INTRAMOLECULAR MANNICH REACTION OF 2-OXOTRYPTAMINE AND HOMOLOGUES WITH OXO REAGENTS YIELDING SPIRO COMPOUNDS. PART II+

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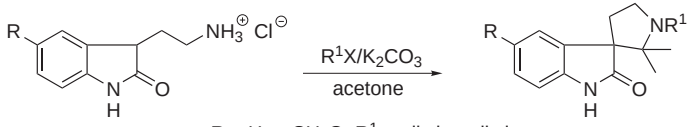
2-Oxotryptamine and its homo derivative undergo intramolecular Mannich-type cyclization with acetone and other ketones to give spiro[indole-3,3′-pyrrolidin]-2-ones and spiro[indole-3,3′-piperidin]-2-ones. A similar reaction with the bis-homologue of 2-oxotryptamine to yield spiro[azepane-3,3′-indol]-2′-ones was unsuccessful.

Keywords: Intramolecular Mannich reaction; Spirocyclic compounds; Oxindoles; Pyrrolidines; Piperidines; Cyclizations; Alkaloids; Ketones; Indoles.

In our previous publication[1], we reported an unexpected intramolecular Mannich cyclization, which occurred when 2-oxotryptamine and 2-oxo-5-methoxytryptamine were treated with acetone in the presence of K_2CO_3 and alkyl halides. In this way, a series of 1′-substituted 2′,2′-dimethylspiro-[indole-3,3′-pyrrolidin]-2-one derivatives has been synthesized (Scheme 1).



R = H or CH_3O; R^1 = alkyl, aralkyl

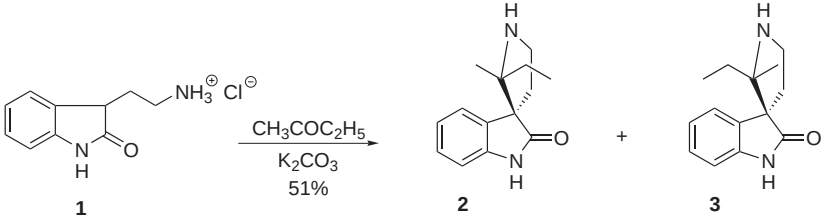
SCHEME 1

3-Substituted indolin-2-ones are considered physiologically active compounds, with potential selectivity to various receptor tyrosine kinases[2] and serotonines; similarly, 2-oxospiroindoles show important biological ef-

+ Part I, see ref.[1]

fects[3]. One of these compounds is a selective antagonist of vasopressin V_2 receptor, and hence a candidate for controlling the clinically debilitating condition of hyponatremia and associated syndromes[4].

Because of the increasing interest, the scope and limitation of this intramolecular Mannich-type ring closure have been investigated. In the course of this research, the reaction of 2-oxotryptamine (**1**) with bulkier ketones was studied first. When ethyl methyl ketone was used as the reagent instead of acetone, the reaction slowed down and the corresponding 2′-ethyl-2′-methyl-2-oxospiropyrrolidine diastereomers (**2** and **3**) could be isolated as a mixture of hydrochlorides (Scheme 2). The actual stereochemistry at chiral center C2′ of this one and similar diastereometric pairs was assigned on the basis of the measured NOE effects between the H4 aromatic proton and one of the C2′ substituents. In the case of diastereomeric mixture **2** + **3**, ^{1}H NMR showed that the ratio of the two compounds was about 10:1 in favour of the sterically less hindered isomer **2**. After repeated recrystallization, the more stable isomer **2** was isolated in a pure form.

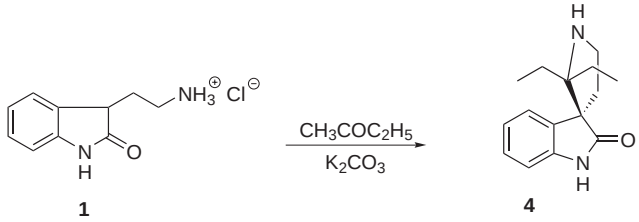


SCHEME 2

A similar result was expected when the reaction was carried out with methyl vinyl ketone; however a great number of products was observed by TLC in the reaction mixture as a consequence of ambivalent reactivity of α,β-unsaturated carbonyl compounds.

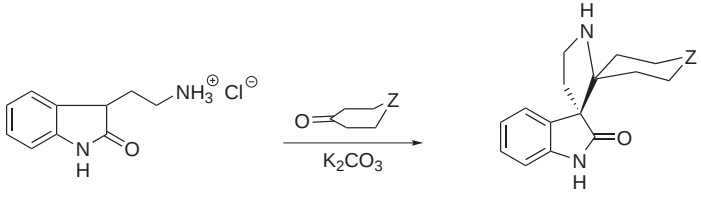
The reaction with bulkier ketones (pentan-3-one, acetophenone, benzophenone) proved unsuccessful. While the formation of a new compound, presumably 2′,2′-diethyl spiro compound **4**, could be observed in the reaction of 2-oxotryptamine with pentan-3-one, this compound turned out to be extremely unstable, and during even a careful work-up a reverse process took place, and only the starting material could be isolated (Scheme 3). No reaction was observed (TLC) with acetophenone and benzophenone.

Surprisingly, cyclic ketones (cyclohexanone and 1-benzyl-4-piperidone) gave good yields of bis-spiro compounds **5** and **6** (Scheme 4).



1 **4**

SCHEME 3

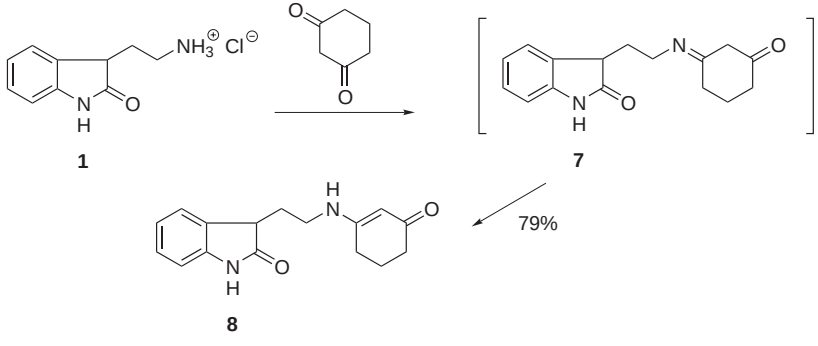


1

	Z	yield
5	CH_2	65%
6	NCH_2Ph	72%

SCHEME 4

With cyclohexane-1,3-dione, however, no cyclization was observed. The Schiff base **7**, the formation of which is assumed to be the initial step of all intramolecular Mannich-type reactions, is stabilized in this case as a conjugated enamine (vinylogous amide **8**) (Scheme 5).

