Synthesis of Azaindenoquinoline Analogs of Amsacrine

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Five azaindenoquinolines were synthesized in order to study their antitumoral activity.

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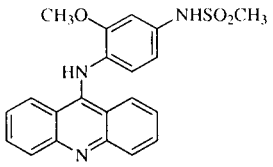
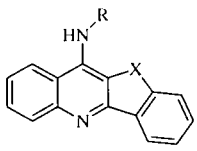
Some analogs **2** of amsacrine **1** [1] with a tetracyclic quinoline structure and an amine moiety R as a side chain, have been synthesized [2]. These authors have shown that the cytotoxic activity is dependant upon R and X. The best activity was obtained when X was a methylene group, an oxygen or a sulfur atom and R an arylamino group bearing an electron-withdrawing substituent such as $NHSO_2CH_3$. These compounds are active against KB-cells (*in vitro* and *in vivo*), P388 leukemia and various solid tumors [3].

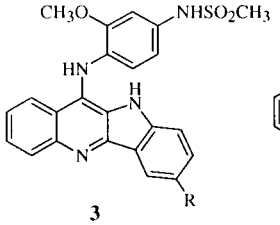


1

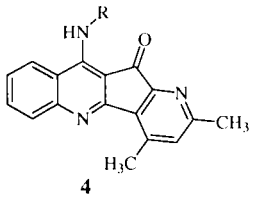


2

Chang has synthesized indolo[3,2-*b*]quinolines **3** [4]. These compounds are cytotoxic against leukemia P388 in mice, in particular when R is a galactopyranosyl moiety.



3

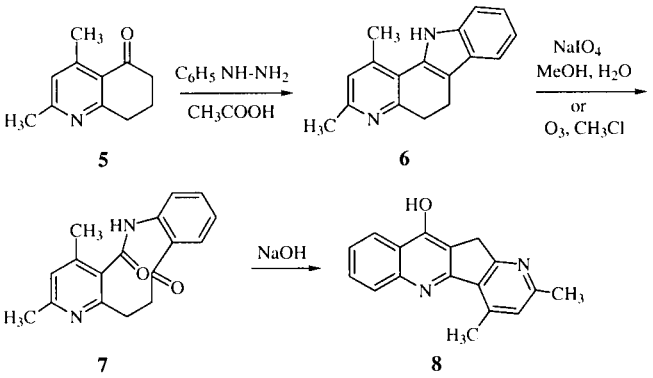


4

In this work we synthesized new tetracyclic compounds **4** and studied the relation between the substitution of the aromatic substituent and the cytotoxic activity.

The 5-oxo-2,4-dimethyltetrahydroquinoline **5** [5] was reacted with phenylhydrazine (Fischer reaction) to give the tetracyclic compound **6**, which led to the ketolactam **7** by either ozonolysis or periodate oxidation. Compound **8** was obtained by cyclization in alkaline medium [6]. Compound **6** is unstable and must be used immediately after preparation. It is quickly oxidized to a 5,6-dehydrogenation product (Scheme 1).

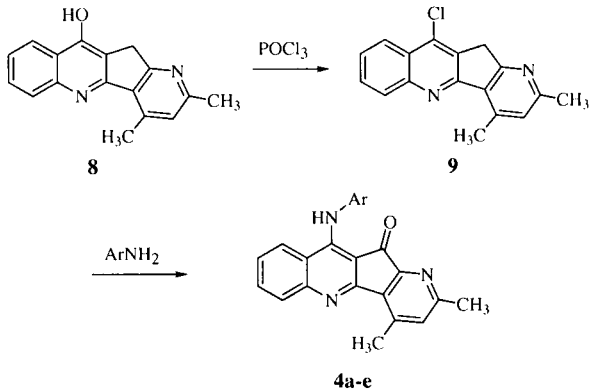
Scheme 1



5 **6** **7** **8**

The chloro derivative **9** was obtained by treatment of **8** with phosphoryl chloride (Scheme 2). At this point, different amines were condensed with **9**. Stirring **9** at room temperature with the appropriate amine in methanol afforded **4** after 15 days in low yields. Heating of these solutions at a reflux temperature led only to degradation products. Other procedures such as stirring the solution of **9** and amines in *N*-methyl-2-pyrrolidinone [7a], heating at 100°C in phenol in the absence [7b] or in the presence of potassium iodide [7c] or at reflux in ethanol [7d], did not give the expected products. Finally, improvement was obtained by the use of Andersen's process (reflux in 2-methoxyethanol instead of 2-ethoxyethanol [8]). Since these substitution reactions were not conducted under an inert atmosphere, the methylene

