Kayed A. Abu Safieh [a], Mustafa M. El-Abadelah* [a], Salim S. Sabri† [b],
Musa H. Abu Zarga [a], Wolfgang Voelter [c] and Cäcilia M.- Mössmer [d]

[a] Chemistry Department, Faculty of Science, University of Jordan, Amman, Jordan,
[b] Faculty of Arts and Sciences, University of Sharjah, Sharjah, P. O. Box 27272, UAE,
[c] Abteilung für Physikalische Biochemie, Physiologisch-chemisches Institut der Universität Tübingen, Hoppe-Seyler Straße 4, D-72076 Tübingen, Germany,
[d] Institut für Anorganische Chemie auf der Morgenstelle 18, Universität Tübingen, D-72076 Tübingen, Germany
Received December 6, 2000

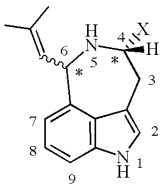
The synthesis of some new pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]indoles (**10a-c**) was achieved *via* regioselective cyclization of the respective 3-(4-acylaminopyrazol-5-yl)indoles (**9a-c**) under Bischler-Napieralski reaction conditions. The latter compounds were obtained by acylation of the corresponding 3-(4-aminopyrazol-5-yl)indoles (**8a,b**) which, in turn, were prepared by reduction of the 3-(4-nitropyrazol-5-yl)indoles precursors (**7a,b**). The latter synthons were accessible from the reaction of indolylzinc chlorides (**5a,b**) with 5-chloro-1,3-dimethyl-4-nitropyrazole. Ms and nmr spectral data of **10a-c** are in agreement with the assigned azepino-indole structure as determined for **10a** by X-ray crystal measurements which demonstrate that the azepine ring is almost completely planar with the indole and pyrazole rings.

J. Heterocyclic Chem., **38**, 623 (2001).

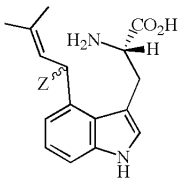
Introduction.

The tetrahydro-azepino[5,4,3-*cd*]indole ring system constitutes the skeleton of some naturally occurring erogt alkaloids exemplified by the claviciptic acids (**1a**,**b**) [1-3] and aurantioclavine (**1c**) [4,5]. These compounds are considered as derailment products in the normal ergot biosynthesis, following the isoprenylation step of (*S*)-tryptophan in forming **2a.** The latter common precursor **2a** [6] is then converted, *via* enzymatic hydroxylation, into **2b** which is subsequently cyclized by internal displacement to give **1a,b** [2,3,7]. Efficient biomimetic pathways toward synthesis of **1a,b** [8] and **1c** [5,9] were reported; other synthetic routes for **1a,b** [3,7,10] and related derivatives [11-14] were also documented. Some of these derivatives were described as selective dopamine D-1 receptor ligands [12], useful for the treatment of circulatory and digestive tract disorders [13], as psychotropics [13], diuretics and smooth muscle relaxants [14].

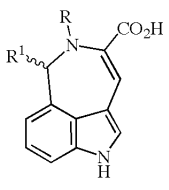
On the other hand, the 5,6-dihydroazepino[5,4,3-*cd*]indoles were less frequently encountered. Types **3a-c** were prepared from α,β-dehydrotryptophan ester and the corresponding alkanal under Pictet-Spengler reaction conditions [15], and **3d** was likewise obtained from its relevant α,β-dehydrotryptophan derivative [16]. These examples demonstrate regioselective cyclization at the 4-position of the indole nucleus, instead of the usual 2-position.



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



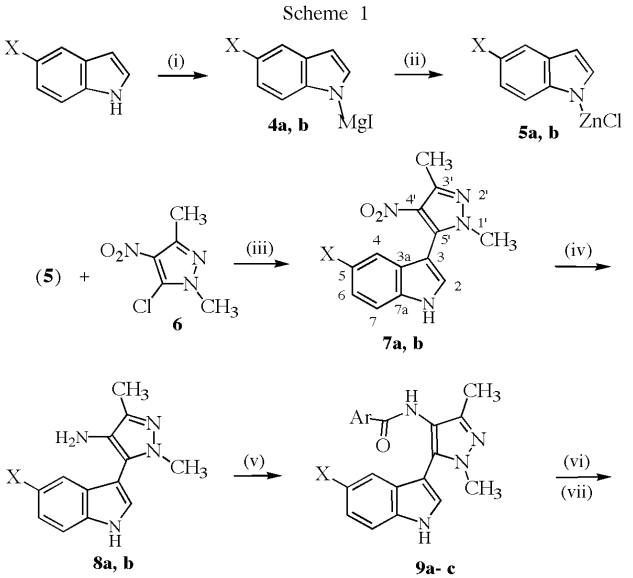
2a (Z = H)
2b (Z = OH)

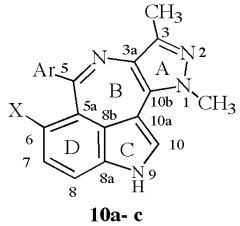


3a (R = H; R' = Me)
3b (R = H; R' = *i*-Pr)
3c (R = H; R' = *i*-Bu)
3d (R = PhCO; R' = H)

To the best of our knowledge, compounds with a fully unsaturated azepino[5,4,3-*cd*]indole nucleus, or encompassing an heteroarene[3,4]-fused to the azepine moiety are hitherto unreported. Accordingly, the present work aims at describing the synthesis and properties of some pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]indoles (**10a-c**) shown in Scheme 1.

