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SYNTHESIS AND DOPAMINE RECEPTOR BINDING OF SOME PYRAZOLO[3',4':6,7]AZEPINO[5,4,3-*cd*]INDOLES

Peter Gmeiner,^a Harald Hübner,^a Kayed A. Abu Safieh,^b Ismail I. Fafous,^b Mustafa M. El-Abadelah,^{b*} Salim S. Sabri,^c and Wolfgang Voelter^d

^aDepartment of Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, D-91052 Erlangen, Germany

^bChemistry Department, Faculty of Science, University of Jordan, Amman, Jordan

^cFaculty of Arts and Sciences, University of Sharjah, Sharjah, UAE

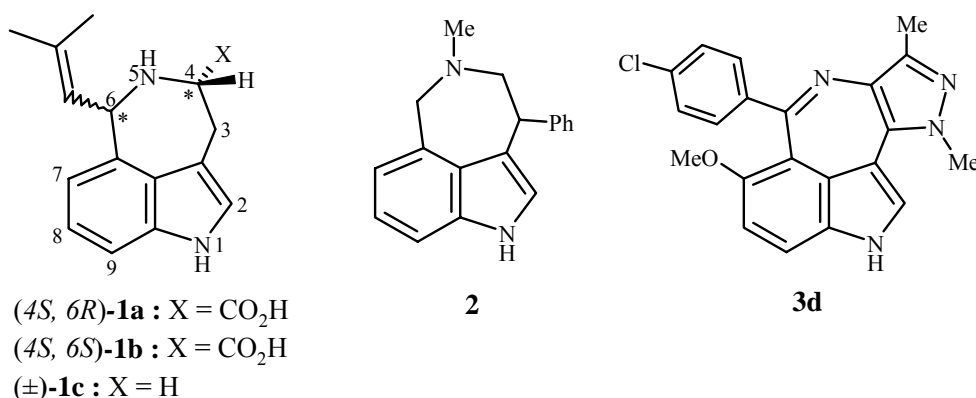
^dAbteilung für Physikalische Biochemie, Physiologisch-chemisches Institut der Universität Tübingen, Hoppe-Seyler Straße 4, D-72076 Tübingen, Germany

Abstract– A synthesis of some substituted pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]-indoles is described and their affinities to dopamine receptors were evaluated. The tested compounds (**3a-d** and **4a,b**) showed micromolar affinity to the bovine D₁ receptor subtype and the human D₂, D₃ and D₄ receptor isoforms.

INTRODUCTION

The clavicipitic acids (**1a, b**)¹ and aurantioclavine (**1c**)² are naturally occurring ergot alkaloids having the uncommon, yet interesting 3,4,5,6-tetrahydroazepino[5,4,3-*cd*]indole nucleus. Numerous synthetic routes of **1a,b**,^{3,4} **1c**,⁵ and of related derivatives⁶⁻⁸ have been reported. These heterocyclic compounds have retained a continued attention for their potential interest in the field of medicinal chemistry.^{7,8}

As part of an ongoing program in search for new selective dopamine D₁- and D₂- like receptor ligands, some 3-phenyltetrahydroazepinoindoles were recently prepared, exemplified by **2** that showed micromolar affinity to the bovine D₁ receptor subtype.⁷ Quite recently, the synthesis of some pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]indoles, exemplified by **3d**, has been described.⁹ From the viewpoint of its chemical structure encompassing a fully unsaturated azepinoindole moiety, compound (**3d**) and related analogs are envisioned worthy of investigating their affinities to dopamine receptors.



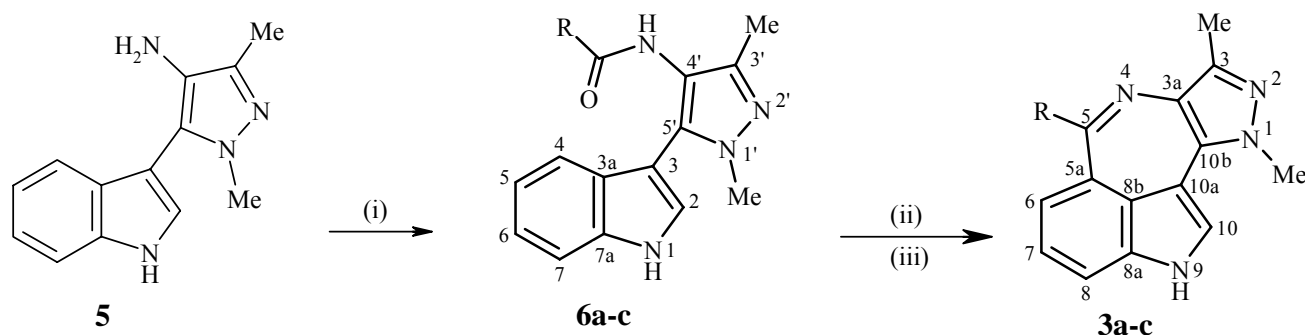
Accordingly, the present work aims at synthesis of a selected set of new substituted pyrazolo-[3',4':6,7]azepino[5,4,3-*cd*]indoles (**3a-c** / Scheme I), (**4a,b** / Scheme II), and evaluation of their binding properties to dopamine D₁, D₂, D₃ and D₄ receptors.

RESULTS AND DISCUSSION

CHEMISTRY

The synthesis of pyrazolo[3',4' : 6,7]azepino[5,4,3-*cd*]indoles (**3a-c**) commenced with 3-(4-amino-1,3-dimethylpyrazol-5-yl)indole (**5**),⁹ as the key precursor, which is acylated with the appropriate acid chlorides to deliver the corresponding 3-(4-acylamino-1,3-dimethylpyrazol-5-yl)indoles (**6a-c** / Scheme I). The latter carboxamides were cyclized by the Bischler-Napieralski reaction, using phosphorous oxychloride in acetonitrile at reflux, to furnish the corresponding condensed azepinoindole derivatives (**3a-c**). Apparently ring closure prevails regioselectively at C-4 of the indole nucleus, rather than at the usual C-2 position. The structural assignments are supported by elemental analyses, IR, MS, ¹H- and ¹³C NMR spectral data listed in EXPERIMENTAL. Carbon-13 assignments are based on DEPT and 2D (COSY, HMQC, HMBC) experiments. These reveal long range H-C correlations, in particular between

