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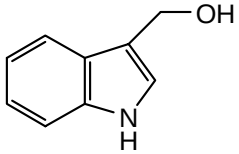
SYNTHESIS AND CYTOTOXIC ACTIVITY OF *N*-ACETYLATED TRIINDOLYLMETHANES

Jun Li[1, 2], Bing Guang[1], Liangbing Wang[1], Bogang Li[1], and Guolin Zhang[1*]

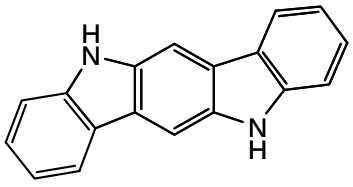
[1]Chengdu Institute of Biology, the Chinese Academy of Sciences, Chengdu 610041, P. R. China, [2]Chengdu Institute of Organic Chemistry, the Chinese Academy of Sciences, Chengdu 610041, P. R. China

Abstract –Triindolylmethanes or *N*-acetylated triindolylmethanes were synthesized with high yields by treating indoles with indole-3-carboxaldehydes in acetic acid and acetic anhydride. *In vitro* screening showed that bis(indole-3-yl)-(*N*-acetylindole-3'-yl)methane (**3a**) and bis(2-methylindole-3-yl)-(*N*-acetylindole-3'-yl)methane (**3b**) possessed moderate cytotoxic activity against Lu-04 cell line with GI_{50} of 19 μM and 33 μM, respectively.

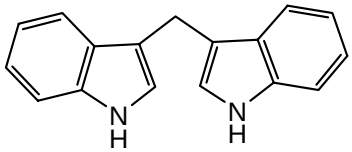
The wide-ranging biological activity associated with indole derivatives, both naturally occurring and synthetic, ensures that the synthesis of indole derivatives remains a topic of current interest.[1~3] Monoindole and bisindole have been intensively studied and the results revealed that most of them have biological activities, such as indole-3-carbinol (**I**), found in *Brassica* plants, is a potential cancer protective agent.[4, 5] Acid treatment of **I** produces a mixture of dimer (ICZ **II** and DIM **III**), which is also active.[6, 7] However, the studies of triindoles, especially triindolylmethanes were only limited to the synthesis and application as dye materials.[8] Up to now there is no report about the biological activities of triindolylmethanes.



I (I3C)



II (ICZ)

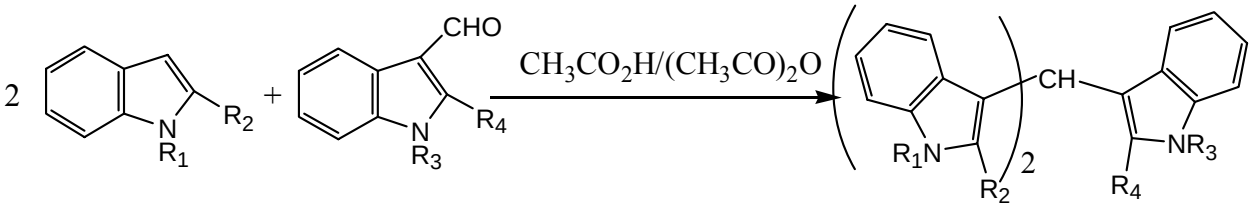


III (DIM)

Triindolylmethanes were firstly synthesized by treatment of indole-3-carboxaldehyde with two equivalents of indole in acetic acid and ethanol with unsatisfactory yields.[9~11] In 1984, another synthetic method was developed by Mueller and co-workers, in which triindolylmethanes were prepared by treatment of 3-substituted indoles with ethyl orthoformate in acidic media. Only symmetric triindolylmethanes could be prepared by this method and the yields were still not adequate in many times. [12] Clay was used to catalyze this reaction by Chakrabarty and co-workers in the absence of solvent, and the yield could reach 78%.[13] But when indole was substituted, several kinds of triindolylmethanes were formed by side reaction. In this paper we wish to disclose an efficient synthesis and evaluation of cytotoxic activities of tri(indole-3-yl)methanes or *N*-acetylated tri(indole-3-yl)methanes (**3a**~**3h**).