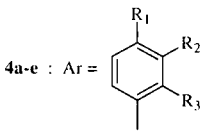
Scheme 2



8 **9** **4a-e**

group was oxidized into the keto group during the process (Scheme 2, Table).

Table



R_1	R_2	R_3	Product
H	H	H	**4a**
OCH_3	H	H	**4b**
H	OCH_3	H	**4c**
$NHSO_2CH_3$	H	H	**4d**
$NHSO_2CH_3$	H	OCH_3	**4e**

Biogical activity was studied with murine leukemic L1210 cells and human leukemic K562 cells. After three days with increasing concentrations of each compounds no growth inhibition of K652 cells was observed (10^{-5} to 10^{-10} *M*); after 24 hours of culture of L1210 cells no toxicity was observed until 10^{-3} *M* and for all compounds a growth inhibition (50%) was obtained at 10^{-5} *M*. These concentrations are very important (for example the IC_{50} of AHMA (3-(9-acridylamino)-5-(hydroxymethyl)aniline) is in the range of 10^{-9} *M* [9]) and thus these results does not present interest for ulterior studies.

EXPERIMENTAL

General Methods.

The melting points are uncorrected. The ir spectra were recorded on a Bomem spectrophotometer. The uv spectra were recorded on a Varian 634 spectrophotometer. The ^1H- and ^{13}C-nmr spectra were measured on a Brucker AC 300 apparatus at 300 MHz and 75 MHz, respectively. High resolution electron impact mass spectra (E = 70 eV) were obtained on a JEOL JMS D-300 spectrometer. Merck Kieselgel 60 PF254 was used for thin layer chromatography and Kieselgel 60 for column chromatography.

1,3-Dimethyl-5,6-dihydro-11*H*-pyrido[3,2-*a*]carbazole (**6**).

Ketone **5** (1.35 g, 7.7 mmoles) and phenylhydrazine hydrochloride (1.07 g, 7.4 mmoles) were dissolved in acetic acid (34.5 ml). The mixture was stirred for 2 hours at room temperature and then treated with concentrated hydrochloric acid (22 ml). The mixture was stirred at reflux for 21 hours. After cooling, the acetic acid was evaporated and the solution was made alkaline with 15% ammonium hydroxide solution. The solution was extracted with dichloromethane and the organic phase was washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was treated with diethyl ether. The white crystals were filtered (815 mg) and the filtrate was evaporated and the residue was purified on a chromatographic column of silica gel (cyclohexane-ethyl acetate 1/9) to give an additional 190 mg. The total yield was 55%, mp 210-211°C; uv (methanol): 208, 241, 336 nm; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 3.05 (t, 2H, J = 15 Hz, H-6), 3.22 (t, 2H, J = 15 Hz, H-5), 6.8 (s, 1H, H-2), 7.10 (t, 1H, J = 18 Hz, H-8), 7.25 (t, 1H, J = 18 Hz, H-9), 7.45 (d, 1H, J = 9 Hz, H-7), 7.60 (d, 1H, J = 9 Hz, H-10), 8.50 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 19.0 (CH_3), 21.2 (CH_3), 23.8 (C-5), 33.3 (C-6), 111.0 (C-10), 113.4 (C-6a), 118.7 (C-7), 120.0 (C-8), 121.6 (C-10a), 122.3 (C-9), 124.6 (C-2), 126.0 (C-6b), 132.1 (C-1), 137.0 (C-11b), 138.6 (C-11a), 154.6 (C-3), 157.7 (C-4a); ms: m/z 247 (100), 232 (9), 148 (37), 124 (13), 120 (30); hrms: Calcd. for $C_{17}H_{16}N_2$: 248.1313. Found: 248.1307.

