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SYNTHESIS OF β-CARBOLINE-BENZODIAZEPINE HYBRID MOLECULES AND THEIR "AMPUTATED" ANALOGUES AS NOVEL LIGANDS OF THE BENZODIAZEPINE RECEPTOR

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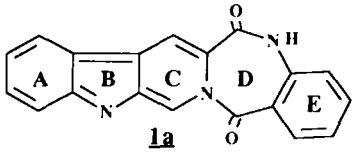
Abstract. Two approaches to the synthesis of substituted β-carboline-benzodiazepine hybrid molecules, novel ligands of the benzodiazepine receptor of the central nervous system, were utilized. The first involved DDQ-promoted dehydrogenation of a tetrahydro-β-carboline-benzodiazepine derivative while the second method made use of a triflic anhydride-activated intramolecular condensation of the carboxylic acid functionality of a C-3 anthranilamide of a β-carboline onto N-2. These two techniques were also applied to the synthesis of "amputated" hybrid derivatives in which important structural features (ring A, ring E, C-1) of these molecules were absent.

We recently described the synthesis of a benzodiazepine-β-carboline hybrid molecule **1a** which exhibited high binding affinity for the central type benzodiazepine receptors *in vitro*.[1] The design of this novel ligand was based on the hypothesis that 3-carboxy-β-carbolines and 1,4-benzodiazepines bind to discrete, though partially overlapping, sites on the receptor complex.[2,3] In an effort to better understand the roles played by both the β-carbolino and the 1,4-benzodiazepino portions of **1a** in ensuring its binding to the receptor, we have selectively modified portions of these two units of the hybrid molecule and investigated the effects of these modifications on binding affinity.



1a

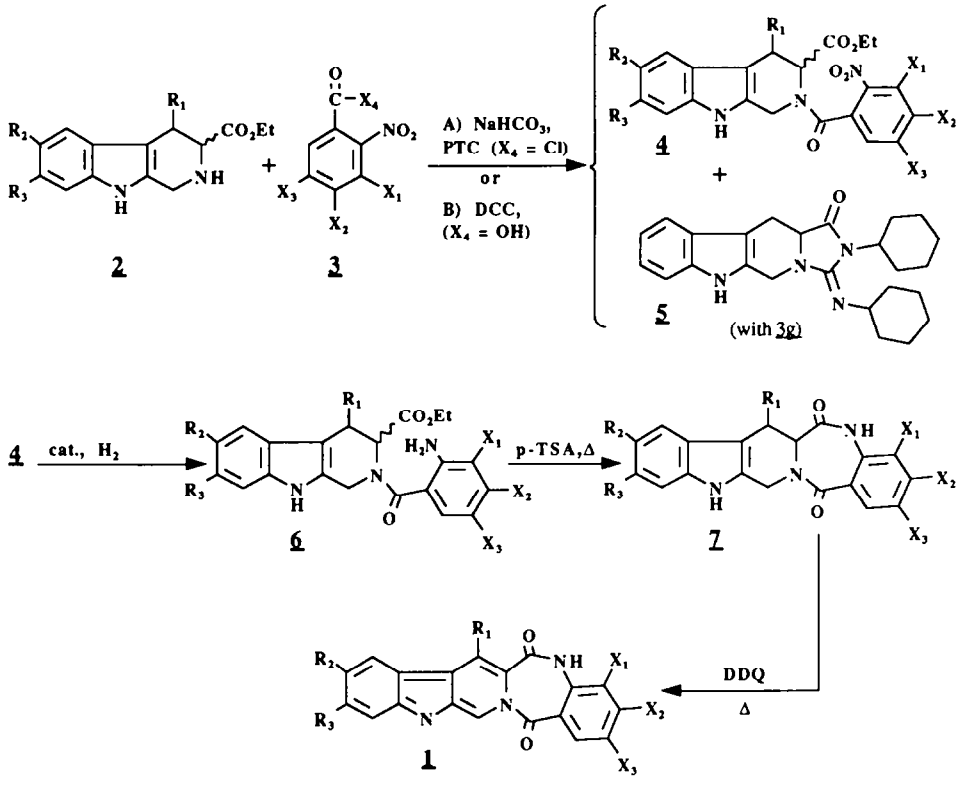
The choice of the structural changes brought to the skeleton of **1a** was based on knowledge of the largely documented structure-activity relationships[4] of the separate 3-carboxy-β-carboline and 1,4-benzodiazepine units of the hybrid **1**. The two principal synthetic approaches used to obtain the desired analogues depended on i) DDQ-promoted dehydrogenation of a tetrahydro derivative of compound **1** or ii) triflate-activated formation of the seven-membered ring starting from a totally aromatic β-carboline derivative. In this paper, we report the results of this synthetic work.

This paper is dedicated to Professor Yu Wang on the occasion of his 80 th birthday.

1) Synthesis of Hybrid Molecules Carrying Ring Substituents.

a) DDQ-promoted dehydrogenation of tetrahydro hybrids .

The synthesis of hybrid molecules of type **1a** carrying substituents on the A,C, and E rings was accomplished using the methodology shown in Scheme 1. [1]



a) $R_1 = R_2 = R_3 = H$
b) $R_1 = H$; $R_2 = R_3 = OCH_3$
c) $R_1 = C_2H_5$; $R_2 = R_3 = H$
d) $R_1 = R_3 = H$; $R_2 = OCH_2C_6H_5$
} $X_1 = X_2 = X_3 = H$

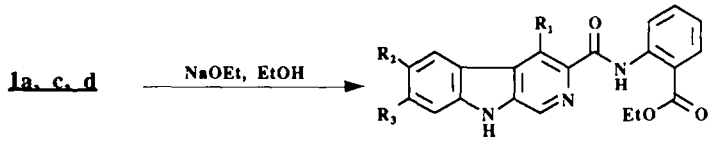
e) $X_1 = X_2 = H$; $X_3 = Cl$
f) $X_1 = X_3 = H$; $X_2 = Cl$
g) $X_1 = Cl$; $X_2 = X_3 = H$
h) $X_1 = OCH_3$; $X_2 = X_3 = H$
} $R_1 = R_2 = R_3 = H$

Scheme 1

Thus, the starting 1,2,3,4-tetrahydro-β-carbolines **2a-d**, prepared according to published procedures,[5] were coupled to the appropriate *o*-nitrobenzoic acid derivatives **3**, either by use of phase transfer catalysis (for **3**, $X_4 = Cl$) or by use of dicyclohexylcarbodiimide (DCC) in dichloromethane (when $X_4 = OH$). Yields were generally in the 50-60% range. One of the by-products isolated, in the case of the synthesis of **4g**, was compound **5** resulting from the addition of DCC to **2a** followed by cyclization. Raney nickel-catalyzed reduction of the nitro group of **4** in ethanol gave the amines **6**. However, when the benzyl derivative **4d** was reduced under these conditions, the product of hydrogenolysis (**6**, $R_2 = OH$) was mainly obtained. The nitro group of **4d** could be selectively reduced by conducting the hydrogenation in ethyl acetate instead of ethanol

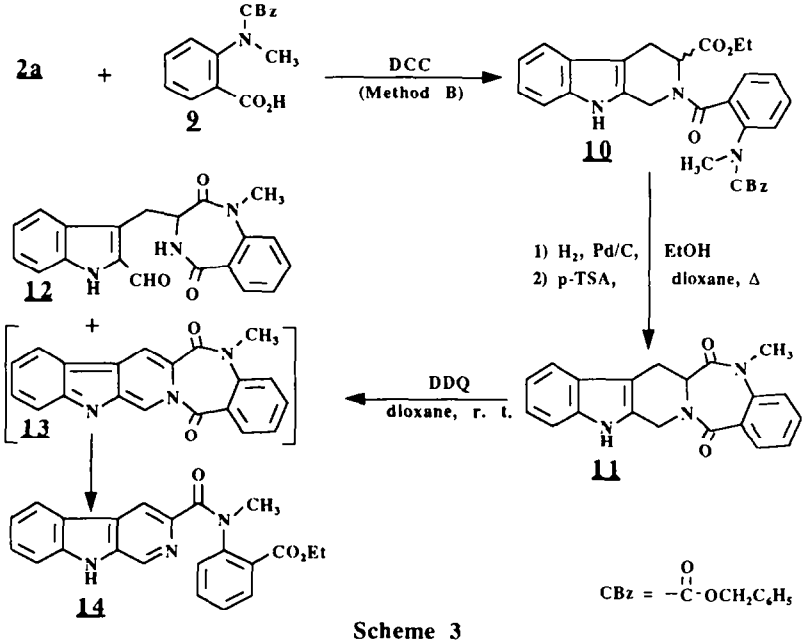
and without the addition of an external source of hydrogen, that adsorbed on the active Raney nickel sufficing. Hydrogenation of the chloro derivatives **4e,g** was also accompanied by formation of minor amounts of the dechlorinated derivative **6a**, but these could be separated by chromatography on silica gel.

