HETEROCYCLES, Vol. 60, No. 7, 2003, pp. 1653 - 1672
Received, 31st March, 2003, Accepted, 9th May, 2003, Published online, 12th May, 2003

SYNTHESIS AND CRYSTALLOGRAPHIC STUDIES OF NEW ACRIDINIC ESTERS AND AMIDES: AN EFFICIENT SYNTHETIC ROUTE TO 4-METHYL FUNCTIONALIZED ACRIDINES

Julien Chiron* and Jean-Pierre Galy

UMR 6009, Laboratoire de Valorisation de la Chimie Fine, case 552, Faculté des Sciences et Techniques de Saint Jérôme, Avenue de l'Escadrille Normandie Niemen, 13397 Marseille Cedex 20, France
Fax: +33 (0) 4 91 28 83 23
E-mail: julien.chiron@univ.u-3mrs.fr

Abstract – In order to open a new way in antitumor drugs research, an efficient synthetic route to mono functional 4-substitued acridine derivatives has been developed on the basis of direct electrophilic substitution of acridine. This method leads to a wide range of simple acridinic patterns that can be linked to various side chains. We present here the synthesis of two new families of acridine ester and amide derivatives, obtained from acridinic alcohol and amine respectively, with high yields. Some crystallographic aspects of one representative compound of each family are discussed.

INTRODUCTION

The constant research in new efficient DNA topoisomerases inhibiting agents is one of the most important challenge in the development of new antitumor drugs.[1-4] Since the discovery of *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA) by Denny *et al*.,[5] many research teams have been working on acridine-4-carboxamide derivatives.[6] Indeed, acridine substituents at the position 4 are known to bind DNA in the major groove[7] and the resulting adduct can inhibit topoisomerase I and/or II action.[8] Although important studies have already been published about acridine-4-carboxamide derivatives, few work has been carried out concerning 4-methyleneacridine derivatives. Such compounds can bear various side chains and could present comparable biological activities as DACA, that would open a new promising way for drug discovery. Recent work[9] has shown that this methylene position is

able to alkylate DNA after acridine intercalation in order to create a covalently linked drug-DNA adduct, thus enhancing mutagenic activity.

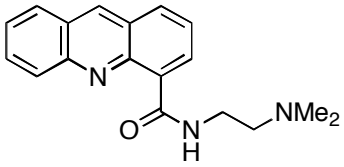
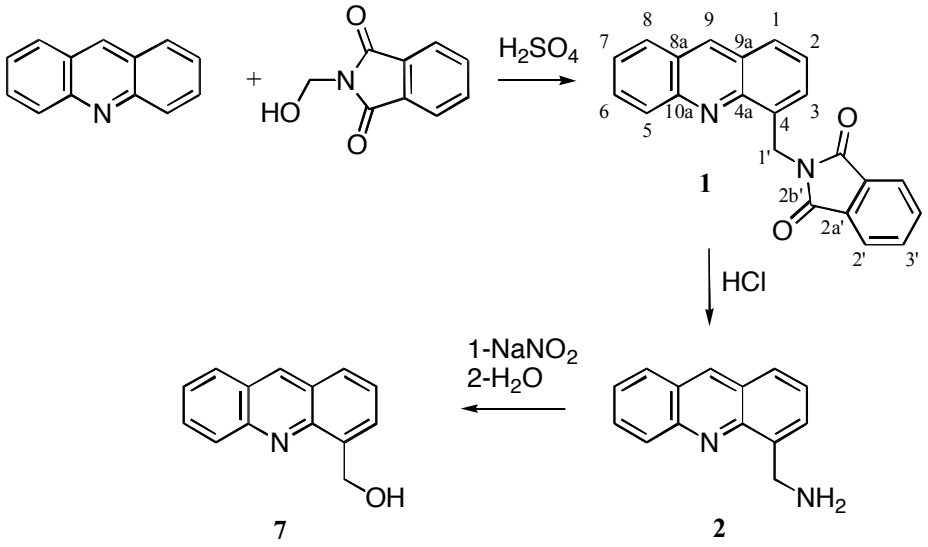


Figure 1. *N*-[2-(Dimethylamino)ethyl]acridine-4-carboxamide (DACA)[5]

According to these results, we report an efficient synthetic route to acridin-4-ylmethanol in three steps from acridine using an original synthetic method of acridin-4-ylmethylamine. Both intermediates are leading precursors to integrate a wide range of functional groups to the acridine scaffold. On that account, we synthesized two new families of 4-methylacridine derivatives, including various *N*-acridin-4-ylmethylamides and *O*-acridin-4-ylmethyl esters.

RESULTS AND DISCUSSION

Several investigations have been carried out in our laboratory to synthesize methylacridine derivatives on positions 2[10]and 4.[11] In order to increase the DNA binding effect of these derivatives, we decided to replace aminoalkyl group with carboxamide and carboxyle.



Scheme 1. Synthesis of precursor (**1**) and intermediates (**2**) and (**7**)

The widely used synthetic pathway to amino- or hydroxymethylacridines, involves a minimum of 6 to 7 steps[11]. Because of such a long synthetic route, the global yield is usually as fairly low as the waste amount is high. Thanks to the particularity of position 4, electrophilic substitution can easily be achieved with high regioselectivity depending on the choice of the electrophilic agent. Indeed, nitration is known to

occur preferentially on position 2.[12] The commercial availability of simple nonsubstituted acridine drove us to use such a synthetic pathway.

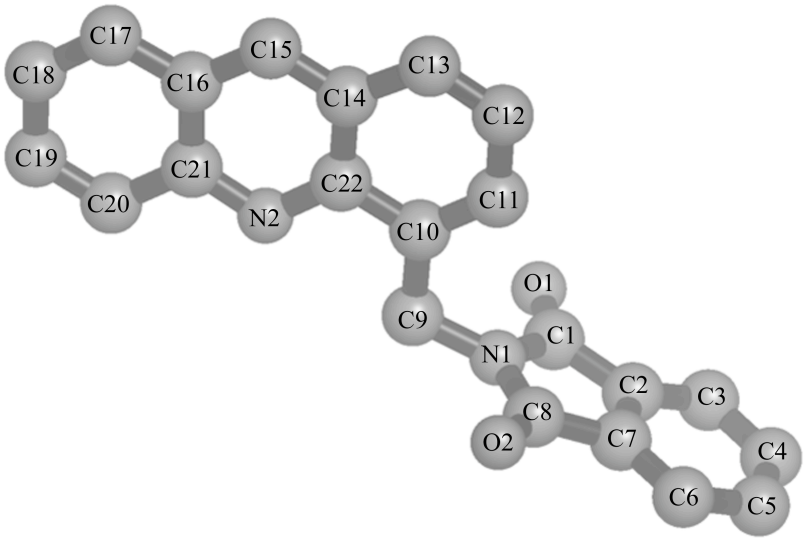
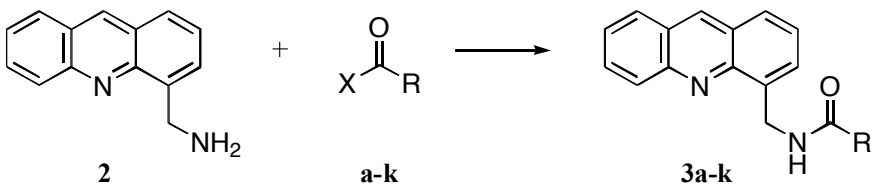


Figure 2. Crystal structure of compound (**1**) crystallized from chloroform

In 1971, Hess[13] first described a synthesis of acridin-4-yl-methylamine using the Tscherniac-Einorn reaction, which leads to the intermediate 2-(acridin-4-ylmethyl)isoindole-1,3-dione (**1**). The acridin-4-ylmethylamine (**2**) was then obtained with a overall yield of 61% after acid hydrolysis of the corresponding phthalimide. Compound (**2**) must be stored as hydrochloride to avoid rapid degradation.

A crystallographic study of phthalimide (**1**) has been carried out (Figure 2) that revealed an angle of 84.35(5)° between the planes of the phthalimide and the acridine groups, and an angle of –0.9(3)° for C11—C10—C9—N1. The molecules are packed along plane (1,0,1) and the acridinic plane is slightly twisted.



2 **a-k** **3a-k**

Scheme 2. Synthesis of amides (**3a-k**)

Compound (**2**) was allowed to react with a representative family of acids and acyl chlorides (**a-k**) to give the corresponding amides (**3a-k**) as shown in Table 1. The *in situ* neutralization of hydrochloride of **2** with conc. aqueous NaOH in acetone did not interfere with acylation using acyl chlorides because of the higher kinetic of amide toward acid formation. The base excess was then used to neutralize the reaction

formed hydrochloride. We did not notice any yield augmentation by using neutral **2** in the reaction. Compounds (**3j-k**) were obtained directly from acids derivatives using classic peptide synthesis methods.[14]

Table 1. List of R groups and yields of the amide series

Reagent	R	X	Product	Yield %
a	Ph	Cl	**3a**[13]	73
b	4-Cl-C_6H_4	Cl	**3b**	89
c	4-F-C_6H_4	Cl	**3c**	73
d	4-MeO-C_6H_4	Cl	**3d**	77
e	$(Ph)_2CH$	Cl	**3e**	90
f	4-$(CH_3)_2N$-C_6H_4	Cl	**3f**	91
g	CH_2=CH	Cl	**3g**	94
h	4-Cl-Prop	Cl	**3h**	92
i	4-(Ph-N=N)-C_6H_4	Cl	**3i**	94
j	4-(CH_3SO_2NH)-2-CH_3O-C_6H_3	OH	**3j**	92
k	$(CH_3)_2N$-CH_2	OH	**3k**	81

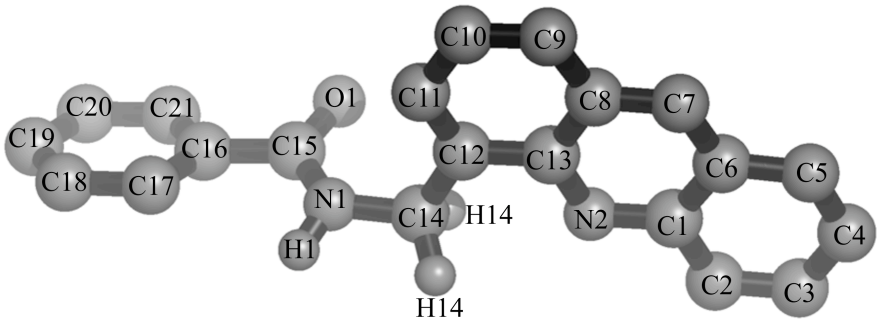
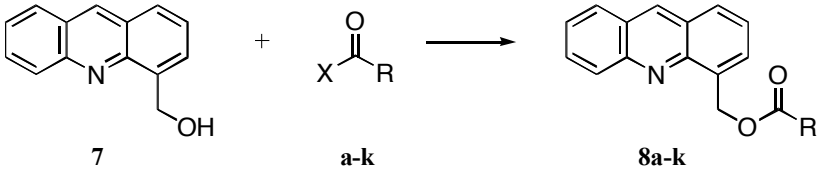


Figure 3. Crystal structure of compound (**3a**) crystallized from acetone

Compound (**3a**) could be crystallized from acetone and a crystallographic study was carried out (Figure 3) that revealed an angle of 78.39(15)° between acridine and phenyl planes and 19.57(19)° between phenyl and amide planes. The packing due to H-bond N1a—H1a O1b occurred along plane (1,1,0).