Scheme 1





10a- c

i) MeMgI (3M in Et_2O)
ii) $ZnCl_2$ (1M in Et_2O)
iii) Et_2O / rt
iv) Sn +conc. HCl
v) ArCOCl, C_6H_6, NEt_3, Δ
vi) $POCl_3$, MeCN, Δ
vii) aq. NaOH (5%)

Compounds **4**, **5**, **7** and **8** (**a**: X=H; **b**: X=OCH_3)
Compounds **9** and **10**

Entry	**a**	**b**	**c**
X	H	OCH_3	H
Ar	4" 1"	Cl 4" 1"	5" S 2"

Results and Discussion.

Chemistry.

Indolylzinc chlorides (**5a,b**), generated *in situ* from **4a,b** and $ZnCl_2$, act as C-3 carbanions in their reaction with 5-chloro-1,3-dimethyl-4-nitropyrazole (**6**) and thus lead to the formation of the corresponding 3-(4-nitropyrazol-5-yl)indoles (**7a,b**) (Scheme 1). Examples of related nucleophilic heteroaromatic substitutions include the reaction of indolyl Grignard reagents (**4a,b**) with 2-bromothiazole in preparing the naturally occurring 3-(2-thiazolyl)indoles (called camalexines) [17], and with 2-chloropyridines to form the respective 3-(2-pyridyl)indoles [18]. The chemistry and applications of indolyl Grignard reagents [19], indolylzinc chlorides [20] and indolylmetal salts [21] were reviewed and revived. Chemical reduction of the 4'-nitro group in **7a,b**, using tin and HCl in the conventional manner, produced the respective 3-(4-aminopyrazol-5-yl)indoles (**8a,b**) which, in turn, were acylated with the appropriate acyl chlorides to afford the corresponding 3-(4-acylaminopyrazol-5-yl)indoles (**9a-c**). Subsequent treatment of the latter carboxamides with phosphorous oxychloride in refluxing acetonitrile furnished the target pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]indoles (**10a-c**). Apparently regioselective intramolecular cyclization of **10a-c**, under Bischler-Napieralski reaction conditions, took place at C-4 of the indole nucleus instead of the usual C-2 position. Related regioselective cyclizations were reported for the reaction of dehydrotryptophan with alkanals, under Pictet-Spengler conditions, whereby dihydroazepino[5,4,3-*cd*]-indoles (**3a-d**) were the main products [15,16].

Spectral Data.

The spectral (ms, nmr) and microanalytical data of compounds (**6, 8-10**) are in agreement with the assigned structures, and are given in the experimental section. Thus, high resolution mass spectral measurements (hrms) for $M^{+\cdot}$ conform with the respective calculated values as suggested by their molecular formulas. Assignments of the ^1H nmr signals are straightforward, and carbon-13 assignments are based on DEPT, HMQC and HMBC experiments. In each of compounds (**6,8,9**), the H-2 proton of the indole nucleus is coupled to the vicinal N-H and appears as a doublet (δ = 7.22-7.56; J = 2.5-2.8 Hz) that collapses to a singlet upon addition of D_2O. The persistent occurrence of this doublet, collapsing to a singlet, in the ^1H nmr spectra of the cyclized products (H-10 in **10a-c**: δ = 7.44; J = 2.4-2.7 Hz) provides conclusive evidence that intracyclization did not take place at the indole C-2 position. Moreover, perspicuous long range correlation between H-6 and the azepine-imino C-5 in HMBC experiments for **10a** and **10c** constitutes a diagnostic criterion that annulation of **9a-c** occurred regioselectively at C-4 of the indole nucleus. These and relevant spectral features are in full agreement with the azepino-indole structure as determined for **10a** by X-ray crystal structure measurements.

X-Ray Crystal Structure Determination of **10a**.

An X-ray crystal structure of **10a** has been determined. The results of crystallographic data are shown in Tables 1-3. The molecular structure of **10a**, based on crystallographic data, is displayed in Figure 1. These data confirm the proposed azepino[5,4,3-*cd*]indole structure in the Bischler-Napieralski cyclization step of the respective carboxamide precursors (**9a-c**). Calculations relating to the plane of the azepine ring (B) show that all atoms comprising that ring lie in the same plane. Hence, the azepine ring is completely planar and is also co-planar with the indole and pyrazole rings A, C and D.

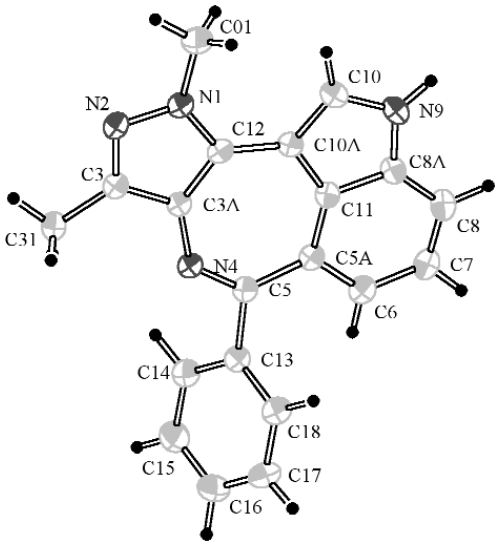


Figure 1. ORTEP Plot of the molecular structure of **10a**.

