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The Biomimetic Synthesis of Marine Alkaloid Related Pyrido- and Pyrrolo[2,3,4-kl]acridines

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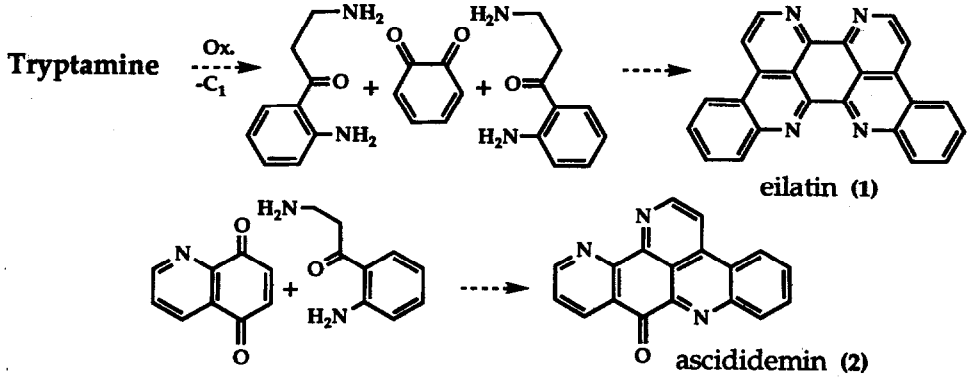
Abstract: A biomimetic reaction between β,β′-diaminoketones (e.g. kynuramine, kynurenine or o,o′-diaminobenzophenone) and a variety of cyclohexanediones and quinones leading to pyrido[2,3,4-*kl*]acridines is described. The synthesis of several di- and tetrahydro--pyrido[2,3,4-*kl*]acridine derivatives (**7**, **10**, **12** and **15**) as well as benzoderivatives of the marine alkaloids eilatin (**1**) and ascididemin (**2**), compounds **28** and **30**, has been accomplished. Additionally, the new heterocycles isoeilatin (**24**), and diazapentacene **19** have also been synthesized. All newly prepared heterocycles have been fully characterized by IR, MS and mainly by NMR spectroscopy. An analogous synthesis has been developed for pyrrolo[2,3,4-*kl*]acridines, the heterocyclic core of the bioactive marine alkaloids the plakinidines (**31** A-C).

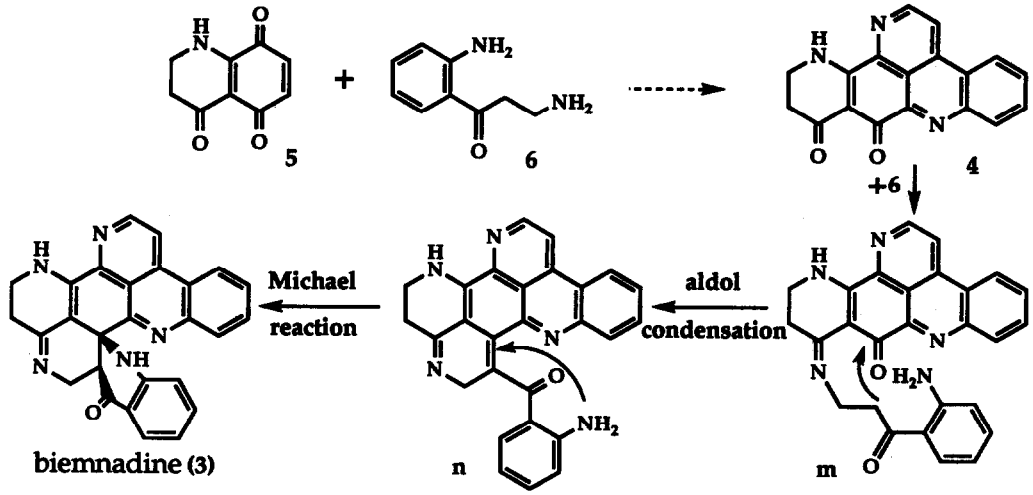
The structures of over 40 pyrido[2,3,4-*kl*]acridine alkaloids have been published over the last decade[1]. This group of alkaloids is currently of great interest due to their significant biological activities[1]. Almost all pyridoacridines have been reported as having significant cytotoxity[1]. Other activities such as the regulation of cellular growth and differentiation, affect on cAMP-mediated processes[2], inhibition of topoisomerase II, and anti-HIV activity[1] have also been reported. Our discovery of six compounds of this group of alkaloids (eilatin, debromoshermilamine and the segolins) which possess interesting biological activities[2,3] brought us to the synthesis of pyrido[2,3,4-*kl*]acridines.

Recently we reported a novel biomimetic synthesis of pyrido[2,3,4-*kl*]acridines by the reaction of kynuramine derivatives with a variety of quinones, hydroquinones and dienes[4,5]. Using this synthesis



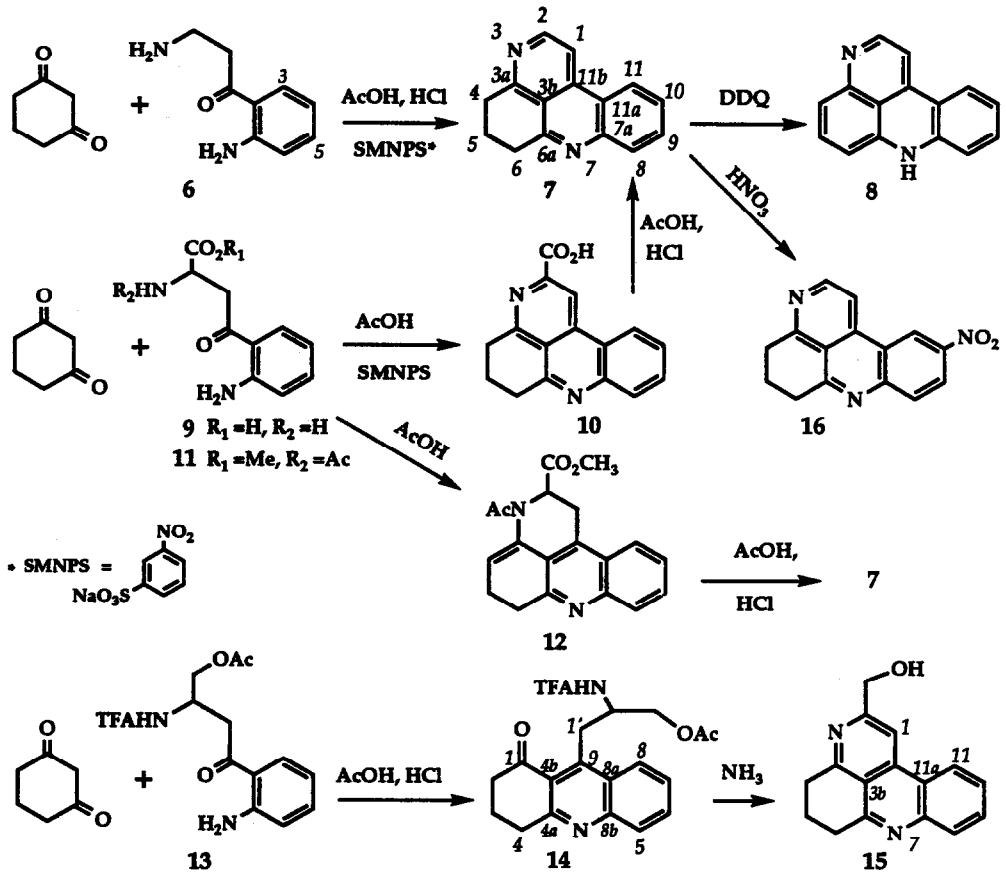
SCHEME 1: Suggested biogenesis for **1** and **2**

we synthesized the marine alkaloids eilatin[5] (1) and ascididemin[6] (2). The existence of kynuramine and quinolinequinones in marine organisms[7,8,9] suggests that the title biomimetic reaction may also describe the biosynthesis of eilatin (1), ascididemin (2) (Scheme 1), and other pyrido[2,3,4-*kl*]acridine alkaloids such as biemnadin[10] (3), as demonstrated in Scheme 2. The latter proposed biogenesis is supported by the fact that in the *Biemna* sponge biemnadin is accompanied by its suggested precursor 8,9-dihydro-11-hydroxyascididemin (4) which itself may be obtained from quinolinequinone 5 and kynuramine (6) (Scheme 2). Compound 4 might react sequentially with a second molecule of kynuramine (6) to give biemnadin (3) *via* intermediates m and n by an aldol addition reaction followed by a Michael reaction (Scheme 2). Similar biogeneses can also be suggested for eudistones A and B[11] and other less complicated members of this pyridoacridine group[1].