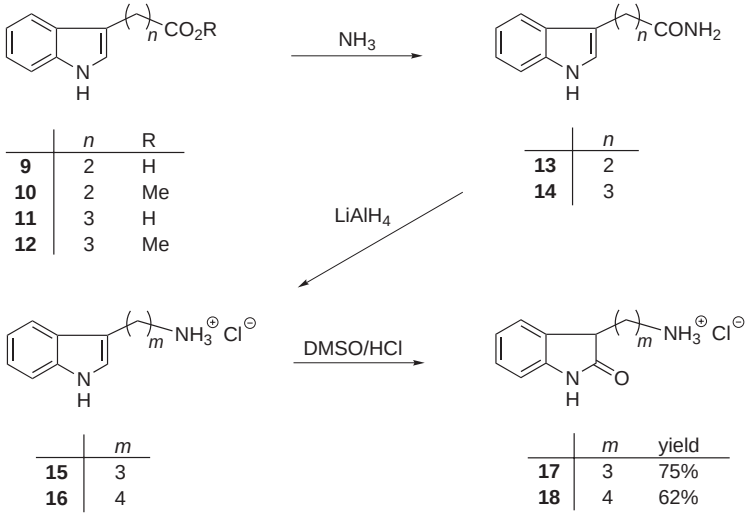


1 **7** **8**

SCHEME 5

Another interesting point was to investigate the reactivity of 3-aminoalkylindol-2-ones. The homologues of 2-oxotryptamine seem to be exciting starting materials for an intramolecular Pictet–Spengler cyclization, not only from the viewpoint of determining the scope and limitation, but also

because of the possibility of preparing new, so far undescribed spiro compounds. For this reason, 2-oxohomotryptamine [3-(3-aminopropyl)indolin-2-one; **17**], and the bis-homo derivative [3-(4-aminobutyl)indolin-2-one; **18**] were synthesized from indole-3-propanoic acid (**9**) and indole-3-butanoic acid (**11**), respectively, as depicted in Scheme 6.



	n	R
9	2	H
10	2	Me
11	3	H
12	3	Me

	n
13	2
14	3

	m
15	3
16	4

	m	yield
17	3	75%
18	4	62%

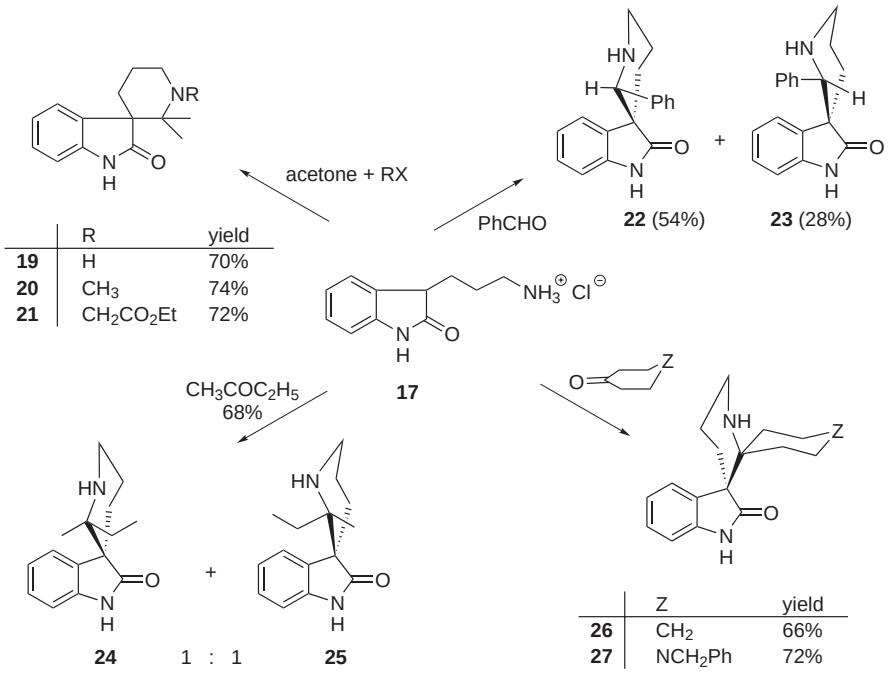
SCHEME 6

Carboxylic acids **9** and **11** were first esterified with MeOH/HCl, and aminolysis of esters **10** and **12** furnished the corresponding amides **13** and **14**. $LiAlH_4$ reduction of **13** and **14** in THF produced tryptamine homologues **15** and **16** as HCl salts; finally, 2-oxotryptamine homologues **17** and **18** were obtained by DMSO/HCl oxidation[1,5]. While investigating the reactivity of the two homologues, we found that compound **17** basically gives all the studied intramolecular Mannich-type reactions with aldehydes and ketones resulting in the formation of spiro[indole-3,3′-piperidin]-2-ones (**19**–**27**). Some representative reactions are shown in Scheme 7.

Interestingly enough, these spiro[indole-3,3′-piperidin]-2-ones are somewhat less stable than the corresponding spiro[indole-3,3′-pyrrolidin]-2-ones; they can be stored as the corresponding HCl salts, but the free bases slowly decompose in a reverse process (TLC and NMR evaluation).

Starting with compound **18**, no intramolecular Mannich reaction leading to spiro[azepane-3,3′-indole]-2′-ones could be effected with any ketone.

In summary, our present and earlier[1] findings show that intramolecular Mannich-type cyclization of 2-oxotryptamine (**1**) and 2-oxohomotrypt-



	R	yield
19	H	70%
20	CH_3	74%
21	CH_2CO_2Et	72%

	Z	yield
26	CH_2	66%
27	NCH_2Ph	72%

SCHEME 7

amine [3-(3-aminopropyl)indolin-2-one; **17**] could be effected not only with aldehydes, but also with some ketones. The scope and limitation concerning both reactants (ketones and amines) were investigated. While the 5 + 5 spiro compounds from 2-oxotryptamine turned out to be more stable than the 5 + 6 ones from the corresponding homologue, only acetone and cyclic ketones could be employed as partners in the reaction. Bulkier ketones failed to react. As a result of our present findings, a new ring system (spiro[indole-3,3′-piperidin]-2-ones) was synthesized and described. No similar reaction leading to spiro[azepane-3,3′-indol]-2′-ones from the bis-homologue of 2-oxotryptamine [3-(4-aminobutyl)indolin-2-one; **18**] was observed.

