Synthesis of Tetrahydroimidazo[1,5-*b*]-β-carboline Derivatives with Complex Basic Substituents

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Novel tetrahydroimidazo[1,5-*b*]-β-carbolines derivatives **6** bearing complex basic chains as substituents on the imidic nitrogen have been prepared in a one-pot reaction. This simple experimental procedure overcomes the direct handle of isocyanates which can be favorably generated "*in situ*" from carbonyldiimidazole (CDI) and different amines. The stereochemistry of the novel compounds was determined by nmr experiments.

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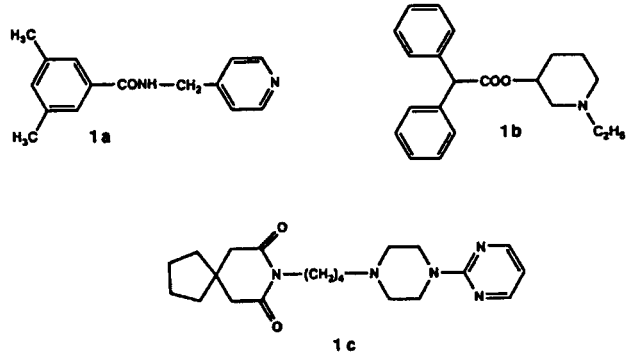
During the last few years, we have developed a program directed toward the synthesis of new compounds active on the CNS. We have carried out the synthesis of these new drugs [1], by combining two important pharmacophores: β-carbolines [2,3], which have been reported as inverse agonists at the benzodiazepine receptor, and the well known anticonvulsant hydantoin [4]. The synthesis of mixed molecules with affinity for different receptors is an interesting approach to the attainment of these novel drugs, which is the focus of our labors.

Scheme 1

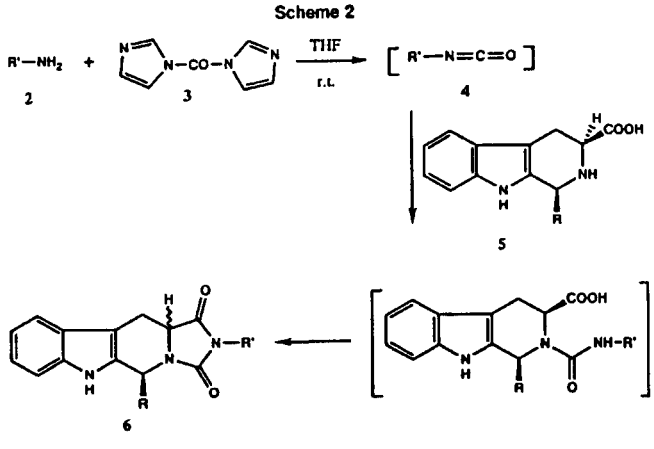


In preliminary work, we reported [5] the synthesis of simpler 2-dialkylaminoalkyl substituted tetrahydroimidazo[1,5-*b*]-β-carbolines (imidazopyridoindole). In this paper, we describe the synthesis of a variety of tetrahydroimidazo[1,5-*b*]-β-carbolines derivatives **6** bearing complex basic alkyl chains on the imidic nitrogen. Thus, we have prepared three groups of molecules: a) compounds **6a** and **6b** bearing the pyridylmethyl group related to the anticholinergic Picobenzide (**1a**) [6], b) 1-ethyl-3-piperidinyl derivative, **6c** related to the anticholinergic Piperidolate (**1b**) [7], c) and the corresponding piperazine derivatives, **6d-h** which include the characteristic moiety present in the molecule of Buspirone (**1c**) [8], widely used for the anxiety treatment.

The novel tetrahydroimidazo[1,5-*b*]-β-carboline derivatives (Table I, **6a-h**) were obtained by reaction of the tetrahydro-β-carboline-3-carboxylic acid derivatives **5** with the corresponding basic isocyanates **4** in dry tetrahydrofuran (THF) at reflux temperature.

