Molecules **2001**, *6*, 300-322

molecules
ISSN 1420-3049
http://www.mdpi.org

Synthesis and Electrophilic Substitution of Pyrido[2,3,4-*kl*]-acridines‡

Avi Koller[1], Amira Rudi[1], Marta Garcia Gravalos[2] and Yoel Kashman[1,*]

[1] School of Chemistry, Tel Aviv University, Ramat Aviv 69978, Israel
[2] PharmaMar, Tres- Cantos, Madrid, Spain

* To whom correspondence should be addressed; E-mail: kashman@post.tau.ac.il; Phone: +972-3-640-8419. Fax: +972-3-640-9293.

‡ Presented at the 4th Electronic Conference on Synthetic Organic Chemistry, September 1-30, 2000, (Paper A0029).

Received: 28 February 2001; in revised form 7 March 2001 / Accepted: 7 March 2001 / Published: 31 March 2001

Abstract: Several new pyrido[2,3,4-*kl*]acridines were synthesized by reacting naphthoquinone, juglone or cyclohexan-1,3-dione with β,β'-diaminoketones in a biomimetic reaction. The structure of all new compounds was elucidated by NMR and MS spectroscopy. Electrophilic substitution, mainly nitration, of the various compounds was undertaken and the substitution positions determined. A series of derivatives was prepared and their cytotoxicity towards P-388 mouse lymphoma cells analysed. The most cytotoxic derivatives were found to have IC50's of 0.05 and 0.1 ug/ml.

Keywords: Pyrido[2,3,4-*kl*]acridines; Biomimetic synthesis; NMR; Electrophilic nitration; Cytotoxicity

---

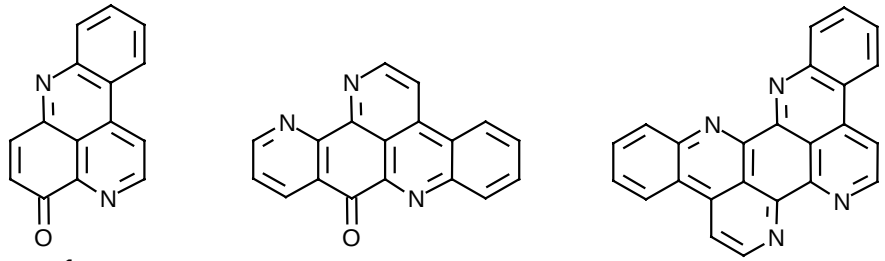
Introduction

Over the last 15 years more than 50 pyridoacridine alkaloids, based on the 4*H*-pyrido[2,3,4-*kl*]acridone (**1**) skeleton (Figure 1), have been isolated from marine organisms [1]. Almost all natural pyridoacridines have been reported to possess significant cytotoxicity against cultured tumor cells [1].

This motivated us to synthesize and study some of the compounds of this group. In 1993 we reported a biomimetic synthesis of the pyrido[2,3,4-*kl*]acridine ring system by the reaction of β,β'-diamino-ketones with a variety of quinones and diketones [2][3]. Using this method we synthesized the marine alkaloid ascididemin (**2**)[4], eilatin (**3**)[3] (Figure 1) and also new pyridoacridine skeletons such as benzoascididemin and isoeilatin [5].

Here we report a biomimetic synthesis of additional new pyridoacridines and a study of their reactions with electrophiles or amines (in the case of the quinoneimines). Most of the new pyridoacridines were tested for *in-vitro* activity against tumor cells and some of them were found to be highly cytotoxic.

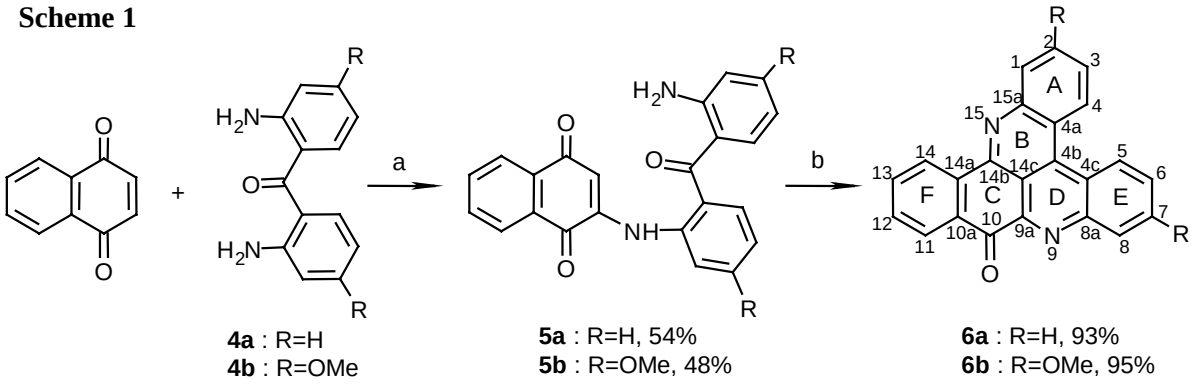
Figure 1

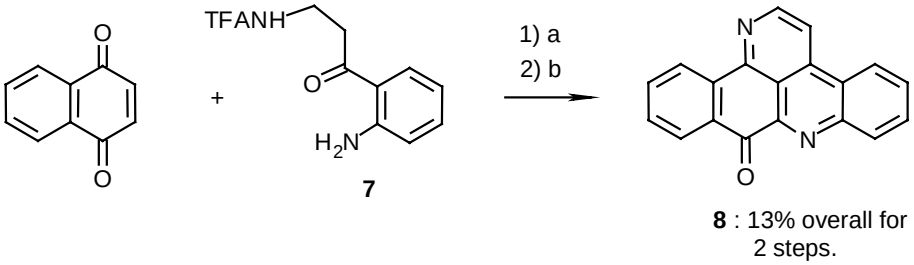


Results and Discussion

Several new pyridoacridines were synthesized in a two step reaction of β,β'-diaminoketones with quinones. Thus, addition of 2,2'-diaminobenzophenone **4a** or **4b** to 1,4-naphthoquinone afforded in the first step the arylaminonaphthoquinones **5a** and **5b** respectively, in approximately 50% yield (Scheme 1).

Scheme 1





Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, Air, E tOH, reflux, 9 h; (b) 25% NH_4OH, MeOH, R.T., 7 days.

The reaction took place in the presence of catalytic amounts of cerous chloride while air was bubbled through the solution to oxidize the intermediate hydroquinone [6-7]. In the second step, treatment of compounds **5a** and **5b** in methanol with NH_4OH at room temperature for 7 days gave the corresponding compounds **6a** and **6b** in over 90% yield (Scheme 1).

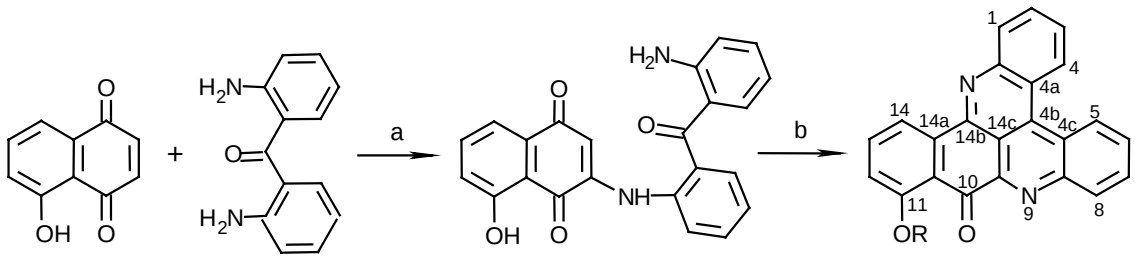
The structures of **6a** and **6b,** possessing the required molecular ions (*m/z* 332 and 392, respectively) were confirmed by 1D and mainly COSY, HMQC and HMBC 2D-NMR spectra (See Table 1 for the HMBC correlations and the Experimental section for the proton and carbon chemical shift assignments).

Characteristic were the resonances of C-10 and C-14b of the quinoneimine system (ring C) and the down-field proton resonances of the spatially close protons H-4 and H-5 (δ_H 9.09 and 9.18 ppm, respectively, for **6a** and δ_H 8.90 and 8.98 ppm, respectively, for **6b**)[5].

Three four-spin systems were observed in the ^{1}H-NMR spectrum of **6a** belonging to rings A, E and F. Rings A and E, bearing the spatially close H-4 and H-5 protons, were distinguished from ring F by NOE measurements. The differentiation between rings A and E was achieved from an NOE between H-1 and H-14 (about 3.7Å apart). This NOE was also the key for determining the structure of the nitration products **21**, **23a** and **23b,** as described below. A second reaction that was performed with naphthoquinone was its reaction with TFA-kynuramine (**7**) [4] (Scheme 1). This reaction afforded 9H-benzo[i]pyrido[2,3,4-*kl*]acridin-9-one (deaza-ascididemin, **8**), earlier synthesized by Zjawiony by a four step reaction [8]. The structure of compound **8** (*m/z* 282) was confirmed by its NMR data (see Experimental) and comparison with the data in the literature [8].

A second naphthoquinone that was tested was juglone. Reacting juglone (5-hydroxy-1,4-naphthoquinone) with diaminobenzophenone **4a** afforded, in a regioselective reaction, a single addition product **9** in 80% yield (Scheme 2).

Scheme 2



4a **9** (80%)

Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, Air, E tOH, R.T., 3 days; (b) E t $_3$N, MeOH, R.T., 10 days; (c) Ac $_2$O, pyridine, R.T., 24 h.

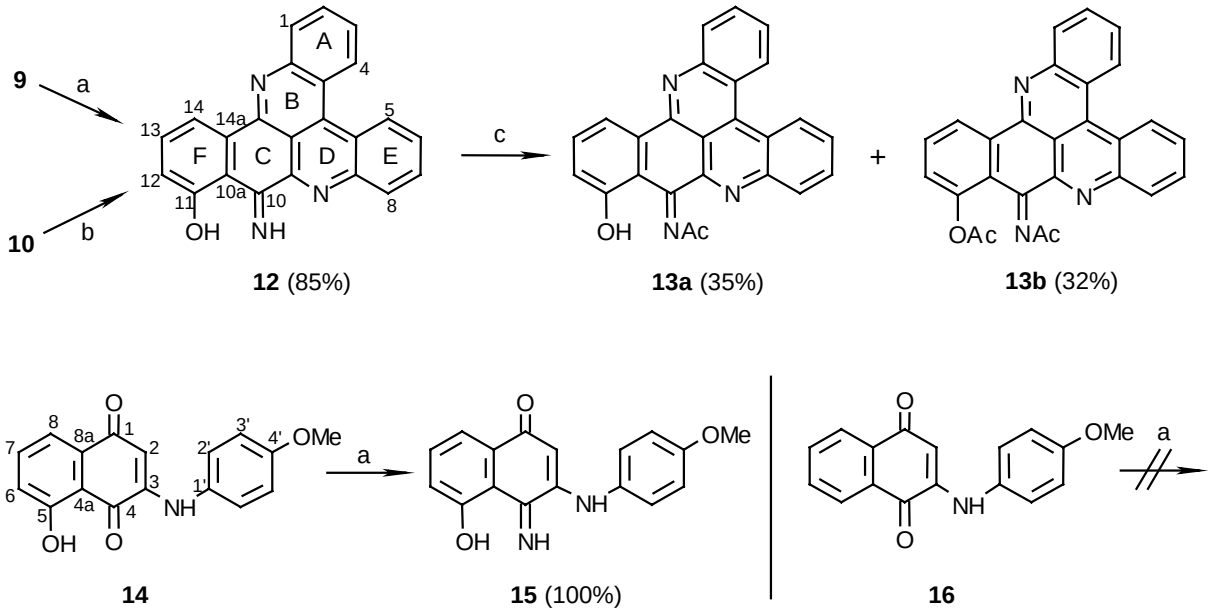
The orientation of this addition was defined by the structure determination of compound **10,** obtained in a second step by stirring compound **9** in methanol with Et_3N. A key HMBC correlation in the structure elucidation was the one between C-14b (δ 147.5) and H-14 (δ 8.73). For other correlations

that assisted with the structure determination see Table 1. The regioselectivity of nucleophilic additions of amines to juglone was observed before by Thomson [9] in the reactions of aniline with the juglone derivatives 5-acetoxy or 5-methoxy-1,4-naphthoquinones. Performing the second step of the latter reaction with ammonia, rather than Et_3N, as used for the preparation of compounds **6a** and **6b**, caused unexpectedly the disappearance of the C-10 carbonyl group. Moreover, acetylation of the obtained pyridoacridine (**12)** (Scheme 3) gave a mono- (**13a**) and a diacetate (**13b**). It is suggested that the carbonyl group of compound **10** is replaced in compound **12** by an imine and indeed, treatment of **10**, obtained with the Et_3N, with NH_3 gave compound **12**. The position of the imine group was defined by a HMBC experiment of compound **13a** namely from correlations between the 11-hydroxylic proton and carbons C-10a, C-11, and C-12 of ring F (see Table 1).