EXPERIMENTAL

Melting points were measured on a Boetius hot-stage apparatus and are uncorrected. IR spectra (wavenumbers in cm^{-1}) were recorded on a Nicolet 205 FT spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a Varian Unity Inova-400 spectrometer, chemical shifts (δ, ppm) are reported relative to TMS; coupling constants (*J*) are given in Hz. Mutual interproton couplings are given only once, at their first occurrence. Selective ^1H-{^1H} NOE

measurements were performed in the difference mode. Two-dimensional heteronuclear single-quantum correlation (HSQC) experiments were used to correlate the protons and the protonated carbons. 2D heteronuclear multiple bond correlation (HMBC) experiment was used for the assignment of quaternary carbon resonances in **19**. Mass spectra were recorded on a VG ZAB2-SEQ tandem mass spectrometer using electron impact ionization. For TLC analyses MN Polygram SIL G/UV_{254} sheets were used. Preparative separations were performed by column chromatography on Merck Kieselgel 60 (0.063–0.200). Elemental analyses (C, H, N) were carried out on a Vario EL III (Elementar Analysen Systeme GmbH) automatic microanalyzer, ionic halide content was measured by the titration with mercuric perchlorate.

General Methods for Intramolecular Mannich-Type Cyclization

Method A [6]. To a suspension of 2-oxotryptamine hydrochloride (**1**) or 3-(3-aminopropyl)indolin-2-one hydrochloride (**15**; 2 mmol) in ethanol (10 ml), ketone or aldehyde (2–5 mmol) and a solution of $NaOAc \cdot 3H_2O$ (0.56 g, 4 mmol) in water (2 ml) were added. The mixture was stirred at room temperature or at reflux for several hours. The reaction time depended on the progress of the cyclization; the reaction was followed by TLC (dichloromethane–methanol 4:1 or dichloromethane–methanol–aqueous NH_4OH 10:1:0.1; the R_F of the product was always higher than that of the starting material **1** or **17**). After completion, the solvent was removed, the residue dissolved in water (10 ml), and the solution acidified with HCl (pH 2–3). The excess ketone was removed by extraction with diethyl ether, and the aqueous phase evaporated to dryness. The final product was dissolved by the digestion of the mixture with chloroform (3 × 20 ml). The $CHCl_3$ phase was evaporated, and the residue crystallized. In some cases, purification by column chromatography was necessary to obtain a pure product.

Method B. In case of lower reactivity or to accomplish parallel alkylation, anhydrous conditions and argon gas protection were employed as follows: To a suspension of 2-oxotryptamine hydrochloride (**1**) or 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol) in a ketone reactant (30–60 mmol), dried K_2CO_3 (0.2 g) and NaI (0.1 g) were added. The suspension was stirred at room temperature or at 60–70 °C for several hours. The reaction time depended on the progress of the cyclization, which was followed by TLC (see method *A*). After completion, the mixture was diluted with water (10 ml), acidified with HCl (pH 2–3), and the excess ketone removed by extraction with diethyl ether. If the product turned out to be sufficiently stable in an alkaline medium, the aqueous phase was neutralized with ammonia (pH 8), and extracted with CH_2Cl_2. After evaporation, the residue was crystallized. If the product was unstable in an alkaline medium, the acidic aqueous phase was evaporated to dryness, and the product separated by digesting the organic product with chloroform (3 × 20 ml). The $CHCl_3$ solution was evaporated, and the residue crystallized. In some cases, purification by column chromatography was necessary to obtain a pure product.

2′-Ethyl-2′-methylspiro[indoline-3,3′-pyrrolidin]-2-one diastereomers (**2** *and* **3**). Method *A*, reactants: 2-oxotryptamine hydrochloride (**1**; 2 mmol) and ethyl methyl ketone (20 equiv.). Temperature/time: 80 °C, 20 h. The hydrochloride salt obtained (0.34 g, 62%) was a 10:1 mixture of the *exo* (**2**) and *endo* (**3**) diastereomers (^{1}H NMR spectroscopy, NOE measurement). Recrystallization of this mixture from dichloromethane/ethyl acetate furnished pure **2**. Yield: 0.28 g (51%), m.p. 199–201 °C. IR (KBr): 1705 (5-membered lactam). ^{1}H NMR (DMSO-d_6 + $CDCl_3$): 0.81 t, J_{vic} = 7.5, 3 H (CH_2-C**H**$_3$); 1.46 + 1.86 2 × dq, J_{gem} = 14.4, 2 × 1 H (C**H**$_2$-CH_3); 1.56 s, 3 H (CH_3); 2.30 + 2.70 2 × ddd, J_{gem} = 13.8, $J_{4',5'}$ = 7.6 + 4.4 and 10.0 + 9.0, 2 × 1 H

(H4′); 3.66 m, 2 H (H5′); 6.98 d, 1 H (H7); 7.02 dd, 1 H (H5); 7.24 dd, 1 H (H6); 7.34 d, 1 H (H4); 8.60 + 10.20 2 × brs, 2 × 1 H (NH_2^+); 10.90 s, 1 H (CONH). NOE: 1.56 (CH_3) → 7.34 (H4). ^{13}C NMR (DMSO-d_6 + $CDCl_3$): 8.35 (CH_2-**C**H_3), 18.51 (CH_3), 27.18 (**C**H_2-CH_3), 31.96 (C4′), 40.48 (C5′), 59.45 (C3), 70.15 (C2′), 110.53 (C7), 122.07 (C5), 125.60 (C4), 126.16 (C3a), 129.33 (C6), 143.03 (C7a), 179.77 (CONH). MS, *m/z* (%): 230 (M^+, 49), 160 (10), 146 (14), 132 (15), 98 (17), 85 (100), 56 (33). For $C_{14}H_{19}ClN_2O$ (266.8) calculated: 63.13% C, 7.18% H, 13.29% Cl, 10.50% N; found: 62.97% C, 7.08% H, 13.41% Cl, 10.37% N.