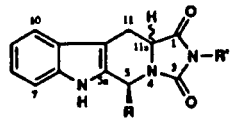
Tetrahydro-β-carboline-3-carboxylic acids **5** were prepared from commercial L-tryptophan by Pictet-Spengler condensation with carbonyl compounds in acidic medium, according to literature procedures [9]. The unstable isocyanates **4** were favorably generated "*in situ*", from the corresponding primary amines **2** and carbonyldiimidazole (CDI) **3**, according to the previously described procedure [10]. The amines **2** used for the synthesis of **4** were obtained from commercial sources. However, the preparation of amines bearing the piperazine moiety used to obtain compounds **4e-h** were synthesized in several steps [11,12].

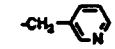
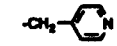
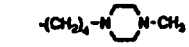
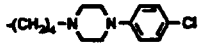
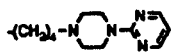
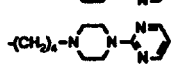
Scheme 2



Formation of compounds **6** can be accounted for by the addition of the amine group of **5**, to the carbon-nitrogen double bond of the isocyanate, **4** to yield the non-isolated trisubstituted urea [13]. Subsequent cyclization with the carboxylic group led to the corresponding tetrahydroimidazo[1,5-*b*]-β-carboline derivatives **6**.

Table 1



Compound	R	R'	M.p.°C	Yield %
6a	H		211-13	40
6b	H		260-62	48
6c	H		120-22	35
6d	H		102-04	40
6e	H		148-50	37
6f	H		180-82	51
6g	CH_3		214-16	44
6h	C_6H_5		146-48	60

Compounds **6** were obtained as racemates when R = H, due to the acidic character of the hydrogen at the chiral center. The presence of starting amine, **2** and free byproduct imidazole in the reaction mixture, could result in the formation of a carbanion. Reintegration of the hydrogen atom would provide the racemic products. Surprisingly, compound **6f** was isolated as a sole stereoisomer from the reaction mixture, showing an optical activity of $[\alpha]_D^{25}$= -116.24 (c = 0.82 in chloroform).

In order to prove that no racemization occurs at the asymmetric center C-11a in compound **6f**, NOE and 2D-NOESY spectra were recorded (Figure 1). In the NOE differential spectrum, the selective irradiation of proton B-H affords enhancements of 23% and 1% of the protons signals C-H and L-H, respectively. On the other hand, the 2D-NOESY spectrum shows, in addition to the expected connection between geminal, neighbor, and the next protons, weak, though significative cross-peaks between N-H/K-H and I-H/E-H protons. This fact might suggest a bent conformation for compound **6f**, where the indol and pyrimidinyl rings are spacially adjacent.

When C-5 is substituted, compounds **6g,h**, only one diastereomer was isolated from the reaction mixture as