SCHEME 2: Suggested biogenesis for biemnadin

We have demonstrated that 1,3-cyclohexanedione reacts with kynuramine (6) under acidic oxidative conditions to give dihydropyrido[2,3,4-*kl*]acridine 7 which oxidizes further to pyridoacridine 8[4]. We show here that kynurenine (9) (the biogenetic precursor of kynuramine which retains the carboxylic group), its acetamido methyl ester derivative 11 (Scheme 5), and the N-trifluoroacetamido-3′-methylene-acetoxy derivative of kynuramine (13)[12] (Scheme 5) also give the di- or tetrahydropyridoacridine systems, namely compounds 10, 12, and compound 15 *via* 14, respectively. Each of these three compounds (10, 12, 15) was fully characterized spectroscopically mainly by 1D and 2D-NMR experiments (COSY, TOCSY, d-NOE, HMQC and HMBC correlations). Both compounds 10 and 12 undergo decarboxylation under stronger acidic conditions (acetic acid - HCl; 20:1) to give compound 7 (Scheme 3). The reaction of 1,3-cyclohexanedione with the kynuramine derivative 13 afforded the dihydroacridanone 14 by the Friedländer quinoline synthesis[13] (*via* a Schiff base followed by condensation between the carbonyl of the kynuramine moiety and the active methylene of the cyclohexanedione) (Scheme 3). The IR and NMR data of 14 (Experimental) clearly point to the formation of the quinoline and to a cyclohexanone

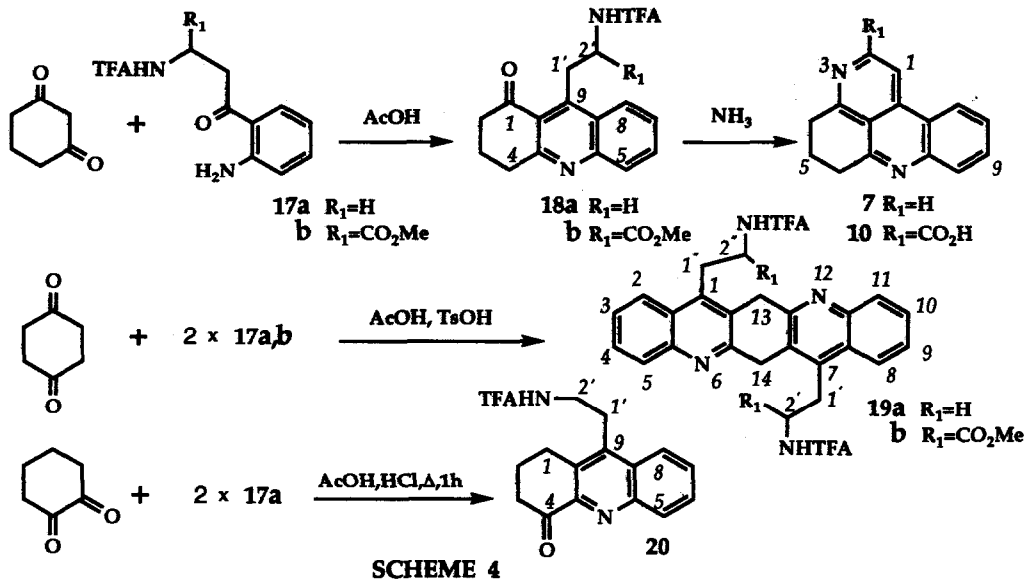


SCHEME 3

group, fused to this quinoline. Treatment of **14** with ammonia afforded compound **15**- the 2-methylene--oxy derivative of compound **7**. Compounds **10**, **12** and **15** may serve as starting materials for the preparation of C2 and/or N3 substituted pyridoacridines.

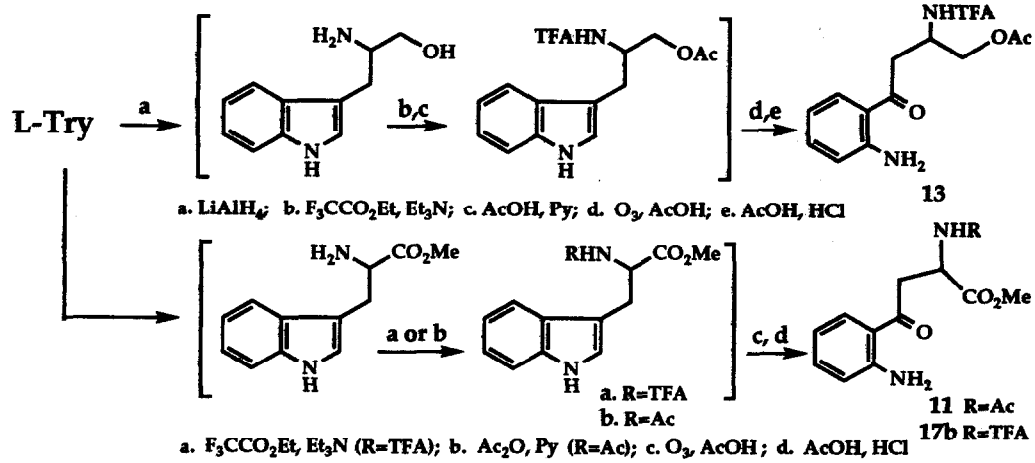
The reaction of 1,3-cyclohexanedione with N-trifluoroacetamidokynuramine (**17a**)[6] in acetic acid for 1h afforded, as with **14**, a dihydroacridanone derivative (compound **18a**, Scheme 4). The IR and NMR data of **18a** (Experimental) secured the remaining of one carbonyl group at C1, conjugated with the quinoline. As with **14**, treatment of dihydroacridanone **18a** with ammonia afforded compound **7**. By the same route the kynurenine derivative **17b** afforded compound **10** *via* compound **18b** (Scheme 5).

Nitration of compound **7** with nitric acid at 100°C gave one major mono nitro derivative (**16**) (Scheme 3). From the proton NMR spectrum [one low field aromatic proton (δ 9.43d, J=1.8Hz; H-11) and an AB spin system (δ 8.60dd, J=8,1.8Hz, H-9 and δ 8.23d, J=8Hz, H-8)], it was clear that the nitration took place on the benzene ring either at C9 or C10. As the doublet of the proton α to the nitro substituent (δ 9.43) exhibited an NOE with H-1 (4%), it was evident that the nitration took place on C10. Compound **16** is expected to be another good starting material for all kinds of C10-substituted pyrido[2,3,4-*kl*]acridines *via* its diazonium derivative.



SCHEME 4

Reacting 1,4-cyclohexanedione with compounds **17a** or **17b**, gave the 1:2 adducts, namely compounds **19a** or **19b**, respectively. The ^{13}C NMR spectrum of both **19a** and **19b**, which demonstrated only ten carbon resonances for the pentacyclic system and only one set of resonances for the two ethyltrifluoroacetamide side chains, pointed clearly to a symmetric molecule. Careful interpretation of the NMR spectra of compound **19a** (Experimental), determined the 1,7-disubstituted-6,12-diazapentacene structure (Scheme 4). The suggested linear heterocycle was preferred over the angular dibenzo-4,7-phenanthroline isomer on the basis of an NOE between H-1'(1") and H-13(14), a spatial proximity which is impossible in the case of the angular structure where the two ethylfluoroacetamido functionalities at positions 1 and 10 of the 4,7-phenanthroline are on the opposite side of the C5,C6 ethylene.

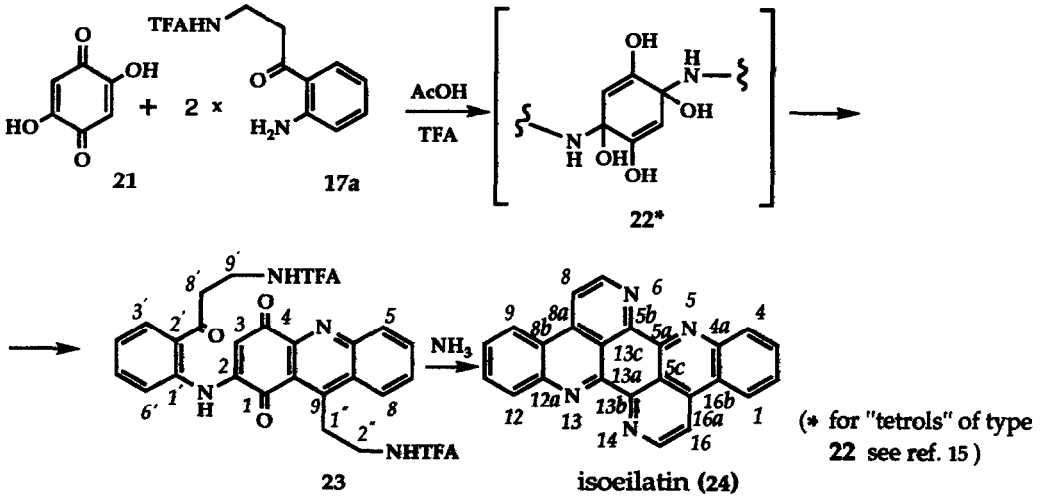


SCHEME 5

Interestingly, in contrast to the carbon NMR spectrum, the proton spectrum of **19a** differentiated between the geminal protons of the various methylenes as is evident from the COSY, HMQC and HMBC experiments. The first experiment determined the geminal pairs, the second confirmed the pairs and determined the carbon resonances of the atoms carrying each pair, and the HMBC experiment gave the correlations between the protons and their neighboring C-atoms. The proton resonances suggest an asymmetric conformation in **19a**, maybe due to strong hydrogen bonds which are responsible for the geminal methylene protons not being equivalent.