In our method, **2** reacted with two equivalents of **1** in acetic acid and acetic anhydride (Scheme 1 and Table 1). Acetic anhydride was not only used as reagent and solvent, but also as additive to remove the water produced by the reaction. So the yield could get up to 94.4%.

Scheme 1



1	**2**	**3(a~h)**
a: R_1=R_2=H	a: R_3=R_4=H	a: R_1= R_2=R_4=H, R_3=CH_3CO
b: R_1=H, R_2 =Me	b: R_3=R_4=H	b: R_1=R_4=H, R_2=Me, R_3=CH_3CO
c: R_1=H, R_2=Ph	c: R_3=R_4=H	c: R_1=R_4=H, R_2=Ph, R_3=CH_3CO
d: R_1=R_2=H	d: R_3=H, R_4=Ph	d: R_1= CH_3CO, R_2= R_3=H, R_4=Ph
e: R_1=H, R_2=CO_2Et	e: R_3=R_4=H	
f: R_1=Ts, R_2=H	f: R_3=R_4=H	
g: R_1=H, R_2=Ph	g: R_3=H, R_4=Ph	g: R_1= R_3=H, R_2=R_4=Ph
h: R_1=n-Bu, R_2 =H	h: R_3=R_4=H	h: R_1= n-Bu, R_2=R_3=R_4=H

RESULTS AND DISCUSSION

The results (Table 1) showed that under our conditions, most of the triindolylmethanes were acetylated by acetic anhydride. Indole and its derivatives are easy to be attacked by electrophiles (such as acetic anhydride) at C-3.[14] In this reaction, indole reacted firstly with indole-3-carboxaldehyde but not acetic anhydride, which only reacted with triindolylmethanes as soon as they formed. The ^{1}H-NMR and MS

spectra suggested the newly formed triindolylmethanes were acetylated at *N*-atoms (**3g** and **3h** were not acetylated). When R_1, R_2, R_3, and R_4 were hydrogen, the yield of **3a** (Entry 1) got to 82.7% and it was acetylated by one acetyl. But when a methyl was introduced onto C-2 of indole, **1b**'s reactivity decreased (Entry 2) and the yield of **3b** was only 51.4%. When phenyl group presented at C-2 of indole (Entry 3), the reaction proceeded well to give **3c** with a yield up to 94.4%. The structure of **3c** was confirmed by crystallographic analysis (Figure 1 and Table 2). The crystals of **3c** from the mixture of THF and petroleum ether with orthorhombic crystal system contain two molecules of THF (not drawn in the Figure 1). It is to be noted that the bond length of C (1)-C (3") (1.508(5) Å) is shorter than that of C (1)-C (3') (1.525(5) Å) or C (1)-C (3) (1.529(5) Å), and the bond angle of C (3")-C (1)-C (3') (113.7(3)°) is different from those of C (3")-C (1)-C (3) (110.5(3)°) and C (3')-C (1)-C (3) (115.1(4)°). According to the possible reaction mechanism (Scheme 2), the substituent at C-2 of indole could have hindrance.[13] However, as phenyl group can stabilize the intermediates and this plays as a dominant factor, 2-phenylindole has a high reactivity. Substituents at C-2 of **2** would block the attack of indole (Entry 4), so the reaction time would get longer and the yield was lower. The MS and ^{1}H-NMR spectra indicated that this triindolylmethane was acetylated by two acetyl groups (**3d**). *N*-Alkylated indole could also react with indole-3-carboxaldehyde to yield corresponding product without acetylating by acetic anhydride (Entry 8, **3h**). And in another reaction (Entry 7), when R_2 and R_4 were phenyl group, the product tri(2-phenyl- indole-3-yl) methane (**3g**) was not acetylated. When electron-withdrawing substituents such as -CO_2Et onto C-2 (Entry 5) or -Ts onto nitrogen (Entry 6) were introduced, indole's nucleophilic reactivity decreased so much that the reaction could not take place.

