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ORIGINAL PAPER

Structure and Antibacterial Activity of 3-(3,4-Dimethoxyphenyl) furan-2(5*H*)-ones

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Abstract Crystalline hydrate of the title compound (**5**), $C_{19}H_{26}N_2O_5{\cdot}2(H_2O)$, was structurally characterized by single crystal X-ray diffraction. It crystallizes in monoclinic system space group *P 21/c* with $a = 7.3987(7)$ Å, $b = 17.8691(16)$ Å, $c = 17.0022(13)$ Å, $\beta = 112.944(3)°$, $V = 2070.0(3)$ Å^3, $Z = 4$, $R_1 = 0.0592$, $wR_2 = 0.1016$, and $T = 298(2)$ K. The X-ray structure determination revealed that the center furanone ring is nearly coplanar with 3,4-dimethoxybenzene ring, making a dihedral angle of 0.860(69)°. Two kinds of centrosymmetric tetramers characterized by graph-set motifs of $R_7^8(36)$ and $R_4^6(32)$ are formed through O–H···O, O–H···N and C–H···O hydrogen bonding interactions, which generate a sheet of edge-fused rings parallel to the (011) plane. These sheets are further linked into a three dimensional network by C–H···π interactions. Nine 3-(3,4-dimethoxyphenyl)furan-2(5*H*)-ones were synthesized and fully characterized by elemental analysis, MS and ^{1}H NMR. All of them were evaluated for antimicrobial activities against three Gram-positive organisms and a Gram-negative organism, and compound **5** was the most active against *Staphylococcus aureus* ATCC 25923.

Keywords Synthesis · Crystal structure · 3-Arylfuran-2(5*H*)-one · Antibacterial

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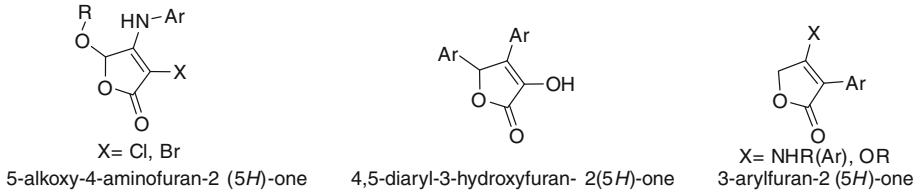
Introduction

Compounds with γ-butyrolactone-core show diverse biological activities such as anti-oxidative, anti-inflammatory and antibacterial activity [1–3], and have been receiving increasing attention in recent years [4, 5]. In 2006, Lattmann et al. [6] reported 5-alkoxy-4-aminofuran-2(5*H*)-ones (Scheme 1) showing good antibacterial activity against multiresistant *Staphylococcus aureus*. Subsequently, Bailly et al. [7] reported 4,5-diaryl-3-hydroxyfuran-2(5*H*)-ones (Scheme 1) being good inhibitors against HIV-1 integrase. Recently, we determined that 3-arylfuran-2(5*H*)-ones (Scheme 1) as potent inhibitors against tyrosyl-tRNA synthetase (TyrRS) [8, 9], which is an aminoacyl-tRNA synthetases (aaRSs). AaRSs are essential enzymes involved in protein biosynthesis in all living organisms. However, these enzymes have been subjected to significant evolutionary divergence, and selective inhibition of bacterial enzymes is therefore a valuable strategy for the production of antibiotics [10]. As a part of our ongoing studies on furan-2(5*H*)-ones, we designed and synthesized a series of 3-(3,4-dimethoxyphenyl)-furan-2(5*H*)-ones for screening antibacterial activity. For confirmation of the structure the obtained compounds (**1–9**), the single crystal structure of 3-(3,4-dimethoxyphenyl)-4-(2-(4-methylpiperazin-1-yl)ethoxy) furan-2(5*H*)-one (**5**) was selected to determine.