Following the study of the 1,3- and 1,4-cyclohexanedione isomers the investigation of the reaction between 1,2-cyclohexanedione and the kynuramine derivative **17a**[6] was undertaken. Mild conditions (reflux for 1h in CH_3CO_2H and catalytic amounts of HCl) afforded a 1:1 adduct, **20**. The spectral data of **20** (Experimental) suggested a single Friedländer quinoline synthesis product (Scheme 4). Compound **20** might be a promising precursor for other substituted benzophenanthrolines[14].

Once compounds **19a** and **19b** were obtained, the preparation of a 13,14-dioxo derivative as a potential intermediate to isoeilatin (**24**) (dibenzo[*l*,*k*]-1,6,7,12-tetraazaperylene) was investigated. For this purpose the reaction between 2,5-dihydroxy-1,4-cyclohexanedione (**21**) and compound **17a**, under acidic conditions, was performed. Indeed, the latter reaction afforded a 2:1, kynuramine-quinone adduct (**23**) (Scheme 6). In contrast to compounds **19a** and **19b**, this adduct was not symmetric according to its spectral data. On the basis of its NMR data (Experimental) compound **23**, has been shown to be the 2-kynuramino-p-acridinequinone. The H-3 singlet at δ 6.65 in the NMR spectrum was characteristic of the suggested structure as were the resonances of the kynuramine moiety (Experimental). Tindale[15] reported the reaction of compound **21** with several amines in ethanol to give the 1:2 "tetrol" adducts of the general structure **22** (Scheme 6). When compound **21** was reacted with **17a** in ethanol rather than in a CH_3CO_2H/ TFA mixture a similar tetrol (**22**) was obtained, as characterized by its proton NMR spectrum [δ 7.51 (d, J=8Hz,1H), 7.32 (d, 8Hz,1H), δ 7.18 (t, J=8Hz,1H), 7.13 (t, J=8Hz,1H), 7.02 (s,1H: the center tetrol ring proton), 3.68 (q, J=6Hz,2H) and 3.00 (t, J=6Hz,2H)]. The symmetric structure of **22** supports the position of the C-N bonds of **23** and hence the structure of **24**.



(* for "tetrols" of type **22** see ref. 15)

SCHEME 6

As demonstrated earlier[4,5] compound **23** could be expected to form two pyridine rings by treatment with ammonia. Indeed, the ammoniacal treatment of **23** afforded a heptacyclic compound, called isoeilatin (**24**) (Scheme 6). The structure of **24** was fully characterized by NMR data (Experimental), including COSY, d-NOE (between H-1(9) and H-16(8)), HMQC and HMBC correlations. Whereas the proton NMR data of **24** were similar to those of eilatin[3] (**1**), the ^{13}C data in the same solvent ($CDCl_3$/TFA; 10:1) were completely different:

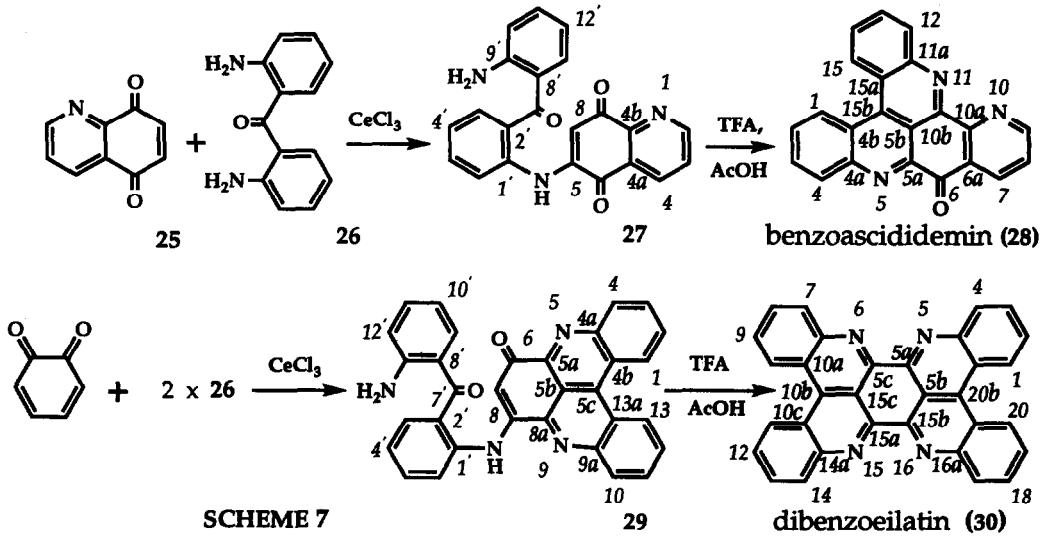
1: δ 147.3d, 144.1s, 142.9s, 142.3s, 141.6s, 136.7s, 134.1d, 128.9d, 125.0d, 123.0d, 121.5d, 116.9s,

24: δ 146.4s, 143.7s, 143.1s, 141.3d, 136.8d, 133.9d, 132.9d, 131.5s, 125.2d, 121.9d, 121.3s, 117.0s.

The synthesis of two additional derivatives of marine pyrido[2,3,4-*kl*]acridine alkaloids (compounds **28** and **30**) is shown in Scheme 7. Benzoascididemin (**28**) and dibenzoeilatin (**30**) were prepared employing the title synthesis using 2,2′-diaminobenzophenone[4] (**26**)and quinolinequinone[6] **25** or o-benzoquinone[16], respectively (Scheme 7). The first synthesis resembles the synthesis of ascididemin[6], using 2,2′-diaminobenzophenone (**26**) instead of kynumarine. Comparison of the NMR data of **27** and benzoascididemin (**28**) with those of ascididemin and its synthetic precursor[6], fully supported the structure of both **27** and **28**. The bioactivity of the latter two compounds is presently under investigation.

In an earlier report[4] we described the synthesis of a quinolinoacridanone ("benzopyrido-[2,3,4-*kl*]--acridine"), the "right" half of **29** (Scheme 7), from o-benzoquinone and 2,2′-diaminobenzophenone (**26**). In that report[4] we also mentioned the formation of an additional 1:2 adduct which has now been obtained in somewhat better yield (36%). The spectroscopic data (Experimental) of this 1:2 adduct, compound **29**, had much in common with that of the above mentioned, earlier reported, 1:1 adduct, quinolinoacridanone[4], and with that of 2,2′-diaminobenzophenone (**26**), these being the two halves of **29**.

Acidic treatment of compound **29** (CH_3CO_2H/H_2SO_4/ TFA; 45:10:45) at 60°C for 40 min, afforded a highly symmetrical compound (**30**), $C_{32}H_{16}N_4$, as judged from the HRMS and carbon NMR spectrum. Only

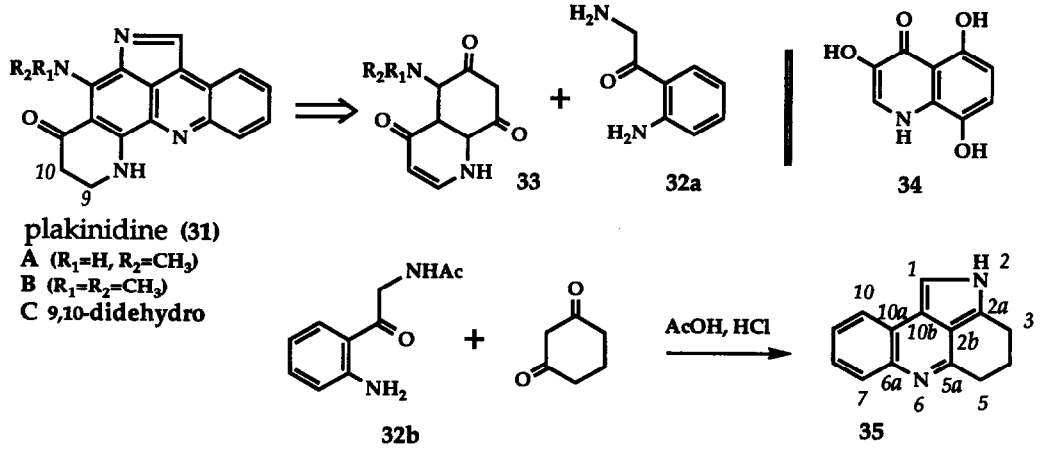


SCHEME 7

nine aromatic resonances were observable in the carbon spectrum and the proton NMR spectrum showed even fewer signals, i.e. only four protons (δ 9.32, 8.85, 8.35, 8.23 ppm), both suggesting the symmetrical nonacyclic dibenzoeilatin structure **30** (tetrabenzo[*b,e,k,n*]-1,6,7,12-tetraazaperylene) (Scheme 7). The latter structure gives a good explanation for the very low resonance of four of the protons (δ 9.32) because of the very crowded structure (overlapping of H-1 (and H-10) and H-20 (and H-11)). It is suggested that the entire molecule of **30** is twisted to a certain degree around the C10b, C15c, C5b, C20b axis due to the expected repulsions between the aforementioned protons.

