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Synthesis, Crystal Structure and Antibacterial Activity of *N'*-(2-Bromobenzylidene)-4-methylbenzohydrazide

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A Schiff base compound, *N'*-(2-bromobenzylidene)-4-methylbenzohydrazide (m.f. $C_{15}H_{13}N_2OBr$) has been synthesized by the condensation of 4-methylbenzohydrazide and 2-bromobenzaldehyde in an ethanol solution. The compound was characterized by ^{1}H NMR, MS and single crystal X-ray diffraction. Here, we first report the crystal structure and antibacterial activities of the title compound. The crystal belongs to the orthorhombic system, space group $Pna2_1$ with a = 9.5295 (6), b = 11.4154 (7), c = 12.5957 (8) Å, Z = 4, V = 1370.20 (15) Å, D_c = 1.538 g/cm^3, M_r = 317.18, λ(MoK$_\alpha$) = 0.71073 Å, μ = 2.993 mm^{-1}, F(000) = 640. The final R = 0.0292, wR = 0.0674 for 1904 observed reflections with I > 2σ (I). The dihedral angle between the two phenyl rings is 16.31°. The structure exhibits intermolecular hydrogen bonding of N-H···O type. The title compound molecules are connected through hydrogen bonds to generate a one-dimensional chain. The preliminary biological activity assay results showed that the title compound exhibited good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

Keywords: Schiff base, *N'*-(2-bromobenzylidene)-4-methylbenzohydrazide, Crystal structure, Synthesis, Antibacterial activity.

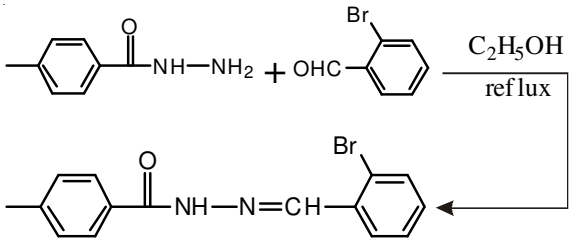
INTRODUCTION

In the past decades, Schiff base compounds and their metal complexes have been extensively investigated due to their wide range of applications including catalysts[1,2], medicine[3,4] and anti-corrosion agents[5]. Schiff bases have also been reported to show a variety of biological actions by virtue of the azomethine linkage, which is responsible for antibacterial, antifungal, antiviral, antiinflammatory and antitumor activities[6-11]. In addition, Schiff bases have been employed as ligands playing an important role in the development of coordination chemistry, which could be attributed to their strong coordination ability and versatile coordination modes[12]. They can form stable complexes with most metal ions[13,14]. Many Schiff base metal complexes have a variety of biological activities[15,16]. Induced by wide variety of biological activities exhibited by Schiff bases and in continuation of our efforts in search of potent molecules exhibiting antibacterial activity, a Schiff base compound, *N'*-(2-bromobenzylidene)-4-methylbenzohydrazide have been synthesized by the condensation of 4-methylbenzohydrazide and 2-bromobenzaldehyde in an ethanolic solution and its crystal structure was determined by X-ray crystallography. Furthermore, preliminary antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* was tested.

EXPERIMENTAL

All chemicals and reagents were of analytical grade and used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE-400 MHz NMR spectrometer using TMS as internal standard. Mass spectrum was obtained with HPLC/MS LCQDECA spectrometer (APCI).

Synthesis of title compound: The synthesis procedure is shown in **Scheme-I**. 4-Methylbenzohydrazide (0.30 g, 2 mmol) and 2-bromobenzaldehyde (0.37 g, 2 mmol) were dissolved in ethanol (10 mL). The mixture was refluxed for 2 h until the disappearance of the starting materials (monitored by TLC) to give a clear white solution. The excess ethanol was evaporated under reduced pressure, the mixture was filtered. The crude product was recrystallized from methanol to give 0.45 g colorless crystals with a yield of 71.02 %. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.43 (s, 3H, CH_3), 7.20-7.38 (m, 5H, ArH), 7.56 (d, *J* = 8 Hz, 1H, ArH), 7.81 (d, *J* = 5.8 Hz, 2H, ArH), 8.63 (s, 1H, NH-N), 9.43 (s, 1H, CH=N); APCI MS: (*m/z*) 329.4 (M + 1, 100). Single crystals suitable for X-ray structural determination were obtained by slowly evaporating the methanol solution of the product under room temperature.



