ЖУРНАЛ СТРУКТУРНОЙ ХИМИИ

2013. Том 54, № 1 *Январь – февраль* *С. 155 – 161*

UDC 548.737:546.17

CRYSTAL STRUCTURES AND ANTIBACTERIAL ACTIVITY OF HYDRAZONE DERIVATIVES FROM 1*H*-INDOL-3-ACETOHYDRAZIDE

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Received October, 7, 2011

A series of three new hydrazone derivatives $C_{22}H_{19}N_3O_2$ (**1**), $C_{17}H_{13}ClN_4O_3$ (**2**), and $C_{21}H_{24}N_4O_2 \cdot CH_4O$ (**3**) obtained by the condensation of 1*H*-indol-3-acetohydrazide with 2-methoxynaphthaldehyde, 2-chloro-5-nitrobenzaldehyde, and 4-diethylaminosalicylaldehyde, respectively, in methanol, ia prepared. The compounds are characterized by elemental analysis, IR spectra, ^{1}H NMR spectra, and single crystal X-ray diffraction. Compound **1** crystallizes in the monoclinic space group $P2_1/n$ with unit cell dimensions $a = 17.740(2)$ Å, $b = 5.621(1)$ Å, $c = 18.573(3)$ Å, $\beta = 92.659(2)°$, $V = 1850.0(6)$ Å^3, $Z = 4$, $R_1 = 0.0610$ and $wR_2 = 0.1155$. Compound **2** crystallizes in the monoclinic space group $C2/c$ with unit cell dimensions $a = 29.178(2)$ Å, $b = 8.195(1)$ Å, $c = 14.372(1)$ Å, $\beta = 109.446(2)°$, $V = 3240.5(5)$ Å^3, $Z = 8$, $R_1 = 0.0452$ and $wR_2 = 0.1028$. Compound **3** crystallizes in the monoclinic space group Pc with unit cell dimensions $a = 6.579(1)$ Å, $b = 15.112(2)$ Å, $c = 10.676(2)$ Å, $\beta = 90.030(2)°$, $V = 1061.4(3)$ Å^3, $Z = 2$, $R_1 = 0.0535$ and $wR_2 = 0.1123$. The single crystal X-ray structural determination reveals that the molecules of the compounds are much twisted due to the lack of efficient conjugation. Preliminary biological tests indicate that the compounds are effective antibacterial material.

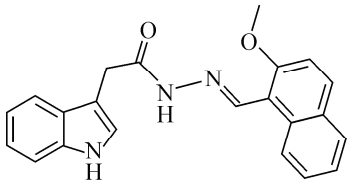
K e y w o r d s: hydrazone derivative, synthesis, X-ray diffraction, antibacterial activity.

INTRODUCTION

The condensation of carbonyl-containing compounds with primary amines produces Schiff base compounds bearing C=N double bonds, which is an essential structural requirement for biological activities, especially for the antibacterial, antimicrobial, antifungi, and antitumor activities [1—4]. Hydrazone derivatives are a kind of special Schiff bases bearing C=N—NH—CO functional groups. As is well known, nicotinohydrazide derivatives exhibit effective activities against pulmonary tuberculosis. In recent years, considerable attention has been focused on the preparation and biological activities of hydrazone derivatives [5—7]. During the search of the literature, we can observe that most of the reported hydrazone derivatives bear a rigid backbone. In order to investigate the crystal structures and antibacterial activities of flexible hydrazone derivatives, in the present paper, 1*H*-indol-3-acetohydrazide, an expensive flexible hydrazide, was used to prepare three hydrazone derivatives: $C_{22}H_{19}N_3O_2$ (**1**), $C_{17}H_{13}ClN_4O_3$ (**2**), and $C_{21}H_{24}N_4O_2 \cdot CH_4O$ (**3**).

EXPERIMENTAL

Materials and methods. 1*H*-Indol-3-acetohydrazide, 2-methoxynaphthaldehyde, 2-chloro-5-nitrobenzaldehyde, and 4-diethylaminosalicylaldehyde were obtained commercially from Lancaster



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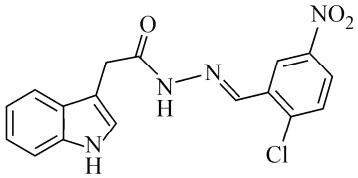

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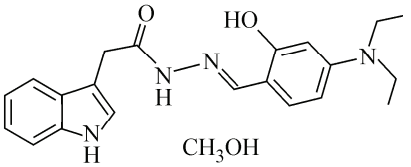

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Research Chemicals. The solvents used were of analytical grade. Elemental analyses (CHN) were performed on a Perkin-Elmer 240C elemental analyzer. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DPX-400 instrument at 400 MHz with tetramethylsilane as the internal reference.

