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NOVEL CARBOHYDRAZIDE AND HYDRAZONE BIOMARKERS BASED ON 9-SUBSTITUTED ACRIDINE AND ANTHRACENE FLUOROGENS[†]

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Abstract – Three series of carbohydrazides or hydrazones bearing either acridine or anthracene pharmacophores were synthesized as potential noncovalent DNA-binding antitumor agents. Carbohydrazides with an acridine or anthracene moiety were prepared from appropriate acridine or anthracene carbaldehydes via cyclocondensation with selected hydrazides whilst hydrazones with a 10*H*-acridin-9-ylidene moiety were obtained by condensation of (acridin-9-yl)hydrazine with various aldehydes or ketones. The spectroscopic properties of the first two series revealed efficient fluorescence implying that the compounds could be amenable for use as biomarkers. The structures of the compounds were characterized by spectral methods (UV-vis, fluorescence, IR, and ¹H, ¹³C, and 2D NMR) and quantum-chemical calculations (DFT, ZINDO, and AM1). The first carbohydrazone series was also tested against human leukemia cell line HL-60 wherein the phenyl-substituted derivative was found to possess the highest activity.

[†] Dedicated to Prof. Emeritus Akira Suzuki on the occasion of his 80th birthday.

INTRODUCTION

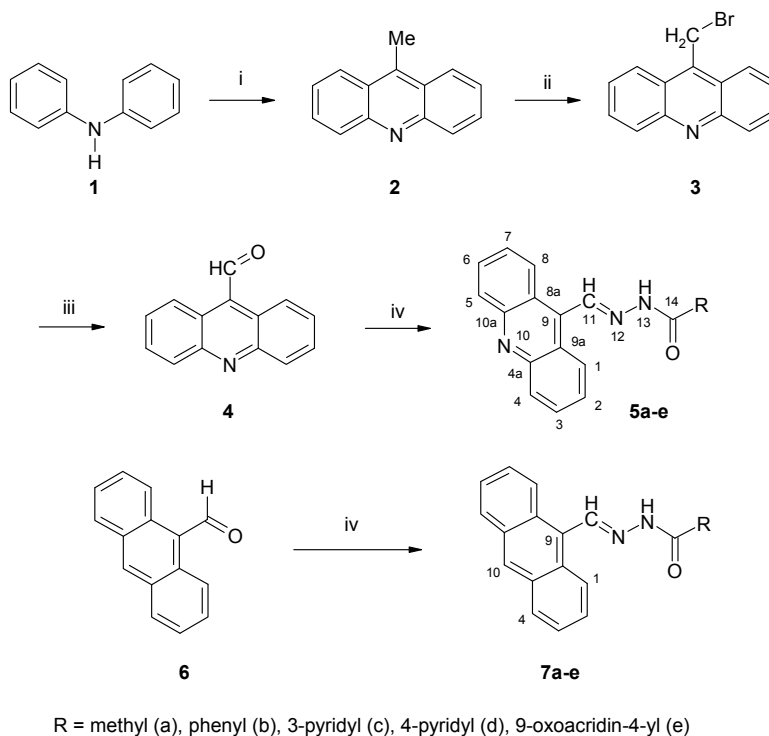
The chemistry and biological properties of acridines^{1–3}, especially their proclivity towards spiro–open-chain tautomerism^{1g–j} as well as intercalating^{1a–g}, fluorescent⁴, and antitumor activities⁵, have been the focal point of our research interest over two decades. Similarly too, because of their intercalating and fluorescent properties, we have paid attention to analogous anthracene substrates.⁶ Analogously, azomethines represent a class of compounds which are interesting not only from chemical^{1b} and spectroscopic² points of view, but also because they are the subject of biological and pharmaceutical research endeavors.^{7,8} Structural studies on the imine double bond of azomethines and ketimines have been conducted⁹ where the azomethines were found to occur as only one geometrical isomer whilst the ketimines were found to be present in the reaction mixture as two geometrical isomers. Recently, we have reported the physico-chemical properties of potentially intercalating 4-acridonecarboxamide imines.²

The aim of this contribution is to explore the effect of acridine vs. anthracene and the effect of substitution in the side-chain on the properties of analogous 9-substituted acridine/anthracene carbohydrazide and hydrazone compounds with respect to conjugation, prototropic tautomerism, intra- and interunit geometry, and spectral properties, in particular fluorescence, as well as their biological activities. The three series of novel carbohydrazides and hydrazones prepared here, together with a previous set,² afforded a comparison between the various permutations regarding the positional placement of the tricyclic aromatic system, i.e. the acridine or anthracene moiety, with respect to the substituent unit.

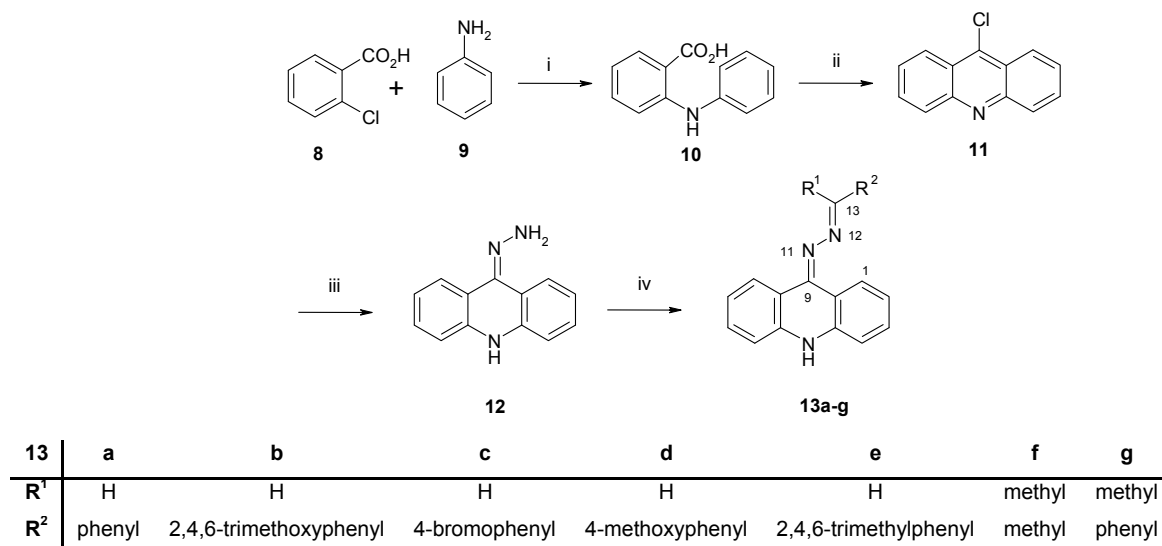
RESULTS AND DISCUSSION

Synthesis

The synthesis of the first series of carbohydrazides **5a–e** (Scheme 1) started from commercially available diphenylamine (**1**) giving, after modification of Bernthsen's reaction,¹⁰ 9-methylacridine (**2**). Following radical bromination of **2**, 9-bromomethylacridine (**3**) was obtained¹¹ and this provided (acridin-9-yl) carbaldehyde (**4**) after oxidation with sodium and 2-nitropropane.¹² Subsequent condensation with various hydrazides (methyl, **a**; phenyl, **b**; 3-pyridyl, **c**; 4-pyridyl, **d**; and (9-oxoacridin-4-yl), **e**) then yielded substituted *N*-(acridin-9-ylmethylene)hydrazides **5a–e** in yields up to 74%. Anthracenyl derivatives of the second series were prepared by the condensation of commercially available 9-anthraldehyde (**6**) with the same set of hydrazides to provide substituted *N*-(anthracen-9-ylmethylene)hydrazides **7a–e** in excellent yields up to 90%. The third series of disubstituted hydrazones of 9,10-dihydroacridine, together with two trisubstituted ones, were prepared as indicated in Scheme 2 starting from the Ullmann–Jourdan condensation of *o*-chlorobenzoic acid (**8**) and aniline (**9**) to provide *N*-phenylanthranilic acid (**10**). Compound **10** upon treatment with POCl₃ yielded



Scheme 1. Reaction sequence leading to carbohydrazide series **5a–e** and **7a–e**. Reagents and conditions: (i) ZnCl_2 , acetic acid, $190\text{ }^\circ\text{C}$; (ii) NBS, AIBN, CCl_4 , reflux; (iii) DMF, MeOH, Na, 2-nitropropane, rt; (iv) MeOH, H^+ , corresponding hydrazides, rt.