Scheme 1 The structures of some furanones



Experimental Section

Reagents and Techniques

2-(3,4-Dimethoxyphenyl)acetic acid was purchased from Aldrich (USA) and the other chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd (China). Separation of the compounds by column chromatography was carried out with silica gel 60 (200–300 mesh ASTM, E. Merck). The quantity of silica gel used was 30–70 times the weight charged on the column. Then, the eluates were monitored using TLC. Melting points (uncorrected) were determined on a XT4 MP apparatus (Taike Corp., Beijing, China). ESI mass spectra were obtained on a Mariner System 5304 mass spectrometer, and ^{1}H NMR spectra were recorded on a Bruker AV-300 spectrometer at 25 °C with TMS and solvent signals allotted as internal standards. Chemical shifts were reported in ppm (δ). Elemental analyses were performed on a CHN-O-Rapid instrument and were within ±0.4% of the theoretical values.

General Procedure for Preparation of Compounds **1–9**

Compounds **1** and **2** were obtained according to the procedure previously described [11, 12], which were further treated as follows to produce compounds **3–9** (Scheme 2; Table 2). A mixture of compound **2** (0.5 mmol) and triethylamine (225 μL, 1.5 mmol) was dissolved in 15 mL of dry DMF and heated to 50 °C. The solution was received 3–4 interval injections of an appropriate amine (0.6 mmol) within 2 h. The mixture was then stirred for 6–10 h. After 30 mL of water was added, the resulted mixture was extracted thrice with EtOAc. The combined organic layer washed with brine and dried over $MgSO_4$. Removement of the solvent under reduced pressure gave a brown oil, which was purified by column chromatography on silica gel, eluting with $CHCl_3$/CH_3OH (saturated with ammonia, from 37/1 to 80/1) to give compounds **3–5**. As for the synthesis of compounds **6–9**, a mixture of compound **1** (0.5 mmol), an appropriately substituted aniline (0.6 mmol) and *p*-toluene sulphonic acid (3.4 mg, 0.02 mmol) was heated to 90 °C for 10 min. Five mL toluene was then added and refluxed for 3–7 h. After toluene was removed under reduced pressure, the residue was purified by column chromatography on silica gel, eluting with EtOAc/petroleum ether.

*3-(3,4-Dimethoxyphenyl)-4-hydroxyfuran-2(5H)-one (**1**)*

Colorless crystal, 53%, mp 210–212 °C, ^{1}H NMR (DMSO-d_6): 3.88 (s, 3H); 3.89 (s, 3H); 4.77 (s, 2H); 6.75 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H); 6.77 (d, J = 2.1 Hz, 1H); 6.93 (d, J = 8.1 Hz, 1H); EIMS *m/z* 236 (M^+). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12; Found: C, 61.47; H, 5.10.

*4-(2-Bromoethoxy)-3-(3,4-dimethoxyphenyl)furan-2(5H)-one (**2**)*

Light yellow crystal, 47%, mp 140–142 °C, ^{1}H NMR ($CDCl_3$): 2.68 (t, J = 5.5 Hz, 2H); 3.88 (s, 3H); 3.90 (s, 3H); 4.20 (t, J = 5.5 Hz, 2H); 4.79 (s, 2H); 6.91 (d, J = 8.4 Hz, 1H); 7.50 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H); 7.56 (d, J = 1.8 Hz, 1H); EIMS *m/z* 342 (M^+). Anal. Calcd for $C_{14}H_{15}BrO_5$: C, 49.00; H, 4.41; Br, 23.28; Found: C, 49.13; H, 4.41; Br, 23.24.

