Bioorganic & Medicinal Chemistry Letters xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis, spectroscopic studies and biological evaluation of acridine derivatives: The role of aggregation on the photodynamic efficiency

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ARTICLE INFO

Article history:
Received 30 November 2017
Revised 25 January 2018
Accepted 2 February 2018
Available online xxxx

Keywords:
Self-aggregation
Organic nanoparticles
9-Amidoacridine
Photodynamic therapy
Singlet oxygen

ABSTRACT

Two new photoactive compounds (**1** and **2**) derived from the 9-amidoacridine chromophore have been synthesized and fully characterized. Their abilities to produce singlet oxygen upon irradiation have been compared. The synthesized compounds show very different self-aggregating properties since only **1** present a strong tendency to aggregate in water. Biological assays were conducted with two cell types: hepatoma cells (Hep3B) and human umbilical vein endothelial cells (HUVEC). Photodynamic therapy (PDT) studies carried out with Hep3B cells showed that non-aggregating compound **2** showed photoxicity, ascribed to the production of singlet oxygen, being aggregating compound **1** photochemically inactive. On the other hand suspensions of **1**, characterized as nano-sized aggregates, have notable antiproliferative activity towards this cell line in the dark.

Introduction

Acridine derivatives are well known biologically active compounds, widely used, for instance, as topical antibacterial and antiparasitic agents.[1] They have been used also as anticancer drugs since the planar structure of this chromophore permits the intercalation into the major groove of DNA and hence disruption of the replication process.[2] Further understanding of their molecular mode of action showed that this biological effect is not only due to their intercalating ability but also can be explained by targeting of overexpressed biomolecules in tumoral cells, such as telomerase, protein kinase and topoisomerases I and II.[3] An abundant collection of acridine-based antiproliferative compounds can be found in the literature, with plethora of structural variants designed to enhance not only their binding abilities at the site of action but also the membrane crossing features and transportation properties of the molecules through the cellular millieu.[4] For example, Delcros et al. have described a series of 9-substituted aminoacridines and amidoacridines linked to polyamine chains capable of inhibiting the growth of L1210 and CHO cells with IC_{50} values in the micromolar range.[5] One strategy followed to enhance the DNA binding efficiency is the introduction of a second acridine moiety in the structure, which improves the stacking to the nucleic acids and hence potentiates the biological effect.[6] Apart from applications in oncology, acridines have also found utility in other therapeutic fields, for instance as antimalarials[7] and as cholinesterase inhibitors for Alzheimer's disease therapy.[8]

In parallel with this conventional approach there is another therapeutic strategy also using acridine-derived compounds and light to inhibit the proliferation of cancerous cells[9] and also to kill microorganisms.[10] Photodynamic therapy (PDT) is a clinical tool that uses a photosensitizer in combination with visible or UV light to produce cytotoxic reactive oxygen species (ROS) including superoxide radical anion ($O_2^{\bullet-}$) and singlet oxygen ($^1O_2$). Numerous types of compounds have been employed so far for the generation of $^1O_2$, not only for photobiological applications,[11,12] but also for synthetic purposes.[13]

The use of acridines in PDT dates back to the very origin of this discipline[14] and currently there is a renewed interest in the development of acridine derivatives for photodynamic applications. In principle, acridine chromophore is an excellent candidate to develop a bioactive photosentitizer, taking into account the very efficient population of the triplet excited state upon irradiation.[15] Energy transfer to molecular triplet oxygen gives rise to very high yields of $^1O_2$ (Φ_Δ) both in polar and apolar medium. For instance, Ogilby et al.[16] have reported Φ_Δ (benzene) = 0.84 and Φ_Δ (acetonitrile) = 0.97. However, compared to the number of acridine derived compounds reported as DNA binding agents, the number of PDT active

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https://doi.org/10.1016/j.bmcl.2018.02.005
0960-894X/

compounds based on this chromophore is relatively low. The aim of this study is to compare the ability of two new 9-amidoacridine compounds (**1** and **2** in Fig. 1) to generate $^1O_2$ upon irradiation. The hypothesis of this work is that the superstructure adopted by the photosensitizing molecules affects dramatically their photobiological efficiency, in such a way that aggregation can favour deactivation pathways of the excited states, leading to quenching of the photosensitizer (like molecule **1**) and hence their invalidation as PDT agents. In this regard, a simpler structure (like molecule **2**) avoiding this aggregation phenomenon would be more favourable for the photogeneration of $^1O_2$ in aqueous medium, and then their use for clinical application more recommendable.

