Reaction of Pyrano[3,4-*b*]indolones with Aliphatic Amines and *N*,*N*-Dimethylhydrazine

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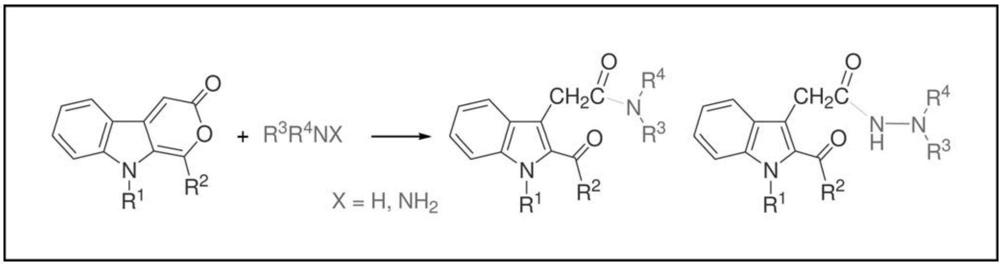

The synthesis of a number of indolylacetamides and indolylacetohydrazides in very good yields from the reaction of pyranoindolones with aliphatic amines and *N*,*N*-dimethylhydrazine, respectively, is described. The reactivity difference with aromatic amines but also with methylhydrazine and aromatic hydrazines is discussed.

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INTRODUCTION

From the reaction between 1-methylpyranoindolone and aromatic amines in boiling bromobenzene, only Schiff bases **1** were isolated [1], whereas from the same reaction in boiling isopropanol, 2-acetyl-indoloacetic acid amides **2** were formed [2] (Fig. 1).

Concerning the reaction of pyranoindolones with aliphatic amines as nucleophiles only some scattered reports were found in the literature. Thus, by refluxing 1-methylpyranoindolone with ethanolic ammonia (2-acetyl-3-indolyl)acetamide was formed [3], whereas with methanolic dimethyl amine, the corresponding *N,N*-dimethylacetamide was isolated in 44% [4]. Recently, the synthesis of the *N*-benzyl-(2-acetyl-3-indolyl)acetamide was reported from the reaction of 1-methylpyranoindolone with benzylamine in boiling DMF, which was eventually cyclized to a β-carbolinone by reflux with triethylamine in acetic acid [5].

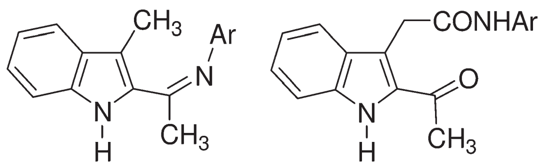
In addition, recently, we studied the reaction of pyranoindolones with bisnucleophiles, such as methylhydrazine, whereupon 1,2-diazepinoindoles were isolated [6], and also the reaction with aromatic hydrazines, such as phenyl- and benzoylhydrazine, leading to the synthesis of β-carbolinones [7].

RESULTS AND DISCUSSION

In the light of the above results and in continuation of our research into the synthesis of compounds containing the indole ring [6,7], we embarked in a more detailed study of the reactions between pyranoindolones and aliphatic amines and also *N*,*N*-dimethylhydrazine.

Since the reaction of pyranoindolone **3a** with dimethylamine in protic solvents (boiling methanol) has been, as mentioned above, reported to give the *N,N*-dimethyl-2-acetyl-1*H*-indole-3-acetamide (**5a**) in 44% yield and since such reactions show a strong solvent effect, initially the pyranoindolones **3a–3f** were allowed to react with two molar equivalents of dimethylamine in refluxing bromobenzene for 20 min, whereupon the indole-3-acetamides **5a–5f** were isolated in much better yields (Table 1, Scheme 1).

The reaction proceeded smoothly also at lower temperatures (refluxing toluene or benzene for 4–6 h) and even at room temperature, though a longer reaction time (12 h) was necessary for the completion of the reaction (Table 1). Next, the reaction was repeated with another secondary amine morpholine, but also with the primary amine benzylamine at room temperature for 12 h, and in all cases, the corresponding indole-3-acetamides 6 and 7 were isolated as the only reaction products in very good yields (Table 1). Indolylacetohydrazides 8 were isolated, when *N,N*-dimethylhydrazine was used as nucleophile. Compounds 7 and 8 were isolated as a mixture of two rotamers, as was confirmed from their NMR spectra ranging from 10:1 (major to minor) in compound **7a** to 2:1 in compound **8d** (see Experimental). The molar ratio of the rotamers depends on their relative stability, which is based on the volume and the electronic properties of



1 2

Figure 1. Products from the reaction of pyranoindolones with aromatic amines.

Table 1

Reaction conditions and products.

