Scientific paper

Synthesis, Characterization and X-Ray Crystal Structures of Aroylhydrazones Derived from 2-Chlorobenzaldehyde with Various Benzohydrazides

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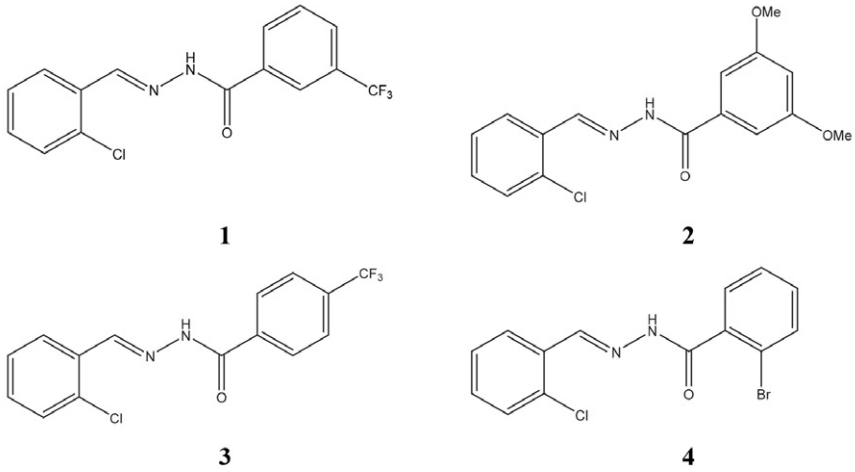
Abstract

Reaction of 2-chlorobenzaldehyde with 3-trifluoromethylbenzohydrazide, 3,5-dimethoxybenzohydrazide, 4-trifluoromethylbenzohydrazide and 2-bromobenzohydrazide, respectively, in methanol afforded four new aroylhydrazones. The newly synthesized compounds were characterized by means of elemental analysis, IR and ^{1}H NMR spectroscopy, and their structures were further confirmed by X-ray single crystal determination. The compounds were assayed for their antibacterial activities against *E. coli, P. aeruginosa, B. subtilis, and S. aureus* and show interesting results.

Keywords: Aroylhydrazones; 2-chlorobenzaldehyde; crystal structure; antibacterial activity.

1. Introduction

Aroylhydrazones containing –C(O)–NH–N=CH– group can be prepared by a facile reaction of carbonyl containing compounds with hydrazides. The compounds have shown interesting biological application such as antibacterial activity,[1] antifungal activity,[2] antitumor activity,[3] anti-inflammatory activity,[4] and cytotoxic activity.[5] The literature work indicates that compounds bearing halide substituents have enhanced biological activities especially for the antibacterial and antifungal aspects.[6] Rai et al. reported some fluoro, chloro, bromo and iodo-containing compounds that show improved antimicrobial activities.[7] Recently, we have reported some hydrazones derived from 4-pyridinecarboxaldehyde.[8] In continuation of such work, we report herein four new aroylhydrazones, *N*'-(2-chlorobenzylidenemethylene)-3-trifluoromethylbenzohydrazide (**1**), *N*'-(2-chlorobenzylidenemethylene)-3,5-dimethoxybenzohydrazide (**2**),



Scheme 1. The aroylhydrazones under study

N'-(2-chlorobenzylidenemethylene)-4-trifluoromethylbenzohydrazide (**3**), and 2-bromo-*N*'- (2-chlorobenzylidenemethylene)benzohydrazide (**4**), and evaluation of their antibacterial activities.

2. Experimental

2. 1. Materials and Measurements

2-Chlorobenzaldehyde, 3-trifluoromethylbenzohydrazide, 3,5-dimethoxybenzohydrazide, 4-trifluoromethylbenzohydrazide, and 2-bromobenzohydrazide were purchased from Sigma-Aldrich, and used as received. The remaining chemicals were obtained from Aladin Chemical Co. Ltd. CHN elemental analyses were carried out with a Perkin-Elmer elemental analyzer. Infrared spectra of the compounds were recorded on a Nicolet AVATAR 360 spectrometer. ^{1}H NMR data were determined with a Bruker 500 MHz instrument. Single crystal X-ray diffraction was performed on a Bruker D8 VENTURE PHOTON diffractometer at room temperature equipped with Mo-Kα radiation.