Compounds **1** and **2** were synthesized by coupling carbobenzyloxy-L-valine with the corresponding amine or diamine, as depicted in Scheme 1, followed by deprotection of the Cbz group and reaction with acridine-9-carbonyl chloride. Compounds were purified by subsequent filtration and washing steps, and were fully characterized by means of HRMS, ^1H and ^{13}C NMR spectroscopy (see Supporting information).

In acetonitrile, compounds **1** and **2** show the typical absorption of the acridine chromophore at 360 nm, displaying optical features appropriate for UVA excitation and weak fluorescence at 419 nm (Fig. 2).[17] In a polar solvent such as water, absorption maximum undergoes opposed shifts (365 nm for **1** and 357 nm for **2**) and fluorescence emission batochromic shifts (439 nm for **1** and 435 nm for **2**). The emission quantum yield in water is notably different: very low for compound **1** and moderate for the mono-acridine derivative **2**. Summarized photophysical properties of the synthesized compounds are shown in Table 1.

The generation of $^1O_2$ upon irradiation was tested using a well-known benchmark reaction like the oxygenation of 1,5-dihydroxynaphthalene (DHN) to juglone, depicted in Scheme 2.[18] Compounds **1** and **2** were irradiated in quartz cuvettes with light of 365 nm. The analysis of the reaction was performed by UV-vis absorption measurements following the decreasing absorption of DHN at 298 nm.

An illustrative example of the spectral changes occurring upon irradiation of acridine derivatives in the presence of DHN can be found in Fig. 3. As it can be seen, the absorption bands of DHN at 298 nm disappear when increasing the irradiation time and,

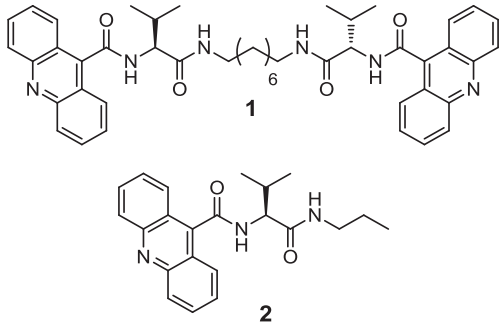


Fig. 1. Synthesized compounds based on the 9-amidoacridine chromphore.

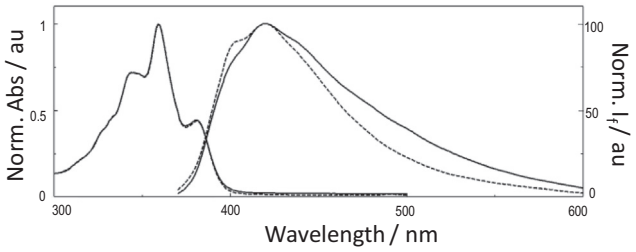
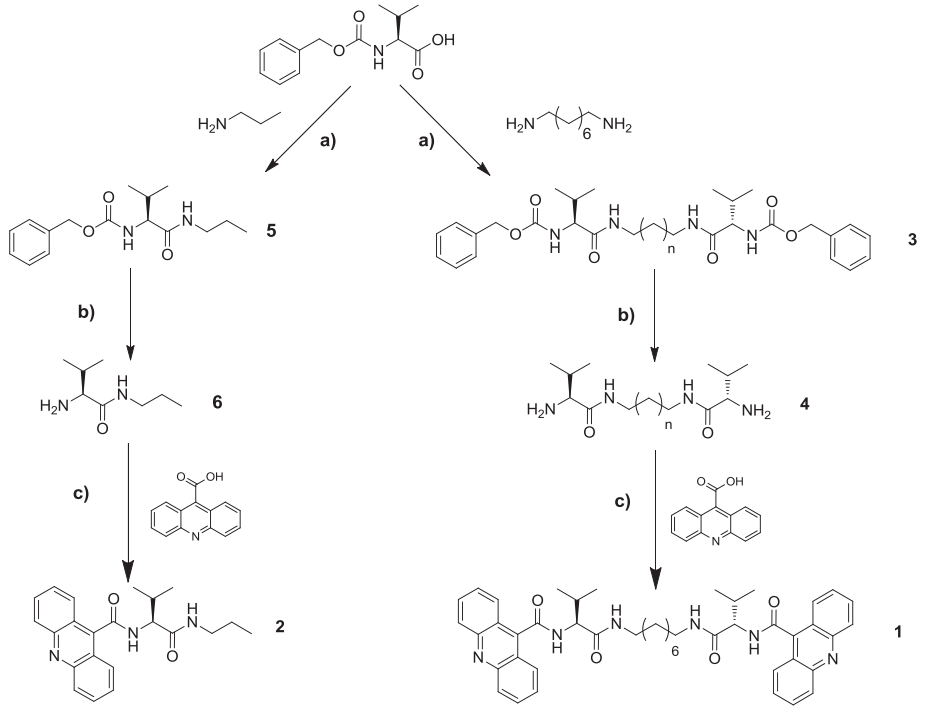