Table 1. Results of indoles reacted with indole-3-carbaldehydes

Entry	**1**	**2**	Reaction conditions	Triindolylmathane (**3**)	Yield (%) [a]
1	**1a**	**2a**	rt, 5 h	**3a** (one acetyl)	82.7
2	**1b**	**2b**	rt, 12 h	**3b** (one acetyl)	51.4
3	**1c**	**2c**	rt, 12 h	**3c** (one acetyl)	94.4
4	**1d**	**2d**	reflux , 5 h	**3d** (two acetyl)	37.1
5	**1e**	**2e**	reflux, 36 h	–	–
6	**1f**	**2f**	reflux, 36 h	–	–
7	**1g**	**2g**	rt, 36 h	**3g** (no acetyl)	55.0
8	**1h**	**2h**	rt, 36 h	**3h** (no acetyl)	42.3

[a] Isolated yields.

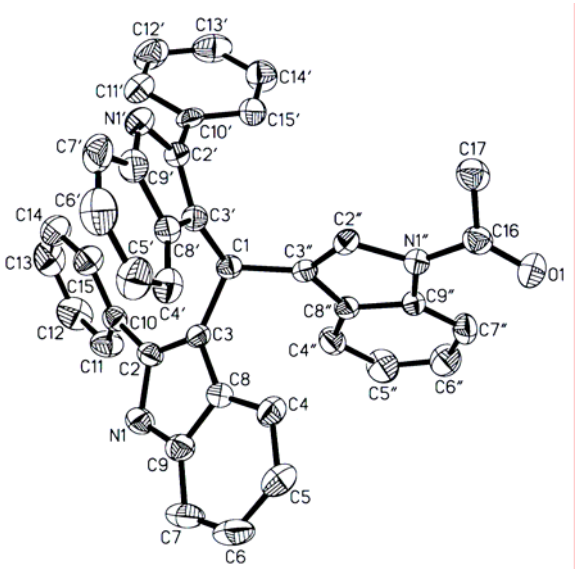


Figure 1 ORTEP diagram of bis(2-phenylindole-3-yl)-(*N*-acetylindole-3'-yl)methane (**3c**) (two THF molecules were omitted).