Scheme I



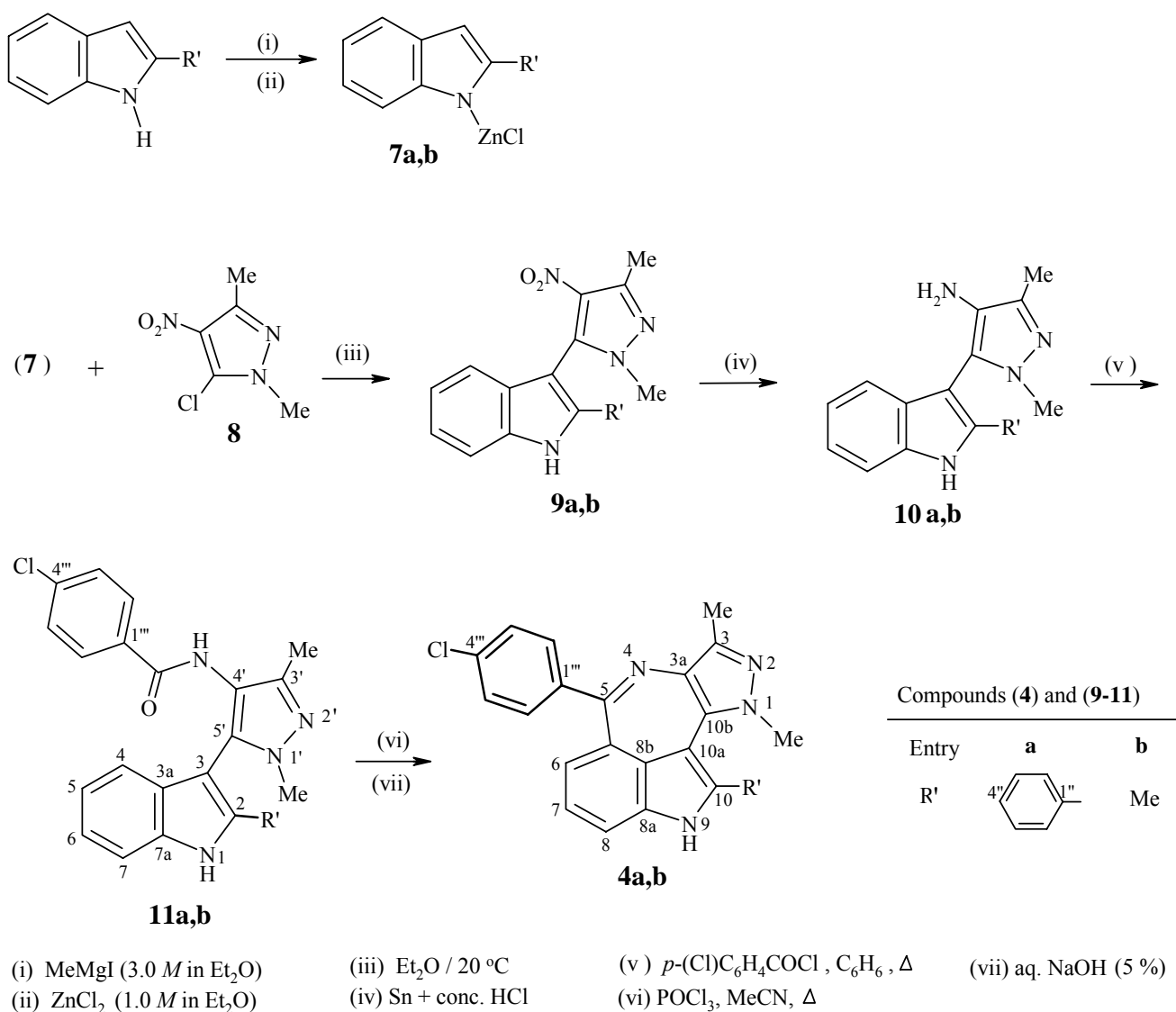
- (i) RCOCl, C₆H₆, NEt₃, Δ
 (ii) POCl₃, MeCN, Δ
 (iii) aq. NaOH (5 %)

Compounds (3) and (6)			
Entry	a	b	c
R	Me		

the indolic H-6 and the azepine C-5. Furthermore, the indolic H-2 of **6a-c** and **3a-c** resonates at *ca.* δ 7.5 as a doublet ($J_{\text{CH-NH}} \approx 2.5$ Hz) that collapses to a singlet upon treatment with D₂O. These diagnostic spectral features are in conformity with an azepine-forming C-4 cyclization reaction as depicted in Scheme I.

The synthesis of substituted 10-phenyl- and 10-methylpyrazoloazepinoindole analogs (**4a,b**) were likewise achieved by acylation of the respective 3-(4-amino-1,3-dimethylpyrazol-5-yl)indole (**10a,b**), followed by annulation of the resulting carboxamides (**11a,b**) using phosphorous oxychloride under Bischler-Napieralski reaction conditions (Scheme II).

Scheme II



Here, the presence of a phenyl or methyl group as substituents at carbon-2 of the indole nucleus, directs the ring closure solely at position-4 with ultimate formation of the corresponding pyrazoloazepinoindoles (**4a,b**). The synthons (**10a,b**) were obtained by chemical reduction of their 3-(1,3-dimethyl-4-nitropyrazol-5-yl)indole precursors (**9a,b** / Scheme 2). The latter were prepared, in turn, by direct coupling between

5-chloro-1,3-dimethyl-4-nitropyrazole (**8**) and the appropriate indolylzinc chloride (**7a,b**), generated *in situ* from the corresponding indolylmagnesium iodide and zinc chloride (Scheme II). Examples of related nucleophilic heteroaromatic substitutions include the reaction of indolyl Grignard reagents, acting as C-3 indolyl carbanions, with 2-bromothiazole in preparing the naturally occurring 3-(thiazol-2-yl)indoles, called camalexins,¹⁰ and with 2-chloropyridines to form the respective 3-(2-pyridyl)indoles.¹¹

