OXAZOLO[4,5-*g*]-β-CARBOLINES AND PYRAZINO[2,3-*g*]-β-CARBOLINES. SYNTHESIS OF MODULATORS OF THE $GABA_A$/CHLORIDE CHANNEL COMPLEX

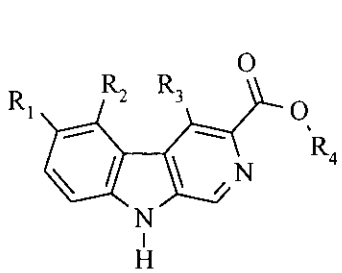
Preben H. Olesen[1*], Dieter Seidelmann[2] and John Bondo Hansen[1]

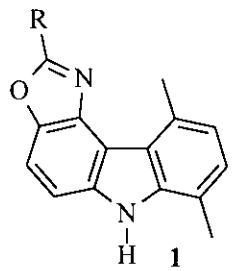
[1]Medicinal Chemistry, Health Care Discovery, Novo Nordisk, Novo Nordisk Park, DK 2760 Maaloev, Denmark

[2]Research Laboratories of Schering AG, 13342 Berlin, Germany

Abstract—The synthesis of oxazolo[4,5-*g*]-β-carbolines and pyrazino[2,3-*g*]-β-carbolines starting from 6-hydroxy-β-carbolines was investigated in order to prepare new ligands for the benzodiazepine site of the $GABA_A$/chloride channel complex.

Derivatives of ethyl β-carboline-3-carboxylate (β-CCE) are potent ligands for the benzodiazepine (BDZ) site of the $GABA_A$/chloride channel complex.[1,2] Isopropyl 6-benzyloxy-4-methoxymethyl-β-carboline-3-carboxylate (Abecarnil) and ethyl 5-benzyloxy-4-methoxymethyl-β-carboline-3-carboxylate (ZK 91296) have been shown to possess anxiolytic and anticonvulsant properties.[3,4]





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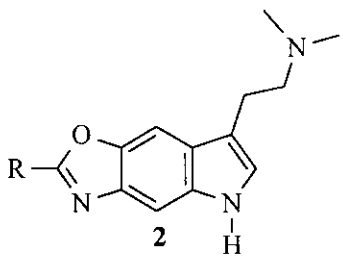