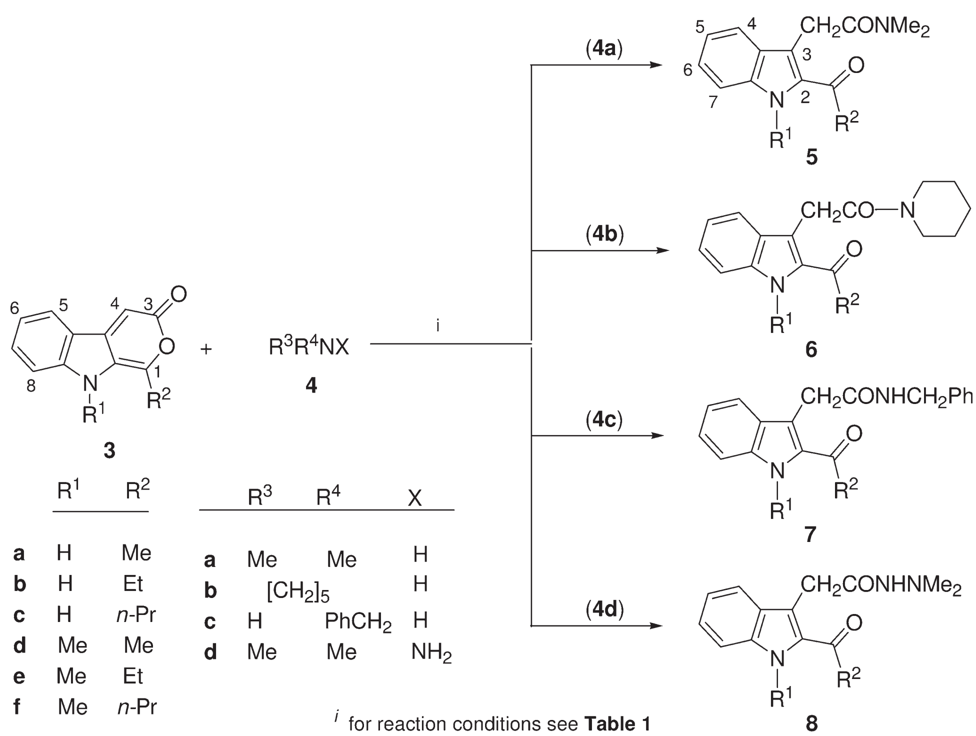
Entry	Amine	Solvent	Temp (°C)	Time	Product	Yield (%)
3a	**4a**	PhBr	156	20 min	**5a**	69
3b	**4a**	PhBr	156	20 min	**5b**	72
3c	**4a**	PhBr	156	20 min	**5c**	65
3d	**4a**	PhBr	156	20 min	**5d**	71
3e	**4a**	PhBr	156	20 min	**5e**	69
3f	**4a**	PhBr	156	20 min	**5f**	66
3e	**4a**	PhMe	111	4 h	**5e**	60
3e	**4a**	C_6H_6	80	6 h	**5e**	78
3e	**4a**	C_6H_6	25	12 h	**5e**	65
3a	**4b**	C_6H_6	25	12 h	**6a**	71
3d	**4b**	C_6H_6	25	12 h	**6d**	68
3e	**4b**	C_6H_6	25	12 h	**6e**	82
3a	**4c**	C_6H_6	25	12 h	**7a**	61
3d	**4c**	C_6H_6	25	12 h	**7d**	65
3e	**4c**	C_6H_6	25	12 h	**7e**	97
3b	**4d**	C_6H_6	25	12 h	**8b**	53
3d	**4d**	C_6H_6	25	12 h	**8d**	51
3e	**4d**	C_6H_6	25	12 h	**8e**	47

the substituents. The formation of the two rotamers is expected due to the high proportion of double bond character of the C—N amide bond resulting thus to hindered free rotation at low and ambient temperatures. As a result, in the case of different *N*-substituents, the NMR spectra of the two rotamers (in products 7 and 8) are practically different. In the case of two identical *N*-substituents (products 5 and 6), these substituents are in different magnetic environment and experience different chemical shifts.

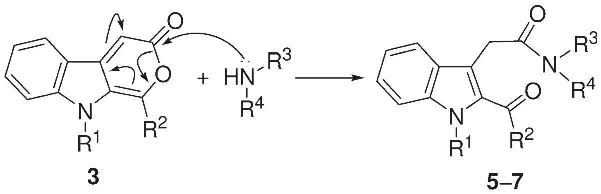
Concerning the reaction mechanism for the formation of products **5–8** attack of the amines to the carbonyl carbon, being the strongest electrophilic center (Scheme 2) is observed in all cases. This result is not in agreement with the results previously obtained with aromatic amines, and also with the bisnucleophiles methylhydrazine, phenyl-, and benzoylhydrazine, where under the same reaction conditions, initial attack to the less electrophilic center, namely C-1 was always observed [1,6,7]. The different behavior can be explained by the enhanced nucleophilicity of the aliphatic amines thus attacking the strongest electrophilic center. All isolated products **5–8** are new, with exception of **5a** and **7a**.

The assigned molecular structures of all compounds **5–8** are based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, COSY, NOESY, HETCOR, and COLOC), MS, and elemental analysis data.

Scheme 1



Scheme 2



Regarding the structure of the isolated indole-3-acetamides **5–8**, the assignment of **5e** is described. The elemental analysis and mass spectra unequivocally established the reaction of one molecule of pyranoindolone **3e** with one molecule of dimethylamine with the loss of a water molecule, a fact that was also confirmed from the ^{13}C NMR spectrum, where 16 different signals were observed. Moreover, in the IR spectra, a carbonyl at 1657 cm^{-1} was identified. In the ^{1}H NMR, the presence of the four indole aromatic protons resonating as a double doublet of doublets at δ 7.60 (J = 8.0 Hz, J = 1.0 Hz, and J = 0.5 Hz), a double doublet of doublets at δ 7.12 (J = 8.0 Hz, J = 7.1 Hz, and J = 1.1 Hz) [8], a multiplet at δ 7.33–7.34 for two protons with their carbons resonating at 120.4, 120.3, 125.3, and 110.2 ppm, respectively, was identified. The 3-position methylene protons appear as a singlet at δ 4.09, whereas in addition to the ethyl group, three *N*-methyl groups appeared at δ 3.00, 3.16, and 3.93 with their carbons resonating at 35.8, 37.4, and 32.6 ppm, respectively. Moreover, in addition to the characteristic COLOC correlations for the indole aromatic ring protons, the indole *N*-methyl group protons gave COLOC correlations with the quaternary carbons at 135.0 (C-2) and at 138.5 ppm (C-7a), whereas the 3-methylene protons correlated with the quaternary carbons at 135.0 (C-2) and at 126.9 (C-3a), 114.9 (C-3), and with the amide carbonyl carbon at 170.0 ppm, as depicted in Figure 2. In **8e**, the amide carbonyl carbon correlates as expected with the amide proton instead of the *N*-methyl protons.