When the amino derivatives **6a-h** were heated in dioxane (**6a,e,f,h**), toluene (**6b,d,g**) or DMSO (**6c**) in the presence of a catalytic quantity of *p*-toluenesulfonic acid, the benzodiazepines **7a-h** were obtained as mixtures of diastereomers. DDQ-promoted dehydrogenation of **7** in refluxing dioxane gave the desired β-carboline-benzodiazepine hybrid molecules **1a-h**, though in somewhat low yields (15-35%). These low yields are partly explained by the sensitive nature of the tertiary amide group of these benzodiazepines. For example, this bond easily undergoes ethanolysis to give the ethyl anthranilates **8** (Scheme 2).



Scheme 2

Because N-1 methylation of 1,4-benzodiazepines is known to favor their activity,[4] analogous substitution on hybrid molecules of type **1** was studied. Direct *N*-alkylation of **1a** or **7a** was precluded due to the noted sensitivity of their tertiary amide bonds. Synthesis starting from the carbobenzoxy *N*-methyl anthranilic acid derivative **9** was thus attempted (Scheme 3).

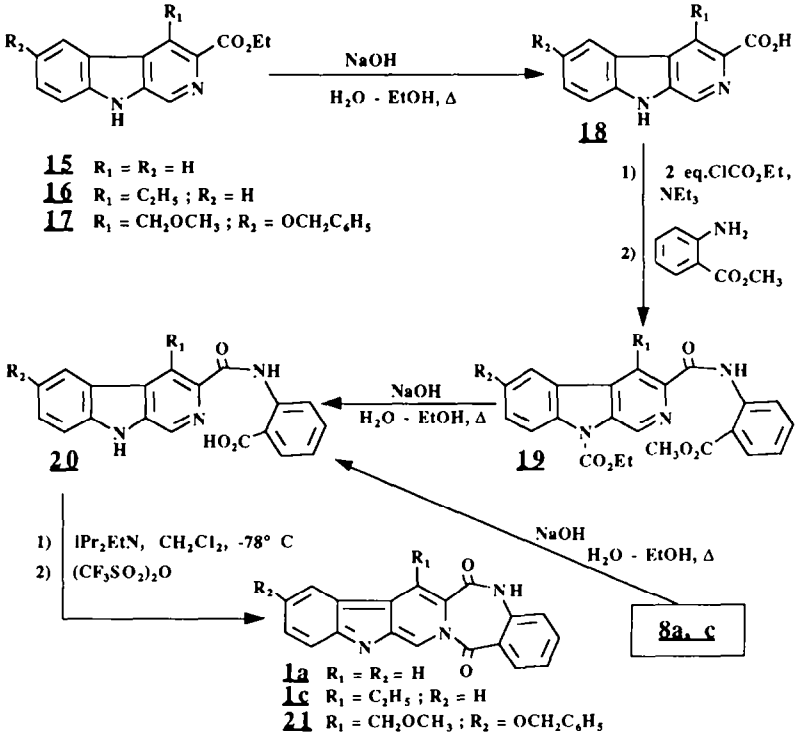


Scheme 3

DCC-promoted coupling of the tetrahydro-β-carboline ester **2a** with **9** in dichloromethane (method B) gave good yields of **10** which, after removal of the carbobenzoxy group by hydrogenolysis followed by acid-catalyzed cyclization of the resulting amine, provided **11**, the tetrahydro form of the desired *N*-methylated hybrid molecule. Treatment of **11** with DDQ in dioxane resulted in the formation of three products as indicated by TLC (CH_2Cl_2-EtOH 15:1): two higher R_f products and one very polar, highly fluorescent compound, typical of the hybrid molecules of type **1**. When the reaction mixture was subjected to column chromatography on silica gel using this eluting mixture, only the two higher R_f compounds could be recovered. One of these, isolated in low yield (<5%) was shown, by mass spectroscopy and NMR, to be the product of hydrolytic ring cleavage **12**. Precedent exists for this type of DDQ-promoted reaction in the β-carboline series.[6] The second, and major, compound isolated was the β-carboline **14**. The latter presumably arose from ethanolysis of hybrid **13** (probably corresponding to the low R_f compound observed in the TLC of the reaction mixture) during the course of purification. Thus, *N*-methylation of the carboxamide group of the hybrid molecules appears to accentuate the fragility of the neighboring tertiary amide bond. Attempts to isolate compound **13** have so far been unsuccessful.

b) Triflate-activated benzodiazepine ring closure.

The generally low yields of hybrids **1a-h** obtained after DDQ treatment of the tetrahydro precursors **7a-h** prompted us to investigate a synthetic route which would avoid this step. Such a route beginning with already aromatized β-carboline derivatives[7] is shown in Scheme 4.



Scheme 4

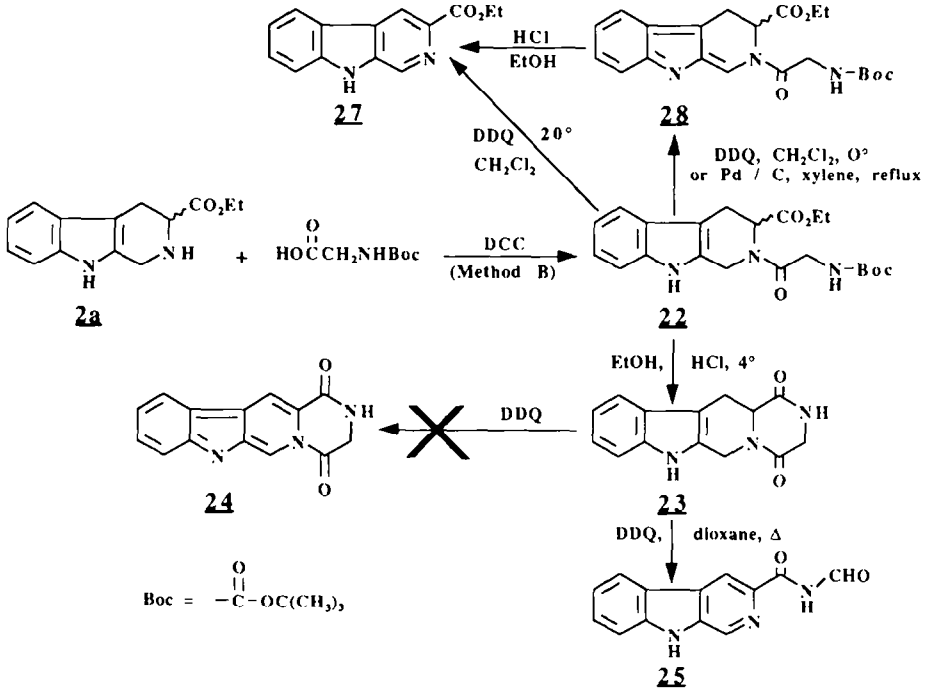
Thus, the esters **15**, **16**, and **17** (the latter corresponding to ZK 93423, a β-carboline resembling diazepam in its pharmacological activity[8]) were first hydrolyzed and the resulting carboxylic acids **18** were coupled to methyl anthranilate *via* their mixed anhydrides (2 equivalents of ethyl chloroformate were used in order to avoid the formation of mixtures due to partial reaction with the indolic amino group). The ester and carbamate blocking groups of the resulting compounds **19** were then removed simultaneously with sodium hydroxide in aqueous ethanol, yielding **20**. The latter could also be obtained by similar treatment of **8a** and **8c**, obtained by a different route (Scheme 2). Activation of the acid group of **20** with triflic anhydride followed by treatment with ethyl isopropyl amine led to clean formation of the hybrids **1a**, **1c** (both identical to those synthesized *via* Scheme 1) and **21**.

2) Synthesis of "Amputated" β-Carboline-Benzodiazepine Hybrids.

As part of our structure-activity study, we wished to investigate the importance of maintaining the integrity of the β-carboline and benzodiazepine moieties of the hybrids in assuring high affinities for the benzodiazepine receptors. For this purpose, the synthesis of three types of "amputated" hybrids, in which important structural elements of these moieties are absent, was envisaged. The results of these studies are presented below.

a) Removal of ring E, the benzo portion of the benzodiazepine moiety.

We first attempted to synthesize the diketopiperazine **24** in which the 2-acyl-3-carboxamide-9-dehydro-β-carboline pattern is no longer part of a benzodiazepine structure. For this purpose (Scheme 5), the tetrahydro-β-carboline **2a** was condensed with BOC-glycine using DCC to give **22**.