Scheme 2. Reaction sequence leading to hydrazone series **13a–g**. Reagents and conditions: (i) Cu, K_2CO_3 , 2-methoxyethanol, reflux; (ii) POCl_3 , reflux; (iii) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, MeOH, reflux; (iv) EtOH, H^+ , appropriate aldehyde or ketone, reflux.

9-chloroacridine (**11**), which then readily yielded (acridin-9-yl)hydrazine (**12**) by the application of hydrazine monohydrate. Disubstituted **13a–e** and trisubstituted 9-(alkyl/benzylidenehydrazono)-9,10-dihydroacridines **13f,g** were then prepared by condensation of **12** with a set of aldehydes and ketones (benzaldehyde, **a**; 2,4,6-trimethoxybenzaldehyde, **b**; 4-bromobenzaldehyde, **c**; 4-methoxybenzaldehyde, **d**; 2,4,6-trimethylbenzaldehyde, **e**; acetone, **f**; acetophenone, **g**) under acidic catalysis in yields of 41–93% for the **13a–e** and 38% and 42% for **13f,g**, respectively.

NMR spectroscopy

In general, the N-10 nitrogen located in the structural framework of the acridine moiety has an extremely strong tendency to retain a proton,^{1b,f,g,i–n,3,13} i.e. if tautomeric interchanges are possible, then the H-10 tautomer usually dominates and the predominance of the equilibrium can easily be ascertained by standard methods of appraisal (correlations and diagnostic NMR chemical shifts compared to previous reports^{1b,f–n,3}). Thus determination that the H-13 tautomer as depicted in Scheme 1 dominates over the H-10 tautomer for the compounds of the acridine series **5a–e** provides a rare exception^{1h} against this general rule, and despite the potential gain from the additional conjugation with the carbonyl double bond that would arise. The H-13 tautomeric structure permits free rotation about the C₉–C₁₁ bond and as a consequence the outer rings of the acridine moiety are rendered equivalent on the NMR timescale. Interestingly, the only two compounds of the three series to displayed two sets of signals in solution for a major and minor species, the first one, **5a**, in the integral intensity ratio 67 : 33 (Figure 1). Upon heating to 80° C the corresponding signals in the ¹H NMR spectrum started to coalesce but resumed their normal appearance upon lowering the temperature back to 25° C. It appears that this equilibrium is due to *E/Z* configurational interchange about the amide bond, i.e. geometrical isomerism, based on the chemical shift differences which exist only in the side-chain for these two species. The other derivatives

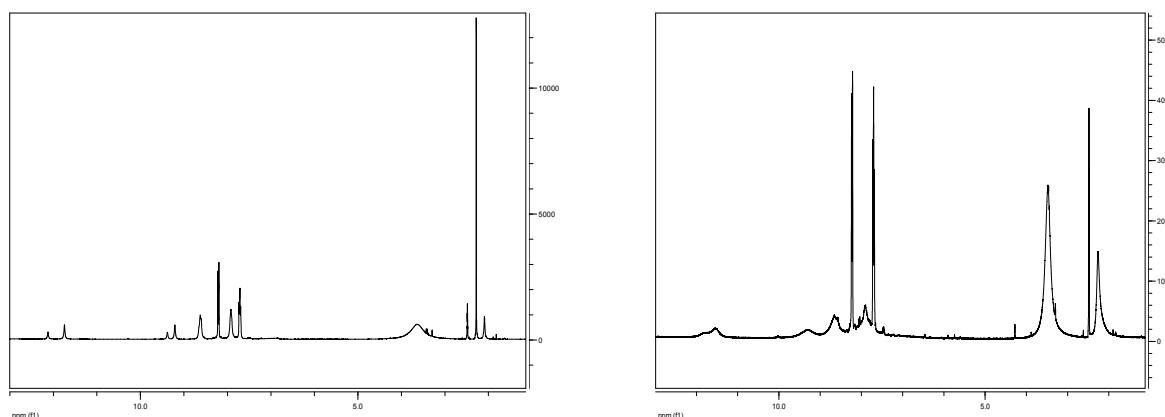


Figure 1. ¹H NMR spectrum of the compound **5a** at 25 °C (left) and 80 °C (right).

5b–e in the series and compounds **7b–e** in the second series are likely to be simply strongly biased in this respect and thus they exhibit only the one set of signals. The corresponding methyl-substituted derivative **7a** in the anthracene series also showed two species in the ratio 69 : 31, the minor one characterized by some typical chemical shifts with other signals overlapped by the signals of the major species.

For the predominant tautomeric structures of **5a–e**, there are two competing mechanisms for conjugation of the lone pair of the N-13 nitrogen atom (structure A, Figure 2). The NMR chemical shifts for C-9, C-11, and the carbonyl carbon C-14 as well as the chemical shifts of the protons in the side-chain are all strongly affected by these mechanisms, in particular if there is a dominant one in effect.

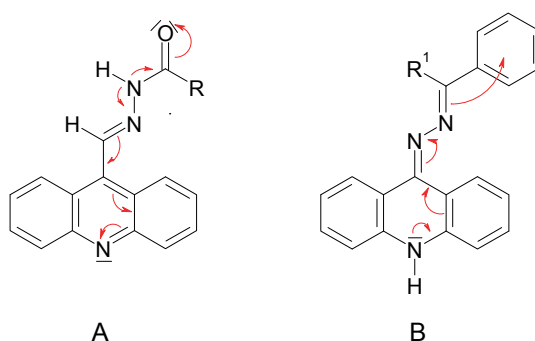


Figure 2. Structures showing the conjugation pathways in the first series for compounds **5a–e** (structure A) and the third series for compounds **13a–g** (structure B).

Conjugation of the considered lone pair with the carbonyl oxygen is affected by the substituents R attached to the carbonyl carbon whilst conjugation extending down into the tricyclic aromatic system is obviously determined to a large extent by whether an acridine or an anthracene moiety is present since replacement of the nitrogen atom N-10 in the acridinyl series by a carbon atom in the anthracenyl series will clearly mitigate any conjugation arising from the tricyclic aromatic system. Hence, comparison of the observed nuclear shifts in series **5a–e** with the analogous series **7a–e** should thus allude to any dominating mechanism. The pertinent chemical shifts presented in Table 1 are in accordance with the expected electronic character of the substituents. For example, the effect of the electron donating character of the methyl substituent in **5a** on carbon C-11 is unequivocal (138.9 ppm) whilst the electron accepting character of the 4-pyridinyl-substituent of **5d** (146.1 ppm) is also evident. Conversely, a reverse substituent effect is obvious for the carbonyl carbon C-14, cf. **5a**, 172.4 ppm and **5d**, 161.9 ppm, and this same effect is also observed for the acridinyl carbon C-9. While the chemical shifts of carbons C-4a and C-10a are affected only very slightly by the substituents, those of carbons C-8a and C-9a are not affected at all. The effects of the substituents on the chemical shifts of the amidic hydrogen H-13 are likewise in concert with the electronic character of the substituents, e.g. cf. **5a**, 11.79 ppm and **5d**, 12.56 ppm.

Table 1. Selected ^1H and ^{13}C NMR chemical shifts of compounds **5a–e**, **7a–e**, and **13a–g**

Cmpd	H-10	H-11	H-13	C-9	C-10	C-11	C-13	C-14
5a , major	–	9.25	11.79	136.8	–	138.9	–	172.4
5a , minor	–	9.42	12.16	– ^a	–	142.0	–	166.2
5b	–	9.69	12.35	134.6	–	144.8	–	163.4
5c	–	9.85	12.96	137.9	–	144.9	–	161.8
5d	–	9.68	12.56	134.3	–	146.1	–	161.9
5e	–	9.75	12.70	– ^a	–	145.9	–	162.7
7a , major	8.70	9.21	11.47	125.1	129.1	141.4	–	171.9
7a , minor	8.64	9.34	11.69	– ^a	– ^a	144.5	–	165.6
7b	8.74	9.71	12.14	125.0	129.6	146.9	–	163.0
7c	8.73	9.69	12.34	124.5	129.8	147.7	–	161.7
7d	8.75	9.70	12.34	124.7	129.9	148.3	–	161.5
7e	8.75	9.76	12.47	124.5	130.1	148.3	–	163.9
13a	10.83	–	8.55	149.8	–	–	154.4	–
13b	10.60	–	8.80	148.8	–	–	150.9	–
13c	10.89	–	8.53	149.9	–	–	153.1	–
13d	10.73	–	8.48	149.2	–	–	154.3	–
13e	10.78	–	8.87	149.6	–	–	155.6	–
13f	10.43	–	–	144.2	–	–	158.0	–
13g	10.68	–	–	145.5	–	–	155.8	–

^a Not detected.