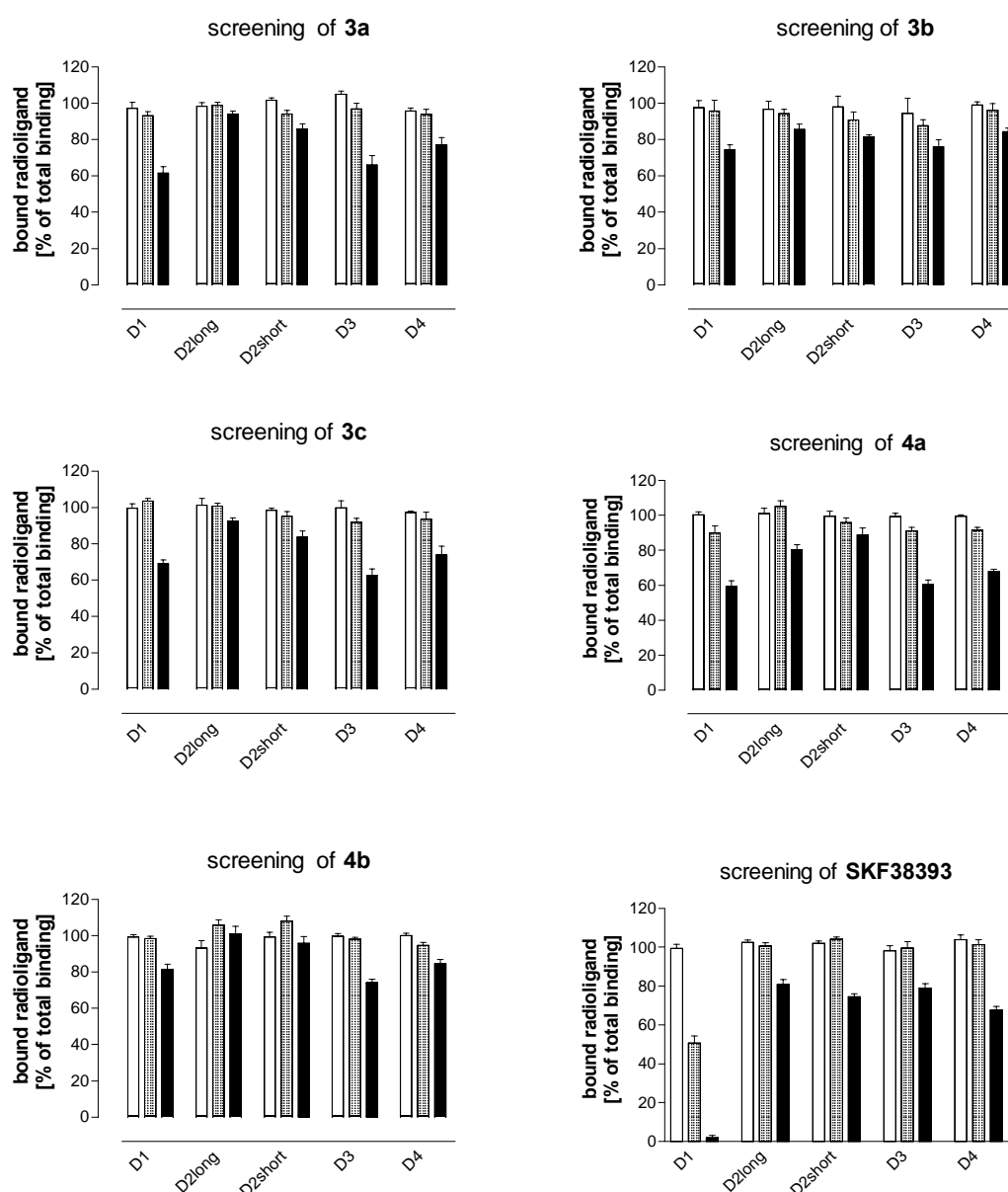


Figure 1. Screening of the test compounds (**3a-c** and **4a,b**) at the dopamine receptor subtypes in comparison with the D₁ selective reference compound SKF 38393 (rate of displacement of the radioligand (in %) caused by the test compounds at three different concentrations: full bars = 10 μM; pointed bars = 100 nM; open bars = 1 nM).

BIOLOGICAL SCREENING

The receptor binding assays with the compounds (**3a-d** and **4a,b**) were performed employing the bovine dopamine D₁ receptor¹² besides the human D_{2 long}, D_{2 short},¹³ D₃¹⁴ and D₄¹⁵ isoforms and three different concentrations of the tested compounds (10 μ M, 100 nM and 1 nM), measuring the displacement of the radioligands [³H]SCH23390 (D₁) and [³H]spiperone (D₂-D₄). The tested compounds (**3a-d** and **4a,b**) showed weak binding affinities to all dopamine receptor subtypes expressed by the ability to displace the corresponding radioligands only incomplete at micromolar concentration. They were less potent than the D₁ selective reference compound SKF 38393, which is characterized by a K_i value of 77 nM.^{7,16} The graphical data of the screening results for these compounds and the reference ligand are illustrated in Figure 1.

EXPERIMENTAL

2-Methylindole and 2-phenylindole were purchased from Acros. 5-Chloro-1,3-dimethyl-4-nitropyrazole, methylmagnesium iodide (3.0 M in ether) and zinc chloride (1.0 M in ether) were purchased from Aldrich. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker WM-400 and a Bruker DPX-300 spectrometers using TMS as internal reference. EIMS spectra and high resolution data were obtained using a Finnigan MAT 731 spectrometer at 70 eV; ion source temperature = 200 °C. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were performed at the Microanalytical Laboratory, Inorganic Chemistry Department, Tübingen University, Germany.

3-[4-(N-Acetylamino)-1,3-dimethylpyrazol-5-yl]indole (**6a**)

Acetyl chloride (0.51 g; 6.5 mmol) was added to a solution of 3-(4-amino-1,3-dimethylpyrazol-5-yl)indole (**5**)⁹ (1.36 g; 6.0 mmol) in dry benzene (40 mL), followed by addition of triethylamine (4 mL, 28.5 mmol). The resulting mixture was refluxed for 4 h. The solvent was then evaporated in vacuo, the solid residue was soaked in water (70 mL), filtered and recrystallized from chloroform / petroleum ether. Yield of **6a** = 0.84 g (52 %), mp 275-277 °C (decomp). *Anal.* Calcd for C₁₅H₁₆N₄O: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.21; H, 6.07; N, 20.74. IR (KBr) : ν 3421, 3247, 3145, 3098, 2986, 2924, 2873, 1664, 1552, 1439, 1327, 1291, 1112 cm⁻¹; MS *m/z* (% rel. int.): 268 (M⁺, 100), 226 (77), 225 (81), 184 (13), 157 (32), 142 (50), 115 (15); HRMS: Calcd for C₁₅H₁₆N₄O: 268.13241. Found: 268.13407; ¹H NMR (300 MHz, DMSO-d₆): δ 1.85 (s, 3H, CO-CH₃), 2.09 (s, 3H, C3'-CH₃), 3.66 (s, 3H, N-CH₃), 7.05 (dd, 1H, H-5, *J* = 7.7 Hz, 8.0 Hz), 7.16 (dd, 1H, H-6, *J* = 7.7 Hz, 8.1 Hz), 7.35 (d, 1H, H-4, *J* = 8.0 Hz), 7.47 (d, 1H, H-7, *J* = 8.1 Hz), 7.52 (d, 1H, H-2, *J* = 2.4 Hz), 8.91 (s, 1H, N1-H), 11.55 (s, 1H, NHCO); ¹³C NMR (75 MHz, DMSO-d₆): δ 11.5 (C3'-CH₃), 22.5 (COCH₃), 37.0 (N-CH₃), 102.9 (C-3), 111.9 (C-7), 115.9 (C-4'), 119.1 (C-4), 119.6 (C-5), 121.6 (C-6), 125.8 (C-3a), 125.9 (C-2), 136.0 (C-

