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Synthesis, Crystal Structures and Antimicrobial Activities of 3-bromo-*N*'-(5-bromo-2-hydroxy-3-methoxybenzylidene)benzohydrazide Monohydrate and 3-Bromo-*N*'-(4-hydroxy-3-methoxybenzylidene)benzohydrazide monohydrate

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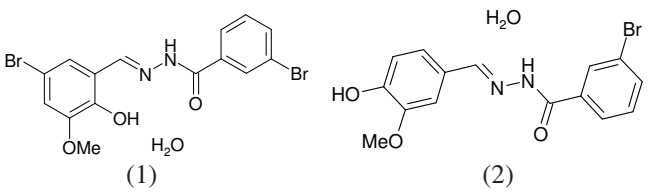
Two new hydrazone compounds, 3-bromo-*N*'-(5-bromo-2-hydroxy-3-methoxybenzylidene)benzohydrazide monohydrate (**1**) and 3-bromo-*N*'-(4-hydroxy-3-methoxybenzylidene)benzohydrazide monohydrate (**2**), have been synthesized and characterized by elemental analysis, IR and single crystal X-ray diffractions. Each compound contains a hydrazone molecule and a water molecule of crystallization. In the crystal structure of (**1**), molecules are linked through O-H···O hydrogen bonds, forming 2D layers parallel to the ab plane. In the crystal structure of (**2**), molecules are linked through N-H···O, O-H···O and O-H···N hydrogen bonds, forming 2D layers parallel to the *bc* plane. The preliminary antimicrobial activities of the compounds were studied.

Key Words: Hydrazone, Synthesis, Hydrogen bonding, X-ray structure analysis, Antimicrobial activity.

INTRODUCTION

Hydrazones have attracted much attention for their excellent biological properties, such as antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular, anticancer and antitumor activities[1-4]. Hydrazones possessing an azomethine –NHN=CH– group constitute an important class of compounds for new drug development. Many researchers have therefore synthesized these compounds as target structures and evaluated their biological activities[5-8]. In this paper, the author reports the syntheses, characterization, crystal structures and antimicrobial activities of two new hydrazone compounds 3-bromo-*N*'-(5-bromo-2-hydroxy-3-methoxy- benzylidene)benzohydrazide monohydrate (**1**) and 3-bromo-*N*'-(4-hydroxy-3- methoxybenzylidene)benzohydrazide monohydrate (**2**) (**Scheme-I**).



(1) (2)

Scheme-I The hydrazone compounds

EXPERIMENTAL

All chemicals with AR grade were commercially available and used without further purification. C, H and N elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. The IR spectra were measured with a FT-IR 170-SX (Nicolet) spectrophotometer.

Synthesis of (1): 5-Bromo-2-hydroxy-3-methoxybenzaldehyde (0.231 g, 1.0 mmol) and 3-bromobenzohydrazide (0.215 g, 1 mmol) were mixed and stirred in methanol (50 mL) for 1 h at ambient temperature to give a colourless solution. The solution was left to slow evaporation of the methanol for a week, yielding colourless block-shaped single crystals. The crystals were filtered out and washed with methanol. Yield 0.37 g (86 %). Analysis calculated for $C_{15}H_{12}N_2O_3Br_2$: C, 42.1; H, 2.8; N, 6.5 %; found: C, 42.3; H, 2.9; N, 6.4 %. Selected IR data (KBr, ν_{max}, cm^{-1}): 3570 (w), 3395 (w), 1650 (s), 1607 (m), 1582 (s), 1561 (m), 1523 (s), 1462 (w), 1345 (s), 1302 (s), 1280 (s), 1132 (w), 1045 (m), 835 (m), 745 (m).

Synthesis of (2): 4-Hydroxy-3-methoxybenzaldehyde (0.152 g, 1.0 mmol) and 3-bromobenzohydrazide (0.215 g, 1 mmol) were mixed and stirred in methanol (50 mL) for 1 h at ambient temperature to give a colourless solution. The solution was left to slow evaporation of the methanol for a week, yielding colourless block-shaped single crystals. The crystals were filtered out and washed with methanol. Yield 0.31 g (89 %). Analysis calculated for $C_{15}H_{13}N_2O_3Br$: C, 51.6; H, 3.8; N, 8.0 %; found: C, 51.3; H, 3.8; N, 8.1 %. Selected IR data (KBr, ν_{max}, cm^{-1}): 3512 (w), 3387 (w), 1646 (s), 1607 (m), 1581 (s), 1562 (m), 1522 (s), 1463 (w), 1345 (s), 1298 (s), 1282 (s), 1135 (w), 1045 (m), 839 (m), 741 (m).