Similar substituent effects are also manifested in the anthracene series **7a–e**. For example, the chemical shift of C-14, cf. **7a**, 171.9 ppm and **7d**, 161.5 ppm, are comparable to the comparison of **5a**. The evident slight difference between the two series is due to the electron accepting character of the N-10 nitrogen atom in acridine compared to the C-10 carbon atom in the anthracene unit.

Thus, from the chemical shift values, it can be concluded that there is an efficient transfer mechanism of electronic effects from the substituents throughout the molecules in these two series of compounds **5a–e** and **7a–e** but it appears there is considerable participation from both mechanisms with neither dominating.

In the case of derivatives **13a–g**, the values of various diagnostic ^{13}C NMR chemical shifts (e.g. C-4a and C-10a, 138–142; C-8a and C-9a, 114–120; and, in particular,^{1i,3} C-4 and C-5, 115–116 ppm) in comparison to previous reports^{1b,f–n,3} clearly indicate that the dihydroacridine structure of the acridine moiety is predominant, i.e. the H-10 tautomer dominates over the H-11 tautomer. For the H-10 tautomer,

interchange between the conformers is slow and as a consequence the outer rings of the acridine moiety are rendered inequivalent on the NMR timescale.

The conjugation between the acridine unit, emanating from the nitrogen heteroatom, and the side-chain is mitigated by the substituents R^1 and R^2 with the phenyl substituents aiding conjugation whilst the methyl substituents in ketimines **13f,g** reduce this conjugation by their inductive effects. These inductive effects manifest themselves on the chemical shift of the carbon of the azomethine group ($C=N$) with some deshielding evident for C-13 in **13g** (phenyl and methyl substituents present) and with greater deshielding for C-13 in **13f** (two methyl substituents present). Conversely, there is some shielding observed for C-9 in **13g** in comparison to the very consistent values for aldimines **13a–e** (149–150 ppm) with greater deshielding evident for the carbon atom C-9 in **13g**. The aiding of conjugation by the phenyl substituents was also evident from the UV spectra (vide infra).

UV-vis absorption spectroscopy

Electronic absorption spectra of compounds **5a–d**, **7a–e**, and **13a–g** measured in methanol are presented in Table 2. Compounds **5a–d** exhibited broad absorption bands with their principal maxima lying in the range 363–367 nm together with a shoulder in the range 402–407 nm. Compounds **7a–d** each displayed only a clear single band in the range 386–413 nm whilst compounds **13a–g** each displayed a long wavelength maximum in the range 406–441 nm together with one or more two bands at ca. 320 and 280 nm. These absorbances are characteristic for $n \rightarrow \pi^*$ transitions and the long wavelength maxima of compounds **13** are shifted to longer wavelengths compared to series **5a–d** and **7a–e** as a consequence of extended conjugation (cf. Figure 2).

In compounds **5a–d**, the positions of the absorption maxima are only slightly influenced by the nature of the substituents (Figure 3) whereas by comparison the changes were more notable for **7a–e** and **13a–g** (Table 2). The largest bathochromic shift was observed for **13c** due to the presence of the 4-bromophenyl substituent which not only extends the conjugation by way of the phenyl unit, but the large effect of which could be attributed also to the electron accepting character of the bromine atom. On the other hand, the shorter conjugation system due to the absence of the phenyl ring in **13f** was confirmed by a distinct hypsochromic shift of the long wavelength maximum to 406 nm.

Conjugation and transitions in the UV-vis spectra for the phenyl-substituted compounds **5b**, **7b**, and **13a** were interpreted by orbital analysis using the semiempirical ZINDO method on structures optimized by DFT at the B3LYP/6-311+G(d,p) level of theory. From the orbitals depicted in Figure 4 it follows that the HOMO and LUMO represent net π and π^* orbitals and these contribute strongly to the conjugation of the acridine moiety and the side-chain. Intriguingly, the phenyl substituent in **5b** and **7b** does not participate in the extended conjugation in contrast to **13a** where the phenyl substituent does appear to participate.

Table 2. UV-vis absorption maxima^a of compounds **5a–d**, **7a–e**, and **13a–g**

Cmpd	λ_{max} (nm)	Absorb.	$\log \epsilon$	Cmpd	λ_{max} (nm)	Absorb.	$\log \epsilon$
5a	402	0.246	4.71	7e	386	0.216	4.65
	363	0.337	4.85				
5b	407	0.224	4.67	13a	434	0.479	5.00
	367	0.273	4.75		323	0.258	4.73
5c					275	0.438	4.96
	407	0.192	4.60	13b	436	0.630	5.12
	360	0.229	4.68		325	0.369	4.89
5d	284	0.241	4.70		290	0.433	4.96
	402	0.173	4.56	13c	441	0.526	5.04
7a	367	0.205	4.63		275	0.487	5.01
				13d	434	0.580	5.08
7b	395	0.408	4.93		320	0.372	4.89
					275	0.505	5.02
7c	411	0.200	4.62	13e	434	0.419	4.94
					326	0.246	4.71
7d	413	0.372	4.89		289	0.297	4.79
				13f	406	0.441	4.96
7e	390	0.444	4.97		288	0.419	4.94
				13g	421	0.417	4.94
					275	0.459	4.98

^a In methanol at 24 °C; conc., 4.8×10^{-6} M.

In the case of **5b**, the contribution to the absorbance band of the lone electron pair of N-10 in the acridine moiety is via the HOMO-4 and HOMO-5 orbitals. A similar contribution by the analogous lone pair in **13a** was not found and it participates via the π (and π^* accordingly) HOMO, HOMO-1, HOMO-2, and LUMO orbitals.

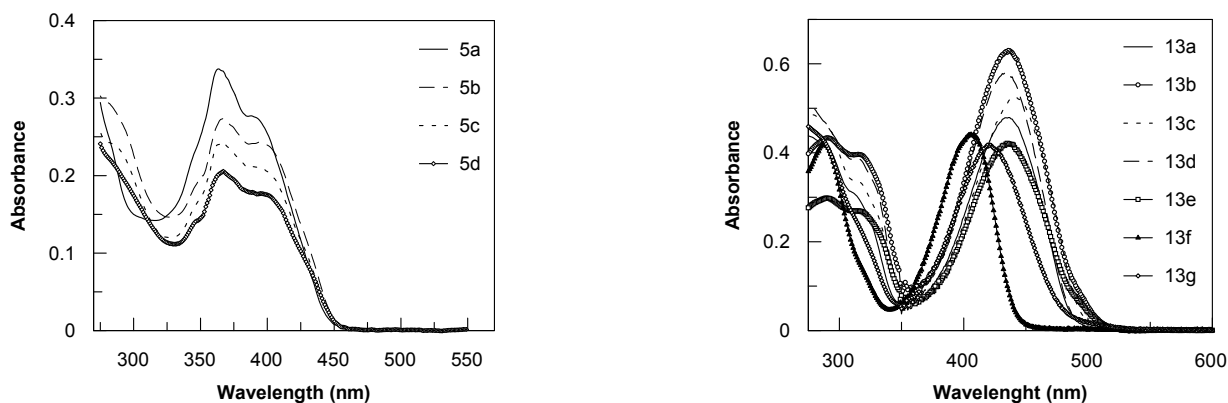


Figure 3. UV-vis spectra of compounds **5a–d** (left) and **13a–g** (right) (in methanol at 24 °C; conc., 4.8×10^{-6} M).