Scheme-I: Synthesis route of the title compound

X-ray crystal structure determination: A yellow single crystal of the title compound (0.40 mm × 0.23 mm × 0.20 mm) was sele-cted and mounted on the top of a glass fiber. X-ray single-crystal diffraction measurement was carried out at 273 (2) K on a Bruker Smart APEX 1000 CCD area diffractometer equipped with a graphite-monochromatic MoK_α radiation (λ = 0.71073 Å) for data collection. The structure was solved by direct methods with SHELXS-97 program and refined by full-matrix least-squares techniques on F^2 with SHELXL-97 program[17,18]. All non-H atoms were refined anisotropically and allowed to ride on their parent carbon atoms. A full-matrix least-squares refinement gave the final R = 0.0292 and wR = 0.0674 ($w = 1/[\sigma^2(F_o^2) + (0.0256\ P)^2 + 0.3938\ P]$, where $P = (F_o^2 + 2F_c^2)/3$). S = 1.019, $(\Delta/\sigma)_{max}$ = 0.001, $(\Delta\rho)_{max}$ = 0.453 e Å^{-3}, $(\Delta\rho)_{min}$ = -0.313 e Å^{-3}. All calculations were performed using the crystal structure crystallographic software package except for the refinement. All H atoms were placed in the geometrically idealized positions and allowed to ride on their respective parent atoms, with the C-H distance of 0.9500-0.9800 Å and U_{iso} (H) = 1.2 or 1.5 U_{eq} (C/O).

Antibacterial activity measurement: The title compound was screened for its antibacterial activity against *S. aureus* and *E. coli* by the agar diffusion method[19]. The compound was dissolved in DMF. After encapsulation, autoclave sterilization at 121 °C for 20 min, nutrient agar was transferred to Petri dish and frozen after cooling. After the test strains were spread on the solid nutrient agar surface, three stainless steel tubes (7.8 mm × 6 mm × 10 mm) were placed on the surface vertically. 100 µL compound with certain concentration was injected into each steel tube. The inhibition was labeled as the diameter of transparent bacteriostatic circle after an incubation period of 24 h at 37 °C. All the samples were tested for three times with the average value as the final result.

RESULTS AND DISCUSSION

The selected bond lengths and bond angles are summarized in Table-1. The hydrogen bond lengths and bond angles are presented in Table-2. The molecular structure and packing diagram of title compound are shown in Figs. 1 and 2, respectively. The two benzene rings are not coplanar with a dihedral angle of 16.31°. The N-N bond length of 1.375 (4) Å is somewhat shorter than that observed in related literature[20]. The N-C bond length (C(7)-N(1)) is 1.356 Å, which is shorter than the isolated N-C single bond (1.4710 Å) and longer than the double bond (1.2730 Å) because of the conjugation effects in the molecule, indicating that a partially conjugated system operates in this Schiff base. The torsion angle C(7)-C(1)-C(2)-C(3), C(14)-C(9)-C(10)-Br(1) and C(9)-C(8)-N(2)-N(1) are 179.0(3)°, -178.7(2)° and -176.0(3)°, respectively. From these results, it is known that all the bond lengths and bond angles are in normal ranges as compared to those observed in a similar Schiff base. In the structure, the intermolecular N-H···O hydrogen bonds link the molecule into a one-dimensional chain which stabilize the molecular structure by causing the formation of supramolecular architecture as shown in Fig. 2.

TABLE-2
HYDROGEN BOND LENGTHS (Å) AND BOND ANGLES (°)

D-H···A	d(D-H)	d(H···A)	d(D···A)	∠DHA/(°)
N(1)-H(1A) ···O(1)#1	0.88	1.93	2.776(4)	159.6

Symmetry transformation used to generate the equivalent atoms: (#1) x-1/2, -y+1/2, z

The antibacterial activity of the title compound was evaluated against *S. aureus* and *E. coli*. The test results are reported in Table-3. It can be observed that the title compound exhibits antibacterial activity against both test bacterial organisms. The inhibition effect is strengthened with the increase of the concentration in the test range. Besides, the

TABLE-1
SELECTED BOND LENGTHS (Å) AND BOND ANGLES (°)