Collection of X-Ray Diffraction Data and the Structure Analysis.

Orange needle-like crystals were grown by allowing a solution of **10a** in 95% ethanol to evaporate slowly at room temperature over 2-3 days. The structure was solved by direct method using the program SHELXS-86 [22].

All non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedure based on F^2 using all unique data with SHELXL-97 [23].

The hydrogen atoms have been found in the difference Fourier map and were refined isotropically. This resulted in *R* values R_1/wR_2= 0.0519/0.1338 for all data and 0.0413/0.1255 for the observed data and 282 parameters. Further information of the crystal structure determination can be ordered from Cambridge Crystallographic Data Center under the depository number CCDC 153321.

Evaluation of the dopamine receptor binding affinity for **10a-c** and relevant analogs is underway, and the results will be communicated in the near future.

Table 1

Summary of the Crystal Data and Structure Refinement Parameters for **10a**

Molecular formula	$C_{20}H_{16}N_4$
Formula weight	312.37
Temperature (K)	213(2)
Crystal system	Monoclinic
Space group	P21/c
Diffractometer	ENRAF-NONIUS CAD 4
Wavelength/ Radiation	1.5418 Å / Cu K_α
Unit cell dimensions	
a (Å)	4.04991(12)
b (Å)	25.5917(8)
c (Å)	14.4012(10)
α(°)	90
β(°)	94.118(4)
γ(°)	90
Volume (Å ^{3})	1488.74(12)
Z	4
Density (calculated) (mg/m^3)	1.394
Absorption coefficient (mm^{-1})	0.672
F(000)	656
Crystal description	Orange needles
Crystal size (mm)	0.4 x 0.1 x 0.1
θ range (Lattice) (°)	12.15-23.60
θ range for data collection (°)	6.04-64.98
Index ranges	$-1 \leq h \leq 4$; $0 \leq k \leq 30$; $-16 \leq l \leq 16$
Reflections collected	3499
Independent reflections	2354{R_{int}= 0.0416}
Reflections observed	1975
Criterion for observation	> 2 σ (I)
Decay	2.5%
Molecular Graphics	PLATON
Refinement method	Full-matrix least- squares on F^2
Weighting scheme	Calc $w=1/[\sigma^2(F_0)^2 + (0.1000P)^2 + 0.0000P]$ where $P = [(F_0)^2 + 2(F_c)^2]/3$
Data/ restraints/parameters	2354/0/282
Goodness-of-fit on F^2	1.061
Extinction coefficient	0.0045(10)
Largest difference peak(e. Å $^{-3}$)	0.211
Largest difference hole(e. Å $^{-3}$)	-0.178

Table 2

Atomic Coordinates and Equivalent Isotropic Displacement Parameters (A^2 x 10^{-3}) for **10a**

Atom	X	Y	Z	U(eq) [a]
N(1)	0.5395 (4)	0.7344 (1)	0.7317 (1)	39(1)
C(01)	0.4869 (7)	0.7850 (1)	0.7727 (2)	52(1)
N(2)	0.4073 (4)	0.7252(1)	0.6431 (1)	41(1)
C(3)	0.4922 (5)	0.6765 (1)	0.6246 (1)	37(1)
C(31)	0.3788 (6)	0.6513 (1)	0.5345 (1)	46(1)
C(3A)	0.6818 (5)	0.6540 (1)	0.7000 (1)	36(1)
N(4)	0.7953 (4)	0.6027 (1)	0.6956(1)	37(1)
C(5)	0.9729 (5)	0.5768 (1)	0.7579(1)	35(1)
C(5A)	1.1223 (4)	0.5946 (1)	0.8503(1)	35(1)
C(6)	1.3361 (5)	0.5615 (1)	0.9024 (1)	40(1)
C(7)	1.4776 (5)	0.5745 (1)	0.9909 (1)	43(1)
C(8)	1.4120 (5)	0.6212 (1)	0.0317 (1)	43(1)
C(8A)	1.2031 (5)	0.6556 (1)	0.9808 (1)	38(1)
N(9)	1.1000 (4)	0.7046 (1)	0.0043 (1)	44(1)
C(10)	0.9072 (5)	0.7249 (1)	0.9313 (1)	43(1)
C(10A)	0.8749(5)	0.6894 (1)	0.8599 (1)	37(1)
C(11)	1.0614 (5)	0.6438 (1)	0.8905 (1)	35(1)
C(12)	0.7055 (5)	0.6924 (1)	0.7686(1)	35(1)
C(13)	1.0323 (5)	0.5214 (1)	0.7286 (1)	38(1)
C(14)	1.1509 (6)	0.5124 (1)	0.6416 (1)	46(1)
C(15)	1.1904 (6)	0.4622(1)	0.6093 (1)	54(1)
C(16)	1.1073 (6)	0.4200 (1)	0.6629(2)	53(1)
C(17)	0.9913 (5)	0.4282 (1)	0.7491 (2)	48(1)
C(18)	0.9539 (5)	0.4786 (1)	0.7821 (1)	42(1)

[a] Equivalent isotropic U is defined as one third of the trace of the orthogonalized U_{eq} tensor.