Table 1. Long-range CH correlations observed in the HMBC experiments of the benzopyridoacridines

C#	H# of correlated protons							
	6a	**6b**	**10**	**12**	**13a**	**20**	**23a**	**23b**
1	3	3	3	3	3			
2	4	4, OMe	4	4	4	4	4, OMe	4, OMe
3	1	1	1	1	1	1		
4	2		2	2	2	2		
4a	1, 3	1, 3	1, 3	1, 3	1, 3	1		
4b	4, 5	4, 5	4, 5	4, 5	4, 5	4, 5	4, 5	4, 5
4c	6, 8	6, 8	6, 8	6, 8	6, 8	6, 8	6	6
5	7		7	7	7	7		
6	8	8	8	8	8	8		
7	5	5, OMe	5	5	5	5	5, OMe	5, OMe
8	6	6	6	6	6	6	6	6
8a	5, 7	5	5, 7	5, 7	5, 7	5, 7	5	5
9a								
10	11	11				11	11	11
10a	12, 14	12, 14	12, 14	12, 14	12,14,OH	12, 14	14	12
11	13	13	13	13	13, OH	13	13	13
12	14	14	14	14	14, OH	14	14	
13	11	11				11	11	11
14	12	12	12	12	12	12		12
14a	11, 13	11, 13	13	13	13	11, 13	11, 13	11, 13
14b	14	14	14	14	14	14	14	
14c								
15a	2, 4	4	2, 4	2, 4	2, 4	2, 4	4	4

Scheme 3



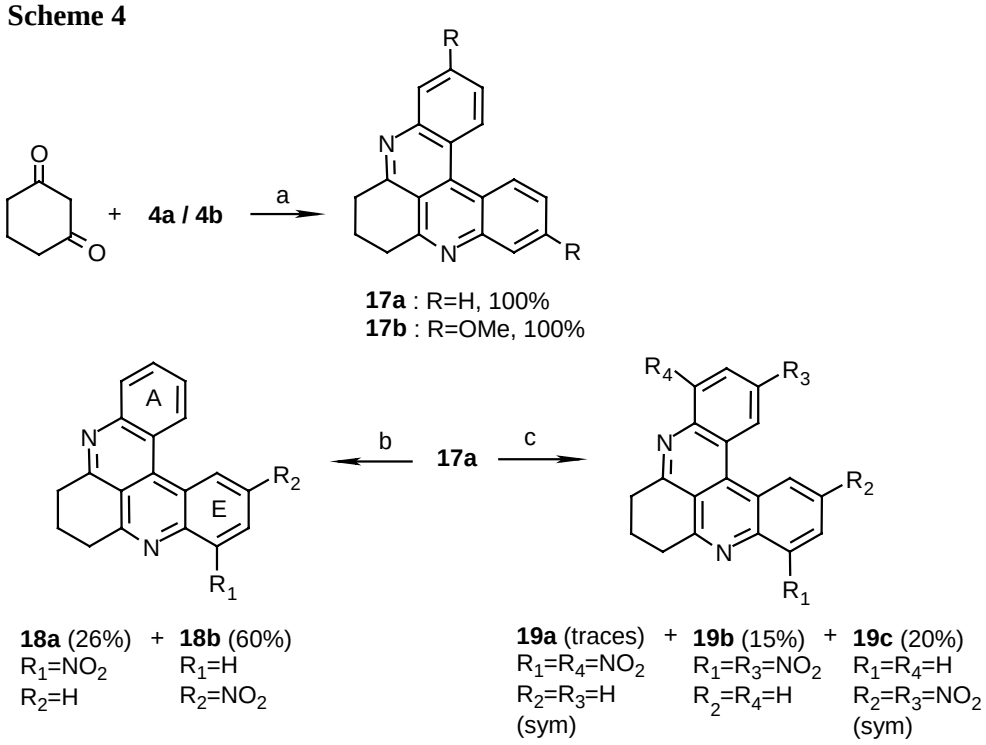
Reagents and conditions: (a) 25% NH_4OH, MeOH, R.T., 7 days; (b) MeOH / NH_3, R.T., 14 days; (c) Ac_2O, pyridine, R.T., 24 h.

Quinoneacetimide systems such as ring C in compounds **13a** and **13b** are stable, e.g. the reported simple acetimides of naphthoquinones and benzoquinones [10]. In contrast, simple quinoneimines are unstable and were seldom isolated [10]. Thus, it was interesting to find that the quinoneimine moiety of compound **12** is stable as was also found to be the case of the natural pyridoacridine calliactine [11] whose structure was determined recently [12]. In both compound **12** and calliactine the hydroxyl group in the β position relative to the imine group seems to stabilize the quinoneimine by a hydrogen- bond. Another example for the latter behaviour was seen in compound **14**, synthesized from juglone and p-anisidine (Scheme 3). Compound **14** in methanol with aqueous ammonia, yielded the quinoneimine **15**, while compound **16** [13] without the β-OH group, did not form the quinoneimine under the same conditions. These results proved the necessity of a hydroxyl group β to the ketone for the imine formation and also suggest that the quinoneimine ring could be obtained, in the synthesis, before the rings closure of compound **10**.

A major target in the present investigation was the study of the electrophilic substitution reactions of pyridoacridines and dihydropyridoacridines for the preparation of derivatives for structure activity relationship studies. It was decided to start with nitration as the nitro groups are easily transformed to other functional groups. Investigating a variety of nitration conditions (HNO_3-TFA, HNO_3-H_2SO_4 and NO_2BF_4 in CH_3CN) brought to the best conditions, namely, the use of HNO_3-H_2SO_4, 1:1 *vide infra*.

The first substrate for nitration was dihydropyridoacridine **17a**. Compounds **17a** and **17b** were obtained in quantitative yields by condensation of compounds **4a** or **4b** with 1,3-cyclohexanedione (Scheme 4). Nitration of compound **17a** gave, after 1 hour, two mononitro isomers **18a** and **18b** and three dinitroisomers **19a**, **19b** and **19c** after 12 hours of reaction at room temperature.

Scheme 4



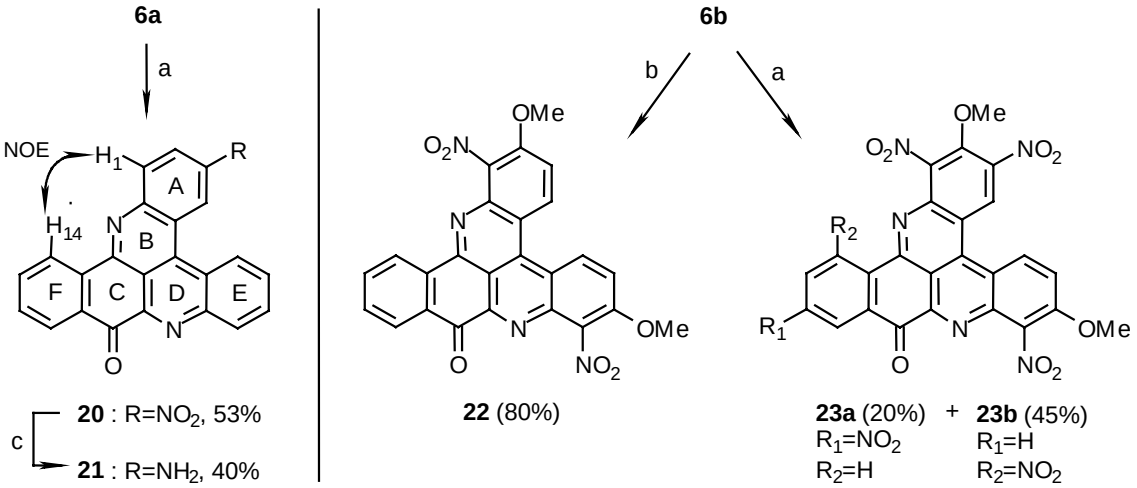
Reagents and conditions: (a) AcOH / conc. HCl (99.5:0.05), 3-Nitrobenzenesulfonic acid Sodium salt, reflux, 2 h.; (b) HNO_3 / H_2SO_4 (1:1), R.T., 1 h.; (c) HNO_3 / H_2SO_4 (1:1), R.T., 12 h.

The structures of the different isomers were determined by ^{1}H-NMR and COSY experiments. In all the products the nitro group(s) are in ring A (or E) in positions *para* or *ortho* to the nitrogen of the attached pyridine ring (*para* or *ortho* positions). The yields of the nitration products indicate that the *para* position in ring A (and E) is more reactive than the *ortho* one under the conditions used. Nitration of quinoline with nitric acid in sulphuric acid at 0^{o}C was reported to yield 5- and 8-nitroquinoline in a ratio of 52% to 48% respectively [14]. The nitration experiments of compound **17a** show that the *para* position of ring A (and E) in the dihydropyridoacridine is more reactive than position- 6 of quinoline, under the same conditions [15]. Positions 4 and 5 in the pyridoacridine, which can be compared to the reactive position- 5 of quinoline, are blocked by steric interference and therefore are not substituted.

The nitration of compound **6a** afforded a mono-nitro product **20** in 53% yield after 12 hours at room temperature. Because of the absence of long range CH-correlations in the NMR experiments between atoms of rings A or E and F to ring C it was difficult to determine whether the nitro group is attached to ring A or E. However, the nitration position, C-3 on ring A, could be determined from a NOE between H-1 and H-14 (2%), which are ca.3.7 Å apart (see Scheme 5). It was found by 1D and 2D NMR experiments (for HMBC correlations see Table 1) that the nitration went to the *para* position of ring A as was found for the nitro derivatives of compound **17a** which were obtained in higher yields (compounds **18b**, **19b** and **19c**).

Catalytic hydrogenation of compound **20** with 5% Pd-C in AcOH / TFA afforded the amino derivative **21**.

Scheme 5



Reagents and conditions: (a) HNO_3 / H_2SO_4 (1:1), R.T., 12 h.; (b) HNO_3 / H_2SO_4 (1:1), R.T., 1 h.; (c) AcOH / TFA (1:2), 5% Pd/C, H_2, 3 Atm, R.T., 1 h.

Nitration of compound **6b**, the electron richer 2,7-dimethoxy derivative of **6a**, gave a dinitro derivative **22** after 1 hour and two tetra nitro isomers **23a** and **23b** (Scheme 5) after 12 hours of reaction at room temperature. That the two nitro groups in **22** substituted C-1 and -8, *ortho* to the quinoline-nitrogen, was clear from the two AB- systems seen in the ^{1}H-NMR spectrum along with the aromatic four- proton system (Experimental).

The structures of **23a** and **23b** were also determined by 1D and 2D-NMR experiments (for HMBC correlations see Table 1). In compounds **23a** and **23b** only one of rings A or E was attacked by the electrophile at the *para* position. The structures of compounds **23a** and **23b** are tentatively suggested on the basis of the structure of compound **20** as depicted in Scheme 5. Because of the nitro groups at the *ortho* positions, it was impossible to prove by NOE that the substitution is at the *para* position of ring A (as in the case of compound **20**). In addition to the nitration of rings A and E, ring F in **23a** and **23b** was also substituted due to long range activation by the methoxyl groups.

The second electrophilic substitution undertaken was bromination. Compounds **6a** and **8** did not react with Br_2 in CH_2Cl_2, Br_2 in AcOH or NBS in CH_2Cl_2 and it seems that severe conditions may be needed in order to brominate these compounds. The use of Lewis acids as catalyst precipitated the compound. Quinoneimine **24** [2] afforded the dibromo derivative **26** (Scheme 6) by reaction with Br_2 in AcOH; a reaction known for quinones [16]. Compound **26** like other dibromoquinones is expected to afford a variety of derivatives by cycloaddition reactions and by reactions with amines and thiols [13, 16-17].