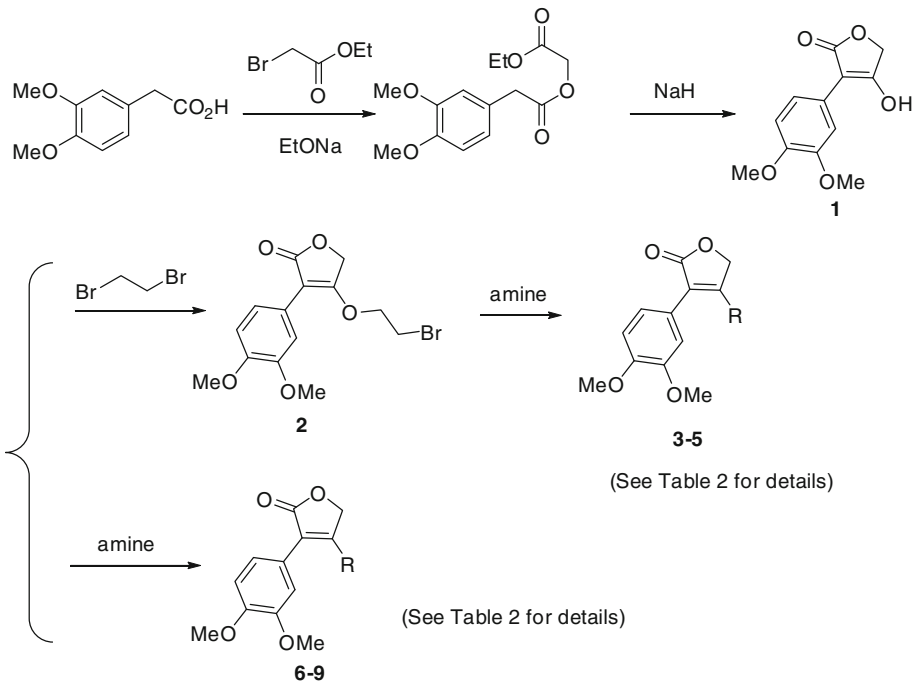
*4-(2-(Cyclohexylamino)ethoxy)-3-(3,4-dimethoxyphenyl)furan-2(5H)-one (**3**)*

Colorless crystal, 68%, mp 137–139 °C, ^{1}H NMR ($CDCl_3$): 0.80–1.02 (m, 3H); 1.23–1.42 (m, 3H); 1.60–1.74 (m, 4H); 1.93 (bs, 1H); 3.23 (t, J = 6.4 Hz, 2H); 3.32–3.43 (m, 1H); 3.54 (t, J = 6.3 Hz, 2H); 3.85 (s, 3H); 3.89 (s, 3H); 4.88 (s, 2H); 6.80 (d, J = 1.8 Hz, 1H); 6.81 (dd, J = 8.0 Hz, J = 1.8 Hz, 1H); 6.86 (d, J = 8.3 Hz, 1H); EIMS *m/z* 361 (M^+). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88; Found: C, 66.51; H, 7.51; N, 3.87.

*3-(3,4-Dimethoxyphenyl)-4-(2-(piperidin-1-yl)ethoxy)furan-2(5H)-one (**4**)*

Colorless crystal, 89%, mp 116–117 °C, ^{1}H NMR ($CDCl_3$): 1.38–1.49 (m, 2H); 1.51–1.67 (m, 4H); 2.46 (t, J = 5.0 Hz, 4H); 2.73 (t, J = 5.5 Hz, 2H); 3.90 (s, 3H); 3.91 (s, 3H); 4.22 (t, J = 5.5 Hz, 2H); 4.87 (s, 2H); 6.89 (d, J = 8.4 Hz, 1H); 7.50 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H); 7.54 (d, J = 1.8 Hz, 1H); EIMS *m/z* 347 (M^+). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03; Found: C, 65.60; H, 7.27; N, 4.04.

Scheme 2 Synthetic rout of 3-(3,4-dimethoxyphenyl)furan-2(5H)-ones



3-(3,4-Dimethoxyphenyl)-4-(2-(4-methylpiperazin-1-yl) ethoxy)furan-2(5H)-one ***(5)***

Colorless crystal, 64%, mp 69–71 °C, ^{1}H NMR (DMSO-d_6): 2.16 (s, 3H); 2.23–2.38 (m, 4H); 2.42–2.55 (m, 4H); 2.73 (t, $J = 5.3$ Hz, 2H); 3.75 (s, 3H); 3.76 (s, 3H); 4.34 (t, $J = 5.4$ Hz, 2H); 5.11 (s, 2H); 6.97 (d, $J = 8.4$ Hz, 1H); 7.49 (d, $J = 2.0$ Hz, 1H); 7.53 (dd, $J = 8.4$ Hz, $J = 2.0$ Hz, 1H); EIMS *m/z* 362 (M^+). Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73; Found: C, 62.88; H, 7.25; N, 7.74.