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 81.59; H, 6.50; N, 11.27.

1,3-Dimethyl-6,7,12,13-tetrahydro-5*H*-pyrido[3,2-*c*][1]benzazonine-7,13-dione (**7**).

Oxidation of **6** with sodium periodate.

To a solution of **6** (125 mg, 0.5 mmole) in methanol (5 ml) was added sodium periodate (270 mg in 2 ml of water). The mixture was stirred for 24 hours at room temperature and then 4 hours at reflux. Then, 100 mg of sodium periodate was added and the reflux was maintained for 12 hours. After cooling, the mixture was extracted with dichloromethane. The organic phase was washed with saturated sodium chloride solution and dried with sodium sulfate. After concentration, the residue was purified on a chromatographic column of silica gel (ethyl acetate) to give 58.8 mg of white crystals (42%).

Oxidation of **6** with ozone.

A solution of **6** (810.5 mg, 3.24 mmoles) in chloroform (100 ml) was cooled at 0°C and ozonized for 30 minutes. Then, dimethyl sulfide (five drops) was added and the solution was stirred for 1 hour. After evaporation of the solvent the residue was crystallized from ethanol to give 581 mg (64%) of white crystals, mp >350°C; uv (methanol): 203 nm; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.05 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.00 (m, 4H, CH_2-CH_2), 6.75 (m, 2H, H-2 and NH), 7.25 (t, 1H, J = 15 Hz, H-10), 7.30 (d, 1H, J = 9 Hz, H-11), 7.45 (t, 1H, J = 15 Hz, H-9), 7.52 (d, 1H, J = 9 Hz, H-8); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 18.0 (CH_3), 23.7 (CH_3), 33.7 (C-6), 40.6 (C-5), 122.2 (C-2), 127.3 (C-9), 127.6 (C-11), 127.8 (C-8), 130.0 (C-13a), 132.1 (C-10), 135.0 (C-7a), 138.0 (C-11a), 142.4 (C-1), 153.6 (C-3), 157.4 (C-4a), 170.4 (C-13), 202.7 (C-7); ms: m/z 280(15), 237 (23), 225 (19), 160 (65), 120 (100); hrms: Calcd. for $C_{17}H_{16}N_2$: 280.1224. Found: 280.1212.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.66; H, 5.49; N, 9.81.

2,4-dimethyl-11*H*-1,5-diazabenzo[*b*]fluoren-10-ol (**8**).

A suspension of **7** (1 g, 3.6 mmoles) in 2*N* NaOH solution (53 ml) was stirred for 4 hours and then the mixture was neutralized with concentrated hydrochloric acid (10.2 ml). The product was filtered, washed with water, and dried at room temperature. White crystals were obtained (849 mg, 90%), mp >350°C; uv (methanol): 193, 203, 258, 313, 342, 358 nm; ^1H nmr (deuteriochloroform): δ 2.52 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.40 (s, 1H, OH), 3.70 (s, 2H, H-11), 7.00 (s, 1H, H-3), 7.20 (t, 1H, J = 13 Hz, H-8), 7.52 (t, 1H, J = 13 Hz, H-7), 7.82 (d, 1H, J = 9 Hz, H-6), 8.15 (d, 1H, J = 9 Hz, H-9); ^{13}C nmr (deuteriochloroform): δ 18.8 (CH_3), 23.1 (CH_3), 48.0 (C-11), 117.7 (C-9a), 118.4 (C-3), 123.6 (C-9), 123.7 (C-8), 124.0 (C-6), 124.3 (C-10a), 125.9 (C-4a), 131.1 (C-7), 139.6 (C-4), 142.6 (C-11a), 142.9 (C-5a), 143.0 (C-4b), 158.7 (C-2),

164.5 (C-10); ms: m/z 262 (100), 247 (9), 233 (20); hrms: Calcd. for $C_{17}H_{14}N_2O$: 262.1101. Found: 262.1106.

Anal. Calcd. for $C_{17}H_{14}N_2O$, 3.3 H_2O: C, 63.34; H, 6.46; N, 8.61. Found: C, 63.50; H, 6.41; N, 8.61.