Several of the synthesized new pyridoacridines were tested for *in-vitro* cytotoxicity against P-388 mouse lymphoma cells (Table 2). It was found that compounds **6a** and **8** are more cytotoxic than other

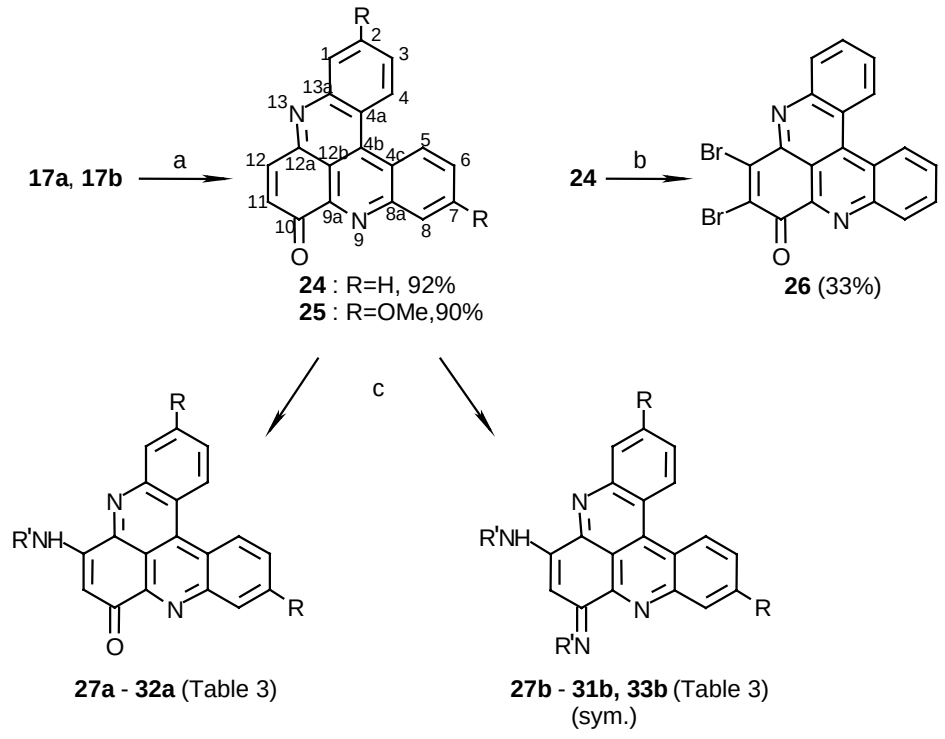
reported natural pyridoacridines for which IC_{50} values of 0.1- 0.4 ug/ml were found [1a]. The cytotoxicity of compound **6a**, the electron richer dimethoxy derivative **6b** and the electron poorer nitro derivatives **21** and **23b**, as well as compound **12** and its acetate derivatives **13a** and **13b** is lower.

Table 2. In- vitro cytotoxicity against P-388 mouse lymphoma cells

Compound	**6a**	**6b**	**8**	**12**	**13a**	**13b**	**24**	**25**	**20**	**21**	**23b**
IC_{50} (ug/ml)	0.05	10	0.1	>10	5	10	1	2.5	0.5	10	2.5

Oxidation of compounds **17a** and **17b**, with cerium ammonium nitrate, afforded benzopyridoacridones **24** and **25,** respectively, in high yields (Scheme 6). Amination of the latter quinoacridones (**24** and **25**) with several primary amines in ethanol afforded two kinds of derivatives; monoamination products (compounds **27a- 32a**) and symmetric diamination ones (compounds **27b-31b** and **33b**). The diamination products were separated easily from the monoamination products, in each reaction, by silica gel chromatography (eluting with chloroform- methanol mixtures). The diamination products are more polar than the monoamination products and the starting material. Performing the amination in acetonitrile instead of ethanol afforded mainly the monoamination products **27a** and **30a** with only traces of the diamination products **27b** and **30b** (Scheme 6). Another derivative, prepared from **24**, was compound **32a** (Scheme 6), which was derived from **24** by hydrazoic acid in methanol under conditions reported for synthesis of aminonaphthoquinones [18].

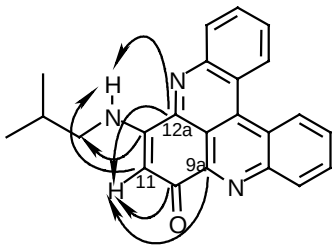
Scheme 6



Reagents and conditions: (a) CAN, CH_3CN, reflux, 10 min.; (b) Br_2, AcOH, 80°C, 2 h.; (c) see Table 3 and Experimental.

The structures of the diamination products were determined by their ^{1}H- and ^{13}C-NMR spectra which indicated symmetric structures (see Experimental). The substitution site in the monoamination product **27a** was determined by a HMBC experiment which showed correlations between proton H-11 and carbons C-9a and C-12a and correlations between the substituent NH- proton and carbons C-12a and C-11 (Scheme 7). As seen in Table 3, the symmetric diamination products are more cytotoxic than the monoamination ones and most of the diamination products are more toxic than their parent compounds **24** and **25** (Table 2). Most active are the symmetric derivatives obtained with isobutylamine and methylamine (compounds **27b**- **29b**) while the more lypophilic derivative obtained with dodecylamine (compound **31a**) (as well as **31b**) and the more hydrophilic derivative obtained with serinol (compound **33b**) are less active.

Scheme 7. CH correlations in HMBC experiment of compound **27a**



27a

Table 3. Amination products of compounds 24 and 25 with amines R'NH_2 and their in-vitro cytotoxicity against P-388 mouse lymphoma cells.

Compound	R	R'	Yield (%)		IC50 (ug/ml)	
			a	b	a	b
27	H	$(CH_3)_2CHCH_2$	36	38	0.25	0.1
28	OCH_3	$(CH_3)_2CHCH_2$	19	37	1	0.1
29	H	CH_3	46	28	0.25	0.1
30	H	$CH_3OC_6H_4$	55	38	1	0.5
31	H	$CH_3(CH_2)_{11}$	24	18	2.5	0.5
32a[a]	H	H	76	-	1	-
33	H	$(HOCH_2)_2CH$	-	50	-	>10

[a] **32a** is the reaction product of **24** with hydrazoic acid (see Experimental).

Experimental

General

Commercially available reagents were purchased from standard chemical suppliers and were used without further purification. 2(N)-(4-methoxyaniline)-1,4-naphthoquinone (**16**) was synthesized by a literature method [13]. IR spectra (KBr disks) were recorded on a Nicolet 205 FT-IR spectrophotometer. MS and HRMS spectra were recorded on a Fisons Autospec Q instrument. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker ARX-500 or a Bruker AMX-360 spectrometer. NOE experiments and 2D NMR spectra (COSY, HMQC and HMBC) were recorded on a Bruker ARX-500 instrument using standard pulse sequences. TLC was performed on Merck precoated Kieselgel 60 F_{254} plates. Column chromatography was performed using Silica gel 60 H (Merck) unless otherwise stated. The silica was washed with methanol, before use, in a Soxhlet apparatus. In all cases silica gel chromatography was performed with vacuum.

2,2'-Diaminobenzophenone (**4a**):

Compound **4a** was performed from 2,2'-dinitrobenzophenone by hydrogenation, instead of the literature method of reduction with iron powder [19]. 2,2'-Dinitrobenzophenone [19] (250 mg, 0.92 mmol) was dissolved in dichloromethane (40 mL), 5% Pd/C (100 mg) was added and the solution was shaken in a Parr apparatus under H_2 (3 atm) for 1 hour. The catalyst was filtered off and the solvent evaporated to afford **4a** (195 mg, quantitative yield), yellow crystals (from 80% aqueous methanol), m.p. 134^{o}C (lit [19], 134-135 ^{o}C).

2,2'-Diamino-4,4'-dimethoxybenzophenone (**4b**):

4b was prepared from 2,2'-Dinitro-4,4'-dimethoxybenzophenone [20] (250 mg, 0.75 mmol) under the same conditions as described for the synthesis of **4a**. The product was recrystallized from methanol to afford **4b** (185 mg, 90%): m.p. 138^{o}C (lit [20], 137-138^{o}C).

General procedure for the reaction between arylamines and 1,4-naphthoquinones

The procedure of Pratt [7] was adopted. The corresponding amine (1 equiv.) was dissolved in ethanol, $CeCl_3 \cdot 7H_2O$ (0.05 equiv.) was added followed by the naphthoquinone (1.5 equiv.). The resulting red solution was refluxed for 9 h. During this time air saturated with ethanol (prepared by passage of air through hot ethanol to avoid evaporation of the ethanol) was bubbled through the reaction mixture. After cooling, the ethanol was evaporated and the residue purified by chromatography on silica gel (eluting with chloroform/methanol) to afford the desired amination product.

2(N)-(2,2'-diaminobenzophenone)-1,4-naphthoquinone (**5a**):

4a (450 mg, 2.1 mmol) was dissolved in ethanol (20 mL) and reacted with naphthoquinone (500 mg, 3.2 mmol) by the above described general procedure. The crude mixture containing the product and starting materials was chromatographed by two subsequent silica gel columns (eluting with $CHCl_3$/MeOH, 50:1) to afford **5a** (420 mg, 54%), red prisms (from EtOH), m.p. 208°C; MS (EI); *m/z*: 368 (100) [M^+, $C_{23}H_{16}N_2O_3$]; IR: $\tilde{\nu}$ = 1667, 1611, 1568, 1512, 1292, 1246 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 6.56 (s, 1 H, 3-H), 6.59 (t, *J*=7.5 Hz, 1 H, 12'-H), 6.72 (d, *J*=7.5 Hz, 1 H, 10'-H), 7.21 (t, *J*=7.5 Hz, 1 H, 11'-H), 7.29 (t, *J*=7.5 Hz, 1 H, 4'-H), 7.40 (d, *J*=7.5 Hz, 1 H, 6'-H), 7.52 (d, *J*=7.5Hz, 1 H, 13'-H), 7.55 (t, *J*=7.5 Hz, 1 H, 5'-H), 7.63 (d, *J*=7.5 Hz, 1 H, 3'-H), 7.65 (t, *J*=7.6 Hz, 1 H, 7-H), 7.75 (t, *J*=7.6 Hz, 1 H, 6-H), 8.08 (d, *J*=7.6 Hz, 1 H, 5-H), 8.09 (d, *J*=7.6 Hz, 1 H, 8-H), 9.30 (br s, 1 H, NH).

2(N)-(2,2'-diamino-4,4'-dimethoxybenzophenone)-1,4-naphthoquinone (**5b**):

4b (200 mg, 0.74 mmol) was dissolved in ethanol (10 mL) and reacted with naphthoquinone (170 mg, 1.1 mmol) by the general procedure described above. After two subsequent silica gel columns (eluting with $CHCl_3$) compound **5b** was isolated (150 mg, 48%): red prisms (from EtOH), m.p. 214°C. – MS (EI); *m/z*: 428 (100) [M^+, $C_{25}H_{20}N_2O_5$]; IR: $\tilde{\nu}$ = 1658, 1624, 1576, 1521, 1448, 1244 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 3.81 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.14 (s, 1 H, 10'-H), 6.17 (d, *J*=8.5 Hz, 1 H, 12'-H), 6.62 (s, 1 H, 3-H) , 6.68 (dd, *J*=8.5, 2.5 Hz, 1 H, 4'-H), 7.11 (d, *J*=2.5Hz, 1 H, 6'-H), 7.36 (d, *J*=8.5 Hz, 1 H, 13'-H), 7.44 (d, *J*=8.5 Hz, 1 H, 3'-H), 7.65 (t, *J*=7.0 Hz, 1 H, 7-H), 7.74 (t, *J*=7.0 Hz, 1 H, 6-H), 8.10 (d, *J*=7.0 Hz, 1 H, 5-H), 8.11 (d, *J*=7.0 Hz, 1 H, 8-H), 9.90 (br s, 1 H, NH).

10H-benzo[i]quino[2,3,4-kl]acridin-10-one (**6a**):

5a (400 mg, 1.1 mmol) was added to a solution of 25% aq. ammonia (10mL) in methanol (100mL) and stirred for 7 days at room temperature. During this time the reaction was monitored by TLC, Rf= 0.7 and 0.5 for **5a** and **6a** respectively (petroleum ether/ethyl acetate, 1:1). The reaction mixture was evaporated and the crude product was chromatographed (eluting with $CHCl_3$/MeOH 30:1) to afford **6a** (335 mg, 93%), amorphous powder ($CHCl_3$/MeOH, 9:1), m.p. 255°C; Analysis: $C_{23}H_{12}N_2O$ (332.1): calcd. C 83.1, H 3.64, N 8.43, found C 82.4, H 3.53, N 8.70; HRMS calcd. for $C_{23}H_{12}N_2O$ [M^+] 332.0950, found 332.0947; IR: $\tilde{\nu}$ = 1678, 1654, 1562, 1396, 1203 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 7.73 (t, *J*=7.5 Hz, 1 H, 12-H), 7.83 (t, *J*=8.0 Hz, 1 H, 3-H), 7.90 (t, *J*=7.5 Hz, 1 H, 13-H), 7.95 (t, *J*=8.0 Hz, 1 H, 6-H), 7.95 (t, *J*=8.0 Hz, 1 H, 2-H), 8.03 (t, *J*=8.0 Hz, 1 H, 7-H), 8.42 (d, *J*=8.0 Hz, 1 H, 1-H), 8.52 (d, *J*=7.5 Hz, 1 H, 11-H), 8.73 (d, *J*=8.0 Hz, 1 H, 8-H), 9.09 (d, *J*=8.0 Hz, 1 H, 4-H), 9.11 (d, *J*=7.5 Hz, 1 H, 14-H), 9.18 (d, *J*=8.0 Hz, 1 H, 5-H); ^{13}C-NMR ($CDCl_3$): δ = 115.8 (s, C-14c), 122.4 (s, C-4a), 124.2 (s, C-4c), 125.9 (d, C-14) , 127.0 (d, C-5), 127.1 (d, C-4), 127.9 (d, C-11), 128.1 (d, C-3), 129.9 (d, C-6), 130.8 (d, C-2), 130.9 (d, C-7), 131.0 (d, C-1), 131.0 (d, C-12), 132.2 (s, C-10a), 132.4 (d, C-8), 134.7 (d, C-13), 136.0 (s, C-14a), 136.1 (s, C-4b), 145.4 (s, C-9a), 147.2 (s, C-15a), 147.3 (s, C-8a), 147.7 (s, C-14b), 182.2 (s, C-10).