In conclusion, a direct method for the systematic synthesis of a number of indolylacetamides and indolylacetohydrazides has been described. Moreover, the reaction of pyranoindolones with aliphatic amines and *N,N*-dimethylhydrazine does not show a solvent effect and proceeds with initial attack to the strongest electrophilic center, a result which is not in agreement with the results previously obtained with aromatic amines, and also with the bisnucleophiles methylhydrazine, phenyl-, and benzoylhydrazine, where initial attack to the less electrophilic center was always observed.

EXPERIMENTAL

Melting points were measured on a Büchi apparatus and are uncorrected. Column chromatography was carried out using Fluka silica gel 60. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} purchased from Macherey–Nagel using a 3:1 mixture of petroleum ether–ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80°C. NMR spectra were recorded at room temperature on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. In the case of insoluble substances, 5–20% of DMSO-d_6 was added, whereas in one case, only DMSO-d_6 was used, as indicated. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra; in the case of DMSO-d_6 solutions, the signal of the solvent at 39.7 ppm was used for calibration. Coupling constants ^nJ are reported in Hz. Second order ^{1}H NMR spectra were analyzed by simulation [8]. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra were recorded on a 6890N GC/MS system (Agilent Technology); in some cases, LC-MS (ESI, 1.65 eV) spectra were recorded on LCMS-2010 EV system (Shimadzu). Elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their IR, MS, and NMR spectra (^{1}H, ^{13}C, DEPT, COSY, NOESY, HETCOR, and COLOC).

General procedure for the reaction of pyrano[3,4-b]indol-3(9H)-ones (3a–3f) with amines 4. To a stirred and refluxing solution of pyranoindolone **3** (1.0 mmol) in bromobenzene (15 mL), amine **4a** (1.5 mmol) was added and refluxing and stirring was continued for 20 min. The solvent was distilled off under reduced pressure and the resulting residue was subjected to column chromatography on silica gel using petroleum ether–EtOAc (5:1) as eluent, slowly increasing the polarity up to 3:1 to give 2-(2-acyl-1H-indol-3-yl)-*N,N*-dimethylacetamide **5**.

The reaction conditions given in Table 1 are followed for the preparation of compounds **6–8**.

From indolopyranones 3 and amine 4a.

2-(2-Acetyl-1H-indol-3-yl)-N,N-dimethylacetamide (5a). 0.168 g, 69% Yield, yellow solid, mp 78–80°C (ethanol); IR (nujol) ν_{max}: 3178, 1663, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.74 (s, 3H, 2-CH_3), 3.07 (s, 3H, 3-NCH_3), 3.21 (s, 3H, 3-NCH_3), 4.07 (s, 2H, 3-CH_2), 7.01 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H, 5-H), 7.06 (dd, J = 7.8, 1.2 Hz, 1H, 7-H), 7.16 (dd, J = 7.8, 7.2 Hz, 1H, 6-H), 7.49 (d, J = 8.0 Hz, 1H, 4-H), 9.92 (s br, 1H, 1-H); ^{13}C NMR ($CDCl_3$): δ = 27.0 (2-CH_3), 30.1 (3-CH_2), 36.1 (N—CH_3), 37.7 (N—CH_3), 110.3 (C-7), 114.9 (C-3), 120.3 (C-5), 120.4 (C-4), 125.4 (C-6), 127.0 (C-3a), 135.1 (C-2), 138.6

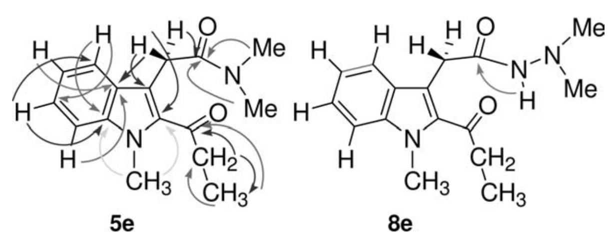


Figure 2. Diagnostic COLOC correlations between protons and carbons (via $^2J_{C-H}$ and $^3J_{C-H}$) in compounds **5e** and **8e**.

(C-7a), 171.7 (3-C=O), 191.6 (2-C=O); EIMS: *m/z* (%) 244 (45, M^+), 199 (35), 172 (100). Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.29): C, 68.83; H, 6.60; N, 11.47%. Found: C, 69.05; H, 6.73; N, 11.35%.