4-(2-Chlorophenylamino)-3-(3,4-dimethoxyphenyl) furan-2(5H)-one ***(6)***

Colorless crystal, 68%, mp 162–164 °C, ^{1}H NMR ($CDCl_3$): 2.28 (s, 3H); 2.31 (s, 3H); 3.42 (s, 2H); 5.41 (d, $J = 8.0$ Hz, 1H); 5.51–5.61 (m, 4H); 5.72 (t, $J = 7.7$ Hz, 1H); 5.79 (s, 1H); 5.91 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (DMSO-d_6):172.77; 160.05; 159.67; 158.90; 140.68; 134.77; 134.11; 127.13; 126.74; 125.85; 125.04;121.07; 114.75; 113.16; 97.47; 66.42; 56.83; 56.69. EIMS *m/z* 345 (M^+). Anal. Calcd for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; Cl, 10.25; N, 4.05; Found: C, 62.48; H, 4.66; Cl, 10.26; N, 4.04.

4-(3-Chlorophenylamino)-3-(3,4-dimethoxyphenyl) furan-2(5H)-one ***(7)***

Colorless crystal, 71%, mp 200–203 °C, ^{1}H NMR ($CDCl_3$): 2.27 (s, 3H); 2.30 (s, 3H); 3.41 (s, 2H); 5.38 (d, $J = 8.8$ Hz, 2H); 5.44–5.55 (m, 4H); 5.60 (d, $J = 8.0$ Hz, 1H); 5.75 (t, $J = 8.0$ Hz, 1H). ^{13}C NMR (DMSO-d_6):172.82; 160.04; 159.63; 158.92; 140.70; 135.58; 133.19; 127.57; 124.78; 124.15; 123.64;123.28; 114.70; 113.21; 97.49; 66.40; 56.83; 56.68. EIMS *m/z* 345 (M^+). Anal. Calcd for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; Cl, 10.25; N, 4.05; Found: C, 62.60; H, 4.67; Cl, 10.23; N, 4.04.

3-(3,4-Dimethoxyphenyl)-4-(2-methoxyphenylamino) furan-2(5H)-one ***(8)***

Colorless crystal, 85%, mp 120–121 °C, ^{1}H NMR ($CDCl_3$): 3.86 (s, 3H); 3.92 (s, 6H); 5.05 (s, 2H); 6.91–6.98 (m, 4H); 7.07–7.19 (m, 3H); 7.57 (s, 1H). ^{13}C NMR (DMSO-d_6):172.78; 160.05; 159.97; 159.64; 158.90; 140.72; 133.17; 127.57; 124.75; 124.22; 123.61;115.06; 114.75; 113.24; 97.49; 66.40; 56.81; 56.68; 55.91. EIMS *m/z* 341 (M^+). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10; Found: C, 66.74; H, 5.62; N, 4.11.

3-(3,4-Dimethoxyphenyl)-4-(2-nitrophenylamino) furan-2(5H)-one ***(9)***

Colorless crystal, 85%, mp 120–121 °C, ^{1}H NMR (DMSO-d_6): 3.60 (s, 3H); 3.73 (s, 3H); 5.09 (s, 2H); 6.79 (s, 1H); 6.92 (s, 2H); 7.19-7.28 (m, 2H); 7.47 (td, $J = 8.4$ Hz, $J = 1.3$ Hz, 1H); 8.03 (dd, $J = 8.3$ Hz, $J = 1.3$ Hz, 1H); 9.78 (s, 1H). ^{13}C NMR (DMSO-d_6):172.75; 160.14; 159.97; 158.90; 140.72; 137.60; 134.12; 133.66; 126.52; 122.58; 118.67;114.98; 114.15; 113.52; 97.43; 66.38;

56.81; 56.66; 55.90. EIMS *m/z* 356 (M^+). Anal. Calcd for $C1_8H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86; Found: C, 60.61; H, 4.54; N, 7.87.