Scheme 5

Treatment of the latter with hydrogen chloride-saturated ethanol for several days at 4°C led to deprotection of the amine group and concomitant intramolecular cyclization, providing the diketopiperazine **23**. This compound was then subjected to the same conditions (DDQ in refluxing dioxane) previously used to aromatize compounds **7a-h**. However, instead of the expected compound **24**, only compound **25** could be isolated from the reaction mixture and this in very minor quantities (10%). Compound **25** was identified by comparison of spectral data with an authentic sample prepared by a direct route.[9] A possible mechanism accounting for the formation of **25** is shown in Figure 1.

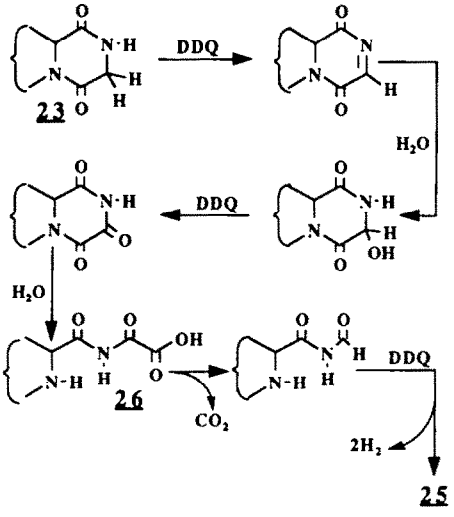


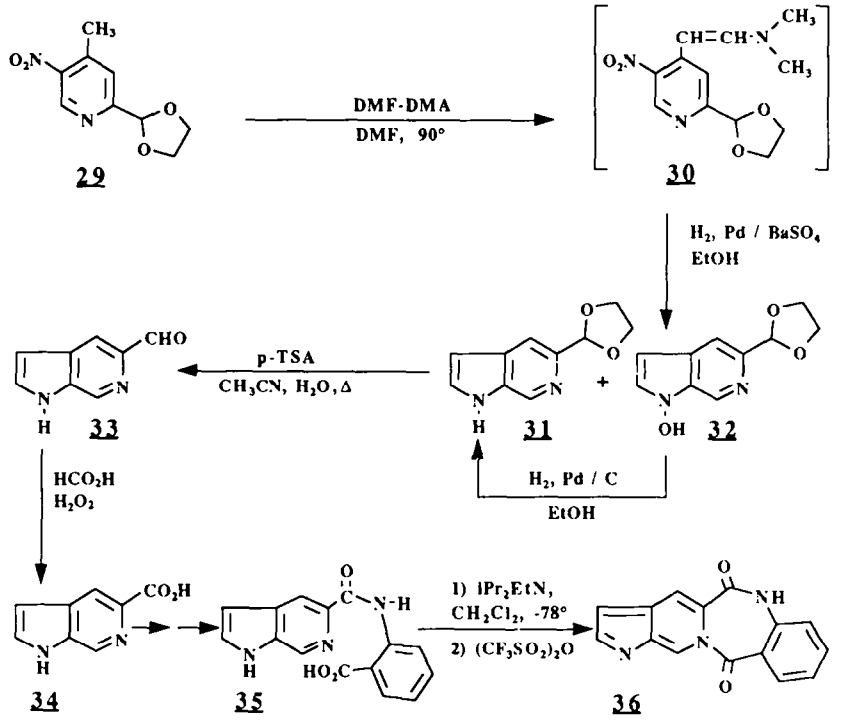
Figure 1

Successive oxidation and hydrolysis (due to traces of water in the reaction mixture) of **23** leads to the carboxylic imide **26**. Decarboxylation of the latter followed by DDQ-promoted aromatization of the β-carboline nucleus finally gives **25**.

In order to obtain **24**, we then considered initial dehydrogenation of the N-2 acylated β-carboline **22** prior to cyclization. However, when **22** was treated with DDQ in dichloromethane at 20°C under anhydrous conditions, dehydrogenation was accompanied by scission of the tertiary amide bond to give **27** as the sole product. When this reaction was conducted at 0°C another product, **28** (30%) in addition to **27** (60%) was isolated. The mass spectrum of **28** showed loss of only 2 hydrogen atoms with respect to **22**. That dehydrogenation of the 1,9 rather than the more usual[6,10] 3,4 positions of the β-carboline skeleton had occurred was indicated by the proton NMR spectrum of **28**. Only one D_2O-exchangeable proton could be observed and, as well, H-4 appeared as a doublet of doublets coupled to H-3. Higher yields (60%) of **28** were obtained when **22** was refluxed in xylene in the presence of palladium on charcoal. An attempt to remove the carbamate blocking group of **28** with hydrogen chloride in ethanol led once more to cleavage of the sensitive tertiary amide bond with formation of the β-carboline **27**.

b) Removal of ring A, the benzo portion of the β-carboline moiety of hybrid ***1a****.*

Compound **36** (Scheme 6) represents the prototype hybrid molecule **1a** amputated of its fused phenyl A ring. Suppression of this ring in the high affinity esters of β-carboline-3-carboxylic acids (e.g. **27**) gives rise to the analogous esters of 6-azaindole-5-carboxylic acids (e.g. esters of **34**) which bind much more poorly to the benzodiazepine receptor.[11] The azaindole-benzodiazepine hybrid **36** should also, if our binding model is correct, bind less strongly than the β-carboline-benzodiazepine hybrid **1a**.

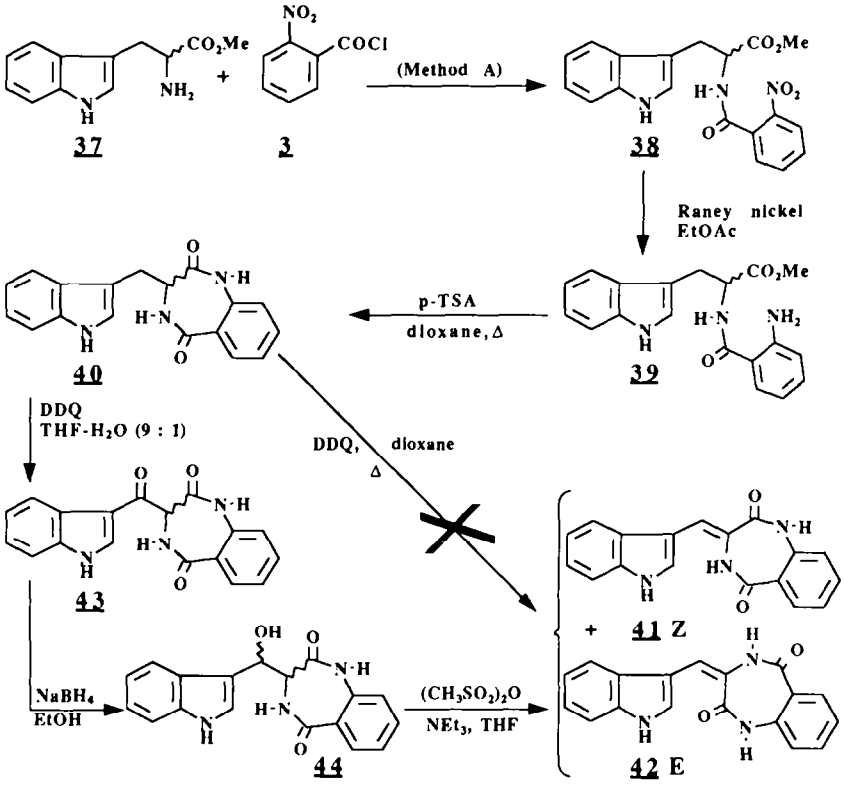


Scheme 6

The trisubstituted pyridine derivative **29**, the preparation of which has previously been described by us[11], was used as the starting material in the synthesis of **36**. Thus, using a modification of an azaindole synthesis described by Yakhontov,[12] compound **29** was condensed with dimethylformamide dimethyl acetal. The resulting intermediate, red vinylic amine **30** underwent reductive cyclization in the presence of palladium on barium sulfate as catalyst to give the azaindole **31** as the major product (52%) as well as a minor amount of the *N*-hydroxy derivative **32** (19%). The latter could be transformed quantitatively into **31** by hydrogenation with palladium on charcoal as catalyst. Removal of the acetal blocking group of **31** with *p*-toluenesulfonic acid in aqueous acetonitrile followed by oxidation of the resulting aldehyde **33** with performic acid[11] yielded 6-azaindole-5-carboxylic acid **34**. The latter was then transformed into the desired benzodiazepino derivative **36** by the method described in Scheme 4 for the conversion of **18** into **1a**.

c) Removal of the C-1 carbon atom of the β-carboline moiety of hybrid ***1a****.*

A second approach was used to verify that an intact β-carboline moiety was required in our hybrids to ensure their high binding affinity to the benzodiazepine receptor. Thus, the synthesis of 3-(3-methyleneindolo)benzodiazepine **41** (Scheme 7) was envisaged since this molecule, though structurally similar to hybrid **1a**, has lost the planar, aromatic character of the β-carboline moiety due to amputation of C-1.