Afterwards, *O*-acridin-4-ylmethanol (**7**) could be obtained from **2** by hydrolyzing the corresponding diazonium salt according to a classical general method.[15]

We did notice that the yield is strongly enhanced using **2** as hydrochloride instead of its neutral form.



7 **a-k** **8a-k**

Scheme 3. Synthesis of esters (**8a**) to (**8k**)

Compounds (**8a-k**) could be synthesized by reacting some of the same acids derivatives (**a-k)** as above in Table 1 with alcohol (**7**) (Table 2). In the case of esters (**8a-h**) formation, the kinetic of the reaction with acyl chlorides is lower than for amides formation and needs drastic anhydrous conditions so as to be completed.

Table 2. Yields of the ester series

Reagent	Product	Yield	Reagent	Product	Yield
a	**8a**	92	**f**	**8f**	91
b	**8b**	90	**g**	**8g**	84
c	**8c**	81	**h**	**8h**	81
d	**8d**	85	**j**	**8j**	98
e	**8e**	79	**k**	**8k**	73

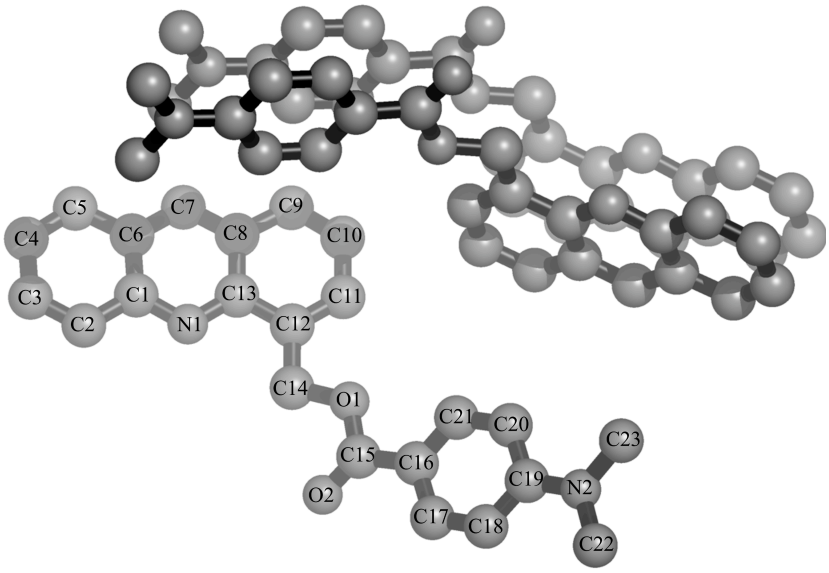


Figure 4. Crystal structure of compound (**8f**) crystallized from ethanol

Compound (**8f**) could be crystallized from ethanol and was studied by X-Ray crystallography (Figure 4). This analysis showed a particular pi stacking of the acridine groups along the plane (1,0,0) with an

inverted molecule out of three that leads to an elementary pattern containing three molecules. The molecules self-assemble along plane (0,1,0) thanks to H-bonds O2 H23B, O4 H69B and O6 H46B. The resulting unit cell contains 12 molecules. The angle formed by phenyl plane and dimethylamino group vary from 1.0(3)° to 1.9(3)° showing an eclipsed conformation.

Compound (**6**) was chosen because of its structural similarity with the m-amsa pattern.[16] It has been prepared in three steps from commercially available 4-Aminosalicylic acid with an overall yield of 66%.

Table 3. LogP calculation using various methods through ALOGP 2.1 program[17]

Compounds	ALOGPs	IAlogP	CLOGP	KOWWIN	XLOGP	ALOGpS ($mg.L^{-1}$)	IAlogS ($mg.L^{-1}$)
DACA	2.76	3.08	3.10	2.23	2.74	-3.88(38.63)	-4.52(8.86)
Amsasacrine	4.67	3.04	4.69	3.89	3.85	-5.11(3.06)	-5.30(1.97)
3a	4.05	3.57	4.10	4.24	4.59	-5.54(0.90)	-5.28(1.64)
3b	4.70	4.21	5.01	4.88	5.22	-5.93(0.40)	-6.08(0.29)
3c	4.28	3.86	4.45	4.44	4.76	-5.75(0.59)	-5.97(0.35)
3d	4.35	3.81	4.30	4.32	4.51	-5.54(0.98)	-5.52(1.03)
3e	5.63	6.59	5.34	5.68	6.07	-6.76(70.63[a])	-5.29(2.06)
3f	4.34	3.67	4.46	4.42	4.80	-5.07(3.03)	-5.31(1.74)
3g	3.34	2.98	2.46	2.69	3.17	-4.73(4.89)	-4.54(7.57)
3h	3.81	3.82	3.14	3.57	3.83	-5.07(2.68)	-5.35(1.40)
3i	6.32	5.18	6.33	6.36	6.71	-6.21(0.26)	-5.65(0.93)
3j	3.60	2.86	3.16	3.51	3.75	-5.09(3.57)	-5.59(1.12)
3k	2.66	2.76	2.49	1.94	2.40	-3.98(30.50)	-4.34(13.41)
8a	4.96	4.17	5.21	4.86	5.13	-5.76(0.56)	-6.38(0.13)
8b	5.50	4.67	5.92	5.51	5.75	-6.45(0.12)	-7.02(33.21[a])
8c	4.92	4.27	5.35	5.06	5.29	-5.45(0.46)	-6.82(50.15[a])
8d	5.00	5.54	5.38	4.94	5.04	-5.77(0.59)	-6.29(0.18)
8e	6.56	8.40	6.21	6.75	6.60	-7.04(37.10[a])	-7.15(28.56[a])
8f	5.07	4.41	5.69	5.43	5.33	-5.30(1.79)	-5.77(0.61)
8g	4.30	3.37	3.84	3.76	3.70	-4.66(5.70)	-4.77(4.47)
8h	4.42	4.02	4.15	4.64	4.36	-5.52(0.95)	-5.71(0.61)
8j	3.81	3.42	4.17	4.14	4.28	-5.77(0.75)	-6.29(0.22)
8k	3.07	3.35	3.18	2.61	2.93	-4.13(21.58)	-4.40(11.72)

[a] $\mu g.L^{-1}$

A comparative LogP calculation of compound (**3a-k**, **8a-k**), DACA and Amsacrine has been performed (Table 3) using various methods[17] that proposes that, compared to DACA, compound (**3k**) has a lower LogP and that **3k** and **8k** have a similar solubility in water. On the other hand, we can see that, compared to Amsacrine, compounds (**3g**-**h**, **3j**-**k, 8h-k**) have a lower LogP and that compounds (**3-8g**, **3-8k**) are more soluble in water**.**

CONCLUSION

In conclusion, in this work, we have enhanced a useful synthetic method to functionalize acridine on position 4 in one step with good yield and we synthesized two precursors of 4-functionalized acridine derivatives. This method will be developed in order to get a wide variety of mono functionalized acridine scaffolds. Using both previously cited precursors, we synthesized 11 amides and 10 esters derivatives of acridine, which will be evaluated in different pharmacological tests. At last, we carried out a crystallographic study on three acridinic compounds and one benzoic acid, and a comparative LogP calculation of all esters and all amides derivatives using various methods.

EXPERIMENTAL

General Remarks: All chemicals were used as purchased unless otherwise stated. Column chromatography was performed on Kieselgel 60. Melting points were performed on a Stuart Scientific Smp3 apparatus and are uncorrected. NMR spectrum was carried out with Bruker AC 300 (300 MHz for ^{1}H; 75 MHz for ^{13}C). Chemical shifts are given in δ relative to the solvent[18]: $CDCl_3$ ($\delta^{1}H$ = 7.28 ppm and $\delta^{13}C$ = 77.0 ppm), DMSO-d_6 ($\delta^{1}H$ = 2.48 ppm and $\delta^{13}C$ = 39.70 ppm) or acetone-d6 ($\delta^{1}H$ = 2.07 ppm and $\delta^{13}C$ = 29.80 ppm). Chemical shift assignments were determined using 1D and 2D experiments including DEPT,[19] gs-COSY,[20] gs-HMQC[21] and gs-HMBC[22] sequences. Chemical shifts of nucleus marked with the same amount of asterisks could not be differentiated. All crystallographic structures were solved by use of SIR-92 software[23] and refined on F^2 with SHELXL-97[24] program, measurements were done with Platon,[25] publication picture were prepared with PyMol.[26] All crystallographic data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]

2-Acridin-4-ylmethylisoindole-1,3-dione (1): A stirred solution of *N*-(hydroxymethyl)phthalimide (25 g, 0.14 mol) in H_2SO_4 (150 mL) was cooled to 0°C. Acridine (25 g, 0.14 mol) in H_2SO_4 (150 mL) was gradually added and the mixture was allowed to stand at rt under N_2 for one week. The reaction mixture was poured into ice (200 g) and the solution pH was adjusted to 10 with aqueous NH_3 (16%). The

precipitate was filtered and the grey solid was thoroughly washed with water. The dried solid was dissolved in $CHCl_3$ (500 mL) and the solution was filtered. The solution was concentrated under vacuo to obtain 50 mL and the resulting mixture was allowed to stand overnight at 0°C. The crystallized product was filtered and recrystallized from CH_2Cl_2 to give pure **1** as a white crystalline powder (30 g, 64%). mp 199°C (from CH_2Cl_2). lit.,[13] mp 199 - 201°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 5.75 (s, 2 H, 1'-H), 7.40 (dd, *J* = 8.3, 7.0 Hz, 1 H, 2-H), 7.48 (dd, *J* = 7.0, 1.5 Hz, 1 H, 3-H), 7.51 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1 H, 7-H), 7.72 (m, 2 H, 3'-H), 7.75 (ddd, *J* = 8.3, 6.6, 1.1 Hz, 1 H, 6-H), 7.89 (dd, *J* = 8.3, 1.5 Hz, 1 H, 1-H), 7.89 (m, 2 H, 2'-H), 7.96 (dd, *J* = 8.5, 1.1 Hz, 1 H, 8-H), 8.22 (dd, *J* = 8.3, 1.0 Hz, 1 H, 5-H), 8.72 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 39.02 (C-1'), 123.34 (C-3'), 125.10 (C-2), 125.82 (C-7), 126.42 (C-9a**), 126.51 (C-8a**), 126.98 (C-3), 127.77 (C-8*), 127.94 (C-1*), 130.01 (C-5), 130.01 (C-6), 132.35 (C-2'a), 133.85 (C-4), 133.94 (C-2'), 135.84 (C-9), 146.87 (C-4a), 148.38 (C-10a), 168.43 (C-2'b) ppm. *Anal.* Calcd for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.21; H, 4.16; N, 8.25.