X-ray Structure Determination of **5**

X-ray diffraction data were collected using a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at room temperature. A crystal with dimensions 0.3 mm × 0.3 mm × 0.2 mm was used. Data having theta less than or equal to 25° were integrated and the structure was solved by the direct method using the SHELXS-97 program [13], which refined by the full-matrix least-squares method using the SHELXL-97 program [13]. Crystal data and experimental details are listed in Table 1. The H atoms bonded to O6 and O7 were located in difference Fourier maps. All other H atoms were positioned geometrically and refined as riding atoms, with C–H of 0.93 Å for aromatic H atoms, 0.96 Å for CH_3 groups and 0.97 Å for CH_2 groups, U_{iso}(H) values were set at 1.2 times U_{eq}(C) for aromatic H atoms and CH_2, and 1.5 times U_{eq}(C) for CH_3.

Table 1 Crystal data and experimental crystallographic details

Empirical formula	$C_{19}H_{30}N_2O_7$
Formula weight	398.45
Temperature (K)	298(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 21/c
Cell dimensions	
a (Å)	7.3987(7)
b (Å)	17.8691(16)
c (Å)	17.0022(13)
α (°)	90
β (°)	112.944(3)
γ (°)	90
Volume (Å^3)	2070.0(3)
Z	4
Density (calculated) (Mg/m^3)	1.279
Absorption coefficient (mm^{-1})	0.097
F_{000}	856
Crystal size	0.2 mm × 0.3 mm × 0.3 mm
θ range for data collection	2.60°–28.28°
Index ranges	$-9 \le h \le 9$
	$-23 \le k \le 22$
	$-15 \le l \le 22$
Reflections collected/unique reflections	13818/5094
R_{int}	0.0520
Refinement method	Full-matrix least-squares on *F*2
Data/restraints/parameters	5094/0/273
Goodness-of-fit on F^2	0.963
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0592$, $wR_2 = 0.1016$
R indices (all data)	$R_1 = 0.1155$, $wR_2 = 0.1193$
Largest diff. peak and hole (eÅ^{-3})	0.167/−0.199

Antimicrobial Activity

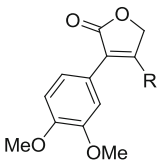
The antibacterial activities of the synthesized compounds were tested against two Gram-positive bacterial strains (*B. subtilis* ATCC 6633, *S. aureus* ATCC 25923) and a Gram-negative bacterial strain (*E. coli* ATCC 35218) using LB medium, while the antifungal activities of the compounds were tested against *C. albicans* ATCC 10231 (Gram-positive) using RPMI-1640 medium. The MIC_{50}s of the test compounds were determined by a colorimetric method using the dye MTT [14]. A stock solution of the synthesized compound (1,000 μg/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid medium (50% (v/v) of DMSO in PBS). A specified quantity of the medium containing the test compound was poured into 96-well plates. Suspension of the microorganism was prepared to contain approximate 10^5 cfu/mL and applied to 96-well plates with serially diluted compounds to be tested and incubated at 37 °C for 24 h. In the case of fungi, plates were incubated at 27 °C for 48 h. Fifty μL of PBS containing 2 mg of MTT/mL was added to each well. Incubation was continued at room temperature for 4–5 h. The content of each well was removed, and 100 μL of 10% sodium dodecyl sulfate containing 5% isopropanol and 1 mol/L HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density (OD) was measured with a microplate reader at 550 nm. The observed MIC_{50}s were presented in Table 2.

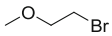
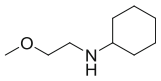
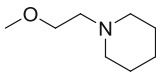
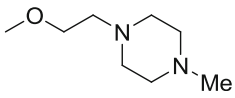
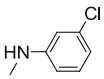
Results and Discussion

Nine 3-(3,4-dimethoxyphenyl)furan-2(5*H*)-ones were synthesized by the routes outlined in Scheme 2. Compounds **2–8** derived from compound **1**, and the structure of lactone-core in these compounds could be determined dependent on that of **1**. At high field in ^{1}H NMR spectrum of **1**, except of methyl group signals at δH 3.88 and 3.89, there are two proton signals displaying as singlet at δH 4.77, which strongly indicated that the lactone-core is furan-2(5*H*)-one (4-hydroxyfuran-2(5*H*)-one) instead of furan-2(3*H*)-one or furan-2,4(3*H*,5*H*)-dione. The furan-2(5*H*)-one skeleton was further confirmed by the crystal structure of compound **5**.