Scheme 7

Compound **41** was synthesized from D,L-tryptophan methyl ester **37**. Condensation of the latter with the acid chloride of *o*-nitrobenzoic acid **3** (X_4 = Cl) under phase transfer catalysis conditions (method A) yielded the nitrobenzamide **38**. Reduction of the nitro group of **38** with Raney nickel in ethyl acetate followed by acid-catalyzed cyclization of the resulting amine **39** gave the benzodiazepine **40**. Direct dehydrogenation of the latter to **41** with DDQ in anhydrous, refluxing dioxane was unsuccessful, only starting material being recovered. Instead, compound **40** was first oxidized to the keto derivative **43** using DDQ in an aqueous medium.[13] Sodium borohydride reduction of this keto function then gave the secondary alcohol **44** as a mixture of diastereomers. Finally, treatment of **44** with mesyl anhydride led to formation of the unsaturated derivative **41** (Z isomer, 52%) together with a minor amount of the E isomer, **42** (3%). The Z isomers of other, similar unsaturated tryptophan derivatives have also been shown to be the more stable ones.[14] Moreover, the exocyclic vinylic proton of the Z isomer **41** was found in the NMR at lower field (7.69 ppm)

than that of the E isomer **42** (7.0 ppm) due to the anisotropic deshielding effects of the neighboring carbonyl group.[15]

3) Biological Results

The affinities of the synthesized β-carboline-benzodiazepine hybrid molecules for the central type benzodiazepine receptors were measured *in vitro* by a previously described procedure.[1] Except for compound **1e** (IC_{50} = 24 nM)[16], all the substituted hybrids **1b-d, 1f-h, 21**, had affinities 10 to 30-fold inferior to that of the prototype hybrid **1a** (23 nM). None of the "amputated" hybrid molecules **36, 41, 42** showed any significant receptor binding, indicating that the β-carboline moiety is essential for receptor binding.

EXPERIMENTAL SECTION

General : Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra of samples were obtained as KBr pellets with a Perkin-Elmer 297 instrument. Proton NMR spectra were determined on Bruker 80 - or 200-MHz instruments. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Mass spectral measurements were done on an AEI MS-9 or an AEI MS 50 spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator generally with use of toluene-ethanol (9:1) or dichloromethane-ethanol (20:1) as developer. The plates were visualized with UV light (254 and 366 nm). Merck silica gel 60 (230-400 mesh) was used for all column chromatography. Substituted o-nitrobenzoic acid derivatives were purchased from Aldrich Chemical Company, as was active Raney nickel in water. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France. High resolution mass spectra were obtained from the Service Central d'Analyse, CNRS, Vernaison, France.

General Procedures

Acylation of tetrahydro-β-carbolines 2a-d and tryptophan methyl ester of 37 with 3 (X_4 = Cl). Method A.

A solution of the β-carboline or tryptophan derivative in dichloromethane containing excess solid, anhydrous sodium hydrogen carbonate (5 eq), and tetrabutylammonium hydrogen sulfate (0.1 eq) was treated at 0°C with O-nitrobenzoyl chloride (1eq). After 3 h at 0°C, the reaction mixture was filtered, the filtrate was washed with water and the organic phase was dried over sodium sulfate. Evaporation of the solvent under vacuum left a yellow solid which was crystallized in the indicated solvents. Besides **4a**[1], the following compounds were prepared in this manner.

4b : 88 % ; m.p. 199-199.5°C ; EIMS, m/z 453 (M^+) ; Anal. Calcd. for $C_{23}H_{23}N_3O_7$:C, 60.93 ; H, 5,08 ; N, 9.27. Found : C, 60.73 ; H, 5,17 ; N, 9,05.

4c : 85 % ; m.p. 176°C (chloroform) ; EIMS, m/z 421 (M^+). Anal. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.55 ; H, 5.46 ; N, 9.97. Found : C, 65.34 ; H, 5.28; N, 9.84.

4d : 52 % ; foam ; EIMS, m/z 499 (M^+) ; Anal. Calcd. for $C_{28}H_{25}N_3O_6$: C, 67.33 ; H, 5.01 ; N, 8.42. Found : C, 67.14 ; H, 5,13 ; N, 8.32.

38 : 65 % ; m.p. 150°C (dichloromethane) ; EIMS, m/z 367 (M^+) ; Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12 ; H, 4.66 ; N, 11.44. Found : C, 61.80 ; H, 4.51 ; N, 11.66.

Acylation of tetrahydro-β-carboline 2a with 3 (X_4 = OH), 9, or N-Boc-glycine Method B.

A solution of ethyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate and 1 eq of 3e-c (X_4 = OH), or of 9 or of N-Boc-glycine in anhydrous dichloromethane was treated under a nitrogen atmosphere with dicyclohexyl carbodiimide (DCC, 1.1 eq). The reaction mixture was stirred for 3h at room temperature and then filtered to remove the precipitated dicyclohexylurea. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using toluene-ethanol (9:1) as developer. The N-2-acylated β-carbolines so-obtained could be further purified by crystallization in the solvents indicated. Following compounds were prepared in this manner :

4e : 64 % ; m.p. 216°C (ethanol) ; EIMS, m/z 427 and 429 (3:1, M^+) ; ^1H NMR (200 MHz, DMSO-d_6) 1.20 (3H, 2t, $CH_2\underline{CH_3}$), 3.00-3.25 (2H, m, H-4), 4.05 (2H, 2q, $\underline{CH_2}CH_3$), 4.46-4.68 (2H, dd, H-1), 5.35 (0.5H, d, H-3), 5.75 (0.5H, d, H-3), 6.76-8.30 (7H, m, Ar), 10.42 (0.5H, S, D_2O-exchangeable, NH), 10.80 (0.5H, D_2O-exchangeable, NH). Anal. Calcd for $C_{21}H_{18}N_3O_5Cl$-2/3 H_2O : C, 57.33 H, 4.39 ; N, 9.55. Found : C, 57.26 ; H, 4.19 ; N, 9.49.

4f : 82 % ; m.p. 192°C (ethanol) ; EIMS,m/z 427 and 429 (3:1, M^+). Anal. Calcd for $C_{21}H_{18}N_3O_5Cl$: C, 58.95 ; H, 4.21 ; N, 9.82. Found : C, 58.66 ; H, 4.42 ; N, 9.80.

4g : 51 % ; m.p. 224°C (ethanol) ; EIMS, m/z 427 and 429 (3:1, M^+) ; ^1H NMR (200 MHz, $CDCl_3$) ; 1.26 (3H, t, CH_3), 3.20-3.37 (2H, m, $\underline{CH_2}CH$), 4.17 (2H, q, $\underline{CH_2}CH_3$), 4.65 (2H, m, H-1), 5.31-5.68 (1H, m, H-3), 7.00-8.20 (7H, m, Ar), 10.70 and 11.00 (1H, 2s, D_2O-exchangeable, NH).

5 : 20 % ; m.p. 139-140.5°C ; EIMS, m/z 404 (M^+) ; ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.30-1.60 and 1.80 (22H, m, 2 x C_6H_{11}), 2.70 (1H, dd, J_{3-4a} = 11 Hz, H-4a), 3.24 (1H, dd, J_{3-4b} = 6 Hz, H-4b), 3.95 (1H, dd, H-3), 4.70 (1H, d, $J_{1a,1b}$ = 16.5 Hz, H-1a), 5.00 (1H, d, H-1b), 7.13-7.30 and 7.50 (7H, m, Ar), 8.18 (1H, S, D_2O-exchangeable, NH).

4h : 78 % ; m.p. 278°C (decomp)(ethanol) ; EIMS, m/z 423 (M^+) ; Anal. calcd for $C_{22}H_{21}N_3O_6$: C, 62.41 ; H, 4.96 ; N, 9.93. Found : C, 62.22 ; H, 4.89 ; N, 10.03.

10 : 65 % ; oil ; EIMS, m/z 511 (M^+) ; Anal. Calcd for $C_{30}H_{29}N_3O_5$: C, 70.45 H, 5.68 ; N, 8.22. Found : C; 70.30 ; H, 5.67 ; N, 8.31.

22 : 98 % ; m.p. 183°C (ether) ; EIMS, m/z 401 (M^+) ; Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.84 ; H, 6.78 ; N, 10.48. Found : C, 62.84 ; H, 6,78 ; N, 10.54.

Preparation of the o-aminobenzamide derivatives.

