Res Chem Intermed
DOI 10.1007/s11164-013-1502-8

Convenient synthesis, antibacterial activity, and crystal structure of some biologically important hydrazinecarbonyl benzenesulfonamides

G. Thiyagarajan · H. S. P. Rao · A. Thamaraichelvan · Peter Mayer · Ashutosh Pandey

Received: 27 September 2013 / Accepted: 30 November 2013

Abstract Microwave-assisted synthesis of a series of hydrazinecarbonyl benzenesulfonamides (**5a**–**r**) is reported, and the products have been characterized by nuclear magnetic resonance and Fourier-transform infrared spectral techniques. A comparison with the conventional method for their preparation has also been done. The crystal and molecular structures of compounds 2-(hydrazinecarbonyl)benzenesulfonamide **3**, 2-({(2*E*)-2-[(3,4-dimethoxy)benzylidene]hydrazine}carbonyl) benzenesulfonamide **5e**, 2-({(2*E*)-2-[(2,4-dimethoxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide **5f**, and 2-({(2*E*)-2-[(4-hydroxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide **5k** have also been established by single-crystal X-ray diffraction. Antibacterial activity of prepared compounds (**5a**–**r**) is reported against *Staphylococcus aureus*, *Bacillus firmus*, and *Escherichia coli*. The preeminent antibacterial activity was shown by 2-({(2*E*)-2-[(2-hydroxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide **5j** against all three tested bacterial organisms.

Keywords Hydrazone · Benzenesulfonamide · Crystallography · Microwave reaction · Antibacterial activity

G. Thiyagarajan · A. Pandey (✉)
Department of Chemistry, Motilal Nehru National Institute of Technology, Allahabad 211 004, India
e-mail: apandey70@yahoo.com

H. S. P. Rao
Department of Chemistry, Pondicherry University, Pondicherry 605 014, India

A. Thamaraichelvan
Department of Chemistry, Thiagarajar College, Madurai 625 020, India

P. Mayer
Department of Chemistry and Biochemistry, Ludwig-Maximilian University Munich, Butenandtstrasse 5-13, 81377 Munich, Germany

Published online: 18 December 2013

Introduction

The synergistic effect of growing population and climate change has resulted in the eruption of several diseases which are affecting humankind [1–4]. There is a continuous need to synthesize prospective drugs for new diseases by fast and efficient methods. Therefore, in-depth focus on the discovery of new drugs has gained tremendous momentum in recent times. Considering the various aspects of drug design, chemists have synthesized a number of compounds by way of conventional heating processes [5]. While these processes are too slow to meet the demand for growing populations, concerns with regards to environmental impact and energy constraints also compel the search for greener synthetic modes [6–9]. Among the available alternatives that may accelerate these synthetic processes, green microwave (MW) technology with power and temperature optimization is a better option which has resulted in dramatic decline in reaction times from days and hours to minutes and seconds [10, 11].

Saccharin is a polyfunctional ligand with three hydrogen-bond acceptors (one carbonyl and two sulfonyl O atoms) and one hydrogen-bond donor (imino group NH). Further, it has been used as an acid in the pharmaceutical industry [12, 13], and the crystal structures and physical properties of several active saccharinates used as pharmaceutical ingredients have also been reported recently [14–16]. Additionally, benzenesulfonamides constitute an important class of drugs with a number of biological activities such as antibacterial [17, 18], hypoglycemic [19], diuretic [20], anticarbonic anhydrase [21], antithyroidal [22], and anticancer activities [23]. Hydrazone derivatives which contain highly reactive azomethine (NH–N=CH) group are also very useful in designing new drugs [24, 25]. Moreover, hydrazones form an interesting class of chelating ligands linked to a nitrogen atom and find extensive application in various fields [26]. By virtue of nitrogen–nitrogen–oxygen (NNO) donor atoms, they have also been introduced into coordination chemistry for preparation of organometallic complexes [27, 28]. Thus, it is expected that the synchronized effect of both sulfonamide and hydrazone groups in a certain stoichiometry should have a strong and manifold effect on the biological applications of the resulting compounds. Therefore, detailed study on the synthesis and molecular structure descriptions of these compounds seems to be important for understanding their biological activities and coordination capabilities.

Herein, we report the synthesis of a series of hydrazinecarbonyl benzenesulfonamides (**5a**–**r**) by MW heating, which have been characterized by ^{1}H and ^{13}C NMR, Distortionless enhancement by polarization transfer (DEPT), and FT-IR spectral studies. The crystal and molecular structures of 2-(hydrazinecarbonyl) benzenesulfonamide **3**, 2-({(2*E*)-2-[(3,4-dimethoxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide **5e**, 2-({(2*E*)-2-[(2,4-dimethoxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide **5f**, and 2-({(2*E*)-2-[(4-hydroxy)benzylidene] hydrazine}carbonyl)benzenesulfonamide **5k** have also been described by single-crystal X-ray crystallography. The antibacterial activities of all the synthesized compounds (**5a**–**r**) were screened against Gram-positive *S. aureus* and *B. firmus* and Gram-negative *Escherichia coli* bacterial strains.

