), 6.91 (t, *J*= 8.5 Hz, 2H), 7.28 (t, *J*= 8.1 Hz, 2H), 7.35 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 20.9 CH_2, 22.3 CH_2, 22.6 CH_2, 27.5 CH_2, 28.0 CH_2, 29.2 CH_2, 29.3 CH_2, 29.5 CH_2 x 4, 31.8 CH_2, 33.4 CH, 36.9 CH_2, 112.8 C, 114.2 C, 115.1 CH x 2 (*J*=21.2 Hz), 117.0 C, 129.6 CH x 2 (*J*=7.8 Hz), 136.7 CH, 140.6 C, 148.4 C, 153.0 C, 161.7 C-F (*J*=244.2 Hz), 180.1 C, 181.8 C, 195.4 C; EIMS *m/z* (%): 493 (M^+, 81), 398 (100), 353 (72), 258 (15); HREIMS**:** 493.2644 (calcd. for $C_{30}H_{36}NO_4F$ (M^+) 493.2628); IR ($CHCl_3$) ν_{max}: 1634, 1608, 1508, 1470, 1403, 1376, 1359, 1330, 1269, 1179, 1136, 774, 842, 742, 709, 603, 530 cm^{-1} .

9-(3-Fluoro-phenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5d). Following the general procedure described above 30.0 mg of embelin (0.1 mmol), 0.021 mL of 3-fluorobenzaldehyde (0.2 mmol), and 2.0 equiv of 3-amino-2-cyclohexen-1-one (22.6 mg, 0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 80W). The crude was purified by flash chromatography with 60% Hex/EtOAc to provide 49.2 mg (98%) of **5d** as an amorphous purple solid; mp 176-177 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.6 Hz, 3H), 1.27 (bs, 16H), 1.44 (m, 2H), 2.07 (m, 2H), 2.40 (m, 2H), 2.63 (m, 2H), 5.21 (s, 1H), 6.83 (t, *J*= 6.8 Hz, 1H), 7.00 (d, *J*= 9.8 Hz, 1H), 7.15 (d, *J*= 7.6 Hz, 1H), 7.20 (t, *J*= 6.0 Hz, 1H), 7.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 20.9 CH_2, 22.4 CH_2, 22.6 CH_2, 27.5 CH_2, 28.0 CH_2, 29.2 CH_2, 29.3 CH_2, 29.5 CH_2, 29.6 CH_2 x 3, 31.8 CH_2, 33.8 CH, 36.9 CH_2, 112.5 C, 113.7 CH (*J*=20.1 Hz), 114.9 CH (*J*=5.1 Hz), 117.1

CH, 123.9 C, 129.6 CH (*J*=8.0 Hz), 136.9 CH, 147.0 C, 148.8 C, 153.0 C, 163 C-F (*J*=244.7 Hz), 180.1 C, 181.7 C, 195.3 C; EIMS *m/z* (%): 493 (M^+, 74), 398 (100), 353 (60), 258 (17); HREIMS: 493.2604 (calcd. for $C_{30}H_{36}NO_4F$ (M^+) 493.2628); IR ($CHCl_3$) ν_{max}: 1636, 1535, 1470, 1404, 1376, 1360, 1332, 1269, 1226, 1185, 1141, 975, 743, 709 cm^{-1}.

9-(4-Nitro-phenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5e). Following the general procedure described above 30.0 mg of embelin (0.1 mmol), 30.8 mg of 4-nitrobenzaldehyde (0.2 mmol), and 22.6 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 76W). The crude was purified by flash chromatography with 50% Hex/EtOAc to provide 47.3 mg (89 %) of **5e** as an amorphous purple solid; mp 197-198 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.5 Hz, 3H), 1.26 (bs, 16H), 1.43 (m, 2H), 2.10 (m, 2H), 2.39 (m, 4H), 2.64 (m, 2H), 5.28 (s, 1H), 7.43 (s, 1H), 7.49 (d, *J*=7.4 Hz, 2H), 8.09 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 20.8 CH_2, 22.4 CH_2, 22.6 CH_2, 27.5 CH_2, 28.0 CH_2, 29.2 CH_2, 29.3 CH_2, 29.5 CH_2 x 4, 31.8 CH_2, 34.5 CH, 36.8 CH_2, 111.5 C, 113.4 C, 117.7 C, 123.8 CHx2, 137.1 C, 146.6 C, 149.5 C, 151.6 C, 153.3 C, 180.0 C, 181.3 C, 195.4 C; EIMS *m/z* (%): 520 (M^+, 59), 398 (100), 380 (27), 258 (14); HREIMS: 520.2549 (calcd. for $C_{30}H_{36}N_2O_6$ (M^+) 520.2573); IR ($CHCl_3$) ν_{max}**:** 1637, 1609, 1469, 1404, 1351, 1269, 1180, 1136, 743, 710, 606 cm^{-1}.