A solution of the nitro or N-carbobenzoxy derivative in ethanol (4a-c, 4e-h, 10) or ethyl acetate (4d, 38) was hydrogenated at atmospheric pressure in the presence of an equivalent weight of 10 % palladium on charcoal (4a, c, h, 10) or active Raney nickel (4b, d, e-g, 38). In the case of 4d, no external source of hydrogen was used. Upon completion of the reaction (as indicated by TLC), the mixture was filtered through celite, the catalyst was washed copiously with the reaction solvent and the combined filtrate and washings were concentrated under reduced pressure. The syrupy residue was purified by column chromatography on silica gel using toluene-ethanol (9:1) as developer or by crystallization. In addition to 6a[1], the following amines were prepared :

6b : 72 % ; m.p. 164-165°C ; EIMS, m/z 423 (M^+) ; Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 65.25 ; H, 5.91 ; N, 9.92. Found : C, 65.27 ; H, 5.86 ; N, 9.84.

6c : 95 % ; m.p. 135°C (ethyl acetate) ; EIMS, m/z 391 (M^+) ; IR (KBr) 3450, 3350 (NH), 1740 cm^{-1} (ester), 1640 (amide) ; ^{1}H NMR (80 MHz, $CDCl_3$) δ4.30 (2H, broad s, D_2O-exchangeable, NH_2).

6d : 96 % ; m.p. 160°C ; EIMS, m/z 469 (M^+) ; Anal. Calcd for $C_{28}H_{27}N_3O_4$: C, 71.64 ; H, 5.76 ; N, 8.95. Found : C, 71.87 ; H, 5.90 ; N, 8.43.

6e : 83 % ; foam ; EIMS m/z 397 and 399 (3:1, M^+) ; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (3H, t, $CH_2\underline{CH_3}$), 3.18 (1H, dd, H-4a), 3.65 (1H, dd, H-4b), 4.15 (2H, q, $\underline{CH_2}CH_3$), 4.25 (2H, broad s, D_2O-exchangeable, NH_2), 4.86 (2H, m, H-1), 5.60 (1H, m, H-3), 6.60-7.45 (7H, m, Ar), 8.00 (1H, broad s, D_2O-exchangeable, NH). Anal.Calcd for $C_{21}H_{20}N_3O_3Cl$: C, 63.40 ; H, 5.03 ; N, 10.57. Found : C, 63.67 ; H, 5.26 ; N, 10.64.

6f : 95 % ; m.p. 118-120°C ; EIMS, m/z 397 and 399 (3:1, M^+) ; ^1H NMR (200 MHz, DMSO-d_6) δ 5.73 (2H, s, D_2O-exchangeable, NH_2).

6g : 75 % ; m.p. 166-168°C ; EIMS, m/z 397 and 399 (3:1, M^+) ; ^1H NMR (200 MHz, DMSO-d_6) δ 4.87 (2H, s, D_2O-exchangeable, NH_2). Anal. Calcd. for $C_{21}H_{20}N_3O_3Cl$: C, 63.39 ; H, 5.03 ; N, 10.56. Found : C, 63.35 ; H, 4.87 ; N, 10.44.

6h : 85 % ; m.p. 228-230°C (ethanol) ; EIMS, m/z 393 (M^+). Anal. Calcd for $C_{22}H_{23}N_3O_4$. 1/2 H_2O : C, 65.67 ; H, 5.97 ; N, 10.45. Found : C, 65.50 ; H, 5.63 ; N, 10.23.

Amine from 10 : 89 % ; foam ; EIMS, m/z 377 (M^+) ; ^1H NMR (200 MHz, $CDCl_3$), δ1.05 (3H, t, $CH_2\underline{CH_3}$), 2.72 (3H, s, NCH_3), 4.75 (1H, broad s, D_2O-exchangeable, $N\underline{H}CH_3$). Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.03 ; H, 6.10 ; N, 11.14. Found : C, 69.87 ; H, 6.15 ; N, 11.15.

39 : 92 % ; m.p. 125-126°C (dichloromethane-hexane) ; EIMS, m/z 337 (M^+) ; Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64 ; H, 5.67 ; N, 12.45. Found : C, 67.37 H, 5.74 ; N, 12.70.

Cyclization of the o-aminobenzamides to 1,4-benzodiazepines.

A solution of the amine in dioxane (6a, e, f, amine from 10, 39), toluene (6b, d, g) or DMSO (6c) was heated at 120°C for 24-48 h under a nitrogen atmosphere in the presence of p-toluenesulfonic acid (0.1 eq). In the case where the product precipitated during the course of the reaction (7a, b, d, g), filtration of the colored reaction mixture followed by column chromatography of the precipitate using toluene-ethanol (9:1) as developer gave a pure product. Where the product did not precipitate, the reaction mixture was concentrated under reduced pressure and the residue was chromatographed as above. In addition to 7a[1], the following compounds were prepared :

7b : 55 % ; EIMS, m/z 377 (M^+) ; ^1H NMR (200 MHz, DMSO-d_6) δ 2.97 (2H, m, $\underline{CH_2}CH$), 3.83 (6H, s, 2xOCH_3), 4.21 (1H, d, H-1a), 4.73 (1H, d, H-1b), 4.97

(1H, dd, H-3), 6.98 (1H, s, H-5), 7.08 (1H, s, H-8), 7.20-7.87 (4H, m, Ar), 10.5 (1H, s, D_2O-exchangeable, amide NH), 10.93 (1H, s, D_2O-exchangeable, indole NH).

7c : 71 % ; m.p. 268°C (dichloromethane) ; EIMS, m/z 345 (M^+) ; Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.04 ; H, 5.50 ; N, 12.17. Found : C, 72.91 ; H, 5.43 ; N, 12.02.

7d : 84 % ; m.p. 245°C (decomp.) ; EIMS, m/z 423 (M^+) ; Anal. Calcd for $C_{26}H_{21}N_3O_3 \cdot 1/2\ H_2O$: C, 72.22 ; H, 5,09 ; N, 9.72. Found : C, 72.57 ; H, 5.00 ; N, 9.79.

7e : 72 % ; m.p. 310°C (decomp)(ethanol) ; EIMS, m/z 351 and 353 (3:1, M^+) ; Anal. Calcd for $C_{19}H_{14}N_3O_2Cl$: C, 64.86 ; H, 3.98 ; N, 11.95. Found : C, 65.12 ; H, 4.00 ; N, 12.03.

7f : 63 % ; m.p. 222°C (decomp); EIMS, m/z 351 and 353 (3:1, M^+); ^1H NMR (200 MHz, DMSO-d_6) : 10.58 and 10.93 (2H, 2s, D_2O - exchangeable, amide NH and indole NH).

7g : 60 %; m.p. 300°C (decomp); EIMS, m/z 351 and 353 (3:1, M^+); ^1H NMR (200 MHz, DMSO-d_6) : 10.14 and 11.10 (2H, 2s, D_2O - exchangeable, amide NH and indole NH).

7h : 55 % ; m.p. 212-215°C (ethanol) ; EIMS, m/z 347 (M^+) ; Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.16 ; H, 4.90 ; N, 12.10. Found : C, 69.20 ; H, 4.63 ; N, 12.21.

11 : 46 % ; m.p. 295°C (ethanol) ; EIMS, m/z 331 (M^+) ; ^1H NMR (200 MHz, $CDCl_3$), 3.06 (1H, dd, J_{gem} = 16 Hz, J_{vic} = 7 Hz, H-4a), 3.38 (3H, s, N-CH_3), 3.56 (1H, dd, J_{gem} = 16 Hz, J_{vic} = 2 Hz, H-4b), 4.66 (1H, m, CHC=O), 4.72 (1H, d, J_{gem} = 18 Hz, H-1a), 5.06 (1H, d, H-1b), 7.06-7.96 (8H, m, Ar), 8.33 (1H, S, D_2O-exchangeable, NH). Anal.Calcd for $C_{20}H_{17}N_3O_2$: C, 72.51 ; H, 5.14 ; N, 12.69. Found : C, 72.19 ; H, 5.04 ; N, 12.75.

40 : 47%; m.p. > 270°C (decomp) (dichloromethane-hexane); EIMS , m/z 305 (M^+); Anal. Calcd for $C_{18}H_{15}N_3O_2 \cdot 1/8\ H_2O$: C, 70.29; H, 5.00; N, 13.66. Found : C, 70.37; H. 5.02; N, 13.88.