7a), 133.3 (C-5'), 143.5 (C-3'), 169.3 (NHCO).

3-[4-(4-Chlorobenzoylamino)-1,3-dimethylpyrazol-5-yl]indole (6b)

This compound was prepared from *p*-chlorobenzoyl chloride (0.48 g; 2.75 mmol) and **5** (0.57 g; 2.5 mmol), following the same procedure described above for **6a**. Yield of **6b** = 0.71g (78 %), mp 243-244 °C (ethanol). *Anal.* Calcd for C₂₀H₁₇N₄OCl: C, 65.84 ; H, 4.70; N, 15.36; Cl, 9.72. Found : C, 65.59; H, 4.92; N, 15.17; Cl, 9.66. IR (KBr) : ν 3412, 3221, 3150, 3104, 3068, 2971, 2914, 2873, 1649, 1592, 1536, 1486, 1311, 1091 cm⁻¹; MS *m/z* (% rel. int.): 364 (M⁺, 27), 225(100), 157 (32), 142 (25), 139 (16), 111(12), HRMS: Calcd for C₂₀H₁₇N₄OCl: 364.10909. Found: 364.10998; ¹H NMR (300 MHz, DMSO-d₆): δ 2.08 (s, 3H, C3'-CH₃) , 3.71(s, 3H, N-CH₃), 6.98 (dd, 1H, H-5, *J* = 7.5 Hz, 7.6 Hz), 7.12 (dd, 1H, H-6, *J* = 7.5 Hz , 7.9 Hz), 7.44 (d, 1H, H-4, *J* = 7.6 Hz), 7.46 (d, 1H, H-7, *J* = 7.9 Hz), 7.49 (d, 2H, H-3"/H-5", *J* = 8.5 Hz), 7.55 (d, 1H, H-2, *J* = 2.6 Hz), 7.84 (d, 2H, H-2"/H-6", *J* = 8.5 Hz), 9.54 (s, 1H, N1-H), 11.50 (s, 1H, NHCO); ¹³C NMR (75 MHz, DMSO-d₆) : δ 11.4 (C3'-CH₃), 37.2 (N-CH₃), 102.7 (C-3), 111.9 (C-7), 115.4 (C-4'), 119.1 (C-4) , 119.5 (C-5), 121.6 (C-6), 125.6 (C-3a), 125.9 (C-2), 128.2 (C-3"/C-5"), 129.3 C-2"/C-6"), 133.0 (C-5'), 133.8(C-1"), 135.9 (C-7a), 136.1 (C-4"), 143.7 (C-3'), 165.4 (NHCO).

3-[4-(2-Furoylamino)-1,3-dimethylpyrazol-5-yl]indole (6c)

This compound was prepared from 2-furoyl chloride (0.72 g; 5.5 mmol) and **5** (1.13 g; 5.0 mmol), following the same procedure described above for **6a**. Yield of **6c** = 1.15 g (72 %), mp 207-209 °C (decomp) (ethanol). *Anal.* Calcd for C₁₈H₁₆N₄O₂ : C, 67.49; H, 5.03; N, 17.49. Found : C, 67.60; H, 4.95; N, 17.23. IR (KBr) : ν 3403, 3308, 2925, 1660, 1547, 1480, 1310, 1125 cm⁻¹; MS *m/z* (% rel. int.): 320 (M⁺, 64), 225 (100), 157 (39), 142 (29), 115 (9), 95 (23); HRMS: Calcd for C₁₈H₁₆N₄O₂ : 320.12733. Found: 320.12950; ¹H NMR (300 MHz, DMSO-d₆): δ 2.06 (s, 3H, C3'-CH₃), 3.69 (s, 3H, N-CH₃), 6.59 (dd, 1H, H-4", *J* = 3.3 Hz, 1.8 Hz), 7.00 (m, 1H, H-5), 7.11 (m, 1H, H-6), 7.13 (dd, 1H, H-3", *J* = 3.3 Hz, 0.5 Hz), 7.40 (d, 1H, H-4, *J* = 8.0 Hz), 7.44 (d, 1H, H-7, *J* = 8.2 Hz), 7.55 (d, 1H, H-2, *J* = 2.6 Hz), 7.79 (dd, 1H, H-5", *J* = 1.8 Hz, 0.5 Hz), 9.40 (s , 1H, N1-H), 11.52 (s, 1H, NHCO); ¹³C NMR (75 MHz, DMSO-d₆) : δ 11.4 (C3'-CH₃), 37.2 (N-CH₃), 102.8 (C-3), 114.0 (C-3"), 111.8 (C-4"), 111.9 (C-7), 114.7 (C-4'), 119.1 (C-4) , 119.6 (C-5), 121.6 (C-6) , 125.8 (C-3a), 126.1 (C-2), 134.2 (C-5'), 136.0 (C-7a), 143.8 (C-3'), 145.2 (C-5"), 147.6 (C-2"), 157.6 (NHCO).