Crystal Data of 1: Yellow prism crystals (0.4 × 0.3 ×0.2) of $C_{22}H_{14}N_2O_2$, M = 338.35, monoclinic, *a* = 15.2460(4) Å, b = 14.0620(6) Å, c = 7.7090(7) Å, β = 97.556(3)°, V = 1638.38(17) Å^3, Z = 4, space group: $P2_1/c$, ρ_{calcd} = 1.372 g cm^{-3}. Data were collected at 293(2) K, Kappa CCD diffractometer, Mo-K_α radiation, λ = 0.71073 Å, ω scan method with 90 frames and $\Delta\omega$ = 2°, θ_{max} = 26.34°, 3283 measured, 2643 were unique with $I>2\sigma(I)$. $R(F)$ = 0.0623 and $wR(F^2)$ = 0.1737 for 3283 reflections, 235 parameters. Residual electron density: 0.332/-0.419 e/Å^3. CCDC-194590 contains the supplementary crystallographic data for this paper.

***C*-Acridin-4-ylmethylamine (2):** Phthalimide (**1**) (10 g, 29.55 mmol) was dissolved in 300 mL of HCl (6N) and the mixture was refluxed for 4 days. The clear yellow solution was cooled with ice and basified with NH_3 (16%). The solution was extracted with CH_2Cl_2 (3 × 100 mL), the organic phase was washed with brine, dried with Na_2SO_4 and the solvent was removed under vacuo to give **2** as a brown oil (5.85 g, 96%, purity > 96% according to NMR data). **2** is used without further purification in the rest of the present work. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 2.45 (s, 2 H, 2'-H), 4.48 (s, 2 H, 1'-H), 7.39 (dd, *J* = 8.5, 6.7 Hz, 1 H, 2-H), 7.48 (ddd, *J* = 8.3, 6.6, 1.1 Hz, 1 H, 7-H), 7.59 (dd, *J* = 6.7, 1.0 Hz, 1 H, 3-H), 7.72 (ddd, *J* = 8.4, 6.6, 1.3 Hz, 1 H, 6-H), 7.91 (dd, *J* = 8.5, 1.0 Hz, 1 H, 1-H), 7.91 (dd, *J* = 8.3, 1.3 Hz, 1 H, 8-H), 8.19 (dd, *J* = 8.4, 1.1 Hz, 1 H, 5-H), 8.64 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 44.78 (C-1'), 125.47 (C-2), 125.66 (C-7), 126.36 (C-9a), 126.72 (C-8), 127.33 (C-1), 127.78 (C-3*), 127.94 (C-8*), 129.84 (C-5), 129.91 (C-6), 136.01 (C-9), 141.20 (C-4), 147.70 (C-4a), 148.25 (C-10a) ppm. *Anal.* Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found C, 80.82; H, 5.82; N, 13.49. In order

to preserve its quality, compound (**2**) was stored as HCl salt: The resulting oil was diluted in 5 mL of methanol and the solution was poured into dry ether (200 mL). Hydrogen chloride saturated ether was gradually added until the precipitate turns pale yellow to bright yellow. The mixture was stirred overnight under dry atmosphere ($CaCl_2$). The hydrochloride of **2** was filtered and washed with dry ether to give a yellow pulverulent solid (m/z = 209).

***N*-Acridin-4-ylmethylbenzamide (3a):** Hydrochloride of **2** (500 mg, 2.04 mmol) was dispersed into Me_2CO (20 mL) at 0°C and NaOH (5N, 2 mL) was added. A solution of benzoyl chloride (316 mg, 2.24 mmol) in Me_2CO (5 mL) was added drop wise and the stirring was maintained for 3 h. The mixture was poured into cold water (100 mL) and stirred for 1 h. The precipitate was filtered and washed with water. The resulting solid was recrystallized from $C_6H_{12}/CHCl_3$ to give a beige powder (462 mg, 72%). mp 160°C (from $C_6H_{12}/CHCl_3$). lit.,[13] mp 160 - 163°C. ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : □ = 5.29 (d, *J* = 5.8 Hz, 2 H, 1'-H), 7.51 (m, 2 H, 4'-H), 7.54 (m, 1 H, 5'-H), 7.57 (dd, *J* = 8.3, 7.0 Hz, 1 H, 2-H), 7.64 (ddd, *J* = 8.0, 6.6, 1.0 Hz, 1 H, 7-H), 7.69 (dd, *J* = 7.0, 1.3 Hz, 1 H, 3-H), 7.88 (ddd, *J* = 8.4, 6.6, 1.5 Hz, 1 H, 6-H), 7.99 (m, 2 H, 3'-H), 8.07 (dd, *J* = 8.3, 1.3 Hz, 1 H, 1-H), 8.19 (dd, *J* = 8.0, 1.5 Hz, 1 H, 8-H), 8.23 (dd, *J* = 8.4, 1.0 Hz, 1 H, 5-H), 9.13 (s, 1 H, 9-H), 9.13 (t, *J* = 5.8 Hz, 1 H, 2'-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : □ = 39.71 (C-1'), 125.67 (C-2), 126.10 (C-7), 126.21 (C-9a*), 126.25 (C-8a*), 127.02 (C-3), 127.40 (C-1), 127.49 (C-3'), 128.54 (C-4'), 128.61 (C-8), 129.43 (C-5), 130.76 (C-6), 131.44 (C-5'), 134.67 (C-3'a), 136.69 (C-4), 136.73 (C-9), 146.73 (C-4a), 147.79 (C-10a), 166.75 (C-2'a) ppm. *Anal.* Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 81.01; H, 5.14; N, 8.94.

Crystal Data of 3a: Yellow prism crystals (0.3 □ 0.2 □ 0.1) of $C_{21}H_{16}N_2O$, M = 312.36, monoclinic, *a* = 15.6510(5) Å, b = 12.2580(10) Å, c = 8.8150(10) Å, □ = 103.157(5)°, V = 1646.8(2) Å^3, Z = 4, space group: $P2_1/c$, □$_{calcd}$ = 1.260 g cm^{-3}. Data were collected at 293(2) K, Kappa CCD diffractometer, Mo-K□ radiation, □ = 0.71073 Å, □ scan method with 90 frames and □□ = 2°, □$_{max}$ = 26.17°, 3128 measured, 2381 were unique with I>2□(I). $R(F)$ = 0.0964 and $wR(F^2)$ = 0.1772 for 3128 reflections, 217 parameters. Residual electron density: 0.161/-0.145 e/Å^3. CCDC-194591 contains the supplementary crystallographic data for this paper.

***N*-Acridin-4-ylmethyl-4-chlorobenzamide (3b):** Same procedure as for **3a** with hydrochloride of **2** (567 mg, 2.32 mmol) and 4-chlorobenzoyl chloride (446 mg, 2,56 mmol). **3b** was obtained as a beige powder (705 mg, 88%). mp 102°C (from $C_6H_{12}/CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : □ = 5.27 (d, *J* = 5.9 Hz, 2 H, 1'-H), 7.57 (dd, *J* = 8.4, 6.9 Hz, 1 H, 2-H), 7.58 (m, 2 H, 4'-H), 7.65 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1 H, 7-H), 7.69 (dd, *J* = 6.9, 1.1 Hz, 1 H, 3-H), 7.88 (ddd, *J* = 8.1, 6.7, 1.5 Hz, 1 H, 6-H), 8.00 (m, 2 H,

3'-H), 8.08 (dd, *J* = 8.4, 1.1 Hz, 1 H, 1-H), 8.19 (dd, *J* = 8.1, 1.5 Hz, 1 H, 8-H), 8.23 (dd, *J* = 8.1, 1.3 Hz, 1 H, 5-H), 9.13 (s, 1 H, 9-H), 9.21 (t, *J* = 5.9 Hz, 1 H, 2'-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : □ = 39.60 (C-1'), 125.66 (C-2), 126.11 (C-7), 126.21 (C-9a*), 126.26 (C-8a*), 127.11 (C-3), 127.47 (C-1), 128.62 (C-8), 128.62 (C-3'), 129.46 (C-5), 129.46 (C-4'), 130.77 (C-6), 133.40 (C-3'a), 136.29 (C-4'a), 136.54 (C-4), 136.70 (C-9), 146.70 (C-4a), 147.80 (C-10a), 165.73 (C-2'a) ppm. *Anal.* Calcd for $C_{21}H_{15}N_2OCl$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.85; H, 4.34; N, 8.10.