2

β-CCE R_1, R_2, R_3: H; R_4: CH_2CH_3

Abecarnil R_1: benzyloxy; R_2: H; R_3: CH_2OCH_3; R_4: $CH(CH_3)_2$

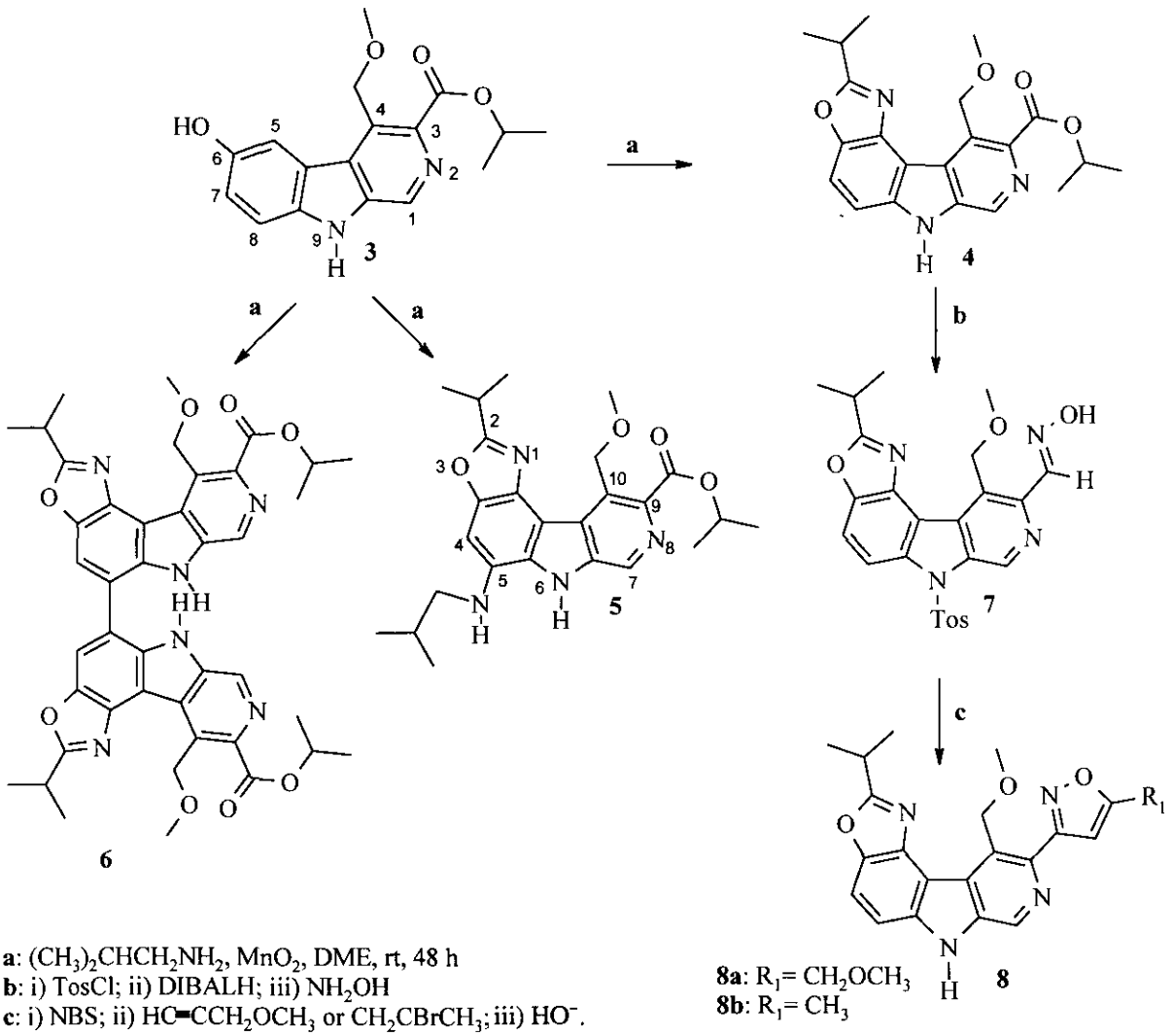
ZK 91296 R_1: H; R_2: benzyloxy; R_3: CH_2OCH_3; R_4:CH_2CH_3

Investigations of these and other analogues have indicated that substituents at the 5- and 6-position of the β-carboline ring system are not only accepted by the BDZ-site but also modify the biological activity

when compared to the parent compound.[1,2,5] This suggests that 5,6 ring annulated β-carbolines as exemplified by the novel oxazolo[4,5-*g*]-β-carbolines **(3, 8)** and pyrazino[2,3-*g*]-β-carbolines **(9, 10)** described in this paper could be of interest as new ligands for the BDZ-site.

Annulated oxazoloindole derivatives have previously been synthesized by an oxidative nucleophilic addition reaction of primary α-unsubstituted amines to 5-hydroxyindole containing compounds.[6-8] Starting from carbazole derivatives[8] MnO_2 oxidation gives, according to the proposed mechanism a quinone-imine intermediate which is attacked by the primary amine at C-4 of the indole ring system. The formed alkylaminophenol is subsequently oxidized by MnO_2 whereupon ring closure forms the annulated oxazolo[5,4-*c*]carbazoles **(1)**.

Scheme 1.



a: $(CH_3)_2CHCH_2NH_2$, MnO_2, DME, rt, 48 h
b: i) TosCl; ii) DIBALH; iii) NH_2OH
c: i) NBS; ii) $HC{\equiv}CCH_2OCH_3$ or CH_2CBrCH_3; iii) HO^-.