Recently, in addition to the above discussed pyrido[2,3,4-*kl*]acridine alkaloids, three novel bioactive pyrrolo[2,3,4-*kl*]acridines, plakinidines A-C (**31**) have been isolated from the marine sponge *Plakortis* sp.[17a,b] These pentacyclic aromatic alkaloids belong to a new class which has not yet been reported from marine or terrestrial origin. Here we suggest a biogenesis for these alkaloids similar to the one proposed for the pyridoacridines, namely a reaction between the lower homologue of kynuramine, 2,β-diaminoacetophenone (**32a**), and an appropriate quinoline (**33**) (Scheme 8). As mentioned above oxygenated quinolines like trihydroxyquinoline **34** have previously been isolated from marine sources[9]. To support this postulate we undertook the synthesis of a pyrrolo[2,3,4-*kl*]acridine through a condensation of 1,3-cyclohexanedione with 2-amino-2′-acetamido-acetophenone **32b**. This reaction afforded ca. 50% yield of the desired tetrahydro pyrroloacridine **35**, $C_{14}H_{12}N_2$. The structure of **35** was unequivocally confirmed by its NMR spectra (Experimental), namely correlations between H-1 and C2b, 6a, 5a, 10b; H-7 with C10a; H-5 with C2b, 5a and H-10 with C10b, 9, 6a as observed in an HMBC experiment, and an 8% NOE between H-1 and H-10. Compound **35** is relatively unstable and so far we have not found the right oxidation conditions to transform it to the pyrroloacridine itself.

The motivation for searching for new marine natural products as potential drugs is that once biologically interesting metabolites are discovered, they, or related compounds, will be synthesized in the laboratory. The above described biomimetic syntheses are very good examples for this concept and indeed several of the newly synthesized compounds which are presently under investigation show interesting bioactivities.



SCHEME 8

EXPERIMENTAL

IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Low resolution mass spectra were recorded on a Finnigan-4021 mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-360 and ARX-500 spectrometers. All chemical shifts are reported with respect to TMS (δ=0). HRMS were taken on a JEOL SX 102 instrument. One and multi bond CH-correlations were established by HMQC and HMBC experiments, respectively, and given as C/H's. Protons locations were determined by COSY (through bond) and by d-NOE (through space) correlations. All chromatographics were carried out by vaccum liquid chromatography on silica-gel H and TLC on silica-gel (Merck 7735).

Dihydropyrido[2,3,4-*kl*]acridine (7).

Method A: Compound **10** (or **12**) (32mg, 0.1mmol) was refluxed in a 20:1 mixture of CH_3CO_2H-HCl (10 mL) for 1h. The mixture was poured over ice (20g), brought to pH 8 with conc. NH_3 and then extracted with CH_2Cl_2 (3x20mL). After evaporation of the solvent the residue was purified chromatographically (eluted with CH_2Cl_2) to give **7** as a yellow oil (13mg, 58%) identical to the earlier reported compound.[4]

Method B: Compound **17a** (34mg, 0.1mmol) was stirred for 24h in a solution of 28% ammonia (0.5mL) in MeOH (5mL). Purification of the residue, after evaporation of the ammoniacal methanol solution, by chromatography afforded compound **7**[4] (14mg, 64%).

2-Carboxy-dihydropyrido[2,3,4-*kl*]acridine (10).

Method A: Kynurenine (21mg, 0.1mmol), 1,3-cyclohexanedione (13mg, 0.11mmol) and sodium m-nitrophenylsulfonate (45mg, 0.2mmol) in CH_3CO_2H (5mL) were refluxed for 1h. Work-up, as described for **7** (method A), afforded compound **10** (13mg, 50%); yellow powder, mp. 168°. MS: *m/z*(%) = 264 (M^+, $C_{16}H_{12}N_2O_2$,6), 263(M^+- H, 33), 262(M^+-2H, 100), 220(M^+- CO_2, 4); IR (KBr): ν = 3436 bs, 1687, 1604, 1583, 1423, 786 cm^{-1}; ^{1}H-NMR (5% $CD_3OD/CDCl_3$): δ 9.17 (s, H-1), 8.61 (d, *J*=8Hz, H-11), 8.18 (d, *J*=8Hz, H-8), δ 7.84 (t, *J*=8Hz, H-9), 7.69(t, *J*=8Hz, H-10), 3.50(t, *J*=5.5Hz, 2H-4), 3.37(t, *J*=5Hz, 2H-6), 2.36 (m, 2H-5). ^{13}C-NMR (5% $CD_3OD/CDCl_3$): δ 167.0(s, CO_2H), 161.4(s, C-7a), 160.6(s, C-6a), 146.9(s, C-3a), 144.9 (s, C-2), 138.7(s, C-11a), 131.8(d, C-11), 130.5(d, C-8), 127.2(d, C-9), 123.2(d, C-10), 122.2(s, C-11b), 119.2(s, C-3b), 113.3(d, C-1), 33.9(t, C-4), 33.6(t, C-6), 22.7(t, C-5). Observed CH-correlations (C to H's): 3a/5,5'; 3b/1,4; 4/5,5',6,6'; 6a/5.5',6,6'; 7a/8,9; 8/9; 9/10,11; 10/8; 11/10; 11a/1, CO_2/1.

Method B: Compound **18b** (20mg, 0.05mmol) gave compound **10** (12mg, 60%) under the same ammoniacal-methanol conditions as described for the synthesis of **7** (method B).

N(3')-Acetamidokynurenine methyl ester (11). A solution of N(2')-acetamidotryptophan methyl ester[18] (2.6g, 10mmol) in CH_3CO_2H (30mL) was treated with ozone for 5 min at r.t.. Conc. HCl (2mL) was then added and the solution was left at r.t. for 24h. The mixture was then poured over ice (50g), made basic with conc. NH_3 (to pH 8) and then extracted with CH_2Cl_2 (3x50 mL). The combined organic phase was washed with brine, dried over anhy. Na_2SO_4 and evaporated to give a brownish oil (2.21g, 84%), Rf=0.5 (ethyl acetate), which was not further purified; MS: *m/z*(%) = 264 (M^+, $C_{13}H_{16}N_2O_4$, 100); IR (KBr): ν = 3341, 1738, 1732, 1658, 1600, 1538, 1216, 987, 850 cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 7.59(d,*J*=8, H-3), 7.29(t, *J*=8, H-5), 6.62(d, *J*=8, H-6), 6.59(t, *J*=8, H-4), 6.17(bs, NH), 4.88(m, H-2'), 3.77(dd, *J*=16,5) and 3.48(dd,*J*=16,5)) (2H-1'), 3.62(s,OMe), 1.98(s, CH_3CO).

1,2,5,6-Tetrahydro-3-acetamido-2-carbomethoxypyrido[2,3,4-*kl*]acridine (12). Compound **11** (264mg, 1mmol), was refluxed together with 1,3-cyclohexanedione (123mg, 1.1mmol) in CH_3CO_2H (20mL) for 1h.