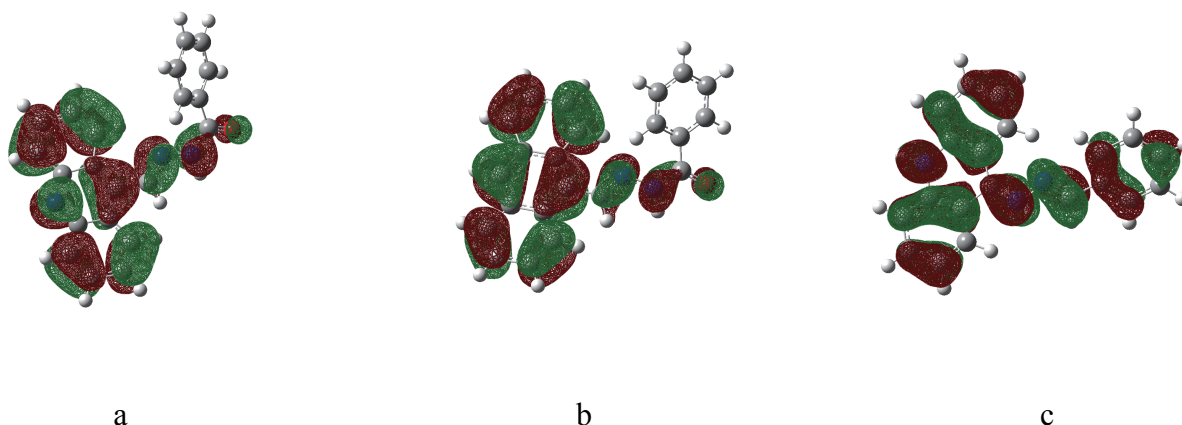


Figure 4. HOMO of derivatives **5b** (a), **7b** (b), and **13a** (c).

Fluorescence emission spectroscopy

Due to the planar aromatic units they contain, acridine and anthracene derivatives express unique chemical and physical properties with substitution at the C-9 position able to improve their luminescent properties.¹⁴ Fluorescence emission spectra taken in methanol of compounds **5a–d**, **7a–d**, and **13b,c** were recorded at excitation wavelengths corresponding to their absorbance maxima. It can be seen from Figure 5 that compounds **5a–d** each had one emission maximum in the range 479–482 nm but that of the reference compound 9-isothiocyanatoacridine (acridine-ITC) exhibited three emission peaks at 479, 457, and 429 nm (Table 3). The highest fluorescence observed, that for derivative **5c**, is almost 14-fold higher by comparison to acridine-ITC, a compound known as a fluorescence marker for amino and thiol groups present in biomacromolecules.¹⁵ The fluorescence emission spectra of compounds **4**, **7a–d**, **13b,c**, and the reference compound acridine are summarized in Table 4 wherein it can be seen that prepared compounds

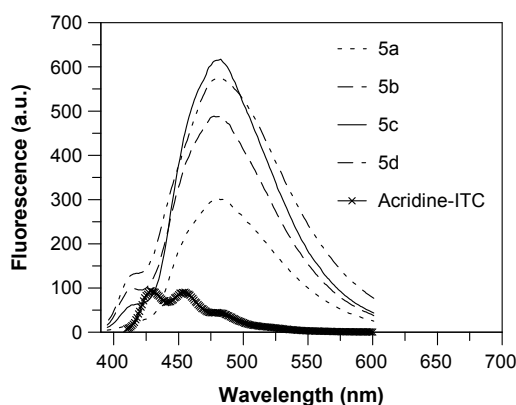


Figure 5. The emission fluorescence spectra of compounds **5a–d** and 9-isothiocyanatoacridine (acridine-ITC) in methanol at 24 °C (conc., 6.0×10^{-6} M).

Table 3. Fluorescence spectral data for **5a–d** and 9-isothiocyanatoacridine (acridine-ITC)

Compound	λ_{em} (nm)	F (a.u.)	F/F_o^a
5a	479	299.14	6.72
5b	482	487.49	10.95
5c	482	615.02	13.82
5d	480	575.51	12.92
acridine-ITC	479, 457, 429	44.51, 84.5, 97.66	1.00

^a Relative fluorescence related to fluorescence of a long wavelength maximum of 6.0×10^{-6} M solution of acridine-ITC in methanol, slit width 10 nm.

Table 4. Fluorescence spectral data for **4**, **7a–d**, **13b,c**, and acridine

Compound	λ_{em} (nm)	F (a.u.)	F/F_o^a
4	427	305.33	3.24
7a	459	341.43	3.63
7b	477	97.28	1.03
7c	478	242.00	2.57
7d	485	206.70	2.20
13b	510	16.96	0.18
13c	501	57.78	0.61
acridine	418	94.15	1.00

^a Relative fluorescence related to fluorescence maximum of 6.0×10^{-6} M solution of acridine in methanol, slit width 20 nm.

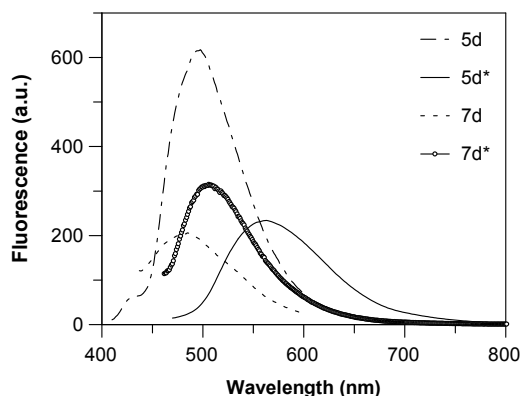


Figure 6. The emission fluorescence spectra of compounds **5d** and **7d** (in methanol at 24 °C; conc., 6.0×10^{-6} M) and their excimer species **5d*** and **7d*** (in methanol at 24 °C; conc., 3.8×10^{-3} M).

excepting **13b,c** exhibited stronger fluorescence than the reference. For samples of varying concentration, the observation of a non-linear concentration dependence of fluorescence is an indication of a change in the oligomeric state of a fluorogen with the most common oligomeric forms of fluorogens, J-aggregates

and excimers, evident by the sharpening of their absorbance spectra and broad red-shifted fluorescence, respectively.¹⁶ At high concentration, 3.8×10^{-3} M, a red-shifted fluorescence ca. 40–70 nm was observed for the acridine derivative **5d** as well as for the analogous anthracene derivative **7d** (Figure 6) but, notably, without any significant perturbations in their absorbance spectra. These changes in the fluorescence spectra are thus ascribed^{15,16} to the formation of excimer species for these two compounds (**5d*** and **7d***, respectively).

The observed reduced fluorescence in **13b,c** and its underlying cause is of interest and the explanation may lie in the structural differences between the ground and the first excited states. For the DFT-optimized structures at the B3LYP/6-311+G(d,p) level of theory of the methyl-substituted derivatives **5a** and **7a**, amongst the probable structures, the most preferable were found to be the *E,E*-configurations (Figure 7a,b) where the HC=N–N–C=O segment is also planar. By contrast, whilst the acridine and anthracene moieties in **5a** and **7a**, respectively, are perfectly planar, the dihydroacridine moiety in the dimethyl-substituted derivative **13f** is considerably deformed (Figure 7c) and no longer forms an ideal plane and instead it forms a shallow and a slightly twisted butterfly conformation folded about the C-9···N-10 axis. This has been confirmed by X-ray analysis in the case of spiroacridine and acridinium derivatives containing a dihydroacridine ring.¹⁷ The calculated first excited state (Figure 7d), however, is essentially planar and thus the supposition that the structural differences between the ground and the first excited states may limit the ability for fluorescence to occur appears to be valid.