Scheme 2

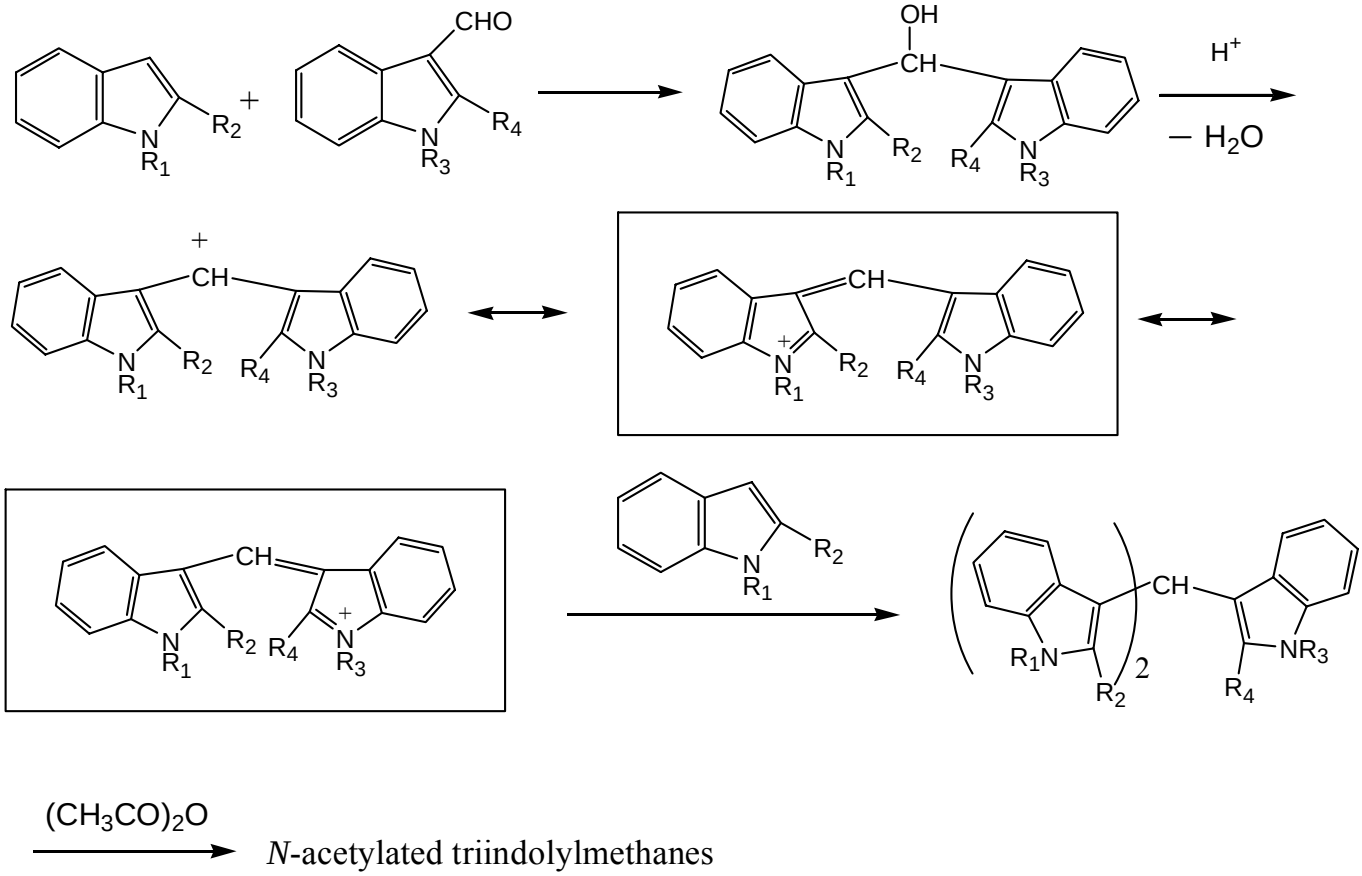


Table 2. Crystallographic data for **3c**

Formula	$[C_{39}H_{29}N_3O].[C_8H_{16}O_2]$	P_{calcd} ($g.cm^{-3}$)	1.197
Fw	699.86 (contain two THF molecules)	μ (Mo Ka)(mm^{-3})	0.075
Crystal system	Orthorhombic	F (000)	1488
Space group	Pca2 (1) |	θ range (deg)	1.52~25.00
a (Å)	17.848 (3)	Indepdt reflens	3552
b (Å)	13.399 (3)	GOF on F^2	0.772
c (Å)	16.232 (4)	R 1[a] [I>2σ(I)][a]	0.0406
V ($Å^3$)	3882.0 (14)	wR2[b]	0.0540
Z	4	abs struct param	-1 (2)
T (K)	296 (2)	Ext coeff	0.0042 (2)
Λ (Mo Ka) (Å)	0.71073	Largest diff peak and hole (e. $Å^3$)	0.127 and –0.125

[a] $R1= \Sigma \| F_0 | - | F_c \| / \Sigma | F_0 |$

[b] $wR2=\{\Sigma w(F_0^2-F_c^2)^2/ \Sigma wF_0^4\}^{1/2}$

The *in vitro* cytotoxic activities of **3a~3d**, **3g** and **3h** were evaluated against Lu-04, N-04 and Bre-04 cell lines using sulforhodamine B (SRB) assay.[15] The results revealed that most of the triindolylmethanes exhibited no activity, only **3a** and **3b** showed reasonable activities. **3a** is cytotoxic to Lu-04, N-04 and Bre-04 cell lines successively with GI_{50} of 19 μM, 47 μM and 28 μM. The GI_{50} of **3b** against Lu-04 and Bre-04 cell lines were 33 μM and 56 μM, respectively, whereas the GI_{50} values of **3c**, **3d**, **3g** and **3h** to Lu-04, N-04 and Bre-04 cell lines exceeded 100 μM.

EXPERIMENTAL

Melting Points were measured on an XRC-1 Micro-Melting Point apparatus and are uncorrected. UV spectra were measured on a GBC Cintra 20 Spectrometer (CH_3CN as solvent). ^1H and ^{13}C NMR spectra were recorded on Vrian^{unity}Ionva-400 or Bruker AC-300P spectrometer. The chemical shifts are reported

in ppm (δ value) downfield from tetramethylsilane (TMS), which was used as an internal standard. IR spectra were measured on Nicolet Protégé 460 Spectrophotometer (KBr disc). HR-ESIMS were measured on API QSTAR Pulsar i system mass spectrometer. ESIMS were carried on Finnigan LCQ^{DECA} Spectrometer. Analytical TLC was carried out on silica gel (10~40 μ) precoated plates.

