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

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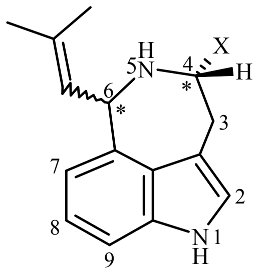
Abstract– A synthesis of some substituted pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]-indoles is described and their affinities to dopamine receptors were evaluated. The tested compounds (**3a-d** and **4a,b**) showed micromolar affinity to the bovine D_1 receptor subtype and the human D_2, D_3 and D_4 receptor isoforms.

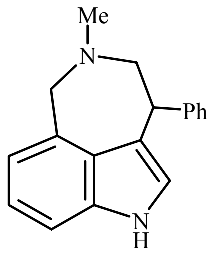
INTRODUCTION

The claviciptic 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 derivatives [6-8] 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 D_1- and D_2- like receptor ligands, some 3-phenyltetrahydroazepinoindoles were recently prepared, exemplified by **2** that showed micromolar affinity to the bovine D_1 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.



(*4S, 6R*)-**1a :** X = CO_2H
(*4S, 6S*)-**1b :** X = CO_2H
(±)-**1c :** X = H



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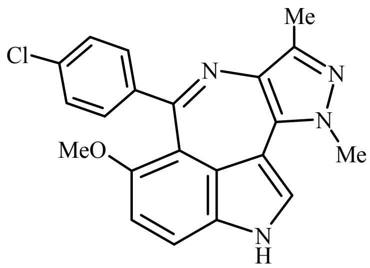


3d

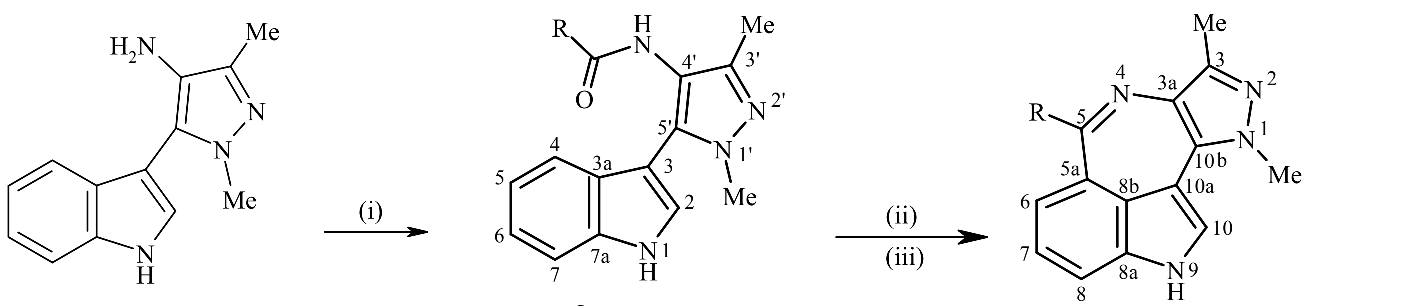
Accordingly, the present work aims at synthesis of a selected set of new substituted pyrazolo-[3',4':6,7]azepino[5,4,3-*cd*]indoles (**3a-c** / Scheme I), (**4a,b** / Scheme II), and evaluation of their binding properties to dopamine D_1, D_2 , D_3 and D_4 receptors.

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 assignements are supported by elemental analyses, IR, MS, ^{1}H- and ^{13}C NMR spectral data listed in EXPERIMENTAL . Carbon-13 assignements are based on DEPT and 2D (COSY, HMQC, HMBC) experiments . These reveal long range H-C correlations, in particular between

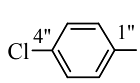
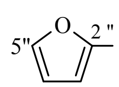
Scheme I



5 **6a-c** **3a-c**

(i) RCOCl, C_6H_6, NEt_3, Δ
(i) $POCl_3$, MeCN, Δ
(iii) aq. NaOH (5 %)

