European Journal of Medicinal Chemistry 45 (2010) 3299–3310

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Structure–activity relationship studies of acridones as potential antipsoriatic agents. 1. Synthesis and antiproliferative activity of simple N-unsubstituted 10*H*-acridin-9-ones against human keratinocyte growth

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ARTICLE INFO

Article history:
Received 12 March 2010
Received in revised form
8 April 2010
Accepted 13 April 2010
Available online 18 April 2010

Keywords:
Acridone
Antiproliferative activity
Antipsoriatic
HaCaT cells
Radical

ABSTRACT

A series of N-unsubstituted hydroxy-10*H*-acridin-9-ones were synthesized and evaluated for inhibitory action against HaCaT keratinocyte growth, in order to explore their potential as antipsoriatic agents. For structure–activity relationship studies, the number and position of the hydroxyl groups were modified, the oxygen functions substituted or replaced, or additional functional groups were introduced into the acridone scaffold. 1,8-Dihydroxy-10*H*-acridin-9-one (**4**), which is an aza-analogue of the antipsoriatic anthralin, was only marginally active. However, 1,3-dihydroxy-substituted **5ee** was the most potent acridone within this series and inhibited keratinocyte growth with an IC_{50} value comparable to that of anthralin. In contrast to anthralin, nearly all members of the acridone series were devoid of radical generating properties, which were determined by their capability to interact with the free radical 2,2-diphenyl-1-picrylhydrazyl. Structures with a phenolic hydroxyl or an aromatic amine arranged *ortho* or *para* to the acridone NH group were exceptions. Also in contrast to anthralin, membrane-damaging effects as documented by the release of lactate dehydrogenase into the culture medium were not observed for acridones.

1. Introduction

Psoriasis is a common, immune-mediated inflammatory and scaling skin disease, mainly characterized by excessive growth of keratinocytes [1]. Despite the importance of systemic treatment for severe and life-threatening forms of psoriasis, most patients can be treated with topical antipsoriatic agents such as vitamin D_3 analogues, anthralin (**1**, dithranol, Chart 1), coal tar and retinoids [2,3]. Among the classical treatments, the anthrone derivative anthralin is best used in hospital or day treatment centers, because it causes substantial skin irritation and staining of skin, clothing and furniture [4]. The methylene moiety at C-10 of the anthrone nucleus has been recognized as a key site of anthralin-derived oxygen radicals [5,6] and anthralin metabolite radicals [7,8], which play a fundamental role in the induction of these undesired effects. Therefore, our strategy to overcome this problem was to modify the molecule by partially blocking the critical 10-position of the pharmacophore, which led to various series of 10-substituted 1,8-dihydroxy-10*H*-anthracen-9-ones [9–12].

In this regard, our interest has focused on acridones, which can be considered as 10-aza-analogues of the anthrone class of antipsoriatic agents. The acridone alkaloids constitute a small group of naturally occurring compounds found exclusively in plants belonging to the order Rutales [13], and interest continues unabated in the synthesis of related synthetic analogues of the tetracyclic acridone alkaloid acronycine (**2**) [14] or acridones showing large numbers of oxygenated groups in particular patterns such as glyfoline (**3**) [15]. In view of the hyperproliferative nature of keratinocytes in psoriatic epidermis, compounds derived from the acridone scaffold may be of special importance because of their demonstrated antiproliferative activity [14–19] as well as other interesting properties associated with cell growth [20–22]. Prominent amongst some acridone alkaloids isolated from two *Boronia* species (Rutaceae) [23,24] and also a *Samadera* species (Simaroubaceae) [25] found in Australia is an atypically substituted, symmetrical acridone alkaloid, 1,8-dihydroxy-10*H*-acridin-9-one (**4**), matching exactly the substitution pattern of anthralin. Although this alkaloid is a relatively simple compound, its structure, which was determined originally by spectroscopic analysis [23], has not yet been accessible by total synthesis.

Abbreviations: DPPA, diphenylphosphoryl azide; DPPH, 2,2-diphenyl-1-picrylhydrazyl; LDH, lactate dehydrogenase; RT, room temperature; TPP, 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine.

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doi:10.1016/j.ejmech.2010.04.013

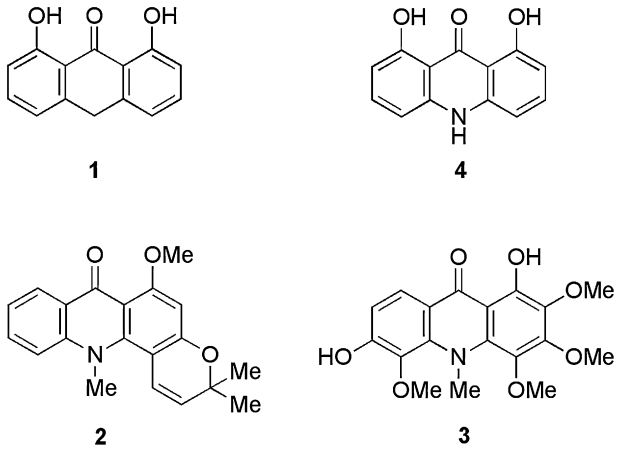


Chart 1. Structures of anthralin (**1**), acronycine (**2**), glyfoline (**3**), and 1,8-dihydroxy-10*H*-acridin-9-one (**4**).

We set out to determine the significant structural features responsible for inhibitory action against keratinocyte growth among a series of simple acridone analogues related to anthralin, particularly by modifying the number and position of the hydroxyl groups, substitution of the oxygen functions or introduction of additional functional groups into the acridone scaffold. As in earlier studies with anthrones, we evaluated the capability of the acridones to interact with a stable free radical by use of 2,2-diphenyl-1-picrylhydrazyl (DPPH), and we also examined the potential of the compounds to exert membrane-damaging effects.

2. Chemistry

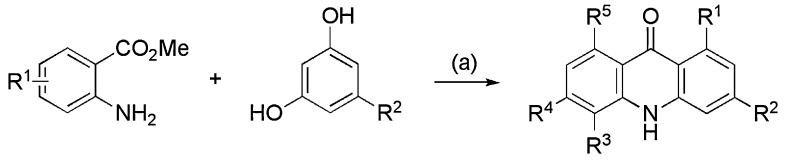
Scheme 1 presents the synthesis of monohydroxy- and 1,3-dihydroxy-substituted acridones **5a**, **5i**, **5t**, **5x**, **5aa**–**5ee** which was accomplished by the classical condensation of a substituted anthranilate with resorcinol or phloroglucinol [26], respectively, in 1-heptanol in the presence of 4-toluenesulfonic acid [27,28]. Methoxy-substituted acridones **5e**–**5h**, **5j**, **5m**, **5p**, **5r**, **5w**, **5z** (Scheme 2), **5gg**, **5ii**, **5oo**, **5ss** (Scheme 3) were obtained by the conventional approach [29]. This involves a polyphosphoric acid-catalyzed ring closure of a requisite phenylanthranilic acid (e.g., **6w**) prepared by Ullmann reaction (Scheme 2). In an alternative approach (Scheme 3), phenylanthranilic acids (**6gg**, **6ii**, **6oo**, **6ss**) were obtained in a modified Ullmann reaction of diphenyliodonium-2-carboxylate with substituted anilines [30]. Hydroxy-substituted acridones were obtained by ether cleavage of appropriate methoxy-substituted acridones with 48% hydrobromic acid (e.g., **5ff**), 36% HCl (e.g., **5y**), boron tribromide (e.g., **5hh**), or aluminum chloride (e.g., **5nn**). Finally, Fries reaction of 1-*O*-acylated acridones **5az** and **5zz**, which were prepared by acylation of **5a**, led exclusively to the *ortho*-substituted **5xx** and **5yy**, respectively (Scheme 4).

In the procedures depicted in Schemes 1 and 2, the final cyclization is compromised by the fact that two possible routes are available, and depending on the substitution pattern, sometimes a mixture of isomers is obtained. For a regiospecific route to the aza-analogous anthralin, 1,8-dihydroxy-10*H*-acridin-9-one (**4**), it was necessary to use starting material that incorporates from the outset the requisite substitution pattern (Scheme 5). The benzophenone precursor **9** was synthesized in high yields by techniques analogous to those described by Franck [31], which have also been employed for the synthesis of (−)-balanol [32]. Accordingly, [4 + 2]-cyloaddition of singlet molecular oxygen ($^1O_2$) in a tetraphenylporphine photosensitized oxidation of tetramethoxyanthracene **7** [33] provided the 9,10-endoperoxide **8** which upon acid cleavage yielded the desired benzophenone **9**. This conversion can be rationalized in a straightforward manner as a process involving regioselective ketal cleavage at C-9 followed by a Baeyer–Villiger type rearrangement of an intermediate peroxide [32]. Methylation of phenolic **9** with dimethyl sulfate to **10**, hydrolysis to the carboxylic acid **11**, and Curtius reaction [34] using diphenylphosphoryl azide (DPPA) afforded the carbamate **12**, which was directly cyclized to the acridone **5** by sodium hydride in dimethyl sulfoxide according to a literature method [35]. Ether cleavage with hydrobromic acid provided the desired aza-anthralin (**4**).

3. Biological assay methods

As antiproliferative action in cell cultures may be critical in the management of the proliferative component of psoriasis, the sensitivity of HaCaT keratinocytes to each N-unsubstituted acridone was determined directly by counting the dispersed cells under a phase-contrast microscope after 48 h of treatment. HaCaT is a rapidly dividing immortalized human keratinocyte line [36], which mimics the hyperproliferative epidermis found in psoriasis, one of the pathological features of the disease.