General procedure for condensation of indole with indole-3-carboxaldehyde

To a solution of the indole-3-carbaldehyde (**2**, 0.5 mmol) in acetic acid (1.0 mL, 17.5 mmol) and acetic anhydride (2.0 mL, 20.0 mmol) was added dropwise indole (**1**, 1.0 mmol) in acetic anhydride (1.0 mL, 10.0 mmol) at rt under nitrogen atmosphere, and the mixture was stirred until the formation of products ceased. To the reaction mixture was added saturated $NaHCO_3$ (aq.) until pH=7 and the mixture was extracted by ethyl acetate. The organic layer was washed with saturated NaCl (aq.), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue, which was purified by silica gel column chromatography. Elution of the column with ethyl acetate/petroleum ether mixture gave the required triindolylmethanes or *N*-acylated triindolylmethanes.

Bis(indole-3-yl)-(*N*-acetylindole-3'-yl)methane (3a): mp 151-153 ºC (petroleum ether/ethyl acetate=5/1 (V/V)); UV λ_{max}^{MeCN} nm: 225.8; HR-ESIMS (positive mode) *m/z*: 403.1685 ($[M]^+$, $C_{27}H_{21}N_3O$, calcd: 403.1684); ESIMS (negative mode) *m/z*: 403 ($[M]^-$), 402 ($[M-1]^-$); IR ν_{max}^{KBr} cm^{-1}: 3424.0, 1675.1, 1451.81, 1390.5, 745.6; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 10.02 (2H, br s, N-H), 8.40 (1H, d, J=8.0 Hz, H-7'), 7.53 (2H, dd, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-4), 7.51 (1H, dd, J_1=8.0 Hz, J_2=0.8 Hz, H-4'), 7.40 (2H, dd, J_1=8.0 Hz, J_2=1.2 Hz, 2 H-7), 7.38 (1H, dd, J_1=2.4 Hz, J_2=0.8 Hz, H-2'), 7.27 (1H, td, J_1=8.0 Hz, J_2=1.2 Hz, H-5'), 7.13 (1H, td, J_1=8.0 Hz, J_2=0.8 Hz, H-6'), 7.07 (2H, td, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-5), 7.02 (2H, dd, J_1=2.4 Hz, J_2=0.8 Hz, 2 H-2), 6.30 (2H, td, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-5), 6.17 (1H, q, J=0.8 Hz, $(indolyl)_3C\underline{H}$), 2.48 (3H, s, $-COCH_3$); ^{13}C-NMR (75 MHz, acetone-d_6): 169.62 (-CO-), 138.01, 137.85, 131.38, 127.87, 126.56, 125.28, 124.88, 124.44, 124.28, 123.70, 121.99, 120.93, 120.06, 119.31, 118.15, 118.10, 117.02, 112.24, 112.18, 31.04 ($(indolyl)_3\underline{C}H$), 23.90 ($-CO\underline{C}H_3$)

Bis(2-methylindole-3-yl)-(*N*-acetylindole-3'-yl)methane (3b): mp 233.5-235 ºC (petroleum ether/ethyl acetate=4/1(V/V)); UV λ_{max}^{MeCN} nm: 203.5, 229.4; HR-ESIMS (positive mode) *m/z*: 431.1974 ($[M]^+$, $C_{29}H_{25}N_3O$, calcd: 431.1997); ESIMS (negative mode) *m/z*: 431 (M^-), 430 ($[M-1]^-$); IR ν_{max}^{KBr} cm^{-1}: 3406.6, 1697.2, 1450.6, 1382.0, 745.1; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 9.91 (2H, br s, 2 N-H), 8.41 (1H, d, J=8.0 Hz, H-7'), 7.25 (6H, m, 1 H-4', 1 H-6', 2 H-4, 2 H-7), 7.13 (1H, d, J=1.6 Hz, H-2'), 7.10 (1H, td, J_1=8.0 Hz, J_2=1.2 Hz, H-5'), 6.95, (2H, td, J_1=8.0 Hz, J_2=1.2 Hz, 2 H-6), 6.76 (2H, td, J_1=8.0 Hz, J_2=1.2 Hz, 2 H-5), 6.17 (1H, d, J=1.6 Hz, $(indolyl)_3C\underline{H}$), 2.44 (3H, s, $-COCH_3$), 2.23 (6H, s, 2 CH_3); ^{13}C-NMR