8a: $R_1 = CH_2OCH_3$
8b: $R_1 = CH_3$

In contrast, it has been described that starting from 5-hydroxy-*N*,*N*-dimethyltryptamine, oxidative nucleophilic addition gives the pyrrolo[2,3-*f*]benzoxazole **(2)** through an attack at the C-6 of the indole nucleus.[9]

Oxazolo[4,5-*g*]-β-carbolines (Scheme 1).

Treatment of isopropyl 6-hydroxy-4-methoxymethyl-β-carboline-3-carboxylate **(3)**[2,10] with α-unsubstituted primary amines in the presence of excess activated MnO_2 afforded the oxazolo[4,5-*g*]-β-carboline **(4)** in moderate yield.

A more thorough examination of the reaction between isobutylamine and the 6-hydroxycarboline **(3)** revealed that in addition to the desired oxazolo[4,5-*g*]-β-carboline **(4)** an isobutylamino adduct **(5)** and a 5,5′-dimer **(6)** were formed. The dimer is presumably a result of the dimerization of C-5 radical cation, analogous to the formation of 7,7′-bisindolyls described by Black,[11] whereas the isobutylamino adduct is probably formed *via* a successive MnO_2 oxidation to the quinone followed by attack of the amine on carbon 5 and then carbon 8. The double substituted phenol is finally cyclized to compound **(5)**.

Table 1. ^{1}H and ^{13}C-NMR spectral data for compound 5

	δ_C	δ_H
2	166.3	
3a	147.1	
4	90.2	7.05
5	132.9	
5a	128.7	
6		12.0
6a	135.4	
7	132.9	8.95
9	140.0	
10	126.4*	
10a	126.3*	
10b	110.8	
10c	124.5	
11	21.6	1.35
12	68.0	5.20
13	167.0	
14	57.4	3.40
15	67.9	5.85
16	20.4	1.45
17	28.0	3.30
18	20.4	1.01
19	27.2	2.02
20	51.2	3.10
21		5.70

*: may be interchanged
coupling constants are given under methods.

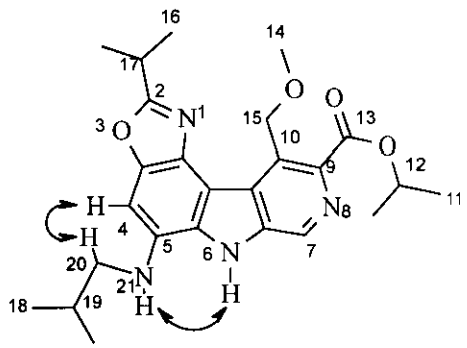


Figure 1. Top:Numbering and important ^{1}H NOESY cross-peaks. Bottom:Important HMBC correlations for compound **(5)**.

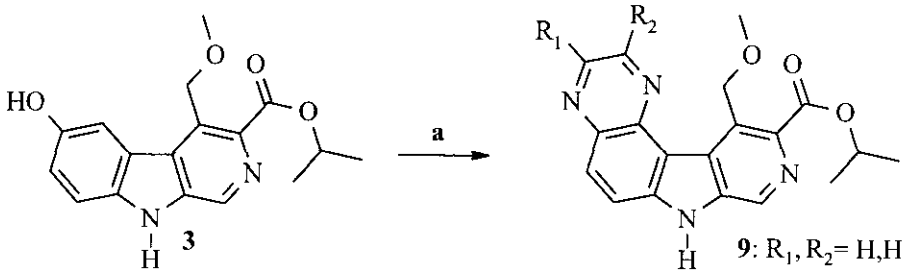
Extensive COSY, HSQC, HMBC and ROSEY measurements allowed the assignment of all the signals and correlations (figure 1 and table 1), confirming the structure of compound **(5)**.

Treatment of **(4)** with tosyl chloride in the presence of base followed by reduction with DIBALH and reaction with hydroxylamine gave the tosyl protected oxime **(7)** as an intermediate. In a one pot procedure compound **(7)** reacted with NBS and triethylamine to generate the nitrile oxide. The nitrile oxide formed *in situ* was, *via* a 1,3-dipolar cycloaddition reaction with acetylene derivatives transformed into 3,5-disubstituted isoxazole derivatives, which after tosyl deprotection with base gave the compounds **(8a)** and **(8b)**.