9-(3,4-Dimethoxy-phenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5f). Following the general procedure described above 30.0 mg of embelin (0.1 mmol), 33.9 mg of 3,4-dimethoxybenzaldehyde (0.2 mmol), and 22.6 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 80W). The crude was purified by flash

chromatography with 40% Hex/EtOAc to provide 44.7 mg (82 %) of **5f** as an amorphous purple solid; mp 141-142 ºC; ^{1}H NMR (400 MHz, C_6D_6) δ: 0.91 (t, *J*=5.7 Hz, 3H), 1.32 (bs, 16H), 1.62 (m, 2H), 1.94 (m, 1H), 2.11 (m, 1H), 2.55 (m, 2H), 3.34 (s, 3H), 3.54 (s, 3H), 5.49 (s, 1H), 6.60 (d, *J*=7.7 Hz, 1H), 6.69 (s, 1H), 6.94 (dd, *J*=7.2 Hz, 1H), 7.36 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 21.0 CH_2, 22.3 CH_2, 22.6 CH_2, 27.5 CH_2, 28.0 CH_2, 29.3 CH_2, 29.4 CH_2, 29.5 CH_2 x 4 , 31.8 CH_2, 33.4 CH, 37.1 CH_2, 55.7 CH_3, 55.9 CH_3, 111.0 CH, 112.2 CH, 113.1 C, 114.3 C, 116.8 C, 119.7 CH, 126.9 C, 129.2 C, 136.6 CH, 137.7 CH, 147.9 C, 148.3 C, 148.7 C, 153.2 C, 180.3 C, 182.4 C, 195.5 C; EIMS *m/z* (%): 535 (M^+, 100), 476 (8), 448 (44), 398 (M^+-C_4H_3O, 62), 395 (69), 258 (16); HREIMS**:** 535.2950 (calcd. for $C_{32}H_{41}NO_6$ (M^+) 535.2934); IR ($CHCl_3$) ν_{max}: 1631, 1604, 1512, 1465, 1421, 1400, 1373, 1355, 1327, 1265, 1224, 1179, 1140, 1027, 895, 739, 705 cm^{-1}.

9-(3,4-Methylenedioxiphenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5g). Following the general procedure described above 30.0 mg of embelin (0.1 mmol), 30.6 mg of piperonal (0.2 mmol), and 22.6 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 70W). The crude was purified by flash chromatography with 40% Hex/EtOAc to provide 37.4 mg (72%) of **5g** as an amorphous purple solid; mp 174-175 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.5 Hz, 3H), 1.26 (bs, 16H), 1.43 (m, 2H), 2.07 (m, 2H), 2.39 (m, 4H), 2.60 (m, 2H), 5.11 (s, 1H), 5.87 (s, 2H), 6.67 (d, *J*= 8.0 Hz, 1H), 6.79 (d, *J*= 8.0 Hz, 1H), 6.81 (s, 1H), 7.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 CH_3, 20.9 CH_2, 22.4 CH_2, 22.6 CH_2, 27.5 CH_2, 28.0 CH_2, 29.3 CH_2, 29.4 CH_2, 29.5 CH_2 x 4, 31.9 CH_2, 33.7 CH, 37.0 CH_2, 100.9 CH_2, 108. 1 CH_2, 108.8 CH, 113.1 C, 114.4 C, 116.9 C, 121.4 CH, 136.5 C, 138.9 C, 146.3 C, 147.6 C, 148.3 C, 153.0 C, 180.2 C, 181.8 C, 195.4 C. EIMS *m/z* (%): 519

(M$^+$, 100), 398 (63), 379 (87), 258 (12); HREIMS**:** 519.2621 (calcd. for $C_{31}H_{37}NO_6$ (M$^+$) 519.2621); IR ($CHCl_3$) ν_{max}: 1627, 1466, 1399, 1372, 1359, 1320, 1228, 1177, 1137, 1115, 1089, 1038, 969, 809, 734, 599 cm^{-1}.

9-(Phenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5h). Embelin (30 mg, 0.1 mmol), 20.76 µL of benzaldehyde (0.2 mmol), and 22.64 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 90W). The crude was purified by flash chromatography with 40% Hex/EtOAc to provide 46.3 mg (96%) of **5h** as an amorphous purple solid; mp 152-153 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, *J*=6.9 Hz, 3H), 1.26 (bs, 16H), 1.43 (m, 2H), 2.06 (m, 2H), 2.39 (m, 4H), 2.62 (m, 2H), 5.22 (s, 1H), 7.23 (t, *J*= 7.6 Hz, 2H), 7.32 (d, *J*= 7.4 Hz, 2H), 7.47 (t, *J*= 7.6 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 CH_3, 20.9 CH_2, 22.4 CH_2, 22.6 CH_2, 27.5 CH_2, 28.0 CH_2, 29.3 CH_2, 29.4 CH_2, 29.5 CH_2, 29.6 CH_2 x 3, 31.8 CH_2, 34.0 CH, 37.0 CH_2 , 113.0 C, 114.2 C, 116.9 C, 126.8 CH, 128.1 CH x 2, 128.4 CH x 2, 136.9 C, 144.7 C, 148.8 C, 153.2 C, 180.2 C, 181.9 C, 195.5 C; EIMS *m/z* (%): 475 (M$^+$, 54), 398 (M$^+$-C_6H_5, 100), 335 (34), 258 (10); HREIMS: 475.2740 (calcd. for $C_{30}H_{37}NO_4$ (M$^+$) 475.2723); IR ($CHCl_3$) ν_{max}: 1635, 1607, 1470, 1404, 1360, 1330, 1269, 1227, 1180, 1136, 899, 743, 709, 605 cm^{-1} .