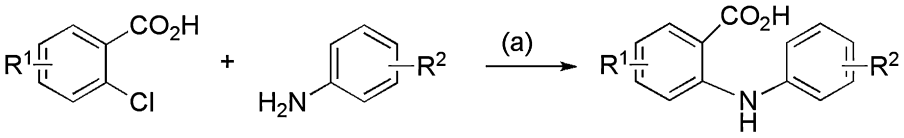
Secondly, the generation of free radicals by anthralin and the resulting dimerization and polymerization is associated with the instability of the drug as well as with undesired side effects such as staining and irritation of the skin [6]. Therefore, we have used the stable free radical DPPH (2,2-diphenyl-1-picrylhydrazyl) [37] as a simple method to compare the capability of the acridones to produce radicals by loss of a hydrogen atom with that of anthralin.



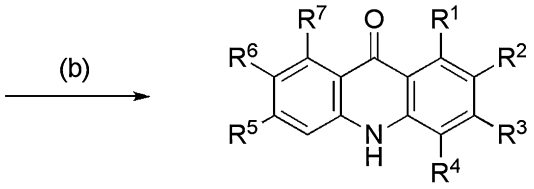
R^1 = H, OMe, Me R^2 = H, OH, Me

5a	R^1 = OH, R^2–R^5 = H
5i	R^1 = R^2 = OH, R^3–R^5 = H
5t	R^1 = R^2 = OH, R^3 = OMe, R^4 = R^5 = H
5x	R^1 = R^2 = OH, R^3 = R^4 = H, R^5 = OMe
5aa	R^1 = OH, R^2 = Me, R^3–R^5 = H
5bb	R^1 = Me, R^2 = OH, R^3–R^5 = H
5cc	R^1 = R^2 = OH, R^3 = Me, R^4 = R^5 = H
5dd	R^1 = R^2 = OH, R^4 = Me, R^3 = R^5 = H
5ee	R^1 = R^2 = OH, R^3 = R^4 = H, R^5 = Me

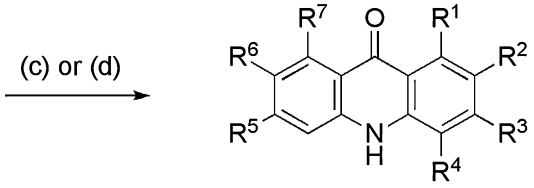
Scheme 1. Reagents: (a) 4-toluenesulfonic acid, 1-heptanol, reflux.



R^1 = H, OMe R^2 = H, OMe **6e**, **6f**, **6g**, **6h**, **6j**, **6m**, **6p**, **6r**, **6w**, **6z**



5e R^1 = OMe, R^2–R^7 = H
5f R^2 = OMe, R^1 = R^3–R^7 = H
5g R^3 = OMe, R^1 = R^2 = R^4–R^7 = H
5h R^4 = OMe, R^1–R^3 = R^5–R^7 = H
5j R^1 = R^3 = OMe, R^2 = R^4–R^7 = H
5m R^1 = R^4 = OMe, R^2 = R^3 = R^5–R^7 = H
5p R^1 = R^5 = OMe, R^2–R^4 = R^6 = R^7 = H
5r R^1 = R^6 = OMe, R^2–R^5 = R^7 = H
5w R^1 = R^3 = R^7 = OMe, R^2 = R^4–R^6 = H
5z R^1 = R^4 = R^7 = OMe, R^2 = R^3 = R^5 = R^{6v} = H



5b R^2 = OH, R^1 = R^3–R^7 = H
5c R^3 = OH, R^1 = R^2 = R^4–R^7 = H
5d R^4 = OH, R^1–R^3 = R^5–R^7 = H
5k R^1 = OH, R^3 = OMe, R^2 = R^4–R^7 = H
5l R^1 = R^4 = OH, R^2 = R^3 = R^5–R^7 = H
5n R^1 = OH, R^4 = OMe, R^2 = R^3 = R^5–R^7 = H
5o R^1 = R^5 = OH, R^2–R^4 = R^6 = R^7 = H
5q R^1 = R^6 = OH, R^2–R^5 = R^7 = H
5v R^1 = R^3 = R^7 = OH, R^2 = R^4–R^6 = H
5y R^1 = R^7 = OH, R^4 = OMe, R^2 = R^3 = R^5 = R^6 = H

Scheme 2. Reagents: (a) $Cu(OAc)_2$, dimethylformamide, 90 °C (b) PPA, 90 °C; (c) 48% HBr, reflux; (d) 36% HCl, reflux.

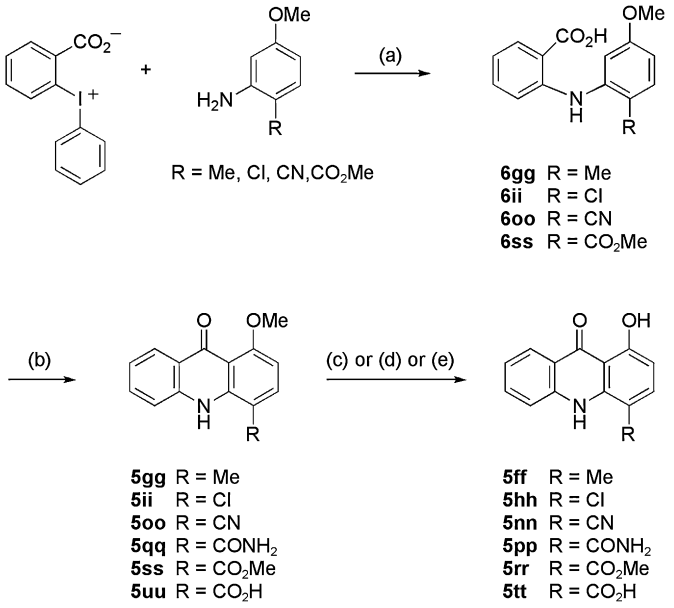
As would be the case with most other free radicals, DPPH does not dimerize by virtue of the delocalization of the unpaired electron over the whole molecule. This also gives rise to a deep-violet color, characterized by absorbance at 520 nm. When DPPH reacts with an electron-donating test compound (i.e., a hydrogen atom donor), it is reduced to the corresponding hydrazine, whereas the primary species derived from the test compound is a free radical.

Thirdly, keratinocytes were also tested for their susceptibility for the action of the most potent inhibitors of keratinocyte growth of the acridone class on plasma membrane integrity. This was assessed by the activity of LDH (lactate dehydrogenase) released into the culture medium, which is commonly used as an indicator of plasma membrane damage [9,38].

4. Results and discussion

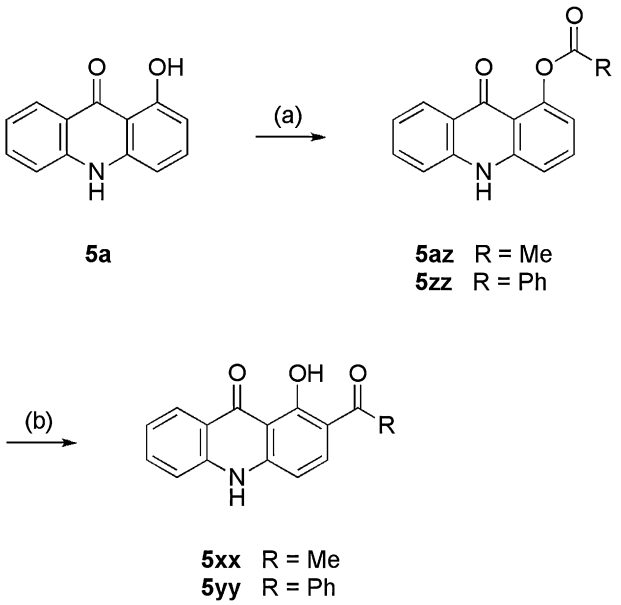
4.1. Inhibition of keratinocyte growth

It can be seen from Table 1 that the bioisosteric replacement of the 10-methylene group of the antipsoriatic anthrone anthralin (**1**)



Scheme 3. Reagents: (a) Cu, K_2CO_3, 1-heptanol, reflux; (b) PPA, 90 °C; (c) 48% HBr, reflux; (d) BBr_3, CH_2Cl_2, −78 °C, N_2; (e) $AlCl_3$, NaCl, 160 °C.

with an NH group to produce acridone **4** resulted in a dramatic loss of antiproliferative potency (IC_{50} of 0.7 μM for **1** versus 39.5 μM for **4**). Nevertheless, based upon the IC_{50} values of some acridone derivatives presented in Table 1 one can quite reasonably suppose that an antipsoriatic potential resides within the acridone scaffold. Our screening of simple acridone analogues for keratinocyte growth inhibitory action revealed that, given the appropriate substitution pattern, representatives with IC_{50} values in the lower micromolar range were obtained. As already seen in the anthrone series of antipsoriatic agents [39], the nature of the substituents, their number and their position at the tricyclic skeleton were critical for the antiproliferative potency of acridones. Thus, the modification of these features led to the establishment of the following structure–activity relationships.



Scheme 4. Reagents: (a) NaH, THF, AcCl or BzCl, RT, N_2; (b) $AlCl_3$, 160 °C.