N,N-dimethyl-2-(2-propionyl-1H-indol-3-yl)acetamide (5b). 0.186 g, 72% Yield, yellow solid, mp 145–147°C (ethanol); IR (nujol) ν_{max}: 3202, 1670, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.77 (t, *J* = 7.1 Hz, 3H, 2-CH_2CH_3), 2.17 (q, *J* = 7.1 Hz, 2H, 2-CH_2CH_3), 3.15 (s, 3H, 3-NCH_3), 3.28 (s, 3H, 3-NCH_3), 4.14 (s, 2H, 3-CH_2), 7.07 (dd, *J* = 8.0, 7.2 Hz, 1H, 5-H), 7.13 (d, *J* = 8.0 Hz, 1H, 7-H), 7.22 (dd, *J* = 7.8, 7.2 Hz, 1H, 6-H), 7.56 (d, *J* = 7.8 Hz, 1H, 4-H), 9.98 (s br, 1H, 1-H). ^{13}C NMR ($CDCl_3$): δ = 7.3 (2-CH_2CH_3), 30.2 (3-CH_2), 36.1 (N—CH_3), 37.7 (N—CH_3), 113.4 (C-7), 115.8 (C-3), 120.0 (C-5), 120.3 (C-4), 125.5 (C-6), 128.2 (C-3a), 132.4 (C-2), 136.4 (C-7a), 171.7 (3-C=O), 194.3 (2-C=O). EIMS: *m/z* (%) 258 (35, M^+), 213 (45), 186 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84%. Found: C, 69.70; H, 6.93; N, 10.93%.

2-(2-Butyryl-1H-indol-3-yl)-N,N-dimethylacetamide (5c). 0.186 g, 65% Yield, yellow solid, mp 153–155°C (ethanol); IR (nujol) ν_{max}: 3321, 3178, 1669, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3H, 2-$CH_2CH_2CH_3$), 1.39 (sextet, *J* = 7.4 Hz, 2H, 2-$CH_2CH_2CH_3$), 2.20 (t, *J* = 7.4 Hz, 2H, 2-$CH_2CH_2CH_3$), 3.13 (s, 3H, $CONCH_3$), 3.27 (s, 3H, $CONCH_3$), 4.15 (s, 2H, 3-CH_2), 7.06 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H, 5-H), 7.10–7.24 (m, 2H, 6-H, 7-H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H, 4-H), 9.82 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$): δ = 13.7 (2-$CH_2CH_2CH_3$), 17.0 (2-$CH_2CH_2CH_3$), 30.3 (3-CH_2), 36.1 ($CONCH_3$), 37.7 ($CONCH_3$), 41.4 (2-$CH_2CH_2CH_3$), 113.2 (C-7), 115.9 (C-3), 120.1 (C-5), 120.3 (C-4), 125.6 (C-6), 126.9 (C-3a), 132.3 (C-2), 136.3 (C-7a), 171.5 (3-CO), 193.8 (2-CO); EIMS: *m/z* (%) 286 (M^+, 37), 241 (25), 214 (100). Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78%. Found: C, 71.37; H, 7.76; N, 9.65%.

2-(2-Acetyl-1-methyl-1H-indol-3-yl)-N,N-dimethylacetamide (5d). 0.183 g, 71% Yield, yellow solid, mp 111–113°C (ethanol); IR (nujol) ν_{max}: 1654, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.58 (s, 3H, 2-CH_3), 2.98 (s, 3H, $CONCH_3$), 3.15 (s, 3H, $CONCH_3$), 3.93 (s, 3H, 1-CH_3), 4.07 (s, 2H, 3-CH_2), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, 5-H), 7.31–7.37 (m, 2H, 6-H, 7-H), 7.60 (dd, *J* = 8.0, 0.9 Hz, 1H, 4-H) [8]; ^{13}C NMR ($CDCl_3$): δ = 30.9 (3-CH_2 and 2-CH_3), 32.6 (1-CH_3), 35.9 ($CONCH_3$), 37.5 ($CONCH_3$), 110.4 (C-7), 116.0 (C-3), 120.4 (C-5), 120.6 (C-4), 125.8 (C-6), 127.0 (C-3a), 135.1 (C-2), 138.8 (C-7a), 170.0 (3-CO), 192.8 (2-CO); EIMS: *m/z* (%) = 258 (45, M^+), 213 (15), 186 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.31): C, 69.74; H, 7.02; N, 10.84%. Found: C, 70.14; H, 6.85; N, 10.45%.

N,N-dimethyl-2-(2-propionyl-1-methyl-1H-indol-3-yl)-acetamide (5e). 0.188 g, 69% Yield, yellow solid, mp 99–100°C (ethanol); IR (nujol) ν_{max}: 1657 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3H, 2-CH_2CH_3), 2.91 (q, *J* = 7.2 Hz, 2H, 2-CH_2CH_3), 3.00 (s, 3H, $CONCH_3$), 3.16 (s, 3H, $CONCH_3$), 3.93 (s, 3H, 1-CH_3), 4.09 (s, 2H, 3-CH_2), 7.12 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, 5-H), 7.328 (ddd, *J* = 7.9, 1.1, 0.5 Hz, 1H, 7-H), 7.332 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, 6-H), 7.60 (ddd, *J* = 8.0, 1.0 Hz, 0.5 Hz, 1H, 4-H) [8]; ^{13}C NMR ($CDCl_3$): δ = 8.3 (2-CH_2CH_3), 30.8 (3-CH_2), 32.6 (1-CH_3), 35.7 (2-CH_2CH_3), 35.8 ($CONCH_3$), 37.4 ($CONCH_3$), 110.2 (C-7), 114.9 (C-3), 120.3 (C-5), 120.4 (C-4), 125.3 (C-6), 126.9 (C-3a), 135.0 (C-2), 138.5 (C-7a), 170.0 (3-CO), 196.4 (2-CO); EIMS: *m/z* (%) = 272 (42, M^+), 200 (100). Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29%. Found: C, 70.47; H, 7.33; N, 9.95%.

