Scientific paper

6-Bromo-2'-(2-chlorobenzylidene)nicotinohydrazide and 6-Bromo-2'-(3-bromo-5-chloro-2-hydroxybenzylidene) nicotinohydrazide Methanol Solvate: Synthesis, Characterization, Crystal Structures and Antimicrobial Activities

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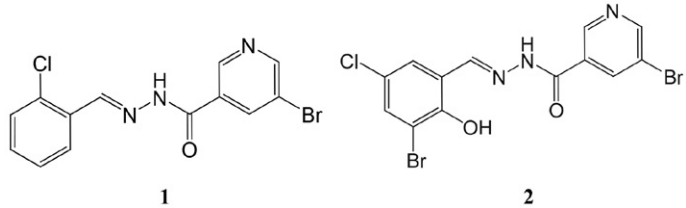
Abstract

Two newly synthesized nicotinohydrazones, 6-bromo-2'-(2-chlorobenzylidene)nicotinohydrazide (**1**) and 6-bromo-2'-(3-bromo-5-chloro-2-hydroxybenzylidene)nicotinohydrazide methanol solvate (**2**), have been obtained and structurally characterized by spectroscopic method and single crystal X-ray determination. The molecules in both compounds are in *E* configuration regarding to the azomethine groups. The molecules of compound **1** are linked *via* hydrogen bonds of N–H···O, generating one dimensional chains running along the *c*-axis direction. The hydrazone molecules of compound **2** are linked by methanol molecules *via* hydrogen bonds of N–H···O and O–H···N, generating dimers. The *in vitro* antimicrobial activities of these compounds indicate that they are interesting antibacterial agents.

Keywords: Hydrazone; synthesis; hydrogen bonding; X-Ray crystal structure; antimicrobial activity

1. Introduction

Hydrazones with the central group –CH=N–NH– are of great importance in biological fields, especially for the new drug investigation.[1] These compounds have been reported to show interesting biological activities like antimicrobial, antifungal, anticonvulsant, analgesic, antiplatelet, antitubercular, antiinflammatory, as well as antitumor.[2] Hydrazones are also a kind of interesting ligands in coordination chemistry.[3] The metal complexes with hydrazones are reported to have interesting biological activities.[4] Isoniazide is a front-line antituberculotic drug. The derivatives of isoniazide have been widely used as attractive drugs in the treatment of various deseases.[5] To date, a number of hydrazones derived from benzohydrazides were reported.[6] However, those derived from nicotinohydrazide are relatively rare. Moreover, the compounds bearing halide substituent such as F, Cl and Br usually possess effective antimicrobial activities.[7] We have reported on some hydrazone compounds with antimicrobial activities.[8] In pursuit of new antimicrobial agents, in this paper, two nicotinohydrazones, 6-bromo-2'-(2-chlorobenzylidene)nicotinohydrazide (**1**) and 6-bromo-2'-(3-bromo-5-chloro-2-hydroxybenzylidene)



Scheme 1. The nicotinohydrazones **1** and **2**

nicotinohydrazide methanol solvate (**2**), possessing simultaneously Cl, Br and isoniazide skeleton are presented (Scheme 1).

2. Experimental

2. 1. Materials and Methods

5-Bromonicotinohydrazide, 2-chlorobenzaldehyde and 3-bromo-5-chloro-2-hydroxybenzaldehyde were purchased from Bide Chemical Reagent Co. Ltd. The other chemicals with AR grade were obtained commercially and used as received. CHN elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. IR spectra were measured with a FT-IR 170-SX (Nicolet) spectrophotometer. ^{1}H NMR and ^{13}C NMR data were measured with a Bruker 500 MHz instrument.