Dispiro[cyclohexane-1,2′-pyrrolidine-3′,3″-indolin]-2″-one (**5**). Method *A*, reactants: 2-oxotryptamine hydrochloride (**1**; 2 mmol) and cyclohexanone (8 mmol). Temperature/time: 25 °C, 24 h. The bis-spiro product **5** was isolated as a base in the form of colourless crystals (dichloromethane/diethyl ether). Yield: 0.35 g (65%), m.p. 166–170 °C. IR (KBr): 1690 (5-membered lactam), 3250 (NH). ^{1}H NMR ($CDCl_3$): 0.90–1.80 m, 10 H (5 × cyclohexyl CH_2); 2.27 t, $J_{4',5'}$ = 7.4, 2 H (H4′); 2.50 brs, 1 H (H1′); 3.18 and 3.29 2 × dt, J_{gem} = 12.1, 2 × 1 H (H5′); 6.90 d, 1 H (H7″); 7.02 dd, 1 H (H5″); 7.20 dd, 1 H (H6″); 7.22 d, 1 H (H4″); 8.70 brs, 1 H (CONH). ^{13}C NMR ($CDCl_3$): 21.80 and 23.15 (C3 and C5), 25.68 (C4), 30.45 and 31.44 (C2 and C6), 35.29 (C4′), 43.27 (C5′), 62.91 (C3′), 69.72 (C2′), 109.60 (C7″), 121.53 (C5″), 125.45 (C4″), 127.68 (C6″), 130.06 (C3″a), 141.78 (C7″a), 183.30 (CO). MS, *m/z* (%): 256 (M^+, 70), 213 (6), 144 (5), 130 (8), 111 (100), 110 (38), 96 (10), 83 (37). For $C_{16}H_{20}N_2O$ (256.4) calculated: 74.97% C, 7.86% H, 10.93% N; found: 74.90% C, 7.98% H, 10.77% N.

1″-Benzyldispiro[indoline-3,3′-pyrrolidine-2′,4″-piperidin]-2-one (**6**). Method *A*, reactants: 2-oxotryptamine hydrochloride (**1**; 2 mmol) and 1-benzylpiperidine (2.5 mmol). Temperature/time: 25 °C, 48 h. The bis-spiro product **6** was isolated as a base in the form of colourless crystals (diethyl ether/hexane). Yield: 0.51 g (72%), m.p. 183–185 °C. IR (KBr): 1685 (5-membered lactam), 3180 and 3400 (NH). ^{1}H NMR ($CDCl_3$): 1.30–1.85 m, 4 H (H3″ + H5″); 1.72 m, 2 H ($H_{ax}2''$ + $H_{ax}6''$); 2.10–2.90 m, 5 H ($H_{eq}2''$ + $H_{eq}6''$ + H4′ + H1′); 3.23 m, 2 H (H5′); 3.46 s, 2 H (N-CH_2-Ph); 6.81 d, 1 H (H7); 6.96 dd, 1 H (H5); 7.14 dd, 1 H (H6); 7.20 d, 1 H (H4); 7.22 m, 5 H (benzylic ring protons); 9.21 brs, 1 H (N1-H). ^{13}C NMR ($CDCl_3$): 30.01 + 31.21 (C3″ and C5″), 35.17 (C4′), 43.18 (C5′), 49.08 and 50.61 (C2″ and C6″), 62.18 (C3), 63.08 (N-CH_2-Ph), 67.62 (C2′), 109.60 (C7), 121.73 (C5), 125.45 (C4), 127.71 (C6), 129.51 (C3a), 141.62 (C7a), 182.73 (CO), benzylic ring carbons: 126.90 (C4‴), 128.08 (C3‴ and C5‴), 129.28 (C2‴ and C6‴), 138.05 (C1‴). MS, *m/z* (%): 347 (M^+, 93), 256 (M^+ – benzyl, 18), 228 (57), 201 (12), 187 (10), 172 (53), 146 (17), 134 (33), 120 (11), 91 (Bn^+, 100), 83 (33), 42 (31). For $C_{22}H_{25}N_3O$ (347.5) calculated: 76.05% C, 7.25% H, 12.09% N; found: 75.91% C, 7.20% H, 12.01% N.

3-{2[(3-Oxocyclohex-1-en-1-yl)amino]ethyl}indolin-2-one (**8**). Method *A*, reactants: 2-oxotryptamine hydrochloride (**1**; 2 mmol) and cyclohexane-1,3-dione (3 mmol). Temperature/time: 25 °C, 24 h. The enamino ketone **8** was isolated as a base in the form of yellow crystals (methanol/diethyl ether). Yield: 0.43 g (79%), m.p. 215–217 °C. IR (KBr): 1680 (5-membered lactam and conjugated ketone C=O), 3280 and 3400 (NH). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 1.87 m, 2 H (H5′); 2.12 m, 2 H (C**H**$_2$-CH_2-NH); 2.17 t, *J* = 6.2, 2 H (H4′); 2.32 t, *J* = 6.1, 2 H (H6′); 3.16 m, 2 H (NH-C**H**$_2$); 3.47 t, *J* = 6.3, 1 H (H3); 4.90 s, 1 H (H2′); 6.85 d, 1 H (H7); 6.95 dd, 1 H (H5); 6.96 brt, *J* = 6.0, 1 H (NH); 7.15 dd, 1 H (H6); 7.20 d, 1 H (H4); 10.30 s, 1 H (CONH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 21.96 (C5′), 28.98 (C4′ and C6′), 36.64 (**C**H_2-CH_2-NH), 39.50 (CH_2-**C**H_2-NH), 43.57 (C3), 95.30 (C2′), 109.67 (C7), 121.56 (C5), 123.86 (C4), 127.85 (C6), 129.13 (C3a), 142.78 (C7a), 164.96 (C1′), 179.03 (CONH), 195.58 (CO). MS, *m/z* (%): 270 (M^+, 41), 146 (7), 133 (13), 125 (100), 110 (7), 97 (25), 77 (6), 55 (12).

For $C_{16}H_{18}N_2O_2$ (270.3) calculated: 71.09% C, 6.71% H, 10.36% N; found: 70.95% C, 6.55% H, 10.50% N.