Table 3

Selected Bond Lengths (Å) and Angles (°) for **10a**

N(4)-C(5)	1.295 (2)	C(5)-N(4)-C(3A)	128.29 (15)
C(5)-C(5A)	1.493 (2)	N(4)-C(5)-C(5A)	129.22 (15)
C(5A)-C(11)	1.415 (2)	C(11)-C(5A)-C(5)	124.37 (15)
C(10A)-C(11)	1.442 (2)	C(5A)-C(11)-C(10A)	134.30 (15)
C(10A)-C(12)	1.441 (2)	C(12)-C(10A)-C(11)	121.82 (15)
C(3A)-C(12)	1.393 (2)	C(3A)-C(12)-C(10A)	127.82 (15)
C(3A)-N(4)	1.391 (2)	N(4)-C(3A)-C(12)	133.82(15)
C(5)-C(13)	1.505 (2)	N(4)-C(5)-C(13)	112.43 (14)
C(5A)-C(6)	1.391 (2)	C(5A)-C(5)-C(13)	118.34 (14)
C(8A)-C(11)	1.416 (2)	C(6)-C(5A)-C(5)	119.48 (15)
C(10)-C(10A)	1.372 (2)	C(10)-C(10A)-C(12)	131.44 (16)
N(1)-C(12)	1.355(2)	N(1)-C(12)-C(10A)	126.24 (15)
C(3)-C(3A)	1.407 (2)	N(4)-C(3A)-C(3)	120.87(14)

EXPERIMENTAL

5-Chloro-1,3-dimethylpyrazole and 5-methoxyindole were purchased from Acros. The acyl chlorides, zinc chloride (1.0 *M* in ether), and methyl-magnesium iodide (3.0 *M* in ether) were purchased from Aldrich.

Melting points (uncorrected) were determined on SMP2 Stuart melting point apparatus. Nmr spectra were recorded on a Bruker WM-400 and a Bruker DPX-300 spectrometers using TMS as internal reference. Electron impact (EI) mass spectra and high resolution data were obtained using a Finnigan MAT 731 spectrometer at 70 eV; ion source temperature = 200 °C. Microanalysis was performed at the Microanalytical Laboratory, Inorganic Chemistry Department, Morgenstelle 18 (Tübingen Universität).

5-Chloro-1,3-dimethyl-4-nitropyrazole (**6**).

This compound was obtained by nitration of 5-chloro-1,3-dimethylpyrazole (10 g; 76 mmol) using a mixture of concentrated nitric acid (40 mL) and concentrated sulfuric acid (60 mL), following a reported procedure [24]. Yield of **6** =12 g (90 %); mp 77-78 °C (Lit. [24] mp 68 °C, from ethanol).

3-(1,3-Dimethyl-4-nitropyrazol-5-yl)indole (**7a**).

To a solution of indole (2.34 g; 20 mmol) in dry ether (30 mL), was added a solution of CH_3MgI (3 *M* in diethyl ether, 7 mL), and the mixture was stirred for 15 minutes. An ethereal solution of $ZnCl_2$ (1 *M*, 20 mL) was then added and stirred at room temperature for 30 minutes. Later on, 5-chloro-4-nitro-1,3-dimethylpyrazole (**6**) (1.76 g; 10 mmol) was added to the reaction mixture, and stirring was continued at room temperature for 6 hours. Water (100 mL) was then added to the reaction mixture, the ether layer was separated and the aqueous layer was further extracted by ether (3x50 mL). The combined ether portions were

dried (anhydrous Na_2SO_4), and the solvent was evaporated. The residual product was recrystallized from chloroform-petroleum ether (bp 40-60 °C) to afford a yellow solid. Yield of **7a** = 1.74 g (68%); mp 141-142 °C; ms: m/z (% rel. int.): 256 ($M^{+\bullet}$, 100), 239 (9), 227 (19), 197 (10), 166 (6), 148 (21), 139 (10), 120 (9); hrms: Calcd for $C_{13}H_{12}N_4O_2$: 256.096. Found: 256.0957268; ^{1}H nmr (300.13 MHz, $CDCl_3$): δ 2.63 (s, 3H, C3'-C*H*$_3$), 3.72 (s, 3H, N-C*H*$_3$), 7.22 (m, 1H, H-5), 7.31 (m, 2H, H-4 and H-6), 7.47 (d, 1H, J = 8.0 Hz, H-7), 7.51 (d, 1H, J = 2.8 Hz, H-2), 8.68 (broad s, 1H, N-*H*); ^{13}C nmr (75.48 MHz, $CDCl_3$): δ 14.3 (C3'-*C*H$_3$), 37.8 (N-*C*H$_3$), 101.8 (C-3), 112.1 (C-7), 119.3 (C-4), 121.2 (C-5), 123.0 (C-6), 125.8 (C-3a), 127.3 (C-2), 131.4 (C-3'), 135.7 (C-7a), 137.7 (C-5'), 146.6 (C-4').

Anal. Calcd. for $C_{13}H_{12}N_4O_2$ (256.26): C, 60.93; H, 4.72; N, 21.86. Found: C, 60.74; H, 4.81; N, 21.90.

3-(1,3-Dimethyl-4-nitropyrazol-5-yl)-5-methoxyindole (**7b**).