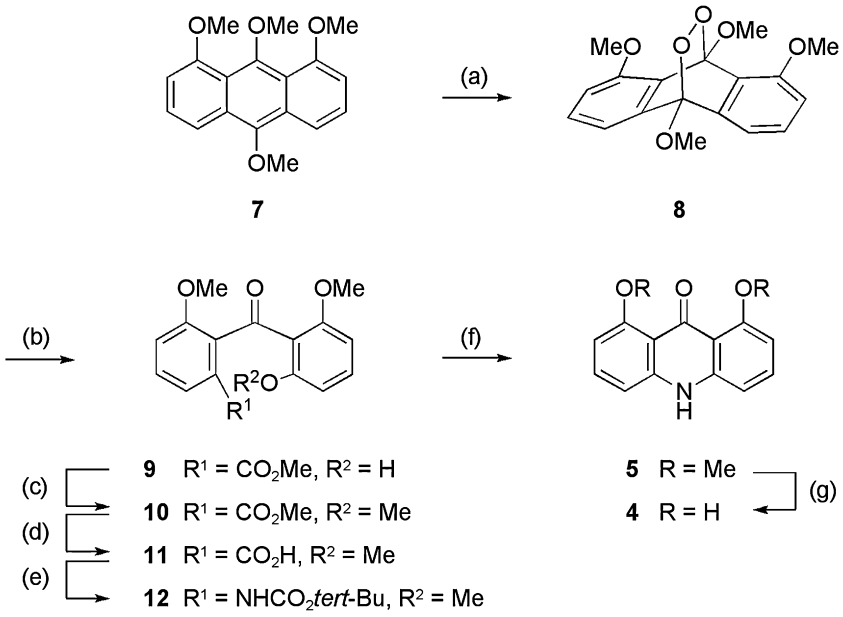
In general, monohydroxy- (**5a**–**5d**), monomethoxy- (**5e**–**5h**), dimethoxy- (**5**, **5j**, **5p**, **5r**), and trimethoxy-substitution (**5w**, **5z**) resulted in almost total loss of activity. However, introduction of an additional hydroxy-substituent into position 3 (**5i**) or 4 (**5l**) of 1-monohydroxy **5a** gave moderate inhibitors of keratinocyte growth, with the 1,6-dihydroxyacridone (**5o**) exhibiting activity even in the lower micromolar range (IC_{50} of 4.5 μM). Improvement over **5a** could also be observed for the 2-acetylated and 2-benzoylated analogues **5xx** and **5yy**, respectively. In particular, **5yy** was markedly active and retained the antiproliferative activity of anthralin, although the potency was somewhat reduced.

The series **5ff**–**5uu** explored the consequences of varying 4-substitution on monohydroxy **5a** and its methyl ether **5e**. An active keratinocyte growth inhibitor was obtained by introduction of a *para*-hydroxyl group (**5l**), but this caused chemical instability. As compared to **5l**, changing the *para*-hydroxyl group to lipophilic or electron-withdrawing (**5ff**, **5hh**, **5jj**, **5nn**) and also electron-donating substituents, as in **5ll**, was disadvantageous for antiproliferative potency. By contrast, substitution of the *para*-position of **5a** with a carboxamide (**5pp**) or methyl ester (**5rr**) group improved potency, while the analogous free carboxylic acid **5tt** was inactive. In each case of the 1-hydroxy-4-substituted analogues, the corresponding O-methylated derivatives were less active or inactive, indicating that the presence of the intramolecular hydrogen bond in 1-hydroxy-10*H*-acridin-9-ones played an important role for their keratinocyte inhibitory action. This is in good agreement with the results obtained for glyfoline analogues against human leukemic cells [15].

Finally, we explored additional substituents on 1,3-dihydroxyacridone (**5i**). Introduction of a 5-hydroxyl group in **5s** improved potency, whereas its 3-O-methylated analogue (**5t**) was less potent. This was in line with the observation that 3-O-alkylation of **5i** with methyl, benzyl or phenylethyl groups in **5k**, **5vv** and **5ww**, respectively, rather impaired antiproliferative action. Most successfully, addition of a *peri*-hydroxyl group provided 1,3,8-trihydroxy-substituted **5v** with an IC_{50} value of 2.0 μM, suggesting the requirement of a 3-hydroxyl group in the aza-analogous anthralin **4** for potent keratinocyte inhibition. Moreover, replacement of the 8-hydroxyl with a methyl group in **5ee** further improved potency. With an IC_{50} value in the submicromolar range the potency of **5ee** to arrest the excessive growth of keratinocytes was comparable to that of the antipsoriatic anthralin. The importance of the position of the methyl substituent on the 1,3-dihydroxyacridone skeleton was investigated by comparing analogues **5cc**–**5ee**. Moving the methyl substituent to the 5- or 6-position produced inactive compounds **5cc** and **5dd**, respectively. Accordingly, even minor changes in the arrangement of a promising substitution pattern such as **5ee** resulted in a dramatic loss of activity.

4.2. Interaction with the stable free radical DPPH

Table 1 shows that in terms of its ineffectiveness to reduce the free radical DPPH, the aza-analogous anthralin (**4**) is devoid of any appreciable radical interacting activity. This is in sharp contrast to anthralin (**1**) itself, which proved to be very effective in donating an electron to the stable free radical DPPH. As a consequence, acridone **4** was also more stable than the corresponding anthrone **1** and did not dimerize or polymerize to dark brown material. Obviously, hydrogen atom abstraction from acridones by free radicals such as DPPH did not easily occur, as most acridones of this study were not reactive with DPPH. In particular, the most potent inhibitors of keratinocyte growth such as **5v** and **5ee**, bearing hydroxyl groups in *meta*-position of the acridone nitrogen atom (i.e., position 1, 3 or 8 at the acridone skeleton), did not exhibit radical generating



Scheme 5. Reagents: (a) Et_2O, TPP, O_2, hν, 5 °C; (b) H_2SO_4, acetone, RT; (c) Me_2SO_4, K_2CO_3, acetone, reflux; (d) 10% NaOH, EtOH, reflux; (e) NEt_3, *tert*-BuOH, DPPA, N_2, reflux; (f) NaH, DMSO, RT; (g) 48% HBr, reflux.

properties. This is not surprising, as radical production from acridones has only been described scarcely in the literature. Only after photoirradiation and laser flash excitation, N-radical formation by hydrogen transfer to pyridine has been observed [40,41].

However, in some cases interaction of acridone derivatives with DPPH did occur. Given a suitable arrangement of their substituents, acridones were capable of interacting with the DPPH radical as effectively as the antioxidants NDGA or α-tocopherol. In fact, our results document the importance of the orientation of hydroxyl or amino groups on the acridone scaffold for the capability of the compounds to generate radicals, with the hydroxy- or amino-substitution *ortho* (**5d**, **5l**, **5s**, **5ll**, **5mm**) or *para* (**5b**, **5q**) to the NH group of acridone being required for effective interacting with DPPH. This observation is in good agreement with a recent report on moderate free radical scavenging activity of some naturally occurring alkaloids consisting of a 1,3,5-trihydroxy-acridone moiety [42]. Furthermore, our findings can be rationalized as a result of the resonance stabilization afforded to the resulting acridone N-radical (e.g., **5b**, Scheme 6). The resulting primary structure **13a** would be stabilized by the so-called captodative effect [43]. In such a scenario, pairs of substituents of opposite polarity, an electron-acceptor group (9-carbonyl) together with an electron-donor group (2-OH) act in synergy on the stabilization of the captodative radical (e.g., **13a**–**13e**) and contribute a stronger stabilization to this radical than pairs of identical substituents. In addition, a second hydrogen abstraction from the radical would give rise to a *para*-quinone-imine derivative **14**.

4.3. Membrane damage

As a result of its potential to generate radicals, LDH release by the standard anthralin significantly exceeded that of the vehicle control. On the other hand, LDH release of the most potent acridones (Table 1) was generally unchanged as compared to controls, documenting that their antiproliferative activity was not related to nonspecific cytotoxic effects. The only exception was the 2-benzoyl-substituted acridone **5yy**. This compound showed enhanced LDH activity, but somewhat less pronounced than anthralin.

5. Conclusions

We screened a series of N-unsubstituted hydroxy-10*H*-acridin-9-ones for their activities against the proliferation of human keratinocytes using HaCaT cells. Structure–activity relationships for acridone derivatives did not follow those observed in the anthrone class of antipsoriatics [39]. 1,8-Dihydroxy-substitution as seen in the anthrone series was not a prerequisite of antiproliferative potency in the HaCaT keratinocyte line, as the aza-analogous representative, 1,8-dihydroxy-10*H*-acridin-9-one (**4**), was only marginally active as compared to the antipsoriatic anthralin. Rather, acridones comprising a 1,3-dihydroxy-substitution pattern were among the most active analogues. Compound **5ee**, with an 8-methyl substituent at the 1,3-dihydroxy-substituted skeleton, was the most potent acridone within this series and displayed keratinocyte growth inhibitory action with an IC_{50} value in the submicromolar concentration range, which was comparable to that of the antipsoriatic anthralin. However, only minor changes in the position of the methyl substituent resulted in loss of activity.

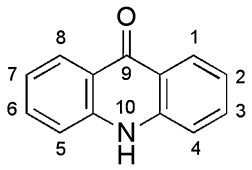
In most cases, acridones were devoid of radical generating properties. The only groups that had a substantial impact on interaction with the free radical DPPH were a phenolic hydroxyl or an aromatic amine arranged *ortho* or *para* (2-, 4-, 5-, or 7-position) to the acridone NH group. Also of note is the fact that in contrast to anthralin, the most potent acridones did not disrupt membrane integrity. The results of this work suggest that the acridone scaffold is a quite reasonable structure for the development of antipsoriatic agents.