2,4-dimethyl-10-chloro-11*H*-1,5-diazabenzo[*b*]fluoren (**9**).

A mixture of **9** (0.5 mg, 1.9 mmole) and phosphoryl chloride (7.4 ml) was refluxed for 3 hours. Aqueous ammonia solution was added and the solution was extracted with dichloromethane. The organic phase was washed with saturated sodium chloride solution and dried with sodium sulfate. The solvent was evaporated *in vacuo* and 399 mg of white product was obtained (75%), mp 179-180°C; uv (methanol): 203, 211, 264, 327, 342 nm; ^{1}H nmr (deuteriochloroform): δ 2.65 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.92 (s, 2H, H-11), 6.90 (s, 1H, H-3), 7.54 (t, 1H, J = 15 Hz, H-8), 7.65 (t, 1H, J = 15 Hz, H-7), 8.03 (d, 1H, J = 9 Hz, H-9), 8.10 (d, 1H, J = 9 Hz, H-6); ^{13}C nmr (deuteriochloroform): δ 19.6 (CH_3), 20.3 (CH_3), 33.4 (C-11), 123.6 (C-3), 123.7 (C-9a), 127.0 (C-9), 127.8 (C-8), 129.7 (C-4a), 130.0 (C-10a), 132.6 (C-6), 133.1 (C-7), 138.4 (C-5a), 148.9 (C-10), 153.5 (C-4), 153.9 (C-4b), 159.2 (C-2), 162.2 (C-11a); ms: m/z 280 (100), 265 (10), 245 (60), 140 (18); hrms: Calcd. for $C_{17}H_{13}N_2{}^{35}Cl$: 280.0703. Found: 280.0767; calcd. for $C_{17}H_{13}N_2{}^{37}Cl$: 282.0647. Found: 280.0737.

Substitution of **9** with amines:

Method A:

A solution of chloride **9** (150 mg, 0.53 mmole) and aniline (50 mg, 0.54 mmole) in methanol (5 ml) was stirred for 15 days at room temperature in the dark. Then, the solution was neutralized with sodium bicarbonate solution, and the product was filtered, dissolved in chloroform, and the organic phase was washed with saturated sodium chloride solution. After drying and concentration, the residue was purified by preparative TLC (silica gel, chloroforme-methanol 98.5/1.5).

Method B:

A solution of chloride **9** (250 mg, 0.89 mmole) and *p*-anisidine (110 mg, 0.99 mmole) in 2-methoxyethanol (25 ml) was refluxed for 48 hours. The solution was neutralized with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic phase was washed with saturated sodium chloride solution, dried, and concentrated *in vacuo*. The residue was purified on a chromatographic column of silica gel (dichloromethane-methanol, 98/2) and crystallized from methanol.

10-Phenylamino-2,4-dimethyl-1,5-diazabenzo[*b*]fluoren-11-one (**4a**).

This compound was obtained by method A in 46% yield; mp 222-223°C; uv (methanol): 203, 223, 241, 268, 289, 324 nm; ^{1}H nmr (deuteriochloroform-methanol-d_4) δ: 2.60 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 7.04 (t, 1H, J = 15 Hz, H-7), 7.08 (s, 1H, H-3), 7.30 (t, 2H, J = 15 Hz, H-2' and H-6'), 7.32 (t, 1H, J = 15 Hz, H-4'), 7.40 (t, 2H, J = 15 Hz, H-3' and H-5'), 7.45 (d, 1H, J = 9 Hz, H-6), 7.55 (1H, t, J = 15 Hz, H-8), 7.91 (d, 1H, J = 9 Hz, H-9), 9.66 (s, 1H, NH); ^{13}C nmr (deuteriochloroform-methanol-d_4): δ 18.3 (CH_3), 23.8 (CH_3), 119.1 (C-9a), 124.7 (C-9), 126.1 (C-4'), 127.9 (C-6), 128.7 (C-3' and C-5'), 128.8 (C-10a), 128.9 (C-4a), 129.3 (C-2' and C-6'), 130.1 (C-8), 131.5 (C-7), 140.3 (C-3), 145.2 (C-1'), 148.5 (C-5a), 151.9 (C-4), 155.5 (C-10), 160.5 (C-4b), 161.8 (C-2), 162.6 (C-11a), 191.5 (C-11); ms: m/z 351 (53), 294 (100), 165 (20), 175 (12); hrms: Calcd. for $C_{23}H_{17}N_3O$: 351.1396. Found: 351.1371.