Synthesis of 3-(3-Aminopropyl)indolin-2-one (**17**) and 3-(4-Aminobutyl)indolin-2-one (**18**)

1. Esterification

A solution of carboxylic acid (0.1 mol) in methanol (100 ml) and 1 M HCl/MeOH (20 ml) was left to stand at ambient temperature for 48 h. The solvent was then evaporated, and the residue dissolved in CH_2Cl_2 (100 ml). The solution was washed with 10% aqueous Na_2CO_3 solution (2 × 20 ml), water (20 ml) and brine (20 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was crystallized from ether/hexane to furnish colourless crystals.

Methyl indole-3-propanoate (**10**). Yield: 18.1 g (88%), m.p. 78–79 °C (ref.[7] gives m.p. 79–80 °C). IR (KBr): 1710 (C=O), 3380 (NH).

Methyl indole-3-butanoate (**12**). Yield: 19.8 g (93 %), m.p. 70–72 °C (ref.[8] gives m.p. 71–72 °C). IR (KBr): 1710 (C=O), 3380 (NH).

2. Aminolysis

The solutions of methyl esters **10** and **12** (40 mmol) in CH_3OH (100 ml) were saturated with ammonia gas at –70 °C. The resultant solutions were left to stand at room temperature for 48 h. The solvents were then evaporated and the residues treated with diethyl ether. The colourless crystals were filtered off. With the residues obtained by evaporating the mother liquors, repeated aminolyses were performed. The crystals obtained in three consecutive procedures were combined.

Indole-3-propanamide (**13**). Yield: 6.77 g (90%), m.p. 133–135 °C (ref.[9] gives m.p. 131.5–133 °C). IR (KBr): 1645 (C=O amide), 3380 (NH).

Indole-3-butanamide (**14**). Yield: 6.72 g (83%), m.p. 117–118 °C (ref.[9] gives m.p. 117–118 °C). IR (KBr): 1645 (C=O amide), 3380 (NH).

3. Reduction

To a vigorously stirred suspension of $LiAlH_4$ (15.2 g, 0.4 mol) in dry THF (500 ml), a solution of amide **13** or **14** (50 mmol) in dry THF (250 ml) was added dropwise at room temperature during *ca* 30 min. The suspension was stirred under argon at room temperature for about 24 h. When the reduction was complete (TLC, CH_2Cl_2–MeOH–NH_4OH 5:1:0.1; R_F amine < R_F amide), the mixture was cooled and the excess reagent decomposed by careful addition of water (15 ml), 15% NaOH solution (15 ml) and water (45 ml) again. After 12 h, the white precipitate was filtered off and washed with chloroform (3 × 100 ml). The aqueous phase was separated, the organic phase was dried (anhydrous Na_2SO_4), acidified with 1 M HCl/MeOH, and the solvent evaporated. On treating the residue with diethyl ether, the hydrochlorides of the tryptamine homologues were obtained as colourless crystals.

3-(Indol-3-yl)propan-1-amine hydrochloride (**15**). Yield: 9.5 g (90%), m.p. 166–169 °C (ref.[10] gives m.p. 169–170 °C). IR (KBr): 2500–3000 (salt), 3360 (NH). For $C_{11}H_{15}ClN_2$ (210.7) calculated: 62.70% C, 7.18% H, 16.83% Cl, 13.29% N; found: 62.54% C, 7.28% H, 16.69% Cl, 12.99% N.

4-(Indol-3-yl)butan-1-amine hydrochloride (**16**). Yield: 9.55 g (85%), m.p. 217–219 °C (ref.[10] gives m.p. 217–218 °C). IR (KBr): 2500–3000 (salt), 3370 (NH). For $C_{12}H_{17}ClN_2$ (224.7) calculated: 64.14% C, 7.62% H, 15.78% Cl, 12.47% N; found: 64.02% C, 7.53% H, 15.59% Cl, 12.71% N.

4. Oxidation

A solution of the amine hydrochloride **15** or **16** (30 mmol) in DMSO (6.5 ml, 7.08 g, 90 mmol) was cooled in an ice bath and concentrated HCl (3.8 ml, *ca* 42 mmol) was added dropwise. The mixture was then stirred at room temperature overnight. The crystalline mass obtained was diluted with ethanol (50 ml), stirred for another 1 h, and then left to stand in a refrigerator for several hours. The crystals were filtered off and washed with ethanol and diethyl ether.

3-(3-Aminopropyl)indolin-2-one hydrochloride (**17**). Yield: 5.18 g (75%), m.p. 179–181 °C. IR (KBr): 1670 (C=O; 5-membered lactam). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 1.64 m, 2 H (CH_2-CH_2-NH_3^+); 1.92 m, 2 H (CH_2-CH_2-CH_2-NH_3^+); 2.79 t, J = 7.5, 2 H (CH_2-NH_3^+); 3.44 t, J = 6.0, 1 H (H3); 6.86 d, 1 H (H7); 6.95 dd, 1 H (H5); 7.17 dd, 1 H (H6); 7.26 d, 1 H (H4); 8.04 brs, 3 H (NH_3^+); 10.40 s, 1 H (CONH). ^{13}C NMR (DMSO-d_6 + $CDCl_3$): 23.75 (CH_2-CH_2-NH_3^+), 27.24 (CH_2-CH_2-CH_2-NH_3^+), 39.23 (CH_2-NH_3^+), 44.98 (C3), 109.70 (C7), 121.61 (C5), 124.25 (C4), 127.96 (C6), 129.45 (C3a), 142.13 (C7a), 178.91 (CONH). MS, *m/z* (%): 190 (M^+, 72), 173 (100), 145 (93), 133 (94), 117 (30), 104 (17), 91 (6), 77 (22), 56 (18), 45 (47). For $C_{11}H_{15}ClN_2O$ (226.7) calculated: 58.28% C, 6.67% H, 15.64% Cl, 12.36% N; found: 58.11% C, 6.80% H, 15.71% Cl, 12.48% N.