(75 MHz, acetone-d_6): 169.37 (-CO-), 137.13, 136.22, 132.55, 131.84, 129.42, 126.51, 125.37, 124.82, 123.78, 120.75, 120.65, 119.35, 119.08,116.95, 112.16, 111.09, 111.04, 31.61 ((indolyl)$_3$C<u>H</u>), 23.91 (-CO<u>C</u>H$_3$), 12.30 (-<u>C</u>H$_3$), 12.32 (-<u>C</u>H$_3$)

Bis(2-phenylindole-3-yl)-(*N*-acetylindole-3'-yl)methane (3c): mp 157-159 ºC (petroleum ether/ethyl acetate=5/1(V/V)); UV λ_{max}^{MeCN} nm: 303.3; HR-ESIMS (positive mode) *m/z*: 555.2307 ([M]$^+$, $C_{39}H_{29}N_3O$, calcd: 555.2310); ESIMS (negative mode) *m/z*: 554.3 ([M-1]$^-$); IR ν_{max}^{KBr} cm^{-1}: 3359.0, 1708.0, 1451.0, 745.9; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 10.44 (2H, br s, 2 N-H), 8.36 (1H, d, J=8.4 Hz, H-7'), 7.45 (8H, m), 7.31 (1H, d, J=1.6 Hz, H-2'), 7.19 (7H, m), 7.01 (4H, m), 6.73 (2H, td, J_1=8.4 Hz, J_2=1.2 Hz, 2 H-5), 6.30 (1H, d, J=1.6 Hz, (indolyl)$_3$C<u>H</u>), 2.45 (3H, s, -COCH$_3$); ^{13}C-NMR (75 MHz, acetone-d_6): 169.45 (-CO-) , 137.42, 137.16, 136.27, 134.19, 131.27, 129.51, 129.11, 129.06, 128.79, 128.06, 127.52, 125.50, 125.41, 123.74, 122.04, 121.68, 120.42, 119.65, 116.98, 114.31, 111.98, 33.26 ((indolyl)$_3$C<u>H</u>), 24.00 (-CO<u>C</u>H$_3$); **3c** was recrystallized from the mixture of THF and petroleum ether to give crystals suitable for X-Ray crystallography. The crystallographic data for **3c** see Table 2.

Bis(*N*-acetylindole-3-yl)-(2-phenylindole-3'-yl)methane (3d): mp 221-222 ºC (petroleum ether/ethyl acetate=4/1(V/V)); UV λ_{max}^{MeCN} nm: 238, 297.5, 302.2; HR-ESIMS (positive mode) *m/z*: 521.2102 ([M]$^+$, $C_{35}H_{27}N_3O_2$, calcd: 521.2103); ESIMS (negative mode) *m/z*: 521 ([M]$^-$), 520 ([M-1]$^-$); IR ν_{max}^{KBr} cm^{-1}: 3427.5, 1701.8, 1450.7, 1386.4, 748.3; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 10.53 (1H, br s, N-H'), 8.39 (2H, d, J=8.0 Hz, 2 H-7), 7.71 (1H, d, J=8.0 Hz, H-4'), 7.62 (2H, dt, J_1=6.8 Hz, J_2=1.6 Hz, aromatic protons), 7.45 (6H, m), 7.27 (2H, td, J_1=8.0 Hz, J_2=1.2 Hz, 2 H-5), 7.20 (2H, dd, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-4), 7.09 (2H, td, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-6), 7.05 (1H, td, J_1=8.0 Hz, J_2=0.8 Hz, H-6'), 6.87 (1H, td, J_1=8.0 Hz, J_2=0.8 Hz, H-5'), 6.18 (1H, t, J=1.6 Hz, (indolyl)$_3$C<u>H</u>), 2.44 (6H, s, 2 (-COCH$_3$)); ^{13}C-NMR (100 MHz, chloroform-d_1): 168.56 (-CO-), 136.28, 136.24, 135.57, 132.61, 129.93, 128.88, 128.46, 128.30, 128.06, 125.22, 124.04, 123.91, 123.40, 122.25, 120.19, 119.82, 119.75, 116.56, 111.60, 111.12, 31.27 ((indolyl)$_3$C<u>H</u>), 24.00 (-CO<u>C</u>H$_3$)