2. 2. Preparation of the compounds

The four compounds were facile synthesized with the following method. 2-Chlorobenzaldehyde (1.0 mmol, 140 mg) was dissolved in MeOH (30 mL), which was slowly added to the methanolic solution (30 mL) containing 3-trifluoromethylbenzohydrazide (1.0 mmol, 204 mg), 3,5-dimethoxybenzohydrazide (1.0 mmol, 196 mg), 4-trifluoromethylbenzohydrazide (1.0 mmol, 204 mg), and 2-bromobenzohydrazide (1.0 mmol, 215 mg), respectively. The mixtures were magnetic stirred for 30 min at room temperature. Single crystals of the compounds with X-ray diffraction quality were grown from the solution after slow evaporation in air for several days.

N'-(2-Chlorobenzylidenemethylene)-3-trifluoromethylbenzohydrazide (1)

Colorless crystals. Yield: 273 mg (83%). Anal. calcd. for $C_{15}H_{10}ClF_3N_2O$: C, 55.15; H, 3.09; N, 8.57; found C, 54.93; H, 3.16; N, 8.65%. Characteristic IR data (cm^{-1}): 3184 (w), 1652 (s), 1598 (m), 1563 (s), 1434 (w), 1370 (w), 1330 (s), 1310 (m), 1276 (s), 1167 (s), 1117 (s), 1073 (m), 953 (w), 934 (w), 914 (w), 810 (w), 755 (m), 701 (s). ^{1}H NMR (500 MHz, d_6-DMSO): δ: 12.24 (s, 1H, NH), 8.88 (s, 1H, CN=N), 8.28 (s, 1H, ArH), 8.26 (d, 1H, ArH), 8.06 (t, 1H, ArH), 7.97 (d, 1H, ArH), 7.78 (t, 1H, ArH), 7.55 (d, 1H, ArH), 7.46 (m, 2H, ArH).

N'-(2-Chlorobenzylidenemethylene)-3,5-dimethoxybenzohydrazide (2)

Colorless crystals. Yield: 281 mg (88%). Anal. calcd. for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79; found C, 60.45; H, 4.81; N, 8.68%. Characteristic IR data (cm^{-1}): 3178 (w), 1652 (s), 1598 (s), 1565 (s), 1454 (m), 1360 (m), 1310 (m), 1206 (m), 1163 (s), 1063 (s), 945 (w), 854 (m), 760 (w), 700 (w), 538 (w). ^{1}H NMR (500 MHz, d_6-DMSO): δ: 11.98 (s, 1H, NH), 8.88 (s, 1H, CN=N), 8.03 (t, 1H, ArH), 7.53 (t, 1H, ArH), 7.45 (m, 2H, ArH), 7.10 (d, 2H, ArH), 6.73 (s, 1H, ArH), 3.83 (s, 6H, CH_3).

N'-(2-Chlorobenzylidenemethylene)-4-trifluoromethylbenzohydrazide (3)

Colorless crystals. Yield: 255 mg (78%). Anal. calcd. for $C_{15}H_{10}ClF_3N_2O$: C, 55.15; H, 3.09; N, 8.57; found C, 54.98; H, 3.16; N, 8.51%. Characteristic IR data (cm^{-1}): 3165 (w), 1655 (s), 1597 (m), 1561 (m), 1445 (w), 1372 (w), 1323 (m), 1313 (w), 1275 (m), 1163 (s), 1098 (m), 1065 (m), 971 (w), 946 (w), 902 (w), 823 (w), 757 (m), 689 (m). ^{1}H NMR (500 MHz, d_6-DMSO): δ: 12.17 (s, 1H, NH), 8.88 (s, 1H, CN=N), 8.19 (d, 2H, ArH), 7.79 (d, 2H, ArH), 7.67 (d, 1H, ArH), 7.53 (d, 1H, ArH), 7.45 (m, 2H, ArH).