3-(4-Aminobutyl)indolin-2-one hydrochloride (**18**). Towards the end of the reaction, the mixture was stirred at 50 °C for 3–4 h. Yield: 4.48 g (62%), m.p. 232–233 °C. IR (KBr): 1670 (C=O; 5-membered lactam). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 1.40 m, 2 H (CH_2-CH_2-CH_2-NH_3^+); 1.68 m, 2 H (CH_2-CH_2-NH_3^+); 1.89 m, 2 H (CH_2-CH_2-CH_2-CH_2-NH_3^+); 2.79 t, J = 7.5, 2 H (CH_2-NH_3^+); 3.37 t, J = 6.0, 1 H (H3); 6.87 d, 1 H (H7); 6.95 dd, 1 H (H5); 7.14 dd, 1 H (H6); 7.21 d, 1 H (H4); 8.20 brs, 3 H (NH_3^+); 10.26 s, 1 H (CONH). ^{13}C NMR (DMSO-d_6 + $CDCl_3$): 22.78 (CH_2-CH_2-CH_2-NH_3^+), 27.30* (CH_2-CH_2-NH_3^+), 29.83* (CH_2-CH_2-CH_2-CH_2-NH_3^+), 39.26 (CH_2-NH_3^+), 45.44 (C3), 109.64 (C7), 121.50 (C5), 123.93 (C4), 127.69 (C6), 129.44 (C3a), 142.87 (C7a), 179.21 (CONH). MS, *m/z* (%): 204 (M^+, 67), 187 (16), 146 (100), 133 (32), 117 (11), 104 (8), 91 (6), 77 (12), 59 (34), 47 (7). For $C_{12}H_{17}ClN_2O$ (240.7) calculated: 59.87% C, 7.12% H, 14.73% Cl, 11.64% N; found: 59.70% C, 7.02% H, 14.85% Cl, 11.49% N.

2′,2′-Dimethylspiro[indoline-3,3′-piperidin]-2-one (**19**). Method *A*, reactants: 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol) and acetone as a solvent. Temperature/time: 60 °C, 3 h. The spiro compound **19** was isolated in the form of a base as colourless crystals (0.33 g, 70%), m.p. 189–191 °C (ethyl acetate). IR (KBr): 1690 (5-membered lactam), 3040 and 3250 (NH), 3400 (amide NH). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 0.84 s, 3 H (CH_3 directed towards the C=O group); 1.30 s, 3 H (CH_3 directed towards the aromatic ring); 1.48 m, 1 H (H_{eq}5′); 1.65 m, 1 H (H_{eq}4′); 2.11 m, 1 H (H_{ax}4′); 2.14 m, 1 H (H_{ax}5′); 2.93 m, 2 H (H6′); 3.20 brs, 1 H (N1′-H); 6.84 d, 1 H (H7); 6.93 dd, 1 H (H5); 7.13 dd, 1 H (H6); 7.24 d, 1 H (H4); 10.19 brs, 1 H (CONH). NOE: 7.24 (H4) → 1.30 (CH_3). ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 20.46 (C5′), 22.70 (CH_3 directed towards the aromatic ring), 25.88 (CH_3 directed towards the C=O group), 28.68 (C4′), 40.44 (C6′), 52.57 (C3), 53.88 (C2′), 109.31 (C7), 121.00 (C5), 124.72 (C4), 127.29 (C6), 133.54 (C3a), 142.04 (C7a), 181.19 (CONH). MS, *m/z*

(%): 230 (M^+, 70), 173 (9), 145 (8), 117 (7), 85 (100), 70 (32), 57 (17), 42 (25). For $C_{14}H_{18}N_2O$ (230.3) calculated: 73.01% C, 7.88% H, 12.16% N; found: 73.14% C, 7.95% H, 12.08% N.

1′,2′,2′-Trimethylspiro[indoline-3,3′-piperidin]-2-one (**20**). Method *B*, reactants: 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol), methyl iodide (0.18 ml, 0.414 g, 2.9 mmol) and acetone (30 ml) as a solvent. Temperature/time: 25 °C, overnight. The spiro compound **20** was isolated in the form of a base as colourless crystals (0.36 g, 74%), m.p. 176–178 °C (ethyl acetate/hexane). IR (KBr): 1690 (5-membered lactam), 3050 and 3180 (NH), 3400 (amide NH). ^{1}H NMR ($CDCl_3$): 0.76 s, 3 H (CH_3 directed towards the aromatic ring); 1.27 s, 3 H (CH_3 directed towards the C=O group); 1.46 + 2.24 2 × ddd, J_{gem} = 13.3, $J_{4',5'}$ = 4.5 + 3.5 and 12.7 + 4.7, 2 × 1 H (H4′); 1.70 + 2.06 2 × m, 2 × 1 H (H5′); 2.23 s, 3 H (N-CH_3); 2.69 + 2.77 2 × ddd, J_{gem} = 12.5, $J_{5',6'}$ = 5.3 + 5.1 and 11.3 + 3.7, 2 × 1 H (H6′); 6.88 d, 1 H (H7); 6.98 dd, 1 H (H5); 7.18 dd, 1 H (H6); 7.94 d, 1 H (H4); 8.59 brs, 1 H (CONH). NOE: 0.76 (CH_3) → 7.94 (H4). ^{13}C NMR ($CDCl_3$): 11.37 + 23.84 [C2′-(CH_3)$_2$], 20.80 (C5′), 29.42 (C4′), 37.45 (N-CH_3), 49.75 (C6′), 55.86* (C3), 57.65* (C2′), 109.07 (C7), 121.22 (C5), 127.22$^+$ (C6), 128.13$^+$ (C4), 133.70 (C3a), 140.45 (C7a), 181.26 (C=O). Peaks with the same signals are interchangeable. MS, *m/z* (%): 244 (M^+, 100), 229 (12), 173 (18), 145 (13), 112 (15), 99 (54), 84 (27), 71 (79), 56 (74), 42 (10). For $C_{15}H_{20}N_2O$ (244.3) calculated: 73.74% C, 8.25% H, 11.47% N; found: 73.58% C, 8.14% H, 11.61% N.