***N*-Acridin-4-ylmethyl-4-fluorobenzamide (3c):** Same procedure as for **3a** with hydrochloride of **2** (500 mg, 2.04 mmol) and 4-fluorobenzoyl chloride (256 mg, 2,24 mmol). **3c** was obtained as a brown powder (483 mg, 72%). mp 138°C (from C_6H_{12}/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : □ = 5.26 (d, *J* = 5.9 Hz, 2 H, 1'-H), 7.33 (m, 2 H, 4'-H), 7.58 (dd, *J* = 8.3, 6.9 Hz, 1 H, 2-H), 7.64 (ddd, *J* = 8.0, 6.6, 1.1 Hz, 1 H, 7-H), 7.69 (dd, *J* = 6.9, 1.3 Hz, 1 H, 3-H), 7.88 (ddd, *J* = 8.1, 6.6, 1.5 Hz, 1 H, 6-H), 8.05 (m, 2 H, 3'-H), 8.08 (dd, *J* = 8.3, 1.3 Hz, 1 H, 1-H), 8.19 (dd, *J* = 8.0, 1.5 Hz, 1 H, 8-H), 8.23 (dd, *J* = 8.1, 1.1 Hz, 1 H, 5-H), 8.99 (t, *J* = 5.9 Hz, 1 H, 2'-H), 9.12 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : □ = 39.71 (C-1'), 115.44 (d, *J* = 22.0 Hz, C-4'), 125.65 (C-2), 126.08 (C-7), 126.20 (C-9a*), 126.25 (C-8a*), 127.06 (C-3), 127.43 (C-1), 128.59 (C-8), 129.43 (C-5), 130.16 (d, *J* = 9.0 Hz, C-3'), 130.73 (C-6), 131.14 (d, *J* = 3.0 Hz, C-3'a), 136.65 (C-9), 136.95 (C-4), 146.72 (C-4a), 147.80 (C-10a), 164.12 (d, *J* = 248.0 Hz, C-4'a), 165.73 (C-2'a) ppm. *Anal.* Calcd for $C_{21}H_{15}N_2OF$: C, 76.35; H, 4.58; N, 8.48. Found: C, 76.28; H, 4.60; N, 8.50.

***N*-Acridin-4-ylmethyl-4-methoxybenzamide (3d):** Same procedure as for **3a** with hydrochloride of **2** (500 mg, 2.04 mmol) and 4-methoxybenzoyl chloride (383 mg, 2,24 mmol). **3d** was obtained as a beige powder (531 mg, 76%). mp 146°C (from C_6H_{12}/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : □ = 3.82 (s, 3 H, 5'-OMe), 5.26 (d, *J* = 5.8 Hz, 2 H, 1'-H), 7.04 (m, 2 H, 4'-H), 7.57 (dd, *J* = 8.3, 6.9 Hz, 1 H, 2-H), 7.64 (ddd, *J* = 8.1, 6.6, 0.9 Hz, 1 H, 7-H), 7.67 (dd, *J* = 6.9, 1.4 Hz, 1 H, 3-H), 7.88 (ddd, *J* = 8.5, 6.6, 1.2 Hz, 1 H, 6-H), 7.97 (m, 2 H, 3'-H), 8.07 (dd, *J* = 8.3, 1.4 Hz, 1 H, 1-H), 8.19 (dd, *J* = 8.1, 1.2 Hz, 1 H, 8-H), 8.23 (dd, *J* = 8.5, 0.9 Hz, 1 H, 5-H), 8.99 (t, *J* = 5.8 Hz, 1 H, 2'-H), 9.12 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : □ = 39.60 (C-1'), 55.52 (5'-OMe'), 113.74 (C-4'), 125.66 (C-2), 126.08 (C-7), 126.21 (C-9a*), 126.24 (C-8a*), 126.89 (C-3'a), 126.98 (C-3), 127.34 (C-1), 128.61 (C-8), 129.33 (C-3'), 129.44 (C-5), 130.73 (C-6), 136.67 (C-9), 136.95 (C-4), 146.75 (C-4a), 147.78 (C-10a), 161.81(C-4'a), 166.25 (C-2'a) ppm. *Anal.* Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.35; H, 5.29; N, 8.16.

***N*-Acridin-4-ylmethyl-2,2-diphenylacetamide (3e):** Same procedure as for **3a** with hydrochloride of **2** (500 mg, 2.04 mmol) and 2,2-diphenylacetyl chloride (471 mg, 2,04 mmol). **3e** was obtained as a beige powder (720 mg, 88%). mp 173°C (from C_6H_{12}/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : δ = 5.08 (d, *J* = 5.7 Hz, 2 H, 1'-H), 5.13 (s, 1 H, 3'-CH), 7.30 (m, 4 H, 4'-H), 7.30 (m, 4 H, 5'-H), 7.30 (m, 2 H, 6'-H), 7.50 (dd, *J* = 8.3, 6.9 Hz, 1 H, 2-H), 7.57 (dd, *J* = 6.9, 1.2 Hz, 1 H, 3-H), 7.63 (ddd, *J* = 8.0, 6.6, 1.1 Hz, 1 H, 7-H), 7.86 (ddd, *J* = 8.3, 6.6, 1.5 Hz, 1 H, 6-H), 8.06 (dd, *J* = 8.3, 1.2 Hz, 1 H, 1-H), 8.14 (dd, *J* = 8.0, 1.5 Hz, 1 H, 8-H), 8.17 (dd, *J* = 8.3, 1.1 Hz, 1 H, 5-H), 8.80 (t, *J* = 5.7 Hz, 1 H, 2'-H), 9.11 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : δ = 39.37 (C-1'), 56.78 (3'-CH), 125.53 (C-2), 126.14 (C-7), 126.20 (C-9a*), 126.25 (C-8a*), 126.82 (C-6'), 127.59 (C-1**), 127.71 (C-3**), 128.42 (C-4'), 128.58 (C-8), 128.76 (C-5'), 129.47 (C-5), 130.73 (C-6), 136.55 (C-4), 136.71 (C-9), 140.65 (C-3'a), 146.70 (C-4a), 147.80 (C-10a), 171.45 (C-2'a) ppm. *Anal.* Calcd for $C_{28}H_{22}N_2O$: C, 83.56; H, 5.51; N, 6.96. Found: C, 83.67; H, 5.49; N, 6.94.

***N*-Acridin-4-ylmethyl-4-dimethylaminobenzamide (3f):** Same procedure as for **3a** with hydrochloride of **2** (508 mg, 2.08 mmol) and 4-dimethylaminobenzoyl chloride (381 mg, 2,08 mmol). **3f** was obtained as a yellow powder (656 mg, 89%). mp 205°C (from C_6H_{12}/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : δ = 2.97 (s, 6 H, 5'-NMe_2), 5.24 (d, *J* = 5.9 Hz, 2 H, 1'-H), 6.73 (m, 2 H, 4'-H), 7.57 (dd, *J* = 8.2, 7.0 Hz, 1 H, 2-H), 7.64 (ddd, *J* = 8.3, 6.6, 1.1 Hz, 1 H, 7-H), 7.66 (dd, *J* = 7.0, 1.1 Hz, 1 H, 3-H), 7.85 (m, 2 H, 3'-H), 7.88 (ddd, *J* = 8.6, 6.6, 1.5 Hz, 1 H, 6-H), 8.06 (dd, *J* = 8.2, 1.1 Hz, 1 H, 1-H), 8.19 (dd, *J* = 8.3, 1.5 Hz, 1 H, 8-H), 8.23 (dd, *J* = 8.6, 1.1 Hz, 1 H, 5-H), 8.77 (t, *J* = 5.9 Hz, 1 H, 2'-H), 9.13 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : δ = 39.47 (C-1'), 39.93 (5'-NMe_2), 111.05 (C-4'), 121.32 (C-3'a), 125.69 (C-2), 126.08 (C-7), 126.21 (C-9a*), 126.23 (C-8a*), 126.93 (C-3), 127.24 (C-1), 128.62 (C-8), 128.82 (C-3'), 129.45 (C-5), 130.73 (C-6), 136.67 (C-9), 137.32 (C-4), 146.79 (C-4a), 147.77 (C-10a), 152.35 (C-4'a), 166.63 (C-2'a) ppm. *Anal.* Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.91; H, 5.94; N, 11.79.

***N*-Acridin-4-ylmethylacrylamide (3g):** Same procedure as for **3a** with hydrochloride of **2** (500 mg, 2.04 mmol) and acryloyl chloride (185 mg, 2,04 mmol). **3g** was obtained as a beige powder (495 mg, 93%). mp 179°C (from C_6H_{12}/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : δ = 5.13 (d, *J* = 5.9 Hz, 2 H, 1'-H), 5.64 (dd, *J* = 10.1, 2.2 Hz, 1 H, 4'-CH*cis*), 6.16 (dd, *J* = 17.2, 2.2 Hz, 1 H, 5'-CH*trans*), 6.41 (dd, *J* = 17.2, 10.1 Hz, 1 H, 3'-CH), 7.58 (dd, *J* = 8.2, 6.9 Hz, 1 H, 2-H), 7.64 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1 H, 7-H), 7.67 (dd, *J* = 6.9, 1.5 Hz, 1 H, 3-H), 7.87 (ddd, *J* = 8.4, 6.6, 1.5 Hz, 1 H, 6-H), 8.08 (dd, *J* = 8.2, 1.5 Hz, 1 H, 1-H), 8.18 (dd, *J* = 8.5, 1.5 Hz, 1 H, 8-H), 8.21 (dd, *J* = 8.4, 1.0 Hz, 1 H, 5-H), 8.68 (t, *J* = 5.9 Hz, 1 H, 2'-H), 9.12 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : δ = 39.05 (C-1'), 125.54

(4'-CH_2), 125.65 (C-2), 126.13 (C-7), 126.22 (C-9a*), 126.28 (C-8a*), 127.57 (C-1**), 127.64 (C-3**), 128.61 (C-8), 129.47 (C-5), 130.76 (C-6), 132.00 (3'-CH), 136.51 (C-4), 136.72 (C-9), 146.70 (C-4a), 147.84 (C-10a), 165.15 (C-2'a) ppm. *Anal.* Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.99; H, 5.36; N, 10.64.