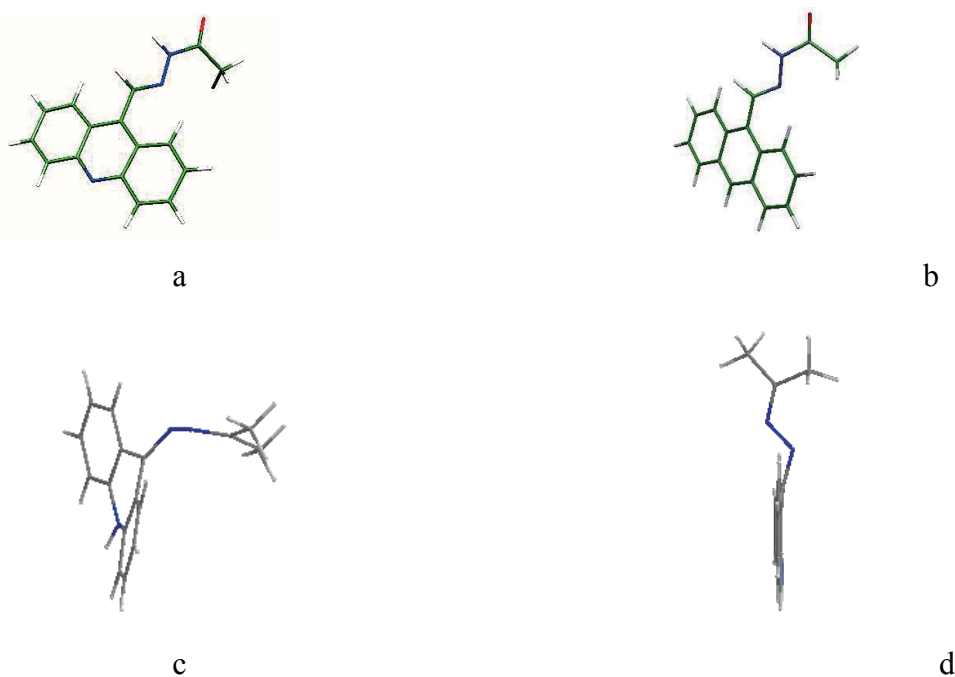


Figure 7. Optimized structures of **5a** (a) and **7a** (b) calculated by DFT at the B3LYP/6-311+G(d,p) level of theory and **13f** in the ground state (c) and in the first excited state (d) as by provided by AM1 calculations.

Biological activities

To evaluate the biological activity potential of the compounds, preliminary investigations were conducted by testing compounds **5a–d** for their cytotoxic effect against human leukemia cell line HL-60. From the concentrations that produced 25% inhibition (IC_{25}) of cell viability (Table 5), it is evident that the tested

Table 5. Cytotoxic effect of compounds **5a–d** on the human leukemia cell line HL-60 cells

Compound	5a	5b	5c	5d
IC_{25} (μ M)	10.5 ± 1.2	1.0 ± 1.3	2.0 ± 0.8	5.6 ± 0.5
IC_{50} (μ M)	> 1000	100 ± 2.5	> 1000	> 1000

derivatives do clearly possess mild cytotoxic properties wherein the most significant activity was observed for the phenyl-substituted derivative **5b**. A more than 100-fold increase of IC_{50} compared to IC_{25} in all studied compounds evidences undoubtedly a good HL-60 cell reparation at higher concentrations of **5**. This can be ascribed either to a hampered incorporation of **5** into tumor cells nuclei due to a binding into other cell organelles or an induction of a repair cell mechanisms. For example, enzymatic pathways enhancing the synthesis of low-molecular intracellular thiols as glutathione (GSH), which can interact by its thiol group with studied derivatives to protect DNA, were proven in a similar case.¹⁸ The protection extent may be high when glutathione is bound to strongly intercalating compound.

EXPERIMENTAL

General

Melting points were determined on a Boetius block and are uncorrected. Elemental analyses were performed using a Perkin–Elmer CHN 2400 analyzer. IR spectra were recorded on a Nicolet 6700 FT IR instrument.

NMR spectra were obtained at room temperature in hexadeuteriodimethyl sulfoxide ($DMSO-d_6$) using a Varian Mercury Plus NMR spectrometer operating at 400.13 MHz for 1H and 100.61 MHz for ^{13}C . Tetramethylsilane was used as an internal standard for both 1H and ^{13}C nuclei ($\delta_{TMS} = 0.00$ ppm for both). NMR chemical shift assignments were rendered by standard application of 1-D and 2-D correlation spectra wherein heteronuclear HSQC and HMBC experiments were optimized on 145 Hz for one-bond couplings and on 8 Hz for long-range couplings. Full descriptions of the NMR methodology have been described elsewhere.^{2,3,19,20}

UV-vis spectra were measured on a Varian Cary 100 UV-vis spectrophotometer in 0.01 M Tris buffer (pH 7.4). The working concentration of all compounds was 4.8×10^{-6} M. All measurements were performed at 24 °C.

Fluorescence measurements were scanned on a Varian Cary Eclipse spectrofluorimeter. The excitation and emission slits were 10 nm for compounds **5a–d** and 9-isothiocyanatoacridine and 20 nm for compounds **4**, **7a–d**, **13b,c** and acridine. Emission spectra were recorded in the range 350–600 nm at concentrations of 6.0×10^{-6} and 3.8×10^{-3} M. The excitation wavelengths, λ_{ex} , were: **4**, 400; **5a–d**, 384; **7a**, 388; **7b**, 434; **7c**, 394; **7d**, 397; **13b**, 436; **13c**, 440; acridine, 355; and 9-isothiocyanatoacridine, 400 nm. Fluorescence intensities are expressed in arbitrary units. All measurements were performed at 24 °C. Semiempirical AM1 calculations²¹ were first performed to obtain the input geometries for DFT calculations at the B3LYP/6-311+G(d,p) level of theory²² using Gaussian03 software.²³ UV spectra were analyzed using the semiempirical ZINDO method.²⁴

(Acridin-9-yl)carbaldehyde (4)

Compound **4** was prepared according to literature methodology starting from commercially available diphenylamine **1** giving, after modification of Bernthsen's reaction,¹⁰ 9-methylacridine (**2**). Following radical bromination of **2**, 9-bromomethylacridine (**3**) was obtained¹¹ which then provided (acridin-9-yl)carbaldehyde (**4**) after oxidation using sodium and 2-nitropropane.¹²

General procedure for the preparation of carbohydrazides 5a–e

To a solution of the appropriate hydrazide (1.46 mmol) in anhydrous methanol, one drop of conc. aq. HCl and (acridin-9-yl)carbaldehyde (**4**, 1.47 mmol) was added. The reaction mixture was left to stir ca. 3½ h at rt until a precipitate had formed. The precipitate was filtered off, washed with methanol and then dried followed by recrystallization from methanol.

N'-(Acridin-9-ylmethylene)acetohydrazide (5a). Yield 59%; mp 244–247 °C; IR (KBr) ν : 3211 (NH), 3076 (CH_{arom}), 1668 (C=O), 1633 (C=N) cm^{-1} . *Major species*: ^1H NMR δ : 11.79 (s, 1H, NH), 9.25 (s, 1H, H-11), 8.67 (m, 2H, H-1,8), 8.25 (d, 2H, H-4,5, $J = 8.4$ Hz), 7.96 (m, 2H, H-3,6), 7.76 (m, 2H, H-2,7), 2.32 (s, 3H, CH_3); ^{13}C NMR δ : 172.4 (C-14), 146.7 (C-4a,10a), 138.9 (C-11), 136.8 (C-9), 131.4 (C-3,6), 128.0 (C-4,5), 127.3 (C-2,7), 125.3 (C-1,8), 123.3 (C-8a,9a), 20.4 (CH_3). *Minor species*: ^1H NMR δ : 12.16 (s, 1H, NH), 9.42 (s, 1H, H-11), 8.67 (m, 2H, H-1,8), 8.25 (d, 2H, H-4,5, $J = 8.4$ Hz), 7.96 (m, 2H, H-3,6), 7.76 (m, 2H, H-2,7), 2.13 (s, 3H, CH_3); ^{13}C NMR δ : 166.2 (C-14), 142.0 (C-11), 21.7 (CH_3); Anal. Calcd For $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}$ (263.30): C, 72.99; H, 4.98; N, 15.96. Found: C, 72.61; H, 5.07; N, 15.75%.