Synthesis of (*E*)-2-(1*H*-indol-3-yl)-N′-((2-methoxynaphthalen-1-yl)methylene)acetohydrazide (1). 1*H*-Indol-3-acetohydrazide (1.0 mmol, 0.189 g) was added with stirring to 2-methoxynaphthaldehyde (1.0 mmol, 0.186 g) in methanol. The mixture was heated under reflux for 1 h and cooled to room temperature. After filtration and slow evaporation in air for a few days, colorless block-shaped single crystals formed. The crystals were collected by filtration, washed three times with methanol. Yield, 0.273 g (76 %). Anal. Calcd. (%) for $C_{22}H_{19}N_3O_2$: C, 73.9; H, 5.4; N, 11.8. Found (%): C, 73.7; H, 5.4; N, 11.9. Characteristic IR data (KBr, cm^{-1}): 1646 (s) ($\nu_{C=N}$). ^{1}HNMR data (*d*-DMSO, ppm): δ = 3.65 (s, 2H), 3.79 (s, 3H), 7.08 (m, 2H), 7.17 (s, 1H), 7.30 (m, 2H), 7.4—8.1 (m, 5H), 8.93 (s, 1H), 11.32 (s, 1H), 12.71 (s, 1H).

Synthesis of (*E*)-N′-(2-chloro-5-nitrobenzylidene)-2-(1*H*-indol-3-yl)acetohydrazide (2) and (*E*)-N′-(4-(diethylamino)-2-hydroxybenzylidene)-2-(1*H*-indol-3-yl)acetohydrazide (3). Compounds **2** and **3** were synthesized by the same method as that described for **1**, with 2-methoxynaphthaldehyde replaced by 2-chloro-5-nitrobenzaldehyde (1.0 mmol, 0.186 g) for **2**, and with 2-methoxynaphthaldehyde replaced by 4-diethylaminosalicylaldehyde (1.0 mmol, 0.193 g) for **3**. The filtrates for the two compounds were stood still in air to slow evaporate the solvent to yield yellow (for **2**) and colorless (for **3**) needle-shaped single crystals. For **2**: Yield, 0.312 g (87 %). Anal. Calcd. (%) for $C_{17}H_{13}ClN_4O_3$: C, 57.2; H, 3.7; N, 15.7. Found (%): C, 57.4; H, 3.6; N, 15.6. Characteristic IR data (KBr, cm^{-1}): 1643 (s) ($\nu_{C=N}$). ^{1}HNMR data (*d*-DMSO, ppm): δ = 3.65 (s, 2H), 7.08 (m, 2H), 7.17 (s, 1H), 7.30 (d, 1H), 7.63 (d, 1H), 7.73 (d, 1H), 8.21 (d, 1H), 8.43 (s, 1H), 8.92 (s, 1H), 11.27 (s, 1H), 12.53 (s, 1H). For **3**: Yield, 0.290 g (73 %). Anal. Calcd. (%) for $C_{22}H_{28}N_4O_3$: C, 66.6; H, 7.1; N, 14.1. Found (%): C, 66.7; H, 7.3; N, 14.3. Characteristic IR data (KBr, cm^{-1}): 1645 (s) ($\nu_{C=N}$). ^{1}HNMR data (*d*-DMSO, ppm): δ = 1.14 (t, 6H), 3.38 (q, 4H), 3.65 (s, 2H), 6.26 (s, 1H), 6.35 (d, 1H), 7.08 (m, 2H), 7.17 (s, 1H), 7.30 (m, 2H), 7.3—7.7 (m, 3H), 8.77 (s, 1H), 11.13 (s, 1H), 12.54 (s, 1H).