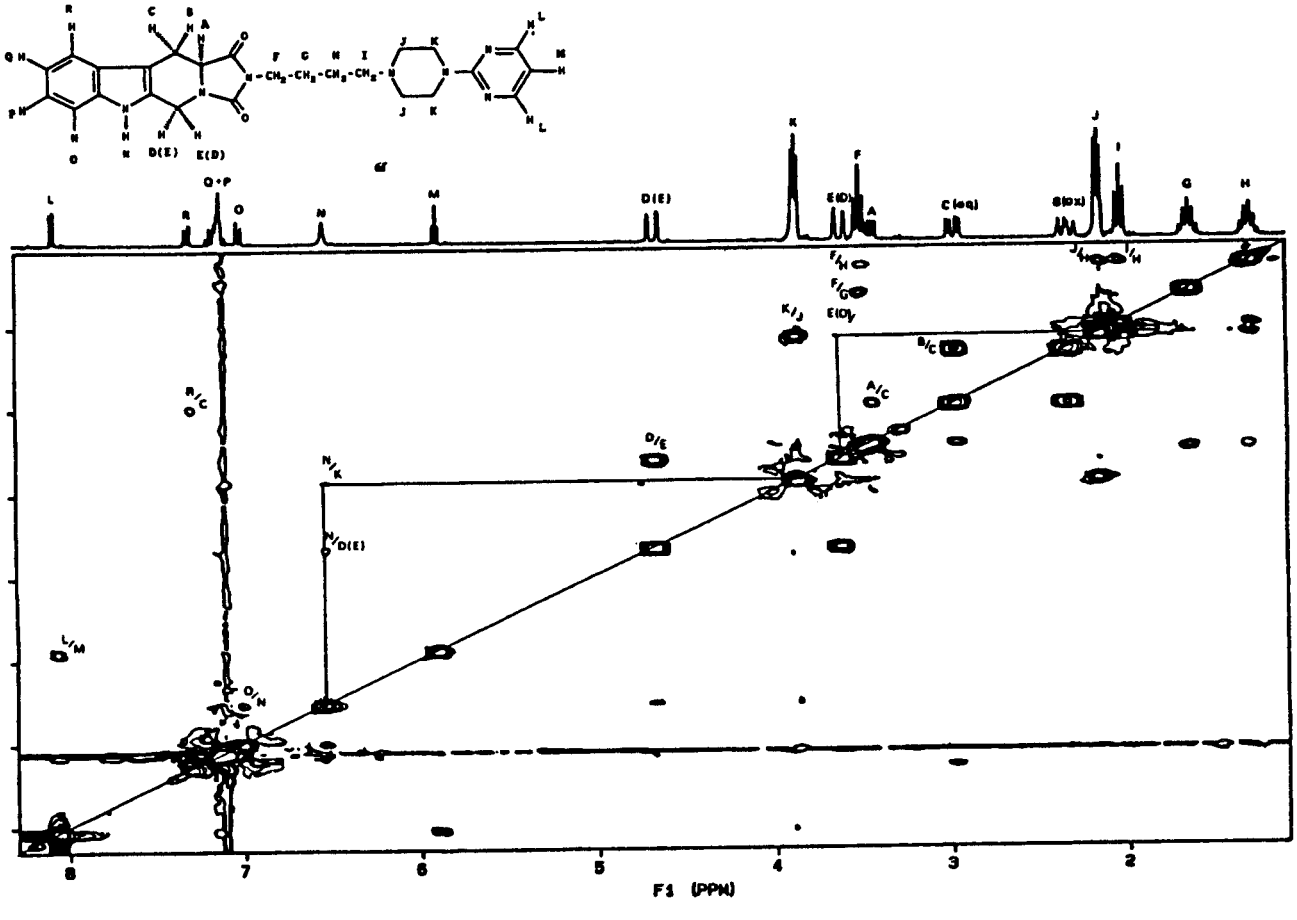


Figure 1. NOSEY spectrum of **6f**.

shown by the high resolution ^{13}C nmr spectra. The stereochemistry of carbons C-11a and C-5 was established according to the different chemical shifts shown by the *cis* and *trans* isomers in the ^{13}C nmr spectra [14].

The ir spectra of these novel compounds **6a-h** showed the NH group at 3380 cm^{-1}, and the two carbonyl groups at 1780 (C=O) and 1715 (N-CO-N) cm^{-1}. The ^1H nmr spectra presented the NH proton as a singlet at 8.40-11.10 ppm, and the proton in 11a, which appeared as a double doublet, at 4.00 ppm (J = 5.3 and 10.9 Hz). The assignments in the ^{13}C nmr were ascertained by comparison with those previously described for 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines [14].

In conclusion, we describe a useful general procedure to prepare, in a one-pot reaction, imidazo[1,5-*b*]-β-carboline derivatives bearing on the imidic nitrogen complex pharmacophores with piperazinyl, piperidyl or pyridyl moieties. This procedure overcomes the practical difficulties of isocyanates, which are now favorably generated "*in situ*" from readily available starting materials.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer model 297 spectrophotometer as potassium bromide discs. The nmr spectra (^1H at 300 MHz and ^{13}C at 75 MHz) were recorded on a Varian VXR-300 spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as an internal standard. The coupling constants are expressed in Hz and in general standard abbreviations are used. Mass spectra were performed on a Varian MAT 711 spectrometer. Microanalyses were performed by the Centro Nacional de Química Orgánica of Madrid (CSIC), and agree with theoretical values to within ±0.4%. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Chemical purity of the final products was checked by analytical tlc using silica gel as adsorbent and ethyl acetate/ethanol as the eluent. The primary amines used as starting materials were commercially obtained, and were used without futher purification. However, in the case of **6e-h** the corresponding amines were prepared in several steps by different routes according to literature procedures [11,12].

