Directed *ortho*-Lithiation of the 2-(*N*,*N*-Dimethylhydrazinecarbonyl)-1-methylindole. Efficient Preparation of Tricyclic Lactones

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Abstract: *N*-Methyl indole-2-hydrazide **1** was lithiated at the 3-position using *t*-BuLi in the presence of TMEDA in THF. The generated *ortho*-lithiated intermediate is reacted with a variety of electrophiles to give regioselectively 2,3-disubstituted indoles in good yields. The hydroxyhydrazides were converted to the corresponding lactones after oxidation with MnO_2.

Key words: indole-hydrazide, directed *ortho*-metalation (DoM), 3-oxofuroindole, 2,3-disubstituted indole, hydrazide cleavage

The process of directed *ortho*-metalation (DoM)[1] of carboxamides,[2] carbamates,[3] carboxylic acids[4] and hydrazides,[5] is one of the better known methods for appending a wide range of substituents onto the aromatic nucleus. Amides, carbamates and oxazolines are excellent substrates for the directed *ortho*-metalation reaction; however, they require harsh conditions for their hydrolysis.[6]

The great majority of studies of *ortho*-metalation have been carried out on the benzene ring, while heterocyclic nuclei have received comparatively less attention. Recently Quéguiner et al.[7] reported studies of metalation of azine rings, whereas Fukuda et al.[8] reported the lithiation of 1-(2,2-diethylbutanoyl)indole and Matsuzomo[9] the directed lithiation at C-3 of 1-(triisopropylsilyl)indole. Previously, Gribble et al.[10] described new indole lithiation methods that allowed the preparation of several substituted indole derivatives, which are not readily available by conventional methodologies.

In general, the directed lithiation at C-3 of the indole-2-carboxylic acids or indole-2-carboxamides presents difficulties. Whereas, the treatment of the secondary amides with *s*-BuLi and subsequent addition of acetaldehyde gives the corresponding alcohol in acceptable yield, the metalation of *N*,*N*-dimethylindole-2-carboxamide using butyllithium suffers ring-opening to an alkyne.[10b]

The directed lithiation of indole-2-carboxylic acids does not appear to be an efficient procedure for preparing the corresponding 2,3-disubstituted indoles. Only few acylated indoles via C-3 lithiation directed by the C-2 carbonyl group are reported.[11]

In an earlier study,[12] we obtained the alkylation of indole-2-amides in excellent yield by metalation, but contrary to our expectations, the hydrolysis step was not straightforward and gave multiple products depending on the reaction conditions. We examined several additional variables in order to increase the yield, but without success. This problem with the hydrolysis of the amide function led us to consider the use of hydrazides as *ortho*-directing function, which seems to be more activating than the carboxylic acid group. The hydrazide function has been introduced into synthetic practice in the DoM process on the benzene ring by Wuts et al.[13] but their application on indole ring is not reported up till now.

Dimethylhydrazides are shown to be excellent substrates for the DoM reaction, and the major interest is the successful oxidative cleavage under relatively mild conditions. This work can be considered an extension of the previous work reported by Wuts et al.[13] about the directed *ortho*-metalation of the *N*,*N*-dimethylhydrazide of benzoic acid.

Based on this aforementioned work, we are interested in the preparation of the 2,3-disubstituted indoles via the *ortho*-lithiated intermediate indole-2-hydrazide. The compounds obtained will be of value for the synthesis of indole alkaloids and also as intermediates in the synthesis of compounds of interest in medicinal chemistry.

We report the lithiation of *N*-methyl-2-(*N*′,*N*′-dimethylhydrazide)indole prepared from the corresponding carboxylic acid under conventional conditions. The *N*-methylindole-2-hydrazide reacts selectively with *t*-butyllithium-TMEDA complex at the 3-position, and forms the corresponding carbanion, which behaves as excellent nucleophile in the presence of electrophilic reagents (Scheme 1). Table 1 depicts an overview of the scope diversity of electrophiles that may be used.

The *N*-methylindole-2-hydrazide **1** is deprotonated at –78 ºC with 3 equivalents of *t*-butyllithium in THF. The reaction works well in THF and TMEDA improves the yield. Normally, the solution of the *ortho*-lithiated intermediate species is reacted with the appropriate electrophile in excess (3 equiv) at –78 ºC and the mixture obtained is allowed to warm to room temperature. The general conditions used were chosen on the basis of preliminary experiments.[12]