X-ray crystallography. Suitable single crystals of the three compounds were mounted on glass fibers for X-ray measurements. Reflection data were collected at room temperature on a Bruker AXS SMART APEX II CCD diffractometer with graphite monochromatized MoK_α radiation (λ = = 0.71073 Å). Crystal structures of the three compounds were solved by the direct method. All non-hydrogen atoms were refined anisotropically. Indole H and amino H atoms were located from difference Fourier maps and refined isotropically with the N—H distances restrained to 0.90(1) Å. The other hydrogen atoms were fixed at calculated positions and refined by using riding models. All calculations were performed using the SHELX-97 program [8]. Crystal data and details of the data collection and the structure refinement are given in Table 1. Hydrogen bonding information is given in Table 2.

Antibacterial test. The compounds were tested for their *in vitro* antibacterial activities against *Staphylococcus aureus* var. Oxford 6538, *Escherichia coli* ATCC 10536, *Klebsiella pneumoniae* ATCC 100131, and *Candida albicans* ATCC 10231 strains using the paper disc diffusion method (for the qualitative determination) and the serial dilutions in the liquid broth method (for the determination of MIC) [9]. Tetracycline was used as the reference drug.

Table 1

Crystal data and refinement parameters for the compounds

Compound	**1**	**2**	**3**
Empirical formula	$C_{22}H_{19}N_3O_2$	$C_{17}H_{13}ClN_4O_3$	$C_{22}H_{28}N_4O_3$
Molecular weight	357.4	356.8	396.5
Crystal color, habit	Colorless, block	Yellow, needle	Colorless, needle
Crystal size, mm	0.17×0.15×0.15	0.30×0.27×0.27	0.17×0.13×0.12
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$C2/c$	Pc
Unit cell dimensions			
a, Å	17.740(2)	29.178(2)	6.579(1)
b, Å	5.621(1)	8.195(1)	15.112(2)
c, Å	18.573(3)	14.372(1)	10.676(2)
β, deg.	92.659(2)	109.446(2)	90.030(2)
V, Å^3	1850.0(6)	3240.5(5)	1061.4(3)
Z	4	8	2
D_{calc}, g·cm^{-3}	1.283	1.463	1.241
Absorption coefficient μ, mm^{-1}	0.084	0.261	0.084
θ range collected, deg.	3.10—27.00	2.59—27.00	2.34—26.99
T_{min} and T_{max}	0.986 and 0.988	0.926 and 0.933	0.986 and 0.990
Reflections collected / unique (R_{int})	10082 / 3986 (0.0620)	8555 / 3505 (0.0340)	5489 / 3614 (0.0416)
Data / restraints / parameters	3986 / 2 / 251	3505 / 2 / 232	3614 / 4 / 272
Observed reflections [$I \geq 2\sigma(I)$]	1577	2109	2372
R_1, wR_2 [$I \geq 2\sigma(I)$]	0.0610, 0.1155	0.0452, 0.1028	0.0535, 0.1123
R_1, wR_2 (all data)	0.1740, 0.1571	0.0866, 0.1224	0.0866, 0.1279
Goodness of fit (GOOF) on F^2	0.984	1.022	0.994
Largest differences in peak/hole, e/Å^3)	0.123 and –0.141	0.167 and –0.211	0.146 and –0.168

Table 2

Geometrical parameters for hydrogen bonds

D—H···*A*	*D*—H, Å	H···*A*, Å	*D*···*A*, Å	*D*—H···*A*, deg.	*D*—H···*A*	*D*—H, Å	H···*A*, Å	*D*···*A*, Å	*D*—H···*A*, deg.
1					**3**				
N2—H2···O1^{i}	0.90(1)	1.98(1)	2.864(3)	170(3)	O2—H2A···N3	0.82	1.95	2.654(3)	143
2					O3—H3···O1^{iv}	0.82	1.92	2.740(4)	174
N2—H2···N1^{ii}	0.90(1)	2.41(1)	3.268(3)	161(2)	N2—H2···O3	0.90(1)	2.01(2)	2.883(4)	164(3)
N1—H1···O1^{iii}	0.90(1)	2.05(1)	2.893(2)	159(2)	N1—H1···O1^{v}	0.90(1)	1.98(2)	2.805(4)	154(4)

Symmetry transformation used to generate the symmetry related atoms: (i) 1–*x*, 1–*y*, –*z*; (ii) *x*, –1+*y*, *z*; (iii) 1/2–*x*, 3/2–*y*, 1–*z*; (iv) 1+*x*, *y*, *z*; (v) 1+*x*, 1–*y*, –1/2+*z*.