2. 2. Synthesis of 6-Bromo-2'-(2-chlorobenzylidene)nicotinohydrazide (1)

5-Bromonicotinohydrazide (0.216 g, 1.0 mmol) and 2-chlorobenzaldehyde (0.140 g, 1.0 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 needle-shaped single crystals. The crystals were filtered out and washed with methanol. Yiled 0.28 g (83%). M.p. 173.2–174.5 °C. Analysis calculated for $C_{13}H_9BrClN_3O$: C, 46.1; H, 2.7; N, 12.4; found: C, 45.9; H, 2.7; N, 12.5. IR data (KBr, cm^{-1}): 3178 (w), 1654 (s), 1598 (m), 1561 (m), 1471 (w), 1437 (w), 1369 (w), 1303 (s), 1158 (w), 1031 (m), 963 (w), 927 (w), 745 (m). ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.24 (s, 1H, NH), 9.05 (s, 1H, PyH), 8.92 (s, 1H, CH=N), 8.83 (s, 1H, PyH), 8.52 (s, 1H, PyH), 8.03 (d, 1H, ArH), 7.55 (d, 1H, ArH), 7.46 (m, 2H, ArH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 160.26, 153.01, 147.34, 144.71, 137.64, 133.36, 131.78, 131.23, 130.48, 129.95, 127.66, 126.97, 120.05.

2. 3. Synthesis of 6-Bromo-2'-(3-bromo-5-chloro-2-hydroxybenzylidene) nicotinohydrazide methanol solvate (2)

5-Bromonicotinohydrazide (0.216 g, 1.0 mmol) and 3-bromo-5-chloro-2-hydroxybenzaldehyde (0.235 g, 1.0 mmol) were mixed and stirred in methanol (50 mL) for 1 h at ambient temperature to give a slight yellow solution. The solution was left to slow evaporation of the methanol for 2 days, yielding light yellow block-shaped single crystals. The crystals were filtered out and washed with methanol. Yiled 0.39 g (84%). M.p. 210.5–211.3 °C. Analysis calculated for $C_{14}H_{12}Br_2ClN_3O_3$: C, 36.1; H, 2.6; N, 9.0; found: C, 35.9; H, 2.7; N, 9.1. IR data (KBr, cm^{-1}): 3457 (w), 3190 (w), 1666 (s), 1600 (w), 1550 (w), 1443 (s), 1344 (m), 1294 (w), 1164 (s), 1078 (s), 955 (s), 861 (s), 734 (m). ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.68 (s, 1H, OH), 12.39 (s, 1H, NH), 9.05 (s, 1H, PyH), 8.92 (s, 1H, CH=N), 8.52 (s, 1H, PyH), 8.50 (s, 1H, PyH), 7.72 (s, 2H, ArH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 160.23, 153.31, 153.25, 147.98, 147.36, 137.71, 133.30, 129.63, 129.28, 123.39, 120.25, 120.07, 110.94.

2. 4. X-Ray Structure Analysis

X-Ray diffraction intensities were collected using a Bruker SMART 1000 CCD area detector equipped with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) at 298(2) K. Absorption corrections were applied by SADABS.[9] The structures of the compounds were solved by direct methods and refined on F^2 by full-matrix least-squares methods with SHELXTL.[10] All non-hydrogen atoms were refined anisotropically. The amino and methanol H atoms in both compounds were located in difference Fourier maps and refined isotropically, with N–H and O–H distances restrained to 0.90(1) Å and 0.85(1) Å, respectively, and with U_{iso}(H) values fixed at 1.2U_{eq}(N) and 1.5U_{eq}(O). The other H atoms were placed in idealized positions and constrained to ride on their parent atoms. The Cl atoms in **1** is disordered over two sites, with occupancies of 0.84(2) and 0.16(2). The details of the crystallographic data are summarized in Table 1. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 850161 and 2022935).