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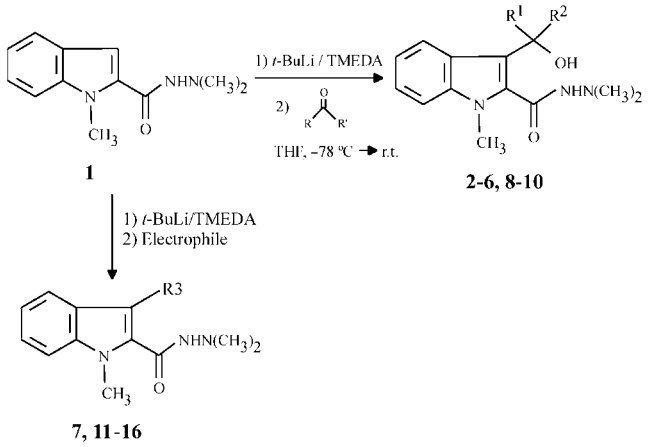
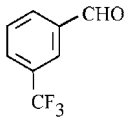
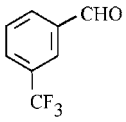
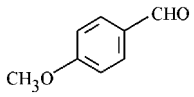
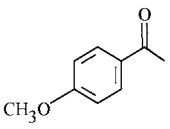
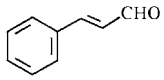
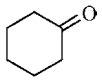
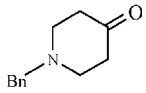
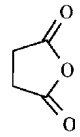
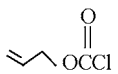
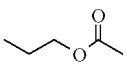


Scheme 1 Lithiation of indole derivatives

The lithiation of **1** leads to an *ortho*-lithiated intermediate, which upon treatment with alkylaldehydes affords racemic alcohols in good yield (entries 1–4, Table 1).

Steric hindrance of the alkyl group could be taken into account on the study of the experimental obtained results (see entry 3, Table 1). The alkylation with aryl or α,β unsaturated aldehydes can be achieved in acceptable yield (entries 5 and 7, Table 1). The condensation with *p*-methoxybenzaldehyde leads to the corresponding ketone instead of the expected alcohol. The alcohol was observed in small amounts when the *p*-methoxybenzaldehyde was used as electrophile due to fast oxidation to the corresponding ketone (entry 6, Table 1). The obtained result suggests that, nucleophilic attack of the *ortho*-lithiated intermediate on the aldehyde occurs and the alcohol formed

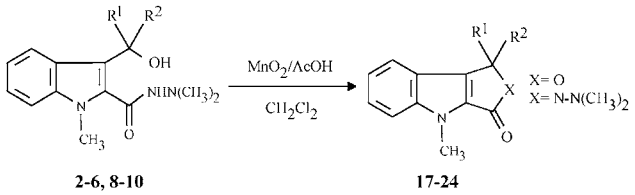
Table 1 Directed *ortho*-Lithiation of Indole-2-hydrazide

Entry	Electrophile	R^1	R^2	R^3	Compound	Yield (%)
1	CH_3CHO	CH_3	H	–	**2**	78
2	$CH_3(CH_2)_5CHO$	$CH_3(CH_2)_5$	H	–	**3**	77
3	$(CH_3)_3CCHO$	$(CH_3)_3C$	H	–	**4**	69
4	$C_6H_5CH_2OCH_2CHO$	$C_6H_5CH_2OCH_2$	H	–	**5**	74
5			H	–	**6**	61
6		–	–		**7**[a]	75
7		$C_6H_5CH=CH$	H	–	**8**	59
8		$-(CH_2)_5-$		–	**9**	63
9		$-(CH_2)_2$-NBn-$(CH_2)_2-$		–	**10**	66
10	$(CH_3)_3SiCl$	–	–	$-Si(CH_3)_3$	**11**	85
11	CH_3I	–	–	CH_3	**12**	81
12	CH_3CH_2I	–	–	CH_3CH_2	**13**	83
13		–	–	$-CO(CH_2)_2CO_2H$	**14**	61
14		–	–		**15**	69
15	 *t*-BuCCl	–	–	 *t*-BuC	**16**	65

[a] Accompanied by trace of the corresponding alcohol.

under the reaction presumably by aerial oxidation under workup conditions, is rapidly oxidized to the corresponding diarylketone. Condensation of the *ortho*-lithiated intermediate with cyclohexanone followed by acid hydrolysis gave the alcohol **9** in acceptable yield as a sole product (entry 8, Table 1). Among the derivatives available by this procedure is the functionalized amine **10** (entry 9, Table 1) obtained using *N*-benzyl-4-piperidone as the electrophilic reagent. The obtained carbinols (**2**–**10**) were proved to be labile, and the crude products were quickly and carefully purified by chromatography and then used directly in the next step.

The addition of trimethylsilyl chloride to the *ortho*-lithiated intermediate gave the desired 3-trimethylsilyl hydrazide in excellent yield (entry 10, Table 1). Moreover, we found that the treatment of the metalated hydrazide with allyl chloroformate led to the corresponding hydrazide acylated in the 3-position (entry 14, Table 1). Alkylations with simple alkyl halides gave the expected alkylhydrazide indoles (entries 11, 12, Table 1). The *ortho*-lithiated hydrazide has proven to be efficient intermediate for the synthesis of diverse acylderivatives (entries 13–15, Table 1). The route involving the use of hydrazide-indole proved to be efficient for the preparation of 2,3-disubstituted indoles, and the obtained compounds may be easily converted to the corresponding lactones or acids by oxidative cleavage (Scheme 2 and Scheme 3).