Work-up, as described for **7** (method A), gave a brown oil which was purified by chromatography (eluted with 2% MeOH in CH_2Cl_2) to afford a brownish oil (145mg, 45%). HRMS (FAB^+): 323.1397 (Δmmu+0.2) (MH^+, $C_{19}H_{19}N_2O_3$, 100%); MS: *m/z* (%)=322 (M^+, $C_{19}H_{18}N_2O_3$,13%), 321(M^+- H, 60), 261(M^+-H-CO_2Me, 10); IR(KBr): ν = 1740, 1656, 1433, 1382, 1216, 1097, 995 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.00(d, *J*=8Hz, H-11), 7.93 (d, *J*=8Hz, H-8), 7.70(t, *J*=8Hz, H-9), 7.57 (t, *J*=8Hz, H-10), 6.13(bs, H-2), 6.06(bs, H-4), 3.96 (d, *J*=17Hz, H-1), 3.68(s, OMe), 3.37(dd, *J*=17,2Hz, H-1′), 3.10 (m, 2H-6), 2.62(m, 2H-5), 2.39(s, $COCH_3$); ^{13}C-NMR ($CDCl_3$): δ 170.5(s, CO_2Me), 169.4(s,$COCH_3$), 156.7(s, C-6a), 146.3(s, C-7a), 133.7(s, C-11a), 132.1(s, C-3a), 129.3(d, C-10), 129.0(d, C-11), 126.4(d, C-9), 125.9(s, C-11b), 123.6(d, C-4), 122.9(d, C-8), 120.9(s, C-3b), 52.5(q, OMe), 50.1(d, C-2), 31.0(t, C-6), 25.9(t, C-1), 22.2(t, C-5), 21.1(q, $COC\underline{H}_3$). Observed CH-correlation (C to H's): CO_2Me/1,1′; 3a/5,5′; 3b/1,1′, 4/5.5′, 6,6′; 6a/5,5′, 6,6′; 7a/8,9; 8/9; 9/10, 11; 10/8; 11/10; 11a/1,1′,8; $\underline{C}O_2CH_3$/$CO_2C\underline{H}_3$.

o-Aminophenyl 2-trifluoroacetamido-3-acetylpropyl ketone (13).

a. N(2′)-Trifluoroacetamidotryptophanol. L-Triptophanol[12] (1.88g, 10mmol) was stirred in methanol (40mL) with CF_3CO_2Et (2.84g, 20mmol) and NEt_3(2g, 20mmol) for 1h at r.t.. The methanol was then removed under vacuum, the residue taken up into CH_2Cl_2 (50mL) washed with 5% aq. NH_3 and then dried over anhy. Na_2SO_4 to give, after evaporation of the CH_2Cl_2 a yellow oil (2.6g, 90%), Rf=0.5 (CH_2Cl_2); MS: *m/z*(%) = 287 (M^++ H, $C_{13}H_{14}N_2O_3F_3$, 73), 286 (M^+,70); IR(KBr): ν = 3386, 1674, 1613, 1522, 1343, 1107, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.62 (d, *J*=8, H-4), 7.31(d, *J*=8, H-7), 7.13(t, *J*=8, H-6), 7.08(t, *J*=8, H-5), 7.02(s, H-2), 4.23(m, H-2′), 3.57(dd, *J*=5,1; 2H-3′), 3.01(d, *J*=7, 2H-1′). The oil was used in the next step without further purification.

b. N(2′)-Trifluoroacetamidotryptophanol acetate. The above oil (2.87g, 10mmol) was stirred overnight at r.t. in a 1:1 mixture of pyridine-acetic anhydride (10 mL). Vacuum distillation of the excess pyridine-acetic anhydride mixture left a yellow oil (3.28g, 100%) which was used in the next step without further purification, Rf=0.6 (EtOAc); MS: *m/z*(%) = 329 (M^++ H, $C_{15}H_{16}N_2O_3F_3$, 23), 328 (M^+, 81); IR (KBr): ν = 3282, 1713, 1682, 1583, 1466, 1238, 1030, 820 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.51(d, J=8, H-4), 7.26(d, *J*=8, H-7), 7.08(m, 2H-5,6), 6.93(s, H-2), 4.46(m, H-2′), 4.09(dd, *J*=5, 2; 2H-3′), 2.94(d, *J*=7, 2H-1′), 1.98(s, CH_3CO).

c. N(3′)-Trifluoroacetamidokynurinol acetate. Ozonolysis of the above oil (3.28g, 10 mmol) under the same conditions as described for the synthesis of **11** gave a yellow oil (1.52g, 45%), Rf=0.8 (CH_2Cl_2-EtOAc; 1:1); MS: *m/z*(%) = 332 (M^+, $C_{14}H_{15}N_2F_3O_4$, 71); IR (KBr): ν= 3178, 1719, 1706, 1674, 1600, 1339, 1061, 910 cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 7.54 (d, *J*=8, H-3), 7.21(t, *J*=8, H-5), 6.60(d, *J*=8, H-6), 6.56(t, *J*=8, H-4), 4.61(m, H-2′), 4.28 (dd, *J*=10,5) and 4.20 (dd, *J*=10,5) (2H-3′), 3.29 (dd, *J*=16,5) and 3.18 (dd, *J*=16,5) (2H-1′), 1.97 (s, CH_3CO).

3,4-Dihydro-9(2′-trifluoroacetamido-3′-acetoxypropyl)-1-acridanone (14). Compound **13** (33mg, 0.1 mmol), and 1,3-cyclohexanedione (13mg, 0.11 mmol) were refluxed in acetic acid (5mL) in the presence of 1 drop of conc. HCl for 1h. After the same work-up as described for **7** (method A) the residue was chromatographed (eluted with 2% MeOH in CH_2Cl_2) to afford compound **14** as a brownish-yellow oil (16mg,55%), Rf=0.7 (EtOAc); HRMS $(FAB)^+$: 409.1384 (Δmmu + 3.1) (MH^+, $C_{20}H_{20}N_2O_4F_3$, 100%); IR (KBr): ν = 3370, 1723, 1706, 1692, 1601, 1566, 1222, 1127, 935 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.18 (d, *J*=8Hz, H-8), 8.07 (d, *J*=8Hz, H-5), 7.81 (t, *J*=8Hz, H-6), 7.63 (t, *J*=8Hz, H-7), 4.62 (m, H-2′), 4.41 (m, 2H-$C\underline{H}_2OAc$), 3.85(t, J=10Hz) and 3.55m (2H-1), 3.31 (t, *J*=6Hz, 2H-4), 2.90 (t, *J*=6Hz, 2H-2), 2.22

(m, 2H-3), 2.18 (s, CH_3CO); ^{13}C-NMR ($CDCl_3$): δ 203.0(s,C-1), 170.0 (s, OAc), 161.5 (s,C-9), 148.0 (s, C-8b), 146.0(s, C-4a), 132.5 (d, C-6), 129.0 (d, C-5), 127.1 (d, C-7), 126.1(s, C-4b), 124.2 (d, C-8), 113.9 (s, C-8a), 65.2 (t, $\underline{C}H_2OAc$), 51.2 (d, C-2'), 40.3 (t, C-1'), 34.1 (t, C-4), 29.2 (t, C-5), 21.6 (t, C-6), 20.0 (q, $\underline{C}H_3CO$). Observed CH-correlations (C to H's): 1/2; $O\underline{C}OCH_3$/3'; 4a/1',1"; 4b/4,1',1"; 5/7; 6/8; 7/5; 8b/6,8.

4,5-Dihydro-2-methylenehydroxypyrido[2,3,4-*kl*]acridine (15). Compound **14** (21mg, 0.05mmol) was treated with NH_3 under the same conditions as described for the synthesis of **7** (method B) to provide after chromatography (eluted with $EtOAc/CH_2Cl_2$; 1:1) compound **15** (13mg, 55%.) as a yellow oil, Rf = 0.4 (EtOAc); HRMS (FAB^+): 251.1176 (Δmmu - 0.8) (MH^+, $C_{16}H_{15}N_2O$, 100%); IR (KBr): ν = 3345, 2961, d_6-1613, 1477, 1209, 863 cm^{-1}; ^{1}H-NMR (d_6-DMSO): δ 8.69 (d,*J* = 8Hz, H-11), 8.51 (s, H-1), 8.03 (d,*J* = 8Hz, H-8), 7.84 (t, *J* = 8Hz, H-9), 7.69 (t, *J* = 8Hz, H-10), 4.75 (s, $C\underline{H}_2OH$), 3.22 (m,4H-4,6), 2.18 (m, 2H-5); ^{13}C-NMR (CDCl3): δ 161.7 (s,C-7a), 160.9 (s,C-6a), 158.5 (s,C-2), 144.9 (s,C-3a), 138.9 (s,C-11a), 131.0 (d,C-11), 128.9 (d,C-8), 126.6 (d,C-9), 122.9 (d,C-10), 121.9 (s,C-11b), 117.3 (s,C-3b), 109.9 (d,C-1), 64.9 (t, $\underline{C}H_2OH$), 34.2 (t,C-4), 33.5 (t,C-6), 22.8 (t,C-5).