2. 5. Antimicrobial Test

Qualitative determination of antimicrobial activity was done using the disk diffusion method. Suspensions in sterile peptone water from 24 hour 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 °C 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. Reading 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

Table 1. Crystal data, data collection and structure refinement for the compounds

Compound	**1**	**2**
Molecular formula	$C_{13}H_9BrClN_3O$	$C_{14}H_{12}Br_2ClN_3O_3$
Molecular weight	338.6	465.5
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$C2/c$
Temperature (K)	298(2)	298(2)
a (Å)	11.482(2)	11.862(1)
b (Å)	14.034(3)	13.494(1)
c (Å)	8.443(2)	19.860(2)
β (°)	90.05(3)	95.485(1)
V (Å^3)	1360.5(5)	1562.1(5)
Z	4	8
D_{calc} (g cm^{-3})	1.653	1.954
Crystal dimensions (mm)	0.23 × 0.20 × 0.20	0.27 × 0.27 × 0.27
Absorption coefficient (mm^{-1})	3.212	5.309
Reflections measured	11289	7887
Total no. of unique data	2963 [R_{int} = 0.0409]	2890 [R_{int} = 0.0434]
No. of observed data, $I > 2\sigma(I)$	1825	1714
No. of variables	184	216
No. of restraints	4	2
Goodness of fit on F^2	1.001	0.961
R_1, wR_2 [I ³ $2\sigma(I)$]^a	0.0486, 0.1097	0.0324, 0.0639
R_1, wR_2 (all data)^a	0.0877, 0.1271	0.0754, 0.0757

$^aR_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$

1 μg/mL. After incubation at 37 °C 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.

3. Results and Discussion

3. 1. Chemistry

The nicotinohydrazones **1** and **2** were facile prepared by the reaction of 1:1 molar ratio of 5-bromonicotinohydrazide with 2-chlorobenzaldehyde and 3-bromo-5-chloro-2-hydroxybenzaldehyde, respectively in methanol. The elemental analyses are in good agreement with the formulae proposed for the compounds determined by single crystal X-ray diffraction. The crystals of the compounds are stable in air at room temperature, and easily soluble in DMF, DMSO, methanol, ethanol, chloroform, dichloromethane, and acetonitrile.

Synthesis of the compounds was indicated in their IR spectra by the presence of bands for imine bonds, *i.e.* 1654 cm^{-1} for **1** and 1666 cm^{-1} for **2**. In ^{1}H NMR, the absence of NH_2 signals and the appearance of peaks for NH protons in the region δ 12.24–12.39 ppm and imine CH proton in the region δ 8.92 ppm confirmed the synthesis of the compounds. The aromatic proton signals were found in their respective regions with different multiplicities, confirming their relevant substitution pattern.

3. 2. Crystal Structure Description of 1 and 2

The molecular structures of compounds **1** and **2** are shown in Figures 1 and 2, respectively. Compound **2** contains a methanol molecule of crystallization. All the related bond lengths and angles (Table 2) in the compounds are similar, and within the ranges of the bond values observed in reported hydrazone compounds.[8a,11] The C7–N1 bond lengths of 1.278(5) Å in **1** and 1.243(4) Å in **2** indicate the double bond nature. The C8–N2 bond lengths of 1.339(4) Å in **1** and 1.335(4) Å in **2**, and the N1–N2 bonds (1.388(4) Å in **1** and 1.340(4) Å in **2**) are shorter than normal, suggesting the existence of delocalization in the molecules.

Table 2. Selected bond lengths (Å) and bond angles (°) for the compounds **1** and **2**

1			
C7–N1	1.278(5)	N1–N2	1.388(4)
N2–C8	1.339(4)	C8–O1	1.226(4)
C1–C7–N1	122.3(3)	C7–N1–N2	113.3(3)
N1–N2–C8	118.8(3)	N2–C8–C9	115.9(3)
N2–C8–O1	123.8(3)	O1–C8–C9	120.3(3)
2			
C7–N1	1.243(4)	N1–N2	1.340(4)
N2–C8	1.335(4)	C8–O1	1.185(4)
C1–C7–N1	118.6(3)	C7–N1–N2	119.3(3)
N1–N2–C8	115.2(3)	N2–C8–C9	115.8(4)
N2–C8–O1	122.7(4)	O1–C8–C9	121.5(3)