N'-(Acridin-9-ylmethylene)benzohydrazide (5b). Yield 43%; mp 262–264 °C; IR (KBr) ν : 3213 (NH), 3057 (CH_{arom}), 1647 (C=O), 1601 (C=N) cm^{-1} ; ^1H NMR δ : 12.35 (s, 1H, NH), 9.69 (s, 1H, H-11), 8.78 (d, 2H, H-1,8, $J = 7.2$ Hz), 8.23 (d, 2H, H-4,5, $J = 8.4$ Hz), 8.06 (m, 2H, H-2',6'), 7.91 (m, 2H, H-3,6), 7.75

(m, 2H, H-2,7), 7.68 (m, 1H, H-4'), 7.64 (m, 2H, H-3',5'); ^{13}C NMR δ : 163.4 (C-14), 148.4 (C-4a,10a), 144.8 (C-11), 134.6 (C-9), 133.0 (C-1'), 132.2 (C-4'), 130.3 (C-3,6), 129.8 (C-4,5), 128.7 (C-3',5'), 127.7 (C-2',6'), 127.2 (C-2,7), 125.3 (C-1,8), 123.4 (C-8a,9a); Anal. Calcd For $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}$ (325.37): C, 77.52; H, 4.65; N, 12.91. Found: C, 77.31; H, 4.87; N, 12.65%.

N'-(Acridin-9-ylmethylene)nicotinohydrazide (5c). Yield 64%; mp 263–266 °C; IR (KBr) ν : 3209 (NH), 3063 (CH_{arom}), 1651 (C=O), 1620 (C=N) cm^{-1} ; ^1H NMR δ : 12.96 (s, 1H, NH), 9.85 (s, 1H, H-11), 9.30 (s, 1H, H-2'), 8.87 (m, 1H, H-6'), 8.82 (d, 2H, H-1,8, $J = 8.8$ Hz), 8.52 (d, 1H, H-4', $J = 6.4$ Hz), 8.29 (d, 2H, H-4,5, $J = 8.8$ Hz), 8.02 (m, 2H, H-3,6), 7.81 (m, 2H, H-2,7), 7.70 (m, 1H, H-5'); ^{13}C NMR δ : 161.8 (C-14), 152.3 (C-6'), 148.5 (C-2'), 145.6 (C-4a,10a), 144.9 (C-11), 137.9 (C-9), 136.2 (C-4'), 132.2 (C-3,6), 128.7 (C-3'), 127.6 (C-2,7), 126.9 (C-4,5), 125.7 (C-1,8), 123.9 (C-5'), 123.4 (C-8a,9a); Anal. Calcd For $\text{C}_{20}\text{H}_{14}\text{N}_4\text{O}$ (326.36): C, 73.61; H, 4.32; N, 17.17. Found: C, 74.01; H, 4.09; N, 16.75%.

N'-(Acridin-9-ylmethylene)isonicotinohydrazide (5d). Yield 74%; mp 249–252 °C; IR (KBr) ν : 3257 (NH), 3072 (CH_{arom}), 1678 (C=O), 1632 (C=N) cm^{-1} ; ^1H NMR δ : 12.56 (s, 1H, NH), 9.68 (s, 1H, H-11), 8.87 (d, 2H, H-2',6', $J = 4.8$ Hz), 8.73 (d, 2H, H-1,8, $J = 8.4$ Hz), 8.22 (d, 2H, H-4,5, $J = 8.8$ Hz), 7.95 (d, 2H, H-3',5', $J = 4.8$ Hz), 7.91 (m, 2H, H-3,6), 7.74 (m, 2H, H-2,7); ^{13}C NMR δ : 161.9 (C-14), 150.5 (C-2',6'), 148.3 (C-4a,10a), 146.1 (C-11), 140.1 (C-4'), 134.3 (C-9), 130.3 (C-3,6), 129.8 (C-4,5), 127.3 (C-2,7), 125.2 (C-1,8), 123.4 (C-8a,9a), 121.6 (C-3',5'); Anal. Calcd For $\text{C}_{20}\text{H}_{14}\text{N}_4\text{O}$ (326.36): C, 73.61; H, 4.32; N, 17.17. Found: C, 73.97; H, 4.02; N, 16.57%.

N'-(Acridin-9-ylmethylene)-9-oxo-9,10-dihydroacridine-4-carbohydrazide (5e). Yield 28%; mp 331–334 °C; IR (KBr) ν : 3275 (NH), 3066 (CH_{arom}), 1647 (C=O_{acridone}), 1616 (C=O_{amide}), 1587 (C=N) cm^{-1} ; ^1H NMR δ : 12.70 (s, 1H, NH), 11.92 (s, 1H, H-10'), 9.75 (s, 1H, H-11), 8.87 (d, 2H, H-1,8, $J = 8.8$ Hz), 8.57 (d, 1H, H-1', $J = 7.6$ Hz), 8.47 (d, 1H, H-3', $J = 7.6$ Hz), 8.27 (m, 3H, H-4,5,8'), 7.94 (m, 2H, H-3,6), 7.92 (m, 1H, H-5'), 7.79 (m, 3H, H-2,7,6'), 7.50 (m, 1H, H-2'), 7.35 (m, 1H, H-7'); ^{13}C NMR δ : 176.4 (C-9'), 162.7 (C-14), 145.9 (C-11), 134.0 (C-6'), 133.6 (C-3'), 130.8 (C-1'), 130.3 (C-3,6), 129.8 (C-4,5), 127.3 (C-2,7), 125.7 (C-8'), 125.1 (C-1,8), 121.8 (C-7'), 119.9 (C-2'), 118.6 (C-5'); Anal. Calcd For $\text{C}_{28}\text{H}_{18}\text{N}_4\text{O}_2$ (442.48): C, 76.01; H, 4.10; N, 12.66. Found: C, 76.28; H, 4.27; N, 12.25%.

General procedure for the preparation of carbohydrazides 7a–e

To a solution of the appropriate hydrazide (1.46 mmol) in anhydrous methanol, one drop of conc. aq. HCl and 9-anthraldehyde (**6**, 1.47 mmol) was added. The reaction mixture was stirred ca. 3½ h at rt. The precipitate that had formed was filtered off, washed with methanol and dried followed by recrystallization

from methanol.

N'-(Anthracen-9-ylmethylene)acetohydrazide (7a). Yield 85%; mp 231–235 °C; IR (KBr) ν : 3199 (NH), 3066 (CH_{arom}), 1666 (C=O), 1624 (C=N) cm⁻¹; *Major species*: ¹H NMR δ : 11.47 (s, 1H, NH), 9.21 (s, 1H, H-11), 8.70 (s, 1H, H-10), 8.59 (d, 2H, H-1,8, J = 8.4 Hz), 8.15 (d, 2H, H-4,5, J = 8.4 Hz), 7.65 (m, 2H, H-2,7), 7.58 (m, 2H, H-3,6), 2.28 (s, 3H, CH₃); ¹³C NMR δ : 171.9 (C-14), 141.4 (C-11), 130.8 (C-4a,10a), 129.4 (C-8a,9a), 129.1 (C-10), 128.9 (C-4,5), 127.0 (C-2,7), 125.4 (C-3,6), 125.1 (C-9), 124.5 (C-1,8), 20.4 (CH₃); *Minor species*: ¹H NMR δ : 11.69 (s, 1H, NH), 9.34 (s, 1H, H-11), 8.64 (s, 1H, H-10), 2.08 (s, 3H, CH₃); ¹³C NMR δ : 165.6 (C-14), 144.5 (C-11), 21.7 (CH₃). Anal. Calcd For C₁₇H₁₄N₂O (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.42; H, 5.07; N, 10.45%.

N'-(Anthracen-9-ylmethylene)benzohydrazide (7b). Yield 90%; mp 279–282 °C; IR (KBr) ν : 3219 (NH), 3061 (CH_{arom}), 1647 (C=O), 1622 (C=N) cm⁻¹; ¹H NMR δ : 12.14 (s, 1H, NH), 9.71 (s, 1H, H-11), 8.79 (d, 2H, H-1,8, J = 8.4 Hz), 8.74 (s, 1H, H-10), 8.17 (d, 2H, H-4,5, J = 8.0 Hz), 8.06 (d, 2H, H-2',6', J = 7.2 Hz), 7.69–7.58 (m, 7H, H-2,3,6,7,3'-5'); ¹³C NMR δ : 163.0 (C-14), 146.9 (C-11), 133.3 (C-1'), 131.8 (C-4'), 130.9 (C-4a,10a), 129.6 (C-10), 129.6 (C-8a,9a), 128.9 (C-4,5), 128.5 (C-2,7), 127.6 (C-2',6'), 127.1 (C-3',5'), 125.5 (C-3,6), 125.0 (C-9), 124.8 (C-1,8); Anal. Calcd For C₂₂H₁₆N₂O (324.38): C, 81.46; H, 4.97; N, 8.64. Found: C, 81.08; H, 4.67; N, 9.02%.