X-ray structure analysis: X-ray diffraction intensities were collected using a Bruker SMART 1000 CCD area detector equipped with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) at 298(2) K. Absorption corrections were applied by SADABS program[9]. The structures were solved by direct methods and refined on F^2 by full-matrix least-squares methods using the SHELXTL package[10]. All non-hydrogen atoms were refined anisotropically. The amino and water H atoms in both compounds were located in difference Fourier maps and refined isotropically, with N-H, O-H and H···H distances restrained to 0.90(1), 0.85(1) and 1.37(2) Å, respectively and with U_{iso}(H) values fixed at 0.08 Å^2. The other H atoms were placed in idealized positions and constrained to ride on their parent atoms. The details of the crystallographic data are summarized in Table-1. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 808427 and 808428).

TABLE-1
CRYSTAL DATA, DATA COLLECTION AND STRUCTURE REFINEMENT FOR THE COMPOUNDS

Compound	(**1**)	(**2**)
Molecular formula	$C_{15}H_{14}N_2O_4Br_2$	$C_{15}H_{15}N_2O_4Br$
Molecular weight	446.1	367.2
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
Temperature (K)	298(2)	298(2)
a (Å)	6.099(2)	8.348(2)
b (Å)	14.340(2)	20.576(3)
c (Å)	19.258(2)	9.317(2)
β (º)	96.626(2)	103.609(2)
V (Å^3)	1673.2(6)	1555.4(5)
Z	4	4
D_{calc} (g cm^{-3})	1.771	1.568
Crystal dimensions (mm)	0.17 × 0.15 × 0.15	0.23 × 0.21 × 0.20
Absorption coefficient (mm^{-1})	4.865	2.662
Radiation λ	MoKα (0.71073 Å)	MoKα (0.71073 Å)
T_{min}/T_{max}	0.492/0.529	0.580/0.618
Reflections measured	8813	8691
Range/indices (h, k, l)	-7, 7; -18, 14; -24, 23	-10, 10; -24, 24; -11, 9
θ limit (º)	2.13–27.00	2.46–27.00
Total no. of unique data	3548 [R_{int} = 0.0697]	3302 [R_{int} = 0.0567]
No. of observed data, I > 2σ(I)	1558	1702
No. of variables	219	210
No. of restraints	4	4
Goodness of fit on F^2	1.045	0.953
R_1, wR_2 [$I \geq 2\sigma(I)$][a]	0.0639, 0.1504	0.0441, 0.0922
R_1, wR_2 (all data)[a]	0.1718, 0.1884	0.1181, 0.1160

[a]$R_1 = \sum||Fo| - |Fc||/\sum|Fo|$, $wR_2 = [\sum w(Fo^2 - Fc^2)^2/\sum w(Fo^2)^2]^{1/2}$

Antimicrobial test: Qualitative determination of antimicrobial activity was done using the disk diffusion method. Suspensions in sterile peptone water from 24-h cultures of microorganisms were adjusted to 0.5 McFarland. Muller-Hinton Petri dishes of 90 mm were inoculated using these suspensions. Paper disks (6 mm in diameter) containing 10 µL of the substance to be tested (at a concentration of 2048 µg/mL in DMSO) were placed in a circular pattern in each inoculated plate. Incubation of the plates was done at 37 ºC for 18-24 h. DMSO impregnated discs were used as negative controls. Toxicity tests of the solvent, DMSO, showed that the concentrations used in antimicrobial activity assays did not interfere with the growth of the microorganisms. Interpretation of the results was done by measuring the diameters of the inhibition zones generated by the test substance. Penicillin was used as a reference.

Determination of MIC was done using the serial dilutions in liquid broth method. The materials used were 96-well plates, suspensions of microorganism, Muller-Hinton broth and stock solutions of each substance to be tested (2048 µg/mL in DMSO). The following concentrations of the substances to be tested were obtained in the 96-well plates: 1024, 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 µg/mL. After incubation at 37 ºC for 18-24 h, the MIC for each tested substance was determined by microscopic observation of microbial growth. It corresponds to the well with the lowest concentration of the tested substance where microbial growth was clearly inhibited.