(3*S*)-2,3,4,9-Tetrahydro-1*H*-pyrido[3 4-*b*]indole-3-carboxylic Acids (**5**).

These compounds were prepared from L-tryptophan by the Pictet-Spengler condensation with the appropriate aldehyde in acidic medium, according to the literature procedure [13].

Synthesis of the 2-Aminoalkyl-substituted Tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indoledione (**6**).

General Procedure.

A solution of carbonyl diimidazole (CDI) (**3**) (2.5 g, 15.4 mmoles) in dry tetrahydrofuran (50 ml), was added dropwise to the corresponding amine **2** (15.4 mmoles), and the reaction mixture was stirred at room temperature for 4-10 hours. Then, **5** (3.33 g, 15.4 mmoles) was added and the mixture was refluxed for 40 hours. The unreacted portion of compound **5**, was removed by filtration and the solvent was evaporated to dryness. The resulting oil was purified by flash-chromatography, using ethyl acetate-ethanol as the eluent. Further purification can be accomplished by recrystallization of the obtained solid in ethanol.

(*RS*)-2-(3-Pyridylmethyl)-5,6,11,11a-tetrahydro-1*H*-imidazo-[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (**6a**).

This compound was prepared according to the general procedure, yield 40%, mp 211-213° (ethanol); ir (potassium bromide): ν 3380 cm^{-1} (NH), 1770 (C=O), 1720 (N-CO-N), 1620 (C=N), 1590, 1460 (ArC=C); ^1H nmr (DMSO-d_6): δ 2.50 (dd, J = 14.9 and 11.4 Hz, 1H, 11-H), 3.00 (dd, J = 14.9 and 5.1 Hz, 1H, 11'-H), 4.10-4.25 (m, 2H, 11a-H and 5-H), 4.39 (s, 2H, CH_2), 4.65 (d, J = 15.8 Hz, 1H, 5'-H), 6.75 (td, J_{9-10} = 7.5, J_{9-8} = 7.1 and J_{9-7} = 1.3 Hz, 9H), 6.80 (td, J_{8-7} = 7.6, J_{8-9} = 7.1 and J_{8-10} = 1.2 Hz, 1H, 8-H), 7.05-7.15 (m, 2H, 4-H and 5-H-pyridine), 7.20 (d, J_{7-8} = 7.6 Hz, 1H, 7-H), 7.45 (d, J_{10-9} = 7.5 Hz, 1H, 10-H), 8.20 (d, J = 4.8 Hz, 1H, 6-H-pyridine), 8.30 (s, 1H, 2-H-pyridine), 10.95 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 22.6 (C-11), 37.8 (C-5), 39.3 (CH_2), 55.1 (C-11a), 104.9 (C-10b), 111.4 (C-7), 118.0 (C-10), 119.0 (C-9), 121.5 (C-8), 123.9 (C-5-pyridine), 126.4 (C-10a), 129.7 (C-5a), 132.5 (C-3-pyridine), 135.5 (C-4-pyridine), 136.5 (C-6a), 148.9 (C-6-pyridine), 149.1 (C-2-pyridine), 154.5 (C-3), 172.8 (C-1).

Anal. Calcd. for $C_{19}H_{16}N_4O_2$ (332): C, 68.67; H, 4.82; N, 16.87. Found: C, 68.53; H, 4.86; N, 16.87.

(*RS*)-2-(4-Pyridylmethyl)-5,6,11,11a-tetrahydro-1*H*-imidazo-[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (**6b**).