N'-(Anthracen-9-ylmethylene)nicotinohydrazide (7c). Yield 83%; mp 265–268 °C; IR (KBr) ν : 3202 (NH), 3084 (CH_{arom}), 1643 (C=O), 1624 (C=N) cm⁻¹; ¹H NMR δ : 12.34 (s, 1H, NH), 9.69 (s, 1H, H-11), 9.28 (s, 1H, H-2'), 8.88 (m, 1H, H-6'), 8.73 (m, 3H, H-1,8,10), 8.39 (m, 1H, H-4'), 8.13 (m, 2H, H-4,5), 7.65 (m, 1H, H-5'), 7.64 (m, 2H, H-2,7), 7.57 (m, 2H, H-3,6); ¹³C NMR δ : 161.7 (C-14), 152.2 (C-6'), 148.5 (C-2'), 147.7 (C-11), 135.5 (C-4'), 130.8 (C-4a,10a), 129.8 (C-10), 129.6 (C-8a,9a), 129.0 (C-4,5), 127.2 (C-2,7), 125.5 (C-3,6), 124.8 (C-1,8), 124.7 (C-3',5'), 124.5 (C-9); Anal. Calcd For C₂₁H₁₅N₃O (325.37): C, 77.52; H, 4.65; N, 12.91. Found: C, 77.23; H, 4.21; N, 12.42%.

N'-(Anthracen-9-ylmethylene)isonicotinohydrazide (7d). Yield 85%; mp 263–265 °C; IR (KBr) ν : 3205 (NH), 3086 (CH_{arom}), 1693 (C=O), 1635 (C=N) cm⁻¹; ¹H NMR δ : 12.34 (s, 1H, NH), 9.70 (s, 1H, H-11), 8.88 (m, 2H, H-2',6'), 8.77 (d, 2H, H-1,8, J = 8.4 Hz), 8.75 (s, 1H, H-10), 8.18 (d, 2H, H-4,5, J = 8.8 Hz), 7.96 (d, 2H, H-3',5', J = 4.8 Hz), 7.68 (m, 2H, H-2,7), 7.61 (m, 2H, H-3,6); ¹³C NMR δ : 161.5 (C-14), 150.4 (C-2',6'), 148.3 (C-11), 140.4 (C-4'), 130.8 (C-4a,10a), 129.9 (C-10), 129.6 (C-8a,9a), 129.0 (C-4,5), 127.3 (C-2,7), 125.5 (C-3,6), 124.7 (C-1,8,9), 121.5 (C-3',5'); Anal. Calcd For C₂₁H₁₅N₃O (325.37): C, 77.52; H, 4.65; N, 12.91. Found: C, 77.27; H, 4.79; N, 13.05%.

N'-(Anthracen-9-ylmethylene)-9-oxo-9,10-dihydroacridine-4-carbohydrazide (7e). Yield 36%; mp 324–327 °C; IR (KBr) ν : 3209 (NH), 3046 (CH_{arom}), 1663 (C=O_{acridone}), 1622 (C=O_{amide}), 1587 (C=N) cm⁻¹; ¹H NMR δ : 12.47 (s, 1H, NH), 12.02 (s, 1H, H-10'), 9.76 (s, 1H, H-11), 8.87 (d, 2H, H-1,8, J = 8.8 Hz), 8.75 (s, 1H, H-10), 8.54 (d, 1H, H-1', J = 8.0 Hz), 8.47 (d, 1H, H-3', J = 6.8 Hz), 8.26 (d, 1H, H-8', J = 8.0 Hz), 8.17 (d, 2H, H-4,5, J = 8.4 Hz), 7.89 (d, 1H, H-5', J = 8.4 Hz), 7.76 (m, 1H, H-6'), 7.69 (m, 2H, H-2,7), 7.62 (m, 2H, H-3,6), 7.46 (m, 1H, H-2'), 7.33 (m, 1H, H-7'); ¹³C NMR δ : 176.5 (C-9'), 163.9 (C-14), 148.3 (C-11), 140.2 (C-4a',10a'), 134.0 (C-6'), 133.5 (C-3'), 130.9 (C-4a,10a), 130.6 (C-1'), 130.1 (C-10), 129.8 (C-8a,9a), 129.1 (C-4,5), 127.4 (C-2,7), 125.8 (C-8'), 125.6 (C-3,6), 124.8 (C-1,8), 124.5 (C-9), 122.1 (C-7'), 121.7 and 118.4 (C-4' and C-9a'), 120.5 (C-8a'), 120.0 (C-2'), 118.7 (C-5'),; Anal. Calcd For C₂₉H₁₉N₃O₂ (441.49): C, 78.90; H, 4.34; N, 9.52. Found: C, 78.55; H, 4.13; N, 9.32%.

General procedure for the preparation of hydrazones 13a–g

To a solution of the appropriate aldehyde or ketone (1.147 mmol) in ethanol (10 mL), (acridin-9-yl) hydrazine (**12**, 200 mg, 0.956 mmol) and several drops of glacial acetic acid were added. The reaction mixture was then refluxed for 3 h following which it was cooled and poured onto chilled water. The resulting precipitate was filtered off, dried and the product recrystallized from methanol.

9-(Benzylidenehydrazono)-9,10-dihydroacridine (13a). Yield: 84%; mp 68–70 °C; IR (KBr) ν : 3271 (NH), 3101, 1626, 1597 (C=N) cm⁻¹; ¹H NMR δ : 10.83 (s, 1H, H-10), 8.99 (dd, 1H, H-1, J = 8.8, 1.6 Hz), 8.55 (s, 1H, HC=N), 8.40 (dd, 1H, H-8, J = 8.0, 1.2 Hz), 7.89 (dd, 2H, H-2',6', J = 8.8, 1.6 Hz), 7.55–7.48 (m, 5H, H-3,6,3'-5'), 7.30 (dd, 1H, H-5, J = 8.4, 1.2 Hz), 7.28 (dd, 1H, H-4, J = 8.4, 0.8 Hz), 7.14–7.05 (m, 2H, H-2,7); ¹³C NMR δ : 154.4 (C-13), 149.8 (C-9), 140.6 (C-4a), 138.6 (C-10a), 135.3 (C-1'), 132.3 (C-1), 131.4 (C-3), 130.9 (C-6), 130.0 (C-4'), 129.0 (C-3',5'), 128.6 (C-2',6'), 125.5 (C-8), 120.9 (C-7), 119.7 (C-2), 119.3 (C-8a), 116.2 (C-5), 115.6 (C-9a), 115.6 (C-4); Anal. Calcd For C₂₀H₁₅N₃ (297.36): C, 80.78; H, 5.08; N, 14.13. Found: C, 80.54; H, 5.01; N, 13.85%.

9-(2,4,6-Trimethoxybenzylidenehydrazono)-9,10-dihydroacridine (13b). Yield 83%; mp 239–240 °C; IR (KBr) ν : 3267 (NH), 3107, 1620, 1599 (C=N) cm⁻¹; ¹H NMR δ : 10.60 (s, 1H, H-10), 9.87 (d, 1H, H-1, J = 8.4 Hz), 8.80 (s, 1H, HC=N), 8.41 (d, 1H, H-8, J = 8.0 Hz), 7.47 and 7.45 (m, m, 2H, H-3,6), 7.22 (d, 1H, J = 8.4 Hz) and 7.18 (d, 1H, J = 8.4 Hz, H-4,5), 7.05 and 7.04 (m, m, 2H, H-2,7), 6.35 (s, 2H, H-3',5'), 3.94 (s, 6H, C-2',6'-OCH₃), 3.87 (s, 3H, C-4'-OCH₃); ¹³C NMR δ : 162.6 (C-4'), 160.4 (C-2',6'), 150.9 (C-13), 148.8 (C-9), 140.2 (C-4a), 138.6 (C-10a), 133.2 (C-1), 131.0 (C-3), 130.4 (C-6), 125.5 (C-8), 120.5 (C-7), 119.6 (C-2), 119.2 (C-8a), 116.4 (C-5), 115.7 (C-9a), 115.3 (C-4), 104.8 (C-1'), 91.0 (C-3',5'), 56.0 (C-2',6'-OCH₃), 55.4 (C-4'-OCH₃); Anal. Calcd For C₂₃H₂₁N₃O₃ (387.44): C, 71.30; H, 5.08; N, 13.62. Found: C, 71.30; H, 5.01; N, 13.85%.