9-Furan-3-yl-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5i). Embelin (30.0 mg, 0.1 mmol), 16.8 µL of furan-2-carbaldehyde (0.2 mmol), and 22.64 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 68W). The crude was purified by flash chromatography with 40% Hex/EtOAc to provide 36.8 mg (78 %) of **5i** as an amorphous purple solid; mp 148-149 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.6 Hz, 3H), 1.26 (bs, 16H), 1.44 (m, 2H), 2.06 (m, 2H), 2.41 (m, 4H), 2.60 (m,

2H), 5.38 (s, 1H), 6.12 (d, *J*= 2.0 Hz, 1H), 6.22 (d, *J*= 2.0 Hz, 1H), 7.19 (s, 1H), 7.51 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 20.9 CH_2, 22.4 CH_2, 22.6 CH_2, 27.6 CH, 28.0 CH_2, 29.3 CH_2, 29.4 CH_2, 29.5 CH_2 x 5, 31.9 CH_2, 36.9 CH_2, 106.2 CH, 109.9 C, 110.6 CH, 111.3 C, 117.1 C, 137.6 C, 141.7 C, 149.5 C, 153.1 C, 155.4 C, 180.0 C, 181.7 C, 195.3 C; EIMS *m/z* (%): 465 (M^+, 100), 398 (M^+-C_4H_3O, 9), 325 (96), 297 (11), 255 (16), 228 (10); HREIMS**:** 465.2510 (calcd. for $C_{28}H_{35}NO_5$ (M^+) 465.2515); IR ($CHCl_3$) ν_{max}: 1622, 1533, 1467, 1398, 1357, 1319, 1219, 1175, 1136, 1072, 1009, 968, 855, 764, 728, 598 cm^{-1}.

9-(3-Fluoro-4-methoxyphenyl)-2-hydroxy-3-undecyl-6,7,9,10-tetrahydro-5H-acridine-1,4,8-trione (5j). Embelin (30 mg, 0.1 mmol), 31.4 mg of 3-fluoro-4-methoxybenzaldehyde (0.2 mmol), and 22.6 mg of 3-amino-2-cyclohexen-1-one (0.2 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 75W). The crude was purified by flash chromatography with 50% Hex/EtOAc to provide 40.4 mg (76%) of **5j** as an amorphous purple solid; mp 199-200 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.6 Hz, 3H), 1.26 (bs, 16H), 1.43 (m, 2H), 2.06 (m, 2H), 2.38 (m, 4H), 2.60 (m, 2H), 3.80 (s, 3H), 5.13 (s, 1H), 6.82 (t, *J*= 8.5 Hz, 1H), 6.98 (dd, *J*= 1.0, 11.1 Hz, 1H), 7.08 (d, *J*= 8.2 Hz, 1H), 7.39 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 20.9 CH_2, 22.3 CH_2, 22.6 CH_2, 27.5 CH_2, 28.0 CH_2, 29.2 CH_2, 29.3 CH_2, 29.5 CH_2, 29.6 CH_2 x 3, 31.8 CH_2, 33.2 CH, 36.9 CH_2, 56.1 CH_3, 112.6 C, 113.0 CH, 114.0 C, 115.7 CH *(J*=18.3 Hz), 117.0 C, 123.9 CH (*J*=2.1 Hz) , 128.3 C, 136.7 C, 137.9 C (*J*=4.6 Hz), 146.4 C (*J*=10.6 Hz), 148.5 C, 180.2 C, 181.7 C, 195.6 C; EIMS *m/z* (%): 523 (M^+, 100), 467 (10), 436 (12), 398 (M^+, 93), 383 (98); HREIMS: 523.2713 (calcd. for $C_{31}H_{38}NO_5F$ (M^+) 523.2734); IR ($CHCl_3$) ν_{max}: 1632, 1514, 1466, 1401, 1355, 1265, 1221, 1181, 1137, 1028, 895, 739, 706, 606, 533 cm^{-1}.

9-Hexyl-2-hydroxy-3-undecyl-6,7-dihydroacridine-1,4,8(5*H,* 8*H,* 10*H)*-trione (5k).