Dihydro-10-nitropyrido[2,3,4-*kl*]acridine (16). Compound **7** (22mg, 0.1mmol) in a mixture of fuming HNO_3-conc. H_2SO_4 (1:1) (5mL) was heated for 1h at 100°C. The mixture was cooled, poured over ice (10g), and conc. NH_3 (20mL) was added. The mixture was then extracted with CH_2Cl_2 (3x 20mL), the organic phase was washed with brine, dried over anhy. Na_2SO_4 and evaporated to give a dark red oil (20mg). Chromatography of the crude oil (eluted with 5% MeOH in CH_2Cl_2) gave pure **16** (14mg, 54%), as a yellowish powder, m.p. 197°, Rf=0.5 (EtOAc); HRMS (FAB^+): 266.0925 (Δmmu-0.5) (MH^+, $C_{15}H_{12}N_3O_2$, 100); MS: *m/z*(%) = 265 (M^+, $C_{15}H_{11}N_3O_2$,100), 235(M^+- NO,11); IR (KBr): ν = 1634, 1588, 1386, 1172, 1008, 910 cm^{-1}; ^{1}H-NMR (5% $CD_3OD/CDCl_3$): δ 9.43(d, *J*=1.8Hz, H-11), 8.88 (d, *J*=5.6Hz, H-2), 8.60 (dd, *J*=8, 1.8Hz, H-9), 8.36 (d, *J*=5.6Hz, H-1), 8.23(d, *J*=8Hz, H-8), 3.38 (m, 4H-4,6), 2.39 (m, 2H-5). An NOE of 4% was measured between H-1 and H-11.

3,4-Dihydro-9-(2'-trifluoroacetamidoethyl)-1-acridanone (18a). Compound **17a**[6] (26mg, 0.1mmol) and 1,3-cyclohexanedione (13mg, 0.11mmol) were refluxed for 1h in acetic acid (5mL). After work-up as described for compound **7**, the product was purified by chromatography (eluted with CH_2Cl_2) to afford compound **18a** (22mg, 61%) as a yellow oil, Rf=0.8 (EtOAc); MS: *m/z*(%)=337 (M^++ H, $C_{17}H_{16}F_3N_2O_2$,19), 336 (M^+, 100), 224 (M^+- $NHCOCF_3$, 20), 223 (M^+- $NHCOCF_3$-H, 98); IR (KBr): ν = 3112, 2941, 1718, 1681, 1561, 1213, 1183, 1156, 784 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.25(d, *J*=8Hz, H-8), 7.99(d, *J*=8Hz, H-5), 7.75(t, *J*=8Hz, H-6), 7.57(t, *J*=8 Hz, H-7), 3.74 (m, 4H-,1',2'), 3.27 (t, *J*=6 Hz, 2H-4), 2.83 (t, *J*=6 Hz, 2H-2), 2.23 (m, 2H-3).

N(3')-trifluoroacetamidokynurenine methyl ester (17b).

a. N-Trifluoroacetamidotryptophan methyl ester. N-Trifluoroacetamidotryptophan methyl ester was synthesized from triptophan methyl ester (2.18g, 10mmol), ethyl trifluoroacetate (2.84g, 20mmol) and NEt_3 (2g, 20mmol) using the same procedure as for compound **13**; yellow oil, Rf=0.9 (EtOAc); MS: *m/z*(%) = 314 (M^+, $C_{14}H_{13}N_2O_3F_3$,97); IR (KBr): ν = 3132, 1722, 1680, 1602, 1514, 1302, 1279, 1116, 863 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.17(bs, NH), 7.39 (d, *J*=8Hz, H-4), 7.30(d, *J*=8Hz, H-7), 7.10(t, *J*=8Hz, H-6), 7.04(t, *J*=8Hz, H-5), 6.91 (d, *J*=2Hz, H-2), 4.82 (m, H-2'), 3.67 (s, OMe), 3.35 (d, *J*=5Hz, 2H-1'). The compound was used without further purification.

b. N(3')trifluoroacetamidokynurenine methyl ester (**17b**). Compound **17b** was prepared by ozonolysis of

the above compound using the same procedure as described for the preparation of **13**. Compound **17b** was obtained as a brown oil, Rf=0.6 (EtOAc). HRMS (FAB^+): 318.0819 (Δmmu-0.8) (MH^+, $C_{13}H_{13}O_4N_2F_3$, 100); IR (KBr): ν = 3219, 1724, 1711, 1683, 1600, 1513, 1398, 1255, 1008, 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.75(d, *J*=8Hz, H-3), 7.30(t, *J*=8Hz, H-5), 6.79(d, *J*=8Hz, H-6), 6.74(t, *J*=8Hz, H-4), 6.37 (bs, NH), 5.03 (m, H-3′), 3.99 (dd, *J*=16,5Hz) and 3.61 (dd, *J*=16,5Hz) (2H-2′), 3.67 (s, OMe).

3,4-Dihydro-9-(2′-trifluoroacetamido-2′-carbomethoxyethyl)-1-acridanone (18b). Compound **17b** (32mg, 0.1mmol) was treated with 1,3-cyclohexanedione (13mg, 0.1mmol) in the same manner as described for the synthesis of **18a**, to afford compound **18b** (23mg, 58%) as a yellowish oil, Rf=0.6 (EtOAc); MS: *m/z*(%) = 394 (M^+, $C_{19}H_{17}F_3N_2O_4$,32), 282 (M^+- $NHCOCF_3$, 19), 281 (M^+- H-$NHCOCF_3$, 100); IR (KBr): ν = 3012, 2986, 1724, 1719, 1658, 1213, 1178, 721 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.29(d, *J*=8Hz, H-8), 8.04(d, *J*=8Hz, H-5), 7.80(t, *J*=8Hz, H-6), 7.63(t, *J*=8Hz, H-7), 4.91 (m, H-2′), 4.04 (d, *J*=10 Hz) and 3.88 (d, *J*=10 Hz) (2H-1′), 3.82 (s, OMe), 3.34 (m, 2H-4), 2.82 (m, 2H-2), 2.23 (m, 2H-3).

1,7-Di(β-trifluoroacetamidoethyl)-6,12-diazapentacene (19a). Compound **17a** (52mg, 0.2mmol) and 1,4-cyclohexanedione (12mg, 0.1mmol) were refluxed in CH_3CO_2H (10mL) with catalytic amounts of p-TsOH acid for 1h. After work-up as described for compound **7** (method A) the residual brown oil was chromatographed (eluted with ethyl acetate/CH_2Cl_2, 1:1) to afford compound **19a** (29mg, 52%), a yellowish oil, Rf=0.7 (EtOAc); HRMS (FAB^+) 561.1722 (Δmmu-0.3) (MH^+, $C_{28}H_{23}F_6N_4O_2$, 100); MS: *m/z*(%): 561 (M^++H, $C_{28}H_{23}F_6N_4O_2$, 14), 560 (M^+, 41); IR (KBr): ν = 1713, 1986, 1402, 1205, 1076, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.20 (d, *J*=8Hz, 2H-2,8), 8.08 (d, *J*=8Hz, 2H-5,11), 7.70 (t, *J*=8Hz, H-4,10), 7.60 (t, *J*=8Hz, H-3,9), 3.62(m) and 2.80(m) (4H-2β,2β′), 3.35(d, *J*=10Hz, 2H-13,14), 3.00 (d=10 Hz, 2H-13′,14′), 370(m) and 3.08(m) (4H-2α,2α′); ^{13}C-NMR ($CDCl_3$): δ 161.0 (s, 2C-6a,12a), 157.1 (q, 2$\underline{C}OCF_3$), 146.0 (s, 2C-5a,11a), 141.0 (s, 2C-1,7), 130.1 (d, 2C-4,10), 128.2 (d, 2C-5, 11), 126.8 (d, 2C-3,9), 126.2 (s, 2C-13a,14a), 125.7 (s, 2C-1a,7a), 124.1 (d, 2C-2,8), 115.0 (q,2CF_3), 40.1 (t, 2C-β,β′), 33.2 (t, 2C-13,14), 28.1 (t, 2C-α,α′). Observed CH-correlations: (C to H′s): 1/2, α,α′; 1a/3; 3/5; 4/2, 3; 5/3; 5a/2,4; 6a/13, 13′, 14,14′; 13a/13,13′, α,α′.