2-(2-Butyryl-1-methyl-1H-indol-3-yl)-N,N-dimethylacetamide (5f). 0.189 g, 66% Yield, yellow solid, mp 109–111°C (ethanol); IR (nujol) ν_{max}: 1654, 1637 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 3H, 2-$CH_2CH_2CH_3$), 1.77 (sextet, *J* = 7.3 Hz, 2H, 2-$CH_2CH_2CH_3$), 2.85 (t, *J* = 7.3 Hz, 2H, 2-$CH_2CH_2CH_3$), 2.98 (s, 3H, $CONCH_3$), 3.13 (s, 3H, $CONCH_3$), 3.90 (s, 3H, 1-CH_3), 4.06 (s, 2H, 3-CH_2), 7.12 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, 5-H), 7.31–7.35 (m, 2H, 6-H, 7-H), 7.62 (dd, *J* = 8.0, 1.0 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$): δ = 13.9 (2-$CH_2CH_2CH_3$), 17.9 (2-$CH_2CH_2CH_3$), 31.0 (3-CH_2), 32.6 (1-CH_3), 35.9 ($CONCH_3$), 37.5 ($CONCH_3$), 44.8 (2-$CH_2CH_2CH_3$), 110.3 (C-7), 114.9 (C-3), 120.4 (C-5), 120.6 (C-4), 125.4 (C-6), 127.0 (C-3a), 135.3 (C-2), 138.6 (C-7a), 170.1 (3-CO), 196.2 (2-CO); EIMS: *m/z* (%) = 286 (M^+, 37), 241 (25), 214 (100). Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78%. Found: C, 71.57; H, 7.76; N, 9.55%.

From indolopyranones 1 and amine 4b.

2-Acetyl-3-(2-oxo-2-piperidin-1-ylethyl)-1H-indole (6a). 0.202 g, 71% Yield, yellow solid, mp 190–191°C (ethanol); IR (nujol) ν_{max}: 3174, 1663, 1623 cm^{-1}; ^1H NMR: δ = 1.60–1.70 (m, 2H, 4′-H), 1.70–1.75 (m, 4H, 3′-H, 5′-H), 1.92 (s, 3H, 2-CH_3), 3.60–3.70 (m, 2H, 2′-H), 3.70–3.80 (m, 2H, 6′-H), 4.15 (s, 2H, 3-CH_2), 7.08 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H, 5-H), 7.15 (dd, *J* = 8.0, 1.2 Hz, 1H, 7-H), 7.23 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, 6-H), 7.57 (dd, *J* = 8.1, 1.0 Hz, 1H, 4-H), 10.09 (s br, 1H, 1-H); ^{13}C NMR ($CDCl_3$): δ = 24.7 (C-4′), 25.9 (C-3′), 26.4 (C-5′), 27.3 (2-CH_3), 30.0 (3-CH_2), 43.5 (C-6′), 47.1 (C-2′), 113.4 (C-7), 116.4 (C-3), 120.2 (C-4), 120.4 (C-5), 125.7 (C-6), 128.2 (C-3a), 132.6 (C-2), 136.4 (C-7a), 169.6 (3-C=O), 191.4 (2-C=O); EIMS: *m/z* (%) 284 (48, M^+), 199 (100), 172 (80), 143 (60), 130 (50), 112 (98). Anal. Calcd for $C_{17}H_{20}N_2O_2$ (284.35): C, 71.81; H, 7.09; N, 9.85%. Found: C, 71.75; H, 7.22; N, 9.82%.

2-Acetyl-1-methyl-3-(2-oxo-2-piperidin-1-ylethyl)-1H-indole (6d). 0.203 g, 68% Yield, yellow solid, mp 138–139°C (ethanol); IR (nujol) ν_{max}: 1657, 1637 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.40–1.55 (m, 4H, 3′-H, 5′-H), 1.55–1.70 (m, 2H, 4′-H), 2.54 (s, 3H, 2-CH_3), 3.47–3.60 (m, 4H, 2′-H, 6′-H), 3.89 (s, 3H, 1-CH_3), 3.98 (s, 2H, 3-CH_2), 7.10 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H, 5-H), 7.30 (ddd, *J* = 8.1, 1.0, 0.8 Hz, 1H, 7-H), 7.32 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, 6-H), 7.57 (ddd, *J* = 8.2, 1.0, 0.8 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$): δ = 24.3 (C-4′), 25.5 (C-3′), 26.3 (C-5′), 30.6 (3-CH_2), 30.7 (2-CH_3), 32.4 (1-CH_3), 43.0 (C-6′), 46.6 (C-2′), 110.1 (C-7), 116.2 (C-3), 120.1 (C-4), 120.4 (C-5), 125.5 (C-6), 126.8 (C-3a), 134.6 (C-2), 138.5 (C-7a), 167.9 (3-C=O), 192.5 (2-C=O); LCMS: *m/z* (%) 321 [100, $(M + Na)^+$], 298 (M^+, 20), 257 (5). Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38): C, 72.46; H, 7.43; N, 9.39%. Found: C, 72.84; H, 7.22; N, 9.28%.