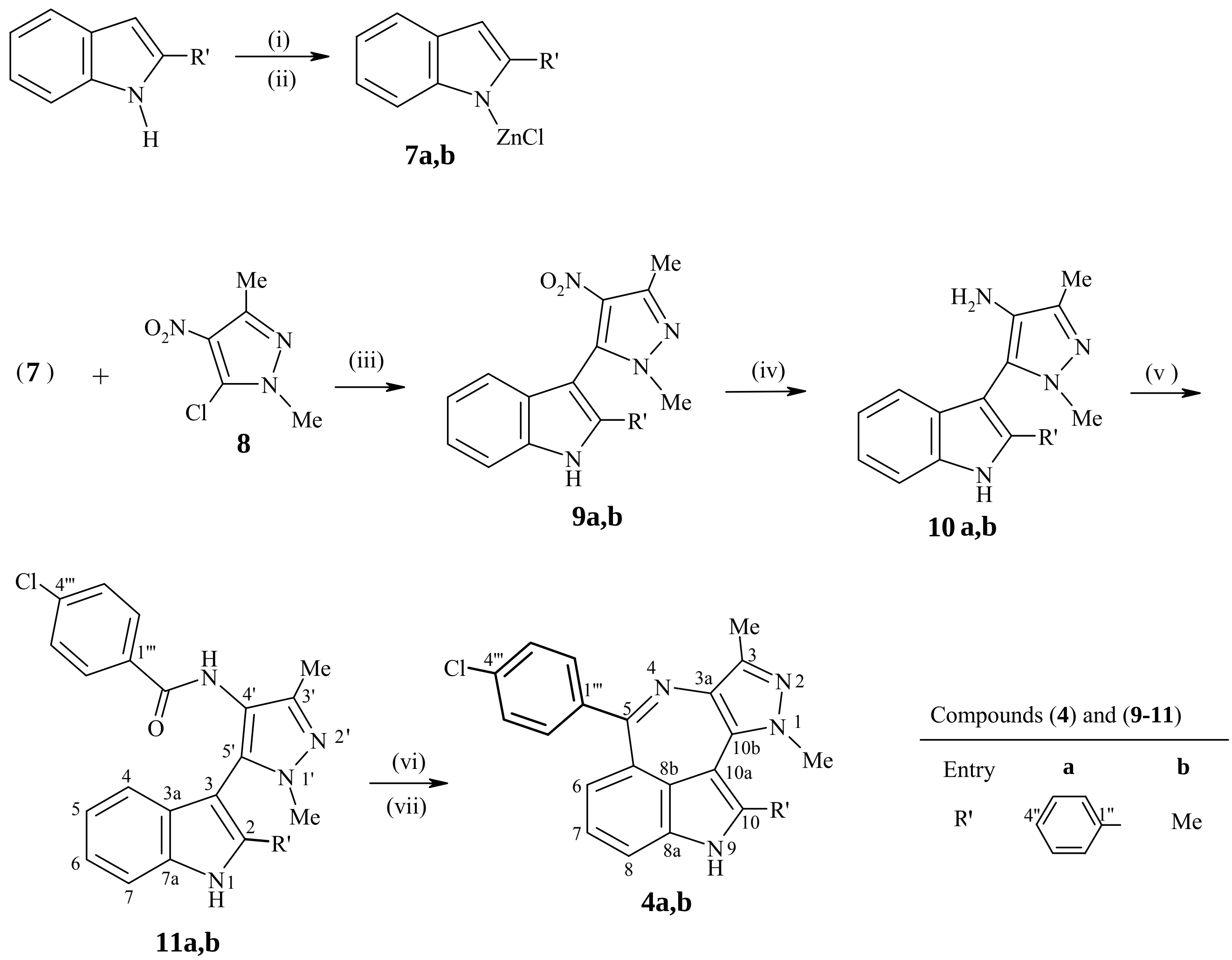
Compounds (**3**) and (**6**)

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 ($J_{CH\text{-}NH}$ ≈ 2.5 Hz) that collapses to a singlet upon treatment with D_2O. 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 likewize 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