2,7-Dimethoxy-10H-benzo[i]quino[2,3,4-kl]acridin-10-one (**6b**):

5b (150 mg, 0.35 mmol) was treated with ammonia in methanol by the same procedure described for the synthesis of **6a**. The product (**6b**) was obtained after chromatography (eluting with chloroform/methanol, 30:1) (130 mg, 95%): amorphous powder ($CHCl_3$/MeOH, 8:2), m.p. 296^oC; Analysis: $C_{25}H_{16}N_2O_3$ (392.4): calcd. C 76.5, H 4.11, N 7.14, found C 76.4, H 3.90, N, 7.84; MS (EI); *m/z*: 392 (100) [M^+], 377 (5) [M^+- CH_3], 361 (14) [(M^+- CH_3O]; IR: $\tilde{\nu}$ = 1676, 1611, 1587, 1564, 1415, 1239, 1218 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 4.08 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 7.40 (dd, 1 H, *J*=9.5, 2.5 Hz, 3-H), 7.54 (dd, 1 H, *J*=9.5, 2.5 Hz, 6-H), 7.64 (t, 1 H, *J*=8.0 Hz, 12-H), 7.77 (d, 1 H, *J*=2.5 Hz, 1-H), 7.88 (t, 1 H, *J*=8.0 Hz, 13-H), 8.04 (d, 1 H, *J*=2.5 Hz, 8-H), 8.49 (d, 1 H, *J*=8.0 Hz, 11-H), 8.90 (d, 1 H, *J*=9.5 Hz, 4-H), 8.98 (d, 1 H, *J*=9.5 Hz, 5-H), 9.07 (d, 1 H, *J*=8.0 Hz, 14-H); ^{13}C-NMR ($CDCl_3$): δ = 55.5 (OCH_3), 55.9 (OCH_3), 108.7 (d, C-8), 110.3 (d, C-1), 113.1 (s, C-14c), 116.0 (s, C-4a), 118.7 (s, C-4c), 119.8 (d, C-3), 122.5 (d, C-6), 126.0 (d, C-14), 128.0 (d, C-11), 128.2 (d, C-5), 128.4 (d, C-4), 131.4 (d, C-12), 131.4 (s, C-10a), 135.0 (d, C-13), 135.3 (s, C-14a), 137.0 (s, C-4b), 143.7 (s, C-9a), 147.6 (s, C-14b), 148.0 (s, C-8a), 149.0 (s, C-15a), 159.0 (s, C-7), 159.4 (s, C-2), 182.3 (s, C-10).

9H-benzo[i]pyrido[2,3,4-kl]acridin-9-one (**8**):

TFA-kynuramine (**7**)[4] (500 mg, 1.9 mmol), naphthoquinone (330 mg, 2.1 mmol) and $CeCl_3 \cdot 7H_2O$ (35 mg, 0.094 mmol) were dissolved in ethanol (25 mL). The reaction mixture was refluxed for 9 h. while air was bubbled through it as described above in the general procedure. After evaporation of the ethanol and chromatography (eluting with $CHCl_3$/MeOH, 50:1) the crude product was added to a solution of 25% aq. ammonia (10 mL) in methanol (100 mL) and was stirred at room temperature for 7 days. The reaction mixture was evaporated and chromatographed (eluting with chloroform/methanol, 30:1) to afford **8** (70mg, 13%), amorphous powder (chloroform/methanol, 9:1), mp 258^oC (lit [8], 260-262^0C).

3(N)-(2,2'-diaminobenzophenone)-5-hydroxy-1,4-naphthoquinone (**9**):

4a (100 mg, 0.47 mmol) and $CeCl_3 \cdot 7H_2O$ (186 mg, 0.50 mmol) were dissolved in ethanol (10 mL) and 5-Hydroxy-1,4-naphthoquinone (juglone) (87 mg, 0.50 mmol) was added. The color of the solution changed immediately from yellow to red. The reaction mixture was stirred at room temperature, with bubbled air, for 3 days. The solvent was then evaporated and the red product purified by chromatography (eluting with $CHCl_3$/MeOH, 100:1) (144mg, 80%): red prisms (from EtOH), m.p. 221^oC; MS (EI); *m/z*: 384 (100) [M^+, $C_{23}H_{16}N_2O_4$]; IR: $\tilde{\nu}$ = 3450, 1625, 1606, 1572, 1513, 1448, 1273, 1242 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 6.2 (br s, 2 H, NH_2), 6.52 (s, 1 H, H-2), 6.58 (t, *J*=7.5 Hz, 1 H, 12'-H), 6.72 (d, *J*=7.5Hz, 1 H, 10'-H), 7.16 (dd, *J*=7.5, 2.0 Hz, 1 H, 6-H), 7.21 (t, *J*=7.5 Hz, 1 H, 11'-H), 7.30 (t, *J*=7.5 Hz, 1 H, 4'-H), 7.40 (d, *J*=7.5 Hz, 1 H, 6'-H), 7.51 (d, *J*=7.5 Hz, 1 H, 13'-H), 7.54 (t, *J*=7.5 Hz, 1 H, 5'-H), 7.60 (d, *J*=7.5 Hz, 1 H, 8-H), 7.61 (d, *J*=7.5 Hz, 1 H, 3'-H), 7.62 (t, *J*=7.5 Hz, 1 H, 7-H), 9.45 (br s, 1 H, NH), 11.60 (s, 1 H, OH).

11-Hydroxy-10H-benzo[i]quino[2,3,4-kl]acridin-10-one (**10**):

9 (70 mg, 0.18 mmol) was added to a solution of Et_3N (2 mL) in methanol (20 mL) and the reaction mixture was stirred at room temperature for 10 days. The solution was evaporated and the residual solid chromatographed (eluting with $CHCl_3$/MeOH, 100:1) to afford **10** (61 mg, 98%), yellow needles ($CHCl_3$-MeOH 50:1), m.p. 292°C; HRMS calcd. for $C_{23}H_{12}N_2O_2$ [M^+] 348.0899, found 348.0899; IR: $\tilde{\nu}$ = 3441, 2924, 1639, 1611, 1567, 1458, 1402, 1277 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 7.30 (d, *J*=8.0 Hz, 1 H, 12-H), 7.83 (t, *J*=8.0 Hz, 1 H, 13-H), 7.88 (t, *J*=8.5 Hz, 1 H, 3-H), 8.00 (t, *J*=8.5 Hz, 1 H, 6-H), 8.00 (t, *J*=8.5 Hz, 1 H, 2-H), 8.08 (t, *J*=8.5 Hz, 1 H, 7-H), 8.67 (d, *J*=8.5 Hz, 1 H, 1-H), 8.73 (d, *J*=8.0 Hz, 1 H, 14-H), 8.83 (d, *J*=8.5 Hz, 1 H, 8-H), 9.08 (d, *J*=8.5 Hz, 1 H, 4-H), 9.17 (d, *J*=8.5 Hz, 1 H, 5-H), 12.90 (s, 1 H, OH); ^{13}C-NMR ($CDCl_3$/CD_3OD, 50:1): δ = 116.9 (s, C-10a), 117.7 (d, C-14), 120.3 (d, C-12), 122.7 (s, C-4a), 124.6 (s, C-4c), 127.2 (d, C-5), 127.3 (d, C-4), 128.4 (d, C-3), 130.4 (d, C-6), 131.1 (d, C-7), 131.2 (d, C-2), 131.3 (d, C-1), 132.7 (d, C-8), 136.1 (s, C-4b), 136.4 (s, C-14a), 137.8 (d, C-13), 145.3 (s, C-9a), 147.5 (s, C-14b), 147.5 (s, C-8a), 147.5 (s, C-15a), 163.9 (s, C-11), 183.6 (s, C-10); C-14c could not be seen due to a long relaxation time.

11-Acetoxy-10H-benzo[i]quino[2,3,4-kl]acridin-10-one (**11**):

10 (10 mg, 0.029 mmol) was acetylated with acetic anhydride-pyridine, 1:1 (1 mL), at room temperature for 24 h. The reaction mixture was evaporated and chromatographed (eluting with $CHCl_3$/MeOH, 40:1) to give **11** (11 mg, 95%), yellow needles ($CHCl_3$/MeOH, 100:1), m.p. 222°C; MS (EI); *m/z*: 390 (5) [M^+, $C_{25}H_{14}N_2O_3$], 348 (100) [M^+-CH_2CO]; IR: $\tilde{\nu}$ = 2924, 1765, 1677, 1563, 1401, 1193 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 50:1): δ = 2.52 (s, 3 H, $COCH_3$), 7.28 (d, *J*=8.0 Hz, 1 H, 12-H), 7.69 (t, *J*=8.0 Hz, 1 H, 13-H), 7.80 (t, *J*=8.0 Hz, 1 H, 3-H), 7.80 (t, *J*=8.0 Hz, 1 H, 2-H), 7.85 (t, *J*=8.0 Hz, 1 H, 6-H), 7.93 (t, *J*=8.0 Hz, 1 H, 7-H), 8.23 (d, *J*=8.0 Hz, 1 H, 1-H), 8.57 (d, *J*=8.0 Hz, 1 H, 14-H), 8.89 (d, *J*=8.0 Hz, 1 H, 8-H), 8.96 (d, *J*=8.0 Hz, 1 H, 4-H), 9.00 (d, *J*= 8.0 Hz, 1 H, 5-H).

11-Hydroxy-10-imino-10H-benzo[i]quino[2,3,4-kl]acridine (**12**):

Method A: **9** (110 mg, 0.28 mmol), was added to a mixture of 25% aq. ammonia (2 ml) and methanol (20 mL) and stirred at room temperature for 7 days. The reaction mixture was then evaporated and the residue chromatographed (eluting with $CHCl_3$/MeOH, 30:1) to afford **12** (83 mg, 85%).
Method B: **10** (10 mg, 0.029 mmol) was stirred in a saturated ammonia/methanol solution (2 mL) for 14 days. The solvent was then evaporated and the residue chromatographed using $CHCl_3$/MeOH, 30:1, as eluant to afford **12** (7 mg, 70%), dark-green needles ($CHCl_3$/MeOH, 20:1), m.p. 266°C; HRMS calcd. for $C_{23}H_{13}N_3O$ [M^+] 347.10586, found 347.10590; IR: $\tilde{\nu}$ = 3384, 1615, 1565, 1488, 1472, 1405, 1124, 1048 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 7.11 (d, *J*=8.0 Hz, 1 H, 12-H), 7.57 (d, *J*=8.0Hz, 1 H, 13-H), 7.77 (t, *J*=8.0 Hz, 1 H, 3-H), 7.88 (t, *J*=8.0 Hz, 1 H, 6-H), 7.89 (t, *J*=8.0 Hz, 1 H, 2-H), 7.97 (t, *J*=8.0 Hz, 1 H, 7-H), 8.32 (d, *J*=8.0 Hz, 1 H, 1-H), 8.37 (d, *J*=7.5 Hz, 1 H, 14-H), 8.40 (d, *J*=8.0 Hz, 1 H, 8-H), 9.00 (d, *J*=8.0 Hz, 1 H, 4-H), 9.10 (d, *J*=8.0 Hz, 1 H, 5-H), 10.81 (br s, 1 H), 14.8 (br s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 113.5 (s, C-10a), 115.9 (d, C-14), 122.4 (s, C-4a), 123.6 (d, C-12), 124.3 (s, C-4c),

127.1 (d, C-4), 127.3 (d, C-5), 127.6 (d, C-3), 129.2 (d, C-6), 130.8 (d, C-7), 130.8 (d, C-2), 131.2 (d, C-8), 131.3 (d, C-1), 133.3 (s, C-14a), 135.2 (d, C-13), 136.1 (s, C-4b), 143.2 (s, C-9a), 146.7 (s, C-8a), 147.9 (s, C-15a), 148.8 (s, C-14b), 162.1 (s, C-10), 171.0 (s, C-11); C-14c could not be seen due to a long relaxation time.