2-Bromo-*N*'-(2-chlorobenzylidenemethylene) benzohydrazide (4)

Colorless crystals. Yield: 260 mg (77%). Anal. calcd. for $C_{14}H_{10}BrClN_2O$: C, 49.81; H, 2.99; N, 8.30; found C, 49.67; H, 3.12; N, 8.37%. Characteristic IR data (cm^{-1}): 3190 (w), 1653 (s), 1597 (s), 1563 (s), 1457 (m), 1371 (m), 1323 (w), 1211 (m), 1160 (m), 1073 (s), 953 (w), 846 (m), 757 (w), 723 (w), 612 (w). ^{1}H NMR (500 MHz, d_6-DMSO): δ: 12.10 (s, 1H, NH), 8.70 (s, 1H, CN=N), 8.03 (d, 1H, ArH), 7.73 (d, 1H, ArH), 7.57 (d, 1H, ArH), 7.51 (m, 3H, ArH), 7.38 (m, 2H, ArH).

2. 3. Single Crystal X-ray Determination

Single crystal X-ray determination for the crystals of the compounds were carried out with Mo-*K*α radiation (λ = 0.71073 Å) at 298(2) K using Bruker D8 VENTURE PHOTON diffractometer. The data were reduced with SAINT.[9] Multi-scan absorption corrections were performed with SADABS.[10] All structures of the compounds were solved by direct method and refined against F^2 by full-matrix least-squares method using SHELXT and SHELXL programs.[11] All non-H atoms were refined anisotropically. The amino H atoms were located from electronic maps and refined isotropically. The N–H distances were restrained to 0.90(1) Å. The remaining H atoms were placed in calculated positions. The crystallographic data are listed in Table 1. The trifluoromethyl groups in compounds **1** and **3** are disordered, with occupancies of 0.46(1) and 0.54(1), and 0.38(1) and 0.62(1), respectively.

Table 1. Crystal data for the compounds

	1	**2**	**3**	**4**
Formula	$C_{15}H_{10}ClF_3N_2O$	$C_{16}H_{15}ClN_2O_3$	$C_{15}H_{10}ClF_3N_2O$	$C_{14}H_{10}BrClN_2O$
M_r	326.70	318.75	326.70	337.60
Crystal color, habit	Colorless, block	Colorless, block	Colorless, block	Colorless, block
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$
Unit cell parameters				
a (Å)	13.2066(10)	21.6544(19)	12.6745(12)	7.4933(7)
b (Å)	12.9373(11)	8.9307(13)	13.1570(13)	25.3971(16)
c (Å)	8.5263(5)	16.3842(17)	8.8105(11)	7.7789(8)
β (°)	97.877(1)	99.034(1)	92.381(1)	114.043(1)
V (Å^3)	1443.0(2)	3129.2(6)	1468.0(3)	1351.9(2)
Z	4	8	4	4
D_{calc} (g cm^{-3})	1.504	1.353	1.478	1.659
μ (mm^{-1})	0.300	0.258	0.295	3.230
F(000)	664	1328	664	672
Collected data	7045	18200	8618	7957
Number of unique data	2672	5821	2734	2511
Number of observed data [$I > 2\sigma(I)$]	1998	2765	1509	1876
Number of parameters	231	408	230	175
Number of restraints	49	2	49	1
R_1, wR_2 [$I > 2\sigma(I)$]	0.0382, 0.0921	0.0559, 0.0949	0.0556, 0.1237	0.0353, 0.0661
R_1, wR_2 (all data)	0.0556, 0.1053	0.1500, 0.1349	0.1161, 0.1550	0.0573, 0.0725
Goodness of fit on F^2	1.073	1.017	1.051	1.022

3. Results and Discussion

3. 1. Chemistry

The four compounds were prepared by facile condensation reaction of 2-chlorobenzaldehyde with aroylhydrazides in methanol. They have good solubility in MeOH, EtOH, acetonitrile, DMSO and DMF. The strong bands in the range 1652–1655 cm^{-1} can be assigned to the vibration of ν(C=O). The bands in the range 1597–1598 cm^{-1} can be assigned to the vibration of ν(C=N).[8,12] The weak bands indicative of the ν(N–H) are observed at 3165–3190 cm^{-1}. The CHN elemental analyses agree well with the proposed chemical formulae by single crystal X-ray determination.