(i) MeMgI (3.0 *M* in Et_2O)
(ii) $ZnCl_2$ (1.0 *M* in Et_2O)
(iii) Et_2O / 20 °C
(iv) Sn + conc. HCl
(v) *p*-(Cl)C_6H_4COCl , C_6H_6 , Δ
(vi) $POCl_3$, MeCN, Δ
(vii) aq. NaOH (5 %)

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)lindole 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 camalexines,[10] and with 2-chloropyridines to form the respective 3-(2-pyridyl)indoles.[11]

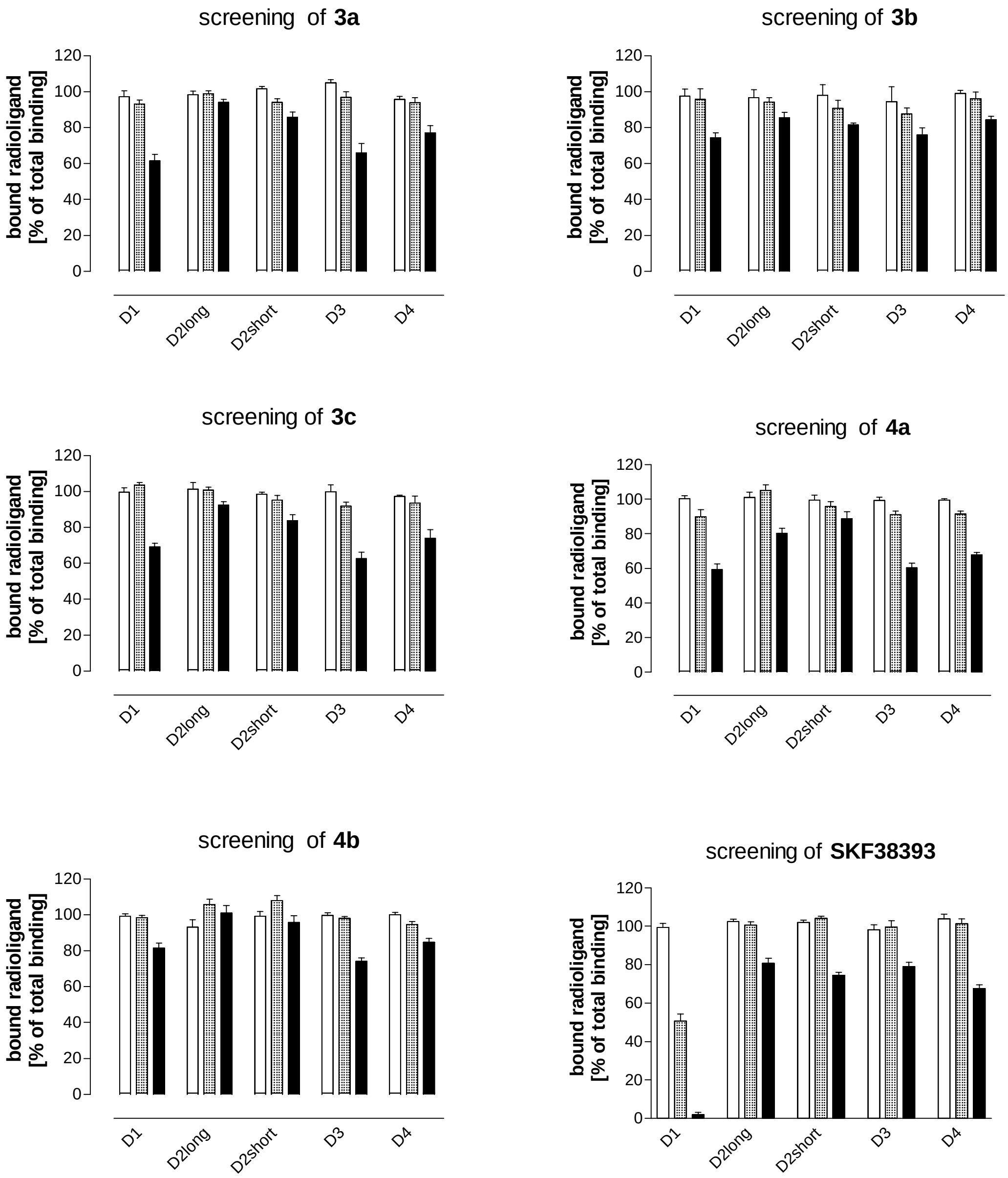


Figure 1. Screening of the test compounds (**3a-c** and **4a,b)** at the dopamine receptor subtypes in comparison with the D_1 selective reference compound SKF 38393 (rate of displacement of the radioligand (in %) caused by the test compounds at three different concentrations: full bars = 10 *µM*; pointed 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 D_1 receptor [12] besides the human $D_{2\ long}$, $D_{2\ short}$,[13] D_3 [14] and D_4 [15] isoforms and three different concentrations of the tested compounds (10 *μM*, 100 *nM* and 1 *nM*), measuring the displacement of the radioligands [^{3}H]SCH23390 (D_1) and [^{3}H]spiperone (D_2-D_4).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 D_1 selective reference compound SKF 38393, which is characterized by a Ki 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 ^oC. 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 ^oC (decomp). *Anal.* Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.21; H, 6.07; N, 20.74. IR (KBr) : *v* 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 $C_{15}H_{16}N_4O$: 268.13241. Found: 268.13407); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.85 (s, 3H, CO-C*H*$_3$), 2.09 (s, 3H, C3'-C*H*$_3$), 3.66 (s, 3H, N-C*H*$_3$), 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, N*H*CO); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.5 (C3'-*C*H$_3$), 22.5 (CO*C*H$_3$), 37.0 (N-*C*H$_3$), 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 (NHC*O*).

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 ^{o}C (ethanol). *Anal.* Calcd for $C_{20}H_{17}N_4OCl$: 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) : *v* 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 $C_{20}H_{17}N_4OCl$: 364.10909. Found: 364.10998; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.08 (s, 3H, C3'-CH_3) , 3.71(s, 3H, N-CH_3), 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, N*H*CO); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 11.4 (C3'-*C*H_3), 37.2 (N-*C*H_3), 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 (NH*C*O).