Acetylation of compound **12** *to afford compounds* **13a** *and* **13b**:

12 (10 mg, 0.029 mmol) was added to a mixture of acetic anhydride/pyridine, 1:1 (1 mL), and the solution was stirred at room temperature for 24 h. The reaction mixture was evaporated and chromatographed. Elution with $CHCl_3$/MeOH, 200:1, afforded the mono N-acetylated product **13a** (4 mg, 35%) and further elution with $CHCl_3$/MeOH, 100:1, afforded the diacetylated product **13b** (4 mg, 32%). Acetylation of **13a** (1 mg, 2.6 μmol) by the same procedure gave the O,N-diacetate derivative **13b** (1 mg). **13a**: MS (EI); *m/z*: 389 (14) [M^+, $C_{25}H_{15}N_3O_2$], 373 (66) [M^+- O], 347 (100) [M^+-CH_2CO]; IR: $\tilde{\nu}$ = 3430, 1698, 1615, 1568, 1404, 1241, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.72 (s, 3 H, $NCOCH_3$), 7.22 (d, *J*=8.5 Hz, 1 H, 12-H), 7.66 (t, *J*=8.5 Hz, 1 H, 13-H), 7.76 (t, *J*=8.5 Hz, 1 H, 3-H), 7.89 (t, *J*=8.5 Hz, 1 H, 2-H), 7.91 (t, *J*=8.0 Hz, 1 H, 6-H), 7.97 (t, *J*=8.0 Hz, 1 H, 7-H), 8.31 (d, *J*=8.5 Hz, 1 H, 1-H), 8.37 (d, *J*=8.0 Hz, 1 H, 8-H), 8.61 (d, *J*=8.5 Hz, 1 H, 14-H), 8.98 (d, *J*=8.5 Hz, 1 H, 4-H), 9.09 (d, *J*=8.5 Hz, 1 H, 5-H); ^{13}C-NMR ($CDCl_3$): δ = 26.6 ($NCOCH_3$), 114.4 (s, C-14c), 114.8 (s, C-10a), 117.8 (d, C-14), 120.3 (d, C-12), 122.5 (s, C-4a), 123.8 (s, C-4c), 127.1 (d, C-4), 127.3 (d, C-5), 128.0 (d, C-3), 129.8 (d, C-6), 131.0 (d, C-7), 131.0 (d, C-2), 131.2 (d, C-8), 131.2 (d, C-1), 134.6 (d, C-13), 135.0 (s, C-14a), 136.5 (s, C-4b), 141.8 (s, C-9a), 146.1 (s, C-8a), 147.8 (s, C-15a), 148.4 (s, C-14b), 153.8 (s, C-10), 161.6 (s, C-11), 183.8 ($NCOCH_3$). **13b**: MS (EI); *m/z*: 433 (17) [$(M+2)^+$, $C_{27}H_{19}N_3O_3$], 389 (15) [M^+-CH_2CO], 373 (100) [$(M+2)^+$-CH_3CO_2H], 347 (82) [M^+- $2CH_2CO$]; IR: $\tilde{\nu}$ = 3430, 1767, 1676, 1640, 1569, 1204 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.47 (s, 3 H, $OCOCH_3$), 2.60 (s, 3 H, $NCOCH_3$), 7.35 (dd, *J*=8.0, 1.5 Hz, 1 H, 12-H), 7.77 (t, *J*=8.0 Hz, 1 H, 13-H), 7.79 (t, *J*=8.0 Hz, 1 H, 6-H), 7.88 (t, *J*=8.0 Hz, 1 H, 3-H), 7.89 (t, *J*=8.0 Hz, 1 H, 7-H), 7.95 (dt, *J*=8.0, 1.5 Hz, 1 H, 2-H), 8.34 (d, *J*=8.0 Hz, 1 H, 8-H), 8.38 (dd, *J*=8.0, 1.5 Hz, 1 H, 1-H), 8.98 (d, *J*=8.0 Hz, 1 H, 14-H), 9.08 (d, *J*=8.0 Hz, 1 H, 4-H), 9.10 (dd, *J*=8.0, 1.5 Hz, 1 H, 5-H).

3N-(4-methoxyaniline)-5-hydroxy-1,4-naphthoquinone (**14**):

p-Anisidine (40 mg, 0.32 mmol) was reacted with juglone (57 mg, 0.33 mmol) in the present of $CeCl_3 \cdot 7H_2O$ (122 mg, 0.33 mmol) by the procedure described for the preparation of compound **9**. The red product was purified by chromatography (eluting with $CHCl_3$/MeOH, 100:1) (65 mg, 69%): red crystals (ethanol), m.p. 211°C. – MS (EI); *m/z*: 295 (100) [M^+, $C_{17}H_{13}NO_4$]; IR: $\tilde{\nu}$ = 3274, 1627, 1590, 1572, 1516, 1240 cm-^{1}; ^{1}H-NMR (CD_3SOCD_3): δ = 3.78 (s, 3 H, OCH_3), 5.87 (s, 1 H, 2-H), 7.01 (d, *J* =8.5 Hz, 2 H, 3'-H), 7.24 (d, *J*=8.5 Hz, 1 H, 6-H), 7.28 (d, *J*=8.5 Hz, 2 H, 2'-H), 7.44 (d, *J*=8.5 Hz, 1 H, 8-H), 7.72 (t, *J*=8.5 Hz, 1 H, 7-H), 9.18 (s, 1 H, NH), 11.54 (s, 1 H, OH); ^{13}C-NMR (CD_3SOCD_3): δ = 55.3 (q, OCH_3), 101.3 (d, C-2), 114.3 (s, C-4a), 114.6 (d, C-3'), 117.6 (d, C-8), 122.1 (d, C-6), 125.8

(d, C-2'), 130.5 (s, C-1'), 133.1 (s, C-8a), 137.6 (d, C-7), 146.9 (s, C-3), 157.1 (s, C-4'), 160.5 (s, C-5), 181.6 (s, C-1), 185.7 (s, C-4).

3(N)-(4-methoxyaniline)-5-hydroxy-1,4-naphthoquinon-4-imine (**15**):

14 (20 mg, 0.068 mmol) was added to a mixture of 25% aq. ammonia (2 mL) and methanol (20 mL) and stirred at room temperature for 7 days. Evaporation of the solvent afforded compound **15** (20 mg, 100%); HRMS calcd. for $C_{17}H_{14}N_2O_3$ [M^+] 394.1004, found 294.1008; IR: $\tilde{\nu}$ = 3300, 1571, 1535, 1513, 1257 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3): δ = 3.77 (s, 3 H, OCH_3), 5.66 (s, 1 H, 2-H), 7.04 (d, *J*=9.0 Hz, 2 H, 3'-H), 7.14 (d, *J*=8.0 Hz, 1 H, 6-H), 7.26 (d, *J*=9.0 Hz, 2 H, 2'-H), 7.39 (d, *J*=8.0 Hz, 1 H, 8-H), 7.49 (t, *J*=8.0 Hz, 1 H, 7-H); ^{13}C NMR (CD_3SOCD_3): δ = 54.9 (q, OCH_3), 100.5 (d, C-2), 113.4 (s, C-4a), 114.3 (d, C-3'), 115.5 (d, C-8), 121.8 (d, C-6), 125.5 (d, C-2'), 130.2 (s, C-1'), 131.6 (s, C-8a), 132.7 (d, C-7), 147.1 (s, C-3), 156.6 (s, C-4'), 161.5 (s, C-5), 161.6 (s, C-4), 181.6 (s, C-1).

10H,11H,12H-dihydroquino[2,3,4-kl]acridine (**17a**):

To a stirred solution of **4a** (400 mg, 1.9 mmol) in AcOH (50 mL) and conc.HCl (0.25 mL), 1,3-cyclohexanedione (425 mg, 3.8 mmol) and sodium m-nitrophenylsulfonate (1.3 g, 5.7 mmol) were added and the reaction mixture was refluxed for 2 h. After cooling, the mixture was poured onto ice (100 g), the solution brought to pH 8 with 25% ammonia and then extracted with chloroform (3 x 30 mL). The chloroform solution was washed with water (2 x 50 mL) and evaporated to afford **17a** (515 mg, quantitative), amorphous powder ($CHCl_3$/MeOH, 20:1), m.p. 186^{o}C; HRMS calcd. for $C_{19}H_{14}N_2$ [M^+] 270.1157, found 270.1157; IR: $\tilde{\nu}$ = 2940, 1585, 1572, 1488, 1400, 1389 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.42 (quintet, *J*=6.0 Hz, 2 H, 11-H), 3.50 (t, *J*=6.0 Hz, 4 H, 10-, 12-H), 7.76 (t, *J*=7.0 Hz, 2 H, 2-, 7-H), 7.89 (t, *J*=7.0 Hz, 2 H, 3-, 6-H), 8.28 (d, *J*=7.0 Hz, 2 H, 1-, 8-H), 9.06 (d, *J*=7.0 Hz, 2 H, 4-, 5-H); ^{13}C-NMR ($CDCl_3$): δ = 22.3 (t, C-11), 34.4 (t, C-10), 116.5 (s, C-12b), 122.4 (s, C-4a), 126.1 (d, C-3), 127.0 (d, C-4), 129.2 (d, C-1), 130.0 (d, C-2), 135.9 (s, C-4b), 146.6 (s, C-8a), 159.5 (s, C-9a).

2,7-Dimethoxy-10H,11H,12H-dihydroquino[2,3,4-kl]acridine (**17b**):

Reacting **4b** (520 mg, 1.9 mmol) with 1,3-cyclohexanedione (425 mg, 3.8 mmol) by the same procedure described for the synthesis of **17a** afforded **17b** (625mg, quantitative), amorphous powder ($CHCl_3$/MeOH, 20:1), mp 218^{o}C; HRMS calcd. for $C_{21}H_{18}N_2O_2$ [M^+] 330.1368, found 330.1368; IR: $\tilde{\nu}$ = 2950, 1612, 1583, 1413, 1219, 1033 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.57 (quintet, *J*=6.5 Hz, 2 H, 11-H), 3.90 (t, *J*=6.5 Hz, 4 H, 10-, 12-H), 4.16 (s, 6 H, OMe), 7.65 (dd, *J*=9.0, 2.5 Hz, 2 H, 3-, 6-H), 8.15 (d, *J*=2.5 Hz, 2 H, 1-, 8-H), 8.95 (d, *J*=9.0Hz, 2 H, 4-, 5-H).

General procedure for nitration of compounds **6a**, **6b** *and* **17a**:

The pyridoacridine (10 mg) was added to a 1:1 mixture of conc.H_2SO_4/fuming HNO_3 (2 mL) at 0°C. The reaction mixture was then allowed to warm up to room temperature and after 1 h. or 12 h. it was poured onto ice (10 g). The solution was neutralized with 10% NaOH and extracted with chloroform (4 x 10 mL). The chloroform solution was evaporated and the residue was chromatographed.

8-Nitro-10H,11H,12H-dihydroquino[2,3,4-kl]acridine (**18a**) *and 6-Nitro-10H,11H,12H- dihydroquino [2,3,4-kl]acridine* (**18b**):

Reaction of **17a** (10 mg, 0.037 mmol) by the above described procedure for 1 h. gave two products that were separated by chromatography. Elution with dichloromethane afforded the less polar isomer **18a** (3 mg, 26%) and further elution with CH_2Cl_2/MeOH, 30:1, afforded the more polar isomer **18b** (7 mg, 60%). **18a**: MS (EI); *m/z*: 315 (100) [M^+, $C_{19}H_{13}N_3O_2$], 285 (37) [M^+- NO], 269 (30) [M^+- NO_2]; IR: $\tilde{\nu}$ = 2925, 1591, 1374, 1139 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 50:1): δ = 2.43 (quintet, *J*=6.0 Hz, 2 H, 11-H), 3.51 (t, *J*=6.0 Hz, 2 H, 12^a-H), 3.75 (t, *J*=6.0 Hz, 2 H, 10^a-H), 7.94 (t, *J*=8.0 Hz, 1 H, 6-H), 8.05 (t, *J*=8.0 Hz, 1 H, 2-H), 8.18 (t, *J*=8.0 Hz, 1 H, 3-H), 8.25 (d, *J*=8.0 Hz, 1 H, 7-H), 9.06 (d, *J*= 8.0 Hz, 1 H, 1-H), 9.07 (d, *J*=8.0 Hz, 1 H, 4-H), 9.21 (d, *J*=8.0 Hz, 1 H, 5-H). **18b**: HRMS calcd. for $C_{19}H_{13}N_3O_2$ [M^+] 315.1008, found 315.1006; MS (EI); *m/z*: 315 (100) [M^+], 269 (33) [M^+- NO_2]; IR: $\tilde{\nu}$ = 2927, 1588, 1339 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 50:1): δ = 2.42 (quintet, *J*=6.0 Hz, 2 H, 11-H), 3.50 (t, *J*=6.0 Hz, 2 H, 12-H, interchangeable), 3.54 (t, *J*=6.0 Hz, 2 H, 10^a-H), 7.87 (t, *J*=7.5 Hz, 1 H, 3-H), 7.97 (t, *J*=7.5 Hz, 1 H, 2-H), 8.32 (d, *J*=7.5 Hz, 1 H, 1-H), 8.36 (d, *J*=7.5 Hz, 1 H, 8-H), 8.63 (dd, *J*=7.5, 2.5 Hz, 1 H, 7-H), 8.95 (d, *J*=7.5 Hz, 1 H, 4-H), 9.93 (d, *J*=2.5 Hz, 1 H, 5-H).