Ethyl 2′,2′-dimethyl-2-oxospiro[indoline-3,3′-piperidine]-1′-acetate (**21**). Method *B*, reactants: 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol), ethyl bromoacetate (0.30 ml, 0.45 g, 2.7 mmol) and acetone (30 ml) as a solvent. Temperature/time: 25 °C, 3 h. The spiro compound **21** was isolated in the form of the hydrochloride salt as colourless crystals (0.51 g, 72%), m.p. 168–170 °C (ethanol/diethyl ether). IR (KBr): 1695 (5-membered lactam), 1740 (C=O ester), 3040 and 3110 (NH^+), 3380 (amide NH). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 1.23 s, 3 H (CH_3 directed towards the C=O group); 1.34 t, J_{vic} = 7.2, 3 H (C**H**$_3$-CH_2O); 1.68 + 2.49 2 × ddd, J_{gem} = 14.2, $J_{4',5'}$ = 3.5 + 1.0 and 13.8 + 4.3, 2 × 1 H (H4′); 1.90 s, 3 H (CH_3 directed towards the aromatic ring); 1.95 + 2.63 2 × m, 2 × 1 H (H5′); 3.59 ddd, J_{gem} = 12.5, $J_{5',6'}$ = 4.5 + 1.0, 1 H (H_{eq}6′); 4.05 m, 1 H (H_{ax}6′); 4.35 q, 2 H (CH_3-C**H**$_2$O); 4.41 d + 4.68 2 × dd, J_{gem} = 17.5, J_{CH_2NH} = 1.0 and 6.5, 2 × 1 H ($^+$N-CH_2-CO); 7.07 dd, 1 H (H5); 7.20 d, 1 H (H7); 7.23 d, 1 H (H4); 7.29 dd, 1 H (H6); 9.74 brs, 1 H (NH^+); 11.63 s, 1 H (CONH). NOE: 1.90 (CH_3) → 7.23 (H4). ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 13.88 (CH_2-C**H**$_3$), 16.77 + 21.61 [C2′-(CH_3)$_2$], 17.89 (C5′), 26.91 (C4′), 51.31 (C6′), 51.40* (C3), 52.94* (C2′), 63.40 (CO_2-C**H**$_2$-CH_3); 67.48 ($^+$N-C**H**$_2$-CO), 111.85 (C7), 122.88 (C5), 124.11 (C4), 129.40 (C6), 129.01 (C3a), 141.67 (C7a), 166.90 (C=O ester), 180.46 (C=O amide). MS, *m/z* (%): 316 (M^+, 100), 301 (7), 243 (26), 184 (14), 173 (40), 158 (10), 144 (16), 117 (7), 98 (70), 84 (15), 56 (6), 42 (9). For $C_{18}H_{25}ClN_2O_3$ (352.9) calculated: 61.27% C, 7.14% H, 10.05% Cl, 7.94% N; found: 61.08% C, 7.11% H, 9.97% Cl, 7.82% N.

2′-Phenylspiro[indoline-3,3′-piperidin]-2-one isomers (**22** *and* **23**). Method *A*, reactants: 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol) and benzaldehyde (0.30 ml, 0.31 g, 3 mmol). Temperature/time: 25 °C, 24 h. The mixture of the spiro diastereomers **22** and **23** (about 2:1) was isolated in the form of a base as pale tan crystals (0.49 g, 88%). Separation of the two isomers was performed by column chromatography ($CHCl_3$–MeOH 9:1, the retention time of **22** was higher than that of **23**).

Isomer **22**. Yield: 0.30 g (54%), m.p. 151–153 °C. IR (KBr): 1690 (5-membered lactam), 3040 and 3200 (NH), 3400 (amide NH). ^{1}H NMR ($CDCl_3$): 1.62 m, 1 H (H_{eq}5′); 2.02 m, 1 H (H_{eq}4′); 2.12 m, 1 H (H_{ax}4′); 2.38 brs, 1 H (NH); 2.46 m, 1 H (H_{ax}5′); 2.94 m, 1 H (H_{ax}6′);

3.47 m, 1 H ($H_{eq}6'$); 4.08 s, 1 H (H2′); 6.51 m, 1 H (H7); 6.92–7.07 m, 7 H (5 × phenyl CH + H5 + H6); 7.29 m, 1 H (H4); 7.90 brs, 1 H (CONH). NOE: 4.08 (H2′) → 7.29 (H4). ^{13}C NMR ($CDCl_3$): 21.08 (C5′), 33.41 (C4′), 47.23 (C6′), 51.30 (C3), 67.71 (C2′), 109.21 (C7), 121.92* (C5), 122.60* (C4), 127.16 (C6), 127.35 + 127.48 (C2″ + C6″ and C3″ + C5″), 127.57 (C4″), 133.22 (C3a), 138.81 (C1″), 140.07 (C7a), 180.26 (CO). MS, *m/z* (%): 278 (M^+, 100), 173 (9), 145 (11), 132 (55), 118 (17), 104 (67), 91 (16), 69 (9), 41 (6). For $C_{18}H_{18}N_2O$ (278.4) calculated: 77.67% C, 6.52% H, 10.06% N; found: 77.48% C, 6.64% H, 9.88% N.

Isomer **23**: Yield: 0.16 g (28%), m.p. 153–155 °C. IR (KBr): 1700 (5-membered lactam), 3050 and 3200 (NH), 3400 (amide NH). ^{1}H NMR ($CDCl_3$): 1.72–1.80 m, 3 H ($H_{eq}4'$ + $H_{eq}5'$ + NH); 2.10–2.26 m, 2 H ($H_{ax}4'$ + $H_{ax}5'$); 3.07 m, 1 H ($H_{ax}6'$); 3.42 m, 1 H ($H_{eq}6'$); 4.20 s, 1 H (H2′); 6.61 d, 1 H (H7); 6.92–7.06 m, 6 H (5 × phenyl CH + H5); 7.11 dd, 1 H (H6); 7.96 brs, 1 H (CONH); 8.07 d, 1 H (H4). ^{13}C NMR ($CDCl_3$): 21.24 (C5′), 33.08 (C4′), 47.60 (C6′), 54.10 (C3), 66.64 (C2′), 109.16 (C7), 121.46 (C5), 127.20 + 127.34 (C4 + C6), 127.38 (C3″ + C5″), 127.49 (C4′), 127.75 (C2″ + C6″), 131.48 (C3a), 139.67 (C1″), 140.21 (C7a), 180.46 (CONH). MS, *m/z* (%): 278 (M^+, 100), 173 (9), 145 (10), 132 (56), 118 (19), 104 (76), 91 (17), 77 (8). For $C_{18}H_{18}N_2O$ (278.4) calculated: 77.67% C, 6.52% H, 10.06% N; found: 77.55% C, 6.49% H, 10.10% N.