3. 2. Crystal Structure Description

The structures of the four compounds are shown in Figures 1–4. Characteristic bond lengths are given in Table 2. The asymmetric unit of **2** contains two independent molecules. There is only one aroylhydrazone molecule in the asymmetric unit in the remaining three compounds. The molecule of each compound has an *E* configuration about the C=N group. The methylidene bonds have distances of 1.26–1.27 Å, which are similar to each other for the four compounds. The C–N bonds are shorter than usual, and the C=O bonds are longer than usual, suggesting the molecules present conjugation effects. The bond lengths in the compounds are within normal values.[8,13] The two benzene rings form dihedral angles of 7.4(3)° for **1**, 35.3(5)° and 4.0(5)° for **2**, 4.3(5)° for **3**, and 15.7(3)° for **4**. It is obvious that the dihedral angle between the two benzene rings in one molecule of compound **2** is larger than the other molecule, which might be caused by the hydrogen bonding. There are two acceptors (O1 and N1) for N4–H4 bond, *viz.* N4–H4···O1 and N4–H4···N1.

The aroylhydrazone molecules of **1** are linked through hydrogen bonds of N–H···O and C–H···O, to form one-dimensional chains along the *c*-axis direction (Table 3, Figure 5). The aroylhydrazone molecules of **2** are linked through hydrogen bonds of N–H···O, N–H···N and

Table 2. Selected bond distances (Å) for the four compounds

	1		
N1–C7	1.268(2)	N1–N2	1.388(2)
N2–C8	1.341(2)	O1–C8	1.230(2)
	2		
N1–C7	1.269(4)	N1–N2	1.378(4)
N2–C8	1.361(4)	O1–C8	1.229(4)
N3–C23	1.270(4)	N3–N4	1.381(4)
N4–C24	1.337(4)	O4–C24	1.228(4)
	3		
N1–C7	1.261(4)	N1–N2	1.388(3)
N2–C8	1.349(4)	O1–C8	1.221(4)
	4		
N1–C7	1.268(3)	N1–N2	1.387(3)
N2–C8	1.344(3)	O1–C8	1.220(3)

C–H···O, to form one-dimensional chains along the *c*-axis direction (Table 3, Figure 6). The aroylhydrazone molecules of **3** are linked through hydrogen bonds of N–H···O and C–H···O, to form one dimensional chains along the *c*-axis direction (Table 3, Figure 7). The aroylhydrazone molecules of **4** are linked through hydrogen bonds of N–H···O and C–H···O, to form one-dimensional chains along the *a* axis direction (Table 3, Figure 8).

3. 3. Antibacterial Activity

The antibacterial experiment was carried out with the method described in literature.[14] Penicillin G was selected as a reference. DMSO was used as a solvent and the solutions were diluted by water. At the tested concentration, DMSO has no activity on the bacteria. The zones of inhibition for the bacteria *E. coli*, *P. aeruginosa*, *S. typhi* and *S. aureus* are summarized in Table 4. MIC values are

Table 3. Hydrogen bond distances (Å) and angles (°) for the four compounds

D–H···*A*	*d*(*D*–H), Å	*d*(H···*A*), Å	*d*(*D*···*A*), Å	Angle (*D*–H···*A*),°
		1		
N2–H2···O1^{i}	0.885(9)	2.036(11)	2.8978(18)	164(2)
C7–H7···O1^{i}	0.93	2.51	3.274(2)	139.5
		2		
N2–H2···O4^{ii}	0.900(10)	2.04(3)	2.853(4)	149(5)
N4–H4···O1^{iii}	0.901(10)	2.11(2)	2.948(4)	155(5)
C7–H7···O4^{ii}	0.93	2.27	3.089(5)	147.1
		3		
N2–H2···O1^{v}	0.897(10)	1.996(16)	2.858(3)	161(3)
C7–H7···O1^{v}	0.93	2.34	3.137(4)	143.2
		4		
C7–H7···O1^{vi}	0.93	2.52	3.292(3)	140.2
N2–H2···O1^{vi}	0.893(10)	1.975(13)	2.842(3)	163(3)

Symmetry codes: i) *x*, 1½ – *y*, ½ + *z*; ii) *x*, *y*, –1 + *z*; iii) *x*, ½ – *y*, ½ + *z*; iv) 1 – *x*, – *y*, – *z*; (v) *x*, 1½ – *y*, ½ + *z*; vi) –½ + *x*, ½ – *y*, –½ + *z*.