This compound was prepared according to the general procedure, yield 48%, mp 260-262° (ethanol); ir (potassium bromide): ν 3200 cm^{-1} (NH), 1775 (C=O), 1720 (N-CO-N), 1620 (C=N), 1580, 1460 (ArC=C); ^1H nmr (DMSO-d_6): δ 2.81 (dd, J = 14.5 and 11.2 Hz, 1H, 11-H), 3.29 (dd, J = 14.5 and 5.2 Hz, 1H, 11'-H), 4.45 (d, J = 16.2 Hz, 1H, 5-H), 4.54 (dd, J = 11.2 and 5.2 Hz, 1H, 11a-H), 4.69 (s, 2H, CH_2), 4.96 (d, J = 16.2 Hz, 1H, 5'-H), 7.02 (td, J_{9-10} = 7.6, J_{9-8} = 7.1 and J_{9-7} = 1.2 Hz, 1H, 9-H), 7.10 (td, J_{8-7} = 8.0, J_{8-9} = 7.1 and J_{8-10} = 1.1 Hz, 1H, 8-H), 7.31 (dd, J = 4.5 and 1.5 Hz, 2H, 3-H and 5-H-pyridine), 7.37 (d, J_{7-8} = 8.0 Hz, 1H, 7-H), 7.50 (d, J_{10-9} = 7.6 Hz, 1H, 10-H), 8.54 (dd, J = 4.5 and 1.5 Hz, 2H, 2-H and 6-H-pyridine), 10.91 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): 22.5 (C-11), 37.6 (C-5), 40.3 (CH_2), 55.0 (C-11a), 104.8 (C-10b), 111.2 (C-7), 117.8 (C-10), 118.8 (C-9), 121.3 (C-8), 122.0 (C-3 and C-5-pyridine), 126.2 (C-10a), 129.5 (C-5a), 136.3 (C-6a), 145.4 (C-4-pyridine), 149.8 (C-2 and C-6-pyridine), 154.3 (C-3), 172.7 (C-1).

Anal. Calcd. for $C_{19}H_{16}N_4O_2$ (332): C, 68.67; H, 4.82; N, 16.87. Found: C, 68.99; H, 4.87; N, 17.00.

(*RS*)-2-(1-Ethyl-3-piperidinyl)-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (**6c**).

This compound was prepared according to the general procedure, yield 35%, mp 120-122° (ethanol-water); ir (potassium bromide): ν 3420 cm^{-1} (NH), 1775 (C=O), 1720 (N-CO-N), 1620, 1470 (ArC=C); ^1H nmr (deuteriochloroform): δ 1.08 (t, J = 7.2 Hz, 3H, CH_3), 1.30-2.54 (m, 7H, $3CH_2$-piperidine, 11-H), 2.73 (q, J = 7.2 Hz, 2H, CH_2-ethyl), 2.86-3.01 (m, 2H, CH_2-piperidine), 3.31 (dd, J = 15.1 and 5.4 Hz, 1H, 11'-H), 4.11 (dd, J

= 10.9 and 5.4 Hz, 1H, 11a-H), 4.21-4.25 (m, 1H, CH-piperidine), 4.32 (d, J = 16.2 Hz, 1H, 5-H), 5.01 (d, J = 16.2 Hz, 1H, 5'-H), 7.10 (td, J_{9-10} = 7.5, J_{9-8} = 6.7 and J_{9-7} = 1.3 Hz, 1H, 9-H), 7.16 (td, J_{8-7} = 7.9, J_{8-9} = 6.7 and J_{8-10} = 1.2 Hz, 1H, 8-H), 7.31 (d, J_{7-8} = 7.9 Hz, 1H, 7-H), 7.44 (d, J_{10-9} = 7.5 Hz, 1H, 10-H), 9.56 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{24}N_4O_2 \cdot H_2O$ (370): C, 64.86; H, 7.03; N, 15.13. Found: C, 64.52; H, 6.99; N, 15.52.

(*RS*)-2-[3-(4-Methyl-1-piperazinyl)propyl]-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (**6d**).