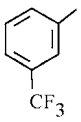
2-6, 8-10 **17-24**

Scheme 2 Oxidation and cyclization of hydrazides

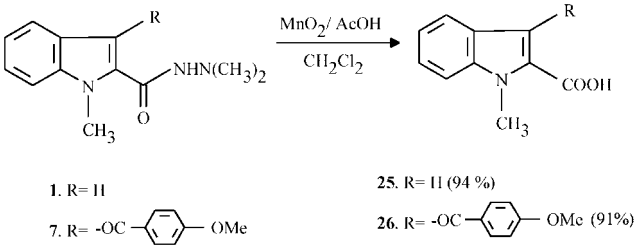
The alcohols obtained from the condensation of *ortho*-lithiated intermediate with aldehydes (entries 1–5 and 7, Table 1) or ketones (entry 8, 9, Table 1) were oxidized by treatment with activated MnO_2 in dichloromethane containing excess acetic acid.[5a] It is interesting to note that the use of $CuCl_2$[13] as oxidizing agent leads to the corresponding keto-hydrazides, whereas MnO_2 by oxidative cleavage gives the expected lactone in good yields (Table 2).

The condensed lactones (entries 1–7, Table 2) can be considered efficient intermediates for the preparation of polycyclic aromatic systems. All attempts to obtain the lactone from the alcohol **8** were unsuccessful, the main product formed was the cyclic hydrazide **24** (entry 8, Table 2). Under the same conditions (MnO_2, HOAc) the hydrazide **1** and the keto-hydrazide **7** were oxidized successfully to the expected indole carboxylic acids **25**[14] and **26** respectively (Scheme 3).

Table 2 Oxidation and Cyclization of Hydrazides

Entry	R^1	R^2	X	Compound	Yield (%)
1	CH_3	H	O	**17**	92
2	$CH_3(CH_2)_5$	H	O	**18**	95
3	$(CH_3)_3C$	H	O	**19**	79
4	$C_6H_5CH_2OCH_2$	H	O	**20**	83
5		H	O	**21**	55
6	$-(CH_2)_5-$		O	**22**	81
7	$-(CH_2)_2$-NBn-$(CH_2)_2-$		O	**23**	85
8	$C_6H_5CH=CH$	H	$N-N(CH_3)_2$	**24**	45[a]

[a] Isolated compound instead of the lactone.



Scheme 3 Oxidation of hydrazides to carboxylic acids

Directed *ortho*-lithiation of indole-2-hydrazides allows easy generation of 2,3-disubstituted indole derivatives which are of general synthetic interest.

The structural assignments of these prepared compounds were based on their analytical data: NMR spectra, IR, MS, and elemental analyses.

Preparation of Indole-hydrazide. The *N*-methylindole-2-carbonyl chloride (obtained from the corresponding acid by treatment with $SOCl_2$ in toluene) was treated with the *N*,*N*-dimethylhydrazine (1.5 mmol) in CH_2Cl_2 and the mixture was stirred overnight at room temperature. The solvent was removed and the residue was purified by column chromatography giving the hydrazide **1** as a white solid (98% yield).

General Procedure for the Introduction of a Substituent at the C-3 of the Hydrazide 1 (2–16).[15] A 25 mL, 3 necked flask, provided with a septum, argon inlet and outlet, and a stirrer, is charged with a solution of **1** (1 mmol) in anhyd THF (5 mL). The solution was cooled to –78 ºC (acetone–solid CO_2 bath) and a 1.6 M solution (3 mmol) of *t*-BuLi in hexane and TMEDA (3 mmol) was added by means of a syringe. The mixture turned brown. Stirring was continued for 3 h at –78 ºC, the corresponding electrophile (3 mmol) added by syringe and the mixture is allowed to warm to r.t. After 8 h, water (ca. 2 mL) was added, and the mixture acidified with HCl 2 N (2 mL). Extraction with Et_2O (3 × 15 mL), washing the combined ether extracts with sat. $NaHCO_3$ solution (15 mL) and with H_2O (15 mL), drying with Na_2SO_4, removal of the Et_2O on the rotary

evaporator and silica gel chromatography of the crude product (SiO_2, 70–230 mesh, hexane–ethyl acetate) gave the products. Oils were isolated directly by column chromatography, and solids were purified by column chromatography, followed by recrystallization (hexane–ethyl acetate). The yields of the pure compounds are indicated on the Table 1.

General Procedure for the Oxidation and Cyclization (17–26).[15] A 50 mL, 1 necked flask, provided with a septum and argon inlet and outlet, and a stirrer was charged with a solution of the hydroxyhydrazide (1 mmol) in dry CH_2Cl_2 (10 mL). The solution was stirred vigorously, and then, activated MnO_2 (10 mmol) and glacial acetic acid (10 mmol) were added sequentially. After stirring for 8 h at r.t. H_2O was added. The reaction mixture was filtered and the solution obtained was further diluted with H_2O (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and washed with H_2O and $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The products were purified by column chromatrography (SiO_2, 70–230 mesh) using hexane–ethyl acetate as eluant. The yields of the prepared compounds are indicated in the Table 2.