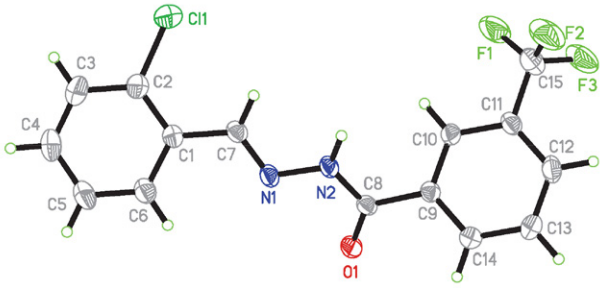


Figure 1. Molecular structure of compound **1** with 30% thermal ellipsoids.

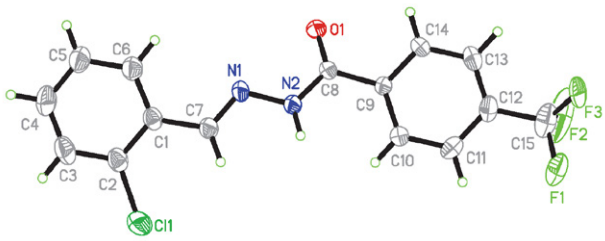


Figure 3. Molecular structure of compound **3** with 30% thermal ellipsoids.

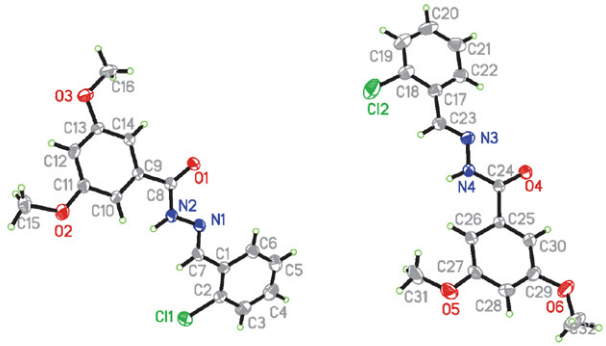


Figure 2. Molecular structure of compound **2** with 30% thermal ellipsoids.

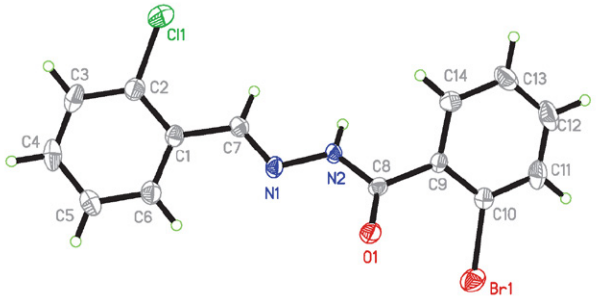


Figure 4. Molecular structure of compound **4** with 30% thermal ellipsoids.

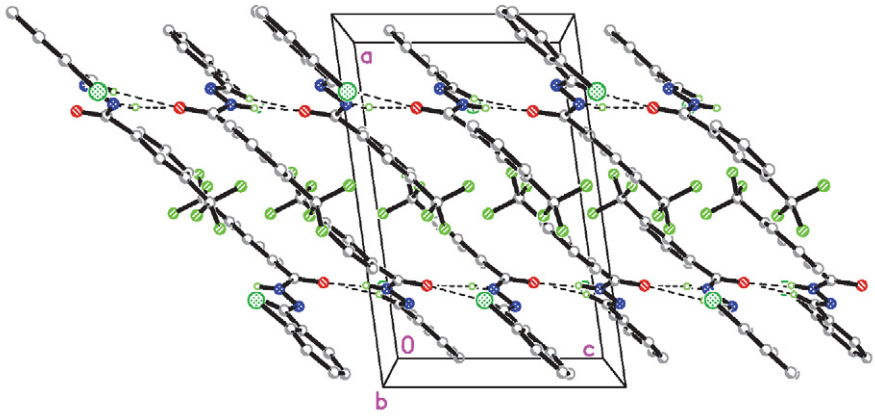


Figure 5. The hydrogen bonds (dashed lines) linked molecular structure of compound **1**. Hydrogen atoms not involved in hydrogen bonding are deleted for clarity.