1-Methyl-3-(2-oxo-2-piperidin-1-ylethyl)-2-propionyl-1H-indole (6e). 0.256 g, 82% Yield, yellow solid, mp 111–113°C (ethanol); IR (nujol) ν_{max}: 1655, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3H, 2-CH_2CH_3), 1.48–1.60 (m, 4H, 3′-H, 5′-H), 1.60–1.70 (m, 2H, 4′-H), 2.92 (q, *J* = 7.2 Hz, 2H, 2-CH_2CH_3), 3.52–3.63 (m, 4H, 2′-H, 6′-H), 3.94 (s, 3H, 1-CH_3), 4.10 (s, 2H, 3-CH_2), 7.13 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, 5-H), 7.35 (dd, J = 8.0, 1.0 Hz, 1H, 7-H), 7.35 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, 6-H), 7.63 (dd, J = 8.1, 1.0 Hz, 1H, 4-H); ^{13}C NMR: δ = 8.4 (2-CH$_2$CH$_3$), 24.6 (C-4′), 25.7 (C-3′), 26.5 (C-5′), 31.1 (3-CH$_2$), 32.7 (1-CH$_3$), 36.0 (2-*C*H$_2$CH$_3$), 43.3 (C-6′), 47.0 (C-2′), 110.3 (C-7), 115.2 (C-3), 120.4 (C-4), 120.6 (C-5), 125.5 (C-6), 127.1 (C-3a), 135.1 (C-2), 138.7 (C-7a), 168.4 (3-C=O), 196.6 (2-C=O); LCMS: *m/z* (%) 335 [100, (M + Na)$^+$], 312 (M$^+$, 20), 257 (5). Anal. Calcd for $C_{19}H_{24}N_2O_2$ (312.41): C, 73.05 H, 7.74; N, 8.97%. Found: C, 73.24; H, 7.37; N, 8.73%.

From indolopyranones 1 and hydrazine 4c.

2-(2-Acetyl-1H-indol-3-yl)-N-benzylacetamide (7a). 0.187 g, 61% Yield, yellow solid, mp 148–149°C (ethanol). IR (nujol) ν_{max}: 3324, 1650, 1638 cm^{-1}. Because of amide partial double bond, two rotamers in a ratio of 10:1 were observed in the NMR spectra of compound **7a**. Major rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.61 (s, 3H, 2-CH$_3$), 4.08 (s, 2H, 3-CH$_2$), 4.35 (d, J = 5.0 Hz, 2H, N—CH$_2$), 7.05–7.45 (m, 9H, 5-H, 6-H, 7-H, CONH and C$_6$H$_5$), 7.77 (d, J = 8.2 Hz, 1H, 4-H), 10.95 (br s, 1H, 1-H); ^{13}C NMR (CDCl$_3$ + DMSO-d$_6$): δ = 28.1 (3-CH$_2$), 33.2 (2-CH$_3$), 43.0 (N—CH$_2$), 112.4 (C-7), 115.8 (C-3), 120.4 (C-5), 120.7 (C-4), 126.0 (C-6), 126.8 (C-4′), 127.0 (C-2′, C-6′), 127.6 (C-3a), 128.2 (C-3′, C-5′), 132.2 (C-2), 136.3 (C-7a), 138.2 (C-1′), 170.6 (3-C=O), 191.7 (2-C=O). Minor rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.62 (s, 3H, 2-CH$_3$), 4.08 (s, 2H, 3-CH$_2$), 4.35 (d, J = 5.0 Hz, 2H, N—CH$_2$), 7.05–7.45 (m, 9H, 5-H, 6-H, 7-H, CONH and C$_6$H$_5$), 7.65 (d, J = 7.8 Hz, 1H, 4-H), 10.50 (br s, 1H, 1-H); ^{13}C NMR (CDCl$_3$ + DMSO-d$_6$): δ = 28.2 (3-CH$_2$), 32.3 (2-CH$_3$), 43.0 (N—CH$_2$), 112.1 (C-7), 116.3 (C-3), 119.9 (C-5), 120.8 (C-4), 125.7 (C-6), 126.8 (C-4′), 128.0 (C-2′, C-6′), 127.6 (C-3a), 128.4 (C-3′, C-5′), 132.5 (C-2), 136.0 (C-7a), 138.2 (C-1′), 174.2 (3-C=O), 191.2 (2-C=O); GCMS: *m/z* (%) 306 (M$^+$, 5), 173 (80), 91 (100). Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306.36): C, 74.49 H, 5.92; N, 9.14%. Found: C, 74.56; H, 5.83; N, 9.17%.

2-(2-Acetyl-1-methyl-1H-indol-3-yl)-N-benzylacetamide (7d). 0.208 g, 65% Yield, yellow solid, mp 129–131°C (ethanol); IR (nujol) ν_{max}: 3285, 1652, 1637 cm^{-1}. Beacuse of amide partial double bond, two rotamers in a ratio of 3.5:1 were observed in the NMR spectra of compound **7d**. Major rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.62 (s, 3H, 2-CH$_3$), 3.96 (s, 3H, 1-CH$_3$), 4.04 (s, 2H, 3-CH$_2$), 4.38 (d, J = 5.9 Hz, 2H, N—CH$_2$), 6.34 (br t, 1H, CONH), 7.05–7.45 (m, 8H, 5-H, 6-H, 7-H and C$_6$H$_5$), 7.74 (d, J = 8.5 Hz, 1H, 4-H); ^{13}C NMR (CDCl$_3$ + DMSO-d$_6$): δ = 29.7 (3-CH$_2$), 31.1 (2-CH$_3$), 34.1 (1-CH$_3$), 43.5 (N—CH$_2$), 110.5 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.5 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.4 (C-2′, C-6′), 128.6 (C-3′, C-5′), 131.8 (C-2), 137.5 (C-7a), 138.9 (C-1′), 170.2 (3-C=O), 192.6 (2-C=O). Minor rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.62 (s, 3H, 2-CH$_3$), 3.85 (s, 3H, 1-CH$_3$), 3.90 (s, 2H, 3-CH$_2$), 4.32 (d, J = 5.9 Hz, 2H, N—CH$_2$), 7.05–7.45 (m, 7H, 5-H, 7-H and C$_6$H$_5$), 7.47 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, 6-H), 7.78 (d, J = 7.8 Hz, 1H, 4-H), 8.34 (br t, 1H, CONH); ^{13}C NMR (CDCl$_3$ + DMSO-d$_6$): δ = 31.3 (2-CH$_3$), 32.9 (3-CH$_2$), 33.8 (1-CH$_3$), 43.3 (N—CH$_2$), 109.2 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.6 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.5 (C-2′, C-6′), 128.7 (C-3′, C-5′), 132.2 (C-2), 136.4 (C-7a), 138.2 (C-1′), 172.4 (3-C=O), 192.5 (2-C=O); LCMS: *m/z* (%) 343 [100, (M + Na)$^+$]. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.39): C, 74.98 H, 6.29; N, 8.74%. Found: C, 74.84; H, 6.18; N, 8.73%.