Compound **5**, 3-(3,4-dimethoxyphenyl)-4-(2-(4-methylpiperazin-1-yl)ethoxy)furan-2(5*H*)-one, co-crystallizes with two water molecules in the monoclinic space group *P*

Table 2 Inhibitory activity (MIC_{50}) of the synthetic compounds against microbes



Compound	*R*	MIC_{50} (μg/mL)			
		A	B	C	D
1	OH	>100	78	>100	>100
2		>100	>100	>100	>100
3		>100	23	>100	>100
4		95	8.7	>100	>100
5		87	7.3	>100	>100
6		>100	49	84	>100
7		>100	62	96	>100
8		>100	79	98	>100
9		>100	31	77	>100

Note: A, *Bacillus subtilis* ATCC 6633; B, *Staphylococcus aureus* ATCC 25923; C, *Candida albicans* ATCC 10231; D, *Escherichia coli* ATCC 35218

21/c and the structure of the crystalline hydrate with the corresponding atomic numbering scheme is shown in Fig. 1. In the center lactone moiety, C8–C11 and C8–O1 are typical double bonds with bond length of 1.350(2) and 1.210(2) Å respectively, while bond distances of others are followed in the range of typical single bonds (Table 3). The center five-member ring is therefore identified as a furan-2(5*H*)-one, which are consistent with the analogues previously reported [11, 12]. An sp^3 orbital of O2, O3, O4 or O5 is conjugated with the attached double bond, which shortens the bond length of C–O from about 1.43 Å [15, 16] to 1.36 Å. O3–C10 (1.333(2) Å) is further shortened by the strong electron withdrawing effect of carbonyl group (C8–O1), which is intermediated by π molecular orbital of C7–C10. However, bond length shortening caused by carbonyl group may be prevent due to the rigidity of center furanone ring [17], and is not observed in C8–O2 (1.362(2) Å).

The furan-2(5*H*)-one motif and the attached benzene ring (3,4-dimethoxy benzene ring) are nearly co-planar, making a dihedral angle of 0.860(69)°. This is consistent with other 4-O-analogues [12, 13], and is quite different

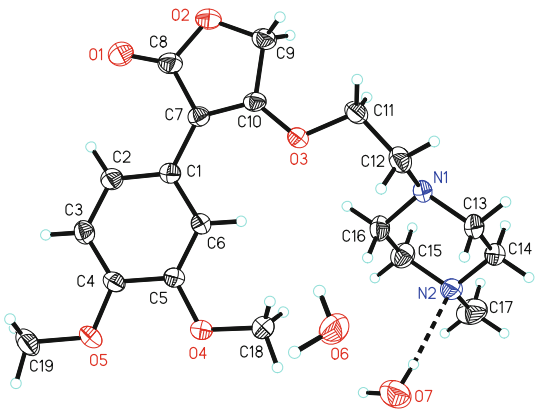


Fig. 1 Molecular structure of compound **5**. Displacement ellipsoids are drawn at the 30% probability level. *Dashed lines* indicate hydrogen bonds

with the 4-N-analogues [11]. In comparison with C7–C8 (1.43–1.47 Å), the bond distance of C7–C10 (1.33–1.37 Å) significantly decreased, causing an increase in steric strain between 4-substituent and 3-benzene ring. Therefore, both