Anal. Calcd. for $C_{23}H_{17}N_3O$, 5.6 H_2O: C, 61.08; H, 6.20; N, 9.29. Found: C, 61.03; H, 6.15; N, 8.93.

10-(4-Methoxyphenylamino)-2,4-dimethyl-1,5-diazabenzo-[*b*]fluoren-11-one (**4b**).

This compound was obtained by method A (22%) and method B (37%); mp 156-157°C; uv (methanol): 204, 211, 265, 299, 312, 327, 334, 343 nm; ^{1}H nmr (deuteriochloroform): δ 2.65 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.25 (d, 2H, J = 9, H-3' and H- 6'), 7.04 (m, 3H, H-4', H-7 and NH), 7.25 (d, 2H, J = 9 Hz, H-2' and H-5'), 7.35 (d, 1H, J = 8 Hz, H-6), 7.50 (t, 1H, J = 9 Hz, H-8), 7.85 (d, 1H, J = 9 Hz, H-9); ^{13}C nmr (deuteriochloroform): δ 18.3 (CH_3), 24.2 (CH_3), 55.4 (OCH_3), 106.9 (C-10a), 114.5 (C-2' and C-6'), 119.0 (C-9a), 124.5 (C-9), 126.8 (C-3' and C-5'), 127.1 (C-6), 128.5 (C-3), 130.8 (C-8), 131.3 (C-7), 133.0 (C-4a), 133.2 (C-4b), 144.8 (C-4'), 145.0 (C-1'), 149.3 (C-5a), 152.0 (C-4), 155.7 (C-10), 160.4 (C-11a), 162.0 (C-2), 191.6 (C-11); ms: m/z 381 (100), 366 (62), 123 (14); hrms: Calcd. for $C_{24}H_{19}N_3O_2$: 381.1477. Found: 381.1485.

Anal. Calcd. for $C_{24}H_{19}N_3O_2$, 3 H_2O: C, 66.21; H, 5.74; N, 9.65. Found: C, 66.35; H, 5.92; N, 9.08.

10-(3-Methoxyphenylamino)-2,4-dimethyl-1,5-diazabenzo[*b*]-fluoren-11-one (**4c**).

This compound was obtained by method A (12%) and method B (15%); mp: 167°C; uv (methanol): 212, 264, 299, 312, 327, 343, 334 nm; ir (potassium bromide): ν NH 3565, CO 1675 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.62 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.81 (s, 1H, H-3), 6.85 (m, 2H, H-2' and H-4'), 7.10 (m, 2H, H-5' and H-6'), 7.28 (t, 1H, J = 9 Hz, H-7), 7.50 (t, 1H, J = 8 Hz, H-8), 7.53 (d, 1H, J = 9 Hz, H-9), 7.92 (d, 1H, J = 8 Hz, H-6), 9.60 (s, 1H, NH). ^{13}C nmr (deuteriochloroform): δ 18.4 (CH_3), 24.2 (CH_3), 55.3 (OCH_3), 108.0 (C-10a), 112.1 (C-6'), 119.3 (C-9a), 124.7 (C-9), 127.3 (C-6), 127.8 (C-5'), 128.7 (C-3), 130.5 (C-4'), 130.8 (C-8), 131.5 (C-7), 132.5 (C-2'), 133.6 (C-1'), 141.8 (C-4a), 145.0 (C-3'), 148.5 (C-5a), 152.1 (C-4), 155.8 (C-10), 160.4 (C-4b), 160.8 (C-11a), 162.0 (C-2), 192.0 (C-11); ms: m/z 381 (100), 366 (8), 337 (16), 294 (41), 265 (10); hrms: Calcd. for $C_{24}H_{19}N_3O_2$: 381.1477. Found: 381.1614.

Anal. Calcd. for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.01. Found: C, 75.55; H, 5.06; N, 11.28.