***N*-Acridin-4-ylmethyl-4-chlorobutyramide (3h):** Same procedure as for **3a** with hydrochloride of **2** (500 mg, 2.04 mmol) and 4-chlorobutyryl chloride (288 mg, 2,04 mmol). **3h** was obtained as a beige powder (577 mg, 90%). mp 112°C (from C_6H_{12}/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : δ = 2.01 (quint, *J* = 6.9 Hz, 2 H, 4'-CH_2), 2.41 (t, *J* = 6.9 Hz, 2 H, 3'-CH_2), 3.98 (t, *J* = 6.9 Hz, 2 H, 5'-CH_2Cl), 5.05 (d, *J* = 5.9 Hz, 2 H, 1'-H), 7.58 (dd, *J* = 8.4, 6.9 Hz, 1 H, 2-H), 7.65 (dd, *J* = 6.9, 1.3 Hz, 1 H, 3-H), 7.65 (ddd, *J* = 8.1, 6.6, 1.1 Hz, 1 H, 7-H), 7.87 (ddd, *J* = 8.4, 6.6, 1.4 Hz, 1 H, 6-H), 8.06 (dd, *J* = 8.4, 1.3 Hz, 1 H, 1-H), 8.17 (dd, *J* = 8.1, 1.4 Hz, 1 H, 8-H), 8.19 (dd, *J* = 8.4, 1.1 Hz, 1 H, 5-H), 8.48 (t, *J* = 5.9 Hz, 1 H, 2'-H), 9.12 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : δ = 28.52 (4'-CH_2), 32.63 (3'-CH_2), 38.98 (C-1'), 45.26 (5'-CH_2Cl), 125.64 (C-2), 126.10 (C-7), 126.19 (C-9a*), 126.24 (C-8a*), 127.29 (C-3), 127.48 (C-1), 128.59 (C-8), 129.46 (C-5), 130.71 (C-6), 136.66 (C-9), 136.80 (C-4), 146.70 (C-4a), 147.79 (C-10a), 171.60 (C-2'a) ppm. *Anal.* Calcd for $C_{18}H_{17}N_2OCl$: C, 69.12; H, 5.48; N, 8.96. Found: C, 69.25; H, 5.46; N, 8.94.

***N*-Acridin-4-ylmethyl-4-phenylazobenzamide (3i):** Same procedure as for **3a** with hydrochloride of **2** (500 mg, 2.04 mmol) and 4-phenylazobenzoyl chloride (500 mg, 2,04 mmol). **3i** was obtained as an orange powder (790 mg, 93%). mp 169°C (from C_6H_{12}/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : δ = 5.32 (d, *J* = 5.8 Hz, 2 H, 1'-H), 7.60 (dd, *J* = 8.3, 6.9 Hz, 1 H, 2-H), 7.63 (m, 2 H, 6'-H), 7.63 (m, 1 H, 7'-H), 7.74 (dd, *J* = 6.9, 1.3 Hz, 1 H, 3-H), 8.24 (dd, *J* = 8.4, 1.0 Hz, 1 H, 5-H), 7.89 (ddd, *J* = 8.4, 6.6, 1.5 Hz, 1 H, 6-H), 7.65 (ddd, *J* = 8.3, 6.6, 1.0 Hz, 1 H, 7-H), 8.20 (dd, *J* = 8.3, 1.5 Hz, 1 H, 8-H), 7.94 (m, 2 H, 5'-H), 8.00 (m, 2 H, 4'-H), 8.09 (dd, *J* = 8.3, 1.3 Hz, 1 H, 1-H), 8.20 (m, 2 H, 3'-H), 9.15 (s, 1 H, 9-H), 9.33 (t, *J* = 5.8 Hz, 1 H, 2'-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : δ = 39.79 (C-1'), 122.64 (C-5'), 122.94 (C-4'), 125.70 (C-2), 126.23 (C-9a*), 147.82 (C-10a), 129.45 (C-5), 130.79 (C-6), 126.13 (C-7), 128.64 (C-8), 126.28 (C-8a*), 127.15 (C-3), 127.50 (C-1), 128.87 (C-6'), 129.74 (C-3'), 132.20 (C-7'), 136.54 (C-3'a), 136.74 (C-9), 136.83 (C-4), 146.73 (C-4a), 152.10 (C-5'a), 153.53 (C-4'a), 166.01 (C-2'a) ppm. *Anal.* Calcd for $C_{27}H_{20}N_4O$: C, 77.87; H, 4.84; N, 13.45. Found: C, 77.65; H, 4.85; N, 13.47.

***N*-Acridin-4-ylmethyl-4-methanesulfonylamino-2-methoxybenzamide (3j)**. Hydrochloride of **2** (500 mg, 2.04 mmol) was treated with Et_3N (1 mL, 7.19 mmol) in Me_2CO (5 mL) and the mixture was added to a solution of acid (**6**) (551 mg, 2,25 mmol), HOBt (304 mg, 2,25 mmol) and DCC (464 mg, 2,25

mmol) in Me_2CO (10 mL). The mixture was stirred at rt under dry atmosphere ($CaCl_2$) for 72 h. The solvent was removed under vacuo and the dry residue was treated with NaOH (1N, 50 mL). The precipitated DCU was filtered off and washed with water, the solution was acidified with 6N HCl to pH 2 in ice bath and basified to pH 8 with 1N NaOH. The resulting precipitate was filtered off and washed with water to give **3j** as a yellow solid (808 mg, 91%). mp 218°C (from $C_6H_{12}/CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 2.97 (s, 3 H, 8'-SO_2Me), 3.66 (s, 3 H, 6'-OMe), 5.33 (d, *J* = 6.0 Hz, 2 H, 1'-H), 6.74 (dd, *J* = 8.5, 1.9 Hz, 1 H, 4'-H), 6.86 (d, *J* = 1.9 Hz, 1 H, 5'-H), 7.47 (dd, *J* = 8.4, 6.8 Hz, 1 H, 2-H), 7.56 (ddd, *J* = 8.3, 6.6, 1.1 Hz, 1 H, 7-H), 7.81 (ddd, *J* = 8.6, 6.6, 1.3 Hz, 1 H, 6-H), 7.85 (dd, *J* = 6.8, 0.9 Hz, 1 H, 3-H), 7.93 (dd, *J* = 8.4, 0.9 Hz, 1 H, 1-H), 8.02 (dd, *J* = 8.3, 1.3 Hz, 1 H, 8-H), 8.18 (d, *J* = 8.5 Hz, 1 H, 3'-H), 8.28 (dd, *J* = 8.6, 1.1 Hz, 1 H, 5-H), 8.77 (s, 1 H, 9-H), 9.23 (t, *J* = 6.0 Hz, 1 H, 2'-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 39.53 (6'-OMe), 41.53 (C-1'), 55.96 (8'-SO_2Me), 102.38 (C-5'), 111.61 (C-4'), 118.47 (C-3'a), 125.75 (C-2**), 125.79 (C-7**), 126.52 (C-9a*), 126.80 (C-8a*), 127.94 (C-3), 128.30 (C-1), 129.57 (C-8), 129.75 (C-5), 130.22 (C-6), 133.85 (C-3'), 136.29 (C-9), 136.38 (C-4), 140.77 (C-4'a), 148.02 (C-4a), 148.29 (C-10a), 158.67 (C-5'a), 164.25 (C-2'a) ppm. *Anal.* Calcd for $C_{23}H_{21}N_3O_4S$: C, 63.43; H, 4.86; N, 9.65. Found: C, 63.22; H, 4.87; N, 9.68.

***N*-Acridin-4-ylmethyl-2-dimethylaminoacetamide (3k):** Hydrochloride of **2** (500 mg, 2.04 mmol) was dissolved in water (1 mL), basified with NH_3 (16%) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried with Na_2SO_4 and reduced to 5 mL under vacuo. A solution of HOBt (304 mg, 2.25 mmol), Et_3N (0.2 mL, 1.44 mmol) and *N,N*-dimethylglycine hydrochloride (314 mg, 2.25 mmol) in CH_2Cl_2 (2 mL) was added at once and the mixture was maintained under dry atmosphere ($CaCl_2$). DCC (506 mg, 2.45 mmol) and triethylamine (0.5 mL, 3.60 mmol) are added after 10 min. The stirring was maintained for 48 h, the mixture was then diluted with EtOAc (20 mL) and filtered. The organic layer was washed with NaOH (1N, 10 mL) and brine (10 mL) and dried with Na_2SO_4. The resulting oil was purified by column chromatography (CH_2Cl_2 /EtOH, 9:1, v/v) to give pure **3k** as brown oil (482 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 2.16 (s, 6 H, 4'-NMe2), 2.95 (s, 2 H, 3'-CH_2), 5.14 (d, *J* = 6.2 Hz, 2 H, 1'-H), 7.44 (dd, *J* = 8.5, 6.8 Hz, 1 H, 2-H), 7.53 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1 H, 7-H), 7.74 (dd, *J* = 6.8, 1.5 Hz, 1 H, 3-H), 7.77 (ddd, *J* = 8.3, 6.6, 1.3 Hz, 1 H, 6-H), 7.90 (dd, *J* = 8.5, 1.5 Hz, 1 H, 1-H), 7.97 (dd, *J* = 8.5, 1.3 Hz, 1 H, 8-H), 8.22 (dd, *J* = 8.3, 1.0 Hz, 1 H, 5-H), 8.62 (t, *J* = 6.2 Hz, 1 H, 2'-H), 8.73 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 40.92 (C-1'), 45.89 (4'-NMe2), 63.28 (3'-CH_2), 125.48 (C-2), 125.78 (C-7), 126.40 (C-9a*), 126.65 (C-8a*), 127.88 (C-1**), 128.04 (C-8**), 129.32 (C-3), 129.67 (C-5), 130.13 (C-6), 135.99 (C-4), 136.15 (C-9), 147.75 (C-4a), 148.28 (C-10a), 170.46 (C-2'a) ppm. *Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.55; H, 6.52; N, 14.28.

4-Amino-2-methoxybenzoic acid methyl ester (4): According to a previously reported procedure,[27] 4-aminosalycilic acid (10.00 g, 63.30 mmol) was dissolved in dry Me_2CO (200 mL) and KOH pellets are added (9.20 g, 163.96 mmol). To the vigorously stirred mixture at 25°C, Me_2SO_4 (14.7 mL, 154.60 mmol) was added drop wise in 1 h and the stirring was maintained for 3 h. The solvent was then removed, the residual solid was dissolved in hot water and the pH was adjusted to 9 with 1N NaOH. After cooling, the precipitate was filtered off and thoroughly washed with water. The dry crude solid was dispersed in EtOAc (50 mL) and the mixture was cooled overnight to 0°C. The precipitate was filtered off and washed with few cold EtOAc to give **4** as a white powder (8.76 g, 74%). mp 155°C (from EtOAc). lit.,[27] mp 153-155°C.