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 ^{o}C (decomp) (ethanol). *Anal.* Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found : C, 67.60; H, 4.95; N, 17.23. IR (KBr) : *v* 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 $C_{18}H_{16}N_4O_2$: 320.12733. Found: 320.12950; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.06 (s, 3H, C3'-CH_3), 3.69 (s, 3H, N-CH_3), 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, N*H*CO); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 11.4 (C3'-*C*H_3), 37.2 (N-*C*H_3), 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 (NH*C*O).

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 $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found : C, 71.84; H, 5.61; N, 22.16. IR (KBr) : *v* 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 $C_{15}H_{14}N_4$: 250.12183. Found: 250.12066; ^{1}H 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-*C*H_3) , 27.6 (C5-*C*H_3) , 39.1 (N-*C*H_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 $C_{20}H_{15}N_4Cl$: 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) : *v* 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 $C_{20}H_{15}N_4Cl$: 346.098504. Found: 346.097129; ^{1}H 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-*C*H_3), 39.0 (N-*C*H_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 $C_8H_{14}N_4O$: C, 71.81; H, 4.67; N, 18.53. Found: C, 71.29; H, 4.69; N, 18.21 . IR (KBr) : *v* 3428, 3141, 3095, 2987, 2920, 2874, 1501, 1423, 1320, 1151cm^{-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 $C_8H_{14}N_4O$: 302.11674. Found: 302.11501; ^{1}H 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-*C*H$_3$) , 39.1 (N-*C*H$_3$) , 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 $ZnCl_2$ (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 (Na_2SO_4), 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 ^{o}C (chloroform / *n*-hexane). *Anal.* Calcd for $C_{19}H_{16}N_4O_2$: 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 $C_{19}H_{16}N_4O_2$: 332.12733. Found: 332.13116; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, C3'-C*H*$_3$), 3.37 (s, 3H, N1'-C*H*$_3$) , 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, $CDCl_3$): δ 14.5 (C3'-*C*H$_3$) , 37.6 (N1'-*C*H$_3$) , 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. $ZnCl_2$ (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 ^{o}C (chloroform / *n*-hexane). *Anal.* Calcd for $C_{14}H_{14}N_4O_2$: 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 $C_{14}H_{14}N_4O_2$: 270.11165. Found: 270.11318; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, C2-C*H*$_3$), 2.65 (s, 3H, C3'-C*H*$_3$), 3.66 (s, 3H, N1'-C*H*$_3$), 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, $CDCl_3$): δ 13.0 (C2-