Fig. 2. Absorption and emission spectra of synthesized compounds in CH_3CN. **1** continuous line, **2** dashed line.



Scheme 1. Synthetic route for compounds **1** and **2** a) THF, Et_3N ClCOOEt, r.t., 12 h b) CH_3OH, Pd/C H_2, r.t., 6 h c) for acridine-9-carboxylic acid activation: CH_2Cl_2, oxalyl chloride, DMF(cat). For activated acid and amine coupling reaction: THF, Et_3N, 16 h.

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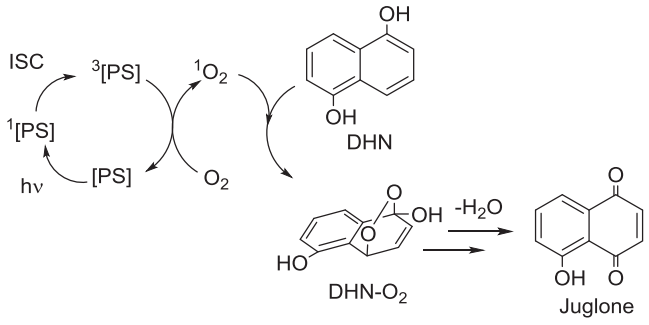
Table 1
Photochemical properties of compounds **1** and **2**.

Compd.	Solvent	λ_{abs} (nm)	λ_{em} (nm)	Φ_F	Φ_Δ
1	CH_3CN	360	418	0.003 ± 0.001	0.96 ± 0.04
	H_2O[a]	365	439	0.04 ± 0.01	0.010 ± 0.008
2	CH_3CN	359	419	<0.001	0.97 ± 0.01
	H_2O[a]	357	435	0.32 ± 0.06	0.263 ± 0.004

[a] Contains 1% CH_3CN from a concentrated stock solution used to prepare the aqueous sample.



Scheme 2. Photooxidation reaction of DHN. PS = Acridine photosensitizer; ISC = Intersystem crossing; DHN = 1,5-dihydroxynaphthalene.

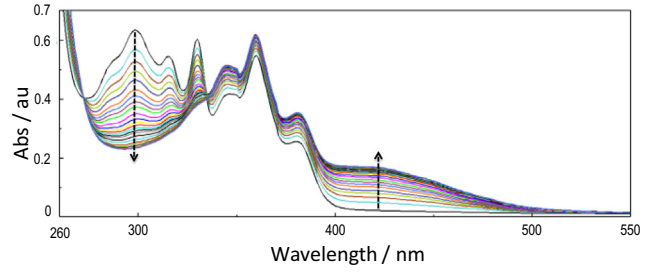


Fig. 3. Photooxidation of DHN by $^1O_2$ induced by irradiation of **1** in CH_3CN, monitored by UV-Vis spectroscopy. [DHN] = 80 μM; [**1**] = 33 μM.

concomitantly, the rise of a new absorption band takes place at 425 nm corresponding to the juglone photoproduct.