RESULTS AND DISCUSSION

The compounds were readily synthesized by the reaction of equimolar quantities of 3-bromobenzohydrazide with 5-bromo-2-hydroxy-3-methoxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde, respectively, in methanol. The elemental analyses are in good agreement with the formulae proposed for the compounds. The single crystals of both compounds are stable in air for at least 3 months, soluble in methanol, ethanol, acetonitrile, chloroform and dichloromethane, insoluble in water.

Figs. 1 and 2 give perspective views of the compounds (**1**) and (**2**), respectively. The structures of the both compounds are very similar, each contains a hydrazone molecule and a water molecule of crystallization. All the bond lengths and angles in the both compounds are comparable to each other and also comparable to those observed in other hydrazone compounds[11,12]. The C8=N1 bond lengths of 1.276(9) Å in (**1**) and 1.273(4) Å in (**2**) confirm them as double bonds. The C8-N2 bonds [1.347(10) Å in (**1**) and 1.345(5) Å in (**2**)] and the N1-N2 bonds [1.377(8) Å in (**1**) and 1.386(4) Å in (**2**)] are relatively short, suggesting some degree of delocalization in the acetohydrazide systems. The dihedral angles between the two benzene rings are 10.1(7)º in (**1**) and 2.0(3)º in (**2**), indicating some distortion of the molecules.

In the crystal structure of (**1**), molecules are linked through O-H···O hydrogen bonds (Table-2), forming 2D layers parallel to the ab plane (Fig. 3). In the crystal structure of (**2**), molecules are linked through N-H···O, O-H···O and O-H···N hydrogen bonds, forming 2D layers parallel to the *bc* plane (Fig. 4).

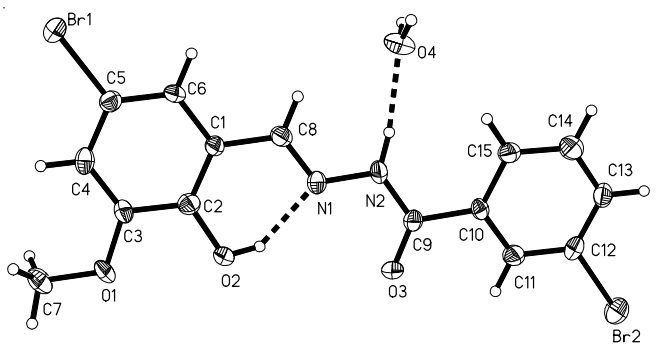


Fig. 1. Molecular structure of (**1**) at 30 % probability displacement. Hydrogen bonds are drawn as dashed lines

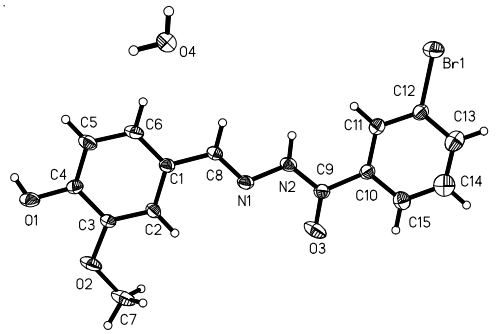


Fig. 2. Molecular structure of (**2**) at 30 % probability displacement.

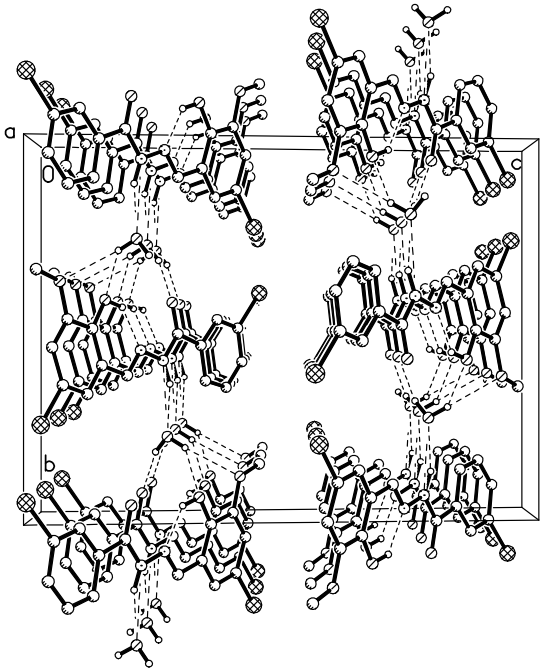


Fig. 3. Molecular packing of (**1**), viewed along the a axis. Hydrogen bonds are drawn as dashed lines.