1,7-Di(β-trifluoroacetamido-β-carbomethoxyethyl)-6,12-diazapentacene (19b). Compound **19b** was synthesized from **17b** (63mg, 0.2mmol) and 1,4-cyclohexanedione (12mg, 0.01mmol) in the same manner as described for **19a** (31mg, 47%). A brownish oil, Rf=0.7 (EtOAc); HRMS (FAB^+) 677.1853 (Δmmu+1.8) (MH^+,$C_{32}H_{27}N_4O_6F_6$, 100%); MS: *m/z*(%) = 564 (M^+-$NHCOF_3$, 100); IR (KBr): ν = 1742, 1724, 1546, 1403, 1217, 1191, 742 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.48 (d, *J*=8Hz, 2H-2,8), 8.11 (d, *J*=8Hz, 2H-5,11), 7.79 (t, *J*=8Hz, 2H-3,9), 7.70 (t, *J*=8Hz, 2H-4,10), 7.01(d, *J*=7 Hz, 2H-NH-), 4.70m (2H-β,β′), 3.96(dd, *J*=13, 4 Hz) and 3.21(dd, *J*=13,4 Hz) (4H-α,α′) 3.36 (d, *J*=10 Hz) and δ 3.13 (d, *J*=10 Hz) (4H-13,14), 3.21 (s, OMe); ^{13}C-NMR ($CDCl_3$): δ 168.0(s, 2$\underline{C}O_2Me$), 161.0(s, 2C-6a,12a), 157.5(q,2 $\underline{C}OCF_3$), 146.8(s, 2C-5a,11a), 137.8 (s, 2C-1,7), 130.2 (d, 2C-4,10), 129.5 (d, 2C-5,11), 127.2 (d, 2C-3,9), 126.2 (s, 2C-1a,7a), 125.9 (s, 2C-13a,14a), 124.3(d, 2C-2,8), 115.0 (q,2CF_3), 53.2 (d, 2C-β,β′), 52.9 (q, 2 OMe), 33.9 (t, 2C-13,14), 32.1 (t, 2C-α,α′). Observed CH-correlations (C to H′s): 1/2, α,α′; 1a/3, α,α′; 2/4; 3/5; 4/2,3; 5a/2,4; 6a/13,13′,14,14′; $\underline{C}OCF_3$/β, $\underline{C}O_2Me$/α,β, $CO_2\underline{C}H_3$.

3,4-Dihydro-9-(2-trifluoroacetamidoethyl)-4-acridanone (20). Compound **20** was synthesized from **17a** (52mg, 0.2mmol) and 1,2-cyclohexanedione (12mg, 0.1mmol) in the same manner as described for **14** (22mg, 30%). A yellowish oil, Rf = 0.5 (EtOAc); HRMS: (FAB^+): 337.1162 (Δmmu + 2.1) (MH^+, $C_{17}H_{16}N_2O_2F_3$, 100%); IR (KBr): ν = 3223, 3081, 2876, 1700, 1690, 1508, 1173, 785 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.23 (d,

J=8Hz, H-8), 8.11 (d, *J*=8Hz, H-5), 7.72 (t, *J*=8Hz, H-6), 7.65 (t, *J*=8Hz, H-7), 3.57 (q, *J*=6Hz, 2H-2'), 3.45 (t, *J*=6Hz, 2H-1'), 3.21 (t, *J*=6.5Hz, 2H-1), 2.85 (t, *J*=6.5Hz, 2H-3), 2.22 (m, 2H-2); ^{13}C-NMR ($CDCl_3$): δ 197.6 (s, C-4), 158.0 (q, $COCF_3$), 146.5s, 142.9s, 134.1s, 131.4d, 130.7s, 129.6d, 129.2d, 128.5s, 122.9d, 39.5t, 38.8t, 27.0t, 26.0t, 21.9t.

3(N)-(β-trifluoroacetamidokynuramine)-9-(2'-trifluoroacetamidoethyl)-acridine-1,4-dione (23). A mixture of β-trifluoroacetamidokynuramine (210mg, 0.8mmol), 2,5-dihydroxy-1,4-benzoquinone (56mg 0.4mmol), in a mixture of CH_3CO_2H/TFA (20:1) (10 mL) was heated under reflux for 2h. After work up, as described for **7** (method A) the residue was chromatographed (eluted with EtOAc) to provide compound **23** (32mg, 7%) as a orange powder, m.p. 287-290°C, Rf= 0.5 (EtOAc); MS: *m/z*(%): 606 (MH^+, $C_{28}H_{20}F_6N_4O_5$, 2), 492 (M^+-($H^+NH_2COCF_3$), 23); IR (KBr): ν = 3263, 1715, 1620, 1498, 1473, 1089, 733 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 10.98 (bs, NH), 9.76 (bs, NH), 9.43 (bs, NH), 8.59 (d, *J*=8Hz, H-8), 8.17 (d, *J*=8Hz, H-5), 8.08 (d, *J*=8Hz, H-3'), 7.91 (t, *J*=8Hz), 7.75 (t, *J*=8 Hz), 7.63 (m, 2H), 7.24 (m, 1H), 6.65 (s, H-3), 3.83 (q, *J*=6Hz, 2H), 3.59 (q, *J*=6Hz, 2H), 3.51 (t, *J*=8 Hz, 2H), 3.37 (t, *J*=8Hz, 2H).

Isoeilatin (24). Compound **23** (20mg, 0.033mmol) was treated with NH_3 under the same condition as described for the synthesis of **7** (method B), to provide after chromatography (eluted with EtOAc/CH_2Cl_2 (1:1)) compound **24** (5mg, 43%) as a yellow powder, m.p. > 300°C, Rf=0.3 (10% MeOH/CH_2Cl_2); HRMS: (FAB^+): 357.1136 (Δmmu - 0.4) (MH^+, $C_{24}H_{13}N_4$, 100%); IR (KBr): ν= 3010, 1590, 1200, 1087 cm^{-1}; ^{1}H-NMR (10% TFA/$CDCl_3$): δ 9.39 (d, *J*=6Hz, 2H-7,15), 9.18 (d, *J*=6Hz, 2H-8,16), 8.89 (d, *J*=8Hz, 2H-1,9), 8.62 (d, *J*=8Hz, 2H-4,12), 8.37 (t, *J*=8 Hz, 2H-3,11), 8.23 (t, *J*=8Hz, 2H-2,10); ^{13}C-NMR (10% TFA/$CDCl_3$): δ 146.4 (s, C-4a), 143.7 (s,C-8a), 143.1 (s, C-5b), 141.3 (d, C-7), 136.8 (d, C-3), 133.9 (d, C-2), 132.9 (d, C-4), 131.5 (s, C-5a), 125.2 (d, C-1), 121.9 (d, C-8), 121.3 (s, C-8b), 117.0 (s,C-5c). Observed CH-correlation (C to H's): 1/3; 2/4; 3/1; 4/2; 4a/1,3; 4b/2,4,16; 5b/7; 5c/16; 7/8.

6-N(o,o'-diaminobenzophenone)-quinoline-5,8-quinone (27). o,o'-Diaminobenzophenone[4] (**26**) (127mg, 0.6mmol) was reacted with 5,8-quinolinequinone under the same conditions as described for the synthesis of **29**. Upon chromatography (eluted with 2% MeOH in ethyl acetate) compound **27** was obtained as a red orange powder, m.p. 184° (32mg, 17%), Rf = 0.8 (EtOAc); MS: *m/z*(%) = 369 (M^+, $C_{22}H_{15}N_3O_2$,48), 333 (M^+- $2H_2O$, 35); IR (KBr): ν = 3267, 1703, 1643, 1600, 1486, 1402, 1313, 1188, 1071, 860 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.28 (bs, NH), 8.94 (dd, *J*=5, 1Hz; H-2), 8.34 (dd, *J*=8, 1Hz; H-4), 7.55 (dd, *J*=8Hz, 5; H-3), 7.52 (t, *J*=8Hz, H-4'), 7.46 (d, *J*=8Hz, H-3') 7.43 (t, *J*=8Hz, H-5'), 7.32 (d, *J*=8Hz, H-13'), 7.22 (t, *J*=8Hz, H-11'), 7.16 (d, *J*=8Hz, H-6'), 6.64 (s, H-7), 6.63 (d, *J*=8Hz, H-10'), 6.50 (t, *J*=8Hz, H-12'); ^{13}C-NMR ($CDCl_3$): 198.0 (s, C-7'), 182.0 (s, C-5), 171.0 (s, C-8), 154.1 (d, C-2), 151.8 (s, C-9'), 148.5 (s, C-4b), 144.8 (s, C-6), 136.8 (s, C-1'), 135.0 (d, C-4), 134.8 (d, C-11'), 134.0 (d, C-13'), 131.5 (d, C-3'), 131.0 (d, C-5'), 132.1 (s, C-2'), 127.5 (s, C-4a), 126.0 (d, C-3), 124.2 (d, C-6'), 122.5 (d, C-4'), 117.3 (s, C-8'), 117.0 (d, C-7), 115.2 (d, C-12'), 104.9 (d, C-10'). Observed CH-correlations (C to H's): 1'/3',5'; 2/3,4; 2'/4'; 3/2; 4a/3; 5/4,7; 5'/3'; 6/7; 6'/4'; 7'/3',13'; 4b/2,4,7; 8'/10',12'; 9'/11',13'; 11'/13'; 12'/10'.