Pyrazino[2,3-*g*]-β-carbolines (Scheme 2).

Pyrazino[2,3-*g*]-β-carbolines **(9** and **10)** were prepared in moderate yields by treatment of isopropyl 6-hydroxy-4-methoxymethyl-β-carboline-3-carboxylate **(3)** with 1,2-diaminoalkanes in the presence of excess MnO_2.[12]

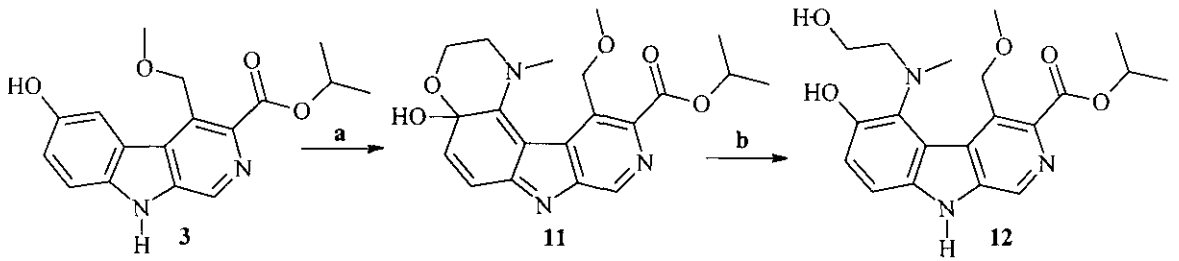
Scheme 2.



a: DME, 1,2-diaminoalkane, MnO_2, rt, 5 h

To verify the reaction mechanism previously described for the oxazole annulation reaction,[12] similar oxidative reaction conditions were used for the formation of a stable König's adduct between *N*-alkylaminoethanol and the intermediate quinone-imine.[13]

Scheme 3.



a: 2-methylaminoethanol/MnO_2 **b**: H_2/10 % palladium on carbon

In this reaction oxazino[3,2-*g*]-β-carboline **(11)** was formed in moderate yield. Hydrogenolysis of compound **(11)** under acidic conditions afforded a stable phenol derivative **(12).**

Comparing ^{1}H NMR data for compounds **(11)** and **(12)** shows that the aminoethanol moiety is fixed in a ring system for compound **(11).** Four separate signals at 3.18, 3.48, 4.32 and 4.35 ppm are observed for the methylene protons. This is not expected for a ring-opened form and in agreement with the NMR data obtained for compound **(12)** where the splitting of the methylene protons into four signals is absent. A geminal coupling, J = 14 Hz, is observed for the methylene protons of the methoxymethyl moiety of compound **(11).** This is caused by steric interaction with the *N*-methyl substituent. Attempts to trap the intermediate quinone-imine with other secondary amines e.g. diisopropylamine failed, which further support the structure determination of compound **(11).** To our knowledge, it is the first time a stable intermediate in this oxidative coupling reactions has been isolated and this provides evidence for the reaction mechanism previously described for the oxazole annulation reaction.[12]

Biology:

The ability of the annulated beta-carboline derivatives to bind to the BDZ-site of the GABA-chloride channel complex was determined by radioligand binding techniques.[3] All the test compounds were potent inhibitors of [^{3}H]-flunitrazepam binding to rat cortical membranes *in vitro*, with IC_{50}'s in the low nM-range (table 2). Inhibition of binding of [^{3}H]-flunitrazepam to mice forebrain membranes by test substances given i.p. showed the *in vivo* binding potency. The data show that several of the compounds were potent in this test. This indicates that the compounds were able to penetrate the blood brain barrier . Furthermore, the biological activity was retained by replacement of the carboxylate functionality in compound **(4)** with an isoxazole heterocycle in compounds **(8a-b).**

Table 2: Receptor binding of test substances:

Compound No.	4	8a	8b	9	10	Abecarnil
In vitro BDZ-binding IC_{50} nM	0.79	1.10	0.86	0.80	0.80	1.75
In vivo BDZ-binding ED_{50} mg/kg	2.9	0.32	1.20	9.6	>30	1.1

MATERIALS AND METHODS

Chemistry:

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 1600 spectrophotometer. ^{1}H NMR was recorded at 400 MHz, on a Bruker BZH-400/52 MHz FT-NMR instrument. Chemical shifts are given in ppm (δ) realtive to tetramethylsilane. MS spectra were recorded with a Finnigan MAT TSQ 70 mass spectrometer with electron impact (EI) ionization or fast atomic bombardment (FAB) techniques. Reactions were followed by thin-layer chromatography performed on a Silica gel 60 F254 (Merck) TLC aluminium sheets. Elemental analyses were performed by Novo Nordisk, Microanalytical Laboratory, Denmark.

Isopropyl 2-isopropyl-10-methoxymethyloxazolo[4,5-*g*]-β-carboline-9-carboxylate (4), isopropyl 4-isobutylamino-2-isopropyl-10-methoxymethyloxazolo[4,5-*g*]-β-carboline-9-carboxylate (5) and 5,5′-bis(isopropyl 2-isopropyl-10-methoxymethyloxazolo[4,5-*g*]-β-carboline-9-carboxylate) (6).

To a suspension of isopropyl 6-hydroxy-4-methoxymethyl-β-carboline-3-carboxylate **(3)**[10] (9.0 g, 28.6 mmol) in 100 mL DME was added 1-amino-2-methylpropane (7.3 g, 100 mmol) and activated MnO_2 (30.0 g, 350 mmol). The reaction mixture was stirred at rt for 48 h, filtered through Celite and concentrated *in vacuo*. The crude compound was purified by column chromatography on silica with ethyl acetate/acetone (1:1, v:v) as eluent. The first fractions contained compound **(6).** Yield 1.7 g (17%); mp >270 °C (methanol/DMF); IR (KBr) 3244, 2976, 1716 (CO), 1557, 1305, 1106; ^{1}H-NMR (DMSO-d_6) δ 1.35 (d, J = 7.5 Hz, 6H); 1.55 (d, J = 7.5 Hz, 6H); 3.45 (s, 3H); 3.50 (m, 1H); 5.20 (m, 1H); 5.95 (s, 2H); 8.20 (s, 1H); 8.75 (s, 1H); 11.75 (s, 1H); FAB-MS *m/z* 761 (M^++1); *Anal.* Calcd for $C_{42}H_{44}N_6O_8$: C, 66.18; H, 5.99; N, 11.01. Found C, 66.12; H, 6.08; N, 11.02. The next fractions contained compound **(4).** Yield 5.7 g (57%); mp 191-93 °C (ethyl acetate/hexane); IR (KBr) 3206, 2975, 1685 (CO), 1552, 1530, 1350, 1311, 1105; ^{1}H-NMR (DMSO-d_6) δ 1.35 (d, J = 7.5 Hz, 6H); 1.50 (d, J = 7.5 Hz, 6H); 3.40 (s, 3H); 3.40 (m, 1H); 5.20 (m, 1H); 5.83 (s, 2H); 7.65 (d, J = 8.3 Hz, 1H); 7.95 (d, J = 8.3 Hz, 1H); 8.90 (s, 1H), 12.30 (s, 1H); EI-MS *m/z* 381 (M^+); *Anal.* Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found C, 65.89; H, 6.09; N, 10.83. The last fractions contained compound **(5)**. Yield 960 mg (8%); mp 221-22 °C (ethyl acetate); IR (KBr) 3379, 3272, 2974, 1698 (CO), 1611, 1594, 1506, 1355, 1308, 1106; ^{1}H-NMR (DMSO-d_6) δ 1.01 (d, J = 7.5 Hz, 6H); 1.35 (d, J = 7.5 Hz, 6H); 1.45 (d, J = 7.5 Hz, 6H); 2.02 (m, 1H); 3.10 (t, J = 5.0 Hz, 2H); 3.30 (m, 1H); 3.40 (s, 3H); 5.20 (m, 1H); 5.70 (br s, 1H); 5.85 (s, 2H); 7.05 (s, 1H); 8.95 (s, 1H); 12.0 (s, 1H); EI-MS *m/z* 452 (M^+); *Anal.* Calcd for $C_{25}H_{32}N_4O_4$,1/4 H_2O: C, 65.71; H, 7.12; N, 12.26. Found C, 65.69; H, 7.19; N, 12.18.