A solution of 5-methoxyindole (2.22 g; 15 mmol) in dry diethyl ether (20 mL) was stirred with excess CH_3MgI (3 *M* in diethyl ether, 5 mL) at 22 °C for 20 minutes. An ethereal solution of $ZnCl_2$ (1.0 *M*, 15 mL) was then added to the reaction mixture. After stirring for 30 minutes, a solution of 5-chloro-1,3-dimethyl-4-nitropyrazole (**6**) (1.23 g, 7 mmol) in dry diethyl ether (40 mL) was added dropwise. The resulting mixture was stirred at room temperature for 6 hours, then water (100 mL) was added and the ether layer was separated. The aqueous layer was extracted with ether (2x100 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and precipitated using petroleum ether to give a yellowish solid which was washed several times with petroleum ether to remove unreacted 5-methoxyindole. Yield of **7b** =1.4 g (70%), mp 173-174 °C; ms: m/z (% rel. int.): 286 ($M^{+\bullet}$, 100), 269 (14), 237 (9), 227(35), 213 (13), 196 (9), 172 (9), 150 (10), 132 (9); hrms: Calcd for $C_{14}H_{14}N_4O_3$: 286.10659. Found: 286.10880; ^{1}H nmr (300.13 MHz, $CDCl_3$): δ 2.64 (s, 3H, C3'-C*H*$_3$), 3.71 (s, 3H, N-C*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 6.69 (d, 1H, J = 2.4 Hz, H-4), 6.89 (dd, 1H, J = 8.9, 2.4 Hz, H-6), 7.29 (d, 1H, J = 8.9 Hz, H-7), 7.39 (d, 1H, J = 2.8 Hz, H-2), 8.77 (broad s, 1H, N-*H*); ^{13}C nmr (75.48 MHz, $CDCl_3$): δ 14.4 (C3'-*C*H$_3$), 37.8 (N-*C*H$_3$), 55.8 (O*C*H$_3$) 100.7 (C-4), 101.6 (C-3), 112.9 (C-7), 113.4 (C-6), 126.5 (C-3a), 127.6 (C-2), 130.6 (C-3'), 131.7 (C-7a), 155.2 (C-5), 137.7 (C-5'), 146.6 (C-4').

Anal. Calcd. for $C_{14}H_{14}N_4O_3$ (286.29): C, 58.74; H, 4.93; N, 19.57. Found: C, 58.63; H, 4.92; N, 19.35.

3-(4-Amino-1,3-dimethylpyrazol-5-yl)indole (**8a**).

To a solution of 3-(1,3-dimethyl-4-nitro-pyrazol-5-yl)indole (**7a**) (2.92 g; 11.4 mmol) in concentrated HCl (30 mL) and 95% ethanol (15 mL) was added tin granules (2.0 g). The mixture was refluxed (water bath) for 1 hour. The resulting solution was cooled, basified with 40% aqueous NaOH solution, and extracted with CH_2Cl_2 (3x100 mL). The combined CH_2Cl_2 extracts were dried (anhydrous Na_2SO_4) and the solvent was distilled *in vacuo* to give a light brown solid. Yield of **8a** = 2.35 g (91%); mp 98-99 °C; ms: m/z (% rel. int.): 226 ($M^{+\bullet}$, 100), 184 (11), 170 (5), 157 (14), 143 (83), 115 (6); hrms: Calcd for $C_{13}H_{14}N_4$: 226.12183. Found: 226.122361; ^{1}H nmr (300.13 MHz, $CDCl_3$): δ 2.28 (s, 3H, C3'-C*H*$_3$), 2.77 (br s, 2H, N*H*$_2$), 3.69 (s, 3H, N-C*H*$_3$), 7.18 (ddd, 1H, J = 8.0, 7.9, 1.0 Hz, H-5), 7.26 (d, 1H, J = 2.5 Hz, H-2), 7.28 (ddd, 1H, J = 8.1, 7.9, 1.0 Hz, H-6), 7.46 (dd, 1H, J = 8.1, 1.0 Hz, H-7), 7.50 (dd, 1H, J = 7.9, 1.0 Hz, H-4), 8.98 (broad s, 1H, N-*H*); ^{13}C nmr (75.48 MHz, $CDCl_3$): δ 11.0 (C3'-*C*H$_3$), 36.9 (N-*C*H$_3$), 105.0 (C-3), 111.6(C-7), 119.8 (C-4), 120.6 (C-5), 122.8 (C-6), 124.2 (C-2), 125.1 (C-3'), 125.4 (C-5'), 126.6 (C-3a), 136.1 (C-7a) 137.4 (C-4').

Anal. Calcd. for $C_{13}H_{14}N_4$ (226.28): C, 69.00; H, 6.24; N, 24.76. Found: C, 69.32; H, 6.09; N, 24.53.

3-(4-Amino-1,3-dimethylpyrazol-5-yl)-5-methoxyindole (**8b**).