6. Experimental section

6.1. Chemistry

Melting points were determined with a Kofler melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with a Varian Gemini 200 (200 and 50,29 MHz, respectively) spectrometer, using tetramethylsilane as an internal standard. Fourier-transform IR spectra (KBr) were recorded on

Table 1
Antiproliferative activity against HaCaT keratinocytes, lactate dehydrogenase release, free radical interacting capability, and method of preparation of N-unsubstituted 10*H*-acridin-9-ones.



Compounds	Substitution pattern	AA[a] IC_{50} (μM)	LDH[b] (mU/mL)	DPPH[d] EC_{50} (μM)	Method[e]
1	anthralin	0.7	122.8[c]	16.7	[60]
4	1,8-$(OH)_2$	39.5	ND	>60	A
5	1,8-$(OMe)_2$	>50	ND	ND	[f]
5a	1-OH	>50	ND	>60	F
5b	2-OH	>50	ND	2.7	A
5c	3-OH	>50	ND	ND	A
5d	4-OH	>50	ND	6.8	A
5e	1-OMe	>50	ND	>60	G
5f	2-OMe	>50	ND	ND	G
5g	3-OMe	>50	ND	ND	G
5h	4-OMe	>50	ND	>60	G
5i	1,3-$(OH)_2$	19.8	ND	>60	F
5j	1,3-$(OMe)_2$	>50	ND	ND	G
5k	1-OH-3-OMe	46.3	ND	ND	B
5l	1,4-$(OH)_2$	10.0	61.2	8.8	A
5m	1,4-$(OMe)_2$	>50	ND	>60	G
5n	1-OH-4-OMe	17.5	ND	>60	B
5o	1,6-$(OH)_2$	4.5	77.7	>60	A
5p	1,6-$(OMe)_2$	>50	ND	ND	G
5q	1,7-$(OH)_2$	48.8	ND	3.9	A
5r	1,7-$(OMe)_2$	>50	ND	ND	G
5s	1,3,5-$(OH)_3$	8.4	69.9	15.0	A
5t	1,3-$(OH)_2$-5-OMe	21.3	ND	ND	F
5u	1-OH-3,5-$(OMe)_2$	34.3	ND	ND	E
5v	1,3,8-$(OH)_3$	2.0	69.3	>60	A
5w	1,3,8-$(OMe)_3$	45.3	ND	ND	G
5x	1,3-$(OH)_2$-8-OMe	28.3	ND	ND	F
5y	1,8-$(OH)_2$-4-OMe	>50	ND	>60	B
5z	1,4,8-$(OMe)_3$	>50	ND	>60	G
5aa	1-OH-3-Me	>50	ND	ND	F
5bb	1-Me-3-OH	27.3	ND	ND	F
5cc	1,3-$(OH)_2$-5-Me	>50	ND	ND	F
5dd	1,3-$(OH)_2$-6-Me	>50	ND	ND	F
5ee	1,3-$(OH)_2$-8-Me	0.8	71.5	>60	F
5ff	1-OH-4-Me	25.7	ND	>60	A
5gg	1-OMe-4-Me	46.7	ND	> 60	G
5hh	1-OH-4-Cl	26.3	ND	>60	C
5ii	1-OMe-4-Cl	43.8	ND	>60	G
5jj	1-OH-4-NO_2	47.3	ND	>60	[56]
5kk	1-OMe-4-NO_2	>50	ND	>60	[f]
5ll	1-OH-4-NH_2	>50	ND	7.6	H
5mm	1-OMe-4-NH_2	>50	ND	7.7	H
5nn	1-OH-4-CN	27.9	ND	>60	D
5oo	1-OMe-4-CN	>50	ND	>60	G
5pp	1-OH-4-$CONH_2$	4.7	68.1	>60	D
5qq	1-OMe-4-$CONH_2$	8.8	66.5	>60	G
5rr	1-OH-4-CO_2Me	5.2	58.8	> 60	C
5ss	1-OMe-4-CO_2Me	10.8	63.7	>60	G
5tt	1-OH-4-CO_2H	49.2	ND	>60	D
5uu	1-OMe-4-CO_2H	>50	ND	>60	[f]
5vv	1-OH-3-OBn	47.8	ND	ND	E
5ww	1-OH-3-O$(CH_2)_2$Ph	21.0	ND	ND	E
5xx	1-OH-2-COMe	17.1	ND	>60	I
5yy	1-OH-2-COPh	1.6	88.9[c]	>60	I
5az	1-OAc	21.5	ND	ND	[57]
5zz	1-OCOPh	12.4	ND	>60	[f]

[a] Antiproliferative activity against keratinocytes. IC_{50}, concentration of test compound required for 50% inhibition of cell growth (HaCaT). Inhibition of cell growth was significantly different with respect to that of the control, $N = 3$, $P < 0.01$.

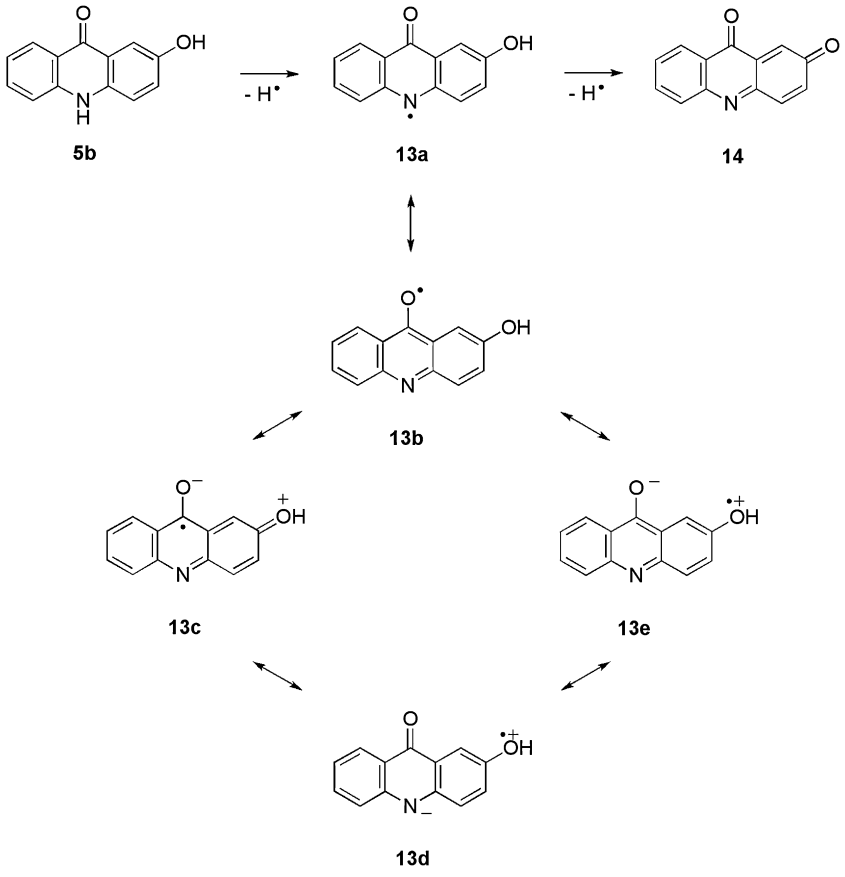
[b] Activity of LDH (mU) release in HaCaT cells after treatment with 2 μM test compound ($N = 3$, SD < 10%).

[c] Values are significantly different with respect to vehicle control. Brij 35 (polyoxyethyleneglycol dodecyl ether)/ultrasound was the positive control (251 mU/mL[c]). ND = not determined.

[d] DPPH radical interacting capability. EC_{50}, effective concentration of test compound ($N = 3$, SD < 10%) required for 50% decrease in DPPH absorbance at 520 nm. NDGA ($IC_{50} = 4.2$ μM) and α-tocopherol ($IC_{50} = 8.2$ μM) were used as positive controls. ND = not determined.

[e] Method of preparation according to the Experimental section.

[f] See Experimental section.



Scheme 6. Hydrogen abstraction from acridone **5b** and resonance stabilization of radical **13a**–**13e** by an electron-withdrawing 9-carbonyl and an electron-donating 2-hydroxyl group.

a Bio-Rad laboratories type FTS 135 spectrometer. Mass spectra were obtained in the EI mode using a MAT GCQ Finnigan instrument. Thin layer chromatography (TLC) was conducted on Merck 60 F_{254} precoated silica gel plates. Chromatography refers to column chromatography, which was performed on Merck silica gel (70–230 mesh) with CH_2Cl_2 as eluant, unless otherwise stated. Yields have not been optimized. Elemental analyses were determined by the Microanalysis Laboratory at the University of Münster, using a Vario EL III elemental analyzer. Elemental analyses were within ±0.4% of calculated values, except where stated otherwise.