4-Methanesulfonylamino-2-methoxybenzoic acid methyl ester (5): Ester (**4**) (4.00 g, 22.08 mmol) and pyridine (4.5 mL, 55.64 mmol) were dissolved in anhydrous $CHCl_3$ (80 mL) at 0°C under N_2. A solution of mesyl chloride (4.3 mL, 55.56 mmol) in dry $CHCl_3$ (25 mL) was added drop wise in 30 min. The solution was stirred for 5 h and the solvent was removed under vacuo. The crude pink oil was dissolved in few mL of Me_2CO and poured into water (150 mL). The precipitate was filtered off and washed with water. The solid was then recrystallized from EtOH to give pure **5** as a white powder (5.24 g, 95%). mp 152°C (from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 3.06 (s, 3 H, 7- SO_2Me), 3.85 (s, 3 H, 6-OMe), 3.87 (s, 3 H, 5-CO_2Me), 6.75 (dd, *J* = 8.5, 2.1 Hz, 1 H, 1-H), 6.88 (d, *J* = 2.1 Hz, 1 H, 3-H), 7.18 (s, 1 H, 4-H), 7.80 (d, *J* = 8.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 39.72 (7-SO_2Me), 52.06 (5-CO_2Me), 56.12 (6-OMe), 102.48 (C-3), 110.06 (C-1), 115.86 (C-2a), 133.61 (C-2), 142.00 (C-1a), 160.76 (C-3a), 165.87 (2b-CO_2Me) ppm. *Anal.* Calcd for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N, 5.40. Found: C, 46.41; H, 5.03; N, 5.39.

4-Methanesulfonylamino-2-methoxybenzoic acid (6): Ester (**5**) (5.00 g, 20.39 mmol) was dissolved in THF (100 mL). A solution of LiOH (4.05 g, 96.52 mmol) in water (100 mL) was added in one portion. The mixture was stirred overnight. THF was removed and the pH was adjusted to 1 with 6N HCl. The precipitate was filtered off and washed with water. After recrystallization from EtOH, pure **6** was obtained as a white powder (4.30 g, 91%). mp 182°C (from EtOH). ^{1}H NMR (300 MHz, acetone-d_6, 25°C) : δ = 3.06 (s, 3 H, 7-SO_2Me), 4.02 (s, 3 H, 6-OMe), 7.02 (dd, *J* = 8.5, 2.1 Hz, 1 H, 1-H), 7.17 (d, *J* = 2.1 Hz, 1 H, 3-H), 7.93 (d, *J* = 8.5 Hz, 1 H, 2-H), 9.06 (s, 1 H, 4-NH), 10.73 (s, 1 H, 5-CO_2H) ppm. ^{13}C NMR (75 MHz, acetone-d_6, 25°C) : δ = 40.01 (7-SO_2Me), 56.71 (6-OMe), 102.86 (C-3), 111.34 (C-1), 114.84 (C-2a), 134.74 (C-2), 145.14 (C-1a), 160.84 (C-3a), 165.77 (2b-CO_2H) ppm. *Anal.* Calcd for $C_9H_{11}NO_5S$: C, 44.08; H, 4.52; N, 5.71. Found: C, 44.20; H, 4.51; N, 5.69.

Acridin-4-ylmethanol (7): According to a previously reported procedure,[15] a solution of $NaNO_2$ (2.54 g, 36.81 mmol) in water (20 mL) was added drop wise to an ice cooled solution of hydrochloride of **2** (3.00 g, 12.26 mmol) in aqueous AcOH (100 mL, 50%). The mixture was stirred overnight at rt, basified with a solution of 5N NaOH and extracted with CH_2Cl_2 (3 × 100 mL). The solvent was reduced to 50 mL under vacuo and a solution of KOH (15 mL, 5% in methanol) was added. The mixture was stirred overnight at rt, washed with brine (2 × 20 mL), dried with $MgSO_4$. After evaporation of the solvent under vacuo, the resulting solid was purified by column chromatography (CH_2Cl_2 / EtOAc, 9:1, v/v) to give pure **7** as a yellow powder (2.33 g, 91%). mp 99.3°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 5.29 (s, 2 H, 1'-H), 5.66 (s, 1 H, 2'-H), 7.46 (dd, *J* = 8.4, 6.8 Hz, 1 H, 2-H), 7.56 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1 H, 7-H), 7.62 (br dd, *J* = 6.8 Hz, 1 H, 3-H), 7.79 (ddd, *J* = 8.3, 6.6, 1.1 Hz, 1 H, 6-H), 7.93 (br dd, *J* = 8.4 Hz, 1 H, 1-H), 8.00 (dd, *J* = 8.4, 1.1 Hz, 1 H, 8-H), 8.20 (dd, *J* = 8.3, 1.2 Hz, 1 H, 5-H), 8.80 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 65.10 (C-1'), 125.28 (C-2), 125.78 (C-7), 126.29 (C-9a), 126.55 (C-8a), 127.66 (C-3), 127.97 (C-8*), 128.01 (C-1*), 129.15 (C-5), 130.38 (C-6), 136.59 (C-9), 137.59 (C-4), 147.48 (C-4a), 148.00 (C-10a) ppm. *Anal.* Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.48; H, 5.18; N, 6.67.

Acridin-4-ylmethyl benzoate (8a): A solution of 4-chlorobenzoyl chloride (460 mg, 2.63 mmol) in Me_2CO (5 mL) was added drop wise to a solution of alcohol (**7**) (500 mg, 2,39 mmol) and Et_3N (0.5 mL, 3.60 mmol) in Me_2CO (15 mL) at 0°C under dry atmosphere ($CaCl_2$). The stirring was maintained for about 6 h (TLC control, CH_2Cl_2/EtOAc, 9:1, v/v) and the mixture was poured into cold water (50 mL). The precipitate was filtered off and washed with water. The dry solid was dissolved in $CHCl_3$ (10 mL), the solution was filtered and the solvent was removed. The crude solid was recrystallized from MeOH to give pure **8a** as a beige powder (758 mg, 92%). mp 129°C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 6.29 (s, 2 H, 1'-H), 7.46 (m, 2 H, 3'-H), 7.53 (dd, *J* = 8.4, 6.8 Hz, 1 H, 2-H), 7.55 (ddd, *J* = 8.5, 6.6, 1.1 Hz, 1 H, 7-H), 7.57 (m, 1 H, 4'-H), 7.76 (ddd, *J* = 8.4, 6.6, 1.4 Hz, 1 H, 6-H), 7.87 (dd, *J* = 6.8, 1.1 Hz, 1 H, 3-H), 7.97 (dd, *J* = 8.4, 1.1 Hz, 1 H, 1-H), 8.00 (dd, *J* = 8.5, 1.4 Hz, 1 H, 8-H), 8.18 (m, 2 H, 2'-H), 8.26 (dd, *J* = 8.4, 1.1 Hz, 1 H, 5-H), 8.72 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 63.58 (C-1'), 125.15 (C-2), 125.79 (C-7), 126.73 (C-9a), 127.00 (C-8a), 127.68 (C-3), 127.94 (C-8), 128.02 (C-1), 128.35 (C-3'), 129.73 (C-2'), 129.96 (C-5), 130.06 (C-6), 130.46 (C-2a'), 132.89 (C-4'), 134.41 (C-4), 135.80 (C-9), 146.73 (C-4a), 148.48 (C-10a), 166.60 (C-2b') ppm. *Anal.* Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47. Found: C, 80.55; H, 4.81; N, 4.46.

Acridin-4-ylmethyl 4-chlorobenzoate (8b): Same procedure as for **8a** with alcohol (**7**) (500 mg, 2,39 mmol) and 4-chlorobenzoyl chloride (460 mg, 2.63 mmol). **8b** was obtained as a beige powder (348 mg,

90%). mp 125°C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : □ = 6.25 (s, 2 H, 1'-H), 7.40 (m, 2 H, 3'-H), 7.51 (dd, *J* = 8.3, 6.8 Hz, 1 H, 2-H), 7.53 (ddd, *J* = 8.0, 6.6, 1.0 Hz, 1 H, 7-H), 7.76 (ddd, *J* = 8.4, 6.6, 1.4 Hz, 1 H, 6-H), 7.84 (dd, *J* = 6.8, 1.0 Hz, 1 H, 3-H), 7.95 (dd, *J* = 8.3, 1.0 Hz, 1 H, 1-H), 7.98 (dd, *J* = 8.0, 1.4 Hz, 1 H, 8-H), 8.07 (m, 2 H, 2'-H), 8.23 (dd, *J* = 8.4, 1.0 Hz, 1 H, 5-H), 8.74 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : □ = 63.84 (C-1'), 125.14 (C-2), 125.88 (C-7), 126.27 (C-9a), 126.55 (C-8a), 127.97 (C-3), 127.97 (C-8), 128.26 (C-1), 128.70 (C-3'), 128.94 (C-2a'), 129.99 (C-5*), 130.15 (C-6*), 131.14 (C-2'), 134.21 (C-4), 135.87 (C-9), 139.33 (C-3a'), 146.79 (C-4a), 148.55 (C-10a), 165.78 (C-2b') ppm. *Anal.* Calcd for $C_{21}H_{14}NO_2Cl$: C, 72.52; H, 4.06; N, 4.03. Found: C, 72.70; H, 4.05; N, 4.02.

Acridin-4-ylmethyl 4-fluorobenzoate (8c): Same procedure as for **8a** with alcohol (**7**) (500 mg, 2,39 mmol) and 4-fluorobenzoyl chloride (417 mg, 2.63 mmol). **8c** was obtained as a beige powder (670 mg, 81%). mp 114°C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : □ = 6.26 (s, 2 H, 1'-H), 7.10 (m, 2 H, 3'-H), 7.51 (dd, *J* = 8.4, 6.8 Hz, 1 H, 2-H), 7.53 (ddd, *J* = 7.7, 6.6, 1.0 Hz, 1 H, 7-H), 7.77 (ddd, *J* = 8.4, 6.6, 1.3 Hz, 1 H, 6-H), 7.85 (dd, *J* = 6.8, 1.1 Hz, 1 H, 3-H), 7.96 (dd, *J* = 8.4, 1.1 Hz, 1 H, 1-H), 7.99 (dd, *J* = 7.7, 1.3 Hz, 1 H, 8-H), 8.16 (m, 2 H, 2'-H), 8.24 (dd, *J* = 8.4, 1.0 Hz, 1 H, 5-H), 8.75 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : □ = 63.71 (C-1'), 115.47 (d, *J* = 21.0 Hz, C-3'), 125.12 (C-2), 125.85 (C-7), 126.24 (C-9a), 126.52 (C-8a), 126.72 (d, *J* = 3.0 Hz, C-2a'), 127.88 (C-3**), 127.95 (C-8**), 128.18 (C-1**), 129.97 (C-5*), 130.10 (C-6*), 132.26 (d, *J* = 9.0 Hz, C-2'), 134.28 (C-4), 135.83 (C-9), 146.77 (C-4a), 148.52 (C-10a), 165.73 (d, *J* = 254.0 Hz, C-3a'), 166.65 (C-2b') ppm. *Anal.* Calcd for $C_{21}H_{14}NO_2F$: C, 76.12; H, 4.26; N, 4.23. Found: C, 76.28; H, 4.25; N, 4.22.