The initial kinetic points of the absorption bleaching of DHN were fitted to a pseudo-first order model ($\ln C/C_0 = -k_{obs}\, t$, where C is the concentration of DHN at a certain time t and C_0 is the initial concentration). The irradiations were performed in a series of media with different water content, from acetonitrile to water. The quantum yields for the $^1O_2$ generation induced by irradiation of **1** and **2** were determined by comparing the slopes of the above mentioned fittings to the same reaction photosensitized by phenalenone, as a well-known photosensitizer standard ($\Phi_\Delta \sim 1$),[19] in acetonitrile. All the fitted kinetics can be visualized in Fig. 4 (see details in the Supporting information file).

As shown in Fig. 5 both mono- (**2**) and bis-acridine (**1**) compounds generate very efficiently singlet oxygen upon irradiation at 365 nm in acetonitrile, as expected, with $\Phi_\Delta = 0.97$ and 0.96 respectively. However, upon addition of water to the medium, this parameter falls dramatically, especially in the case of the bichromophoric compound **1** (in water $\Phi_\Delta = 0.010$). However the decrease for monochromophoric derivative **2** is not so pronounced, affording a moderate yield (in water $\Phi_\Delta = 0.263$).

This differential behaviour prompted us to investigate the reason for the absence of photo-reactivity in the case of bichromophoric compound **1**. Aqueous samples of **1** and **2** were analysed by dynamic light scattering (DLS) revealing a clear difference between them: whereas the larger compound **1** formed nanostructures in suspension with an average diameter of 122 ± 11 nm, monochromophoric acridine **2** did not form any detectable colloidal species (Fig. 6(a)). Further experiments confirmed that **1** undergoes self-aggregation in different polar and apolar solvents.

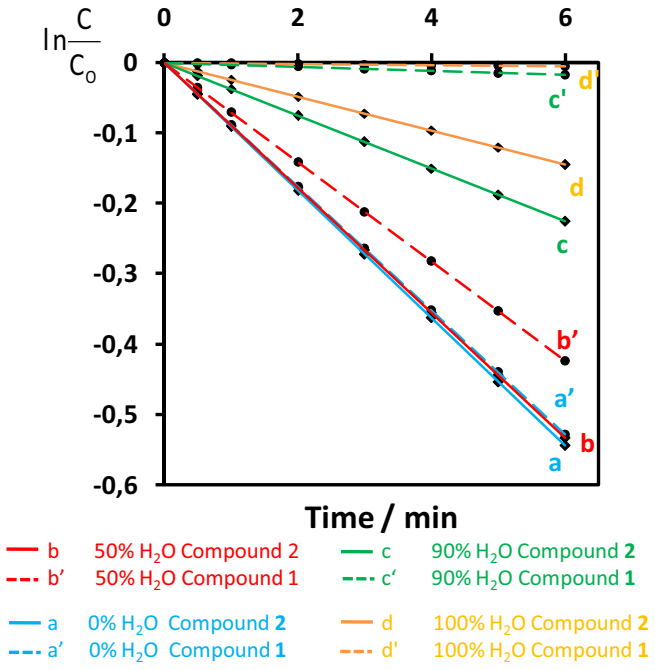


Fig. 4. Comparison of pseudo-first order linear fitting for the production of $^1O_2$ by **1** and **2** in different media (CH_3CN/H_2O).

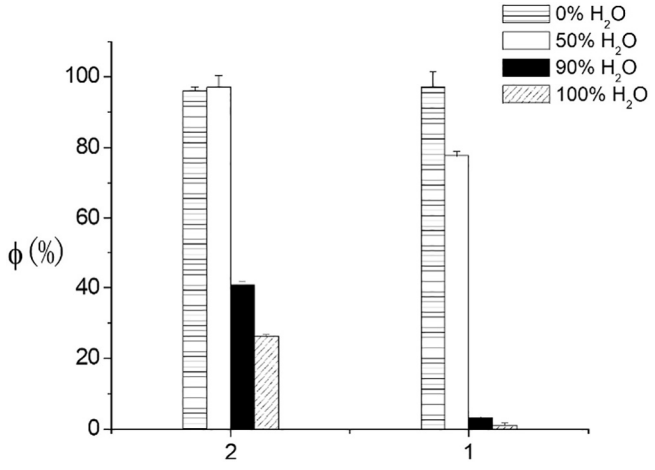


Fig. 5. $^1O_2$ generation quantum yield (ϕ_Δ) by compounds **2** and **1** in different media (CH_3CN/H_2O).