6.1.1. General procedure for the cleavage of methyl ethers

*6.1.1.1. Method A: 1,8-dihydroxy-10H-acridin-9-one (**4**).* A solution of **5** (0.56 g, 2.20 mmol) in 48% HBr (30 mL) was refluxed for 10 h. The solution was allowed to cool to RT. Then the precipitating crystals were filtered by suction and dissolved in MeOH (30 mL). A solution of 10% KH_2PO_4 (20 mL) was added to induce crystallization of the product. The precipitate was filtered, washed with water, and then purified by chromatography (SiO_2; CH_2Cl_2/MeOH, 99/1) to provide bright yellow crystals; 82% yield; mp 298 °C (lit. [24] 252 °C); ^{1}H NMR (DMSO-d_6) δ 12.65 (s, 2H), 12.30 (s, 1H,), 7.63 (t, J = 8.2 Hz, 2H), 6.96 (d, J = 8.1 Hz, 2H), 6.57 (d, J = 8.0 Hz, 2H); FTIR 1654 cm^{-1} (CO); MS m/z = 227 (100, M^+).Anal. $C_{13}H_9NO_3$ (C, H, N).

*6.1.1.2. 1,6-Dihydroxy-10H-acridin-9-one (**5o**).* The title compound was obtained from **5p** by method A to provide bronze needles; 66% yield; mp 275 °C; ^{1}H NMR (DMSO-d_6) δ 14.20 (s, 1H), 11.77 (s, 1H, br), 10.70 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.50 (t, J = 8.2 Hz, 1H), 6.85–6.74 (m, 3H), 6.46 (d, J = 7.7 Hz, 1H); FTIR 1649 cm^{-1} (CO); MS m/z = 227 (100, M^+).Anal. $C_{13}H_9NO_3$ (C, H, N).

*6.1.1.3. 1-Hydroxy-4-methyl-10H-acridin-9-one (**5ff**).* The title compound was obtained from **5gg** by method A to provide a yellow powder; 55% yield; mp 285–286 °C; ^{1}H NMR (DMSO-d_6) δ 13.97 (s, 1H), 10.86 (s, 1H, br), 8.21 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 8.3 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 8.2 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 181.9, 159.9, 141.0, 139.7, 118.9, 113.1, 108.5, 136.5, 134.0, 124.8, 121.7, 118.0, 105.4, 17.0; FTIR 1643 cm^{-1} (CO); MS m/z = 225 (100, M^+). Anal. $C_{14}H_{11}NO_2$ (C, H, N).

Acridones **5b** [20], **5c** [44], **5d** [45], **5l** [46], **5q** [47], **5s** [48], and **5v** [49] were prepared from the corresponding methyl ethers (**5f**, **5g**, **5h**, **5m**, **5r**, **5t**, and **5w**, respectively) by method A.

*6.1.1.4. Method B: 1,8-dihydroxy-4-methoxy-10H-acridin-9-one (**5y**).* A mixture of **5z** (0.57 g, 2.0 mmol), 1-octanol (16 mL) and 36% HCl (7 mL) was heated to reflux for 4 h. The mixture was allowed to cool to RT and then neutralized with NaOH (5 mol/L) on an ice-bath. The crude product was isolated by suction, washed with n-hexane (3 × 100 mL), dissolved in CH_2Cl_2 (100 mL), and dried over Na_2SO_4. The solution was concentrated and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) to provide yellow plates; 33% yield; mp 98 °C; ^{1}H NMR (DMSO-d_6) δ 12.74 (s, 1H), 12.00 (s, 1H), 11.77 (s, 1H, br), 7.90–7.08 (m, 3H), 6.86–6.16 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 184.5, 160.5, 153.2, 131.8, 141.7, 139.1, 107.8, 107.5, 136.1, 116.6, 107.4, 106.4, 104.3, 56.6; FTIR 1650 cm^{-1} (CO···HO); MS m/z 257 (50, M^+), 242 (100). Anal. ($C_{14}H_{11}NO_4$) C, H, N.

Acridones **5k** [20] and **5n** [50] were prepared from **5i** and **5m**, respectively, by method B.

*6.1.1.5. Method C: 4-chloro-1-hydroxy-10H-acridin-9-one (**5hh**).* To a solution of **5ii** (0.26 g, 1.0 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of BBr_3 in CH_2Cl_2 (1 mol/L, 3 mL) at −78 °C under N_2. The solution was stirred for 4 h, then it was allowed to warm to RT and stirred for an additional 18 h. Water (50 mL) was added, the solution was stirred for 2 h at RT, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 phase was washed with water (2 × 75 mL), dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 99/1) to provide yellow plates; 52% yield; mp 262 °C; ^{1}H NMR (DMSO-d_6) δ 14.17 (s, 1H), 11.29 (s, 1H, br), 8.22 (dd, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.92–7.70 (m, 2H), 7.37 (t, $J = 8.1$ Hz, 1H), 6.59 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 181.7, 161.1, 140.9, 137.6, 119.1, 109.1, 107.7, 135.6, 134.7, 124.9, 122.5, 118.4, 106.7; FTIR 1641 cm^{-1} (CO···HO); MS m/z 245 (100, M$^+$). Anal. ($C_{13}H_8ClNO_2$) C, H, N.

*6.1.1.6. Methyl 1-hydroxy-9-oxo-9,10-dihydroacridine-4-carboxylate (**5rr**).* The title compound was obtained from **5ss** by method C to provide light-yellow crystals; 31% yield; mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ 15.05 (s, 1H), 12.15 (s, 1H, br), 8.29 (d, $J = 8.2$ Hz, 1H), 8.20 (d, $J = 8.7$ Hz, 1H), 7.78–7.55 (m, 1H), 7.46–7.10 (m, 2H), 6.52 (d, $J = 9.0$ Hz, 1H), 3.88 (s, 3H); FTIR 1688 (CO_2Me), 1633 cm^{-1} (CO); MS m/z = 269 (68, M$^+$), 237 (100). Anal. $C_{15}H_{11}NO_4$ (C, H, N).

*6.1.1.7. Method D: 1-hydroxy-9-oxo-9,10-dihydroacridine-4-carbonitrile (**5nn**).* A mixture of **5oo** (0.50 g, 2.0 mmol), anhydrous $AlCl_3$ (1.33 g, 10.0 mmol), and NaCl (2.7 g, 46.2 mmol) was triturated and then heated to 160 °C for 30 min. Then it was allowed to cool to RT, and the solidified mixture was stirred with HCl (1 mol/L, 100 mL) for 20 min. The precipitate was isolated by suction, washed with water (100 mL), and then heated to reflux in a mixture of EtOH (50 mL) and NaOH (2 mol/L, 100 mL) for 2 h. The hot mixture was filtered, the filtrate was acidified with HCl (2 mol/L), and the crude product was crystallized on an ice-bath. The precipitate was isolated by suction, washed with water (200 mL) and dried with toluene (Dean–Stark). The product was isolated by suction and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) to provide yellow crystals; 34% yield; mp 279 °C; ^{1}H NMR (DMSO-d_6) δ 15.18 (s, 1H), 11.93 (s, 1H, br), 8.60–7.62 (m, 4H), 7.38 (t, $J = 7.0$ Hz, 1H), 6.63 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 181.5, 167.1, 117.0, 87.4, 143.0, 141.1, 119.4, 108.0, 141.8, 134.9, 124.8, 123.1, 118.7, 107.5; FTIR 2221 (CN), 1637 cm^{-1} (CO···HO); MS m/z 236 (100, M$^+$). Anal. ($C_{14}H_8N_2O_2$) C, H, N.

*6.1.1.8. 1-Hydroxy-9-oxo-9,10-dihydroacridine-4-carboxamide (**5pp**).* The title compound was obtained from **5qq** (0.30 g, 1.1 mmol) by method D to provide yellow needles; 46% yield; mp 304 °C; ^{1}H NMR (DMSO-d_6, hydroxylimine tautomer) δ 14.98 (s, 1H), 13.70 (s, 1H), 8.54–8.05 (m, 3H), 7.95–7.51 (m, 3H), 7.38 (t, $J = 7.3$ Hz, 1H), 6.62 (d, $J = 8.6$ Hz, 1H); FTIR 1684 ($CONH_2$), 1634 cm^{-1} (CO); MS $m/z = 254$ (90, M$^+$), 237 (100). Anal. $C_{14}H_{10}N_2O_3$ (C, H, N).

*6.1.1.9. 1-Hydroxy-9-oxo-9,10-dihydroacridine-4-carboxylic acid (**5tt**).* The title compound was obtained from **5uu** (2.0 g, 7.1 mmol) by method D to provide a yellow powder; 50% yield; mp 275 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 15.29 (s, 1H, br), 14.57 (s, 1H), 8.32 (d, $J = 8.3$ Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 7.76 (t, $J = 7.3$ Hz, 1H), 7.58 (d, $J = 8.3$ Hz, 1H), 7.30 (t, $J = 7.4$ Hz, 1H), 6.50 (d, $J = 8.3$ Hz, 1H); FTIR 1631, 1604 cm^{-1}; MS $m/z = 255$ (62, M$^+$), 237 (100). Anal. $C_{14}H_9NO_4$ (C, H, N).

6.1.2. General procedure for alkylation of 3-hydroxyacridones

*6.1.2.1. Method E:3-(benzyloxy)-1-hydroxy-10H-acridin-9-one (**5vv**).* A mixture of **5i** (0.23 g, 1.0 mmol), dry K_2CO_3 (3 mmol) and benzyl chloride in dry acetone (30 mL) was stirred for 5 h. Then the mixture was filtered by suction, the residue dissolved in CH_2Cl_2 and filtered. The combined filtrate was evaporated and the residue was purified by chromatography (SiO_2; CH_2Cl_2) to provide yellow crystals; 13% yield; mp 293 °C; ^{1}H NMR (DMSO-d_6) δ 14.24 (s, 1H), 8.16 (d, $J = 7.9$ Hz, 1H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.51–7.24 (m, 8H), 6.44 (d, $J = 1.9$ Hz, 1H), 6.24 (d, $J = 1.8$ Hz, 1H), 5.22 (s, 2H); FTIR 1656 cm^{-1} (CO); MS $m/z = 317$ (100, M$^+$). Anal. $C_{20}H_{15}NO_3$ (C, H, N).