CH_3), 14.5 (C3'-*C*H_3) , 37.6 (N1'-*C*H_3), 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-dimethypyrazol-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 CH_2Cl_2 (3 x 100 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and the solvent was distilled off to give a light white solid. Yield of **10a** = 2.4 g (80 %), mp 150-151 ^oC (chloroform / *n*-hexane). *Anal*. Calcd for $C_{19}H_{18}N_4$: 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 $C_{19}H_{18}N_4$: 302.15315. Found: 302.15658; ^1H NMR (300 MHz, DMSO-d_6): δ 2.11 (s, 3H, C3'-C*H_3*), 2.50 (br s, 2H, N*H_2*), 3.37 (s, 3H, N1'-C*H_3*), 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*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.0 (C3'-*C*H_3), 36.0 (N1'-*C*H_3) , 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-dimethypyrazol-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 ^oC (dichloromethane / petroleum ether). *Anal*. Calcd for $C_{14}H_{16}N_4$: 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 $C_{14}H_{16}N_4$: 240.13748. Found: 240.13866; ^1H NMR (300 MHz, DMSO-d_6): δ 2.08 (s, 3H, C3'-C*H_3*), 2.28 (s, 3H, C2-C*H_3*), 3.33 (s, 2H, N*H_2*), 3.42 (s, 3H, N-C*H_3*) , 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*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.0 (C3'-*C*H_3), 12.2 (C2-*C*H_3), 36.4 (N-*C*H_3) , 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-dimethypyrazol-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 ^oC. *Anal*. Calcd for $C_{26}H_{21}N_4OCl$:

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; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H, C3-C*H*$_3$) , 3.51 (s, 3H, N-C*H*$_3$), 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, N*H*CO), 11.75 (s , 1H, N1-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4 (C3'-*C*H$_3$), 37.2 (N-*C*H$_3$), 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(NH*C*O).

3-[4-(4-Chlorobenzoylamino)-1,3-dimethypyrazol-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; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 2.09 (s, 3H, C2-C*H*$_3$) , 2.22 (s, 3H, C3'-C*H*$_3$) 3.57 (s, 3H, N1'-C*H*$_3$), 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, N*H*CO), 11.36 (s, 1H, N1-*H*); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 11.7 (C2-*C*H$_3$), 12.1 (C3'-*C*H$_3$), 36.9 (N1'-*C*H$_3$) , 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 (NH*C*O).

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; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 2.02 (s, 3H, C3-C*H*$_3$), 2.83 (s, 3H, N-C*H*$_3$), 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-CH_3), 39.4 (N-CH_3) , 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 ^{o}C (ethanol). *Anal*. Calcd for $C_{21}H_{17}N_4Cl$: 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 $C_{21}H_{17}N_4Cl$: 360.114154. Found: 360.113798; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.95 (s, 3H, C3-CH_3), 2.49 (s, 3H, C10-CH_3), 3.69 (s, 3H, N-CH_3) , 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-CH_3), 16.4 (C10-CH_3), 39.1 (N-CH_3) , 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 D_1 selective radioligand [^{3}H]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}, D_3 and D_4 receptors were incubated with [^{3}H]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 D_1 receptor was measured in the presence of 10 *μM* butaclamol and to the D_2, D_3 and D_4 receptors with 10 *μM* haloperidol. Each value was normalized and the mean values (+/- S.E.M.) calculated with PRISM.

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