5.46; N, 10.85. Found: C, 71.48; H, 5.53; N, 10.77%.

9-(4-Bromobenzylidenehydrazono)-9,10-dihydroacridine (13c). Yield 93%; mp 99–101 °C; IR (KBr) ν : 1630, 1597 (C=N) cm^{-1} ; ^1H NMR δ : 10.89 (s, 1H, H-10), 8.91 (d, 1H, H-1, $J = 8.0$ Hz), 8.53 (s, 1H, HC=N), 8.39 (d, 1H, H-8, $J = 7.6$ Hz), 7.82 (m, 2H, H-2',6'), 7.72 (m, 2H, H-3',5'), 7.51 (m, 2H, H-3,6), 7.31 (d, 1H, $J = 8.4$ Hz) and 7.27 (d, 1H, $J = 8.4$ Hz, H-4,5), 7.12 and 7.07 (m, m, 2H, H-2,7); ^{13}C NMR δ : 153.1 (C-13), 149.9 (C-9), 140.5 (C-4a), 138.5 (C-10a), 134.5 (C-1'), 132.2 (C-1), 131.9 (C-3',5'), 131.4 (C-6), 130.9 (C-3), 129.3 (C-2',6'), 125.4 (C-8), 123.2 (C-4'), 120.8 (C-7), 119.8 (C-2), 119.1 (C-8a), 116.1 (C-5), 115.6 (C-4), 115.4 (C-9a); Anal. Calcd For $\text{C}_{20}\text{H}_{14}\text{BrN}_3$ (376.26): C, 63.85; H, 3.75; N, 11.17. Found: C, 63.58; H, 3.53; N, 10.84%.

9-(4-Methoxybenzylidenehydrazono)-9,10-dihydroacridine (13d). Yield 78%; mp 68–70 °C; IR (KBr) ν : 3269 (NH), 3130, 1624, 1597 (C=N) cm^{-1} ; ^1H NMR δ : 10.73 (s, 1H, H-10), 9.05 (dd, 1H, H-1, $J = 8.4$, 1.2 Hz), 8.48 (s, 1H, HC=N), 8.37 (dd, 1H, H-8, $J = 8.4$, 1.2 Hz), 7.83 (m, 2H, H-2',6'), 7.51–7.46 (m, 2H, H-3,6), 7.27 (dd, 1H, $J = 8.4$, 1.2 Hz) and 7.23 (dd, 1H, $J = 8.4$, 0.8 Hz, H-4,5), 7.11–7.03 (m, 4H, H-2,7,3',5'), 3.84 (s, 3H, OCH_3); ^{13}C NMR δ : 160.8 (C-4'), 154.3 (C-13), 149.2 (C-9), 140.5 (C-4a), 138.5 (C-10a), 132.3 (C-1), 131.2 (C-6), 130.7 (C-3), 129.2 (C-2',6'), 127.9 (C-1'), 125.3 (C-8), 120.7 (C-7), 119.5 (C-2), 119.3 (C-8a), 116.0 (C-9a), 115.7 (C-5), 115.4 (C-4), 114.4 (C-3',5'), 55.3 (OCH_3); Anal. Calcd For $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}$ (327.39): C, 77.04; H, 5.23; N, 12.83. Found: C, 76.38; H, 5.53; N, 12.64%.

9-(2,4,6-Trimethylbenzylidenehydrazono)-9,10-dihydroacridine (13e). Yield 41%; mp 79–81 °C; IR (KBr) ν : 3259 (NH), 3103, 1628, 1595 (C=N) cm^{-1} ; ^1H NMR δ : 10.78 (s, 1H, H-10), 9.06 (dd, 1H, H-1, $J = 8.0$, 1.2 Hz), 8.87 (s, 1H, HC=N), 8.42 (dd, 1H, H-8, $J = 8.0$, 1.6 Hz), 7.49 and 7.47 (m, m, 2H, H-3,6), 7.27 (dd, 1H, $J = 8.0$, 0.4 Hz) and 7.25 (dd, 1H, $J = 7.6$, 0.8 Hz, H-4,5), 7.10 (ddd, 1H, $J = 8.0$, 7.2, 1.2 Hz H-7), 6.96 (m, 3H, H-2,3',5'), 2.51 (s, 6H, C-2',6'- CH_3), 2.28 (s, 3H, C-4'- CH_3); ^{13}C NMR δ : 155.6 (C-13); 149.6 (C-9); 140.3 (C-4a); 138.6 (C-10a); 138.4 (C-4'), 137.5 (C-2',6'), 131.8 (C-1), 131.3 (C-3), 130.7 (C-6), 129.5 (C-3',5'), 128.9 (C-1'), 125.5 (C-8); 120.7 (C-7); 119.2 (C-8a); 119.2 (C-2); 116.0 (C-5); 115.6 (C-9a); 115.5 (C-4); 21.3 (C-2',6'- CH_3), 20.7 (C-4'- CH_3); Anal. Calcd For $\text{C}_{23}\text{H}_{21}\text{N}_3$ (339.44): C, 81.38; H, 6.24; N, 12.38. Found: C, 80.98; H, 5.94; N, 12.06%.

9-(Propan-2-ylidenehydrazono)-9,10-dihydroacridine (13f). Yield 38%; mp 76–78 °C; IR (KBr) ν : 3277 (NH), 3132, 2995, 2939 (CH), 1622, 1595 (C=N) cm^{-1} ; ^1H NMR δ : 10.43 (s, 1H, H-10), 8.74 (d, 1H, H-1, $J = 7.6$ Hz), 8.24 (d, 1H, H-8, $J = 7.6$ Hz), 7.40 (m, 2H, H-3,6), 7.18 and 7.15 (m, m, 2H, H-4,5), 7.02 (m,

1H, H-7), 6.94 (m, 1H, H-2), 2.12 (s, 3H, CH₃), 1.99 (s, 3H, CH₃); ¹³C NMR δ: 158.0 (C-13), 144.2 (C-9), 140.5 (C-4a), 138.4 (C-10a), 131.7 (C-1), 130.7 (C-3), 130.1 (C-6), 125.2 (C-8), 120.5 (C-7), 119.9 (C-8a), 119.0 (C-2), 115.9 (C-9a), 115.6 (C-4), 115.2 (C-5), 24.6 (CH₃), 17.9 (CH₃); Anal. Calcd For C₁₆H₁₅N₃ (249.32): C, 77.08; H, 6.06; N, 16.85. Found: C, 76.88; H, 5.94; N, 17.06%.

9-((1-Phenylethylidene)hydrazono)-9,10-dihydroacridine (13g). Yield 42%; mp 86–89 °C; IR (KBr) ν: 2923, 1638, 1613 (C=N) cm⁻¹; ¹H NMR δ: 10.68 (s, 1H, H-10), 8.58 (d, 1H, H-1, *J* = 7.6 Hz), 8.38 (d, 1H, H-8, *J* = 7.6 Hz), 7.97 (m, 2H, H-2',6'), 7.52–7.45 (m, 5H, H-3,6,3'-5'), 7.24 (m, 2H, H-4,5), 7.11 (m, 1H, H-7), 6.95 (m, 1H, H-2), 2.46 (s, 3H, CH₃); ¹³C NMR δ: 155.8 (C-13), 145.5 (C-9), 140.6 (C-4a), 138.4 (C-10a), 138.3 (C-1'), 131.5 (C-1), 131.1 (C-3), 130.5 (C-6), 129.1 (C-4'), 128.5 (C-3',5'), 126.0 (C-2',6'), 125.4 (C-8), 120.7 (C-7), 119.8 (C-8a), 119.4 (C-2), 115.7 (C-5), 115.4 (C-4), 115.4 (C-9a), 14.3 (CH₃); Anal. Calcd For C₂₁H₁₇N₃ (311.39): C, 81.00; H, 5.50; N, 13.49. Found: C, 79.83; H, 5.34; N, 13.46%.

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