6-Tosyl-2-isopropyl-10-methoxymethyloxazolo[4,5-*g*]-β-carboline-9-carboxaldehyde oxime (7).

To a solution of isopropyl 2-isopropyl-10-methoxymethyloxazolo[4,5-*g*]-β-carboline-9-carboxylate **(4)** (1.9 g, 5 mmol) in dichloromethane (85 mL) were added *p*-toluenesulfonyl chloride (1.0 g, 5 mmol) *N,N-dimethylaminopyridine (0.65 g, 5.3 mmol) and triethylamine* (1.0 g, 10 mmol). The reaction mixture was stirred at rt overnight. The organic phase was washed with saturated sodium hydrogen carbonate (2 x 30 mL) then water (2 x 30 mL). The organic phase was dried over magnesium sulfate and evaporated *in vacuo*. The crystalline material was washed with petroleum ether and dissolved in dry toluene (100 mL). Under a nitrogen atmosphere at -78 °C diisobutylaluminium hydride (DIBALH) (7.0 ml, 1.0 M solution in toluene) was added, and the reaction mixture stirred at -78 °C for 2 h. The reaction was carefully quenched with methanol (5 mL) and poured into water (200 mL). The phases were separated and the water phase extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate (2 x 50 mL) then water (2 x 50 mL), dried over magnesium sulfate and evaporated *in vacuo*. The crude compound was dissolved in DMF (30 mL) and hydroxylamine hydrochloride (0.44 g, 5.0 mmol) and potassium hydroxide (0.5 g dissolved in ethanol (10 mL)) were added. The reaction mixture was stirred at rt for 1 h. Water (100 mL) was added and the precipitated crystals were filtered, washed with water and dried, giving the title compound in 1.6 g (65%) yield. The compound was sufficiently pure for the next reaction step. ^{1}H-NMR (DMSO-d_6) δ 1.50 (d, 6H); 2.35 (s, 3H); 3.40 (s, 3H); 3.40 (m, 1H); 5.83 (s, 2H); 7.45 (d, 2H); 7.65 (d, 1H); 7.85 (d, 2H); 7.95 (d, 1H); 8.45 (s, 1H); 8.90 (s, 1H); 10.50 (br s, 1H); 12.30 (s, 1H).

2-Isopropyl-10-methoxymethyl-9-(5-methoxymethyl-3-isoxazolyl)oxazolo[4,5-*g*]-β-carboline (8a).

6-Tosyl-2-isopropyl-10-methoxymethyloxazolo[4,5-*g*]-β-carboline-9-carboxaldehyde oxime **(7)** (0.75 g, 1.5 mmol) was dissolved in dry DMF (20 mL). NBS (0.3 g, 1.7 mmol) dissolved in dry DMF (5 mL) was added and the reaction mixture stirred at rt for 15 min. Methyl propargyl ether (0.7 g, 10 mmol) was added, and triethylamine (0.5 g, 5 mmol) in DMF (5 mL) was added dropwise. The reaction mixture was stirred at rt for 6 h, potassium hydroxide (0.56 g, 10 mmol in methanol (10 mL)) was added, and the reaction mixture heated to 60 °C for 5 min. The reaction mixture was poured into water (100 mL) and the water phase extracted with ethyl acetate (3 x 30 mL). The organic phase was concentrated *in vacuo* and the crude compound was purified by column chromatography with acetone: ethyl acetate (1:1, v:v) as eluent. The title compound was isolated in 260 mg (42%) yield. mp 121-122 °C (ethyl acetate/hexane); IR (KBr) 3256, 2975, 1558, 1433, 1374, 1099; ^{1}H-NMR (DMSO-d_6) δ 1.50 (d, J = 7.5 Hz, 6H); 3.40 (s, 3H); 3.45 (m, 1H); 3.45 (s, 3H); 4.65 (s, 2H); 5.80 (s, 2H); 6.92 (s, 1H); 7.65 (d, J = 9.0 Hz, 1H); 7.98 (d, J =