*6.1.2.2. 1-Hydroxy-3-phenethoxy-10H-acridin-9-one (**5ww**).* The title compound was obtained from **5i** and 2-bromoethylbenzene by method E, but the mixture was refluxed for 48 h. Purification afforded yellow crystals; 87% yield; mp 242 °C; ^{1}H NMR (DMSO-d_6) δ 14.21 (s, 1H), 11.86 (s, 1H, br), 8.15 (d, $J = 8.0$ Hz, 1H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 8.3$ Hz, 1H), 7.33–7.21 (m, 6H), 6.36 (d, $J = 1.4$ Hz, 1H), 6.12 (d, $J = 1.4$ Hz, 1H), 4.27 (t, $J = 6.8$ Hz, 2H), 3.06 (t, $J = 6.7$ Hz, 2H); FTIR 1655 cm^{-1} (CO); MS $m/z = 331$ (19, M$^+$), 227 (100). Anal. $C_{21}H_{17}NO_3$ (C, H, N).

Acridone **5u** [48] was prepared from **5t** and iodopropane by method E.

*6.1.3. 1,8-Dimethoxy-10H-acridin-9-one (**5**)*

To a solution of carbamate **12** (2.84 g, 7.3 mmol) in DMSO (55.0 mL) was added 60% NaH (1.0 g) with stirring. The reaction mixture was stirred for 24 h at RT, then it was poured into water (100 mL) and extracted with EtOAc (3 × 50 mL), and the organic phase was dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 99/1) to provide orange crystals; 13% yield; mp 239 °C; ^{1}H NMR (DMSO-d_6) δ 11.11 (s, 1H, br), 7.98–6.59 (m, 6H), 3.79 (s, 6H); FTIR 1638 cm^{-1} (CO); MS m/z = 255 (100, M$^+$). Anal. $C_{15}H_{13}NO_3$ (C, H, N).

6.1.4. General procedure for the condensation of anthranilates with phloroglucinol

*6.1.4.1. Method F: 1,3-dihydroxy-8-methoxy-10H-acridin-9-one (**5x**).* Methyl 2-amino-6-methoxybenzoate (3.62 g, 20.0 mmol), phloroglucinol (2.52 g, 20.0 mmol) and 4-toluenesulfonic acid (0.2 g, 1.2 mmol) in 1-heptanol (40 mL) were refluxed for 4 h. The mixture was allowed to cool to RT, and petroleum ether (150 mL) was added with stirring. The precipitate was filtered, washed with petroleum ether (3 × 100 mL) and CH_2Cl_2 (2 × 50 mL), and then purified by chromatography (SiO_2; CH_2Cl_2/MeOH, 94/6) to provide yellow crystals; 77% yield; mp 326 °C; ^{1}H NMR (DMSO-d_6) δ 14.81 (s, 1H), 11.51 (s, 1H), 10.37 (s, 1H, br), 7.54 (t, $J = 8.3$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 6.66 (d, $J = 8.0$ Hz, 1H), 6.17 (d, $J = 2.1$ Hz, 1H), 5.90 (d, $J = 2.0$ Hz, 1H), 3.83 (s, 3H); FTIR 1653 cm^{-1} (CO); MS $m/z = 257$ (100, M$^+$). Anal. $C_{14}H_{11}NO_4$ (C, H, N).

Analogously, acridones **5i** [28], **5t** [48], **5cc**–**5ee** [51] were prepared by method F. Also, compound **5a** [50] was prepared from methyl 2-aminobenzoate and resorcinol, compounds **5aa** [52] and **5bb** [52] were prepared from 2-aminobenzoate and methylresorcinol.

6.1.5. General procedure for the cyclization of phenylanthranilic acids to acridones

*6.1.5.1. Method G: 1,3,8-trimethoxy-10H-acridin-9-one (**5w**).* 6-Methoxy-2-(3,5-dimethoxyphenylamino)benzoic acid (**6w**, 5.76 g, 19.0 mmol) and polyphosphoric acid (PPA, 15.0 g) were heated at 90 °C for 6 h with stirring. The mixture was cooled to 50 °C, triturated with ice (100 g), and buffered to pH 5 with NaOH (2 mol/L). The mixture was stirred at RT for 5 h, and the precipitate was filtered by

suction. The crude product was dissolved in CH_2Cl_2 (200 mL), and the filtrate was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) to provide beige crystals; 37% yield; mp 299 °C; ^{1}H NMR (DMSO-d_6) δ 11.02 (s, 1H, br), 7.43 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.18 (d, J = 2.2 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H); FTIR 1638 cm^{-1} (CO); MS m/z = 285 (100, M$^+$). Anal. $C_{16}H_{15}NO_4$ (C, H, N).

*6.1.5.2. 1,4,8-Trimethoxy-10H-acridin-9-one (**5z**).* The title compound was obtained from **6z** by method G to provide yellow crystals; 46% yield; mp 255 °C; ^{1}H NMR (DMSO-d_6) δ 10.45 (s, 1H), 7.58–7.26 (m, 2H), 7.12 (d, J = 8.7 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 175.8, 159.7, 153.2, 132.5, 142.5, 140.7, 113.4, 112.9, 132.6, 112.4, 109.4, 102.7, 101.6, 56.3, 55.9, 55.5; FTIR 1627 cm^{-1} (CO); MS m/z = 285 (53, M$^+$), 270 (100). Anal. $C_{16}H_{15}NO_4$ (C, H, N).

*6.1.5.3. 1-Methoxy-4-methyl-10H-acridin-9-one (**5gg**).* The title compound was obtained from **6gg** by method G. The crude product was refluxed in toluene (Dean–Stark). Then it was filtered by suction, washed with petroleum ether (3 × 100 mL), and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 97/3) to provide lemon yellow plates; 80% yield; mp 274 °C; ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H, br), 8.11 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 3.80 (s, 3H), 2.45 (s, 3H); FTIR 1628 cm^{-1} (CO); MS m/z = 239 (82, M$^+$), 210 (100). Anal. $C_{15}H_{13}NO_2$ (C, H, N).

*6.1.5.4. 4-Chloro-1-methoxy-10H-acridin-9-one (**5ii**).* The title compound was obtained from **6ii** by method G to provide pale yellow crystals; 59% yield; mp 259 °C; ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H, br), 8.11 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.67 (t, J = 8.2 Hz, 1H), 7.25 (t, J = 8.2 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 3.73 (s, 3H); FTIR 1623 cm^{-1} (CO); MS m/z = 259 (79, M$^+$), 230 (100). Anal. $C_{14}H_{10}ClNO_2$ (C, H, N).

*6.1.5.5. 1-Methoxy-9-oxo-9,10-dihydroacridine-4-carbonitrile (**5oo**).* The title compound was obtained from **6oo** by method G to provide pale yellow needles; 87% yield; mp 250–251 °C; ^{1}H NMR (DMSO-d_6) δ 11.10 (s, 1H), 8.22–8.01 (m, 2H), 7.92 (d, J = 8.3 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 3.94 (s, 3H); FTIR 2217 (CN), 1627 cm^{-1} (CO); MS m/z = 250 (84, M$^+$), 221 (100). Anal. $C_{15}H_{10}N_2O_2$ (C, H, N).

*6.1.5.6. 1-Methoxy-9-oxo-9,10-dihydroacridine-4-carboxamide (**5qq**).* The title compound was obtained from **6oo** by method G, but the mixture was stirred for 1.5 h. The crude product was refluxed in toluene (Dean–Stark). Then it was filtered by suction, washed with petroleum ether (3 × 100 mL), and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 95/5) to provide light-yellow crystals; 64% yield; mp 298 °C; ^{1}H NMR (DMSO-d_6, hydroxylimine tautomer) δ 13.41 (s, 1H), 8.34 (s, 1H, br), 8.25 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.86–7.58 (m, H-6, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H); FTIR 1680 cm^{-1} ($CONH_2$); MS m/z = 268 (99, M$^+$), 251 (100). Anal. $C_{15}H_{12}N_2O_3$ (C, H, N).

Analogously, methoxy-substituted acridones **5e** [29], **5f** [53], **5g** [29], **5h** [29], **5j** [20], **5m** [54], **5p** [55] and **5r** [47] and **5ss** [30] were prepared by method G.

*6.1.6. 1-Methoxy-4-nitro-10H-acridin-9-one (**5kk**)*

A solution of 1-chloro-4-nitro-10*H*-acridin-9-one [56] (2.0 g, 7.3 mmol) and NaOMe (1.18 g, 21.9 mmol) in absolute MeOH (300 mL) was refluxed for 48 h. The solution was allowed to cool to RT, water was added (100 mL), the precipitate isolated by suction and washed with water (200 mL). The product was dissolved in CH_2Cl_2, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 97/3) to provide a dark-yellow powder; 61% yield; mp 253–254 °C; ^{1}H NMR (DMSO-d_6) δ 11.83 (s, 1H, br), 8.67 (d, J = 9.6 Hz, 1H), 8.40 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H,), 7.82–7.62 (m, 1H), 7.48–7.30 (m, 2H,), 6.75 (d, J = 9.6 Hz, 1H), 4.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.8, 168.3, 139.6, 138.2, 123.8, 112.1, 110.0, 134.0, 133.5, 127.3, 123.9, 117.4, 102.6, 57.2; FTIR 1643 cm^{-1} (CO); MS m/z = 270 (100, M$^+$). Anal. $C_{14}H_{10}N_2O_4$ (C, H, N).