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(15) Analytical data of some representative synthesized compounds: **2-(*N*,*N*-Dimethylhydrazinecarbonyl)-1-methylindole (1)**: Mp: 168–170 ºC (hexane–ethyl acetate 2:8). IR (KBr): ν (cm^{-1}) = 3218 (N-H), 1648 [$CONHN(CH_3)_2$]. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 2.71 [s, 6 H, $N(CH_3)_2$], 4.01 (s, 3 H, NCH_3), 6.81 (br s, 1 H, NH), 7.08–7.39 (m, 3 H, H-4, H-5, H-6), 7.35 (s, 1 H, C3H), 7.61 (d, *J* = 7, 1 H, H-7). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 31.4 (CH_3, NCH_3), 47.5 [CH_3, $N(CH_3)_2$], 103.6 (CH, C3H), 109.9 (CH, C7H), 120.3 (CH, C6H), 121.6 (CH, C4H), 123.9 (CH, C5H), 125.8 (C, C3a), 130.5 (C, C2), 138.8 (C, C7a), 160.5 (C, C=O). MS: *m/z* = 218 [M^+ + 1]. Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.3; H, 7.0; N, 19.3%. Found: C, 66.2; H, 6.9; N, 19.2%. **2-(*N*,*N*-Dimethylhydrazinecarbonyl)-1-methyl-3-(4-methoxyphenylcarbonyl)indole (7)**: Mp: 129–132 ºC (hexane–ethyl acetate 3:7). IR (KBr): ν (cm^{-1}) = 3196 (N-H), 1674 (ArCOAr), 1610 [$CONHN(CH_3)_2$]. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 2.49 [s, 6 H, $N(CH_3)_2$], 3.53 (s, 3 H, NCH_3), 3.87 (s, 3 H, OCH_3), 6.97 (d, *J* = 8.8, 2 H, C3′H, and C5′H), 7.01–7.30 (m, 3 H, H-4, H-5, H-6), 7.49 (d, *J* = 8, 1 H, H-7), 7.80 (d, *J* = 8.8, 2 H, H-2′ and H-6′), 9.97 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm): 31.2 (CH_3, NCH_3), 46.5 [CH_3, $N(CH_3)_2$], 55.4 (CH_3, OCH_3), 109.9 (CH, C7H), 113.6 (CH, C3′H and C5′H), 121.3 (C, C2), 121.0, 121.3 and 123.4 (CH, C4H, C5H and C6H), 125.3 (C, C3), 131.8 (CH, C2′H and C6′H), 132.5 (C, C3a), 136.2 (C, C7a and C1′), 159.0 (C, C4′), 163.4 [C, *C*$ONHN(CH_3)_2$], 190.8 (C, C=O). MS: *m/z* = 352 [M^+ + 1]. Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.4; H, 6.0; N, 12.0%. Found: C, 68.5; H, 5.7; N, 12.1%. **2-(*N*,*N*-Dimethylhydrazinecarbonyl)-1-methyl-3-trimethyl-silylindole (11)**: Mp: 148–149 ºC (hexane–ethyl acetate 4:6). IR (KBr): ν (cm^{-1}) = 3181 (N-H), 1650 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 0.07 [s, 9 H, $Si(CH_3)_3$], 2.36 [s, 6 H, $N(CH_3)_2$], 3.35 (s, 3 H, NCH_3), 6.66 (br s, 1 H, NH), 6.70–6.96 (m, 3 H, H-4, H-5, H-6), 7.41 (d, *J* = 7.8, 1 H, H-7). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 0.73 [CH_3, $Si(CH_3)_3$], 30.4 (CH_3, NCH_3), 46.9 [CH_3, $N(CH_3)_2$], 109.6 (CH, C7H), 119.8 (CH, C6H), 121.9 (C, C3), 122.4 and 122.6 (CH, C4H and C5H), 131.8 (C, C2), 137.8 (C, C3a), 139.0 (C, C7a), 162.3 (C, C=O). MS: *m/z* = 290 [M^+ + 1]. Anal. Calcd for $C_{15}H_{23}N_3OSi$: C, 62.2; H, 8.0; N, 14.5%. Found: C, 62.0; H, 7.7; N, 14.4%. **1,3-Dimethyl-2-(*N*,*N*-dimethylhydrazinecarbonyl)indole (12)**: Mp: 161–163 ºC (hexane–ethyl acetate 2:8). IR (KBr): ν (cm^{-1}): 3242 (N-H), 1651 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 2,43 (2, 3 H, C3-CH_3), 2.73 [s, 6 H, $N(CH_3)_2$], 3.80 (s, 3 H, NCH_3), 6.71–6.79 (br s, 1 H, NH), 7.07–7.39 (m, 3 H, H-4, H-5, H-6), 7.56 (d, *J* = 8, 1 H, H-7). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 10.1 (CH_3, C3-CH_3), 31.0 (CH_3, NCH_3), 47.7 [CH_3, $N(CH_3)_2$], 109.6 (CH, C7H),), 111.8 (C, C3), 119.4 (CH, C6H), 119.8 (CH, C4H), 123.8 (CH, C5H), 127.0 (C, C3a), 128.9 (C, C2), 137.7 (C, C7a), 160.8 (C, C=O). MS: *m/z* = 232 [M^+ + 1]. Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.5; H, 7.4; N, 18.2%. Found: C, 67.4; H, 7.6; N, 18.3%. **3-Ethyl-2-(*N*,*N*-dimethylhydrazinecarbonyl)-1-methylindole (13)**: Mp: 146–149 ºC (hexane–ethyl acetate 2:8). IR (KBr): ν (cm^{-1}) = 3202 (N-H), 1651 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1.32 (t, *J* = 7.6, 3 H, CH_2CH_3), 2.76 [s, 6 H, $N(CH_3)_2$], 2.93 (q, *J* = 7.6, 2 H, CH_2CH_3), 3.85 (s, 3 H, NCH_3), 6.58–6.60 (br s, 1 H, NH), 7.05–7.37 (m, 3 H, H-4, H-5, H-6), 7.63 (d, *J* = 8.2, 1 H, H-7). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 16.1 (CH_3, CH_2CH_3), 18.3 (CH_2, CH_2CH_3), 31.0 (CH_3, NCH_3), 47.6 [CH_3, $N(CH_3)_2$], 109.7 (CH, C7H), 111.8 (C, C3), 119.4 (CH, C6H), 119.9 (CH, C4H), 123.7 (CH, C5H), 126.1 (C, C3a), 128.5 (C, C2), 137.7 (C, C7a), 160.9 (C, C=O). MS: *m/z* = 246 [M^+ + 1]. Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.5; H, 7.8; N, 17.1. Found: C, 68.4; H, 7.6; N, 17.3. **3-(2-Carboxyethyl-1-carbonyl)-2-(*N*,*N*-dimethylhydrazinecarbonyl)-1-methylindole (14)**: Mp: 120–123 ºC (ethyl acetate–methanol 9:1). IR (KBr): ν (cm^{-1}): 3483 (O-H), 3201 (N-H), 1725 (C=O), 1649 (C=O, $CONHNMe_2$). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 2.74 (t, *J* = 5.6, 2 H, CH_2CO_2H), 2.83 [s, 6 H, $N(CH_3)_2$], 3.20 (t, *J* = 5.6, 2 H,