9.0 Hz, 1H); 9.00 (s, 1H); 12.25 (s, 1H); EI-MS *m/z* 406 (M^+); *Anal.* Calcd for $C_{22}H_{22}N_4O_4$,1 H_2O: C, 62.26; H, 5.66; N, 13.20. Found C, 62.60; H, 5.66; N, 13.10.

2-Isopropyl-10-methoxymethyl-9-(5-methyl-3-isoxazolyl)oxazolo[4,5-*g*]-β-carboline (8b).

Compound **(8b)** was prepared by the same procedure as described for compound **(8a)** starting from 6-tosyl-2-isopropyl-10-methoxymethyl-oxazolo[4,5-*g*]-β-carboline-9-carboxaldehyde oxime **(7)** followed by a cyclization with 2-bromopropene. mp 252-255 °C (ethyl acetate/ethanol); IR (KBr) 3286, 2973, 1605, 1560, 1435, 1377, 1094; ^{1}H-NMR (DMSO-d_6) δ 1.50 (d, J = 7.5 Hz, 6H); 2.40 (s, 3H); 3.40 (s, 3H); 3.35 (m, 1H); 5.85 (s, 2H); 6.65 (s, 1H); 7.65 (d, J = 9.0 Hz, 1H); 7.95 (d, J = 9.0 Hz, 1H); 9.05 (s, 1H); 12.25 (s, 1H); EI-MS *m/z* 376 (M^+); *Anal.* Calcd for $C_{21}H_{20}N_4O_3$, ½ H_2O: C, 65.45; H, 5.45; N, 14.54. Found C, 65.70; H, 5.45; N, 14.44.

Isopropyl 11-methoxymethylpyrazino[2,3-*g*]-β-carboline-10-carboxylate (9).

A mixture of isopropyl 6-hydroxy-4-methoxymethyl-β-carboline-3-carboxylate **(3)** (0.63 g, 2.0 mmol), 1,2-diaminoethane (0.60 g, 10 mmol) and activated MnO_2 (2.0 g, 23 mmol) in DME (10 mL) was stirred at rt for 4 h. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude compound was purified by column chromatography with acetone as eluent. The title compound was obtained in 150 mg (21%) yield. mp 238 °C (ethyl acetate/ethanol); IR (KBr) 3189, 2978, 1714 (CO), 1615, 1518, 1326, 1300, 1104; ^{1}H-NMR (DMSO-d_6) δ 1.35 (d, J = 7.5 Hz, 6H); 3.30 (s, 3H); 5.20 (m, 1H); 5.90 (s, 2H); 8.20 (d, J = 9.0 Hz, 1H); 8.25 (d, J = 9.0 Hz, 1H); 8.98 (s, 1H); 9.02 (s, 1H); 9.12 (s, 1H); 12.90 (s, 1H); FAB-MS *m/z* 351 (M^++1); *Anal.* Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found C, 65.27; H, 5.08; N, 15.75.

Isopropyl 12-methoxymethyl-1,2,3,4-tetrahydroquinoxalino[2,3-*g*]-β-carboline-11-carboxylate (10).