Dehydrogenation of the tetrahydro hybrid precursors 7 and 11

A solution of the tetrahydro derivative (7a-h, 11) and dichlorodicyanobenzoquinone (DDQ 2 eq) was refluxed (room temperature for 11)

for 30 min under a nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and, after 2-3h the quinol which had precipitated was removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the residue was chromatographed on a column of silica gel using toluene-ethanol (9:1) as developer. Besides 1a[1], the following compounds were obtained :

1b : 20% ; EIMS, m/z 373 (M^+)

1c : 35%; m.p. 281°C (ethanol); EIMS , m/z 341 (M^+); ^1H NMR (200 MHz, DMSO-d_6): 1.48 (3H, t, $CH_2\underline{CH}_3$), 3.50 (2H, q, $\underline{CH}_2CH_3$), 7.25 (1H, d.Ar), 7.60 (4H, m, ring E Ar), 7.82 (1H, t, Ar), 8.14 and 8.19 (2H, 2d, Ar), 8.81 (1H, s,CH-N), 12.00 (1H, broad s, D_2O-exchangeable, amide NH). Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.88; H, 4.42 ; N, 12.31. Found : C, 73.56 ; H, 4.21 ; N, 12.12.

1d : 15 % ; m.p. 331°C ; EIMS, m/z 419 (M^+) ; ^1H NMR (200 MHz, DMSO-d_6) : 5.40 (2H, s, $\underline{CH}_2Ph$), 7.44-7.82 (8H, m, Ar), 7.96 (1H, m, Ar), 8.12 (1H, m, Ar), 8.34 (1H, m, Ar), 9.20 (1H, s, H-4 of β-carboline), 9.32 (1H, s, H-1 of β-carboline), 12.12 (1H, s, D_2O-exchangeable, amide NH). Anal. Calcd. for $C_{26}H_{17}N_3O_3 \cdot 1/2\ H_2O$: C, 72.89 ; H, 4.20 ; N, 9.81. Found : C, 73.08 ; H, 4.17 ; N, 9.43.

1e : 22 % ; > 320°C (decomp)(ethanol-dioxane) ; EIMS, m/z 347 and 349 (3:1, M^+). Anal. Calcd for $C_{19}H_{10}N_3O_2Cl$: C, 65.61 ; H, 2.88 ; N, 12.09. Found : C, 65.28 ; H, 3.04 ; N, 12.00.

1f : 33 % ; m.p. 220-221°C ; EIMS, m/z 347 and 349 (3:1, M^+) ; ^1H NMR (200 MHz, DMSO-d_6) ; 7.50 (3H, t, Ar), 7.97 (1H, d, Ar) ; 8.27 (1H, d, Ar), 8.55 (1H, d, Ar), 9.14 (1H, s, CH, H-4 of β-carboline), 9.26 (1H, s, H-1 of β-carboline), 12.16 (1H, s, D_2O-exchangeable, amide NH).

1g : 22 % ; m.p. 314°C ; EIMS, m/z 347 and 349 (3:1, M^+) ; ^1H NMR (200 MHz, DMSO-d_6) : 7.45 (1H, t, Ar), 7.67-7.79 (3H, m, Ar), 8.23 (2H, m, Ar), 8.58 (1H, d, Ar), 9.26 (1H, s, H-4 of β-carboline), 9.27 (1H, s, H-1 of β-carboline).

1h : 28 % ; m.p. 285° (decomp) (ethanol-hexane) ; EIMS, m/z 343 (M^+) ; Anal. Calcd for $C_{20}H_{13}N_3O_3 \cdot 1/3\ H_2O$: C, 68.77 ; H, 3.92 ; N, 12.03. Found : C, 68.80 ; H, 3.75 ; N, 12.25.

12 : 5 % ; m.p. 208-210°C (ethanol) ; EIMS, m/z 347 (M^+) ; ^1H NMR (200 MHz, DMSO-d_6) 3.52 (3H, s, CH_3), 3.65 (1H, m, CH_a), 3.89 (1H, dd, J_{gem} = 15 Hz, J_{vic} = 6 Hz, CH_b), 4.32 (1H, q, $CH_2\underline{CH}$), 7.12-7.98 (8H, q, Ar), 8.98 (1H, d, D_2O-exchangeable, NHC=O), 10.31 (1H, s, CHO), 11.91 (1H, s, D_2O-exchangeable,

NH). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.16 ; H, 4.90 ; N, 12.10. Found : C, 69.10 ; H, 4.94 ; N, 12.23.

14 : 42 % : oil ; EIMS, m/z 373 (M^+) ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (3H, t, $CH_2\underline{CH_3}$), 3.55 (3H, s, N-CH_3), 4.30 (2H, q, $\underline{CH_2}CH_3$) , 7.15-7.90 (8H, m, Ar), 8.24 (1H, s, H-4), 8.35 (1H, s, H-1), 9.18 (1H, broad, s, D_2O-exchangeable, NH).

Ethanolysis of hybrids 1a,c,d.

A solution of 1a, 1c, or 1d in anhydrous ethanol was treated with sodium (0.1 eq). After 30 min, the reaction mixture was neutralized with acetic acid and concentrated under reduced pressure. The resulting solid was dissolved in dichloromethane and washed with water. Drying of the organic phase over sodium sulfate followed by evaporation of the solvent in vacuo gave crude 8a, c, d which were purified by chromatography on silica gel using dichloromethane-ethanol (20:1) as developer followed by crystallization from ethyl acetate. Compound 8a was identical to that prepared by another route[7].

8c : 74 % ; m.p. 254°C ; EIMS, m/z 387 (M^+), 342 (M^+-OCH_2CH_3) ; IR (KBr) 1680 (ester), 1570 cm^{-1} (amide) ; ^{1}H NMR (200 MHz, DMSO-d_6) : δ 1.42 (3H, t, $CH_2\underline{CH_3}$), 3.73 (2H, q, $\underline{CH_2}CH_3$), 4.31 (2H, q, $OCH_2\underline{CH_3}$), 7.06 (1H, t, Ar), 7.12 (1H, d, Ar), 7.51 (3H, m, Ar), 7.87 (1H, d, H-5), 8.12 (1H, d, H-8), 8.67 (2H, m, Ar), 11.83 and 12.52 (2H, 2 broad s , D_2O-exchangeable, 2xNH). Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 71.30 ; H, 5.46 ; N, 10.84. Found : C, 71.13 ; H, 5.35 ; N, 10.96.

8d : 69 % ; m.p. 188°C ; EIMS, m/z 465 (M^+), 392 (M^+-CO_2Et) ; ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.19 (3H, t, $CH_2\underline{CH_3}$), 4.22 (2H, q, $\underline{CH_2}CH_3$), 4.95 (2H, s, $OCH_2\underline{Ph}$), 6.86-7.54 (9H, m, Ar), 7.82-7.97 (2H, m, Ar), 8.74-8.85 (2H, m, Ar), 13.00 (1H, s, D_2O-exchangeable, NH).

Hydrolysis of the ester derivatives 8a, 8c, 15-17.

To a solution of the ester in 90 % ethanol was added an aqueous solution of 1N sodium hydroxide (10 eq) and the reaction mixture was refluxed for 30 min. The solution was then cooled and the solution was concentrated to half volume under reduced pressure. The mixture was neutralized with acetic acid, whereupon the product precipitated. After standing for 2 h at 4°C, the mixture was filtered, the solid was washed abundantly with water, dried and crystallized from ethanol (acetic acid for 18 (R_1=R_2=H)). Compound 20 (R_1=R_2=H), obtained from 8a, was identical in all respects to that obtained

from 19 (R_1=R_2=H)[7]. Compound 20 (R_1=C_2H_5, R_2=H) was obtained in 94 % yield, m.p. 289°C ; IR (KBr) 1660 (c=o), 1580 cm^{-1} (amide) ; CIMS, m/z 360 (MH^+) ; ^1H NMR (200 MHz, DMSO-d_6) : 1.12 (3H, t, $CH_2\underline{CH_3}$), 3.30 ($CO_2\underline{H}$ + H_2O of DMSO), 3.77 (2H, q, $\underline{CH_2}CH_3$), 7.51 (4H, m, Ar), 7.92 (1H, d, H-5), 8.21 (1H, d, H-8), 8.77 (3H, m, Ar), 11.88 and 12.63 (2H, 2 broad s, D_2O-exchangeable, 2xNH). Anal. Calcd. for $C_{21}H_{17}N_3O_3$. 1/2 H_2O : C, 68.46 ; H, 4.92 ; N, 11.40. Found : C, 68.27 ; H, 4.98 ; N, 11.89.

Compounds 18 were identical to those already reported[5].