6.1.7. Method H: general procedure for the reduction of nitroacridones

*6.1.7.1. 4-Amino-1-hydroxy-10H-acridin-9-one (**5ll**).* To a solution of 1-hydroxy-4-nitro-10*H*-acridin-9-one [56] (**5jj**, 5.12 g, 20.0 mmol) in EtOH (75 mL) was added a solution of $Na_2S_2O_4$ (13.95 g, 80 mmol) in water (75 mL) with stirring. The solution was refluxed for 4 h and the solvent evaporated in vacuo. The residue was isolated by suction, washed with water (200 mL), and dried with toluene (Dean–Stark). Then it was filtered by suction, washed with petroleum ether (150 mL), and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) under light protection to provide a dark-red powder; 69% yield; mp 246–247 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 13.18 (s, 1H), 10.92 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.96–7.50 (m, 2H), 7.44–7.16 (m, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.40 (d, J = 8.3 Hz, 1H), 4.90 (s, 2H, br); ^{13}C NMR (DMSO-d_6) δ 181.8, 152.9, 140.7, 130.3, 126.4, 118.8, 108.8, 133.9, 125.0, 121.4, 120.7, 117.6, 105.1; FTIR 1644 cm^{-1} (CO); MS m/z = 226 (100, M$^+$). Anal. $C_{13}H_{10}N_2O_2$ (C, H, N).

*6.1.7.2. 4-Amino-1-methoxy-10H-acridin-9-one (**5mm**).* The title compound was obtained from **5kk** by method H to provide a dark-red powder; 73% yield; mp 234–235 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 10.21 (s, 1H, br), 8.10 (d, J = 8.1 Hz, 1H), 7.79–7.51 (m, 2H), 7.30–7.10 (m, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.53 (d, J = 8.5 Hz, 1H), 4.95 (s, 2H, br), 3.72 (s, 3H); FTIR 1625 cm^{-1} (CO); MS m/z = 240 (64, M$^+$), 225 (100). Anal. $C_{14}H_{12}N_2O_2$ (C, H, N).

*6.1.8. 1-Methoxy-9-oxo-9,10-dihydroacridine-4-carboxylic acid (**5uu**)*

A solution of **5ss** (2.00 g, 7.1 mmol) in EtOH (60 mL) and NaOH (2 mol/L, 120 mL) was refluxed for 2 h. The solution was acidified with HCl (2 mol/L), and the product was crystallized on an ice-bath, isolated by suction, washed with water (200 mL), and dried with toluene (Dean–Stark). Then it was filtered by suction, washed with petroleum ether (100 mL), and recrystallized from MeOH to provide light-yellow crystals; 89% yield; mp 264 °C (lit. [30] 266–268 °C); ^{1}H NMR (DMSO-d_6) δ 12.34 (s, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.87–7.44 (m, 2H), 7.26 (t, J = 7.1 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H); FTIR 1678 (COOH), 1619 cm^{-1} (CO); MS m/z = 269 (98, M$^+$), 223 (100). Anal. $C_{15}H_{11}NO_4$ (C, H, N).

6.1.9. Method I: general procedure for the Fries reaction of 1-acyloxyacridones

*6.1.9.1. 2-Acetyl-1-hydroxy-10H-acridin-9-one (**5xx**).* A mixture of 9-oxo-9,10-dihydroacridin-1-yl acetate [57] (**5az**, 0.25 g, 1.0 mmol) and anhydrous $AlCl_3$ (0.73 g, 5.5 mmol) was triturated and then heated to 160 °C for 2 h. The mixture was allowed to cool to RT, and the solidified product was stirred with HCl (0.2 mol/L, 50 mL) on an ice-bath for 20 min. The precipitate was washed with water (100 mL) and dried with toluene (Dean–Stark). The product was isolated by suction, washed with petroleum ether (75 mL),

recrystallized from MeOH and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) to provide yellow-orange crystals; 53% yield; mp 272 °C; ^{1}H NMR (DMSO-d_6) δ 15.89 (s, 1H), 12.44 (s, 1H, br), 8.20 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 195.0, 182.1, 165.0, 144.8, 140.4, 119.4, 115.2, 107.7, 135.8, 134.9, 125.2, 123.0, 117.8, 106.7, 31.9; FTIR 1639, 1620 cm^{-1} (CO); MS m/z = 253 (46, M$^+$), 238 (100). Anal. $C_{15}H_{11}NO_3$ (C, H, N).

*6.1.9.2. 2-Benzoyl-1-hydroxy-10H-acridin-9-one (**5yy**).* The title compound was obtained from (**5zz**) by method I to provide orange crystals; 42% yield; mp 285 °C; ^{1}H NMR (DMSO-d_6) δ 15.04 (s, 1H), 12.44 (s, 1H, br), 8.22 (d, J = 7.6 Hz, 1H), 7.85 (t, 1H), 7.78 (d, 1H), 7.76 (d, 2H), 7.63 (d, 1H), 7.61 (t, 1H), 7.50 (t, 2H), 7.39 (t, 1H), 7.05 (d, J = 8.8 Hz, 1H); FTIR 1654, 1635 cm^{-1} (CO); MS m/z = 315 (100, M$^+$). Anal. $C_{20}H_{13}NO_3$ (C, H, N).

*6.1.10. 9-Oxo-9,10-dihydroacridin-1-yl benzoate (**5zz**)*

A mixture of **5a** (0.1 g, 1.0 mmol) and 60% sodium hydride (0.1 g) in THF (25 mL) was stirred under N_2 for 30 min. Then a solution of benzoyl chloride (0.12 g, 0.84 mmol) in THF (5 mL) was added and stirring was continued for 1.5 h. The mixture was poured into ice-water (20 mL), extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) to provide light-yellow crystals; 35% yield; mp 262 °C; ^{1}H NMR (DMSO-d_6) δ 11.85 (s, 1H, br), 8.36–8.10 (m, 2H), 8.04 (d, J = 8.2 Hz, 1H), 7.93–7.39 (m, 7H), 7.20 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H); FTIR 1738 (OCOPh), 1636 cm^{-1} (CO); MS m/z = 315 (30, M$^+$), 105 (100). Anal. $C_{20}H_{13}NO_3$ (C, H, N).

6.1.11. General procedures for the synthesis of phenylanthranilic acids

*6.1.11.1. Method J: 6-methoxy-2-(3,5-dimethoxyphenylamino)benzoic acid (**6w**).* To a solution of 2-chloro-6-methoxybenzoic acid (3.64 g, 19.5 mmol) and 3,5-dimethoxyaniline (3.98 g, 26.0 mmol) in 1-heptanol (20 mL) was added powdered copper (0.50 g). Then anhydrous K_2CO_3 was added in portions with gentle heating and stirring. The mixture was refluxed for 7 h, and then treated with ice-water (300 mL), alkalinized with NaOH (0.1 mol/L), and filtered. The solution was washed with Et_2O (3 × 50 mL) and acidified with 18% HCl on an ice-bath with stirring. The precipitating crude product was filtered by suction, dried in a drying apparatus in vacuo and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) to provide white crystals; 13% yield; mp 152 °C; ^{1}H NMR (acetone-d_6) δ 9.75 (s, 1H br), 7.35 (t, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 6.31 m, 3H), 4.06 (s, 3H), 3.78 (s, 6H); FTIR 1697 cm^{-1} (COOH); MS m/z = 303 (100, M$^+$). Anal. $C_{16}H_{17}NO_5$ (C, H, N).

*6.1.11.2. 2-(2,5-Dimethoxyphenylamino)-6-methoxybenzoic acid (**6z**).* The title compound was obtained from 2-chloro-6-methoxybenzoic acid and 2,5-dimethoxyaniline by method J. The solution of the crude product was extracted with CH_2Cl_2 (3 × 150 mL), the combined extracts were dried over Na_2SO_4, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 97/3) to provide a light-yellow powder; 26% yield; mp 106 °C; ^{1}H NMR (DMSO-d_6) δ 7.78 (s, 1H, br), 7.29 (t, J = 8.3 Hz, 1H), 7.06–6.84 (m, H-3, 2H), 6.76 (d, J = 2.8 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.44 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.2, 158.3, 153.4, 131.9, 143.3, 142.3, 111.6, 131.6, 112.2, 109.2, 104.8, 103.7, 103.3, 56.2, 55.8, 55.2; FTIR 1692 cm^{-1} (COOH); MS m/z = 303 (100, M$^+$). Anal. $C_{16}H_{17}NO_5$ (C, H, N).