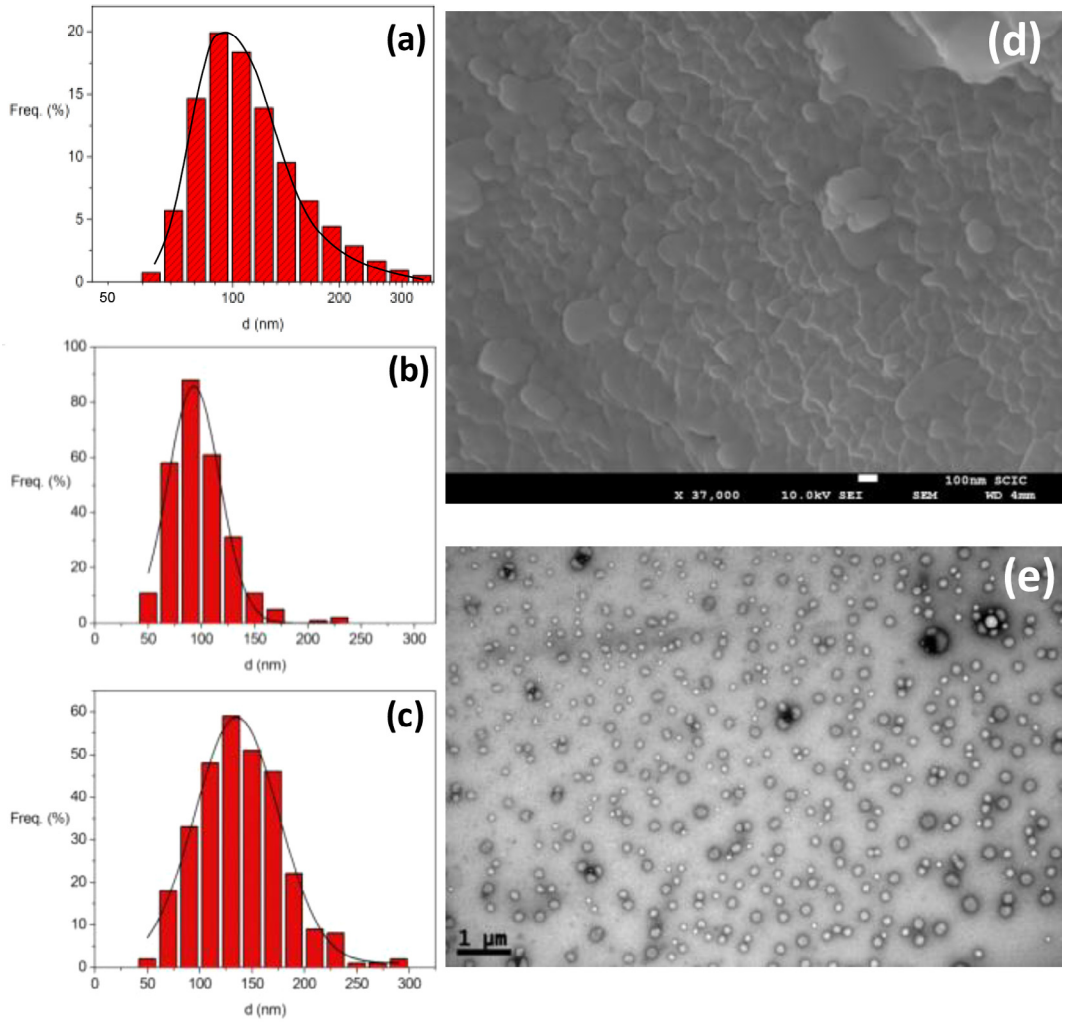


Fig. 6. (a) Representative DLS analysis of **1** aggregates; (b) SEM analysis of **1** aggregates; (c) TEM analysis of **1** aggregates; (d) SEM micrograph of **1**; (e) TEM micrograph of **1.**

Aggregates of bis-acridine compound **1** were also observed by electron microscopy (SEM and TEM) with average diameters of 93 ± 24 nm and 135 ± 40 nm, respectively (Fig. 6b–e).