RESULTS AND DISCUSSION

Structural description of the compounds. The molecular structures of compounds **1** and **2**, and methanol solvated compound **3** are shown in Figs. 1, 2, and 3 respectively. In each compound, the hydrazone molecule adopts an *E* configuration with respect to C=N double bonds. The distances between

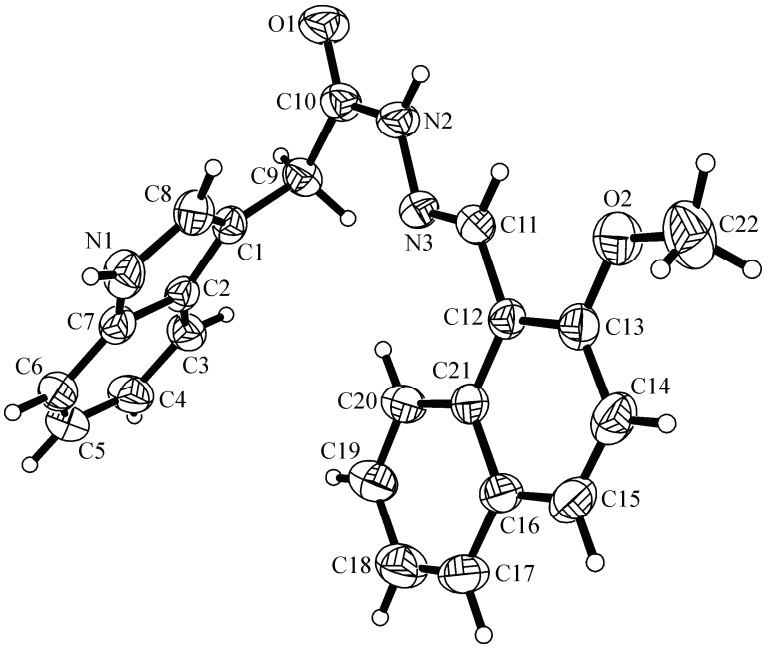

Fig. 1. Thermal ellipsoid plot (30 % probability level) of **1** showing the numbering scheme

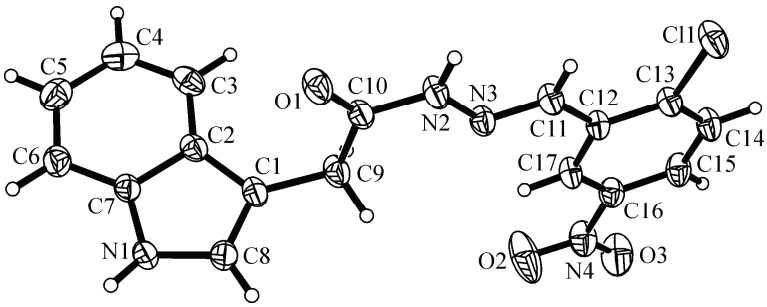

Fig. 2. Thermal ellipsoid plot (30 % probability level) of **2** showing the numbering scheme

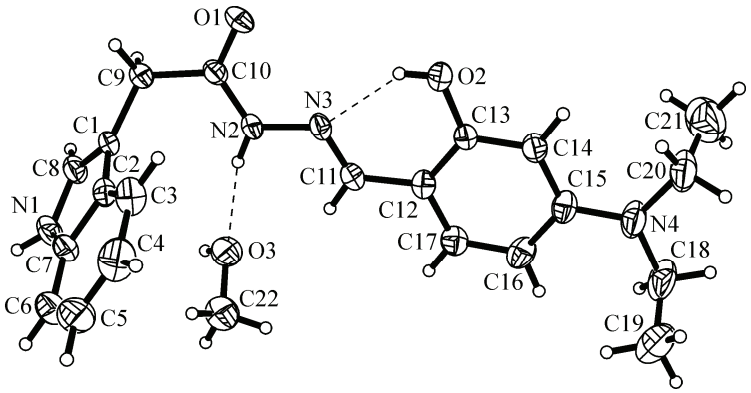

Fig. 3. Thermal ellipsoid plot (30 % probability level) of **3** showing the numbering scheme