1,3,5-Trimethylpyrazolo[3',4' : 6,7]azepino[5,4,3-cd]indole (3a)

To a stirred solution of **6a** (0.62 g; 2.3 mmol) in acetonitrile (35 mL) was added phosphorous oxychloride (6 mL, 64.2 mmol), and the resulting mixture was refluxed for 6 h. Excess acetonitrile and phosphorous oxychloride were removed under vacuum, the residue was poured onto ice-cold water (100 mL), basified with 10% aqueous NaOH solution and extracted with dichloromethane (3 x 80 mL). The

combined organic extracts were dried (MgSO_4) and the solvent was evaporated leaving a crude orange solid. The product was purified on silica gel TLC plates, eluting with MeOH: CH_2Cl_2 (3 : 97, v/v). Yield of **3a** = 0.25 g (43 %), mp 277-278 °C (decomp). *Anal.* Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_4$: C, 71.98; H, 5.64; N, 22.38. Found : C, 71.84; H, 5.61; N, 22.16. IR (KBr) : ν 3430, 3156, 3106, 3047, 2991, 2915, 1608, 1507, 1420, 1322, 1165 cm^{-1} ; MS *m/z* (% rel. int.): 250 (M^+ , 100), 208 (46), 194 (13), 167 (17), 140 (21), 125 (18), 84 (21); HRMS: Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_4$: 250.12183. Found: 250.12066; ^1H NMR (300 MHz, DMSO- d_6): δ 2.04 (s, 3H, C3- CH_3), 2.22 (s, 3H, C5- CH_3), 3.84 (s, 3H, N- CH_3), 6.89 (d, 1H, H-6, J = 7.6 Hz), 6.94 (dd, 1H, H-7, J = 7.6 Hz, 7.8 Hz), 7.19 (d, 1H, H-8, J = 7.8 Hz), 7.43 (d, 1H, H-10, J = 2.5 Hz), 11.42 (s, 1H, N9- H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 10.2 (C3- CH_3), 27.6 (C5- CH_3), 39.1 (N- CH_3), 107.6 (C-10a), 113.9 (C-8), 117.6 (C-10), 119.8 (C-6), 123.2 (C-7), 126.0 (C-10b), 128.4 (C-8b), 130.6 (C-3), 131.1 (C-5a), 136.9 (C-8a), 146.6 (C-3a), 154.1 (C-5).

5-(4-Chlorophenyl)-1,3-dimethylpyrazolo[3',4' : 6,7]azepino[5,4,3-*cd*]indole (**3b**)

This compound was prepared from **6b** (0.80 g; 2.2 mmol) and phosphorous oxychloride (6 mL, 64.2 mmol), following the same procedure described above for **3a**. Yield of **3b** = 0.16 g (21 %), mp 285-286 °C (decomp) (ethanol). *Anal.* Calcd for $\text{C}_{20}\text{H}_{15}\text{N}_4\text{Cl}$: C, 69.26; H, 4.36; N, 16.15; Cl, 10.22. Found : C, 69.52; H, 4.17; N, 16.08; Cl, 10.13. IR (KBr) : ν 3442, 3145, 2986, 2920, 2868, 1593, 1507, 1483, 1312, 1255, 1168, 1143 cm^{-1} ; MS *m/z* (% rel. int.): 346 (M^+ , 100), 304 (22), 263 (21), 254 (30), 228 (16), 201(13), 156 (44), 105 (28); HRMS: Calcd for $\text{C}_{20}\text{H}_{15}\text{N}_4\text{Cl}$: 346.098504. Found: 346.097129; ^1H NMR (300 MHz, DMSO- d_6): δ 1.96 (s, 3H, C3- CH_3), 3.85 (s, 3H, N- CH_3), 6.31 (d, 1H, H-6, J = 7.8 Hz), 6.80 (dd, 1H, H-7, J = 7.8 Hz, 8.0 Hz), 7.14 (d, 1H, H-8, J = 8.0 Hz), 7.40 (d, 2H, H-2"/H-6", J = 8.3 Hz), 7.45 (d, 1H, H-10, J = 2.3 Hz), 7.46 (d, 2H, H-3"/H-5", J = 8.3 Hz), 11.48 (s, 1H, N9- H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 10.1 (C3- CH_3), 39.0 (N- CH_3), 107.7 (C-10a), 114.1 (C-8), 118.4 (C-10), 122.2 (C-6), 122.9 (C-7), 126.6 (C-10b), 126.9 (C-3), 128.1(C-2"/C-6"), 129.6 (C-8b), 129.8 (C-3"/C-5"), 130.7 (C-5a), 132.1(C-4"), 137.4 (C-8a), 142.0 (C-1"), 147.4 (C-3a), 156.2 (C-5).

5-(2-Furyl)-1,3-dimethylpyrazolo[3',4' : 6,7]azepino[5,4,3-*cd*]indole (**3c**)

This compound was prepared from compound (**6c**) (0.83 g; 2.6 mmol) and phosphorous oxychloride (7 mL, 75 mmol), following the same procedure described above for **3a**. Yield of **3c** = 0.48 g (61 %), mp 203-205 °C (decomp) (ethanol). *Anal.* Calcd for $\text{C}_8\text{H}_{14}\text{N}_4\text{O}$: C, 71.81; H, 4.67; N, 18.53. Found: C, 71.29; H, 4.69; N, 18.21. IR (KBr) : ν 3428, 3141, 3095, 2987, 2920, 2874, 1501, 1423, 1320, 1151 cm^{-1} ; MS *m/z* (% rel. int.): 302 (M^+ , 100), 260(7), 246 (13), 232 (60), 217 (10), 191 (6), 164 (18), 151 (17); HRMS: Calcd for $\text{C}_8\text{H}_{14}\text{N}_4\text{O}$: 302.11674. Found: 302.11501; ^1H NMR (300 MHz, DMSO- d_6): δ 1.99 (s, 3H, C3- CH_3), 3.82 (s, 3H, N- CH_3), 6.56 (dd, 1H, H-4", J = 3.3 Hz, 2.0 Hz), 6.67 (dd, 1H, H-3", J = 3.3 Hz, 0.5 Hz), 6.84 (dd, 1H, H-6, J = 7.7 Hz, 1.1 Hz), 6.89 (dd, 1H, H-7, J = 7.7 Hz, 7.8 Hz), 7.16 (dd, 1H, H-8, J = 7.8 Hz, 1.1 Hz), 7.45 (d, 1H, H-10, J = 2.7 Hz), 7.69 (dd, 1H, H-5", J = 2.0

Hz, 0.5 Hz), 11.44 (s, 1H, N9-H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 10.0 (C3-CH₃), 39.1 (N-CH₃), 107.6 (C-10a), 110.1 (C-3''), 110.8 (C-4''), 114.3 (C-8), 118.6 (C-10), 120.8 (C-7), 123.1 (C-6), 126.2 (C-8b), 129.5 (C-10b), 129.6 (C-3), 130.1 (C-5a), 137.5 (C-8a), 142.0 (C-5''), 147.3 (C-2''), 147.6 (C-3a), 154.6 (C-5).