A mixture of 3-(1,3-dimethyl-4-nitropyrazol-5-yl)-5-methoxyindole (**7b**) (1.43 g, 5 mmol), tin granules (4.5 g) in ethanol (10 mL) and concentrated HCl (20 mL) was refluxed (water bath) for 2 hours. Work-up of the reaction mixture as described for **8a** above gave a solid product, which was recrystallized from CH_2Cl_2-petroleum ether to afford a white solid. Yield of **8b** = 0.78 g (61%); mp 185-186 °C (dec.); ms: m/z (% rel. int.): 256 ($M^{+\bullet}$, 100), 239 (4), 223 (10), 200(10), 187 (10), 173 (85), 157 (15), 149 (18), 147 (25), 129 (16); hrms: Calcd for $C_{14}H_{16}N_4O$: 256.13241. Found: 256.13353; ^{1}H nmr (300.13 MHz, $CDCl_3$): δ 2.28 (s, 3H, C3'-C*H*$_3$), 2.56 (br s, 2H, N*H*$_2$), 3.68 (s, 3H, N-C*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 6.89 (d, 1H, J = 2.4 Hz, H-4), 6.93 (dd, 1H, J = 8.7, 2.4 Hz,H-6), 7.22 (d, 1H, J = 2.6 Hz, H-2), 7.32 (d, 1H, J = 8.7 Hz, H-7), 8.95 (broad s, 1H, N-*H*); ^{13}C nmr (75.48 MHz, $CDCl_3$): δ 11.1 (C3'-*C*H$_3$), 36.9 (N-*C*H$_3$), 55.8 (O*C*H$_3$), 100.8 (C-4), 104.7 (C-3), 112.4 (C-7), 113.4 (C-6), 124.8 (C-2), 125.2 (C-3'), 125.4 (C-5'), 127.1 (C-3a), 137.3 (C-7a), 137.4 (C-4'), 154.9 (C-5).

Anal. Calcd. for $C_{14}H_{16}N_4O$ (256.29): C, 58.74; H, 4.93; N, 19.57. Found: C, 58.71; H, 5.09; N, 19.68.

3-[4-(*N*-Benzoyl)amino-1,3-dimethylpyrazol-5-yl)]indole (**9a**).

Benzoyl chloride (0.77 g; 5.5 mmol) was added to a solution of (**8a**) (1.13 g; 5 mmol) in dry benzene (20 mL), followed by addition of triethylamine (2 mL). The resulting mixture was refluxed (oil bath; 90 °C) for 4 hours. The solvent was then evaporated *in vacuo*, and the residue was soaked in water (40 mL), filtered and finally washed with petroleum ether to give a white solid.Yield of **9a** =1.17 g (71%); mp 242-244 °C; ms: m/z (% rel. int.): 330 ($M^{+\bullet}$, 49), 225 (100), 157 (33), 142 (22), 115 (5), 105 (32); hrms: Calcd for $C_{20}H_{18}N_4O$: 330.14806. Found: 330.15061; ^{1}H nmr (400.14 MHz, DMSO-d_6): δ 2.09 (s, 3H, C3'-C*H*$_3$), 3.71(s, 3H, N-C*H*$_3$), 6.99 (dd, 1H, J = 7.4, 7.5 Hz, H-5), 7.11 (dd, 1H, J = 7.2, 7.5 Hz, H-6), 7.38 (d, 1H, J = 7.4Hz, H-4), 7.50(d, 1H, J = 7.2 Hz, H-7), 7.56 (d, 1H, J = 2.4 Hz, H-2), 7.40 (m, 3H, H-3"/H-5" and H-4"), 7.83 (d, 2H, J= 7.2 Hz, H-2"/H-6"), 9.45 (s, 1H, N*H*CO), 11.50 (broad s, 1H, N-*H*); ^{13}C nmr (100.62 MHz, DMSO-d_6): δ 11.4 (C3'-*C*H$_3$), 37.2 (N-*C*H$_3$), 102.9 (C-3), 111.9 (C-7), 115.7 (C-4'), 119.2 (C-4), 119.6 (C-5), 121.6 (C-6), 125.7 (C-3a), 125.8 (C-2), 127.4(C-3"/C-5"), 128.8(C-2"/C-6"), 131.3(C-4"), 134.0 (C-5'), 134.4(C-1"), 136.0 (C-7a), 143.8 (C-3'), 166.5 (NH*C*O).

Anal. Calcd. for $C_{20}H_{18}N_4O$ (330.39): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.75; H, 5.38; N, 16.63.

The following amides were prepared *via* the interaction of the appropriate acid chloride and the respective 5-aminopyrazole derivative (**8**) following the same above procedure, and experimental conditions:

3-[4-(4'-Chlorobenzoyl)amino-1,3-dimethylpyrazol-5-yl]-5-methoxyindole (**9b**).

This compound was prepared from *p*-chlorobenzoyl chloride (0.87 g; 5 mmol) and (**8b**) (1.2 g; 4.7 mmol); Yield of **9b** = 1.24 g (67%); mp 192 - 194 °C; ms: m/z (% rel. int.): 394 ($M^{+\bullet}$, 27), 281(5), 255 (39), 224 (24), 210(8), 187 (12), 156 (17), 139 (100),