This finding suggests that, upon aggregation, a competing pathway is favoured at the expense of energy transfer to triplet oxygen to yield $^1O_2$. This situation does not occur to the same extent in the non-aggregated photosensitizer **2**, which retains certain capacity to generate $^1O_2$ in aqueous medium.

Compounds **1** and **2** have also very different properties from the photobiological viewpoint. When Hep3B cells incubated with the compounds were irradiated with light of 365 nm, only **2** was capable of inducing some PDT effect. As it can be seen in Fig. 7, Hep3B cells were incubated for 1 h in the presence of **2** (10 μM) and then irradiated for 3 min. Propidium iodide (PI) was used to test the photodamage, monitored by means of confocal fluorescence laser scanning microscopy (CLSM). Cells stained with PI after irradiations would indicate dead or damaged cells. In the control cells (no photosensitizer added) the number of damaged or dead cells was very low (only several per field) meaning that the irradiation *per se* was not deleterious. However, the number of PI-positive cells was dramatically increased in the cell population that was irradiated after up-take of **2**, pointing to the existence of a particularly harmful effect on cell viability when the two stimuli (**2** + irradiation) were combined. The observed effect was confirmed by the quantitative assessment of PI fluorescence using fluorescence microscopy coupled with static cytometry (see Supporting information). While the presence of **2** without irradiation only slightly enhances the number of PI^+ cells (3.38% of the cells were PI positive after exposure to 20 μM **2** in comparison to 1.25% of the untreated cells), this number is notably higher when both stimuli are present and reaches the highest value with 20 μM of **2** (8.7%). For compound **1**, no induced photodamage was detected under the same experimental conditions. This observation confirms that aggregation must be avoided for photosensitizers based on acridine, at the designing stage, since this process hampers the generation of $^1O_2$. The negative effect of aggregation on the PDT activity is already well known for porphyrins and phthalocyanines, and efforts are devoted to the design of photosensitizers circumventing this process.[20] According to the observations here reported, the same kind of considerations should be taken into account when dealing with acridine-based photosensitizers.

Despite the lack of PDT activity of **1**, this compound apparently retains the DNA binding ability. MTT (3-4,5-dimethylthiazol-2-yl-2,5-diprenyl tetrazolium bromide) assays showed that exposure to **1** diminished cell viability in a concentration-dependent manner while exposure of **2** had no effect. The primary cell line Human umbilical vein endothelial cells (HUVEC) was slightly more susceptible than hepatoma cells Hep3B which is in line with previous reports of pharmacological toxicities using both cell models.[21] After 3 h exposure to the highest concentration of **1** employed,