Results and discussion

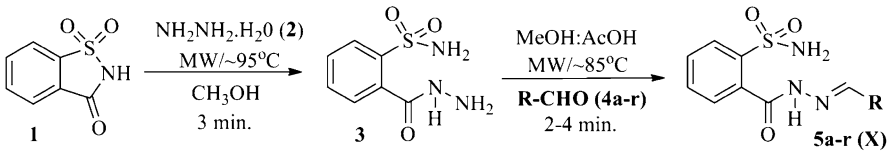
Synthesis

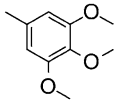
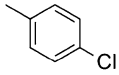
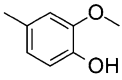
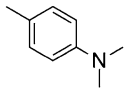
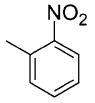
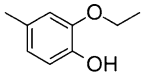
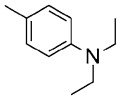
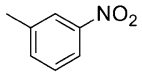
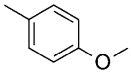
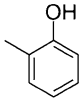
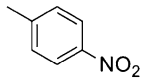
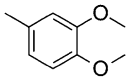
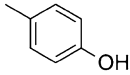
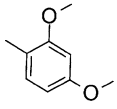
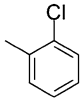
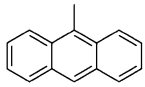
A series of hydrazinecarbonyl benzenesulfonamide derivatives (**5a**–**r**) were synthesized by microwave heating (Scheme 1), encompassing two types of mechanistic pathway. As a consequence of an addition–elimination reaction, saccharin **1** reacts with hydrazine **2** to form 2-hydrazinecarbonyl-benzenesulfonamide **3** by ring opening, then the aromatic aldehydes (**4a**–**r**) react with **3** to form the corresponding products (**5a**–**r**) by way of "aldehyde–amine" condensation. Notably, we synthesized compound **3** using a new synthetic approach which is greener, easier, and economical in comparison with earlier synthetic methods [17]. Wang et al. synthesized **3** by refluxed reaction of 2-methoxycarbonyl benzenesulfonamide with hydrazine hydrate in excess amount of methanol for 5 h. On the other hand, we prepared compound **3** within 3 min from saccharin **1** and hydrazine hydrate in methanol (1 mL) by microwave heating. Similarly, our final products (**5a**–**r**) have also been synthesized by MW heating in higher yields within 2–4 min, while lacking any additional requirement for complex purification processes such as column chromatography etc. All the synthesized products were purified simply by crystallization in methanol. For comparison with microwave-assisted reaction, the products have also been synthesized by the conventional heating method. Evidently, the compounds **3** and **5a**–**r** have been prepared in higher yields and lesser reaction times (Table 1). Therefore, the synthetic procedure adopted in the present work is a much greener and more economical approach to obtain high-purity products.

NMR spectra

All the synthesized compounds gave the expected spectral data in accordance with their proposed structures (Scheme 1). The appearance of four aromatic signals in the ^{1}H NMR spectrum of compound **3** in the δ 7.59–7.95 region confirms its proposed molecular structure. Furthermore, the two separate singlets at δ 7.09 and 7.02 confirm the presence of exchangeable SNH_2 protons. In the ^{13}C NMR spectrum of compound **3**, six carbon signals at δ values between 141.2 and 126.9 correspond to the aromatic carbons, and one peak due to the C=O group at δ 167.5 further substantiates its proposed structure. The aromatic protons of **3** are also confirmed by DEPT spectra by the four carbon signals appearing at values of δ 131.7, 129.9, 129.1, and 126.9.

In ^{1}H NMR of all the final products (**5a**–**r**), the two separate singlets for the exchangeable NH protons were found between δ 12.30 and 11.76. The peaks at δ 12.24 and 12.22 correspond to the occurrence of exchangeable NH proton of **5l**. Likewise, proton signals at δ 11.78 and 11.76 confirm the existence of exchangeable NH proton of **5h**. Similar peaks are also observed in ^{1}H NMR of **5d** and **5n**; i.e., the peaks at δ 11.89, 11.87 and 12.27, 12.06, respectively, correspond to their exchangeable NH protons. In addition, the aldehydic proton, which appeared at $\delta \sim 10$ in the starting aromatic aldehydes (**4a**–**r**), was absent from the ^{1}H NMR spectra of our final products (**5a**–**r**). The appearance of new single peaks in the δ



X	R	X	R	X	R
5a		5g		5m	
5b		5h		5n	
5c		5i		5o	
5d		5j		5p	
5e		5k		5q	
5f		5l		5r	

Scheme 1 Synthesis of hydrazinecarbonyl benzenesulfonamides

8.60–8.04 range in the ^{1}H NMR spectra of compounds **5a**–**r** due to the existence of azomethene (CH=N) groups confirms their proposed structures (Scheme 1). The proton signals appearing at δ 8.73 and 8.45 in **5l** also indicate the presence of exchangeable azomethene (N=CH) group. In the same way, the two exchangeable protons at δ 7.02, 6.92 in **5g** and at δ 7.02, 6.84 in **5h** also appeared as two singlets due to the presence of S-NH_2 groups. However, two singlets at δ 7.15, 7.05 in **5j** and 7.13, 6.92 in **5r** indicate the exchangeable SNH_2 protons.