1,8-Dinitro-10H,11H,12H-dihydroquino[2,3,4-kl]acridine (**19a**), *3,8-Dinitro-10H,11H, 12H-dihydro-quino[2,3,4-kl]acridine* (**19b**) *and 3,6-Dinitro-10H,11H,12H-dihydroquino [2,3,4-kl]acridine* (**19c**):

Reaction of **17a** (10 mg, 0.037mmol) in conc.H_2SO_4/fuming HNO_3 , 1:1 (2ml), by the general above procedure for 12 h. gave three products that were separated by chromatography. Elution with dichloromethane/petroleum ether, 4:1, afforded isomer **19a** (0.5 mg). Elution with dichloromethane afforded isomer **19b** (2 mg, 15%) and isomer **19c** (3 mg, 20%). **19a**: MS (EI); *m/z*: 360 (47) [M^+, $C_{19}H_{12}N_4O_4$], 330 (60) [M^+- NO], 300 (100) [M^+- 2NO]; IR: $\tilde{\nu}$ = 2925, 1620, 1583, 1534 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.39 (quintet, *J*=7.0 Hz, 2 H, 11-H), 3.50 (t, *J*=7.0 Hz, 4 H, 10-, 12-H), 7.83 (t, *J*= 7.5 Hz, 2 H, 3-, 6-H), 8.13 (d, *J*=7.5 Hz, 2 H, 2-, 7-H), 9.10 (d, *J*=7.5 Hz, 2 H, 4-, 5-H). **19b**: HRMS calcd. for $C_{19}H_{12}N_4O_4$ [M^+] 360.0859, found 360.0858; MS (EI); *m/z*: 360 (100) [M^+], 330 (23) [M^+- NO], 302 (29) [$(M+2)^+$- 2NO], 267 (31) [$(M-1)^+$- $2NO_2$]; IR: $\tilde{\nu}$ = 2925, 1618, 1589, 1535, 1341 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.43 (quintet, *J*=7.0 Hz, 2 H, 11-H), 3.52 (t, *J*=7.0 Hz, 2 H, 12^a-H), 3.59 (t, *J*= 7.0 Hz, 2 H, 10-H, interchangeable), 7.95 (t, *J*=8.0 Hz, 1 H, 6-H), 8.19 (d, *J*=8.0 Hz, 1 H, 7-H), 8.55 (d, *J*=8.0 Hz, 1 H, 1-H), 8.73 (dd, *J*=8.0, 2.0 Hz, 1 H, 2-H), 9.16 (d, *J*=8.0 Hz, 1 H, 5-H), 9.90 (d, *J*= 2.0 Hz, 1 H, 4-H). **19c**: MS (EI); *m/z*: 360 (100) [M^+, $C_{19}H_{12}N_4O_4$], 315 (49) [$(M+1)^+$- NO_2], 267 (53) [$(M-1)^+$- $2NO_2$]; IR: $\tilde{\nu}$ = 2925, 1600, 1588, 1506, 1346 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.54 (quintet, *J*=

6.0 Hz, 2 H, 11-H), 3.67 (t, *J*=6.0 Hz, 4 H, 10-, 12-H), 8.60 (d, *J*=8.0 Hz, 2 H, 1-, 8-H), 8.79 (dd, *J*= 8.0, 2.0 Hz, 2 H, 2-, 7-H), 9.96 (d, *J*=2.0 Hz, 2 H, 4-, 5-H).

3-Nitro-10H-benzo[i]quino [2,3,4-kl]acridin-10-one (**20**):

Reaction of **6a** (80 mg, 0.24 mmol) in conc.H_2SO_4/fuming HNO_3, 1:1 (5mL), for 12 h. by the above general procedure followed by crystallization of the crude product from pyridine afforded **20** (48 mg, 53%), yellow needles, m.p. 339°C; MS (EI); *m/z*: 377 (100) [M^+, $C_{23}H_{11}N_3O_3$], 347 (36) [(M^+- NO], 330 (41) [$(M-1)^+$- NO_2]; IR: $\tilde{\nu}$ = 1682, 1513, 1404, 1388, 1340, 1276 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 7.79 (t, *J*=8.0 Hz, 1 H, 12-H), 7.93 (t, *J*=8.0 Hz, 1 H, 13-H), 8.12 (t, *J*=8.0 Hz, 1 H, 7-H), 8.12 (t, *J*= 8.0 Hz, 1 H, 6-H), 8.50 (d, *J*=8.0 Hz, 1 H, 11-H), 8.54 (d, *J*=9.0 Hz, 1 H, 1-H), 8.71 (d, *J*=8.0 Hz, 1 H, 8-H), 8.72 (dd, *J*=9.0, 2.5 Hz, 1 H, 2-H), 9.09 (d, *J*=8.0 Hz, 1 H, 14-H), 9.11 (d, *J*=8.0 Hz, 1 H, 5-H), 10.01 (d, *J*=2.5 Hz, 1 H, 4-H); ^{13}C-NMR ($CDCl_3$/CF_3CO_2D, 100:1): δ = 116.5 (s, C-14c), 121.6 (s, C-4a), 123.6 (d, C-4),123.7 (s, C-4c), 124.7 (d, C-2), 126.4 (d, C-5), 126.7 (d, C-14), 128.4 (d, C-11), 131.5 (d, C-6), 131.8 (d, C-7), 131.9 (d, C-8), 132.2 (s, C-10a), 132.3 (d, C-12), 132.6 (d, C-1), 134.8 (s, C-14a), 135.3 (d, C-13), 136.8 (s, C-4b), 146.0 (s, C-3), 146.7 (s, C-8a), 149.0 (s, C-9a), 149.8 (s, C-15a), 151.3 (s, C-14b), 181.1 (s, C-10).

3-Amino-10H-benzo[i]quino[2,3,4-kl]acridin-10-one (**21**):

20 (40 mg, 0.11 mmol) was dissolved in AcOH (3 mL) and TFA (6mL), 5% Pd-C (25 mg) was added and the reaction mixture was shaken in a Parr apparatus under H_2 (3 atm) for 1 h. The catalyst was then filtered off, the solution poured onto ice (10 g), brought to pH 8 with 25% ammonia and then extracted with chloroform (3 x 20 mL). After evaporation of the solvent the residue was chromatographed (eluting with $CHCl_3$/MeOH, 30:1) to afford **21** (15 mg, 40%); HRMS calcd. for $C_{23}H_{13}N_3O$ [M^+] 347.1059, found 347.1058; IR: $\tilde{\nu}$ = 1677, 1646, 1540, 1515 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3): δ = 7.42 (d, *J*=8.0 Hz, 1 H, 2-H), 7.71 (t, *J*=8.0 Hz, 1 H, 12-H), 7.93 (t, *J*=8.0 Hz, 1 H, 13-H), 8.05 (t, *J*=8.0 Hz, 1 H, 6-H), 8.09 (t, *J*=8.0 Hz, 1 H, 7-H), 8.13 (d, *J*=8.0 Hz, 1 H, 1-H), 8.28 (d, *J*=2.0 Hz, 1 H, 4-H), 8.30 (d, *J*=8.0 Hz, 1 H, 11-H), 8.53 (d, *J*=8.0 Hz, 1 H, 8-H), 8.91 (d, *J*=8.0 Hz, 1 H, 14-H), 9.31 (d, *J*=8.0 Hz, 1 H, 5-H).

2,7-Dimethoxy-1,8-dinitro-10H-benzo[i]quino[2,3,4-kl]acridin-10-one (**22**):

Reaction of **6b** (10 mg, 0.026 mmol) in conc.H_2SO_4/fuming HNO_3, 1:1 (2ml), by the above general procedure for 1 hr afforded **22** (10 mg, 80%); HRMS calcd. for $C_{25}H_{14}N_4O_7$ [M^+] 482.0862, found 482.0855, 452 (100) [(M^+- NO]; MS (EI); *m/z*: 482 (79) [M^+], 452 (100) [M^+-NO]; IR: $\tilde{\nu}$ = 1687, 1617, 1540, 1375, 1290 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3): δ = 4.21 (s, 3 H, OCH_3), 4.24 (s, 3H, OCH_3), 7.85 (t, *J*=8.5 Hz, 1 H, 12-H), 7.97 (d, *J*=10.0 Hz, 1 H, 3-H), 7.99 (t, *J*=8.5 Hz, 1 H, 13-H), 8.13 (d, *J*=10.0 Hz, 1 H, 6-H), 8.27 (d, *J*=8.5 Hz, 1 H, 11-H), 8.66 (d, *J*=8.5 Hz, 1 H, 14-H), 9.28 (d, *J*=10.0 Hz, 1 H, 4-H), 9.36 (d, *J*=10.0 Hz, 1 H, 5-H).

2,7- Dimethoxy-1,3,8,12-tetrainitro-10H-benzo[i]quino[2,3,4-kl]acridin-10-one (**23a**) *and 2,7-dimethoxy-1,3,8,14-tetranitro-10H-benzo[i]quino[2,3,4-kl]acridin-10-one* (**23b**):

Reaction of **6b** (10 mg, 0.026 mmol) in conc.H_2SO_4/fuming HNO_3, 1:1 (2 ml), by the above general procedure for 12 hr gave two products that were separated by chromatography. Elution with dichloromethane afforded first the less polar isomer **23a** (3 mg, 20%) and then the more polar isomer **23b** (7 mg, 45%). **23a**: MS (EI); *m/z*: 572 (100) [M^+, $C_{25}H_{12}N_6O_{11}$], 542 (45) [M^+- NO], 482 (78) [M^+- 3NO], 452 (32) [M^+- 4NO]; IR: $\tilde{\nu}$ = 2925, 1706, 1619, 1547, 1375 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3/CF_3CO_2D, 100:1): δ = 4.18 (s, 3 H, OCH_3), 4.29 (s, 3 H, OCH_3), 8.28 (d, *J*=10.0 Hz, 1 H, 6-H), 8.82 (dd, *J*=8.5, 2.5 Hz, 1 H, 13-H), 8.90 (d, *J*=8.5 Hz, 1 H, 14-H), 8.90 (d, *J*=2.5 Hz, 1 H, 11-H), 9.48 (d, *J*=10.0 Hz, 1 H, 5-H), 9.86 (s, 1 H, 4-H); ^{1}H-NMR (CD_3CN): δ = 4.30 (s, 3 H, OCH_3), 4.32 (s, 3 H, OCH_3), 8.15 (d, *J*=10.0 Hz, 1 H, 6-H), 8.70 (dd, *J*=8.5, 2.0 Hz, 1 H, 13-H), 8.99 (d, *J*= 8.5 Hz, 1 H, 14-H), 9.05 (d, *J*=2.0 Hz, 1 H, 11-H), 9.30 (d, *J*=10.0Hz, 1 H, 5-H), 9.75 (s, 1 H, 4-H). **23b**: HRMS calcd. for $C_{25}H_{12}N_6O_{11}$ [M^+] 572.0564, found 572.0562; IR: $\tilde{\nu}$ = 2925, 1692, 1629, 1557, 1547, 1376 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3): δ = 4.14 (s, 3 H, OCH_3), 4.27 (s, 3 H, OCH_3), 8.06 (t, *J*=8.0 Hz, 1 H, 12-H), 8.22 (d, *J*=8.0 Hz, 1 H, 13-H), 8.26 (d, *J*=9.5 Hz, 1 H, 6-H), 8.54 (d, *J*=8.0 Hz, 1 H, 11-H), 9.43 (d, *J*=9.5 Hz, 1 H, 5-H), 9.79 (s, 1 H, 4-H).

10H-quino[2,3,4-kl]acridin-10-one (**24**):

To a solution of **17a** (300 mg, 1.1 mmol) in acetonitrile (120 mL) cerium ammonium nitrate (2.4 g, 4.4 mmol) was added and the reaction mixture was refluxed for 10 min. The acetonitrile was evaporated and the residue dissolved in chloroform (100 mL), washed with 0.1% aq. ammonia (2 x 100 mL) and evaporated to afford **24** (290 mg, 92%), amorphous powder ($CHCl_3$/MeOH, 20:1), m.p. 254°C; HRMS calcd. for $C_{19}H_{10}N_2O$ [M^+] 282.0793, found 282.0799; IR: $\tilde{\nu}$ = 1663, 1565, 1493, 1280 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 7.11 (d, *J*=11.0 Hz, 1 H, 11-H), 7.90 (t, *J*=8.5 Hz, 1 H, 3-H), 7.98 (t, *J*= 8.5 Hz, 1 H, 2-H), 7.98 (t, *J*=8.5 Hz, 1 H, 6-H), 7.99 (d, *J*=11.0 Hz, 1 H, 12-H), 8.05 (t, *J*=8.5 Hz, 1 H, 7-H), 8.43 (d, *J*=8.5 Hz, 1 H, 1-H), 8.73 (d, *J*=8.5 Hz, 1 H, 8-H), 9.14 (d, *J*=8.5 Hz, 1 H, 4-H), 9.19 (d, *J*=8.5 Hz, 1 H, 5-H).