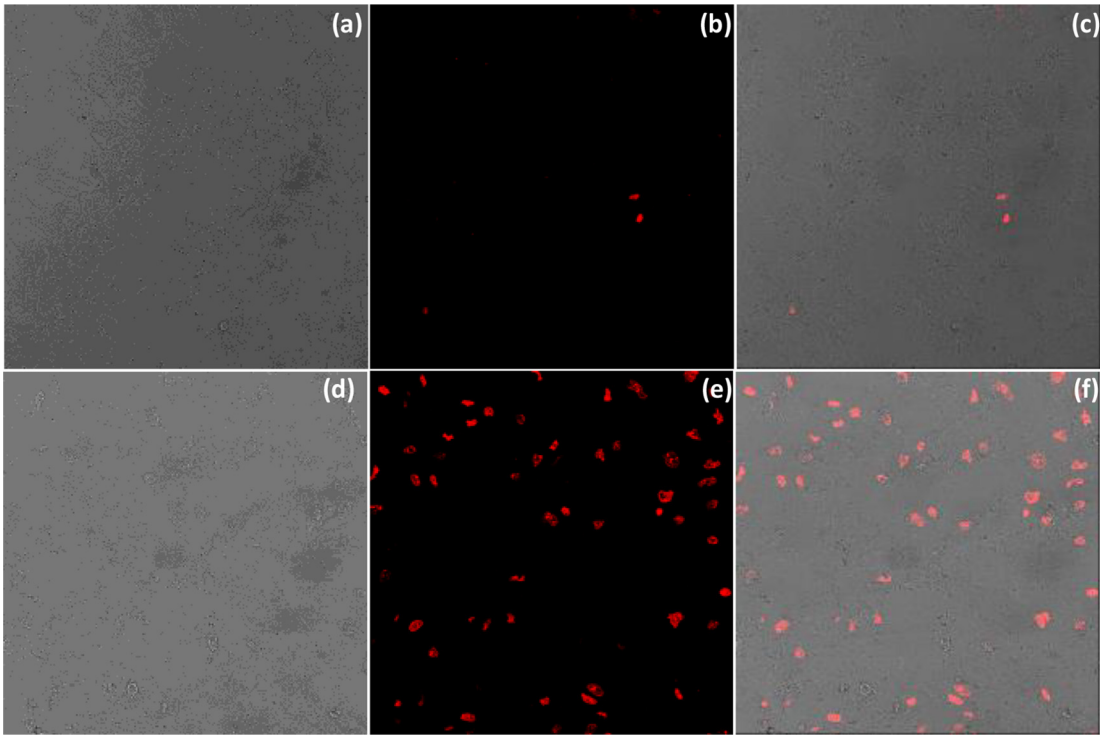


Fig. 7. CLSM images of Hep3B cells (30.000 cell/well) stained with propidium iodide used to mark damaged or dead cells (visualized in red color) (1 μM). Top row: Irradiated set of wells in absence of **2** (10 μM); (a) bright field; (b) PI fluorescence, λ_{ex} = 488 nm, $\Delta\lambda_{em}$ = 500–700 nm; (c) merged channels. Bottom row: Irradiated control set of wells in presence of **2**; (d) bright field; (e) PI fluorescence, λ_{ex} = 488 nm, $\Delta\lambda_{em}$ = 500–700 nm; (f) merged channels. Irradiation performed with UV lamp at 365 nm, 6 W, for 3 min. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