Bond	Dist.	Bond	Dist.	Bond	Dist.
C(1)-C(6)	1.389(5)	C(5)-C(6)	1.376(6)	C(10)-C(11)	1.386(5)
C(1)-C(2)	1.401(5)	C(7)-O(1)	1.227(4)	C(11)-C(12)	1.376(6)
C(1)-C(7)	1.485(5)	C(7)-N(1)	1.356(4)	C(12)-C(13)	1.367(6)
C(2)-C(3)	1.369(6)	C(8)-N(2)	1.276(4)	C(13)-C(14)	1.381(5)
C(3)-C(4)	1.404(5)	C(8)-C(9)	1.475(6)	N(1)-N(2)	1.375(4)
C(4)-C(5)	1.381(6)	C(9)-C(10)	1.387(5)	N(1)-H(1A)	0.8800
C(4)-C(15)	1.505(6)	C(9)-C(14)	1.409(5)	Br(1)-C(10)	1.905(4)
Angle	(°)	Angle	(°)	Angle	(°)
C(6)-C(1)-C(2)	118.1(4)	C(5)-C(6)-C(1)	120.7(3)	C(11)-C(10)-Br(1)	116.8(3)
C(6)-C(1)-C(7)	117.4(3)	O(1)-C(7)-N(1)	122.2(3)	C(9)-C(10)-Br(1)	121.3(3)
C(2)-C(1)-C(7)	124.5(3)	O(1)-C(7)-C(1)	121.3(3)	C(12)-C(11)-C(10	119.3(4)
C(3)-C(2)-C(1)	120.6(3)	N(1)-C(7)-C(1)	116.4(3)	C(13)-C(12)-C(11)	120.0(4)
C(2)-C(3)-C(4)	121.4(3)	N(2)-C(8)-C(9)	118.9(3)	C(12)-C(13)-C(14)	121.5(4)
C(5)-C(4)-C(3)	117.3(3)	C(10)-C(9)-C(14)	117.7(4)	C(13)-C(14)-C(9)	119.6(4)
C(5)-C(4)-C(15)	122.2(4)	C(10)-C(9)-C(8)	123.1(3)	C(7)-N(1)-N(2)	119.1(3)
C(3)-C(4)-C(15)	120.5(4)	C(14)-C(9)-C(8)	119.1(3)	C(8)-N(2)-N(1)	115.5(3)
C(6)-C(5)-C(4)	121.9(3)	C(11)-C(10)-C(9)	121.9(4)	–	–

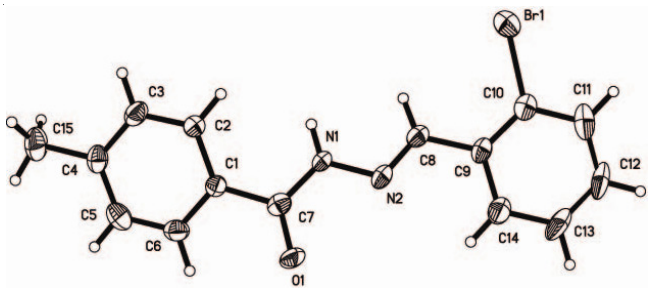


Fig. 1. Molecular structure of the title compound

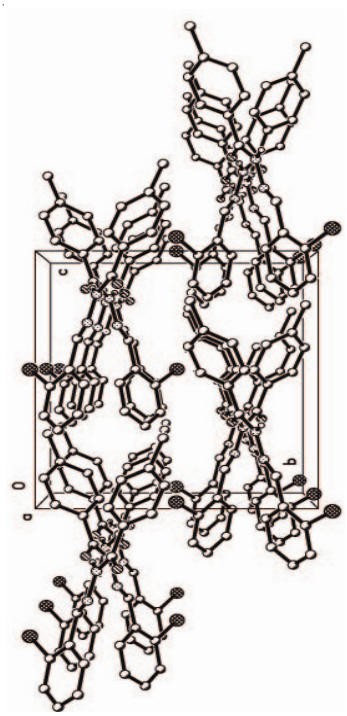


Fig. 2. Packing diagram of the title compound

TABLE-3
ANTIBACTERIAL ACTIVITY OF THE TITLE COMPOUND

Compound	Concentration (mg/mL)	Diameter of inhibition zone (mm)	
		S. aureus	*E. coli*
Title compound	5.0	12.8	13.8
	2.5	12.0	13.5
	1.25	11.8	12.8
	0.625	11.5	12.5
DMF (control)		10.0	11.0

title compound shows more abvious activity against *E. coli* as compared to *S. aureus*. At the concentration of 2.5 and 0.625 mg/mL, the diameters of inhibition zone are 12.0 and 11.5 mm against *S. aureus* while 13.5 and 12.5 mm against *E. coli*.

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