CH_2CO), 3.66 (s, 3 H, NCH_3), 7.05–7.39 (m, 4 H, H-4, H-5, H-6, CO_2H), 7.89 (d, *J* = 8, 1 H, H-7), 8.43 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 28.5 (CH_2, CH_2CO), 31.4 (CH_3, NCH_3), 36.5 (CH_2, CH_2CO_2H), 46.7 [CH_3, $N(CH_3)_2$], 110.5 (CH, C7H), 115.0 (C, C3), 121.3 (CH, C6H), 121.4 (CH, C4H), 124.1 (CH, C5H), 121.3 (C, C2), 124.3 (C, C3a), 136.6 (C, C7a), 160.6 (C, *C*ONHNMe$_2$), 177.1 (C, CO_2H), 195.5 (C, C=O). MS: *m/z* = 318 [M^+ + 1]. Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.6; H, 6.0; N, 13.2. Found: C, 60.3; H, 6.2; N, 13.2. **3-(Allyloxycarbonyl)-2-(*N*,*N*-dimethylhydrazinecarbonyl)indole (15)**: Hexane–ethyl acetate 2:8. IR (NaCl): ν (cm^{-1}) = 3200 (N-H), 1693 (COOR), 1670 [CONHN$(CH_3)_2$]. ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 2.77 [s, 6 H, $N(CH_3)_2$], 4.01 (s, 3 H, NCH_3), 4.89 (d, *J* = 6, 2 H, CH_2O), 5.37 (m, 2 H, C***H*****$_2$**=CH), 6.10 (m, 1 H, CH_2=C***H***), 6.80 (br s, 1 H, NH), 7.32 (m, 3 H, H-4, H-5, H-6), 8.15 (d, *J* = 7, 1 H, H-7). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 32.4 (CH_3, NCH_3), 47.3 [CH_3, $N(CH_3)_2$], 65.5 (CH_2, CH_2O), 113.3 (CH, C7H), 118.6 (CH_2, *C*H**$_2$**=CH), 121.2 (C, C3), 122.8 (CH, C6H), 122.9 (CH, C4H), 124.4 (CH, C5H), 125.3 (C, C2), 132.1 (CH, CH_2=*C*H), 136.8 (C, C7a), 137.2 (C, C3a), 159.6 (C, COO-), 165.8 (C, CON-). MS: *m/z* = 302 [M^+ + 1]. Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.8; H, 6.4; N, 13.9. Found: C, 63.5; H, 6.7; N, 13.8. **3-(*t*-Butylcarbonyl)-2-(*N*,*N*-dimethylhydrazinecarbonyl)-1-methylindole (16)**: Mp: 149–150 ºC (hexane–ethyl acetate 3:7). IR (KBr): ν (cm^{-1}) = 3226 (N-H), 1662 (C=O, CONHNMe$_2$). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1.28 [s, 9 H, $C(CH_3)_3$], 2.67 [s, 6 H, $N(CH_3)_2$], 3.93 (s, 3 H, NCH_3), 7.05–7.38 (m, 3 H, H-4, H-5, H-6), 7.51 (d, *J* = 8, 1 H, H-7), 7.52 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 27.1 [CH_3, $C(CH_3)_3$], 31.3 (CH_3, NCH_3), 45.9 [C, *C*$(CH_3)_3$], 47.5 [CH_3, $N(CH_3)_2$], 110.2 (CH, C7H), 116.8 (C, C3), 121.0 (CH, C6H), 121.4 (CH, C4H), 124.1 (CH, C5H), 124.2 (C, C3a), 129.6 (C, C2), 136.7 (C, C7a), 159.7 (C, CONHNMe$_2$), 213.7 (C, C=O). MS: *m/z* = 302 [M^+ + 1]. Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.7; H, 7.7; N, 13.9. Found: C, 67.5; H, 7.9; N, 13.6. **1,4-Dimethyl-3-oxo-(1*H*)-furo[3,4-*b*]indole (17)**: Mp: 84–85 ºC (hexane–ethyl acetate 8:2). IR (KBr): ν (cm^{-1}) = 2932 (C-H), 1751 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1.70 (d, *J* = 6.6, 3 H, CHC***H*****$_3$**), 3.91 (s, 3 H, NCH_3), 5.64 (q, *J* = 6.6, 1 H, C*H*CH_3), 7.20–7.27 (m, 1 H, H-7), 7.41–7.60 (m, 2 H, H-6, H-8), 7.61 (d, *J* = 8, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 20.7 (CH_3, CH*C*H**$_3$**), 30.0 (CH_3, NCH_3), 75.4 (CH, *C*HCH_3), 111.2 (CH, C5H), 119.8 (C, C8b), 120.6 and 120.8 (CH, C6H and C8H), 125.9 (CH, C7H), 128.5 (C, C3a), 138.2 (C, C8a), 143.9 (C, C4a), 163.2 (C, C=O). MS: *m/z* = 202 [M^+ + 1]. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.5; H, 5.7; N, 6.8. **1-Hexyl-4-methyl-3-oxo-(1*H*)-furo[3,4-*b*]indole (18)**: Hexane–ethyl acetate 9:1. IR (NaCl): ν (cm^{-1}) = 2928 (C-H), 1752 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 0.91 [d, *J* = 6, 3 H, $(CH_2)_5CH_3$], 1.21–1.63 [m, 8 H, $CH_2(CH_2)_4CH_3$], 1.82–2.10 [m, 2 H, C***H*****$_2$**$(CH_2)_4CH_3$], 3.94 (s, 3 H, NCH_3), 5.58 (q, *J* = 6, 1 H, C1H), 7.23–7.46 (m, 3 H, H-6, H-7, H-8), 7.62 (d, *J* = 8, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 14.0 [CH_3, $(CH_2)_5CH_3$], 22.5 [CH_2, (CH_2)$_5CH_3$], 24.8 [CH_2, (CH_2)$_5CH_3$], 29.0 [CH_2, (CH_2)$_5CH_3$], 30.0 (CH_3, NCH_3), 31.6 [CH_2, (CH_2)$_5CH_3$], 34.6 [CH_2, (CH_2)$_5CH_3$], 79.4 (CH, C1H), 111.2 (CH, C5H), 120.1 (C, C8b), 120.8 and 121.0 (CH, C6H and C8H), 125.8 (CH, C7H), 128.8 (C, C3a), 137.0 (C, C8a), 144.0 (C, C4a), 163.4 (C, C=O). MS: *m/z* = 272 [M^+ + 1]. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.2; H, 7.8; N, 5.2. Found: C, 75.1; H, 7.7; N, 4.9. **1-*t*-Butyl-4-methyl-3-oxo-(1*H*)-furo[3,4-*b*]indole (19)**: Mp: 171–173 ºC (hexane–ethyl acetate 9:1). IR (KBr): ν (cm^{-1}) = 2963 (C-H), 1749 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1.11 [s, 9 H, $C(CH_3)_3$], 3.97 (s, 3 H, NCH_3), 5.26 (s, 1 H, H-1), 7.21–7.28 (m, 1 H, H-7), 7.39–7.45 (m, 2 H, H-6, H-8), 7.68 (d, *J* = 8, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 25.5 [CH_3, $C(CH_3)_3$], 30.0 (CH_3, NCH_3), 35.4 [C, *C*$(CH_3)_3$], 87.6 (CH, C1H), 111.2 (CH, C5H), 120.8 (C, C8b), 120.9 and 122.2 (CH, C6H and C8H), 125.9 (CH, C6H), 129.9 (C, C3a), 134.7 (C, C8a), 144.0 (C, C4a), 163.6 (C, C=O). MS: *m/z* = 244 [M^+ + 1]. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.0; N, 5.8. Found: C, 74.3; H, 6.9; N, 5.8. **1-Benzyloxymethyl-4-methyl-3-oxo-(1*H*)-furo[3,4-*b*]indole (20)**: Mp: 116–118 ºC (hexane–ethyl acetate 9:1). IR (KBr): ν (cm^{-1}) = 2932 (C-H), 1748 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 3.90 (d, *J* = 6, 2 H, CH_2O), 3.91 (s, 3 H, NCH_3), 4.65 (s, 2 H, CH_2O), 5.70 (q, *J* = 6, 1 H, C1H), 7.24 (m, 1 H, Ar), 7.42 (m, 5 H, Ar), 7.46 (m, 2 H, Ar), 7.64 (d, *J* = 8, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 30.0 (CH_3, NCH_3), 71.4 (CH_2, CH_2O), 73.8 (CH_2, CH_2O), 77.8 (CH, C1H), 111.1 (CH, C5H), 120.4 (C, C8b), 121.0 and 121.6 (CH, C6H and C8H), 126.0 (CH, C4′H), 127.6 (CH, C7H), 127.7 (CH, C2′H and C6′H), 128.3 (CH, C3′H and C5′H), 128.9 (C, C3a), 134.7 (C, C8a), 137.3 (C, C1′), 144.0 (C, C4a), 162.9 (C, C=O). MS: *m/z* = 308 [M^+ + 1]. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.3; H, 5.6; N, 4.6. Found: C, 74.0; H, 5.7; N, 4.4. **1-(3′-(Trifluoromethane)phenyl)-4-methyl-3-oxo-(1*H*)-furo[3,4-*b*]indole (21)**: Hexane–ethyl acetate 8:2. IR (NaCl): ν (cm^{-1}) = 2919 (C-H), 1759 (C=O), 1331 (C-F). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 4.02 (s, 3 H, NCH_3), 6.59 (s, 1 H, H-1), 7.19–7.60 (m, 6 H, H-4′, H-5′, H-6′, H-6, H-7, H-8), 7.64 (d, *J* = 7, 1 H, H-5), 7.71 (s, 1 H, H-2′). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 30.0 (CH_3, NCH_3), 79.2 (CH, C1H), 111.5 (CH, C5H), 120.2 (C, C8b), 120.8 and 121.5 (CH, C6H and C8H), 125.6 (C, *J* = 288, CF_3), 125.9 (CH, *J* = 3.6, C4′H), 126.4 (CH, C7H), 128.5 (CH, *J* = 3.6, C2′H), 128.9 (C, C3a), 129.4 (CH, C5′H), 130.3 (CH, C6′H), 130.6 (C, *J* = 32, C3′), 131.9 (C, *J* = 1, C1′), 141.0 (C, C8a), 144.4 (C, C4a), 162.7 (C, C=O). MS: *m/z* = 332 [M^+ + 1]. Anal. Calcd for $C_{18}H_{12}F_3NO_2$: C, 65.3; H, 3.7; N, 4.2. Found: C, 65.5; H, 3.9; N, 4.4. **4′-Methyl-3-oxo-(1*H*)spiro{cyclo-hexyl[1,1′]furo[3,4-*b*]indole} (22)**: Mp: 152–154 ºC (hexane–ethyl acetate 9:1). IR (KBr): ν (cm^{-1}): 2921 (C-H), 1749 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1.50–2.08 (m, 10 H, CH_2), 3.93 (s, 3 H, NCH_3), 7.18–7.27 (m, 1 H, H-7), 7.39–7.44 (m, 2 H, H-6, H-8), 7.68 (d, *J* = 8, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz):
δ (ppm) = 22.5 (CH_2, C3′H and C5′H), 24.6 (CH_2, C4′H), 30.0 (CH_3, NCH_3), 36.7 (CH_2, C2′H and C6′H), 86.0 (C, C1), 111.2 (CH, C5H), 119.8 (C, C8b), 120.7 and 121.1 (CH, C6H and C8H), 125.7 (CH, C7H), 128.2 (C, C3a), 138.2 (C, C8a), 143.9 (C, C4a), 163.2 (C, C=O). MS: *m/z* = 256 [M^+ + 1]. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5. Found: C, 75.2%, H, 6.9; N, 5.2. **1′-Benzyl-4-methyl-3-oxo-(1*H*)-spiro{furo[3,4-*b*]indole-1,4′-piperidine} (23)**: Hexane–ethyl acetate 8:2. IR (NaCl): ν (cm^{-1}) = 1755 (C=O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 1.87 (d, *J* = 12.8, 2 H, H_{ax}-3′ and H_{ax}-5′), 2.47 (dt, *J* = 11.8, *J*′ = 4.4, 2 H, H_{eq}-3′ and H_{eq}-5′), 2.70 (dt, *J* = 11.6, *J*′ = 2, 2 H, H_{ax}-2′ and H_{ax}-6′), 3.01 (d, *J* = 11.2, 2 H, H_{eq}-2′ and H_{eq}-6′), 3.74 (s, 2 H, CH_2Ar), 3.92 (s, 3 H, NCH_3), 7.11–7.42 (m, 8 H, H-6, H-7, H-8, H-2″, H-3″, H-4″, H-5″ and H-6″), 7.63 (d, *J* = 8, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 30.1 (CH_3, NCH_3), 35.7 (CH_2, C3′ and C5′), 49.2 (CH_2, C2′ and C6′), 62.5 (CH_2, CH_2Ar), 82.9 (C, C1), 111.2 (CH, C5H), 119.6 (C, C8b), 120.8 and 121.0 (CH, C6H and C8H), 126.0 (CH, C7H), 127.5 (CH, C4″H), 128.1 (C, C3a),