Embelin (15.0 mg, 0.05 mmol), 14.2 μL of heptanal (0.1 mmol) and 11.3 mg of 3-amino-2-cyclohexen-1-one (0.1 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 75 W). The crude was purified by flash chromatography with 40% Hex/EtOAc to provide 22.8 mg (93%) of **5k** as an amorphous green solid; mp 144-145 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (m, 6H), 1.25 (bs, 22H), 1.44 (m, 4H), 2.06 (m, 2H), 2.40 (m, 4H), 2.50 (m, 2H), 4.18 (s, 1H), 7.13 (s, 1H, OH), 7.58 (s, 1H, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1 CH_3, 21.1 CH_2, 22.4 CH_2, 25.2 CH_2, 27.6 CH, 27.8 CH_2, 28.1 CH_2, 29.4 CH_2, 29.5 CH_2, 29.4 CH_2, 29.6 CH_2 x 3, 29.7 CH_2 x2, 31.8 CH_2, 31.9 CH_2 x 2, 35.3 CH_2, 37.2 CH_2, 112.9 C, 113.6 C, 116.5 C, 138.4 C, 149.8 C, 153.0 C, 180.5 C, 181.9 C, 195.9 C; EIMS *m/z* (%): 483 (M^+, 1), 398 (M^+-C_6H_{13}, 100), 399 (30), 370 (7), 258 (8); HREIMS: 483.3329 (calcd. for $C_{30}H_{45}NO_4$ (M^+) 483.3349); IR ($CHCl_3$) ν_{max}: 1621, 1531, 1464, 1404, 1382, 1358, 1226, 1227, 1180, 1137, 1113, 967, 766 cm^{-1}.

9-Ethyl-2-hydroxy-3-undecyl-6,7-dihydroacridine-1,4,8(5*H,* 9*H,* 10*H)*-trione (5l). Embelin (15.0 mg, 0.05 mmol), 7.41 μL of propionaldehyde (0.1 mmol), and 11.3 mg of 3-amino-2-cyclohexen-1-one (0.1 mmol) were suspended in 5 mL of EtOH. The reaction mixture was irradiated for 15 min (150 ºC, 78 W). The crude was purified by flash chromatography with 40% Hex/EtOAc to provide 18 mg (83%) of **5l** as an amorphous green solid; mp 153-154 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.73 (3H, t, *J* = 7.5 Hz), 0.87 (3H, t, *J* = 6.8 Hz), 1.24 (16H, bs), 1.48 (4H, m), 2.07 (2H, m), 2.38 (4H, m), 2.52 (2H, m), 4.20 (1H, t, *J* = 4.8 Hz), 7.13 (1H, bs, OH), 7.58 (1H, bs, N-H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 9.3 CH_3, 14.1 CH_3, 21.1 CH_2, 22.4 CH_2, 22.7 CH_2, 27.4 CH_2, 27.6 CH_2, 28.1 CH_2, 28.7 CH, 29.3 CH_2, 29.4 CH_2, 29.6 CH_2 x 2, 29.7 CH_2 x 2, 31.9 CH_2, 37.2 CH_2, 112.3 C, 112.4 C, 116.6 C, 138.6 C, 150.2 C, 153.1 C, 180.5 C, 181.9 C, 196.1 C; EIMS *m/z* (%): 427 (M^+, 10), 398 (M^+-C_6H_{13}, 100), 399 (35), 370 (4),

258 (10); HREIMS: 427.2744 (calcd. for $C_{26}H_{37}NO_4$ (M^+) 427.2723); IR ($CHCl_3$) ν_{max} : 1725, 1614, 1530, 1465, 1359, 1265, 1225, 1181, 1137, 1111, 763 cm^{-1}

General procedure for the preparation of dihydropyran embelin derivatives (6a-6i)

Embelin (20.0 mg, 0.07 mmol), 2.0 equiv of aldehyde, and 2.0 equiv of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one in 5 mL of toluene were refluxed, until disappearance of the starting benzoquinone. Then the reaction mixture was cooled and the toluene was removed under reduced pressure. The crude was purified by silica gel column chromatography with hexanes/EtOAc as solvent.

9-(4-Chloro-phenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6a). Following the procedure described above, 20 mg of embelin (0.068 mmol) in 5 mL of toluene were treated with 19.1 mg of 4-chlorobenzaldehyde (0.14 mmol) and 22.7 mg of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 30% hexanes/EtOAc to yield 27.9 mg (76%) of **6a** as an amorphous yellow solid; mp 124-125 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*= 6.4 Hz, 3H), 1.02 (s, 3H), 1.12 (s, 3H), 1.26 (bs, 16H), 1.44 (m, 2H), 2.21 (d, *J*= 16.4 Hz, 1H), 2.27 (d, *J*= 16.4 Hz, 1H), 2.42 (t, *J*= 7.5 Hz, 2H), 2.59 (d, *J*= 17.9 Hz, 1H), 2.67 (d, *J*= 17.9 Hz, 1H), 4.87 (s, 1H), 7.24 (m, 4H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 CH_3, 22.5 CH_2, 22.6 CH_2, 27.4 CH_3, 28.0 CH_2, 28.9 CH_3, 29.2 CH_2, 29.3 CH_2, 29.4 CH_2x 2, 29.5 CH_2 x 2, 31.8 CH_2, 32.0 C, 32.3 CH, 40.7 CH_2, 50.6 CH_2, 113.9 C, 117.9 C, 119.5 C, 128.7 CH x 2, 129.9 CH x 2, 133.2 C, 140.7 C, 148.2 C, 151.0 C, 162.9 C, 179.9 C, 181.7 C, 196.0 C; EIMS *m/z* (%): 538 (M^+, 97), 521 (7), 427 (24), 398 (100), 384 (6), 288 (16); HREIMS: 538.2473 (calcd. for $C_{32}H_{39}O_5Cl$ (M^+) 538.2486); IR ($CHCl_3$) ν_{max}:

1652, 1615, 1531, 1489, 1465, 1370, 1319, 1264, 1192, 1161, 1149, 1112, 1072, 997, 813, 738, 735, 621 cm^{-1}.

9-(4-Bromo-phenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6b). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene were treated with 25.2 mg of 4-bromobenzaldehyde (0.14 mmol) and 22.7 mg of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 30% hexanes/EtOAc to yield 29.7 mg (75%) of **6b** as an amorphous yellow solid; mp 120-121 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*= 5.5 Hz, 3H), 1.02 (s, 3H), 1.19 (s, 3H), 1.26 (bs, 16H), 1.44 (m, 2H), 2.21 (d, *J*= 13.2 Hz, 1H), 2.27 (d, *J*= 13.2 Hz, 1H), 2.44 (t, *J*= 8.7 Hz, 2H), 2.60 (d, *J*= 14.4 Hz, 1H), 2.66 (d, *J*= 14.2 Hz, 1H), 4.86 (s, 1H), 7.20 (d, *J*= 6.7 Hz, 2H), 7.39 (d, *J*= 6.7 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 CH_3, 22.5 CH_2, 22.6 CH_2, 27.4 CH_3, 28.0 CH_2, 28.9 CH_3, 29.3 CH_2, 29.4 CH_2, 29.5 CH_2x 2, 29.6 CH_2x 2, 31.9 CH_2, 32.0 C, 32.3 CH, 40.7 CH_2, 50.6 CH_2, 113.9 C, 117.9 C, 119.6 C, 121.4 C, 130.2 CH x 2, 130.2 CH x 2, 141.2 C, 148.2 C, 151.0 C, 162.9 C, 179.9 C, 181.7 C, 196.0 C; EIMS *m/z* (%): 584 (M^+, 100), 456 (3), 443 (84), 427 (33), 288 (15), 288 (15); HREIMS: 584.1993 (calcd. for $C_{32}H_{39}O_5Br^{79}$ (M^+) 584.1981); IR ($CHCl_3$) ν_{max}: 1659, 1623, 1488, 1469, 1427, 1372, 1340, 1269, 1200, 1167, 1075, 1014, 743, 710 cm^{-1}.

9-(4-Fluoro-phenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6c). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene were treated with 2.0 equiv of 4-fluorobenzaldehyde (14.5μL, 0.14 mmol) and 2.0 equiv of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (22.7 mg, 0.14 mmol). The reaction mixture was heated

under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 10% hexanes/EtOAc to yield 25.0 mg (70 %) of **6c** as an amorphous yellow solid; mp 128-129 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.87 (t, *J*= 6.8 Hz, 3H), 1.02 (s, 3H), 1.11 (s, 3H), 1.24 (bs, 16H), 1.42 (m, 2H), 2.21 (d, *J*=16.3 Hz, 1H), 2.27 (d, *J*=16.4 Hz, 1H), 2.40 (m, 2H), 2.60 (d, *J*=18.0 Hz, 1H), 2.66 (d, *J*=18.6 Hz, 1H), 4.87 (s, 1H), 6.94 (m, 2H), 7.27 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1 CH_3, 22.6 CH_2, 27.4 CH_3, 28.1 CH_3, 29.0 CH_2, 29.3 CH_2, 29.4 CH_2, 29.6 CH_2, 29.7 CH_2 x 3, 31.7 CH_2, 31.9 C, 32.6 CH, 40.7 CH_2, 50.7 CH_2, 114.2 C, 115.5 CH x 2 (*J*=21.5 Hz), 118.2 C, 119.5 C, 130.1 CH x 2 (*J*=7.7 Hz), 138.0 C, 148.2 C, 151.0 C, 161.9 C-F (*J*=244.9 Hz), 162.9 C, 180.0 C, 182.0 C, 196.3 C; EIMS *m/z* (%): 522 (M^+, 84), 427 (M^+- C_6H_4F, 17), 382 (100), 288 (9), 228 (6); HREIM**:** 522.2792 (calcd. for $C_{32}H_{39}O_5F$ (M^+) 522.2782); IR ($CHCl_3$) ν_{max}: 1656, 1620, 1338, 1265, 1196, 739, 706 cm^{-1}.