This compound was prepared according to the general procedure, yield 40%, mp 102-104° (ethanol); ir (potassium bromide): ν 3350 cm^{-1} (NH), 1770 (C=O), 1710 (N-CO-N), 1610, 1470 (ArC=C); ^1H nmr (deuteriochloroform) : δ 1.84 (quint, J = 7.1 Hz, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.17-2.52 (m, 10H, $4CH_2$-piperazine, CH_2-N), 2.75 (dd, J = 14.8 and 11.2 Hz, 1H, 11-H), 3.36 (dd, J = 14.8 and 5.3 Hz, 1H, 11'-H), 3.63 (t, J = 6.9 Hz, 2H, N-CH_2), 4.18 (dd, J = 11.2 and 5.3 Hz, 1H, 11a-H), 4.37 (d, J = 15.9 Hz, 1H, 5-H), 5.06 (d, J = 15.9 Hz, 1H, 5'-H), 7.15 (td, J_{9-10} = 7.4, J_{9-8} = 6.8 and J_{9-7} = 1.3 Hz, 1H, 9-H), 7.21 (td, J_{8-7} = 8.1, J_{8-9} = 6.8 and J_{8-10} = 1.2 Hz, 1H, 8-H), 7.34 (d, J_{7-8} = 8.1 Hz, 1H, 7-H), 7.50 (d, J_{10-9} = 7.4 Hz, 1H, 10-H), 8.76 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 23.0 (C-11), 25.2 (CH_2), 37.2 (CH_2-N), 37.7 (C-5), 45.8 (CH_3), 52.9 and 54.9 (CH_2-piperazine), 55.0 (C-11a), 55.5 (N-CH_2), 105.9 (C-10b), 110.9 (C-7), 117.9 (C-10), 119.8 (C-9), 122.3 (C-8), 126.2 (C-10a), 128.3 (C-5a), 136.4 (C-6a), 155.3 (C-3), 172.8 (C-1).

Anal. Calcd. for $C_{21}H_{27}N_5O_2 \cdot 2H_2O$ (417): C, 60.43; H, 7.43; N, 16.79. Found: C, 60.92; H, 7.43; N, 16.79.

(*RS*)-2-[2-(4-(3-Chlorophenyl)-1-piperazinyl)ethyl-5,6,11,11a-tetrahydro-1*H*-imdazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (**6e**).

This compound was prepared according to the general procedure, yield 35%, mp 148-150° (ethanol); ir (potassium bromide): ν 3400 cm^{-1} (NH), 1780 (C=O), 1720 (N-CO-N), 1600, 1500 (ArC=C); ^1H nmr (deuteriochloroform) : δ 2.40-2.65 (m, 7H, CH_2-N, 2N-CH_2-piperazine, 11-H), 3.05 (t, J = 5.0 Hz, 4H, $2CH_2$-*N*-piperazine), 3.22 (dd, J = 14.8 and 5.2 Hz, 1H, 11'-H), 3.42 (t, J = 7.0 Hz, 2H, N-CH_2), 3.66 (dd, J = 10.9 and 5.2 Hz, 1H, 11a-H), 4.15 (d, J = 15.9 Hz, 1H, 5-H), 5.12 (d, J = 15.9 Hz, 1H, 5'-H), 6.61-7.20 (m, 8H, ArH), 8.72 (s, 1H, NH).

Anal. Calcd. for $C_{25}H_{26}ClN_5O_2$ (463.5): C, 64.72; H, 5.61; Cl, 7.66; N, 15.10. Found: C, 65.02; H, 5.43; Cl, 7.40; N, 15.30.

(-)-2-[4-(4-(2-Pyrimidinyl)-1-piperazinyl)butyl]-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (**6f**).

This compound was prepared according to the general procedure, yield 42%, mp 180-182° (absolute ethanol), $[\alpha]_D^{25}$ = -116.24 (c = 0.82 in chloroform); ir (potassium bromide): ν 3350 cm^{-1} (NH), 1775 (C=O), 1715 (N-CO-N), 1620 (C=N), 1590, 1550, 1500, 1450 (ArC=C); ^1H nmr (deuteriochloroform): δ 1.52-1.63 (m, 2H, CH_2), 1.66-1.78 (m, 2H, CH_2), 2.41 (t, J = 7.3 Hz, 2H, CH_2-N), 2.49 (t, J = 5.0 Hz, 4H, 2N-CH_2-piperazine), 2.76 (dd, J = 14.8 and 11.2 Hz, 1H, 11-H), 3.37 (dd, J = 14.8 and 5.5 Hz, 1H, 11'-H), 3.61 (t, J = 7.0 Hz, 2H, N-CH_2), 3.82 (t, J = 5.0 Hz, 4H, $2CH_2$-N-piperazine), 4.21 (dd, J = 11.2 and 5.5 Hz, 1H, 11a-H), 4.38 (d, J = 16.1 Hz, 1H, 5-H), 5.06 (d, J = 16.1 Hz, 1H, 5'-H), 6.47 (t, J = 4.7 Hz, 1H, 5-H-pyrimidine), 7.13 (td, J_{9-10} = 7.6, J_{9-8} = 7.1 and J_{9-7} = 1.3 Hz, 1H, 9-H), 7.19 (td, J_{8-7} = 8.0, J_{8-9} = 7.1 and J_{8-10} = 1.2 Hz, 1H, 8-H), 7.32 (d, J_{7-8} = 8.0 Hz, 1H, 7-H), 7.48 (d, J_{10-9} = 7.6 Hz, 1H, 10-H), 8.29 (d, J = 4.8 Hz, 2H, 4-H and 6-H-pyrimidine), 8.65 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 22.9 (C-11), 23.7 (CH_2), 26.0 (CH_2), 37.5 (C-5), 38.4 (CH_2-N), 43.4 and 52.7 (CH_2-piperazine), 54.9 (C-11a), 57.7 (N-CH_2), 105.7 (C-10b), 109.6 (C-5-pyrimidine), 110.8 (C-7), 117.8 (C-10), 119.6 (C-9), 122.1 (C-8), 126.1 (C-10a), 128.3 (C-5a), 136.3 (C-6a), 155.1 (C-3), 157.4 (C-4 and C-6-pyrimidine), 161.3 (C-2-pyrimidine), 172.7 (C-1); ms: (100 eV), m/z (%) 459 (21) [M+], 364 (15), 351 (26), 339 (21), 296 (6), 226 (7), 197 (7), 177 (100), 143 (43), 108 (29), 80 (25), 56 (7).