128.3 (CH, C2″H and C6″H), 129.6 (CH, C3″H and C5″H), 136.4 (C, C1″), 140.4 (C, C8a), 143.9 (C, C4a), 162.5 (C, C=O). MS: *m/z* = 347 [M^+ + 1]. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.3; H, 6.4; N, 8.1. Found: C, 76.1; H, 6.6; N, 8.3. **1-(Cynnamyl)-2-(*N*,*N*-dimethylamino)-4-methyl-3-oxo-(1*H*)-pirrolo[3,4-*b*]indole (24)**: Mp: 170–172 ºC (hexane–ethyl acetate 7:3). IR (KBr): ν (cm^{-1}): 2925 (C-H), 1682 (C=O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm): 3.01 [s, 6 H, $N(CH_3)_2$], 4.00 (s, 3 H, NCH_3), 5.19 (d, *J* = 8.4, 1 H, H-1), 6.13 (dd, *J* = 15.7, *J*′ = 8.2, 1 H, C*H*CHAr), 6.79 (d, *J* = 15.6, 1 H, CHC*H*Ar), 7.10–7.45 (m, 8 H, H-2′, H-3′, H-4′, H-5′, H-6′, H-6, H-7, H-8), 7.56 (d, *J* = 8, 1 H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 30.2 (CH_3, NCH_3), 45.0 [CH_3, $N(CH_3)_2$], 60.6 (CH, C1H), 110.1 (CH, C8H), 120.0 (CH, C5H), 120.5 (CH, C6H), 121.7 (C, C8b), 124.2 (CH, C7H), 124.6 (C, C8a), 126.3 (CH, *C*HCHAr), 126.6 (CH, C3′H and C5′H), 128.0 (CH, C4′H), 128.6 (CH, C2′H and C6′H), 132.5 (C, C3a), 133.9 (CH, CH*C*HAr), 136.3 (C, C1′), 141.9 (C, C4a), 162.5 (C, C=O). MS: *m/z* = 332 [M^+ + 1]. Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.1; H, 6.4; N, 12.7. Found: C, 76.2; H, 6.7; N, 12.5. **1-Methyl-3-(4-methoxyphenylcarbonyl)indole-2-yl-carboxylic acid (26)**: Mp: 124–126 ºC (hexane–ethyl acetate, 7:3). IR (KBr): ν (cm^{-1}): 2959 (O-H), 1715 (C=O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 3.93 (s, 3 H, NCH_3), 4.25 (s, 3 H, OCH_3), 6.98 (d, *J* = 8.8, 2 H, C3′H, and C5′H), 7.03–7.45 (m, 4 H, H-4, H-5, H-6, CO_2H), 7.54 (d, *J* = 8.4, 1 H, H-7), 7.84 (d, *J* = 8.8, 2 H, H-2′ and H-6′). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) = 33.0 (CH_3, NCH_3), 55.6 (CH_3, OCH_3), 111.0 (CH, C7H), 113.7 (CH, C3′H and C5′H), 116.8 (C, C2), 122.6, 122.8 and 125.6 (CH, C4H, C5H and C6H), 125.8 (C, C3), 131.0 (C, C1′), 132.7 (CH, C2′H and C6′H), 133.2 (C, C3a), 137.5 (C, C7a), 161.4 (C, C4′), 164.1 (C, CO_2H), 194.6 (C, C=O). MS: *m/z* = 310 [M^+ + 1]. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.9; H, 4.9; N, 4.5. Found: C, 69.7; H, 5.2; N, 4.2.