2,7-Dimethoxy-10H-quino[2,3,4-kl]acridin-10-one (**25**):

Oxidation of **17b** (360 mg, 1.1 mmol) by the same procedure described for the synthesis of **24** afforded **25** (340 mg, 90%), amorphous powder ($CHCl_3$/MeOH, 20:1), m.p. 291°C; HRMS calcd. for $C_{21}H_{14}N_2O_3$ [M^+] 342.1004, found 342.1004; IR: $\tilde{\nu}$ = 1666, 1608, 1415, 1259, 1225 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 50:1): δ = 4.03 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 7.02 (d, *J*=10 Hz, 1 H, 11-H), 7.43 (dd, *J*=8.5, 2.5 Hz, 1 H, 3-H), 7.51 (dd, *J*=8.5, 2.5 Hz, 1 H, 6-H), 7.72 (d, *J*=2.5 Hz, 1 H, 1-H), 7.93 (d, *J*=10 Hz, 1 H, 12-H), 7.94 (s, 1 H, 8-H), 8.88 (d, *J*=8.5 Hz, 1 H, 4-H), 8.92 (d, *J*=8.5 Hz, 1 H, 5-H).

11,12-Dibromo-10H-quino[2,3,4-kl]acridin-10-one (**26**):

24 (30 mg, 0.11 mmol) was dissolved in acetic acid (5 mL) and Br_2 (0.2 mL, 3.9 mmol) was added at room temperature. The mixture was stirred at 80°C for 2 h. and then allowed to cool to room temperature. Water (25 mL) and chloroform (25 mL) were added. The organic phase was extracted with 5% $NaHSO_3$ (10 mL) and evaporated. The crude product was chromatographed (eluting with chloroform) to afford **26** (16 mg, 33%); HRMS calcd. for $C_{19}H_8Br_2N_2O$ [M^+] 439.8988, found 439.9000; IR: $\tilde{\nu}$ = 3425, 1669, 1491, 1394, 1242, 767 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 7.86 (t, *J*=8.0 Hz, 1 H, 3-H), 7.93 (t, *J*=8.0 Hz, 1 H, 2-H), 7.93 (t, *J*=8.0 Hz, 1 H, 6-H), 7.99 (t, *J*=8.0 Hz, 1 H, 7-H), 8.39 (d, *J*=8.0 Hz, 1 H, 1-H), 8.56 (d, *J*=8.0 Hz, 1 H, 8-H), 8.97 (d, *J*=8.0 Hz, 1 H, 4-H), 9.04 (d, *J*=8.0 Hz, 1 H, 5-H).

12-Isobutylamino-10H-quino[2,3,4-kl]acridin-10-one (**27a**):

24 (40 mg, 0.14 mmol) and isobutylamine (0.12 mL, 1.2 mmol) in acetonitrile (10 mL) were stirred at room temperature for 48 h. The reaction mixture was then evaporated and the residue chromatographed by a silica gel column (eluting with $CHCl_3$/MeOH, 30:1) to afford **27a** (18 mg, 36%); HRMS calcd. for $C_{23}H_{19}N_3O$ [M^+] 353.1528, found 353.1525; MS (EI); *m/z*: 353 (20) [M^+], 310 (100) [M^+- $(CH_3)_2CH$]; IR: $\tilde{\nu}$ = 2925, 1609, 1514, 1466, 1258, 761 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.15 (d, *J*=7.0 Hz, 6 H, 3'-H), 2.20 (quintet, *J*=7.0 Hz, 1 H, 2'-H), 3.31 (t, *J*=7.0 Hz, 2 H, 1'-H), 6.09 (s, 1 H, 11-H), 7.49 (br s, 1 H, NH), 7.76 (t, *J*=8.0 Hz, 1 H, 3-H), 7.79 (t, *J*=8.0 Hz, 1 H, 6-H), 7.86 (t, *J*= 8.0 Hz, 1 H, 2-H), 7.89 (t, *J*=8.0 Hz, 1 H, 7-H), 8.21 (d, *J*=8.0 Hz, 1 H, 1-H), 8.60 (d, *J*=8.0 Hz, 1 H, 8-H), 8.91 (d, *J*=8.0 Hz, 1 H, 5-H), 8.93 (d, *J*=8.0 Hz, 1 H, 4-H); ^{13}C-NMR ($CDCl_3$): δ = 20.5 (q, C-3'), 28.0 (d, C-2'), 50.5 (t, C-1'), 100.7 (d, C-11), 115.3 (s, C-12b), 123.5 (s, C-4c), 123.8 (s, C-4a), 126.8 (d, C-5), 127.3 (d, C-4), 129.0 (d, C-3), 129.3 (d, C-6), 130.7 (d, C-2), 130.8 (d, C-7), 131.0 (d, C-1), 132.9 (d, C-8), 134.9 (s, C-4b), 144.6 (s, C-9a), 145.7 (s, C-12a), 147.0 (s, C-13a), 147.6 (s, C-8a), 152.1 (s, C-12), 180.4 (s, C-10).

10,12-Di(isobutylamino)quino[2,3,4-kl]acridine (**27b**):

24 (100 mg, 0.36 mmol) and isobutylamine (0.30 mL, 3.0 mmol) in ethanol (25 mL) were stirred at room temperature for 18 h. The reaction mixture was evaporated and the residue chromatographed by two subsequent silica gel columns (eluting with $CHCl_3$/MeOH/trifluoroacetic acid, 20:1:0.01) to afford **27b** (56 mg, 38%); HRMS calcd. for $C_{27}H_{26}N_4$ [(M - 2)$^+$] 406.2157, found 406.2156; IR: $\tilde{\nu}$ = 3445, 1611, 1559, 1462, 1386, 1125, 766 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 20:1): δ = 1.13 (d, *J*=7.0 Hz, 12 H, 3'-H), 2.25 (quintet, *J*=7.0 Hz, 2 H, 2'-H), 3.59 (d, *J*=7.0 Hz, 4 H, 1'-H), 6.19 (s, 1 H, 11-H), 7.99 (t, *J*=8.0 Hz, 2 H, 3-, 6-H), 8.05 (t, *J*=8.0 Hz, 2 H, 2-, 7-H), 8.46 (d, *J=8*.0 Hz, 2 H, 1-, 8-H), 9.16 (d, *J*=8.0 Hz, 2 H, 4-, 5-H), 9.49 (br s, 1 H, NH); ^{13}C-NMR ($CDCl_3$/CD_3OD, 20:1): δ = 20.1 (q, C-3'), 28.4 (d, C-2'), 51.1 (t, C-1'), 87.6 (d, C-11), 113.0 (s, C-12b), 124.2 (s, C-4a), 127.4 (d, C-4), 131.1 (d, C-3), 132.0 (d, C-2), 132.2 (d, C-1), 136.1 (s, C-4b), 141.1 (s, C-9a), 146.2 (s, C-8a), 156.0 (s, C-10).

2,7-Dimethoxy-12-isobutylamino-10H-quino[2,3,4-kl]acridin-10-one (**28a**) *and 10,12-Di (isobutylamino)-2,7-dimethoxyquino[2,3,4-kl]acridine* (**28b**):

25 (50 mg, 0.15 mmol) was reacted with isobutylamine (0.20 mL, 2.0 mmol) by the described procedure for the synthesis of **27b**. Two obtained compounds were separated by chromatography; elution with $CHCl_3$/MeOH, 30:1, afforded the monoamination product (**28a**) (12 mg, 19%) and further elution with $CHCl_3$/MeOH, 10:1, afforded the diamination product (**28b**) (25mg, 37%). **28a**: MS (EI); *m/z*: 413 (29) [M^+, $C_{25}H_{23}O_3N_3$], 370 (100) [M^+- $(CH_3)_2CH$]; IR: $\tilde{\nu}$ = 2959, 1658, 1612, 1562, 1467, 1450, 1422, 1223, 1134 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.11 (d, *J*=7.0 Hz, 6 H, 3'-H), 2.17 (quintet, *J*= 7.0 Hz, 1 H, 2'-H), 3.25 (t, *J*=7.0 Hz, 2 H, 1'-H), 4.03 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 6.07 (s, 1 H, 11-H), 7.40 (d, *J*=10.0 Hz, 1 H, 3-H), 7.42 (d, *J*=10.0 Hz, 1 H, 6-H), 7.50 (br s, 1 H, NH), 7.58 (s, 1 H, 1-H), 8.00 (s, 1 H, 8-H), 8.83 (d, *J*=10.0 Hz, 1 H, 5-H), 8.86 (d, *J*=10.0 Hz, 1 H, 4-H). **28b**: MS (EI); *m/z*: 466 (61) [$(M-2)^+$, $C_{29}H_{30}N_4O_2$], 423 (100) [$(M-2)^+$- $(CH_3)_2CH$]; IR: $\tilde{\nu}$ = 2924, 1658, 1612, 1564, 1467, 1412, 1252, 1219, 669 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 1.14 (d, *J*=7.0 Hz, 12 H, 3'-H), 2.28 (quintet, *J*=7.0 Hz, 2 H, 2'-H), 3.67 (d, *J*=7.0 Hz, 4 H, 1'-H), 4.06 (s, 6 H, OCH_3), 5.89 (s, 1 H, 11-H), 7.36 (dd, *J*=9.0, 1.5 Hz, 2 H, 3-, 6-H), 7.70 (d, *J*=1.5 Hz, 2 H, 1-, 8-H), 8.58 (d, *J*=9.0 Hz, 2 H, 4-, 5-H), 9.78 (br s, 1 H, NH); ^{13}C-NMR ($CDCl_3$): δ = 20.6 (q, C-3'), 28.7 (d, C-2'), 51.4 (t, C-1'), 56.2 (OCH_3), 87.3 (d, C-11), 110.4 (s, C-12b), 111.3 (d, C-1), 117.6 (s, C-4a), 121.9 (d, C-3), 128.0 (d, C-4), 134.8 (s, C-4b), 141.5 (s, C-9a), 148.1 (s, C-8a), 155.3 (s, C-10), 161.7 (s, C-2).

12-Methylamino-10H-quino[2,3,4-kl]acridin-10-one (**29a**):

24 (40 mg, 0.14 mmol), methylamine (0.20 mL of 33% methylamine in ethanol, 1.6 mmol) and $CeCl_3 \cdot 7H_2O$ (52 mg, 0.14 mmol) were mixed together in ethanol (10 mL).The reaction mixture was stirred at room temperature for 15 min. then evaporated and chromatographed by two subsequent silica gel columns (eluting with $CHCl_3$/MeOH, 30:1) to afford **29a** (20 mg, 46%); MS (EI); *m/z*: 311 (100) [M^+, $C_{20}H_{13}N_3O$]; IR: $\tilde{\nu}$ = 3430, 1610, 1560, 1419 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 20:1): δ = 3.11 (s, 3 H, NCH_3), 5.97 (s, 1 H, 11-H), 7.74 (t, *J*=8.0 Hz, 1 H, 3-H), 7.78 (t, *J*=8.0 Hz, 1 H, 6-H), 7.82 (t, *J*= 8.0 Hz, 1 H, 2-H), 7.89 (t, *J*=8.0 Hz, 1 H, 7-H), 8.14 (d, *J*=8.0 Hz, 1 H, 1-H), 8.51 (d, *J*=8.0 Hz, 1 H, 8-H), 8.90 (d, *J*=8.0 Hz, 1 H, 5-H), 8.92 (d, *J*=8.0 Hz, 1 H, 4-H).

10,12-Di(methylamino)quino[2,3,4-kl]acridine (**29b**):

24 (30 mg, 0.11 mmol) was reacted with methylamine (0.20 mL of 33% methylamine in ethanol, 1.6 mmol) in ethanol (10 mL) at room temperature for 24 h. The product (**29b**) was purified by silica gel column chromatography eluting with $CHCl_3$/MeOH, 10:1 (10 mg, 28%); MS (EI); *m/z*: 322 (100) [$(M-2)^+$, $C_{21}H_{14}N_4$], 294 (44) [$(M-2)^+$- CH_2N]; IR: $\tilde{\nu}$ = 3405, 1618, 1564, 1419 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 20:1): δ = 3.38 (s, 6 H, NCH_3), 5.83 (s, 1H, 11-H), 7.83 (t, *J*=8.0 Hz, 2 H, 3-, 6-H), 7.90 (t, *J*=8.0 Hz, 2 H, 2-, 7-H), 8.21 (d, *J*=8.0 Hz, 2 H, 1-, 8-H), 8.79 (d, *J*=8.0 Hz, 2 H, 4-, 5-H).

12-(4-methoxyanilino)-10H-quino[2,3,4-kl]acridin-10-one (**30a**):

24 (10 mg, 0.036 mmol) and p-anisidine (5 mg, 0.041 mmol) were refluxed in acetonitrile for 48 h. The solvent was evaporated and the residue chromatographed on a silica gel column (eluting with $CHCl_3$/MeOH, 50:1) to afford **30a** (8 mg, 55%); MS (EI); *m/z*: 403 (100) [M^+, $C_{26}H_{17}N_3O_2$], 372 (36) [M^+- CH_3O]; IR: $\tilde{\nu}$ = 3448, 1614, 1556, 1512, 1245 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 6.54 (s, 1 H, 11-H), 7.00 (d, *J*=9.0 Hz, 2 H, 3'-H), 7.38 (d, *J*=9.0 Hz, 2 H, 2'-H), 7.88 (t, *J*=8.5 Hz, 1 H, 3-H), 7.88 (t, *J*=8.5 Hz, 1 H, 6-H), 7.96 (t, *J*=8.5 Hz, 1 H, 2-H), 7.96 (t, *J*=8.5 Hz, 1 H, 7-H), 8.37 (d, *J*=8.5 Hz, 1 H, 1-H), 8.67 (d, *J*=8.5 Hz, 1 H, 8-H), 9.07 (d, *J*=8.5 Hz, 1 H, 5-H), 9.10 (d, *J*=8.5 Hz, 1 H, 4-H).