111 (32); hrms: Calcd for $C_{21}H_{19}N_4O_2Cl$: 394.11965. Found: 394.12203; ^{1}H nmr (400.14 MHz, DMSO-d_6): δ 2.07 (s, 3H, C3'-C*H*$_3$), 3.59 (s, 3H, N-C*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 6.72 (dd, 1H, J = 8.8, 2.4 Hz, H-6), 6.84 (d, 1H, J = 2.4 Hz, H-4), 7.30 (d, 1H, J = 8.8 Hz, H-7), 7.54 (d, 1H, J = 2.7 Hz,H-2), [*p*-C_6H_4Cl : 7.51(d, 2H, J = 8.5 Hz, H-3''/H-5''), 7.87(d, 2H, J = 8.5 Hz, H-2''/H-6'')], 9.57 (s, 1H, N*H*CO), 11.41 (broad s, 1H, N-*H*); ^{13}C nmr (100.62 MHz, DMSO-d_6): δ 11.5 (C3'-*C*H$_3$), 37.1 (N-*C*H$_3$), 55.0 (O*C*H$_3$), 100.3 (C-4), 102.7 (C-3), 112.3 (C-7), 112.6 (C-6), 115.5 (C-4'), 126.2 (C-3a), 126.3 (C-2), 128.3 (C-3''/C-5''), 129.4 (C-2''/C-6''), 130.9 (C-5'), 133.0 (C-7a), 133.8(C-1''), 136.2(C-4''), 143.7 (C-3'), 153.8 (C-5), 165.3 (NH*C*O).

Anal. Calcd. for $C_{21}H_{19}N_4O_2Cl$ (394.86): C, 63.88; H, 4.85; N, 14.19; Cl, 8.98. Found: C, 64.07; H, 5.12; N, 14.01; Cl, 8.92.

3-[4-(2-Thenoyl)amino-1,3-dimethylpyrazol-5-yl]indole (**9c**).

This compound was prepared from 2-thiophenecarbonyl chloride (0.81 g; 5.5 mmol) and (**8a)** (1.13 g; 5.0 mmol); Yield of **9c** = 1.25 g (74%); mp 217 - 220 °C; ms: m/z (% rel. int.): 336 ($M^{+\bullet}$, 47), 225 (100), 157 (41), 142 (33), 115(9), 111 (33); hrms: Calcd for $C_{18}H_{16}N_4OS$: 336.10448. Found: 336.10614; ^{1}H nmr (400.12 MHz, DMSO-d_6): δ 2.08 (s, 3H, C3'-C*H*$_3$), 3.70 (s, 3H, N-C*H*$_3$), 6.99 (ddd, 1H, J~ 8.0, 8.0, 0.7 Hz, H-5), 7.09 (dd, 1H, J = 4.9, 3.6 Hz, H-3''), 7.11 (m, 1H, H-6), 7.43 (dd overlapped, 2H, J~ 8.0 Hz, H-4 and H-7), 7.54 (d, 1H, J = 2.4 Hz, H-2), 7.74 (dd, 1H, J = 4.9, 1.1 Hz, H-4''). 7.77(dd, 1H, J = 1.1, 3.6 Hz, H-5''), 9.48 (s, 1H, N*H*CO), 11.50 (broad s, 1H, N-*H*); ^{13}C nmr (100.62 MHz, DMSO-d_6): δ 11.4 (C3'-*C*H$_3$), 37.2 (N-*C*H$_3$), 102.8 (C-3), 111.9 (C-7), 115.1 (C-4'), 119.2 (C-4), 119.6 (C-5), 121.6 (C-6), 125.8 (C-3a), 126.0 (C-2), 127.9 (C-4''), 128.6 (C-5''), 131.1(C-3''), 134.2 (C-5'), 136.0 (C-7a), 139.7 (C-2''), 143.8 (C-3'), 161.2 (NH*C*O).

Anal. Calcd. for $C_{18}H_{16}N_4OS$ (336.42): C, 64.27; H, 4.79; N, 16.65, S, 9.53. Found: C, 64.44; H, 4.82; N, 16.31, S, 9.52.

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

To a stirred solution of compound (**9a**) (0.86 g; 2.6 mmol) in acetonitrile (30mL) was added phosphorous oxychloride (7 mL). The resulting mixture was refluxed (oil bath, 110 °C) for 6 hours under continuous stirring. Excess acetonitrile and phosphorous oxychloride were removed under vacuum and the residue was poured onto ice-cooled water (100 mL). The cold aqueous solution was basified with 10% NaOH solution and extracted with dichloromethane (3x100 mL). The combined organic extracts were dried (anhydrous $MgSO_4$), and upon evaporation of the CH_2Cl_2, gave a crude orange solid. Yield 0.63 g (78%). The product was further purified on silica gel TLC plates, eluting with CH_2Cl_2:MeOH (97:3 v/v) to afford the title compound in analytically pure form. Yield of **10a** = 0.41 g (50%); mp 255-257 °C; ms: m/z (% rel. int.): 312 ($M^{+\bullet}$, 100), 270 (24), 256 (9), 229 (45), 201 (9), 175 (6), 156 (32), 148 (21), 134 (15), 107 (16), 101 (12); hrms: Calcd for $C_{20}H_{16}N_4$: 312.13748. Found: 312.138158; ^{1}H nmr (400.12 MHz, DMSO-d_6): δ 1.95 (s, 3H, C3-C*H*$_3$), 3.84 (s, 3H, N-C*H*$_3$), 6.33 (d, 1H, J = 8.0 Hz, H-6), 6.78 (dd, 1H, J = 8.1, 8.0 Hz, H-7), 7.11 (d, 1H, J = 8.1Hz, H-8), 7.37 (m, 5H, C_6H_5), 7.44 (d, 1H, J = 2.4 Hz, H-10), 11.43 (broad s, 1H, N-*H*); ^{13}C nmr (100.62 MHz, DMSO-d_6): δ 10.2 (C3-*C*H$_3$), 39.1 (N-*C*H$_3$), 107.9 (C-10a), 114.0 (C-8), 118.3 (C-10), 122.5 (C-7), 122.9 (C-6), 126.5 (C-8b), 127.6 (C-4''), 127.8 (C-2''/ C-6''), 128.1 (C-3''/C-5''), 129.6 (C-5a), 130.6 (C-10b), 131.0 (C-3), 137.4 (C-8a), 143.3 (C-1'), 147.4 (C-3a), 157.8 (C-5).

