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Synthesis, Characterization and Crystal structure Studies of 2-[(4-chlorophenyl)(1H-indol-3-yl)methyl]-1H-indole

R. Anil Kumar^{1#}, S. Naveen^{2#}, T. O. Shrunghesh Kumar¹, K. M. Mahadevan¹,
M. N. Kumara³ and N. K. Lokanath^{4*}

¹Department of Chemistry, Kuvempu University, P. G. Centre Kadur 577548, India

²Institution of Excellence, Vijnana Bhavana, Manasagangotri, University of Mysore, Mysuru 570 006, India

³Department of Chemistry, Yuvaraja's College, University of Mysore, Mysuru 570 005, India

⁴Department of Studies in Physics, Manasagangotri, University of Mysore, Mysuru 570 006, India

ABSTRACT

The title compound, 2-[(4-chlorophenyl)(1H-indol-3-yl)methyl]-1H-indole was synthesized in good yield by condensation reaction between commercially available indole and 4-chlorobenzaldehyde under constant stirring in glacial acetic acid as a catalyst and solvent. The product obtained was characterized by spectroscopic techniques and finally the structure was confirmed by X-ray diffraction studies. The compound crystallizes in the triclinic crystal system with the space group *P*-1 with unit cell parameters $a = 7.4955(4) \text{ \AA}$, $b = 12.0832(7) \text{ \AA}$, $c = 13.7889(8) \text{ \AA}$, $\alpha = 106.727(2)^\circ$, $\beta = 103.691(2)^\circ$, $\gamma = 96.829(2)^\circ$ and $Z=2$. The crystal structure features a strong N-H...O hydrogen bond with different packing motifs. In the crystal string N-H... π , C-H... π and C-H...Cl interactions occur, forming a three dimensional network.

Keywords: Indoles, Crystal structure, Hydrogen Bonds, N-H... π and C-H... π interactions.

INTRODUCTION

Indole ring system is important class of heterocyclic compounds. These compounds have received increasing attention due to their wide range of pharmaceutical properties [1-4]. Specially, bis(indolyl)methane scaffolds are attractive synthetic targets [5] because of their widespread occurrence in natural products and the biological activities [6]. There are many bisindolylmethanes that are reported as potential anticancer agents [7]. Moreover, the bisindolylmethane derivatives were found to be potent and selective mitochondrial H⁺-ATP synthase inhibitors [8]. More importantly they are the antagonists of Nur-77 receptor as well [9]. Many methods have been developed for the synthesis of bisindolylmethane [10]. The Friedel-Crafts synthesis using indoles and aldehydes or ketones remains the most widely used synthetic procedure [11]. In view of their broad spectrum of biological properties and as a part of our ongoing work on synthesis and characterization of novel compounds [12-17], the title compound was synthesized. The compound obtained was characterized spectroscopically and finally the structure was confirmed by X-ray diffraction studies.

MATERIALS AND METHODS

Commercially available chemicals were used directly as received. Melting point was determined in open capillary and is uncorrected. FTIR was recorded (400–4000 cm⁻¹) using KBr pellet method on Shimadzu-8400S spectrometer. ¹H NMR was recorded at 400MHz in CDCl₃ solvent. Mass spectra was recorded on a Jeol SX 102=DA-6000 (10 kV) mass spectrometer.

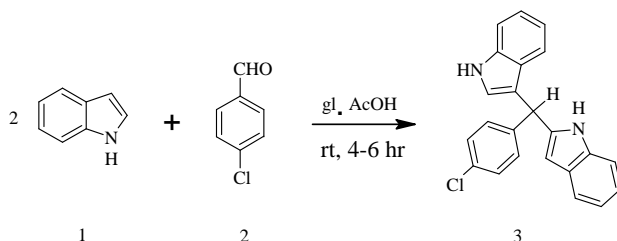
Synthesis of 2-[(4-chlorophenyl)(1H-indol-3-yl)methyl]-1H-indole:

To a flask containing 5 ml of glacial acetic acid, indole (2 mmol, 0.23 g) was added under stirring until all the indole

was dissolved. Then 4-chlorobenzaldehyde (1 mmol, 0.13 g) was added under vigorous stirring. The reaction mixture was allowed to stir for over 4 to 6 hrs, where the reaction solution turned from light yellow to light pink and then to dark red colour. The product was detected by TLC (100 % CH₂Cl₂). After, completion of the reaction, the reaction mixture was added to the ice cold water. The product separated out from the reaction mixture was filtered and washed with water. The crude product was further purified by recrystallization by using methanol as solvent to get white crystals in good yield (80.5%). M.P=76-78° C.

IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3386 (N-H), 3121(C-H), 1274(C-N), 756(C-Cl).; ¹H NMR (400 MHz, CDCl₃): δ =, 5.01 (s, 2H), 5.34 (s, 1H), 6.37 (s, 2H), 7.02 (d, J = 8.40 Hz, 2H), 7.12 (d, J = 6.80 Hz, 2H), 7.23-7.25 (m, 8H) ppm.

Mass spectra of the compound showed molecular ion peak at m/z = 357[M+1].



Scheme:1 Synthesis of 2-[(4-chlorophenyl)(1H-indol-3-yl)methyl]-1H-indole

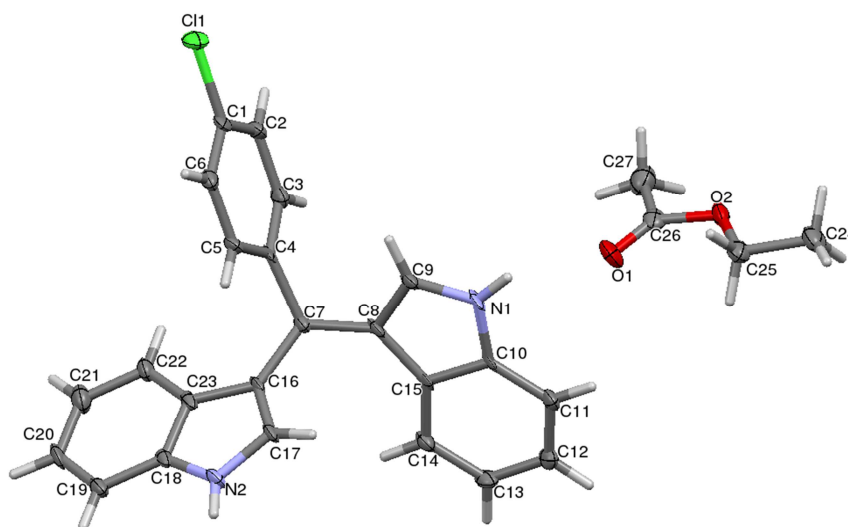


Figure 1: ORTEP of the molecule with thermal ellipsoids drawn at 50% probability

Crystal Structure Determination

A white coloured rectangle shaped single crystal of dimensions 0.29×0.27×0.22 mm of the title compound was chosen for an X-ray diffraction study. The X-ray intensity data were collected at a temperature of 296 K on a Bruker Proteum2 CCD diffractometer equipped with an X-ray generator operating at 45 kV and 10 mA, using CuK α radiation of wavelength 1.54178 Å. Data were collected for 24 frames per set with different settings of ϕ (0° and 90°), keeping the scan width of 0.5°, exposure time of 2 s, the sample to detector distance of 45.10 mm and 2 θ value at 46.6°. A complete data set was processed using *SAINTE PLUS* [18]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs [19]. All the non-hydrogen atoms were revealed in the first difference Fourier map itself. All the hydrogen atoms were positioned geometrically (C–H = 0.93 Å, O–H = 0.82 Å) and refined using a riding model with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}$ and $1.5 U_{\text{eq}}(\text{O})$. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residuals saturated to 0.0345. The geometrical calculations were carried out using the program *PLATON* [20]. The molecular and packing diagrams were generated using the software *MERCURY* [21]. The details of the crystal structure and data refinement are given in **Table 1**. **Tables 2** and **3** gives the list of bond lengths and bond angles which are in

good agreement with the standard values. **Figure 1** represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

Table 1: Crystal data and structure refinement table

Parameter	Value
CCDC deposit No.	CCDC 1497585
Empirical formula	C ₂₇ H ₂₅ N ₂ O ₂ Cl
Formula weight	444.94
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system, space group	Triclinic, <i>P</i> -1
Unit cell dimensions	<i>a</i> = 7.4954(4) Å <i>b</i> = 12.0841(7) Å <i>c</i> = 13.7902(7) Å α = 106.730(2)° β = 103.6920(10)° γ = 96.822(2)°
Volume	1138.49(11) Å ³
Z, Calculated density	2, 1.298 Mg/m ³
Absorption coefficient	1.693 mm ⁻¹
<i>F</i> ₍₀₀₀₎	468
Crystal size	0.29 x 0.27 x 0.22 mm
Theta range for data collection	24.15° to 58.90°
Limiting indices	-7 ≤ <i>h</i> ≤ 8, -13 ≤ <i>k</i> ≤ 8, -15 ≤ <i>l</i> ≤ 15
Reflections collected / unique	2981 / 2526 [R(int) = 0.0167]
Refinement method	Full-matrix least-squares on <i>F</i> ²
Data / restraints / parameters	2526 / 0 / 291
Goodness-of-fit on <i>F</i> ²	1.070
Final R indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0889, <i>wR</i> 2 = 0.2702
R indices (all data)	<i>R</i> 1 = 0.1011, <i>wR</i> 2 = 0.3073
Largest diff. peak and hole	0.580 and -0.821 e. Å ⁻³