10,12-Di(4-methoxyanilino)quino[2,3,4-kl]acridine (**30b**):

24 (10 mg, 0.036 mmol) and p-anisidine (10 mg, 0.081 mmol) in ethanol (4 mL) were stirred at 50°C for 12 h. The ethanol was then evaporated and the residue chromatographed (eluting with $CHCl_3$/MeOH, 10:1) to afford **30b** (7 mg, 38%); MS (EI); *m/z*: 509 (100) [$(M+1)^+$], 508 (99) [M^+, $C_{33}H_{24}N_4O_2$]; IR: $\tilde{\nu}$ = 3440, 2925, 1607, 1548, 1506, 1460, 1253, 1171, 1105, 1025 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3OD, 20:1): δ = 3.89 (s, 6 H, OCH_3), 6.71 (s, 1 H, 11-H), 7.00 (d, *J*=8.0 Hz, 4 H, 3'-H), 7.47 (d, *J*=8.0 Hz, 4 H, 2'-H), 7.91 (t, *J*=8.0 Hz, 2 H, 3-, 6-H), 7.99 (t, *J*=8.0 Hz, 2 H, 2-, 7-H), 8.53 (d, *J*=8.0 Hz, 2 H, 1-, 8-H), 8.99 (d, *J*=8.0 Hz, 2 H, 4-, 5-H).

12-Dodecylamino-10H-quino[2,3,4-kl]acridin-10-one (**31a**) *and 10,12-Di(dodecylamino)quino-[2,3,4-kl]acridine* (**31b**):

24 (10 mg, 0.036 mmol) and dodecylamine (0.030 mL, 0.13 mmol) were stirred in ethanol (4 mL) at 50°C for 12 h. After evaporation of the ethanol, the two products were separated by silica gel chromatography; elution with $CHCl_3$/MeOH, 30:1, to afford the monoamination product (**31a**) (4 mg, 24%) and by elution with $CHCl_3$/MeOH, 10:1, the diamination product (**31b**) which was further purified on a Sephadex LH-20 column (eluting with $CHCl_3$/MeOH/petroleum ether, 1:1:2) (4 mg, 18%). **31a**: MS (EI); *m/z*: 465 (64) [M^+, $C_{31}H_{35}N_3O$], 310 (100) [M^+- $(CH_2)_{10}CH_3$]; IR: $\tilde{\nu}$ = 2923, 2852, 1610, 1561, 1466 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 0.90 (t, *J*=7.5 Hz, 3 H, 12'-H), 1.35 (br m, 14 H, 5'-H - 11'-H), 1.46 (m, 2 H, 4'-H), 1.54 (quintet, *J*=7.5 Hz, 2 H, 3'-H), 1.91 (quintet, *J*=7.5 Hz, 2 H, 2'-H), 3.45 (m, 2 H, 1'-H), 6.25 (s, 1 H, 11-H), 7.63 (br s, 1 H, NH), 7.87 (t, *J*=8.0 Hz, 1 H, 3-H), 7.87 (t, *J*=8.0 Hz, 1 H, 6-H), 7.96 (t, *J*=8.0 Hz, 1 H, 2-H), 7.98 (t, *J*=8.0 Hz, 1 H, 7-H), 8.35 (d, *J*=8.0 Hz, 1 H, 1-H), 8.68 (d, *J*=8.0 Hz, 1 H, 8-H), 9.06 (d, *J*=8.0 Hz, 1 H, 5-H), 9.09 (d, *J*=8.0 Hz, 1 H, 4-H). **31b**: MS (EI); *m/z*: 630 (100) [$(M- 2)^+$, $C_{43}H_{58}N_4$], 475 (33) [$(M- 2)^+$- $(CH_2)_{10}CH_3$]; IR: $\tilde{\nu}$ = 2922, 2851, 1640, 1611, 1563, 1467, 1442, 1408 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 0.85 (t, *J*=7.0 Hz, 6 H, 12'-H), 1.2 (br m, 28 H, 5'-H - 11'-H), 1.38 (m, 4 H, 4'-H), 1.55 (m, 4 H, 3'-H), 1.96 (m, 4 H, 2'-H), 3.91 (m, 4 H, 1'-H), 6.22 (s, 1 H, 11-H), 7.92 (t, *J*=8.0 Hz, 2 H, 3-, 6-H), 8.00 (t, *J*=8.0 Hz, 2 H, 2-, 7-H), 8.55 (d, *J*=8.0 Hz, 2 H, 1-, 8-H), 8.99 (d, *J*=8.0 Hz, 2 H, 4-, 5-H), 9.83 (br s, 1 H, NH).

12-Amino-10H-quino[2,3,4-kl]acridin-10-one (**32a**):

The procedure of Couladouros [17] was adopted. To a solution of **24** (10 mg, 0.036 mmol) in methanol (2 mL), under nitrogen, was added a solution of sodium azide (14 mg, 0.22 mmol) in water (0.5 mL) and the solution was acidified to pH 4 with 1N HCl. After stirring at room temperture for 15 h. the reaction mixture was extracted with chloroform (2 x 10 mL) and the combined organic layer was washed with water (20 ml) and evaporated to afford **32a** (8 mg, 76%); HRMS calcd. for $C_{19}H_{11}N_3O$ [M^+] 297.0902, found 297.0901; IR: $\tilde{\nu}$ = 3425, 1644, 1616, 1546, 1515 cm^{-1}; ^{1}H-NMR ($CDCl_3/CD_3OD$, 20:1): δ = 6.23 (s, 1 H, 11-H), 7.77 (t, *J*=8.0 Hz, 1 H, 3-H), 7.80 (t, *J*=8.0 Hz, 1 H, 6-H), 7.86 (t, *J*=8.0 Hz, 1 H, 2-H), 7.89 (t, *J*=8.0 Hz, 1 H, 7-H), 8.20 (d, *J*=8.0 Hz, 1 H, 1-H), 8.49 (d, *J*=8.0 Hz, 1 H, 8-H), 8.94 (d, *J*=8.0 Hz, 1 H, 5-H), 8.96 (d, *J*=8.0 Hz, 1 H, 4-H).

10,12(N,N)-Di(2-amino-1,3-propanediol)quino[2,3,4-kl]acridine (**33b**):

24 (10 mg, 0.036 mmol) and 2-amino-1,3-propanediol (serinol) (10 mg, 0.11 mmol) were reacted in ethanol (5 mL) to afford **33b** (8mg, 50%), by the procedure described for the synthesis and purification of **30b**. MS (FAB); *m/z*: 445 (100) [$(M+1)^+$, $C_{25}H_{25}N_4O_4$]; IR: $\tilde{\nu}$ = 3332, 1613, 1559, 1415, 1390, 1050 cm^{-1}; ^{1}H-NMR (CD_3SOCD_3): δ = 3.84 (m, 8 H, 2'-H), 4.45 (quintet, *J*=5.0 Hz, 2 H, 1'-H), 5.37 (t, *J*=5.0 Hz, 4 H, OH), 6.91 (s, 1 H, 11-H), 8.08 (t, *J*=7.5 Hz, 2 H, 3-, 6-H), 8.16 (t, *J*=7.5 Hz, 2 H, 2, 7-H), 8.47 (d, *J*=7.5 Hz, 2 H, 1-, 8-H), 9.28 (d, *J*=7.5 Hz, 2 H, 4-, 5-H).

References

1. (a) Molinski, T. F. Marine pyridoacridine alkaloids: structure, synthesis and biological chemistry. *Chem.Rev.* **1993**, *93*, 1825-1838. (b) Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* **2001**, *18*, 1-49, and earlier reports in this series.
2. Gellerman, G.; Rudi, A.; Kashman, Y. Biomimetic synthesis of pyrido[2,3,4-kl]acridines. *Tetrahedron Lett.* **1993**, *34*, 1823-1826.
3. Gellerman, G.; Babad, M.; Kashman, Y. A two step biomimetic total synthesis of Eilatin. *Tetrahedron Lett.* **1993**, *34*, 1827-1830.
4. Gellerman, G.; Rudi, A.; Kashman, Y. Biomimetic synthesis of ascididemin and derivatives. *Syn.* **1994**, 239-241.
5. Gellerman, G.; Rudi, A.; Kashman, Y. The biomimetic synthesis of marine alkaloid related pyrido- and pyrrolo[2,3,4-kl]acridines. *Tetrahedron*, **1994**, *50*, 12959-12972.
6. Schurman, J. V.; Becker, E. I. Synthesis of naphthylaminonaphthoquinones. *J. Org. Chem.* **1953**, *18*, 211-217.
7. Pratt, Y. T. Quinolinequinones. VI. Reactions with aromatic amines. *J. Org. Chem.* **1962**, *27*, 3905-3910.
8. Peterson, J. R.; Zjawiony, J. K.; Liu, S.; Hufford, C. D.; Clark, A. M.; Rogers, R. D. Copyrine alkaloids: synthesis, spectroscopic characterization, and antimycotic/ antimycobacterial activity of A- and B-ring-functionalized sampangines. *J. Med. Chem.* **1992**, *35*, 4069-4077.

9. Macleod, J. W.; Thomson, R. H. Studies in the juglone series. VI. The addition of aniline and toluene-p-thiol to 5-substituted 1,4-naphthoquinones. *J. Org. Chem.* **1960**, *25*, 36-42.
10. (a) Patai, S.; Rappoport, Z. The chemistry of the quinonoid compounds. Vol. 2, **1988**, 1249. (b) Patai, S. The chemistry of the carbon- nitrogen double bond, **1970**, 663.
11. (a) Cimino, G.; Crispino, A.; De Rosa, S.; De Stefano, S.; Gavagnin, M.; Sodano, G. Studies on the structure of calliactine, the zoochrome of the sea anemone calliactis parasitica. *Tetrahedron*, **1987**, *43*, 4023-4030. (b) Schmitz, F. J.; DeGuzman, F. S.; Hossain, M. B.; van der Helm, D. Cytotoxic aromatic alkaloids from the ascidian amphicarpa meridiana and leptoclinides sp.: meridine and 11-hydroxyascididemin. *J. Org. Chem.* **1991**, *56*, 804-808.
12. Kitahara, Y.; Nakahara, S.; Yonezawa, T.; Nagatsu, M.; Shibano, Y.; Kubo, A. Synthetic studies on pentacyclic aromatic alkaloids, kuanoniamine A, 11-hydroxyascididemin, and neocalliactine acetate. *Tetrahedron*, **1997**, *53*, 17029-17038.
13. Luo, Y. L.; Chou, T. C.; Cheng, C. C. Design of antineoplastic agents on the basis of the "2-phenyl-naphthalene-type" structural pattern. 3. synthesis and biological activity evaluation of 5H-benzo[b]naphtho[2,3-d]pyrrole-6,11-dione derivatives. *J. Heterocyclic Chem*. **1996**, *33*, 113-117.
14. Dewar, M. J. S.; Maitlis, P. M. Electrophilic substitution. Part XI. Nitration of some six-membered nitrogen-heterocyclic compounds in sulphuric acid. *J. Chem. Soc*. **1957**, 2521-2528.
15. Crout, D. H. G.; Penton, J. R.; Schofield, K. Heteroaromatic reactivity. Part V. A quantitative study of the products of nitration of quinolinium ion in sulphuric acid. *J. Chem. Soc*. (B) **1971**, 1254-1256.
16. Thomson, R. H. Studies in the juglone series. I. Some halogen derivatives and their reaction with aniline. *J. Org. Chem.* **1948**, *13*, 377-383.
17. Han, G.; Shin, K. J.; Kim, D. C.; Yoo, K. H.; Kim, D. J.; Park, S. W. A new synthetic route to 6,7-dichloro-5,8-quinoxaline-dione and synthesis of its derivatives. *Heterocycles*, **1996**, *43*, 2495-2502.
18. Couladouros, E. A.; Plyta, Z. F.; Haroutounian, S. A. Efficient synthesis of aminonaphthoquinones and azidobenzohydroquinones: mechanistic considerations of the reaction of hydrazoic acid with quinones. An overview. *J. Org. Chem*. **1997**, *62*, 6-10.
19. Partridge, M. W.; Vipond, H. J. 3,6-phenanthrolines derived from 2,2'-diaminobenzophenone. *J. Chem. Soc.* (C) **1962**, 632-635.
20. Gorvin, J. H.; Whalley, D. P. Aromatic nitro-group displacement reactions. Part 1. A novel route to substituted 10-phenylacridones. *J. Chem. Soc. Perkin Trans.* **1979**, *1*, 1364-1370.

Sample availability: Samples not available.