Acridin-4-ylmethyl 4-methoxybenzoate (8d): Same procedure as for **8a** with alcohol (**7**) (500 mg, 2,39 mmol) and 4-methoxybenzoyl chloride (449 mg, 2.63 mmol). **8d** was obtained as a beige powder (698 mg, 85%). mp 132°C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : □ = 3.85 (s, 3 H, 4'-OMe), 6.25 (s, 2 H, 1'-H), 6.92 (m, 2 H, 3'-H), 7.51 (dd, *J* = 8.3, 6.8 Hz, 1 H, 2-H), 7.53 (ddd, *J* = 8.0, 6.6, 1.0 Hz, 1 H, 7-H), 7.76 (ddd, *J* = 8.4, 6.6, 1.4 Hz, 1 H, 6-H), 7.86 (dd, *J* = 6.8, 1.1 Hz, 1 H, 3-H), 7.95 (dd, *J* = 8.3, 1.1 Hz, 1 H, 1-H), 7.99 (dd, *J* = 8.0, 1.4 Hz, 1 H, 8-H), 8.11 (m, 2 H, 2'-H), 8.25 (dd, *J* = 8.4, 1.0 Hz, 1 H, 5-H), 8.75 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : □ = 55.40 (4'-OMe), 63.29 (C-1'), 113.62 (C-3'), 122.92 (C-2'a), 125.22 (C-2), 125.82 (C-7), 126.27 (C-9a), 126.54 (C-8a), 127.61 (C-3), 127.95 (C-8**), 127.97 (C-1**), 130.03 (C-5*), 130.07 (C-6*), 131.78 (C-2'), 134.73 (C-4), 135.83 (C-9), 146.82 (C-4a), 148.52 (C-10a), 163.35 (C-3'a), 166.37 (C-2'b) ppm. *Anal.* Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 77.24; H, 4.97; N, 4.07.

Acridin-4-ylmethyl 2,2-diphenylacetate (8e): Same procedure as for **8a** with alcohol (**7**) (500 mg, 2,39 mmol) and 2,2-diphenylacetyl chloride (606 mg, 2.63 mmol). **8e** was obtained as a white powder (765 mg, 79%). mp 117°C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 5.17 (s, 1 H, 2'-CH), 6.08 (s, 2 H, 1'-H), 7.40 (dd, *J* = 8.3, 6.8 Hz, 1 H, 2-H), 7.52 (ddd, *J* = 8.0, 6.6, 0.8 Hz, 1 H, 7-H), 7.58 (dd, *J* = 6.8, 1.1 Hz, 1 H, 3-H), 7.75 (ddd, *J* = 8.3, 6.6, 1.2 Hz, 1 H, 6-H), 7.92 (dd, *J* = 8.3, 1.1 Hz, 1 H, 1-H), 7.98 (dd, *J* = 8.0, 1.2 Hz, 1 H, 8-H), 8.18 (dd, *J* = 8.3, 0.8 Hz, 1 H, 5-H), 8.72 (s, 1 H, 9-H), 7.26-7.35 (m, 4 H, 3'-H), 7.26-7.35 (m, 4 H, 4'-H), 7.26-7.35 (m, 2 H, 5'-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 57.27 (2'-CH), 63.88 (C-1'), 125.06 (C-2), 125.79 (C-7), 126.19 (C-9a), 126.48 (C-8a), 127.18 (C-5'), 127.92 (C-3), 128.17 (C-8**), 128.22 (C-1**), 128.51 (C-3'), 128.75 (C-4'), 129.99 (C-5*), 130.03 (C-6*), 134.03 (C-4), 135.77 (C-9), 138.77 (C-3a'), 146.73 (C-4a), 148.45 (C-10a), 172.38 (C-2a') ppm. *Anal.* Calcd for $C_{28}H_{21}NO_2$: C, 83.35; H, 5.25; N, 3.47. Found: C, 83.15; H, 5.26; N, 3.47.

Acridin-4-ylmethyl 4-Dimethylaminobenzoate (8f): Same procedure as for **8a** with alcohol (**7**) (500 mg, 2,39 mmol) and 4-dimethylaminobenzoyl chloride (483 mg, 2.63 mmol). **8f** was obtained as a yellow powder (775 mg, 91%). mp 187°C (from MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 3.01 (s, 6 H, 4'-NMe2), 6.24 (s, 2 H, 1'-H), 6.65 (m, 2 H, 3'-H), 7.48 (dd, *J* = 8.3, 6.9 Hz, 1 H, 2-H), 7.51 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1 H, 7-H), 7.75 (ddd, *J* = 8.5, 6.6, 1.5 Hz, 1 H, 6-H), 7.86 (dd, *J* = 6.9, 1.2 Hz, 1 H, 3-H), 7.90 (dd, *J* = 8.3, 1.2 Hz, 1 H, 1-H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1 H, 8-H), 8.05 (m, 2 H, 2'-H), 8.25 (dd, *J* = 8.5, 1.0 Hz, 1 H, 5-H), 8.70 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 40.01 (4'-NMe_2), 62.76 (C-1'), 110.70 (C-3'), 117.20 (C-2a'), 125.26 (C-2), 125.72 (C-7), 126.22 (C-9a), 126.47 (C-8a), 127.22 (C-3), 127.62 (C-8), 127.94 (C-1), 129.95 (C-5), 130.02 (C-6), 131.45 (C-2'), 135.20 (C-4), 135.74 (C-9), 146.79 (C-4a), 148.43 (C-10a), 153.31 (C-3a'), 166.92 (C-2b') ppm. *Anal.* Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.72; H, 5.64; N, 7.84.

Crystal Data of 8f: Yellow prism crystals (0.4 × 0.3 × 0.05) of $C_{69}H_{60}N_6O_6$, M = 1069.23, monoclinic, *a* = 23.1280(7) Å, b = 13.1660(7) Å, c = 21.099(1) Å, β = 122.839(2)°, V = 5398.0(4) Å^3, Z = 4, space group: *Cc*, ρ_{calcd} = 1.316 g cm^{-3}. Data were collected at 293(2) K, Kappa CCD diffractometer, Mo-K_α radiation, λ = 0.71073 Å, ω scan method with 90 frames and $\Delta\omega$ = 2°, θ_{max} = 26.37°, 5236 measured, 4062 were unique with $I>2\sigma(I)$. $R(F)$ = 0.0525 and $wR(F^2)$ = 0.1683 for 5236 reflections, 730 parameters. Residual electron density: 0.188/-0.197 e/Å^3. CCDC-194592 contains the supplementary crystallographic data for this paper.

Acridin-4-ylmethyl acrylate (8g): A solution of acryloyl chloride (460 mg, 2.63 mmol) in Me_2CO (5 mL) was added drop wise to a solution of alcohol (**7**) (500 mg, 2,39 mmol) and Et_3N (0.5 mL, 3.60

mmol) in Me_2CO (15 mL) at 0°C under dry atmosphere ($CaCl_2$). The stirring was maintained for about 6 h (TLC control, CH_2Cl_2/EtOAc, 9:1, v/v) and the mixture was poured into cold water (50 mL). The resulting oil was extracted with CH_2Cl_2 (3 × 20 mL), dried with Na_2SO_4 and purified by column chromatography (CH_2Cl_2/EtOAc, 9:1, v/v) to give pure **8g** as a yellow solid (527 mg, 84%). mp 75°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 5.87 (dd, *J* = 10.4, 1.5 Hz, 1 H, 3'-CH*cis*), 6.11 (s, 2 H, 1'-H), 6.27 (dd, *J* = 17.4, 10.4 Hz, 1 H, 2'-CH), 6.52 (dd, *J* = 17.4, 1.5 Hz, 1 H, 4'-CH*trans*), 7.50 (dd, *J* = 8.3, 6.9 Hz, 1 H, 2-H), 7.52 (ddd, *J* = 7.9, 6.5, 1.3 Hz, 1 H, 7-H), 7.76 (ddd, *J* = 8.4, 6.5, 1.1 Hz, 1 H, 6-H), 7.79 (dd, *J* = 6.9, 1.3 Hz, 1 H, 3-H), 7.94 (dd, *J* = 8.3, 1.3 Hz, 1 H, 1-H), 7.98 (dd, *J* = 7.9, 1.1 Hz, 1 H, 8-H), 8.24 (dd, *J* = 8.4, 1.3 Hz, 1 H, 5-H), 8.73 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 63.17 (C-1'), 125.18 (C-2), 125.86 (C-7), 126.27 (C-9a), 126.55 (C-8a), 127.97 (C-8), 128.01 (C-3), 128.16 (C-1*), 128.61 (2'-CH), 130.02 (C-5), 130.11 (C-6), 130.92 (3'-CH_2), 134.25 (C-4), 135.86 (C-9), 146.80 (C-4a), 148.54 (C-10a), 166.28 (C-2a') ppm. *Anal.* Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.69; H, 4.97; N, 5.31.