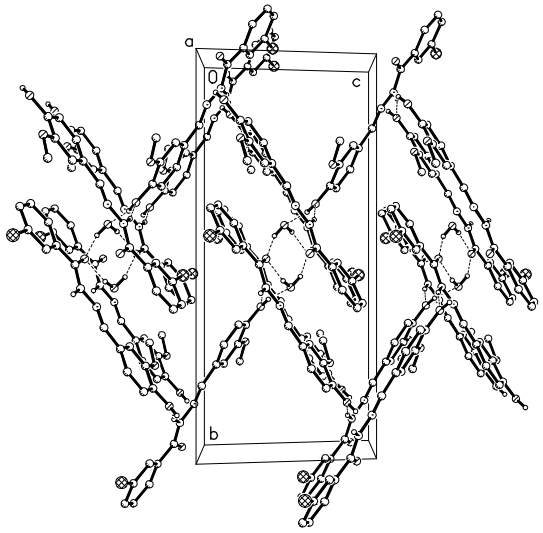


Fig. 4. Molecular packing of (**2**), viewed along the a axis. Hydrogen bonds are drawn as dashed lines.

The MIC values of the antibacterial activities of both hydrazone compounds are listed in Table-3. The organisms used in the present investigation included *Stereptococcus pyogenes, Stereptococcus agalactiae, Staphylococcus aureus, Bacillus anthracis, Klebsiella pneumonia* and *Pseudomonas aeruginosa*. The results show that the compound (**1**) has strong antimicrobial activities against *Klebsiella pneumonia*, but have relatively poor activities against other bacteria when compared to those of the Penicillin. It is notable that the activities of (**1**) are stronger than those of (**2**), indicating that the bromo-substitute group of the C1-C6 benzene ring is a good choice in the search for antimicrobial materials.

TABLE-2
DISTANCES (Å) AND ANGLES (º) INVOLVING HYDROGEN BONDING OF THE COMPOUNDS

D–H···A	d(D–H) (Å)	d(H···A) (Å)	d(D···A) (Å)	Angle (D–H···A) (°)
(**1**)				
N2–H2···O4	0.902(10)	1.96(3)	2.826(9)	162(9)
O4–H4B···O3^{i}	0.850(10)	1.93(3)	2.758(8)	164(8)
O4–H4A···O1^{ii}	0.850(10)	2.38(6)	3.087(9)	141(9)
O4–H4A···O2^{ii}	0.850(10)	2.33(6)	3.047(9)	143(8)
O2–H2A···N1	0.82	1.89	2.579(8)	141
(**2**)				
O4–H4A···O3^{iii}	0.841(10)	2.15(3)	2.883(4)	146(4)
O4–H4B···N1^{iv}	0.846(10)	2.66(4)	3.187(4)	121(3)
O4–H4B···O3^{iv}	0.846(10)	2.022(13)	2.859(4)	170(4)
N2–H2···O1^{iv}	0.896(10)	2.181(15)	3.057(4)	166(4)
O1–H1···O4^{v}	0.82	1.80	2.605(4)	168

Symmetry codes: i) 3/2 – *x*, 1/2 + *y*, 1/2 – *z*; ii) 1/2 – *x*, 1/2 + *y*, 1/2 – *z*; iii) 3/2 – *x*, –1/2 + *y*, 3/2 – *z*; iv) 1/2 + *x*, 3/2 – *y*, –1/2 + *z*; v) *x*, *y*, 1 + *z*.

TABLE-3
ANTIMICROBIAL ACTIVITIES OF THE COMPOUNDS AS MIC VALUES (μg/mL)

	(**1**)	(**2**)	Penicillin
Stereptococcus pyogenes	256	512	230
Stereptococcus agalactiae	128	512	65
Staphylococcus aureus	256	–	250
Bacillus anthracis	16	64	12
Klebsiella pneumonia	4	32	5
Pseudomonas aeruginosa	512	–	–

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