Table 3. Distances (Å) and angles (°) involving hydrogen bonding of the compounds **1** and **2**

D–H···A	*d*(*D*–H) (Å)	*d*(H···*A*) (Å)	*d*(*D*···*A*) (Å)	*Angle*(*D*–H···*A*) (°)
1				
N2–H2···O1^{i}	0.90(1)	2.02(2)	2.859(4)	157(4)
C7–H7···O1^{i}	0.93	2.32(2)	3.133(4)	146(4)
2				
O2–H2A···N1	0.82	1.81	2.518(4)	144(3)
N2–H2···O3	0.90(1)	1.93(1)	2.817(4)	168(4)
O3–H3···N3^{ii}	0.85(1)	1.96(1)	2.799(4)	172(4)

Symmetry code for i: *x*, 1/2 – *y*, 1/2 + *z*; ii: 1 – *x*, – *y*, 1 – *z*.

Table 4. π–π interactions

Cg	Distance between ring centroids (Å)	Dihedral angle (°)	Perpendicular distance of *Cg*(I) on *Cg*(J) (Å)	Perpendicular distance of *Cg*(J) on *Cg*(I) (Å)
1				
*Cg*1···*Cg*1^{iii}	3.9762	0	3.5858	3.5859
*Cg*1···*Cg*2^{iv}	4.1626	7.201	3.4858	–3.7417
*Cg*2···*Cg*2^{v}	3.8892	0	–3.4367	–3.4367
2				
*Cg*1···*Cg*2^{v}	3.6959	3.876	–3.4413	–3.5234
*Cg*1···*Cg*2^{vi}	4.8932	0	3.3600	3.3600

*Cg*1 and *Cg*2 are the centroids of the N3-C12-C11-C10-C9-C13 and C1-C2-C3-C4-C5-C6 rings, respectively. Symmetry codes: iii: 1 – *x*, 1 – *y*, 1 – *z*; iv: *x*, 1/2 – *y*, 1/2 + *z*; v: – *x*, – *y*, 1 – *z*; vi: 1/2 – *x*, 1/2 – *y*, 1 – *z*.

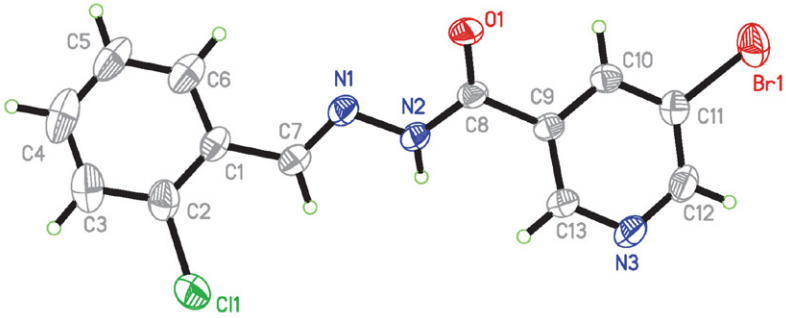


Figure 1. Molecular structure of **1** at 30% probability displacement. Only the major component of the disordered group is shown.