10-(4-Methanesulfonamidophenylamino)-2,4-dimethyl-1,5-diazabenzo[*b*]fluoren-11-one (**4d**).

This compound was obtained by method B in a 14% yield [10]; mp 262°C; uv (methanol): 202, 256, 296 nm; ir (potassium bromide): ν CO 1687 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.62 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.05 (s, 3H, SO_2CH_3), 7.05 (s, 1H, H-3), 7.10 (t, 1H, J = 15 Hz, H-7), 7.23 (d, 2H, J = 9 Hz, H-2' and H-6'), 7.28 (d, 2H, J = 9 Hz, H-3' and H-5'), 7.50 (d, 1H, J = 9 Hz, H-6), 7.60 (t, 1H, J = 15 Hz, H-8), 7.98 (d, 1H, J = 9 Hz, H-9), 9.01 (m, 2H, NH and $NHSO_2$); ^{13}C nmr (deuteriochloroform): δ 18.6 (CH_3), 23.8 (CH_3), 39.2 (SO_2CH_3), 108.0 (C-10a), 119.4 (C-9a), 121.5 (C-2' and C-6'), 124.4 (C-9), 125.8 (C-3' and C-5'), 128.7 (C-3), 129.5 (C-6), 131.1 (C-7), 132,1 (C-8), 133.9 (C-1'), 136.2 (C-4'), 137.3 (C-4a), 145.9 (C-5a), 152.2 (C-4), 155.8 (C-10), 160.0 (C-4b), 160.7 (C-11a), 162.1 (C-2), 191.6 (C-11); ms: m/z 444 (22), 365 (100), 337 (36), 322 (10); hrms: Calcd. for $C_{24}H_{20}N_4O_3S$: 444.1141. Found: 444.1256.

Anal. Calcd. for $C_{24}H_{20}N_4O_3S$, 2H_2O: C, 59.98; H, 5.05; N, 11.62. Found: C, 59.89; H, 4.93; N, 11.63.

10-(4-Methanesulfamido-3-methoxyphenylamino)-2,4-dimethyl-11-oxo-1,5-diazabenzo[*b*]fluoren-11-one (**4e**).

This compound was obtained by method B in a 41% yield [9]; mp 288°C; uv (methanol): 202, 265, 297 nm; ir (potassium bromide): ν NH 3244, CO 1697 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.52 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.10 (s, 3H, SO_2CH_3), 3.72 (s, 3H, OCH_3), 6.82 (dd, 1H, dd, J = 4 Hz, J = 9 Hz, H-5'), 7.00 (d, 1H, J = 9 Hz, H-6'), 7.20 (s, 1H, H-3), 7.30 (m, 2H, H-6 and H-7), 7.60 (t, 1H, J = 15 Hz, H-8), 7.70 (d, 1H, J = 15 Hz, H-9), 7.95 (d, 1H, J = 4 Hz, H-2'), 9.40 (s, 1H, NH), 9.60 (s, 1H, $NHSO_2$); ^{13}C nmr (deuteriochloroform): δ 18.1 (CH_3), 23.9 (CH_3), 39.1 (SO_2CH_3), 55.7 (OCH_3), 106.9 (C-10a), 119.9 (C-9a), 125.0 (C-6'), 125.1 (C-3'), 125.5 (C-5'), 125.6 (C-9), 126.1 (C-3), 128.6 (C-1'), 130.6 (C-8), 132.0 (C-7), 132.9 (C-6), 137.7 (C-4a), 144.3 (C-2'), 148.1 (C-4'), 149.2 (C-5a), 150.6 (C-4), 153.6 (C-10), 155.3 (C-11a), 160.4 (C-4b), 161.9 (C-2), 190.0 (C-11); ms: m/z 474 (17), 395 (65), 381 (100), 366 (82), 288 (42), 229 (43), 199 (66), 141 (68); hrms: Calcd. for $C_{25}H_{22}N_4O_4S$: 474.1373. Found: 474.1361.

Anal. Calcd. for $C_{25}H_{22}N_4O_4S$, H_2O: C, 60.96; H, 4.91; N, 11.37. Found: C, 60.95; H, 4.78; N, 11.31.

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