Benzo[a]ascididemin (28). Compound **27** (20mg, 0.054mmol) dissolved in a mixture of HOAc/H_2SO_4/TFA (45: 10: 45) (5 mL) was heated to 60°C for 40 min. After cooling the reaction mixture it was poured over ice (10mg) and the solution was made basic with conc. NH_3 (15 mL). The mixture was extracted with CH_2Cl_2(3x20 mL), the organic phase was washed with brine, dried over anhy. Na_2SO_4 and evaporated. Chromatography of the residue (eluted with 5% MeOH in EtOAc) afforded compound **28**, (13mg,65%);

amorphous yellow powder, m.p. > 300°C, Rf=0.6 (10% MeOH/CH_2Cl_2); HRMS (FAB^+): 334.0992 (Δmmu+1.1) (MH^+, $C_{22}H_{12}N_3O$,100%); IR (KBr): ν = 1669, 1623, 1596, 1423, 1317, 1196, 1050, 974, 780 cm^{-1}; ^{1}H-NMR (5% $CD_3OD/CDCl_3$): δ 9.29 (dd, *J*=5.5, 1.5Hz, H-9), 9.21 (d, *J*=8Hz, H-15), 9.13 (d, *J*=8Hz, H-1), 8.85 (dd, *J*=8, 1.5Hz; H-7), 8.75 (d, *J*=8Hz, H-4), 8.72 (d, *J*=8Hz, H-12), 8.05 (t, *J*=8Hz, H-13), 8.00 (t, *J*=8Hz, H-3), 7.97 (t, *J*=8Hz, H-14), 7.90 (t, *J*=8Hz, H-2), 7.71 (dd, *J*=8, 5.5Hz; H-8); ^{13}C-NMR (5% $CD_3OD/CDCl_3$): δ 182.0 (s, C-6), 155.8 (d, C-9), 152.4 (s, C-10a), 147.3 (s, C-4a), 147.2 (s, C-11a), 147.1 (s, C-5b), 144.2 (s, C-5a), 136.6 (s, C-15b), 136.5 (d, C-7), 133.1 (d, C-4), 132.5 (d, C-12), 131.3 (d, C-13), 130.5 (d, C-14), 130.0 (s, C-6a), 129.2 (d, C-2), 127.4 (d, C-1), 127.3 (d, C-15), 125.7 (d, C-8), 124.3 (s, C-15a), 123.2 (s, C-4b), 116.2 (s, C-10b). Observed CH-correlations (C to H's): 4a/1; 6/7; 6a/8; 7/9; 9/7,8; 10a/7; 11a/15; 15a/1,14; 15b/1,15.

8-N(o,o'-diaminobenzophenone)-6-one-quinline[2,3,4-kl]acridine (29). A mixture of compound **26** (128mg, 0.6mmol), o-benzoquinone[15] (32mg, 0.3mmol) and $CeCl_3 \cdot 7H_2O$ (223mg, 0.6mmol) in ethanol (10 mL) was stirred at r.t. overnight. During this time the color changed from yellow to deep red. Water was then added (40 mL) and the mixture was extracted with 5% MeOH in CH_2Cl_2 (3x30 mL). The combined organic phase was washed with brine, dried (anhy. Na_2SO_4) and evaporated to give after chromatography (eluted with EtOAc-CH_2Cl_2, 1:1) compound **29**, (53mg, 36%); an amorphous orange powder, m.p. 263°C; Rf=0.8 (EtOAc); HRMS (FAB^+): 493.1667 (Δmmu+0.3) (MH^+, $C_{32}H_{21}N_4O_2$,100); IR (KBr): ν = 3213, 1652, 1566, 1337, 1194, 870 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.04 (d, *J*=8Hz, 2H-1,13), 8.65 (d, *J*=8 Hz, H-4 or 10), 8.37 (d, *J*=8Hz, H-10 or 4), 7.78(m, 4H), 7.47(m, 2H), 7.40 (d, *J*=8Hz, 1H), 7.28(m, 2H), 6.85(s, H-7), 6.67 (d, *J*=8Hz, H-12'), 6.56(t, *J*=8Hz, H-10'), 6.29(bs, NH); ^{13}C-NMR ($CDCl_3$): δ 186.8 (s, C-7'), 182.1 (s, C-6), 151.4s, 149.1s, 147.8s, 146.5s, 145.9s, 144.8s, 137.1s, 134.9d, 134.4d, 133.4d, 132.5d, 131.8d, 131.5d, 131.1d, 130.5d, 129.5d, 129.1d, 127.2d, 126.9d, 125.7s, 124.3 (d,2C), 123.8s, 122.7s, 122.2s, 118.3s, 117.0d, 115.5d, 115.3s, 103.8d.

Dibenzoeilatin (30). Compound **29** (50mg, 0.11mmol) was treated with a CH_3CO_2H/ H_2SO_4/ TFA mixture (45:10:45) (5 mL) at 60°C for 40 min. Work-up as described for compound **28**, except that the alkalified reaction mixture was filtered, instead of extracted. Compound **30** was obtained as a yellow amorphous powder, m.p. > 300°C; Rf=0.4 (10% MeOH/CH_2Cl_2); HRCIMS (Isobutane) *m/z*, (%): 457.1448 (Δmmu - 0.8) (MH^+, $C_{32}H_{17}N_4$,100); IR (KBr): ν = 1636, 1604, 1523, 1369, 1198, 1002, 890 cm^{-1}; ^{1}H-NMR (5% TFA/$CDCl_3$): δ 9.32 (d, *J*=8Hz, H-1), 8.85 (d, *J*=8Hz, H-4), 8.35 (t, *J*=8Hz, H-3), 8.23 (t, *J*=8Hz, H-2); ^{13}C-NMR (5% TFA/$CDCl_3$): δ 140.3 (s, C-4a), 138.9 (s, C-5a), 131.2 (d, C-2), 134.1 (d, C-3), 127.5 (s, C-10b), 126.5 (d, C-1), 125.6 (d, C-4), 121.7 (s, C-4b), 119.3 (s, C-5b). Observed CH-correlations (C to H #): 2/4; 3/1; 4/2,3; 4a/1; 4b/1,4.

Dihydropyrrolo[2,3,4-*kl*]acridine (35). 2'-acetamido-2-aminoacetophenone (**32b**) prepared from the corresponding nitro compound[19] by catalytic hydrogenation over 5% Pt/C in MeOH, at 2 atm. [(δ 7.61 (d, *J*=8Hz, H-3), 7.26 (t, *J*=8Hz, H-4), 6.68 (d, J=8Hz, H-6), 6.64 (t, *J*=8Hz, H-5), 4.67 (d, *J*=4.6 Hz, 2H-2'), 2.08 (s, $NHCOCH_3$); IR (KBr): ν = 3186, 1676, 1612, 1566, 1410, 1311 cm^{-1}; MS: *m/z*(%) = 192, (M^+, $C_{10}H_{12}N_2O_2$,100)] (192mg, 1 mmol) was refluxed with 1,3-cyclohexanedione (123mg, 1.1 mmol) in a mixture of CH_3CO_2H/ HCl (20:1) (20 mL) for 1h. After work-up, as described for compound **7**, the crude product was chromatographed (eluted with CH_2Cl_2) to give compound **35** (125 mg, 60%) as an unstable yellow oil; Rf=0.6 (EtOAc); MS: *m/z*(%) = 210 (M^++2H,1), 208 (M^+, $C_{14}H_{12}N_2$,28); IR (KBr): ν= 3099, 1617, 1560, 1460, 1366, 1247, 1016, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.99 (d, *J*=8 Hz, H-10), 7.76(d, *J*=8Hz,

H-7), 7.44 (s, H-1), 7.35 (t, *J*=8Hz, H-9), 7.34 (t, *J*=8Hz, H-8), 2.97 (t, *J*=6Hz, 2H-5,5'), 2.87 (t, *J*=6Hz, 2H-3,3'), 2.20 (t, *J*=6Hz, 2H-4,4'); ^{13}C NMR ($CDCl_3$): δ 159,1 (s, C-2a), 143.8 (s, C-6a), 128.1 (d, C-7), 128.1 (s, C-5a), 124.8 (d, C-9), 123.9 (d, C-8), 122.9 (d, C-10), 122.8 (s, C-10a), 116.2 (s, C-10b), 115.2 (s, C-2b), 106.4 (d, C-1), 29.7 (t, C-3), 23.8 (t, C-4), 21.4 (t, C-5). Observed CH-correlations (C to H's): 1/NH; 2a/3,3',4,4'; 2b/1,3,3',5,5'; 3/NH; 5a/1,4,4'; 5,5'; 6a/1,8,10; 7/8,9; 9/10; 10a/7; 10b/1,10.

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