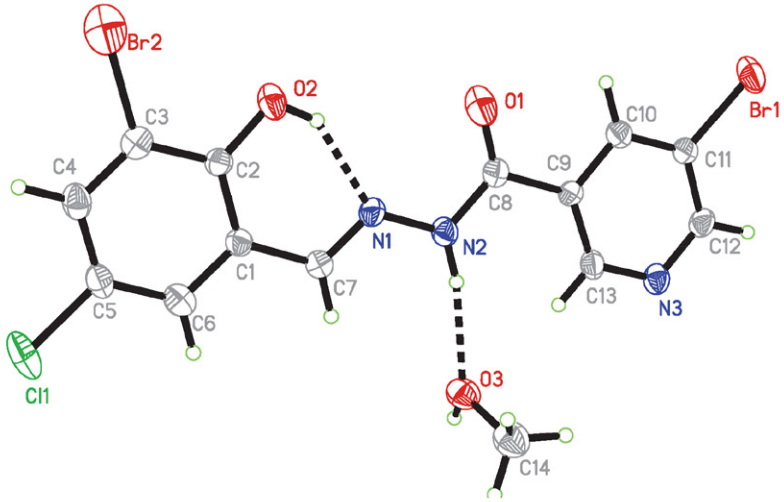


Figure 2. Molecular structure of **2** at 30% probability displacement. Intramolecular O–H···N and N–H···O hydrogen bonds are drawn as dashed lines.

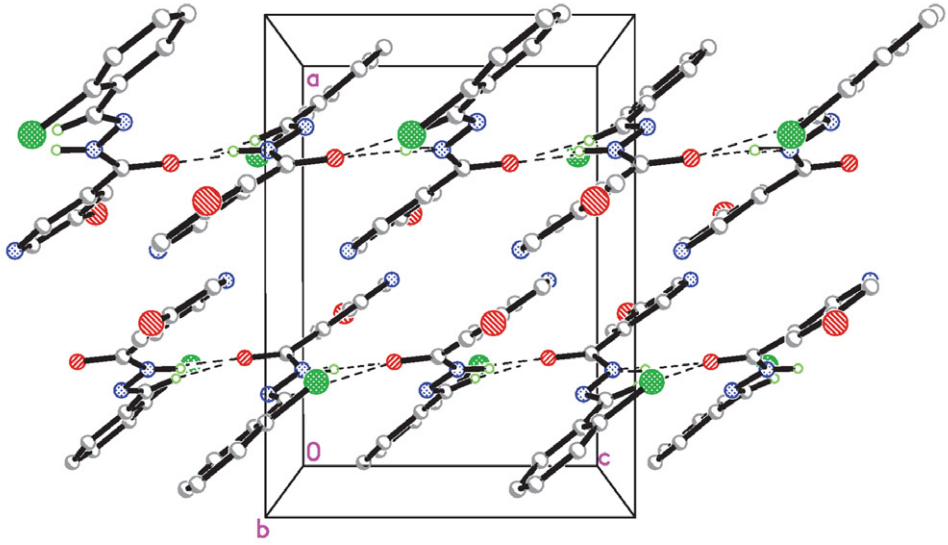


Figure 3. Molecular packing of **1**, viewed along the *b* axis. Hydrogen bonds are drawn as dashed lines.

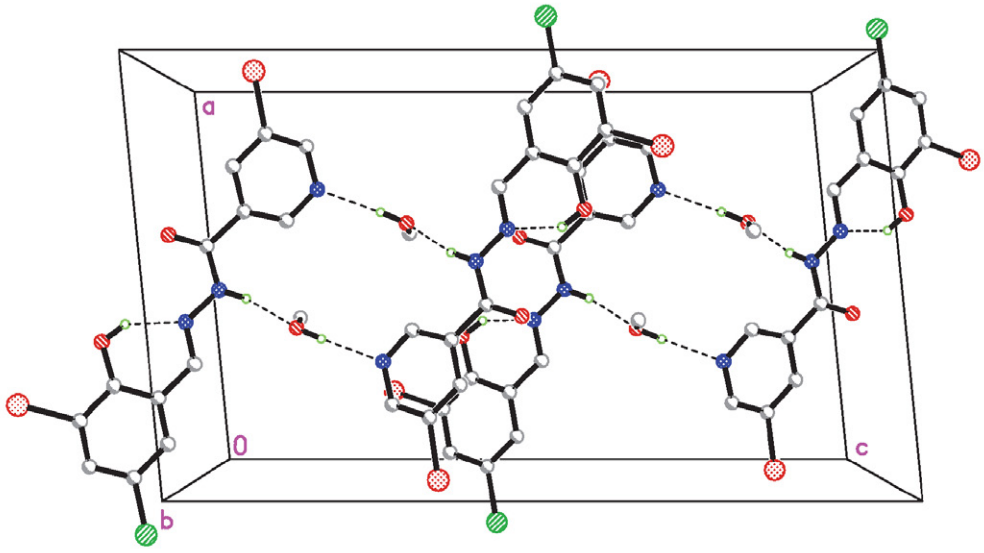


Figure 4. Molecular packing of **2**, viewed along the *b* axis. Hydrogen bonds are drawn as dashed lines.