Triflic anhydride-activated hybrid synthesis

A solution of the N-acyl anthranilic acid derivative (20, 35)[8] in anhydrous dichloromethane was treated under a nitrogen atmosphere with diisopropylethylamine (0.12 eq) at room temperature. After stirring for 30 min, the solution was cooled to -78°C and triflic anhydride (0.12 eq) was slowly added. After 2 h at -78°C, the reaction mixture was allowed to come to room temperature and was washed with water. The organic phase was dried over sodium sulfate, the solvent removed under reduced pressure and the residual solid was purified by crystallization. In addition to 1a (95 % yield) and 1c (83 % yield), identical in all respects with the same compounds prepared via Scheme 1, the following derivatives were prepared :

21 : 83 % ; m.p. 245°C (ethanol) ; IR (KBr) 1735, 1620 cm^{-1} (amides) ; EIMS, m/z 463 (M^+) ; ^1H NMR (200 MHz, DMSO-d_6) : 3.38 (3H, t, OCH_3), 5.23 (2H, s, OCH_2), 5.28 (2H, s, OCH_2), 7.40 (4H, m, Ar), 7.53 (2H, m, Ar), 7.63-7.80 (4H, m, Ar), 8.05 (1H, t, Ar), 8.25 (1H, d, Ar), 9.00 (1H, s, H-1 of β-carboline), 12.00 (1H, broad s, D_2O-exchangeable NH). Anal. Calcd for $C_{28}H_{21}N_3O_4$: C, 72.56 ; H, 4.56 ; N, 9.06. Found : C, 72.43 ; H, 4.64 ; N, 9.17.

36 : 70 % ; m.p. 307-310°C (ethanol-ethyl acetate) ; EIMS, m/z 263 (M^+) ; ^1H NMR (200 MHz, DMSO-d_6) : 6.80 (1H, s, H-3), 7.68 (1H, t, J = 8 Hz H-8), 7.80 (2H, m, H-2, H-10), 8.00 (1H, dd, J = 8 Hz and 1 Hz, H-9), 8.22 (1H, d, J = 1Hz, H-7), 8.70 (1H, s, H-4), 8.97 (1H, s, H-13), 12.07 (1H, s, D_2O-exchangeable, NH). HRMS (EI) m/z calcd for $C_{15}H_9N_3O_2$: 263.0695. Found : 263.0696.

(RS)-1,2,3,4,6,6a,12,12a-octahydro-7H-indolo 3',2' : 4,5 pyrido 2,1-c pyridazine-1,4-dione (23)

A solution of 22 (25 mmol) in hydrogen chloride-saturated methanol (600 ml) was allowed to stand at 4°C for 6 days. The reaction mixture was then

neutralized with concentrated ammonium hydroxide and the yellow precipitate which formed was collected by filtration. Recrystallization of this material in ethanol gave compound 23 in 85 % yield, m.p. 275-280°C ; EIMS, m/z 255 (M^+) ; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.98 and 3.27 (2H, dd, J = 14 Hz, H-12), 3.97 and 4.15 (2H, dd, J = 18 Hz, H-3), 4.28 (1H, m, J_{12-12a} = 4 Hz and 12 Hz, H-12a), 4.33 and 5.50 (2H, 2d, J = 17 Hz, H-6), 7.22-7.57 (4H, m, Ar), 8.40 (1H, s, D_2O-exchangeable, NHCO), 11.08 (1H, s, D_2O-exchangeable, indole NH). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.88 ; H, 5.10 ; N, 16.47. Found : C, 66.04 ; H, 5.04 ; N, 16.41.

N-Formyl-β-carboline-3-carboxamide (25).

A solution of compound 23 (2 mmol) in dioxane (75ml) was refluxed for 2h in the presence of DDQ (4 mmol). The reaction mixture was cooled to room temperature, the quinol precipitate was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography on reversed-phase silica gel using water-methanol (60:40) as developer. Compound 25 was obtained as a white solid in 10% yield, identical in all respects with an authentic sample.

(R,S)-Ethyl 3,4-dihydro-2-(N-Boc-glycinyl)-β-carboline-3-carboxylate (28). Method A :

A solution of compound 22 (1 mmol) in xylene (100ml) was refluxed for 48 h in the presence of 10% palladium on charcoal (50mg). The reaction mixture was then cooled, filtered on Celite and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel using toluene-ethanol (9:1) as developer, giving compound 28 (50%) as a solid as well as unreacted starting material (25%) : m.p. 174°C; EIMS, m/z 399 (M^+); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (3H, t, CH_2CH_3), 1.42 (9H, s, Boc), 3.10 (1H, d, $J_{4a,4b}$= 17Hz, H-4a), 3.26 (1H, dd, J_{4b-3} = 7Hz, H-4b), 3.80 and 4.08 (2H, 2d, CH_2-NH), 3.95 (2H, m, OCH_2CH_3), 5.43 (1H, d, $J_{3,4b}$ = 7Hz, H-3), 6.55 (1H,s, H-1), 7.10-7.30 (4H,m, Ar), 9.35 (1H, s, D_2O-exchangeable, NH-Boc). Anal. Calcd for $C_{21}H_{25}N_3O_5$. 1/2 H_2O : C.61.76, H, 6.37 ; N. 10.29. Found : C, 61.75; H, 6.45; N. 9.77.

Method B : A solution of compound 22 (0.75mmol) in anhydrous dichloromethane was cooled to 0°C and DDQ (0.75mmol) was added. After stirring for 1h at 0°C, the reaction mixture was filtered to remove the precipitated quinol, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using toluene-ethanol (9:1) as developer. Compound 28, identical to that obtained above, was isolated in 30% yield. The major product was 27 (60% yield)[17]. When the reaction was conducted at 20°C, similar work-up gave 27 as the sole, recoverable product (85% yield).

Attempted removal of the Boc group of 28. A solution of 28 (0.25mmol) in hydrogen chloride-saturated ethanol (10ml) was held at 4°C for 24h. The reaction mixture was neutralized with concentrated ammonium hydroxide and the precipitated ammonium chloride was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using toluene-ethanol (9:1) as developer. Compound 27[17] was thus obtained in 95% yield.

5-(1,3-Dioxolan)-1H-pyrrolo [2,3-C] pyridine (31) and 1-hydroxy-5-(1,3-dioxolan)-pyrrolo [2,3-C]pyridine (32).

A solution of 2-(1,3-dioxolan)-4-methyl-5-nitropyridine[11] (29, 2.48 mmol) and dimethylformamide dimethyl acetal (3.36 mmol) in anhydrous dimethylformamide (5ml) was heated at 90°C until complete consumption of starting material was indicated by TLC (silica gel; toluene-ethyl acetate 3.5:1.5) (approximately 4h). The reaction mixture was then cooled and the solvent removed under reduced pressure. The crude product was dissolved in ethanol (5ml) and hydrogenated at atmospheric pressure in the presence of 5% palladium on barium sulfate (500mg). After hydrogen absorption had ceased, the reaction mixture was filtered on Celite, the filtrate was concentrated *in vacuo* and the crude material was purified by column chromatography on silica gel using dichloromethane-ethanol (15:1) as developer. Compound 31 was first eluted (yield = 52%). Crystallization from dichloromethane-hexane gave off-white crystals, m.p. 192-193°C (decomp) : IR (KBr) 1070,1110, 1150 (acetal), 3100 cm^{1} (NH) ; EIMS, m/z 190 (M^+) ; ^1H NMR (200 MHz, $CDCl_3$) δ 4.18 (4H, d of octets, OCH_2CH_2O), 6.08 (1H, s, OCHO), 6.63 (1H, d, J = 3Hz, H-3), 7.50 (1H, d, J=3Hz, H-2), 7.86 (1H, s, H-4), 8.93 (1H, s, H-7), 10.36 (1H, broad s, D_2O -exchangeable, NH). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C 63.16, H, 5.26; N, 14.74. Found : C, 63.24; H, 5.32 ; N, 14.54 .

Continued elution of the column gave the N-hydroxy derivative 32 (19%) which was crystallized from dichloromethane-hexane, m.p. 140-150°C (decomp); IR (KBr) 1090,1140 (acetal), 3300 cm^{1} (OH); EIMS, m/z 206 (M^+), 189 (M^+-OH); ^1H NMR (60 MHz, $CDCl_3$) δ 3.96 (4H, s, OCH_2CH_2O), 5.76 (1H, s, OCHO), 6.27 (1H, d, H-3), 7.48 (1H, d, H-2), 7.59 (1H, s, H-4), 8.14 (1H, S, H-7), 11.29 (1H, broad s, OH). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.88; N, 13.59. Found : C, 57.99; H, 5.12; N, 13.41.

Transformation of 32 into 31 :

To the crude filtered reaction mixture of 31 and 32 in ethanol obtained above was added 10% palladium on carbon (200 mg). The mixture was hydrogenated at atmospheric pressure until hydrogen absorption had ceased.

TLC of the reaction mixture (silica gel, dichloromethane-ethanol 95:5) showed that the lower R_f N-hydroxy derivative 32 had disappeared, leaving only 31. The reaction mixture was treated as described above.