3-(1,3-Dimethyl-4-nitropyrazol-5-yl)-2-phenylindole (9a)

To a solution of 2-phenylindole (11.6 g; 60 mmol) in dry ether (100 mL), an ethereal solution of methylmagnesium iodide (3 M, 21 mL, 63 mmol) was added, and the mixture was stirred at rt for 30 min. An ethereal solution of ZnCl₂ (1 M, 63 mL, 63 mmol) was then added and stirred at rt for 30 min. Thereafter, a solution of 5-chloro-1,3-dimethyl-4-nitropyrazole (**8**) (3.5 g; 20 mmol) in dry benzene (20 mL) was added dropwise to the mixture, and stirring was continued at rt for 6 h. Water (100 mL) was then added to the reaction mixture, the ether layer was separated and the aqueous layer was further extracted with ether (3 x 50 mL). The combined ether portions were dried (Na₂SO₄), and the solvent was evaporated. The crude product was purified by silica gel chromatography to afford the title compound as yellow solid. Yield of **9a** = 2.7 g (41 %), mp 80-82 °C (chloroform / *n*-hexane). *Anal.* Calcd for C₁₉H₁₆N₄O₂: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.45; H, 4.82; N, 16.78. MS *m/z* (% rel. int.): 332 (M⁺, 64), 300 (4), 286 (51), 271 (38), 241 (14), 224 (12), 218 (8), 146 (14), 143 (38), 135 (29), 120 (10), 105 (100); HRMS: Calcd for C₁₉H₁₆N₄O₂: 332.12733. Found: 332.13116; ^1H NMR (300 MHz, CDCl₃): δ 2.66 (s, 3H, C3'-CH₃), 3.37 (s, 3H, N1'-CH₃), 7.18 (m, 1H, H-5), 7.28 (m, 5H, H-2''/ H-6'', H-3''/ H-5'' and H-4''), 7.36 (m, 2H, H-4 and H-6), 7.47 (d, 1H, H-7, *J* = 8.0 Hz), 8.66 (s, 1H, N1-H); ^{13}C NMR (75 MHz, CDCl₃): δ 14.5 (C3'-CH₃), 37.6 (N1'-CH₃), 99.7 (C-3), 111.5 (C-7), 119.4 (C-4), 121.4 (C-5), 123.5 (C-6), 126.7 (C-2''/ C-6''), 127.0 (C-3a), 127.8 (C-3'), 128.9 (C-4''), 129.4 (C-3''/ C-5''), 131.3 (C-1''), 135.8 (C-7a), 137.4 (C-2), 138.0 (C-5'), 146.7 (C-4').

3-(1,3-Dimethyl-4-nitropyrazol-5-yl)-2-methylindole (9b)

2-Methylindole (2.0 g; 15 mmol) in dry ether (20 mL) was stirred with methylmagnesium iodide (3 M in ether, 5 mL, 15 mmol) at rt for 20 min. ZnCl₂ (1 M in ether, 15 mL, 15 mmol) was then introduced under stirring for 30 min. After that, a solution of **8** (1.23 g; 7 mmol) in dry benzene (15 mL) was added dropwise to the reaction mixture which was stirred at rt for 6 h and worked-up as described above for **9a**. Yield of **9b** = 1.3 g (69 %), mp 165-166 °C (chloroform / *n*-hexane). *Anal.* Calcd for C₁₄H₁₄N₄O₂: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.88; H, 5.13; N, 20.56. MS *m/z* (% rel. int.): 270 (M⁺, 100), 253 (54), 239 (46), 236 (40), 182 (12), 180 (17), 155 (28), 128 (13), 120 (35), 118 (16); HRMS: Calcd for C₁₄H₁₄N₄O₂: 270.11165. Found: 270.11318; ^1H NMR (300 MHz, CDCl₃): δ 2.33 (s, 3H, C2-CH₃), 2.65 (s, 3H, C3'-CH₃), 3.66 (s, 3H, N1'-CH₃), 7.12 (m, 1H, H-5), 7.17 (m, 1H, H-6), 7.21 (m, 1H, H-4), 7.36 (dd, 1H, H-7, *J* = 7.8, 1.0 Hz), 8.45 (br s, 1H, N1-H); ^{13}C NMR (75 MHz, CDCl₃): δ 13.0 (C2-

CH₃), 14.5 (C3'-CH₃), 37.6 (N1'-CH₃), 99.3 (C-3), 111.1 (C-7), 118.3 (C-6), 121.0 (C-5), 122.2 (C-4), 127.0 (C-3a), 131.7 (C-3'), 135.5(C-7a), 137.2 (C-5'), 137.7 (C-2), 146.7 (C-4').

3-(4-Amino-1,3-dimethylpyrazol-5-yl)-2-phenylindole (10a)

To a solution of **9a** (3.3 g; 10 mmol) in conc. HCl (35 mL) and 95 % ethanol (10 mL) was added tin granules (6 g), and the mixture was refluxed for 2 h. The resulting solution was cooled, basified with 40 % aqueous NaOH solution and extracted with CH₂Cl₂ (3 x 100 mL). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and the solvent was distilled off to give a light white solid. Yield of **10a** = 2.4 g (80 %), mp 150-151 °C (chloroform / *n*-hexane). *Anal.* Calcd for C₁₉H₁₈N₄: C, 75.47; H, 6.00; N, 18.53. Found: C, 75.24; H, 5.92; N, 18.28. MS *m/z* (% rel. int.): 302 (M⁺, 100), 260 (14), 246 (18), 233 (33), 219 (21), 204 (13), 193 (8), 151 (9), 116 (7), 102 (6); HRMS: Calcd for C₁₉H₁₈N₄: 302.15315. Found: 302.15658; ¹H NMR (300 MHz, DMSO-d₆): δ 2.11 (s, 3H, C3'-CH₃), 2.50 (br s, 2H, NH₂), 3.37 (s, 3H, N1'-CH₃), 7.05 (dd, 1H, H-5, *J* = 7.2 Hz, 7.1 Hz), 7.19 (m, 2H, H-4 and H-6), 7.34 (d, 1H, H-7, *J* = 7.3 Hz), 7.41 (dd, 2H, H-3"/ H-5", *J* = 7.1 Hz, 7.7 Hz), 7.50 (m, 3H, H-2"/ H-6" and H-4"), 11.82 (br s, 1H, N1-H); ¹³C NMR (75 MHz, DMSO-d₆): δ 11.0 (C3'-CH₃), 36.0 (N1'-CH₃), 100.5 (C-3), 111.5 (C-7), 118.9 (C-4), 119.7 (C-5), 122.1 (C-6), 122.9 (C-5'), 126.2 (C-5'), 126.4 (C-2"/ C-6"), 126.7 (C-3'), 127.6 (C-4"), 128.3 (C-3a), 128.7 (C-3"/ C-5"), 132.0 (C-1"), 135.5 (C-7a), 135.7 (C-2), 136.1 (C-4').