The benzene ring and the pyridine ring form a dihedral angle of 6.4(4)° in **1** and 3.8(4)° in **2**.

In the crystal structure of **1**, the molecules are linked through hydrogen bonds of N2–H2···O1 and C7–H7···O1 (Table 3), generating one dimensional chains running along the *c*-axis direction (Figure 3). In the crystal structure of **2**, the adjacent two hydrazone molecules are linked by two methanol molecules through hydrogen bonds of N2–H2···O3 and O3–H3···N3 (Table 3), generating a dimer (Figure 4). In addition, in both compounds the presence of short π-electron ring – π-electron ring interactions with *Cg-Cg* distances < 6.0 Å and β < 60.0° that are specified in Table 4 was detected.[12]

3. 3. Antimicrobial Activity of the Compounds

The antimicrobial activities of the compounds against the organisms *Streptococcus pyogenes* (*S. pyogenes*), *Streptococcus agalactiae* (*S. agalactiae*), *Staphylococcus aureus* (*S. aureus*), *Bacillus anthracis* (*B. anthracis*), *Klebsiella pneumonia* (*K. pneumonia*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) are summarized in Table 5. The results show that both compounds have effective antimicrobial activities against *S. pyogenes*, *S. agalactiae*, and *B. anthracis*, and have relatively poor or negative activities against other bacteria when compared to the Penicillin. Compounds **1** and **2** have similar activities against *S. agalactiae* and *B.*

anthracis. Interestingly, compound **2** has stronger activities against *S. pyogenes*, *K. pneumonia* and *P. aeruginosa* than compound **1**. This indicates that the Br and Cl substitunts are a good choice in the search for new antimicrobial agents. The activities of the nicotinohydrazone compounds in this work are stronger than the benzohydrazones with Br as substituent.[6a] The compounds are more active against *S. pyogenes*, *S. agalactiae*, *B. anthracis* and *P. aeruginosa* than the benzohydrazone compound with Br, NO_2 and Cl as the substituent.[13] Thus, the present compounds show promising activity against *S. pyogenes*, *S. agalactiae* and *B. anthracis*, which deserves further investigation for developing new antimicrobial drugs.

Table 5. Antimicrobial activities of the compounds as MIC values (μg/mL)

	1	**2**	**Penicillin**
S. pyogenes	32	16	230
S. agalactiae	8	8	65
S. aureus	> 1024	> 1024	250
B. anthracis	2	2	12
K. pneumonia	128	16	5
P. aeruginosa	256	64	> 1024

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Povzetek

Pripravili smo dva nova predstavnika nikotinohidrazonov: 6-bromo-2'-(2-klorobenziliden)nikotinohidrazid (**1**) in 6-bromo-2'-(3-bromo-5-kloro-2-hidroksibenziliden)nikotinohidrazid metanolni solvat (**2**). Strukturi obeh produktov smo določili s spektroskopskimi metodami in z rentgensko difrakcijsko analizo monokristalov. Molekule obeh spojin imajo v azometinski skupini *E* konfiguracijo. Molekule v spojini **1** so povezane v enodimenzionalne verige vzdolž *c* osi z vodikovimi vezmi N–H···O. Hidrazonske molekule spojine **2** so z metanolnimi povezane v dimere preko vodikovih vezi N–H···O in O–H···N. Določitev *in vitro* antimikrobnih aktivnosti za ti dve spojini je pokazala, da bi lahko bili potencialno zanimivi antibakterijski učinkovini.