2(-Ethyl-2(-methylspiro[indoline-3,3′-piperidin]-2-one isomers (**24**) *and* (**25**). Method *B*, reactants: 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol) and ethyl methyl ketone (10 ml, 8.04 g, 112 mmol). Temperature/time: 25 °C, 4 h. The mixture of the spiro diastereomers **24** and **25** (*ca* 1:1) was isolated in the form of the hydrochloride salt as pale tan crystals (0.38 g, 68%). The two diastereomers could not be separated either by crystallization or by chromatography, but their ratio could be calculated: from the ^{1}H NMR spectrum. IR (KBr): 1695 (5-membered lactam), 3060 and 3280 (NH_2^+), 3420 (amide NH). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 0.78 t + 0.97 t, J_{vic} = 7.3, 3 H (C**H**$_3$-CH_2); 1.18 s + 1.65 s, 3 H (CH_3); 1.20–3.40 m, 8 H (CH_3-C**H**$_2$ + H4′ + H5′ + H6′); 6.92–7.06 m, 2 H (H5 + H6); 7.20–7.48 m, 2 H (H4 + H7); 7.75 brt + 8.27 br and 9.18 br + 9.35 brd, 2 × 1 H (H1′); 11.00 s + 11.07 s, 1 H (CONH). MS, *m/z* (%): 244 (M^+, 100), 173 (12), 145 (10), 132 (23), 117 (8), 99 (86), 84 (53), 70 (16), 56 (13). For $C_{15}H_{21}ClN_2O$ (280.8) calculated: 64.16% C, 7.54% H, 12.63% Cl, 9.98% N; found: 64.08% C, 7.70% H, 12.54% Cl, 9.86% N.

Dispiro(cyclohexane-1,2′-piperidine-3′,3″-indolin)-2″-one (**26**). Method *B*, reactants: 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol) and cyclohexanone (8 mmol). Temperature/time: 60 °C, 24 h. The bis-spiro product **26** was isolated as the hydrochloride salt in the form of colourless crystals (dichloromethane/diethyl ether). Yield: 0.41 g (66%), m.p. 231–233 °C. IR (KBr): 1690 (5-membered lactam), 3250 (NH). ^{1}H NMR (base, $CDCl_3$): 0.96 m, 1 H ($H_{ax}4$); 1.03 ddd, 1 H ($H_{ax}2$); 1.24–1.76 m, 9 H ($H_{eq}4'$ + $H_{ax}5'$ + $H_{eq}2$ + H3 + $H_{eq}4$ + H5 + H_A6); 1.98 brs, 1 H (H1′); 2.10–2.30 m, 3 H ($H_{ax}4'$ + $H_{eq}5'$ + H_B6); 2.87 + 2.98 2 × m, 2 × 1 H (H6′); 6.86 d, 1 H (H7); 7.00 dd, 1 H (H5); 7.19 dd, 1 H (H6); 7.31 d, 1 H (H4); 8.30 brs, 1 H (CONH). ^{13}C NMR ($CDCl_3$): 20.53 (C5′), 20.61 (C3 + C5), 25.87 (C4), 27.81 and 32.21 (C2 + C6), 28.17 (C4′), 39.13 (C6′), 54.60* (C3″), 56.50* (C2′), 109.17 (C7″), 121.56 (C5″), 125.82 (C4″), 127.39 (C6″), 133.54 (C3″a), 140.95 (C7″a), 181.69 (CONH). MS, *m/z* (%): 270 (M^+, 100), 173 (11), 145 (12), 132 (17), 125 (76), 117 (15), 110 (37), 97 (33), 82 (24), 54 (22), 36 (15). For $C_{17}H_{23}ClN_2O$ (306.8) calculated: 66.55% C, 7.56% H, 11.55% Cl, 9.13% N; found: 66.39% C, 7.70% H, 11.65% Cl, 9.05% N.

1″-Benzyldispiro[indoline-3,3′-piperidine-2′,4″-piperidin]-2-one (**27**). Method *A*, reactants: 3-(3-aminopropyl)indolin-2-one hydrochloride (**17**; 2 mmol) and 1-benzyl-4-piperidone (2.5 mmol). Temperature/time: 25 °C, 24 h. Crystalline product was precipitated from the

reaction mixture. After diluting with water (4 ml), pH was adjusted to 8 by the addition of ammonia, and the product was filtered off. Compound **27** was obtained as a base (colourless crystals). Yield: 0.52 g (72%), m.p. 199–200 °C; m.p. of **27**·HCl 211–212 °C. IR (KBr): 1695 (5-membered lactam), 3050, 3080, 3150 and 3240 (NH). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): 1.36 m, 2 H (H3″); 1.47 m, 1 H (H_{eq}5′); 1.65 m, 1 H (H_{eq}4′); 1.82 m, 1 H (H_{ax}5″); 2.10–2.20 m, 3 H (H_{ax}4′ + H_{ax}5′ + H_{eq}5″); 2.36–2.62 m, 5 H (H2″ + H6″ + H1′); 2.84 m, 1 H (H_{ax}6′); 2.95 m, 1 H (H_{eq}6′); 3.42 s, 2 H (N-CH_2-Ph); 6.82 d, 1 H (H7); 6.94 dd, 1 H (H5); 7.12 dd, 1 H (H6); 7.15–7.25 m, 5 H (benzylic ring protons); 7.23 d, 1 H (H4); 9.62 brs, 1 H (CONH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 20.46 (C5′), 27.19 (C5″), 28.20 (C4′), 32.16 (C3″), 38.82 (C6′), 47.99 and 48.13 (C2″ + C6″), 53.55* (C3), 54.82* (C2′), 62.95 (N-CH_2-Ph), 109.24 (C7), 121.12 (C5), 125.52 (C4), 127.22 (C6), 132.98 (C3a), 141.75 (C7a), 181.10 (CONH), benzyl: 126.63 (C4‴), 127.92 (C3‴ + C5‴), 129.00 (C2‴ + C6‴), 138.65 (C1‴). MS, *m/z* (%): 361 (M^+, 93), 270 (M^+ – benzyl, 16), 242 (82), 215 (25), 187 (11), 172 (31), 145 (7), 134 (16), 120 (12), 91 (Bz, 100), 82 (17), 56 (7), 42 (21). For $C_{23}H_{27}N_3O$ (361.5) calculated: 76.42% C, 7.53% H, 11.62% N; found: 76.37% C, 7.72% H, 11.55% N.

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