9-(3-Fluoro-phenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6d). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene were treated with 2.0 equiv of 3-fluorobenzaldehyde (14.3 μL, 0.14 mmol) and 2.0 equiv of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (22.7 mg, 0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 20% hexanes/EtOAc to yield 24.6 mg (69 %) of compound **6d** as an amorphous yellow solid; mp 155-156 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*= 6.6 Hz, 3H), 1.04 (s, 3H), 1.12 (s, 3H), 1.26 (bs, 16H), 1.43 (m, 2H), 2.22 (d, *J*=16.5 Hz, 1H), 2.28 (d, *J*=16.9 Hz, 1H), 2.41 (m, 2H), 2.60 (d, *J*=17.9 Hz, 1H), 2.68 (d, *J*=17.8 Hz, 1H), 4.89 (s, 1H), 6.87 (t, *J*= 7.4 Hz, 1H), 7.00 (d, *J*= 8.9 Hz, 1H), 7.09 (d, *J*= 7.3 Hz, 1H), 7.21 (t, *J*= 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ: 14.0 CH_3, 22.5 CH_2, 22.6 CH_2, 27.4 CH_3, 28.0 CH_2, 28.8 CH_3, 29.3 CH_2, 29.5 CH_2 x 4, 29.6 CH_2, 31.8 CH_2, 32.1 C, 32.3 CH, 40.7 CH_2, 50.6 CH_2, 113.9 C, 114.3 CH (*J*=20.4 Hz), 115.5 CH, 117.8 C, 119.5 C, 124.1 CH, 129.9 CH (*J*=8.0 Hz), 144.5 C, 148.3 C, 151.0 C, 162.9 C (*J*=244.6 Hz), 163.1 C, 179.8 C, 181.7 C, 196.0 C; EIMS *m/z* (%): 522 (M^+, 100), 427 (26), 382 (82), 369 (4); HREIMS**:** 522.2761 (calcd. for $C_{32}H_{39}O_5F$ (M^+) 522.2782). IR ($CHCl_3$) ν_{max}**:** 1655, 1615, 1592, 1484, 1465, 1369, 1333, 1264, 1193, 1173, 1110, 981, 739, 706, 618 cm^{-1}.

9-(4-Nitro-phenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6e). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene was treated with 20.5 mg of 4-nitrobenzaldehyde (0.14 mmol) and 22.7 mg of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 40% hexanes/EtOAc to yield 23.0 mg (62%) of **6e** as an amorphous yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*= 6.7 Hz, 3H), 1.02 (s, 3H), 1.13 (s, 3H), 1.25 (bs, 16H), 1.44 (m, 2H), 2.21 (d, *J*= 16.4 Hz, 1H), 2.29 (d, *J*= 16.4 Hz, 1H), 2.43 (t, *J*= 7.3 Hz, 2H), 2.63 (d, *J*=16.4 Hz, 1H), 2.69 (d, *J*=16.4 Hz, 1H), 5.00 (s, 1H), 7.50 (d, *J*= 8.7 Hz, 2H), 8.13 (d, *J*= 8.7 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 CH_3, 22.5 CH_2, 22.6 CH_2, 27.4 CH_3, 28.0 CH_2, 28.9 CH_2, 29.2 CH_2, 29.4 CH_2, 29.5 CH_2 x 4, 31.8 CH_2, 32.3 C, 32.6 CH, 40.7 CH_2, 50.5 CH_2, 113.3 C, 117.1 C, 119.9 C, 123.7 CHx2, 129.5 CHx2, 147.0 C, 148.4 C, 149.1 C, 150.9 C, 163.4 C, 179.5 C, 181.6 C, 195.9 C; EIMS *m/z* (%): 549 (M^+, 100), 427 (30), 409 (61), 397 (7); HREIMS**:** 549.2703 (calcd. for $C_{32}H_{39}O_7N$ (M^+) 549.2727); IR ($CHCl_3$) ν_{max}: 1655, 1619, 1523, 1464, 1424, 1346, 1265, 1196, 1163, 1071, 895, 858, 738, 705, 584, 534 cm^{-1}.