RESULTS AND DISCUSSION

Both the indole ring systems are essentially planar with dihedral angles of 3.0(1)° and 0.42(1)° between the two fused ring systems N1/C8-C15 and N2/C16-C23 respectively. These values are in good agreement with those reported for 2-[(2-Fluorophenyl)(1H-indol-3-yl)methyl]-1H-indole. The indole ring systems makes a dihedral angle of 69.73(16)° with respect to each other. The chlorophenyl ring is nearly perpendicular to both the indole ring systems as indicated by the dihedral angle values of 86.7(2)° and 85.7(2)° respectively. The crystal structure features a strong N--H...O hydrogen bond between the indole ring system and the solvent molecule. In the crystal string N--H... π , C--H... π and C--H...Cl interactions occur, forming a three dimensional network. The packing of the molecules when viewed down the *a* axis indicates that the molecule exhibit layered stacking and are interlinked by the intermolecular hydrogen bond to form a three dimensional network(**Figure 2**).

Table 2. Bond Lengths (Å)

Atoms	Length	Atoms	Length
C11-C1	1.750(4)	C8-C15	1.434(7)
O1-C26	1.219(6)	C10-C11	1.382(7)
O2-C26	1.347(6)	C10-C15	1.422(6)
O2-C25	1.452(7)	C11-C12	1.391(7)
N1-C9	1.359(6)	C12-C13	1.400(7)
N1-C10	1.382(6)	C13-C14	1.379(7)
N2-C18	1.375(6)	C14-C15	1.401(7)
N2-C17	1.378(6)	C16-C17	1.357(7)
C1-C6	1.379(7)	C16-C23	1.440(6)
C1-C2	1.384(7)	C18-C23	1.395(7)
C2-C3	1.395(7)	C18-C19	1.400(6)
C3-C4	1.377(7)	C19-C20	1.376(7)
C4-C5	1.395(7)	C20-C21	1.384(8)
C4-C7	1.530(6)	C21-C22	1.388(7)
C5-C6	1.393(7)	C22-C23	1.397(7)
C7-C16	1.510(6)	C24-C25	1.495(7)
C7-C8	1.514(6)	C26-C27	1.470(8)
C8-C9	1.370(6)		

Table 3. Bond Angles (°)

Atoms	Angle	Atoms	Angle
C26-O2-C25	117.1(4)	C11-C12-C13	121.0(4)
C9-N1-C10	109.3(3)	C14-C13-C12	121.4(4)
C18-N2-C17	108.6(4)	C13-C14-C15	119.1(4)
C6-C1-C2	121.8(4)	C14-C15-C10	118.2(4)
C6-C1-C11	119.8(3)	C14-C15-C8	134.7(4)
C2-C1-C11	118.4(4)	C10-C15-C8	107.1(4)
C1-C2-C3	118.4(4)	C17-C16-C23	106.2(4)
C4-C3-C2	121.3(4)	C17-C16-C7	128.2(4)
C3-C4-C5	119.1(4)	C23-C16-C7	125.5(4)
C3-C4-C7	120.0(4)	C16-C17-N2	110.2(4)
C5-C4-C7	120.8(4)	N2-C18-C23	107.6(4)
C6-C5-C4	120.6(4)	N2-C18-C19	130.5(4)
C1-C6-C5	118.8(4)	C23-C18-C19	121.9(4)
C16-C7-C8	113.1(4)	C20-C19-C18	117.5(4)
C16-C7-C4	112.6(3)	C19-C20-C21	121.7(4)
C8-C7-C4	110.2(3)	C20-C21-C22	120.7(5)
C9-C8-C15	106.3(3)	C21-C22-C23	119.0(5)
C9-C8-C7	127.3(4)	C18-C23-C22	119.2(4)
C15-C8-C7	126.3(4)	C18-C23-C16	107.4(4)
N1-C9-C8	110.5(4)	C22-C23-C16	133.4(4)
C11-C10-N1	130.2(4)	O2-C25-C24	107.5(4)
C11-C10-C15	122.9(4)	O1-C26-O2	121.1(4)
N1-C10-C15	106.8(4)	O1-C26-C27	127.0(4)
C10-C11-C12	117.2(4)	O2-C26-C27	111.9(4)