*6.1.11.3. Method K: 2-(5-methoxy-2-methylphenylamino)benzoic acid (**6gg**).* To a solution of diphenyliodonium-2-carboxylate [58] (3.40 g, 10.5 mmol) and 5-methoxy-2-methylaniline (1.37 g, 10.0 mmol) in dry dimethylformamide (20 mL) was added anhydrous $Cu(OAc)_2$ (0.10 g), and the mixture was heated at 90 °C for 15 h. Then it was poured into HCl (0.2 mol/L, 300 mL) on an ice-bath, and the precipitate was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed consecutively with HCl (0.2 mol/L, 2 × 75 mL) and water (3 × 100 mL), and then extracted with NaOH (0.2 mol/L, 3 × 100 mL). The combined extracts were acidified with 35% HCl (pH 4–5), and the precipitate was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with water (3 × 100 mL), dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 97/3) to provide a white powder; 67% yield; mp 159 °C; ^{1}H NMR (DMSO-d_6) δ 9.50 (s, 1H, br), 7.88 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.73 (t, J = 7.7 Hz, 1H), 6.64 (dd, J_1 = 8.2 Hz, J_2 = 2.2 Hz, 1H), 3.70 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.0, 158.1, 147.5, 139.5, 122.8, 112.1, 134.1, 131.7, 131.5, 116.9, 113.6, 109.5, 108.0, 55.0, 16.7; FTIR 1654 cm^{-1} (COOH); MS m/z = 257 (100, M$^+$). Anal. $C_{15}H_{15}NO_3$ (C, H, N).

*6.1.11.4. 2-(2-Chloro-5-methoxyphenylamino)benzoic acid (**6ii**).* The title compound was prepared from 2-chloro-5-methoxyaniline by method K to provide a light-grey powder; 51% yield; mp 152–153 °C; ^{1}H NMR (DMSO-d_6) δ 9.80 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.56–7.34 (m, 2H), 7.28 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.87 (t, J = 7.8 Hz, 1H), 6.66 (dd, J_1 = 8.9 Hz, J_2 = 2.8 Hz, 1H), 3.73 (s, 3H); FTIR 1657 cm^{-1} (COOH); MS m/z = 277 (63, M$^+$), 224 (100). Anal. $C_{14}H_{12}ClNO_3$ (C, H, N).

*6.1.11.5. 2-(2-Cyano-5-methoxyphenylamino)benzoic acid (**6oo**).* The title compound was prepared from 2-amino-4-methoxybenzonitrile by method K to provide a light-grey powder; 45% yield; mp 198–199 °C; ^{1}H NMR (DMSO-d_6) δ 10.10 (s, 1H), 7.96 (d, J = 6.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.12–6.88 (m, 2H), 6.73 (dd, J_1 = 8.8 Hz, J_2 = 2.2 Hz, 1H), 3.80 (s, 3H); FTIR 2214 (CN), 1665 cm^{-1} (COOH); MS m/z = 268 (100, M$^+$). Anal. $C_{15}H_{12}N_2O_3$ (C, H, N).

*6.1.12. 1,8,9,10-Tetramethoxy-9,10-dihydro-9,10-epidioxyanthracene (**8**)*

A solution of 1,8,9,10-tetramethoxyanthracene [33] (**7**, 2.0 g, 6.70 mmol) and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP, 20 mg) in absolute Et_2O (300 mL) was irradiated with halogen lamps (Osram Halostar, 200 W) under continuous oxygen bubbling in a water-cooled immersion well (Haake cryostat KT 33.0) for 90 min at 5 °C. A solution of 40% KNO_2 in water was used as a cutoff filter (350 nm). The solvent was removed, the precipitate filtered and washed with Et_2O (3 × 10 mL) to provide colorless crystals; 80% yield; mp 230 °C; ^{1}H NMR ($CDCl_3$) δ 7.26–7.07 (m, 4H), 6.81 (dd, J = 7.0, 2.0 Hz, 2H), 3.90 (s, 3H), 3.83 (s, 3H). The crude product was used in the subsequent reaction.

*6.1.13. Methyl 2-(2-hydroxy-6-methoxybenzoyl)-3-methoxybenzoate (**9**)*

To a solution of endoperoxide **8** (0.33 g, 1.0 mmol) in dry acetone (300 mL) was added a solution of 96% H_2SO_4 (0.2 mL) in dry acetone (10 mL). The solution was stirred for 3 h at RT, then diluted with water, extracted with CH_2Cl_2 (3 × 100 mL), and the organic phase was washed with water and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98/2) to provide light-green crystals; 72% yield; mp 184 °C; ^{1}H NMR ($CDCl_3$) δ 12.87 (s, 1H), 7.62 (d,

$J = 8.0$ Hz, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 6.62 (d, $J = 8.0$ Hz, 1H), 6.22 (d, $J = 8.0$ Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.30 (s, 3H); FTIR 1700 (CO_2Me), 1620 cm^{-1} (CO); MS $m/z = 316$ (31, M^+), 253 (100). Anal. $C_{17}H_{16}O_6$ (C, H).

*6.1.14. Methyl 2-(2,6-dimethoxybenzoyl)-3-methoxybenzoate (**10**)*

To a suspension of **9** (0.15 g, 4.74 mmol) and anhydrous K_2CO_3 (4.5 g, 3.26 mmol) in dry acetone (150 mL) was added dimethyl sulfate (1.99 g, 15.78 mmol), and the mixture was heated to reflux for 16 h. The reaction mixture was then filtered by suction, the filtrate was cooled on an ice-bath, diluted with water, and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was concentrated, and the residue was purified by column chromatography (SiO_2; CH_2Cl_2/acetone, 99/1) to provide colorless prisms; 73% yield; mp 150 °C; ^1H NMR ($CDCl_3$) δ 7.43 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.31 (t, $J = 8.0$ Hz, 1H), 7.28 (t, $J = 8.0$ Hz, 1H), 7.01 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.52 (d, $J = 8.0$ Hz, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H); FTIR 1700 (CO_2Me), 1650 cm^{-1} (CO); MS $m/z = 330$ (48, M^+), 165 (100). Anal. $C_{18}H_{18}O_6$ (C, H).

*6.1.15. 3-Methoxy-2-(2,6-dimethoxybenzoyl)benzoic acid (**11**)*

A solution of **10** (3.30 g, 10.0 mmol) in EtOH (16 mL) and 10% NaOH (8 mL) was refluxed for 6 h. The solution was allowed to cool to RT, then acidified with HCl (0.1 mol/L), extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4 and concentrated in vacuo. The product was crystallized by addition of small amounts of petroleum ether. The precipitate was isolated by suction and washed with petroleum ether to provide white crystals; 90% yield; mp 176 °C; ^1H NMR ($CDCl_3$) δ 7.44–6.61 (m, 6H), 3.59 (s, 3H), 3.54 (s, 6H); FTIR 1735 cm^{-1} (COOH); MS $m/z = 316$ (4, M^+), 241 (100). Anal. $C_{17}H_{16}O_6$ (C, H).

*6.1.16. Tert-butyl 3-methoxy-2-(2,6-dimethoxybenzoyl) phenylcarbamate (**12**)*

A solution of **11** (3.16 g, 10.0 mmol), diphenylphosphoryl azide (DPPA, 2.75 g, 10.0 mmol) and NEt_3 in *tert*-BuOH (40 mL) was refluxed under N_2 for 4 h. Then the solution was concentrated and column chromatography (SiO_2; CH_2Cl_2/n-hexane, 50/50) afforded yellow crystals of the crude product; 73% yield; m/z (%) = 387 (6, $M^{\bullet+}$), 299 (100). The crude product was used for the subsequent reaction.

6.2. Biological assay methods

6.2.1. Keratinocyte culture and determination of cell growth

HaCaT cells [36] were cultivated and the cell proliferation assay was performed as described [59]. After 48 h of incubation, cell growth was determined by enumerating the dispersed cells by phase-contrast microscopy. Inhibition was calculated by the comparison of the mean values of the test compound ($N = 3$) with the control ($N = 6$–8) activity: (1 − test compound/control) × 100. Inhibition was statistically significant compared to that of the control (Student's t-test; $P < 0.05$). IC_{50} values were obtained by nonlinear regression.

6.2.2. Determination of DPPH radical interacting capability

A radical interacting test compound reduces the violet-colored DPPH (2,2-diphenyl-1-picrylhydrazyl) radical with an absorbance at 520 nm to a yellow-colored 2,2-diphenyl-1-picrylhydrazine (non-radical). A solution of the test compound (3.75–120.0 μM) in EtOH (0.1 mL) was added to a 96-well microtiter plate. DPPH (0.1 mL of a 60 μM solution in EtOH) was added, the mixture was shaken vigorously for 30 s in a Spectramax 340 microplate reader (Molecular Devices) by the built in shaker and allowed to stand in the dark at RT for 20 min. Then it was again shaken for 30 s, and the decrease in absorbance at 520 nm of the resulting solution was measured. Appropriate vehicle and DPPH controls as well as positive controls with NDGA (nordihydroguaiaretic acid) and α-tocopherol were performed. Data were analyzed with the software Softmax Pro. The capability to interact with DPPH radical (%) was calculated by the comparison of the mean values of the test compound ($N = 3$) with those of the control ($N = 8$): (1 − absorbance of test compound/absorbance of control) × 100. Results were expressed as EC_{50}, the effective concentration of the test compound required for 50% decrease in DPPH absorbance at 520 nm. Values were obtained by nonlinear regression.

6.2.3. Lactate dehydrogenase release

The assay was performed as described [9,38]. HaCaT cells were incubated with the test compounds (2 μM) for 4 h at 37 °C. Extracellular LDH activity was measured using the UV method with pyruvate and NADH and is expressed in mU/ml. Appropriate controls with the vehicle were performed ($P < 0.01$; $N = 3$, SD < 10%). Brij 35 (polyoxyethyleneglycol dodecyl ether)/ultrasound was the positive control.

Appendix. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejmech.2010.04.013.

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