9-(3,4-Dimethoxy-phenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6f). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene was treated with 2.0 equiv of 3,4-dimethoxybenzaldehyde (22.6 mg, 0.14 mmol) and 2.0 equiv of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (22.7 mg, 0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 30% hexanes/EtOAc to yield 22.0 mg (57%) of **6f** as an amorphous yellow solid; mp 114-115 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*= 6.7 Hz, 3H), 1.05 (s, 3H), 1.12 (s, 3H), 1.25 (bs, 16H), 1.45 (m, 2H), 2.26 (m, 2H), 2.43 (m, 2H), 2.60 (d, *J*=18.4 Hz, 1H), 2.67 (d, *J*=17.8 Hz, 1H), 3.81 (s, 3H), 3.87 (s, 3H), 4.84 (s, 1H), 6.75 (s, 1H), 6.76 (m, 1H), 6.91 (d, *J*= 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 CH_3, 22.5 CH_2, 22.6 CH_3, 27.3 CH_3, 28.0 CH_2, 29.0 CH_3, 29.2 CH_2, 29.3 CH_2, 29.4 CH_2, 29.5 CH_2 x 2, 31.6 CH, 31.9 CH_2, 32.3 C, 40.8 CH_2, 50.6 CH_2, 55.7 CH_3, 55.9 CH_3, 111.1 CH, 112.3 CH, 114.4 C, 118.5C, 119.3 C, 120.5 CH, 134.9 C, 147.9 C, 148.3 C, 148.9 C, 151.0 C, 162.6 C, 180.2 C, 181.9 C, 196.1 C; EIMS *m/z* (%): 564 (M^+, 100), 547 (8), 437 (15), 424 (72), 411 (7), 288 (9). HREIMS**:** 564.3058 (calcd. for $C_{34}H_{44}O_7$ (M^+) 564.3087). IR ($CHCl_3$) ν_{max}**:** 1656, 1513, 1464, 1422, 1369, 1336, 1265, 1195, 1142, 739, 706, 478 cm^{-1} .

9-(3,4-Methylenedioxiphenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6g). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene was treated with 20.4 mg of piperonal (0.14 mmol) and 22.7 mg of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 30% hexanes/EtOAc to yield 27.7 mg (74 %) of **6g** as an amorphous yellow solid; mp 115-

116 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, *J*= 6.2 Hz, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.24 (bs, 16H), 1.44 (m, 2H), 2.26 (bs, 2H), 2.42 (m, 2H), 2.58 (d, *J*=17.8 Hz, 1H), 2.67 (d, *J*=18.4 Hz, 1H), 4.81 (s, 1H), 5.89 (s, 2H), 6.68 (d, *J*=7.5 Hz, 1H), 6.75 (d, *J*=7.3 Hz, 1H), 6.82 (s, 1H), 7.00 (bs, OH, 1H);^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2 CH_3, 22.6 CH_2, 22.7 CH_2, 27.6 CH_3, 28.1 CH_2, 28.9 CH_3, 29.3 CH_2, 29.4 CH_2, 29.6 CH_2 x4, 29.7 CH_2, 31.9 CH, 32.4 C, 40.7 CH_2, 50.7 CH_2, 101.1 CH_2, 108.3 CH, 109.2 CH, 114.4 C, 118.4 C, 119.4 C, 121.9 CH, 136.2 C, 146.8 C, 147.8 C, 147.9 C, 151.0 C, 162.9 C, 180.1C, 182.1 C, 196.4 C; EIMS *m/z* (%): 548 (M^+, 92), 531 (9), 407 (100), 394 (9), 288 (10); HREIMS: 548.2748 (calcd. for $C_{33}H_{40}O_7$ (M^+) 548.2774); IR ($CHCl_3$) ν_{max}: 1659, 1622, 1490, 1469, 1373, 1340, 1269, 1198, 1125, 1044, 743, 709 cm^{-1}.

9-phenyl-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6h). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene was treated with 13.86 µL of benzaldehyde (0.14 mmol) and 22.7 mg of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 30% hexanes/EtOAc to yield 25.8 mg (75 %) of compound **6h** as an amorphous yellow solid; mp 157-158 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.88 (t, *J*= 6.9 Hz, 3H), 1.03 (s, 3H), 1.11 (s, 3H), 1.24 (bs, 16H), 1.43 (m, 2H), 2.22 (d, *J*=16.4 Hz, 1H), 2.27 (d, *J*=16.4 Hz, 1H), 2.41 (bs, 2H), 2.60 (d, *J*=17.8 Hz, 1H), 2.68 (d, *J*=17.8 Hz, 1H), 4.90 (s, 1H), 6.96 (bs, 1H, OH), 7.18 (t, *J*=7.1 Hz, 1H), 7.27 (m, 2H), 7.32 (d, *J*=7.3 Hz, 2H);^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2 CH_3, 22.6 CH_2, 22.7 CH_2, 27.5 CH_3, 28.1 CH_2, 29.0 CH_3, 29.4 CH_2 x2, 29.6 CH_2 x 2, 29.7 CH_2 x2, 31.9 CH_2, 32.4 CH, 40.8 CH_2, 50.7 CH_2, 114.4 C, 118.4 C, 119.4 C, 127.4 CH, 128.6 CH x 4, 142.2 C, 148.1 C, 151.1 C, 162.9 C, 180.2 C, 181.9 C, 196.2 C. EIMS *m/z* (%): 504 (M^+, 96), 427 (M^+-C_6H_5, 25), 364 (100),

288 (7), 202 (2). HREIMS: 504.2858 (calcd. for $C_{32}H_{40}O_5$ (M^+) 504.2876). IR ($CHCl_3$) ν_{max}: 1731, 1666, 1646, 1618, 1556, 1459, 1370, 1320, 1197, 1165, 1115, 1073, 988, 769, 701, 617 cm^{-1} .