Anal. Calcd. for $C_{25}H_{29}N_7O_2 \cdot 1/2H_2O$ (468): C, 64.10; H, 6.41; N, 20.94. Found: C, 64.44; H, 6.51; N, 20.91.

(-)-(5*S*,11a*S*)-5-Methyl-2-[4-(4-(2-pyrimidinyl)-1-piperazinyl)-butyl]-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]pyrido[3,4-*b*]-indole-1,3(2*H*)-dione (**6g**).

This compound was prepared according to the general procedure, yield 45%, mp 214-216° (absolute ethanol), $[\alpha]_D^{25}$ = -105 (c = 0.6 in chloroform); ir (potassium bromide): ν 3330 cm^{-1} (NH), 1765 (C=O), 1700 (N-CO-N), 1620 (C=N), 1580, 1550, 1480, 1450 (ArC=C); ^1H nmr (DMSO-d_6): δ 1.44-1.49 (m, 2H, CH_2), 1.57-1.62 (m, 2H, CH_2), 1.85 (d, J = 6.4 Hz, 3H, CH_3), 2.32 (t, J = 7.0 Hz, 2H, CH_2-N), 2.39 (t, J = 4.9 Hz, 4H, 2N-CH_2-piperazine), 2.69 (ddd, J = 14.5, 11.5 and 2.0 Hz, 1H, 11-H), 3.17 (dd, J = 14.5 and 4.5 Hz, 1H, 11'-H), 3.44 (t, J = 6.7 Hz, 2H, N-CH_2), 3.70 (t, J = 4.9 Hz, 4H, $2CH_2$-N-piperazine), 4.37 (dd, J = 11.5 and 4.5 Hz, 1H, 11a-H), 4.94 (q, J = 6.4 Hz, 1H, 5-H), 6.60 (t, J = 4.7 Hz, 1H, 5-H-pyrimidine), 7.00 (td, J_{9-10} = 7.6, J_{9-8} = 7.0 and J_{9-7} = 1.3 Hz, 1H, 9-H), 7.08 (td, J_{8-7} = 8.1, J_{8-9} = 7.0 and J_{8-10} = 1.2 Hz, 1H, 8-H), 7.33 (d, J_{7-8} = 8.1 Hz, 1H, 7-H), 7.49 (d, J_{10-9} = 7.6 Hz, 1H, 10-H), 8.34 (d, J = 4.7 Hz, 2H, 4-H and 6-H-pyrimidine), 11.08 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ = 20.5 (CH_3), 22.2 (C-11), 23.6 (CH_2), 25.9 (CH_2), 37.9 (CH_2-N), 43.5 (CH_2-piperazine), 48.3 (C-5) 52.8 (CH_2-piperazine), 57.6 (C-11a and CH_2), 105.0 (C-10b), 110.2 (C-5-pyrimidine), 111.4 (C-7), 118.2 (C-10), 119.0 (C-9), 121.5 (C-8), 126.2 (C-10a), 136.0 (C-5a), 136.4 (C-6a), 155.3 (C-3), 158.0 (C-4 and C-6-pyrimidine), 161.4 (C-2-pyrimidine), 171.9 (C-1); ms: (100 eV) m/z (%) 473 (5) [M+], 365 (6), 307 (6), 262 (5), 212 (8), 199 (45), 177 (100), 157 (13), 148 (45), 122 (55), 108 (41), 78 (26), 56 (14), 45 (40).