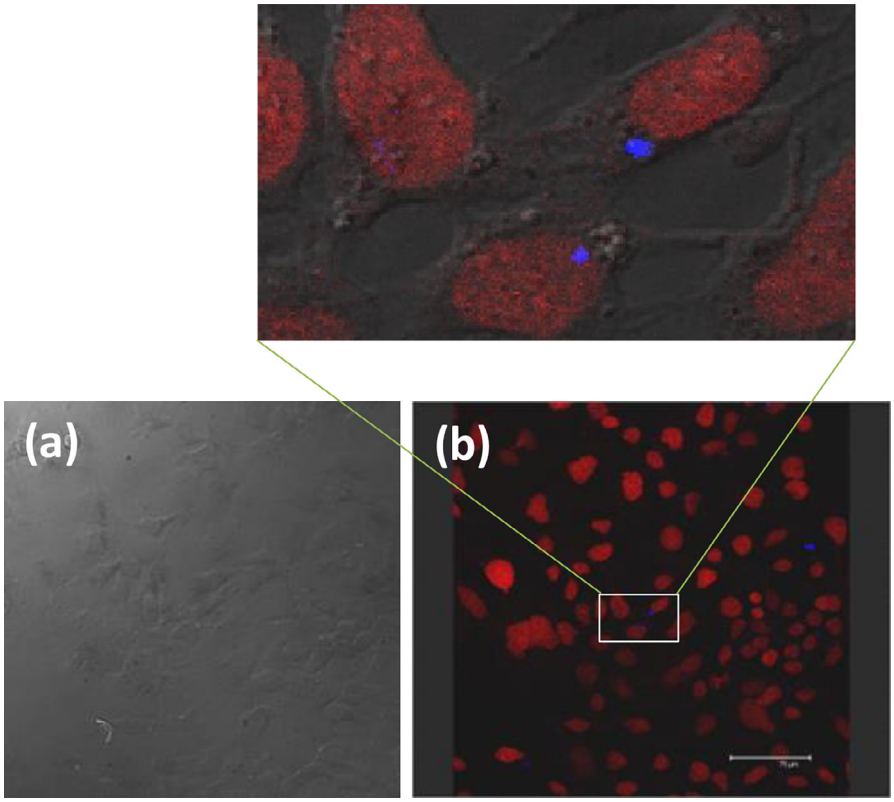


Fig. 8. CLSM images of Hep3B cells (30.000 cell/well) of **1** (10 μM) incubated for 1 h stained with Draq5 (1 μM). (a) Bright field; (b) Merged images of Draq5 fluorescence (nuclei stained in red) and **1** fluorescence (blue) sequentially acquired (**1** fluorescence, λ_{ex} = 405 nm, $\Delta\lambda_{em}$ = 410–550 nm, Draq5 fluorescence, λ_{ex} = 488 nm, $\Delta\lambda_{em}$ = 600–700 nm). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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the calculated IC_{50} was 29.5 μM for Hep3B cells and 18.62 μM for HUVEC. Of note, prolonged incubation (24 h) with **1** did not exacerbate the effect on cellular viability recorded after 3 h-exposure, in Hep3B cells. In HUVEC cells, the prolonged incubation did have a greater effect (46% and 27% vs control after 3 h- and 24 h-incubation respectively). Also, we observed the capacity of both cell lines to recover from exposure to **1** and **2** (21 h recovery after the 3 h-treatment, see Fig. S4 in the supporting information file). The calculated IC_{50} value lies within the range of reported toxicities of similar compounds. Thus, Kožurková et al. described antitumor and binding studies of acridine dialkyldiureas in HeLa and HCT-116 cell lines with an IC_{50} of 3.1 μM.[22] Analogously Arya et al. described several 9-aminoacridine derivatives showing IC_{50} on the 5–10 μM range in different cell lines: breast T47D, lung NCI-H522, colon HCT-15, ovary PA-1, liver HEPG2 and COS-1 cells.[23] This fact could be related to the best binding ability of bichromphoric acridines as compared to the monochromophoric ones.[6] Notably compound **2** is not toxic at concentrations lower than 20 μM.

The cellular uptake of compound **1** was examined by means of CLSM. As it can be seen in Fig. 8, the uptake and subcellular localization of compound **1** was studied by live cell confocal fluorescence microscopy using Hep3B cells. These experiments revealed that after 1 h of incubation with 10 μM of **1**, fluorescence can be visualized inside cells and tend to localize in the perinuclear area, often in association with the nuclear membrane (Fig. 8 inset). Co-localization experiments using organelle-specific fluorochromes failed to show correlation of **1** with any of the subcellular compartments studied: ER, mitochondria and lysosomes (data not shown).

In summary, the synthesis and chemical characterization of two new acridine derived compounds, one monochromophoric (**2**) and the other bichromophoric (**1**), has been presented. Photophysical and photobiological studies of these compounds have been carried out. Their ability to produce $^1O_2$ upon irradiation has been compared, focusing the attention on the influence of chemical structure. The synthesized compounds show very different self-aggregating properties since only the bichromophoric molecule (**1**) presents a strong tendency to aggregate in water, which blocks the ability to produce $^1O_2$. On the contrary, the non-aggregating molecule (**2**) still retains the $^1O_2$ production capacity, even in water (Φ_Δ = 0.263). In biological medium both compounds also show a distinct behaviour, probably due to their different self-aggregating properties. Thus, PDT studies were carried out with Hep3B cells which showed that only non-aggregated monochromophoric compound (**2**) has some efficiency after irradiation with UV light, probably due to production of $^1O_2$. Hence, it can be stated that aggregation influence the dynamics of the excited states of **1**, discarding its use as a PDT agent. Nevertheless, despite this lack of photoactivity, suspensions of this molecule, characterized as nano-sized aggregates, have notable antiproliferative activity in the dark, which opens the way for future studies on this class of compounds.

Acknowledgments

Ministerio de Economía y Competitividad of Spain (Grant CTQ2015-71004-R) and Universitat Jaume I (Grant P1.1B2015-76) are acknowledged for financial support. C.F.-L. thanks Ministerio de Economía y Competitividad of Spain for a FPI fellowship (CTQ2012-37735 and BES-2013-063296). Technical support from SCIC of University Jaume I is acknowledged.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmcl.2018.02.005.

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