2-(1-Methyl-2-propionyl-1H-indol-3-yl)-N-benzylacetamide (7e). 0.324 g, 97% Yield, yellow solid, mp 149–151°C (ethanol); IR (nujol) ν_{max}: 3285, 1652, 1637 cm^{-1}. Beacuse of amide partial double bond, two rotamers in a ratio of 3.5:1 were observed in the NMR spectra of compound **7e**. Major rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.62 (s, 3H, 2-CH$_3$), 3.96 (s, 3H, 1-CH$_3$), 4.04 (s, 2H, 3-CH$_2$), 4.38 (d, J = 5.9 Hz, 2H, N—CH$_2$), 6.34 (br t, 1H, CONH), 7.05–7.45 (m, 8H, 5-H, 6-H, 7-H and C$_6$H$_5$), 7.74 (d, J = 8.5 Hz, 1H, 4-H); ^{13}C NMR (CDCl$_3$ + DMSO-d$_6$): δ = 29.7 (3-CH$_2$), 31.1 (2-CH$_3$), 34.1 (1-CH$_3$), 43.5 (N—CH$_2$), 110.5 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.5 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.4 (C-2′, C-6′), 128.6 (C-3′, C-5′), 136.4 (C-2), 138.9 (C-7a), 140.6 (C-1′), 170.2 (3-C=O), 192.6 (2-C=O). Minor rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.62 (s, 3H, 2-CH$_3$), 3.85 (s, 3H, 1-CH$_3$), 3.90 (s, 2H, 3-CH$_2$), 4.32 (d, J = 5.9 Hz, 2H, N—CH$_2$), 7.05–7.45 (m, 7H, 5-H, 7-H, and C$_6$H$_5$), 7.47 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, 6-H), 7.78 (d, J = 7.8 Hz, 1H, 4-H), 8.34 (br t, 1H, CONH); ^{13}C NMR (CDCl$_3$ + DMSO-d$_6$): δ = 31.3 (2-CH$_3$), 32.9 (3-CH$_2$), 33.8 (1-CH$_3$), 43.3 (N—CH$_2$), 109.2 (C-7), 115.6 (C-3), 120.8 (C-5), 121.2 (C-4), 126.6 (C-6), 126.7 (C-3a), 127.3 (C-4′), 127.5 (C-2′, C-6′), 128.7 (C-3′, C-5′), 137.5 (C-2), 138.2 (C-7a), 143.5 (C-1′), 172.4 (3-C=O), 192.5 (2-C=O); GCMS: *m/z* (%) 334 (30, M$^+$), 277 (5), 227 (10), 202 (90), 200 (100), 172 (75), 144 (42). Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.41): C, 75.42; H, 6.63; N, 8.38%. Found: C, 75.34; H, 6.55; N, 8.43%.

From indolopyranones 1 and hydrazine 4d.

N′,N′-dimethyl-2-(2-propionyl-1H-indol-3-yl)acetohydrazide (8b). 0.145 g, 53% Yield, yellow solid, mp 216–217°C (ethanol); IR (nujol) ν_{max}: 3354, 3194, 1669, 1651, 1644 cm^{-1}. Beacuse of amide partial double bond, two rotamers in a ratio of 7:3 were observed in the NMR spectra of compound **8b**. Major rotamer: ^{1}H NMR: δ = 1.18 (t, J = 7.1 Hz, 3H, 2-CH$_2$C*H$_3$*), 2.49 (s, 6H, N(CH$_3$)$_2$), 2.85 (q, J = 7.1 Hz, 2H, 2-C*H$_2$*CH$_3$), 3.97 (s, 2H, 3-CH$_2$), 3.97 (s, 3H, 1-CH$_3$), 7.01 (brs, 1H, CONH), 7.13–7.18 (m, 1H, 5-H), 7.26–7.35 (m, 2H, 6-H and 7-H), 7.74 (d, J = 8.3 Hz, 1H, 4-H), 9.51 (br s, 1H, 1-H). Minor rotamer: ^{1}H NMR: δ = 1.13 (t, J = 7.1 Hz, 3H, 2-CH$_2$C*H$_3$*), 2.61 (s, 6H, N(CH$_3$)$_2$), 2.87 (q, J = 7.2 Hz, 2H, 2-C*H$_2$*CH$_3$), 4.34 (s, 2H, 3-CH$_2$), 6.29 (br s, 1H, CONH), 7.08–7.12 (m, 1H, 5-H), 7.26–7.35 (m, 2H, 6-H and 7-H), 7.68 (d, J = 8.0 Hz, 1H, 4-H), 9.34 (br s, 1H, 1-H); LCMS: *m/z* (%) = 296 [100, (M + Na)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O_2$ (273.33): C, 65.91; H, 7.01; N, 15.37%. Found: C, 65.97; H, 7.13; N, 15.45%.