Anal. Calcd. for $C_{26}H_{31}N_7O_2 \cdot 1/2H_2O$ (482): C, 64.73; H, 6.64; N, 20.33. Found: C, 65.01; H, 6.77; N, 19.99.

(+)-(5*S*,11a*R*)-5-Phenyl-2-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,11,11a-tetrahydro-1*H*-imidazo[1,'5':1,6]-pyrido[3,4-*b*]indole-1,3(2*H*)-dione (**6h**).

This compound was prepared according to the general procedure, yield 60% mp 146-148° (ethylene glycol) $[\alpha]_D^{25}$ = +164 (c = 0.7 in chloroform); ir (potassium bromide): ν 3350 cm^{-1} (NH), 1765 (C=O), 1705 (N-CO-N), 1620 (C=N), 1590, 1550, 1500, 1450 (ArC=C); ^1H nmr (DMSO-d_6): δ = 1.39-1.43 (m, 2H, CH_2), 1.54-1.59 (m, 2H, CH_2), 2.26 (t, J = 7.1 Hz, 2H, CH_2-N), 2.32 (t, J = 4.8 Hz, 4H, 2N-CH_2-piperazine), 2.83 (ddd, J = 14.7, 11.1 and 1.2 Hz, 1H, 11-H), 3.37-3.46 (m, 3H, 11'-H and N-CH_2), 3.67 (t, J = 4.8 Hz, 4H, $2CH_2$-*N*-piperazine), 4.59 (dd, J = 11.1 and 5.6 Hz, 1H, 11a-H), 6.26 (s, 1H, 5-H), 6.58 (t,

J = 4.7 Hz, 1H, 5-H-pyrimidine), 7.03 (td, J_{9-10} = 7.5, J_{9-8} = 7.2 and J_{9-7} = 1.3 Hz, 1H, 9-H), 7.10 (td, J_{8-7} = 7.9, J_{8-9} = 7.2 and J_{8-10} = 1.2 Hz, 1H, 8-H), 7.31-7.40 (m, 6H, ArH), 7.55 (d, J_{10-9} = 7.5 Hz, 1H, 10-H), 8.33 (d, J = 4.7 Hz, 2H, 4-H and 6-H-pyrimidine), 10.93 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ = 22.9 (C-11), 23.6 (CH_2), 25.7 (CH_2), 38.1 (CH_2-N), 43.5 (CH_2-piperazine), 51.7 (C-11a), 52.7 (CH_2-piperazine), 53.1 (C-5), 57.5 (N-CH_2), 106.2 (C-10b), 110.2 (C-5-pyrimidine). 111.6 (C-7), 118.4 (C-10), 119.0 (C-9), 121.9 (C-8), 126.0 (C-10a), 128.0 (C-2-phenyl or C-3-phenyl), 128.3 (C-4-phenyl), 128.9 (C-3-phenyl or C-2-phenyl), 131.4 (C-5a), 136.9 (C-6a), 140.3 (C-l-phenyl), 154.5 (C-3), 158.0 (C-4 and C-6-pyrimidine), 161.4 (C-2-pyrimidine), 172.8 (C-l); ms: (100 eV) m/z (%) 535 (73) [M+], 316 (9), 440 (42), 427 (78), 415 (81), 245 (21), 219 (9), 218 (43), 177 (100), 148 (24), 122 (56), 108 (10).

Anal. Calcd. for $C_{31}H_{33}N_7O_2 \cdot 1/2H_2O$ (544): C, 68.38; H, 6.25; N, 18.01. Found: C, 68.70; H, 7.32; N, 18.01.

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