Acridin-4-ylmethyl 4-chlorobutyrate (8h): A solution of 4-chlorobutyryl chloride (371 mg, 2.63 mmol) in Me_2CO (5 mL) was added drop wise to a solution of alcohol (**7**) (500 mg, 2,39 mmol) and Et_3N (0.5 mL, 3.60 mmol) in Me_2CO (15 mL) at 0°C under dry atmosphere ($CaCl_2$). The stirring was maintained for about 6 h (TLC control, CH_2Cl_2) and the mixture was poured into cold water (50 mL). The resulting oil was extracted with EtOAc (3 × 25 mL), washed with brine, dried with Na_2SO_4 and purified by column chromatography (CH_2Cl_2) to give pure **8h** as a brown oil (604 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 2.16 (quint., *J* = 6.8 Hz, 2 H, 3'-CH_2), 2.64 (t, *J* = 6.8 Hz, 2 H, 2'- CH_2), 3.63 (t, *J* = 6.8 Hz, 2 H, 4'- CH_2Cl), 6.01 (s, 2 H, 1'-H), 7.48 (dd, *J* = 8.4, 7.0 Hz, 1 H, 2-H), 7.51 (ddd, *J* = 8.5, 6.6, 0.8 Hz, 1 H, 7-H), 7.75 (ddd, *J* = 8.7, 6.6, 1.3 Hz, 1 H, 6-H), 7.76 (dd, *J* = 7.0, 0.8 Hz, 1 H, 3-H), 7.92 (dd, *J* = 8.4, 0.8 Hz, 1 H, 1-H), 7.95 (dd, *J* = 8.5, 1.3 Hz, 1 H, 8-H), 8.22 (dd, *J* = 8.7, 0.8 Hz, 1 H, 5-H), 8.70 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 27.75 (3'- CH_2), 31.38 (2'- CH_2), 44.10 (4'- CH_2Cl), 63.30 (C-1'), 125.09 (C-2), 125.83 (C-7), 126.23 (C-9a), 126.50 (C-8a), 127.94 (C-3), 128.29 (C-1), 128.29 (C-8), 129.93 (C-5*), 130.11 (C-6*), 134.10 (C-4), 135.84 (C-9), 146.77 (C-4a), 148.51 (C-10a), 172.63 (C-2a') ppm. *Anal.* Calcd for $C_{18}H_{16}NO_2Cl$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.99; H, 5.13; N, 4.47.

Acridin-4-ylmethyl 4-methanesulfonylamino-2-methoxybenzoate (8j): A solution of alcohol (**7**) (500 mg, 2.39 mmol), acid (**6**) (645 mg, 2.63), DMAP (321 mg, 2.63) and DCC (542 mg, 2.63) in Me_2CO (10 mL) was stirred for 72 h at rt under dry atmosphere ($CaCl_2$). Me_2CO (50 mL) was then added and the precipitated DCU was filtered off. The solvent was reduced under vacuo to 5 mL and the mixture was poured into cold water (50 mL). pH was adjusted to 2 with 1N HCl and then to 9 with 1N NaOH. The

precipitate was filtered off and washed with cold water. The resulting solid was recrystallized from MeOH to give pure **8j** as a yellow powder (989 mg, 95%). mp 291°C (from MeOH). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C) : δ = 2.60 (s, 3 H, 5'-SO_2Me), 3.74 (s, 3 H, 6'-OMe), 5.98 (s, 2 H, 1'-H), 6.43 (dd, *J* = 8.5, 2.1 Hz, 1 H, 3'-H), 6.45 (d, *J* = 2.1 Hz, 1 H, 4'-H), 7.60 (d, *J* = 8.5 Hz, 1 H, 2'-H), 7.65 (dd, *J* = 8.5, 6.8 Hz, 1 H, 2-H), 7.66 (ddd, *J* = 8.5, 6.6, 1.1 Hz, 1 H, 7-H), 7.88 (ddd, *J* = 8.4, 6.6, 1.5 Hz, 1 H, 6-H), 7.95 (dd, *J* = 6.8, 1.3 Hz, 1 H, 3-H), 8.12 (dd, *J* = 8.5, 1.3 Hz, 1 H, 1-H*), 8.19 (dd, *J* = 8.5, 1.5 Hz, 1 H, 8-H*), 8.21 (dd, *J* = 8.4, 1.1 Hz, 1 H, 5-H), 9.15 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25°C) : δ = 39.58 (5'-SO_2Me), 55.24 (6'-OMe), 61.82 (C-1'), 102.61 (C-4'), 104.69 (C-2'a), 111.85 (C-3'), 125.78 (C-2), 126.05 (C-9a), 126.19 (C-7), 126.35 (C-8a), 127.31 (C-3), 127.91 (C-8*), 128.69 (C-1*), 129.36 (C-5), 130.91 (C-6), 132.73 (C-2'), 135.06 (C-4), 136.79 (C-9), 146.20 (C-4a), 147.87 (C-10a), 158.78 (C-3'a), 161.27 (C-4'a), 165.40 (C-2'b) ppm. *Anal.* Calcd for $C_{23}H_{20}N_2O_5S$: C, 63.29; H, 4.62; N, 6.42. Found: C, 63.41; H, 4.61; N, 6.41.

Acridin-4-ylmethyl 2-(*N,N*-dimethylamino)acetate (8k): A solution of alcohol (**7**) (500 mg, 2.39 mmol), *N,N*-dimethylglycine hydrochloride (367 mg, 2.63), DMAP (321 mg, 2.63) and DCC (542 mg, 2.63) in Me_2CO (15 mL) was stirred for 96 h at rt under dry atmosphere ($CaCl_2$). Me_2CO (50 mL) was then added and the precipitated DCU was filtered off. The solvent was removed under vacuo, the mixture was dissolved in CH_2Cl_2 (20 mL), washed with NaOH (1N, 10 mL) and extracted with HCl (1N, 3 × 10 mL). The acidic aqueous layer was neutralized with 1N NaOH, extracted with CH_2Cl_2 (3 × 20 mL),the resulting organic layer was dried with Na_2SO_4 and the solvent was removed under vacuo. The resulting oil was purified by column chromatography (CH_2Cl_2/EtOAc, 5:5, v/v) to give pure **8k** as a brown oil (515 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) : δ = 2.39 (s, 6 H, 3'-NMe_2), 3.30 (s, 2 H, 2'-CH_2), 6.05 (s, 2 H, 1'-H), 7.48 (dd, *J* = 8.5, 7.0 Hz, 1 H, 2-H), 7.52 (ddd, *J* = 7.8, 6.8, 0.8 Hz, 1 H, 7-H), 7.75 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 1 H, 6-H), 7.77 (dd, *J* = 7.0, 1.2 Hz, 1 H, 3-H), 7.94 (dd, *J* = 8.5, 1.2 Hz, 1 H, 1-H), 7.97 (dd, *J* = 7.8, 1.3 Hz, 1 H, 8-H), 8.22 (dd, *J* = 8.5, 0.8 Hz, 1 H, 5-H), 8.73 (s, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) : δ = 45.31 (3'-NMe2), 60.57 (2'-CH_2), 63.28 (C-1'), 125.11 (C-2), 125.85 (C-7), 126.28 (C-9a), 126.53 (C-8a), 127.96 (C-3), 128.38 (C-8**), 128.59 (C-1**), 129.95 (C-5*), 130.14 (C-6*), 134.05 (C-4), 135.87 (C-9), 146.84 (C-4a), 148.54 (C-10a), 170.66 (C-2a') ppm. *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.30; H, 6.17; N, 9.51.

REFERENCES

1. D. K. Kim and N. Lee, *Mini Rev. Med. Chem.,* 2002, **2**, 611.
2. M. L. Rothenberg, *Ann. Oncol.,* 1997, **8**, 837.
3. H. K. Wang, S. L. Morris-Natschke and K. H. Lee, *Med. Res. Rev.*, 1997, **17**, 367.

4. Y. S. Vassetzky, G. C. Alghisi, and S. M. Gasser, *BioEssays*, 1995, **17**, 767.
5. G. J. Atwell, B. F. Cain, B. C. Baguley, G. J. Finlay, and W.A. Denny, *J. Med. Chem.,* 1984, **27**, 1481.
6. C. B. Carlson and P. A. Beal, *Org. Lett.,* 2000, **2**, 1465.
7. C. B. Carlson and P. A. Beal, *Bio. Med. Chem. Lett.,* 2000, **10**, 1979.
8. L. P. G. Wakelin, A. Adams, and W. A. Denny, *J. Med. Chem.,* 2002, **45**, 894.
9. F. Charmantray, A. Duflos, J. Lhomme, and M. Demeunynck, *J. Chem. Soc., Perkin Trans. 1,* 2001, 2962.
10. N. Filloux and J. P. Galy, *Synlett,* 2001, 1137.
11. V. Sourdon, S. Mazoyer, V. Pique, and J. P. Galy, *Molecules,* 2001, **6**, 673.
12. A. R. Katritzky, 'Handbook of Helectrocyclic Chemistry', Pergamon Press, Oxford, 1985, p. 207.
13. F. Hess, E. Cullen, and K. Grozinger, *Tetrahedron Lett.,* 1971, 2591.
14. D. E. Ward, Y. Gai, R. Lazny, M. Soledade and C. Pedras, *J. Org. Chem.,* 2001, **66**, 7832.
15. K. D. Hargrave, *J. Med. Chem.,* 1991, **34**, 2231.
16. B. F. Cain and G. J. Atwell, *Eur. J. Cancer,* 1974, **10**, 539.
17. I. V. Tetko and V. Y. Tanchuk, *J. Chem. Inf. Comput. Sci.*, 2002, **42**, 1136.
18. H. Günther, 'La spectroscopie de RMN', Masson, Paris, 1994, p. 60.
19. D. M. Doddrell, D. T. Pegg, and M. R. Bendall, *J. Magn. Res.*, 1982, **48**, 323.
20. R. E. Hurd, *J. Magn. Reson.*, 1990, **87**, 422.
21. R. E. Hurd and B. K. John, *J. Magn. Reson.*, 1991, **91**, 648.
22. W. Willker, D. Leibfritz, R. Kerssebaum, and W. Bermel, *Magn. Reson. Chem.*, 1993, **31**, 287.
23. A. Altamore, G. Cascarano, C. Giacovazzo, and A. Guagliardi, *Appl. Cryst.,* 1993, **26**, 343.
24. G. M. Sheldrick, SHELXL97, Universität Göttingen, Germany, 1997**.**
25. A. L. Spek, 'PLATON, A Multipurpose Crystallographic Tool', Utrecht University, Utrecht, The Netherlands, 2002**.**
26. W. L. DeLano, 'The PyMOL Molecular Graphics System', DeLano Scientific, San Carlos, CA, USA. 2002**.**
27. W. A. Hewlett, T. De Paulis, N. S. Mason, D. E. Schmidt, B. L. Trivedi, Z. J. Zhang, and M. H. Ebert, *Chem. Pharm. Bull.,* 1997, **45**, 2079.