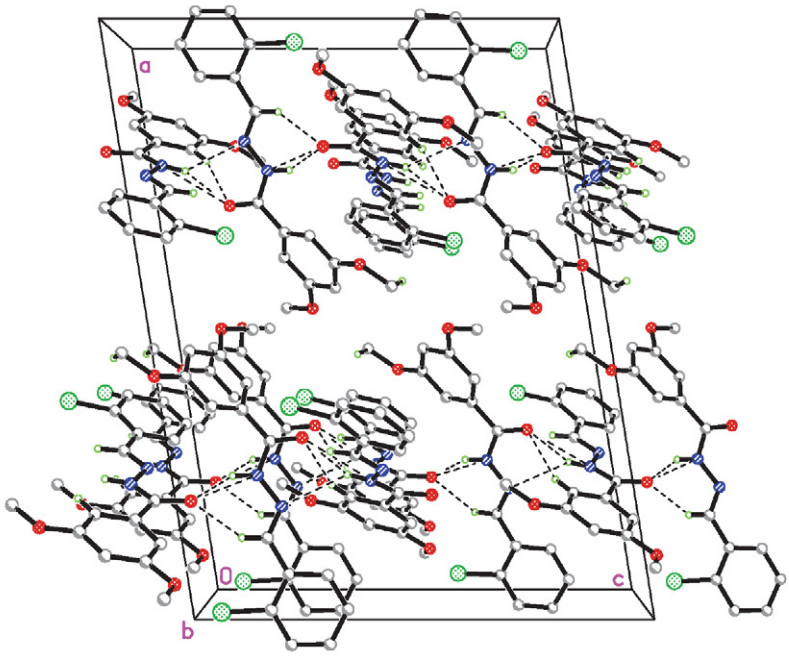


Figure 6. The hydrogen bonds (dashed lines) linked molecular structure of compound **2**. Hydrogen atoms not involved in hydrogen bonding are deleted for clarity.

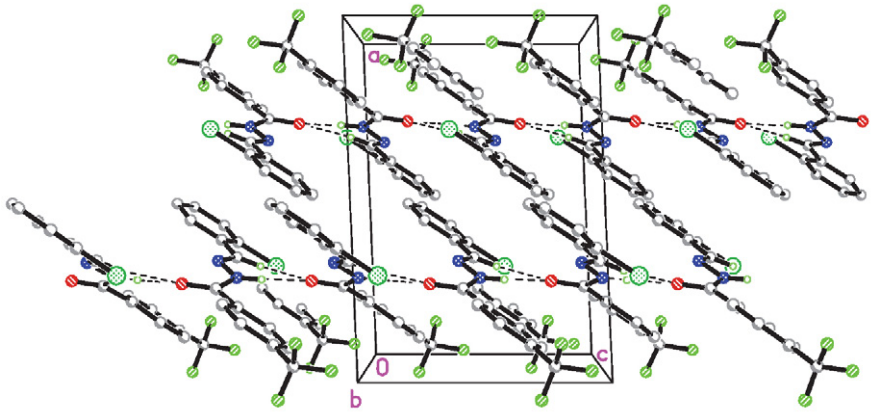


Figure 7. The hydrogen bonds (dashed lines) linked molecular structure of compound **3**. Hydrogen atoms not involved in hydrogen bonding are deleted for clarity.