Table 3 Selected bond lengths (Å) and bond angles (°) for compound I

Bond	Dist.	Bond	Dist.
C(1)–C(7)	1.469(2)	C(11)–O(3)	1.445(2)
C(4)–O(5)	1.366(2)	C(12)–N(1)	1.463(2)
C(5)–O(4)	1.363(2)	C(13)–N(1)	1.462(2)
C(7)–C(8)	1.459(3)	C(16)–N(1)	1.455(2)
C(7)–C(10)	1.350(2)	C(14)–N(2)	1.459(3)
C(8)–O(1)	1.210(2)	C(15)–N(2)	1.455(2)
C(8)–O(2)	1.362(2)	C(17)–N(2)	1.469(3)
C(9)–C(10)	1.491(2)	C(18)–O(4)	1.425(2)
C(9)–O(2)	1.423(2)	C(19)–O(5)	1.426(2)
C(10)–O(3)	1.333(2)		
Angle	**(°)**	**Angle**	**(°)**
C(1)–C(7)–C(8)	124.63(18)	C(12)–N(1)–C(13)	111.08(16)
C(1)–C(7)–C(10)	129.97(17)	C(12)–N(1)–C(16)	111.93(14)
C(4)–O(5)–C(19)	117.30(15)	C(13)–N(1)–C(16)	108.17(16)
C(5)–O(4)–C(18)	116.92(15)	C(14)–N(2)–C(15)	108.86(17)
C(7)–C(10)–O(3)	126.06(17)	C(14)–N(2)–C(17)	110.19(17)
C(9)–C(10)–O(3)	122.85(17)	C(15)–N(2)–C(17)	110.43(18)
C(10)–O(3)–C(11)	117.18(14)		

4-O-analogues and 4-N-analogues show larger angle of C1–C7–C10 (128.9°–131.3°) than that of C1–C7–C8 (120.6°–125.1°).

In the packing diagram, a molecule of **5** anchors a water molecule, which is defined as **I**, with O–H···N and C–H···O hydrogen bonding interactions to form a graph-set motif of $R_2^2(6)$ (Fig. 2). On one hand, another water molecule forms two hydrogen bonds utilizing O atom in the motif of $R_2^2(6)$ and N2 as the acceptors respectively. These two hydrogen bonds and the hydrogen bond with O1 as the acceptor (Table 4) alternatively link four molecules of **I** in discontinuity, forming a centrosymmetric tetramer characterized by a graph-set motif of $R_7^8(36)$ (Fig. 2). On the other hand, the above mentioned three hydrogen bonds also link four molecules of **I** but in continuity, forming another centrosymmetric tetramer characterized by a graph-set motif of $R_4^6(32)$ (Fig. 2). The combination of these motifs ($R_7^8(36)$ and $R_4^6(32)$) generates a sheet of edge-fused rings parallel to the (011) plane.

In the structure of **5**, C–H···π interactions were found between C9s and the benzene rings with H···π distances of 2.710 Å (Fig. 3). These weak intermolecular contacts consequently link the above mentioned sheets into a three dimensional network.

As shown in Table 2, all the tested compounds inactive against Gram-negative organism (*E. coli* ATCC 35218). They showed moderate to good activities against *S. aureus* ATCC 25923, while show quite weak activities against the other Gram-positive organisms. The effect of 4-substituent was described based on MIC_{50}s against *S. aureus* ATCC 25923. Substitution of arylamino group (**6–9**) for 4-hydroxyl group (**1**) maintained the potency or showed a mild increase in activity, while the 2-bromoethoxy group is present at this place, leading to an inactive compound (**2**). However, the bromine atom in the side chain of **2** was replaced by an aliphatic amino group (**3–5**), resulting in a 3- to 10-fold increase in activity, with compound **5** being the most active (MIC_{50} = 7.3 μg/mL).

Conclusions

Among the obtained nine 3-(3,4-dimethoxyphenyl)furan-2(5*H*)-ones, compound **5** shows good antibacterial activity against *S. aureus* ATCC 25923 with MIC_{50} of 7.3 μg/mL, which could be used as a lead compound for further modification to search novel antibacterials. The central