A mixture of isopropyl 6-hydroxy-4-methoxymethyl-β-carboline-3-carboxylate **(3)** (1.2 g, 4.0 mmol), 1,2 diaminocyclohexane (1.86 g, 20.0 mmol) and activated MnO_2 (4.0 g, 46 mmol) in DME (20 mL) was stirred at rt for 5 h. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude compound was purified by column chromatography with acetone as eluent. The title compound was obtained in 250 mg (15%) yield. mp 244-45 °C (ethyl acetate/hexane); IR (KBr) 3211, 2935, 1716 (CO), 1613, 1503, 1357, 1310, 1105; ^{1}H-NMR (DMSO-d_6) δ 1.35 (d, J = 7.5 Hz, 6H); 2.00 (m, 4H); 3.10 (m, 2H); 3.25 (m, 2H); 3.30 (s, 3H); 5.20 (m, 1H); 6.05 (s, 2H); 8.05 (d, J = 9.0 Hz, 1H); 8.10 (d, J = 9.0 Hz,

1H); 8.95 (s, 1H); 12.70 (s, 1H); EI-MS *m/z* 404 (M^+); *Anal.* Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found C, 68.19; H, 6.08; N, 13.67.

Isopropyl 4a-hydroxy-11-methoxymethyl-1-methyl-1,2,3,4a-tetrahydrooxazino[3,2-*g*]-β-carboline-10-carboxylate (11).

To a suspension of isopropyl 6-hydroxy-4-methoxymethyl-beta-carboline-3-carboxylate **(3)** (3.14 g, 10.0 mmol) in DME (75 mL) were added 2-methylaminoethanol (3.0 g, 40.0 mmol) and activated MnO_2 (12.0 g, 140 mmol). The reaction mixture was stirred at rt for 2 h, filtered through Celite and concentrated *in vacuo*. The crude compound was crystallised from ethyl acetate/ethanol, giving the title compound as yellow crystals in 1.5 g (39 %) yield. mp 202-203 °C; IR (KBr) 3135, 2977, 2936, 1716 (CO), 1667, 1589, 1298, 1105, 1039; ^{1}H-NMR (DMSO-d_6) δ 1.28 (d, J = 7.5 Hz, 6H); 2.10 (s, 3H); 3.18 (m, 1H); 3.19 (s, 3H); 3.48 (m, 1H); 4.32 (m, 1H); 4.35 (m, 1H); 4.90 (d, 1H, J_{gem} = 14 Hz); 5.04 (d, 1H, J_{gem} = 14 Hz); 5.12 (m, 1H); 6.10 (d, J = 10 Hz, 1H); 7.65 (d, J = 10 Hz, 1H); 8.72 (s, 1H); 12.45 (br s, 1H); EI-MS *m/z* 385 (M^+); *Anal.* Calcd for $C_{20}H_{23}N_3O_4$,3/2 H_2O: C, 58.52; H, 5.97; N, 10.90. Found C, 58.25; H, 6.31; N, 10.19.

Isopropyl 5-((2-hydroxyethyl)methylamino)-6-hydroxy-4-methoxymethyl-β-carboline-3-carboxylate (12).

To a solution of **(11)** (1.16 g, 3.0 mmol) in ethanol (50 mL) were added 1N hydrochloric acid (5 mL) and palladium on activated carbon (10%, 200 mg). The reaction mixture was stirred under a hydrogen atmosphere at rt for 1 h filtered through Celite and concentrated *in vacuo*. The crude compound was purified by column chromatography with methanol:ethyl acetate (1:3, v:v) as eluent. The title compound was recrystallised from ethyl acetate. Yield 0.78 g (67%). mp 163-165 °C; IR (KBr) 3228, 2979, 2934, 1708 (CO), 1594, 1500, 1453, 1304, 1103; ^{1}H-NMR (DMSO-d_6) δ 1.45 (d, J = 7.5 Hz, 6H); 2.45 (s, 3H); 2.70 (t, J = 4.0 Hz, 2H); 3.25 (s, 3H); 3.4 (br s, 2H); 4.05 (t, J = 4.0 Hz, 2H); 5.15 (m, 1H); 5.42 (s, 2H); 7.18 (d, J = 9.0 Hz, 1H); 7.25 (d, J = 9.0 Hz, 1H); 8.68 (s, 1H); 11.8 (s, br., 1H); EI-MS *m/z* 387 (M^+); *Anal.* Calcd for $C_{20}H_{25}N_3O_5$: C, 62.02; H, 6.46; N, 10.85. Found C, 61.74; H, 6.75; N, 10.72.

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