N′,N′-dimethyl-2-(1-methyl-2-acetyl-1H-indol-3-yl)acetohydrazide (8d). 0.139 g, 51% Yield, yellow solid, mp 176–177°C (ethanol); IR (nujol) ν_{max}: 3193, 1657, 1640 cm^{-1}. Because of amide partial double bond, two rotamers in a ratio of 2:1 were observed in the NMR spectra of compound **8d**. Major rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.40 (s, 6H, N(CH$_3$)$_2$), 2.68 (s, 3H, 2-CH$_3$), 3.92 (s, 2H, 3-CH$_2$), 4.00 (s, 3H, 1-CH$_3$), 7.05 (brs, 1H, NH), 7.21 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.74 (d, J = 8.1 Hz, 1H, 4-H); ^{13}C NMR (CDCl$_3$ + DMSO-d$_6$): δ = 29.4 (3-CH$_2$), 30.9 (2-CH$_3$), 32.6 (1-CH$_3$), 47.1 (N(CH$_3$)$_2$), 110.3 (C-7), 115.4 (C-3), 120.6 (C-5), 120.8 (C-4), 126.2 (C-6), 126.5 (C-3a), 134.9 (C-2), 138.6 (C-7a), 167.6 (3-C=O), 192.7 (2-C=O). Minor rotamer: ^{1}H NMR (CDCl$_3$ + DMSO-d$_6$): δ = 2.49 (s, 6H, N(CH$_3$)$_2$), 2.57 (s, 3H, 2-CH$_3$), 3.96 (s, 3H, 1-CH$_3$), 4.29 (s, 2H, 3-CH_2), 6.56 (br s, 1H, NH), 7.15 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.71 (d, J = 8.1 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ = 8.4 (2-CH_2*CH_3*), 30.7 (3-CH_2), 32.4 (2-CH_3), 32.7 (1-CH_3), 48.4 ($N(CH_3)_2$), 110.1 (C-7), 115.5 (C-3), 120.1 (C-5), 120.7 (C-4), 125.5 (C-6), 127.2 (C-3a), 134.7 (C-2), 138.5 (C-7a), 172.6 (3-C=O), 192.6 (2-C=O); LCMS: *m/z* (%) = 296 [100, (M + Na)$^+$]. Anal. Calcd for $C_{15}H_{19}N_3O_2$ (273.33): C, 65.91; H, 7.01; N, 15.37%. Found: C, 65.86; H, 7.15; N, 15.30%.

N′,N′-dimethyl-2-(1-methyl-2-propionyl-1H-indol-3-yl)acetohydrazide (8e). 0.135 g, 47% Yield, yellow solid, mp 186–188°C (ethanol); IR (nujol) ν_{max}: 3195, 1661, 1645 cm^{-1}. Beacuse of amide partial double bond, two rotamers in a ratio of 7:3 were observed in the NMR spectra of compound **8e**. Major rotamer: ^{1}H NMR: δ = 1.25 (t, J = 7.2 Hz, 3H, 2-CH_2*CH_3*), 2.47 (s, 6H, $N(CH_3)_2$), 2.95 (q, J = 7.2 Hz, 2H, 2-*CH_2*CH_3), 3.93 (s, 2H, 3-CH_2), 3.98 (s, 3H, 1-CH_3), 6.80 (brs, 1H, NH), 7.22 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.72 (dd, J = 8.1, 1.0 Hz, 1H, 4-H); ^{13}C NMR: δ = 8.4 (2-CH_2*CH_3*), 29.7 (3-CH_2), 33.1 (1-CH_3), 36.2 (2-*CH_2*CH_3), 47.3 ($N(CH_3)_2$), 110.5 (C-7), 114.5 (C-3), 120.7 (C-5), 121.1 (C-4), 126.2 (C-6), 126.7 (C-3a), 135.3 (C-2), 138.8 (C-7a), 167.8 (3-C=O), 196.55 (2-C=O). Minor rotamer: ^{1}H NMR: δ = 1.24 (t, J = 7.2 Hz, 3H, 2-CH_2*CH_3*), 2.55 (s, 6H, $N(CH_3)_2$), 3.02 (q, J = 7.2 Hz, 2H, 2-*CH_2*CH_3), 3.91 (s, 3H, 1-CH_3), 4.27 (s, 2H, 3-CH_2), 6.16 (brs, 1H, NH), 7.12–7.17 (m, 1H, 5-H), 7.32–7.45 (m, 2H, 6-H and 7-H), 7.70 (dd, J = 8.1, 1.0 Hz, 1H, 4-H); ^{13}C NMR: δ = 8.4 (2-CH_2*CH_3*), 32.5 (3-CH_2), 32.9 (2-*CH_2*CH_3), 35.8 (1-CH_3), 48.7 ($N(CH_3)_2$), 110.3 (C-7), 114.3 (C-3), 120.3 (C-5), 120.8 (C-4), 125.4 (C-6), 127.2 (C-3a), 135.1 (C-2), 138.6 (C-7a), 172.8 (3-C=O), 196.62 (2-C=O); EIMS: *m/z* (%) = 287 (42, M$^+$), 200 (100). Anal. Calcd for $C_{16}H_{21}N_3O_2$ (287.36): C, 66.88; H, 7.37; N, 14.62%. Found: C, 66.76; H, 7.23; N, 14.68%.

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