3-(4-Amino-1,3-dimethylpyrazol-5-yl)-2-methylindole (10b)

To a solution of **9b** (1.4 g; 5.2 mmol) in conc. HCl (35 mL) and 95 % ethanol (10 mL) was added tin granules (5 g). The mixture was refluxed for 2 h and worked up as described above for **9a** to give the title compound as pale white solid. Yield of **10b** = 1.1 g (88 %), mp 76-77 °C (dichloromethane / petroleum ether). *Anal.* Calcd for C₁₄H₁₆N₄: C, 69.97; H, 6.71; N, 23.31. Found: C, 69.64; H, 6.58; N, 23.12. MS *m/z* (% rel. int.): 240 (M⁺, 100), 225 (4), 198 (28), 172 (7), 171 (15), 157 (40), 149 (14), 130 (9), 120 (7), 112 (3); HRMS: Calcd for C₁₄H₁₆N₄: 240.13748. Found: 240.13866; ¹H NMR (300 MHz, DMSO-d₆): δ 2.08 (s, 3H, C3'-CH₃), 2.28 (s, 3H, C2-CH₃), 3.33 (s, 2H, NH₂), 3.42 (s, 3H, N-CH₃), 6.97 (m, 1H, H-5), 7.02 (m, 1H, H-4), 7.10 (m, 1H, H-6), 7.34 (d, 1H, H-7, *J* = 7.9 Hz), 11.30 (br s, 1H, N1-H); ¹³C NMR (75 MHz, DMSO-d₆): δ 11.0 (C3'-CH₃), 12.2 (C2-CH₃), 36.4 (N-CH₃), 100.6 (C-3), 110.9 (C-7), 118.0 (C-6), 119.2 (C-5), 120.5 (C-4), 123.4(C-5'), 126.2 (C-3'), 127.6 (C-3a), 135.1 (C-1), 135.6 (C-4'), 135.7 (C-7a).

3-[4-(4-Chlorobenzoylamino)-1,3-dimethylpyrazol-5-yl]-2-phenylindole (11a)

This compound was prepared from **10a** (0.9 g; 3 mmol) and *p*-chlorobenzoyl chloride (0.56 g; 3.2 mmol), following the same procedure described above for **6a**. The solid product was recrystallized from benzene / petroleum ether. Yield of **11a** = 1.1 g (84 %), mp 180-181 °C. *Anal.* Calcd for C₂₆H₂₁N₄OCl:

C, 70.82; H, 4.80; N, 12.711; Cl, 8.04. Found: C, 70.66; H, 4.62; N, 12.58; Cl, 7.90. MS m/z (% rel. int.): 440 (M^+ , 100), 301 (67), 285 (8), 260 (45), 233 (28), 218 (39), 189 (6), 167 (4), 149 (34), 139 (26), 111 (20); HRMS: Calcd for $C_{26}H_{21}N_4OCl$: 440.140364. Found: 440.142966; 1H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H, C3- CH_3), 3.51 (s, 3H, N- CH_3), 6.94 (dd, 1H, H-5, $J = 7.4$ Hz, 7.3 Hz), 7.13 (dd, 1H, H-6, $J = 7.4$ Hz, 7.3 Hz), 7.34 (dd, 1H, H-4, $J = 7.3$ Hz, 1.6 Hz), 7.40 (m, 5H, H-2"/H-6", H-3"/H-5", H-4"), 7.44 (d, 2H, H-3"/H-5", $J = 8.5$ Hz), 7.57 (d, 1H, H-7, $J = 7.3$ Hz), 7.78 (d, 1H, H-2"/H-6", $J = 8.5$ Hz), 9.33 (s, 1H, NHCO), 11.75 (s, 1H, N1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4 (C3'- CH_3), 37.2 (N- CH_3), 100.6 (C-3), 111.6 (C-7), 115.9 (C-4'), 119.4 (C-4), 121.1 (C-5), 123.2 (C-6), 127.0 (C-3"/C-5"), 128.0 (C-3a), 128.5 (C-2"/C-6"), 128.6 (C-4"), 128.7 (C-3"/C-5"), 129.4 (C-2"/C-6"), 131.7 (C-1"), 132.5 (C-1"), 133.1 (C-5'), 136.1 (C-4"), 136.7 (C-7a), 137.7 (C-2), 144.7 (C-3'), 165.1 (NHCO).

3-[4-(4-Chlorobenzoylamino)-1,3-dimethylpyrazol-5-yl]-2-methylindole (11b)

This compound was prepared from **10b** (0.72 g; 3 mmol) and *p*-chlorobenzoyl chloride (0.56 g; 3.2 mmol), following the same procedure and experimental conditions described above for **6a**. Yield of **11b** = 0.79 g (70 %), mp 281-282 °C (decomp) (benzene / petroleum ether). *Anal.* Calcd for $C_{21}H_{19}N_4OCl$: C, 66.58; H, 5.05; N, 14.79; Cl, 9.36. Found: C, 66.25; H, 5.06; N, 14.54; Cl, 9.18. MS m/z (% rel. int.): 378 (M^+ , 58), 239 (100), 224 (24), 222 (11), 198 (5), 171 (12), 156 (20), 139 (23), 111 (13); HRMS: Calcd for $C_{21}H_{19}N_4OCl$: 378.12474. Found: 378.12604; 1H NMR (400 MHz, DMSO- d_6): δ 2.09 (s, 3H, C2- CH_3), 2.22 (s, 3H, C3'- CH_3), 3.57 (s, 3H, N1'- CH_3), 6.95 (dd, 1H, H-5, $J = 7.3$ Hz, 7.7 Hz), 7.04 (dd, 1H, H-6, $J = 7.3$ Hz, 7.7 Hz), 7.23 (d, 1H, H-4, $J = 7.7$ Hz), 7.32 (d, 1H, H-7, $J = 7.7$ Hz), 7.48 (d, 2H, H-3"/H-5", $J = 8.3$ Hz), 7.84 (d, 2H, H-2"/H-6", $J = 8.3$ Hz), 9.49 (s, 1H, NHCO), 11.36 (s, 1H, N1-H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 11.7 (C2- CH_3), 12.1 (C3'- CH_3), 36.9 (N1'- CH_3), 99.9 (C-3), 110.9 (C-7), 116.5 (C-5'), 118.2 (C-4), 119.3 (C-5), 120.8 (C-6), 127.4 (C-3a), 128.3 (C-3"/C-5"), 129.4 (C-2"/C-6"), 133.2 (C-4'), 133.3 (C-2), 135.5 (C-1"), 135.6 (C-7a), 136.1 (C-4"), 143.7 (C-3'), 165.1 (NHCO).