1H-Pyrrolo [2,3-c]pyridine-5-carboxaldehyde (33).

A solution of the acetal 31 (4.21 mmol) in 10% aqueous acetonitrile (50ml) was refluxed for 5h in the presence of p-toluenesulfonic acid monohydrate (0.63mmol). The reaction mixture was cooled and concentrated in vacuo to remove excess acetonitrile. The residue was diluted with dichloromethane, the organic extracts were combined and washed with saturated aqueous sodium chloride solution. The organic phase was dried over magnesium sulfate, the solvents were removed under vacuum and the residue was crystallized in acetonitrile-hexane (95% yield), m.p. 191-194°C, IR (KBr) 1690 cm^{-1} (C=O); EIMS, m/z 146 (M^+), 117 (M^+-CHO) ; ^1H NMR (200 MHz, DMSO-d_6) δ 6.93 (1H, d, J = 3Hz, H-3), 7.94 (d, 1H, J = 3Hz, H-2); 8.42 (1H, s, H-4), 9.11 (1H, s, H-7), 10.21 (1H, s, CHO), 12.26 (1H, broad s, NH). Anal Calcd for $C_8H_6N_2O$: C 65.74; H, 4.14; N, 19.17 Found :C 65.88; H, 4.14; N, 19.11.

1H-Pyrrolo [2,3-c]-5-carboxylic acid (34).

The aldehyde 33 (2.76mmol) was dissolved in a minimum of formic acid, the solution was cooled to 0°C and cold , excess 32% hydrogen peroxide was added. The reaction mixture was allowed to stand overnight at 4°C. The solid which formed was then collected by filtration, washed with water and dried. To the mother liquor was added dropwise aqueous saturated sodium hydrogen carbonate in sufficient quantity to bring the pH to 4.5. The solution was again stored at 4°C overnight , where upon a second crop of crystals of 34 was obtained. The total yield of 34 was 92%, m.p. 325-332°C (decomp); IR (KBr) 3400-3350 (OH), 1705 cm-1 (C=O); EIMS , m/z 162 (M^+), 118 (M^+-CO_2); ^1H NMR (200 MHz, DMSO-d_6) δ 4.06 (broad s, CO_2H partly buried under H_2O), 6.86 (1H, d, J = 3Hz, H-3), 7.96 (1H, d, J =3Hz, H-2), 8.52 (1H, s, H-4), 8.96 (1H, s, H-7), 12.22 (1H, broad s, NH). Anal.Calcd for $C_8H_6N_2O_2$. 1/8 H_2O : C, 58.44 ; H , 3.75; N, 17.04 Found : C, 58.76; H, 3.89; N, 17.11.

(R,S)-3-[(1H-indol-3-yl)carbonyl)] -3H-1,4-benzodiazepine-2,5 (1H,4H)-dione (43)

To a solution of dichlorodicyanobenzoquinone (DDQ, 2.9 mmol) in a mixture of THF-water (9:1) at 0°C was added under a nitrogen atmosphere, the indolobenzodiazepine 40 (1.26mmol). The reaction mixture was allowed to come to room temperature and stirring was maintained for 12h. After this period , more DDQ (2.5 mmol) was added and, after 24h stirring, the solvents were removed under reduced pressure. The residue was then taken up in ethyl

acetate and washed with 10% aqueous sodium hydrogen carbonate (2X) and water (2X). The organic phase was dried over sodium sulfate, the solvent was removed in vacuo and the oily residue was chromatographed on silica gel using toluene-ethanol (8:1) as developer. Compound 43 was obtained as a white solid which crystallized in ethanol (yield:30%) : m.p. 281°C (decomp); IR (KBr) 1640,1685 (C=O), 3100-3380 cm^{-1} (NH); CIMS, m/z 319 (M^+); ^1H NMR (400 MHz, DMSO-d_6) δ 5.40 (1H, d, J=6.5 Hz , COCHCO), 7.20 (1H, d, J=8Hz, Ar), 7.28 (2H, t, J = 8Hz, Ar), 7.35 (1H, t, J = 8Hz, Ar), 7.62 (2H, m, Ar),7.85 (1H, d, J=7Hz, Ar), 8.10 (1H, broad d, Ar), 8.55 (2H, s, partly exchangeable with D_2O, Ar + NHCO), 10.87 (1H, broad S, D_2O-exchangeabe, indole NH), 11.20 (1H, broad s, D_2O-exchangeable, Ø NHCO). Anal. Calcd for $C_{18}H_{13}N_3O_3$. 1/2 C_2H_5OH : C, 66.66; H 4.71; N, 12.27. Found : C, 66.65; H, 4.68; N, 12.36.

Reduction of 43 to the alcohol 44.

To a stirred suspension of sodium borohydride (1.56mmol) in 95% ethanol (20ml) was added a solution of 43 (0.31mmol) in ethanol (5ml). After stirring for 4h at room temperature, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate and the solution was washed with water. The organic phase was then dried over anhydrous sodium sulfate and, after removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel using toluene-ethanol (8:3) as developer. Compound 44, obtained as a white powder, was crystallized from ethanol (yield :30%) : m.p. 245°C (decomp); IR (KBr) 1635-1675 (C=O) 3350 cm^{-1} (NH,OH); FABMS, m/z 322 (MH^+); ^1H NMR (200 MHz, DMSO-d_6) δ4.04 (1H, dd, J=10 and 8 Hz, H-3), 4.96 (1H, dd, J=10 and 5Hz, CHOH), 5.39 (1H, d, J=5Hz, D_2O -exchangeable , OH), 6.93 (1H, t, J=7.5 Hz, Ar), 7.06 (1H, t, J=7.5 Hz, Ar), 7.23 (3H, m, Ar), 7.38 (2H, t, J = 9Hz, Ar) 7.58 (1H, td , J=7 and 2 Hz, Ar), 7.69 (1H, d, J=7Hz, Ar), 8.31 (1H, d, J=8Hz, D_2O -exchangeable, NHCO), 10.51 (1H, S, D_2O-exchangeable, indole NH), 11.14 (1H, S, D_2O-exchangeable, Ø NHCO).HRMS, MH^+ calcd for $C_{18}H_{16}N_3O_3$: 322.1192 . found : 322.1170.

(Z)- and (E)-3-(3-indolylmethylene)-1,4-benzodiazepine-2,5 (1H,4H)-dione (41 and 42,respectively). The hydroxy derivative 44 (0.96mmol) was dissolved in anhydrous THF (40ml) and treated at room temperature with triethylamine (3.23mmol) and methane sulfonic anhydride (1.92 mmol). The solution was stirred for 2.5h, the solvent was removed in vacuo and the solid residue was suspended in ethyl acetate. The solid was collected by filtration and crystallized from THF giving compounds 41 as a pale yellow powder (yield=52%): m.p. > 300°C (decomp); IR (KBr) 1620 (conjugated C=C), 1645-1685 (CO of cyclic amide), 3200 cm^{-1} (NH); EIMS , m/z 303 (M^+); ^1H NMR (400 MHz, DMSO-d_6) δ 7.09 (1H, t, J=8Hz, Ar), 7.16 (3H,m,Ar), 7.21 (1H, S, exocyclic

CH), 7.46, 7.51, 7.73, 7.79 (4x1H, d,t,d,d, J=7.5Hz, Ar), 7.86 (1H, s, H-2 of indole), 9.74 (1H, broad S, D_2O-exchangeable, NHCO), 10.24 (1H, s, D_2O-exchangeable , indole NH), 11.78 (1H,s, D_2O-exchangeable, Ø NHCO). HRMS , m/z calcd for $C_{18}H_{13}N_3O_2$: 303.1007. Found : 303.1023.

The mother liquor from the crystallization of 41 was concentrated in vacuo and purified by column chromatography on silica gel using toluene-ethanol (9:1) as developer. Compound 42 was obtained as a pale yellow solid which could be crystallized from THF (yield = 3%): m.p. 290-295°C; IR (KBr) 1620 (conjugated C=C), 1655-1690 (cyclic amide), 3400cm-1 (NH); EIMS, m/z 303 (M^+); ^1H NMR (400 MHz, DMSO-d_6) δ 6.87 (1H, s, exocyclic CH), 7.04 (1H, t;J=7.5 Hz, Ar), 7.13 (2H, m; Ar), 7.23, 7.39, 7.48, 7.61, 7.77 (5x1H, t, d, t, d, d,Ar), 7.91 (1H, s, H-2 of indole), 9.99 (1H, s ,D_2O - exchangeable, NHCO), 10.59 (1H, s, D_2O-exchangeable, indole NH), 11.54 (1H, S, D_2O-exchangeable, Ø NHCO).HRMS , m/z calcd for $C_{18}H_{13}N_3O_2$: 303.1008. Found : 303.1014.

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