Tri(2-phenylindole-3-yl)methane (3g): mp >290 ºC (petroleum ether/ethyl acetate=5/1(V/V)); UV λ_{max}^{MeCN} nm, 208, 232.9, 305.9; HR-ESIMS (positive mode) *m/z*: 589.2509 ([M]$^+$, $C_{43}H_{31}N_3$, calcd: 589.2517); ESIMS (negative mode) *m/z*: 589 (M$^-$), 588 ([M-1]$^-$); IR ν_{max}^{KBr} cm^{-1}: 3415.7 , 1452.0, 741.4 ; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 10.33 (3H, br s, N-H), 7.40 (3H, dt, J_1=8.0 Hz, J_2=0.8 Hz, 3 H-4), 7.28 (6H, m, aromatic protons), 7.20 (3H, d , J=8.0 Hz, 3 H-7), 7.07 (9H, m, aromatic protons), 7.01 (3H, td, J_1=8.0 Hz, J_2=0.8 Hz, 3 H-6), 6.66 (3H, td, J_1=8.0 Hz, J_2=0.8 Hz, 3 H-5), 6.33 (1H, s, (indolyl)$_3$C<u>H</u>); ^{13}C-NMR (100 MHz, acetone-d_6): 137.37¸136.09, 134.44, 130.52, 129.03, 128.67, 127.64, 122.35, 121.87,

119.63, 117.85, 111.80, 111.75, 34.23 ((indolyl)$_3$CH).

Bis(*N*-n-butylindole-3-yl)-(indole-3'-yl)methane (3h): mp 132-133.5 ºC (petroleum ether/ethyl acetate=20/1(V/V)); UV λ_{max}^{MeCN} nm: 228.2, 287.7; HR-ESIMS (positive mode) *m/z*: 473.2828 ($[M]^+$, $C_{33}H_{35}N_3$, calcd: 473.2830); ESIMS (positive mode) *m/z*: 473 (M^+), 472 ($[M-1]^+$); IR ν_{max}^{KBr} cm^{-1}: 3413.5, 1465.1, 1362.2, 1335.2, 739.0; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 9.95 (1H, br s, N-H'), 7.47 (2H, dt, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-4), 7.45 (1H, d, J=8.0 Hz, H-4'), 7.38 (3H, dd, J_1=8.0 Hz, J_2=0.8 Hz, 3 H-7), 7.08 (2H, td, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-6), 7.05 (1H, td, J_1=8.0 Hz, J_2=0.8 Hz, H-6'), 6.92 (3H, d, J=0.8 Hz, 3 H-2), 6.88 (1H, td, J_1=8.0 Hz, J_2=0.8 Hz, H-5'), 6.87 (2H, td, J_1=8.0 Hz, J_2=0.8 Hz, 2 H-5), 6.15 (1H, d, J=0.8 Hz, (indolyl)$_3$CH), 4.08 (4H, t, J=6.8 Hz, 2 (N-CH_2CH$_2$CH$_2$CH$_3$)), 1.72 (4H, p, J=7.2 Hz, 2 (N- CH$_2$CH_2CH$_2$CH$_3$)), 1.26 (4H, m, 2 (N-CH$_2$CH$_2$CH_2CH$_3$)), 0.85 (6H, t, J=3.6 Hz, 2 (N-CH$_2$CH$_2$-CH$_2$CH_3)); ^{13}C-NMR (100 MHz, acetone-d_6): 138.09, 137.72, 128.66, 128.13, 127.72, 124.22, 121.82, 121.67, 120.75, 120.48, 119.81, 119.02, 118.88, 112.09, 110.24, 46.18, 33.13, 32.18 ((indolyl)$_3$CH), 20.60, 13.93.

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