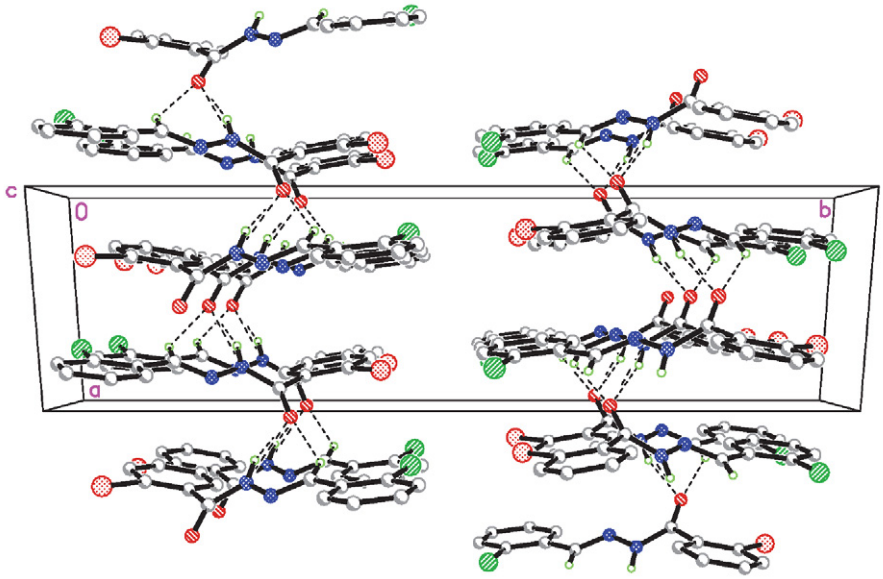


Figure 8. The hydrogen bonds (dashed lines) linked molecular structure of compound **4**. Hydrogen atoms not involved in hydrogen bonding are deleted for clarity.

listed in Table 5. The compounds show from weak to strong activities on the bacteria strains. Compounds **1** and **3** have strong activity on *E. coli*, *P. aeruginosa* and *B. subtilis*, and medium activity on *S. aureus*. Compound **2** has medium activity on *E. coli*, *P. aeruginosa* and *B. subtilis*, and weak activity on *S. aureus*. Compound **4** has strong activity on *E. coli*, and medium activity on *P. aeruginosa*, *B. subtilis* and *S. aureus*. Among the compounds, compounds **1** and **3** have the most activity on *E. coli* and *P. aeruginosa* with MIC values of 1.56 and 6.25 μg mL^{-1}, respectively, which are stronger or similar to penicillin G. The compounds have higher activity on *E. coli*, *B. subtilis* and *S. aureus* than the pyrroles bearing thiazole moiety.[15] The trifluoromethyl containing compounds **1** and **3** have better activity on the bacteria than the fluoro-substituted aroylhydrazones.[16] The present compounds have higher activity than the benzohydrazones.[8]

After careful comparison we noticed that the electronic withdrawing substituent groups like Cl, CF_3 and Br might contribute to the activity on the bacteria strains. The trifluoromethyl group can enhance the activity.

Table 4 Antibacterial results

Compound	Zone of inhibition (mm)			
	E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*
1	32 ± 2.2	23 ± 2.1	22 ± 1.7	15 ± 1.5
2	16 ± 1.7	15 ± 1.4	11 ± 1.5	9.3 ± 1.2
3	33 ± 1.8	21 ± 2.2	25 ± 2.0	16 ± 1.3
4	25 ± 2.0	17 ± 1.5	14 ± 1.7	12 ± 1.6
Penicillin G	30 ± 2.8	26 ± 3.1	30 ± 3.2	24 ± 2.9

Table 5 Antibacterial activities (MIC, μg mL^{-1})

Compound	*E. coli*	*P. aeruginosa*	*B. subtilis*	*S. aureus*
1	1.56	6.25	3.13	12.5
2	12.5	6.25	25	25
3	1.56	6.25	3.13	12.5
4	6.25	12.5	12.5	12.5
Penicillin G	3.13	6.25	1.56	6.25

4. Conclusions

In conclusion, a series of four aroylhydrazones were synthesized and characterized. The antibacterial activities against *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus* were determined. *N*'-(2-Chlorobenzylidenemethylene)-3-trifluoromethylbenzohydrazide and *N*'-(2-chlorobenzylidenemethylene)-4-trifluoromethylbenzohydrazide have strong activity on *E. coli* and *P. aeruginosa*, with MIC values of 1.56 and 6.25 μg mL^{-1}, respectively. The trifluoromethyl substituent group is a preferred factor for the exploration of new antibacterial drugs.

5. Supplementary Material

CCDC–2380982 (**1**), 2380983 (**2**), 2380984 (**3**) and 2380985 (**4**) are the crystallographic data for this work. The data can be obtained 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.

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Povzetek

Reakcija 2-klorobenzaldehida s 3-trifluorometilbenzohidrazidom, 3,5-dimetoksibenzohidrazidom, 4-trifluorometilbenzohidrazidom in 2-bromobenzohidrazidom v metanolu je dala štiri nove aroilhidrazone. Na novo sintetizirane spojine smo okarakterizirali z elementno analizo, IR in ^{1}H NMR spektroskopijo, njihove strukture pa smo potrdili z rentgensko monokristalno analizo. Pri spojinah smo določili njihovo antibakterijsko delovanje proti *E. coli*, *P. aeruginosa*, *B. subtilis* in *S. aureus*.