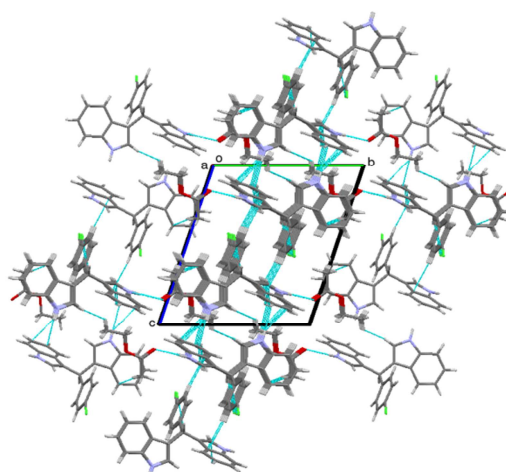


Figure 2: Packing of the molecules exhibiting layered stacking when viewed down the *a* axis. The dotted lines represent the intermolecular hydrogen bond

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REFERENCES

- [1] S. H. Siadatifard, M. Abdoli-Senejani, M. Ali Bodaghifard, *Cogent Chem.*, **2016**, 2, 1188435.
- [2] Y. Zhou, B. Shi, KL Han, Q. N Guo, Y. Yang, B.B. Song, Y.O. Teng, P. Yu. *Chem Pharm Res.*, **2013**, 5, 1024-1028.
- [3] H.R. Bokesch, L.K. Pannell, T.C. McKee, M.R. Boyd, *Chem Pharm Res.*, **2000**, 41, 6305-6308.
- [4] C. Chawla, S. Indoriya, R. Jain, S Sharma, *Chem Pharm Res.*, **2014**, 6, 2097-2104.
- [5] P. F. Xu, X. W. Sun, L. M. Zhang and Z. Y. Zhang, *J. Chem. Res.*, **1999**, 2, 170-171
- [6] F. Shirini, A. Fallah-Shojaei, L. Samavi, MasoumehAbedini. *RSC Adv.*, **2016**, 6, 48469–48478.
- [7] X. Ge, F. A. Fares, S. Yannai, *Anticancer Res.*, **1999**, 19, 3199–3203.
- [8] Y. Gong, H. Sohn, L. Xue, G. L. Firestone, L. F. Bjeldanes, *Cancer Res*, **2006**, 66, 4880–4887.
- [9] D. C. Sung, K. Yoon, S. Chintharlapalli, M. Abdelrahim, P. Lei, S. Hamilton, *Cancer Res.*, **2007**, 67, 674–683.

- [10] M. Shiri, M. A. Zolfigol, H. G. Kruger, Z. Tanbakouchian. *Chem. Rev.*, **2010**, 110, 2250–2293.
- [11] Z.-B. Xie, D-Zh Sun, G.-F. Jiang, Zh-G Le. *Molecules*, **2014**, 19, 19665–19677.
- [12] T. O. Shrunghesh Kumar, S. Naveen, M. N. Kumara, K. M. Mahadevan, N. K. Lokanath, *ActaCryst.* **2015**, E71, 0121.
- [13] P. S. Pradeep, S Naveen, M. N. Kumara, K. M. Mahadevan, N. K. Lokanath., *ActaCryst.* **2015**, E70 (9), 0121.
- [14] P. S. Pradeep, S Naveen, M. N. Kumara, K.M. Mahadevan, N. K. Lokanath., *ActaCryst.* **2015**, E70 (9), 0981.
- [15] R. Anil Kumar, S. Naveen, T. O. Shrunghesh Kumar, K. M. Mahadevan, M. N. Kumara, N. K. Lokanath, *IUCr Data*, **2016**, 1, x160838
- [16] H.N Harishkumar, K.M Mahadevan, H.C Kiran Kumar, N. D Satyanarayan. *Org. Comm.*, **2011**, 4, 26-32.
- [17] A. Sudhakara, H. Jayadevappa, K.M. Mahadevan, VijaykumarHulikal, *Syn. Comm.*, **2009** 39, 2506-2515.
- [18] Bruker, **2004**, APEX2, SAINT-Plus and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.
- [19] G. M. Sheldrick, *ActaCryst.*, **2015**, A71, 3-8.
- [20] A. L. Spek, *Acta. Cryst.*, **1990**, A46, C34-C37.
- [21] C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek, P. A. Wood, *J. Appl. Cryst.*, **2008**, 41, 466.