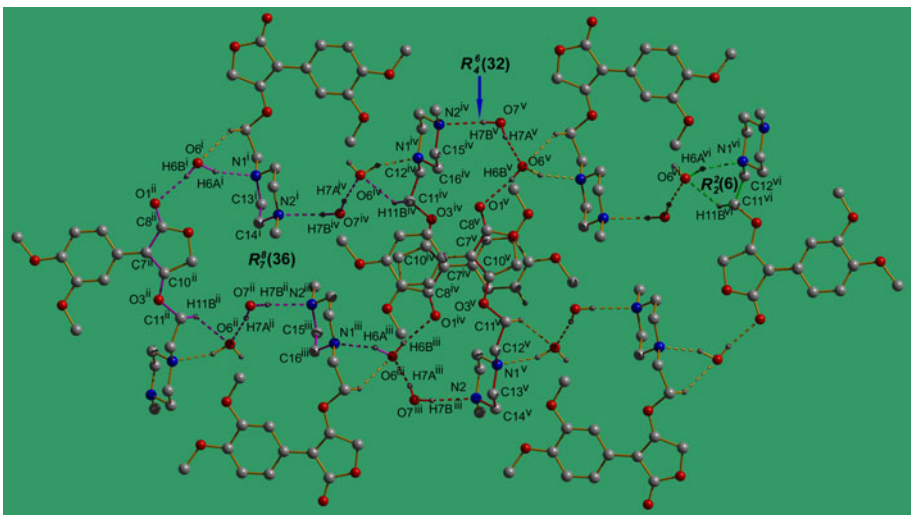


Fig. 2 Part of the crystal structure of **5**, showing the formation of $R_7^8(36)$ and $R_4^6(32)$ motifs, built from O–H···O, C–H···O and O–H···N hydrogen bonds (*dashed lines*). For the sake of clarity, the H atoms not involved in the hydrogen bonds have been omitted

Table 4 Hydrogen-bond geometry (Å, °)

D–H···A	D–H	H···A	D···A	D–H···A
C2–H2···O1	0.93	2.29	2.965(2)	128.7
C6–H6···O3	0.93	2.30	2.963(2)	127.6
O7–H7B···N2	0.84(3)	2.18(3)	3.004(3)	171(3)
O6–H6A···N1^{i}	0.98(3)	2.05(3)	2.993(2)	160(2)
O6–H6B···O1^{ii}	0.83(3)	2.07(3)	2.883(2)	169(3)
O7–H7A···O6^{iii}	0.90(3)	2.10(3)	2.989(3)	170(3)
C11–H11B···O6^{iv}	0.97	2.47	3.293(3)	142.1
C9–H9A···Cg^{v}	0.970	2.710	3.543(2)	145.0

Symmetry transformations used to generate equivalent atoms: i = $x-1$, $-y+1.5$, $z-0.5$; ii = $-x+1$, $-y+2$, $-z+1$; iii = $x+1$, y, z; iv = $x+1$, $-y+1.5$, $z+0.5$; v = $-x+2$, $-y$, $-z+1$, Cg is the centroid of C1–C6

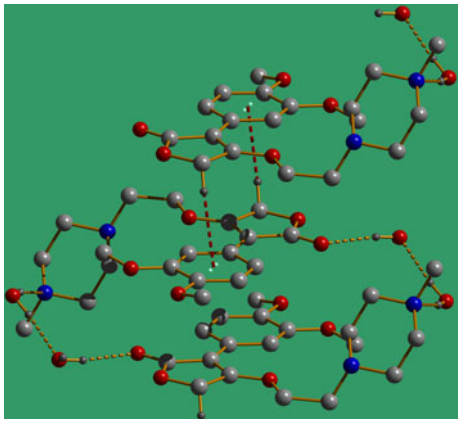


Fig. 3 C–H···π contacts link the sheets parallel to (011) into a three dimensional network. *Solid dashed lines* indicate C–H···π interactions. For the sake of clarity, the H atoms not involved in the hydrogen bonds have been omitted

furan-2(5*H*)-one skeleton was confirmed by the crystal structure of compound **5**, which disclosed that furan-2(5*H*)-ones with 4-OR or 4-NHR show larger angle of C(–O or –N)–C–C(Ar) than that of C(=O)–C–C(Ar).

Supplementary Material

CCDC deposit number of CCDC 827892 for **5** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223-336033; e-mail:deposit@ccdc.cam.ac.uk].

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