5-(4-Chlorophenyl)-1,3-dimethyl-10-phenylpyrazolo[3',4': 6,7]azepino[5,4,3-*cd*]indole (4a)

To a stirred solution of **11a** (0.7 g; 1.6 mmol) in acetonitrile (30 mL) was added phosphorous oxychloride (7 mL, 75 mmol). The resulting mixture was refluxed for 24 h, and worked-up as described above for **3a**. The crude orange product was purified on silica gel TLC plates, eluting with CH_2Cl_2 : MeOH (98 : 2, v/v) to afford 0.20 g (29 %) of **4a**, mp 164-165 °C (ethanol). *Anal.* Calcd for $C_{26}H_{19}N_4Cl$: C, 73.84; H, 4.53; N, 13.25; Cl, 8.38. Found: C, 73.56; H, 4.41; N, 13.08; Cl, 8.15. MS m/z (% rel. int.): 422 (M^+ , 100), 380 (21), 366 (5), 330 (12), 303 (5), 279 (3), 211 (14), 193 (38), 172 (15), 152 (16), 149 (65); HRMS: Calcd for $C_{26}H_{19}N_4Cl$: 422.129804. Found: 422.130797; 1H NMR (400 MHz, DMSO- d_6): δ 2.02 (s, 3H, C3- CH_3), 2.83 (s, 3H, N- CH_3), 6.43 (d, 1H, H-6, $J = 7.5$ Hz), 6.90 (dd, 1H, H-7, $J = 7.5$ Hz, 8.3 Hz), 7.16 (d, 1H, H-8, $J = 7.8$ Hz), 7.40 (d, 2H, H-3"/H-5", $J = 7.8$ Hz), 7.50

(m, 5H, H-2"/H-6", H-3"/H-5", H-4"), 7.60 (d, 2H, H-2"/H-6", $J = 7.8$ Hz), 11.74 (s, 1H, N9-H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 10.4 (C3-CH₃), 39.4 (N-CH₃), 104.1 (C-10a), 113.5 (C-8), 122.9 (C-6), 123.2 (C-7), 127.4 (C-3), 128.1 (C-2"/C-6"), 128.4 (C-2"/C-6"), 128.8 (C-4"), 129.1 (C-3"/C-5"), 129.7 (C-5a), 130.2 (C-3"/C-5"), 131.8 (C-10b), 132.6 (C-4"), 132.7 (C-10), 133.4 (C-1"), 134.8 (C-8b), 137.1 (C-8a), 142.0 (C-1"), 147.4 (C-3a), 159.3 (C-5).

5-(4-Chlorophenyl)-1,3,10-trimethylpyrazolo[3',4':6,7]azepino[5,4,3-cd] indole (4b)

This compound was prepared from **11b** (0.80 g; 2.1 mmol) and phosphorous oxychloride (8 mL, 85.5 mmol). The resulting mixture, dissolved in acetonitrile (45 mL), was refluxed for 48 h and worked-up following the same procedure described above for **3a**. Yield of **4b** = 0.17g (23 %), mp 264-265 °C (ethanol). *Anal.* Calcd for C₂₁H₁₇N₄Cl: C, 69.90; H, 4.75; N, 15.53; Cl, 9.82. Found: C, 69.62; H, 4.63; N, 15.44; Cl, 9.70. MS *m/z* (% rel. int.): 360 (M⁺, 100), 318 (28), 304 (11), 277 (15), 254 (12), 180 (13), 162 (42), 155 (16), 141 (18), 121 (14); HRMS: Calcd for C₂₁H₁₇N₄Cl: 360.114154. Found: 360.113798; ^1H NMR (400 MHz, DMSO- d_6): δ 1.95 (s, 3H, C3-CH₃), 2.49 (s, 3H, C10-CH₃), 3.69 (s, 3H, N-CH₃), 6.26 (d, 1H, H-6, $J = 7.7$ Hz), 6.72 (dd, 1H, H-7, $J = 7.7$ Hz, 7.9 Hz), 6.99 (d, 1H, H-8, $J = 7.9$ Hz), 7.30 (d, 2H, H-2"/H-6", $J = 8.5$ Hz), 7.41 (d, 2H, H-3"/H-5", $J = 8.5$ Hz), 11.29 (s, 1H, N9-H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 10.8 (C3-CH₃), 16.4 (C10-CH₃), 39.1 (N-CH₃), 105.2 (C-10a), 113.3 (C-8), 122.5 (C-6), 122.9 (C-7), 127.3 (C-3), 128.6 (C-2"/C-6"), 129.0 (C-10b), 129.8 (C-8b), 130.6 (C-3"/C-5"), 132.8 (C-5a), 134.3 (C-4"), 136.7 (C-10), 137.5 (C-8a), 142.6 (C-1"), 148.0 (C-3a), 158.9 (C-5).

Screening of the Receptor Binding Affinity

The screening of receptor binding properties of the test compounds was determined as described in the literature.¹² In brief, homogenates of bovine striatal membranes were incubated with the D₁ selective radioligand [³H]SCH 23390 (0.3 nM) and the test compounds with final concentrations of 10 μM , 100 nM and 1 nM in triplicates. In the same manner, preparations of membranes from CHO cells stably expressing the human D_{2long}, D_{2short}, D₃ and D₄ receptors were incubated with [³H]spiperone (0.1 nM) and test compounds. After 60 min at 37 °C the mixtures were harvested on GF/C filter, which were counted in a Microbeta Trilux scintillation counter. Unspecific binding to the D₁ receptor was measured in the presence of 10 μM butaclamol and to the D₂, D₃ and D₄ receptors with 10 μM haloperidol. Each value was normalized and the mean values (+/- S.E.M.) calculated with PRISM.

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(*) Corresponding author, e-mail: mustelab@ju.edu.jo

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