C11 and N3 (1.276(3) Å in **1**, 1.275(3) Å in **2**, and 1.262(4) Å in **3)** conform them as typical double bonds. The distances between C10 and N2 (1.345(3) Å in **1**, 1.360(3) Å in **2**, and 1.317(4) Å in **3**) are intermediate between single and double bonds due to the conjugation effects of C11···N3···N2···C10···O1 moieties. It is notable that the C11—N3 and C10—N2 distances are comparable to each other in **1** and **2**, and they are much longer than those in **3**. This might be caused by the formation of N2—H2···O3 hydrogen bonds. The other bond lengths in the three compounds are comparable to each other and are also within normal values [6, 10—13]. The molecules of the three compounds are much distorted, as evidenced by the dihedral angles between the indole ring and the aromatic ring: 71.2(3)° for **1**, 81.1(3)° for **2**, and 67.9(3)° for **3**. The C1—C9—C10—N2 torsion angles

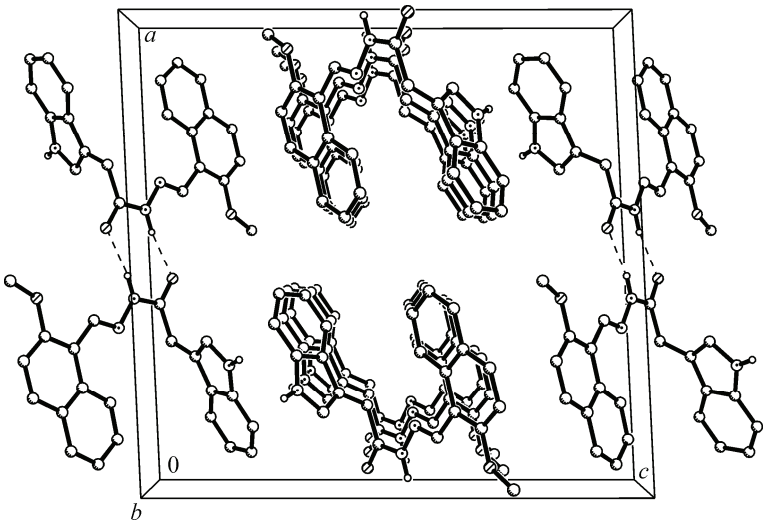

Fig. 4. Packing diagram for **1** viewed along the *b* axis. Hydrogen bonds are drawn as dashed lines

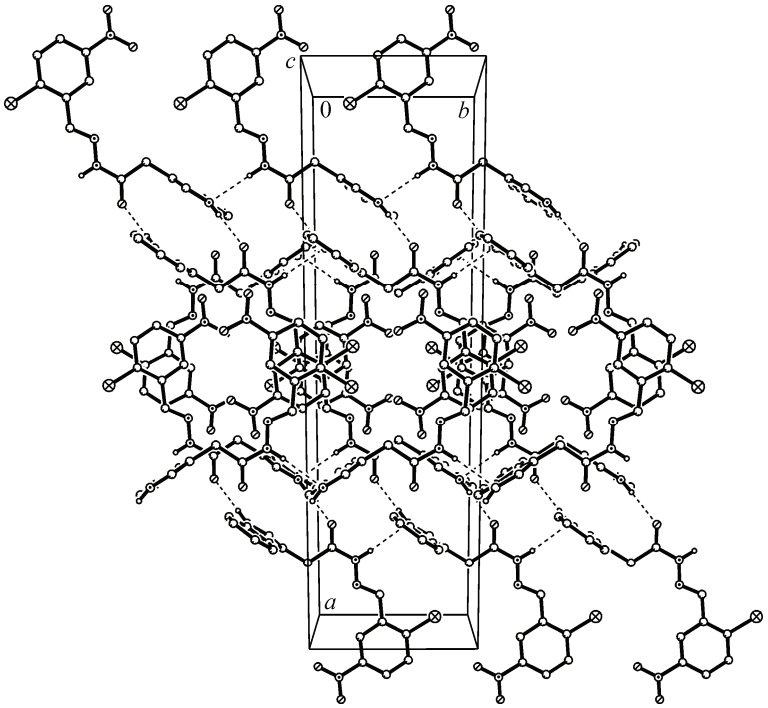

Fig. 5. Packing diagram for **2** viewed along the *c* axis. Hydrogen bonds are drawn as dashed lines