9-(3-Fluoro-4-methoxyphenyl)-2-hydroxy-6,6-dimethyl-3-undecyl-5,6,7,9-tetrahydro-xanthene-1,4,8-trione (6i). Following the procedure described above, 20.0 mg of embelin (0.068 mmol) in 5 mL of toluene was treated with 21.5 mg of 3-fluoro-4-methoxybenzaldehyde (0.14 mmol) and 25.5 mg, of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (0.14 mmol). The reaction mixture was heated under reflux for 8h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 20% hexanes/EtOAc to yield 25.5 mg (68 %) of **6i** as an amorphous yellow solid; mp 118-119 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*= 6.6 Hz, 3H), 1.04 (s, 3H), 1.11 (s, 3H), 1.26 (bs, 16H), 1.44 (m, 2H), 2.22 (d, *J*=16.2 Hz, 1H), 2.28 (d, *J*=16.4 Hz, 1H), 2.42 (t, *J*= 7.2 Hz, 2H), 2.59 (d, *J*=17.7 Hz, 1H), 2.67 (d, *J*=17.9 Hz, 1H), 3.82 (s, 3H), 4.83 (s, 1H), 6.84 (t, *J*= 8.2 Hz, 1H), 7.00 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 CH_3, 22.5 CH_2, 22.6 CH_2, 27.5 CH_3, 28.0 t CH_2, 28.9 C, 29.4 CH_2 x 4, 31.4 CH_2, 31.9 CH_2, 32.3 CH_2, 40.7 CH_2, 50.6 CH_2, 56.1 CH, 113.1 CH, 114.0 C, 116.1 CH (*J*=18.7 Hz), 118.1 C, 119.5 C, 124.3 CH, 135.2 C, 146.8 C, 148.1 C, 152.3 C-F (*J*=245.3 Hz), 162.8 C, 179.9 C, 181.8 C, 196.2 C; EIMS *m/z* (%): 552 (M^+, 49), 535 (9), 425 (15), 412 (100), 399 (7), 288 (10); HREIMS**:** 552.2873 (calcd. for $C_{33}H_{41}O_6F$ (M^+) 552.2887); IR ($CHCl_3$) ν_{max}:1728, 1659, 1623, 1519, 1468, 1446, 1373, 1341, 1269, 1198, 1148, 1127, 1075, 1032, 899, 743, 709 cm^{-1}.

10-benzyl-9-(4-chlorophenyl)-2-hydroxy-3-undecyl-6,7-dihydroacridine-1,4,8(5H,9H,10H)-trione (7). 12.6 mg of embelin (0.04 mmol) in 5 mL of toluene was treated with 9.7 mg (0.07 mmol) of 4-chlorobenzaldehyde and 13.9 mg of 3-(benzylamino)cyclohex-2-enone (0.07 mmol) which was prepared following the

procedure described in reference 22. The reaction mixture was heated under reflux for 6h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography with 40% hexane/EtOAc to yield 8.7 mg (29%) of **7** as an amorphous red solid; m.p 160-161 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J*= 6.3 Hz), 1.24 (16H, bs), 1.38 (2H, t, *J*= 6.9 Hz), 1.99 (2H, m), 2.39 (4H, m), 2.57 (1H, m), 2.80 (1H, m), 5.08 (1H, d, *J*= 16.2 Hz), 5.36 (1H, s), 5.64 (1H, d, *J*= 16.1 Hz), 6.97 (2H, d, *J*= 8.2 Hz), 7.03 (2H, d, *J*= 6.4 Hz), 7.09 (2H, d, *J*= 8.1 Hz), 7.25 (1H, s), 7.28 (2H, d, *J*= 6.6 Hz);^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.2 CH_3, 22.7 CH_2, 23.2 CH_2, 27.0 CH_2, 28.2 CH_2, 29.4 CH_2, 29.5 CH_2, 29.6 CH_2 x 2, 29.7 CH_2 x 3, 31.8 CH, 31.9 CH_2, 36.6 CH_2, 51.9 CH_2, 116.7 C, 119.5 C, 126.8 C, 127.3 CH x 2, 128.0 CH, 128.4 CH x 2, 129.0 CH x 2, 129.3 CH x 2, 130.1 C, 137.3 C, 141.6 C, 142.4 C, 150.5 C, 155.3 C, 180.9 C, 183.8 C, 196.1 C; EIMS *m/z* (%): 599 (M^+, 77), 559 (13), 508 (47), 488 (20), 466 (22), 398 (26), 91 (100); HREIMS: 599.2778 (calcd. for $C_{37}H_{42}O_4NCl$ (M^+) 599.2802); IR ($CHCl_3$) ν_{max}: 2923, 1635, 1565, 1418, 1356, 1218, 1172, 1089, 1013, 946, 831 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by MINECO (SAF 2012-37344-C03-01 and SAF 2009-13296-C02-01 to A.E-B.) and Instituto de Salud Carlos III (PS09/00106 to F. M. and PI10/00125 to S. M.-A.).

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