Anal. Calcd. for $C_{20}H_{16}N_4$ (312.37): C, 76.90; H, 5.16; N, 17.94. Found: C, 77.03; H, 5.24; N, 17.65.

The following azepino[5,4,3-*cd*]indoles were prepared *via* the cyclization of the appropriate amide (**9**) using phosphorous oxychloride and following the same above procedure and experimental conditions.

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

This compound was prepared from compound (**9b**) (1.18 g; 3 mmol) and phosphorous oxychloride (8 mL); Yield of **10b** = 0.85 g (75%); mp 267-269 °C (dec.); ms: m/z (% rel. int.): 376 ($M^{+\bullet}$, 100), 361 (21), 326 (15), 304 (9), 284 (14), 270 (17), 254 (6), 215 (7), 188 (24), 155 (18), 115 (21); hrms: Calcd for $C_{21}H_{17}N_4OCl$: 376.10779. Found: 376.10909; ^{1}H nmr (400.12 MHz, DMSO-d_6): δ 2.03 (s, 3H, C3-C*H*$_3$), 3.19 (s, 3H, N-C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 6.77 (d, 1H, J = 8.2 Hz, H-7), 7.21 (d, 1H, J = 8.2 Hz, H-8), 7.24 (d, 2H, J = 8.4 Hz, H-2''/H-6''), 7.31 (d, 2H, J = 8.4 Hz, H-3''/H-5'') 7.44 (br d, 1H, J = 2.7 Hz, H-10), 11.33 (broad s, 1H, N-*H*); ^{13}C nmr (100.62 MHz, DMSO-d_6): δ 10.1 (C3-*C*H$_3$), 38.7 (N-*C*H$_3$), 55.1 (O*C*H$_3$), 107.7 (C-10a), 111.9 (C-7), 115.0 (C-8), 117.2 (C-5a), 120.0 (C-10), 126.1 (C-8b), 127.1 (C-2''/C-6''), 127.7 (C-3''/C-5''), 131.0 (C-10b), 131.1 (C-3), 132.8(C-4''), 132.9 (C-8a), 145.2(C-1''), 146.0 (C-3a), 152.1 (C-6), 155.8 (C-5).

Anal. Calcd. for $C_{21}H_{17}N_4OCl$ (376.85): C, 66.93; H, 4.55; N, 14.87; Cl, 9.41. Found: C, 66.74; H, 4.38; N, 14.65; Cl, 9.28.

1,3-Dimethyl-5-(2-thienyl)pyrazolo[3',4':6,7]azepino[5,4,3-*cd*]-indole (**10c**).

This compound was prepared from compound (**9c**) (0.84 g; 2.5 mmol) and phosphorous oxychloride (7 mL); Yield of **10c** = 0.35 g (44%); mp 224-225 °C (dec.); ms: m/z (% rel. int.): 318 ($M^{+\bullet}$, 100), 276 (16), 262 (26), 235 (19), 232 (9), 164 (7), 159 (14), 125 (6); hrms: Calcd for $C_{18}H_{14}N_4S$: 318.0939. Found: 318.093321; ^{1}H nmr (400.12 MHz, DMSO-d_6): δ 2.01 (s, 3H, C3-C*H*$_3$), 3.82 (s, 3H, N-C*H*$_3$), 6.91 (dd, 1H, J = 8.0, 8.2 Hz, H-7), 7.03 (dd, 1H, J = 5.0, 3.2 Hz, H-4''), 7.07 (d, 1H, J = 8.0 Hz, H-6), 7.18 (d, 1H, J = 8.2 Hz, H-8), 7.33 (dd, 1H, J = 3.2, 1.0 Hz, H-3''), 7.45(d, 1H, J = 2.7 Hz, H-10), 7.51 (dd, 1H, J = 5.0, 1.0 Hz, H-5''), 11.46 (broad s, 1H, N-*H*); ^{13}C nmr (100.62 MHz, DMSO-d_6): δ 10.1 (C3-*C*H$_3$), 39.0 (N-*C*H$_3$), 107.7 (C-10a), 114.4 (C-8), 118.7 (C-10), 121.4 (C-7), 123.0 (C-6), 126.1 (C-3''), 126.4 (C-4''), 126.6 (C-5''), 129.6 (C-8b), 129.9 (C-5a), 130.5 (C-3), 130.6 (C-10b), 137.6 (C-8a), 147.0 (C-3a), 147.3 (C-2''), 150.7 (C-5).

Anal. Calcd. for $C_{18}H_{14}N_4S$ (318.40): C, 67.90; H, 4.43; N, 17.60, S, 10.07. Found : C, 67.70; H, 4.32; N, 17.46, S, 10.03.

Acknowledgements.

We are grateful to the BMBF, Bonn, Germany and the University of Sharjah, U A E, for financial support. K. A. S. wishes to thank the Hashemite University, Zarqa, Jordan for the scholarship.

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[*] E-mail: mustelab@ ju.edu.jo

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