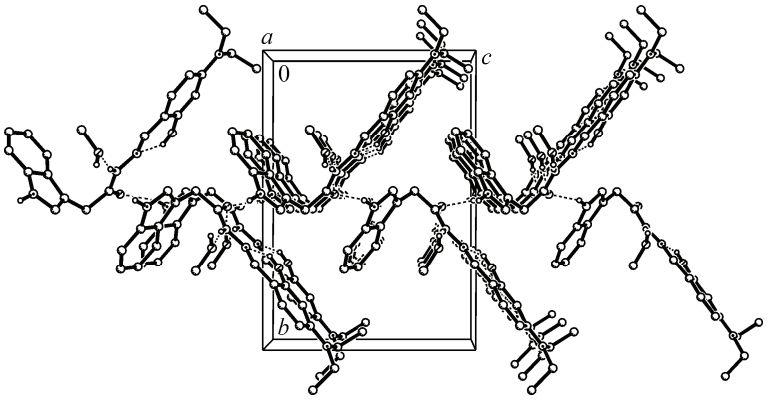

Fig. 6. Packing diagram for **3** viewed along the *a* axis. Hydrogen bonds are drawn as dashed lines

Table 3

Parameters between the planes for **2**

Cg	Distance between ring centroids, Å	Dihedral angle, deg.	Perpendicular distance of Cg(I) on Cg(J), Å	Perpendicular distance of Cg(J) on Cg(I), Å
Cg1···Cg1^{vi}	3.621	0.02	3.245	3.245
Cg2···Cg2^{vii}	3.719	0.03	3.551	3.551

Note: Cg1 and Cg2 are the centroids of N1—C7—C2—C1—C8 and C12—C13—C14—C15—C16—C21, respectively. Symmetry codes: (vi) 1/2–*x*, 5/2–*y*, 1–*z*; (vii) –*x*, 1–*y*, 1–*z*.

Table 4

Antibacterial activity of the compounds as MIC values, μg/mL

Test material	*Staphylococcus aureus*	*Escherichia coli*	*Klebsiella pneumoniae*	*Candida albicans*
1	16	8	32	512
2	4	4	16	64
3	16	32	64	256
Tetracycline	0.22	1.5	1.2	> 1024

are 75.5(3)° for **1**, 0.6(3)° for **2**, and 28.7(3)° for **3**. In the molecule of **3**, an intramolecular O2—H2A···N3 hydrogen bond exists.

In the crystal structure of **1**, the two adjacent molecules are linked through intermolecular N—H···O hydrogen bonds to form a dimer (Fig. 4). In the crystal structure of **2**, the molecules are linked through intermolecular N—H···O and N—H···N hydrogen bonds to form chains running along the *b* axis (Fig. 5). In the crystal structure of **3**, hydrazone and methanol molecules are linked through intermolecular O—H···O and N—H···O hydrogen bonds to form 2D layers parallel to the *ac* plane (Fig. 6). In addition, there are π···π stacking interactions in compound **2** (Table 3). The crystals of the three compounds contain also C—H···π and N—H···π interactions.

Antibacterial activity. The antibacterial activities of the compounds as well as the reference drug are summarized in Table 4. The results indicate that the compounds show from moderate to effective activities against the growth of the tested strains. It is obvious that the activity of **2** is much more effective than that of **1** and **3**, which might be caused by the Cl substituent in the compound. The Cl-containing compounds have been proved to have interesting biological properties. The activities against *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* are somewhat weak as compared to the reference drug Tetracycline. However, all the compounds have stronger activities against *Candida albicans* than Tetracycline.

CONCLUSIONS

Three flexible hydrazone compounds derived from the condensation of 1*H*-indol-3-acetohydrazide with 2-methoxynaphthaldehyde, 2-chloro-5-nitrobenzaldehyde, and 4-diethylaminosalicylaldehyde, respectively, in methanol, were prepared and structurally characterized. The preliminary biological tests indicate that the compounds are effective antibacterial materials.

Supplementary material. CCDC-843105 for **1**, 843106 for **2**, and 843107 for **3** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/const/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgments. The authors thank the Third Affiliated Hospital of Suzhou University for supporting this work.

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