A singlet peak equivalent to the two methoxy groups in **5e** appeared as six protons at δ 3.88, while in **5f** the peaks at δ 3.86 and 3.66 correspond to the existence of two methoxy groups. The proton signal in **5d** equivalent to the methoxy group also appeared at δ 3.83, integrating as three protons. The OH protons of compounds **5b** and **5c** appeared as singlets at δ 9.32 and 9.19, while the same for **5j** and **5k** were found at δ 9.69 and 9.79, respectively. The peaks corresponding to the

Table 1 Conventional versus microwave heating of **3** and **5a–r**

S. no.	Nature	Conventional			Microwave		
		Time (h)	Temp. (°C)	Yield (%)	Time (min)	Temp. (°C)	Yield (%)
3	White crystalline solid	5	95	86.5	4	85	95.4
5a	White solid	8	85	86.4	2	84	93.8
5b	Pale-yellow solid	8	85	81.5	4	82	92.6
5c	Pale-yellow solid	8	85	84.8	3	79	95.3
5d	White crystalline solid	8	85	76.2	3	83	96.4
5e	Pale-yellow solid	8	85	84.9	3	88	93.2
5f	Pale-yellow solid	8	85	79.3	3	89	98.2
5g	White crystalline solid	8	85	80.7	3	86	94.6
5h	Orange crystalline solid	8	85	77.3	3	85	95.2
5i	White solid	8	85	89.2	3	83	93.4
5j	White solid	8	85	86.1	3	86	94.7
5k	White solid	8	85	88.4	3	81	96.3
5l	White crystalline solid	8	85	84.7	3	87	95.4
5m	White solid	8	85	85.3	3	86	94.7
5n	White solid	8	85	83.5	3	84	96.4
5o	Pale-yellow solid	8	85	89.1	3	87	91.6
5p	Pale-yellow solid	8	85	87.9	3	77	97.5
5q	Pale-yellow solid	8	85	90.7	3	81	95.3
5r	Yellow solid	8	85	86.6	3	92	93.8

two methyl groups in **5h** are visible at δ 2.95 as singlet by integrating six protons. Compound **5l** showed aromatic signals in the δ 8.14–7.38 range as multiplet by integrating eight protons.

The carbon signals due to –CHO group in **4a–r** were observed in the range of δ 185–180, which disappeared in **5a–r**, and new signals due to the presence of N=CH group originated at δ values between 144.0 and 149.7. The carbon signals of C=O group in all our synthesized products appeared at $\delta \sim 164$. Hence, the carbon signals of C=O group in **5l** and **5h** appeared at δ 164.6 and 164, respectively. The carbon signal anticipated for methoxy group in **5b** appeared at δ 55.4. The carbon signal at δ 54.9 also confirms the presence of one methoxy group in **5d**, and the peaks corresponding to the two methyl groups of **5h** are observed at δ 39.9. In ^{13}C NMR of **5d** and **5n**, the peaks at δ 148.3 and 148.1 appeared, respectively, due to the presence of N=CH group. The appearance of signals at δ 144.4 and 149.2 in **5l** and **5h**, respectively, is also attributed to the same. All protons of the aromatic rings in the final compounds were further confirmed by the observed carbon signals in the range of δ 150 and 109 in DEPT spectra. In the DEPT spectrum of compound **5c**, the carbon signal at δ 14.6 is due to the methyl group, while another signal at δ 63.8 in the reverse direction indicates the presence of methylene (CH_2) group. The carbon signals in **5f** at δ 55.4 confirm the appearance of two methoxy groups, while the peaks at δ 59.8 and 55.7 in **5g** correspond to the three methoxy groups. Thus, the

proposed molecular structures of all our synthesized compounds were clearly substantiated by ^{1}H and ^{13}C NMR and DEPT spectral data.

FT-IR spectra

The structures of all the compounds were also examined by IR spectral data. Compounds **5a**–**r** showed absorption bands at ~1,676–1,639 cm^{-1} due to the presence of C=O groups, while the IR peak corresponding to the azomethene (N=CH) group in the region of ~1,604–1,558 cm^{-1} provided confirmatory evidence for the condensation reaction between aldehyde and hydrazide. IR spectra of compounds **5e** and **5f** showed absorption bands at 1,661 and 1,651 cm^{-1} due to the presence of C=O group, while the bands observed at 1,603 and 1,568 cm^{-1} correspond to CH=N linkages, respectively. The peaks between ~3,333 and 3,267 cm^{-1} correspond to the presence of NH and NH_2 groups in all the compounds. The observed IR peaks at 3,245 and 3,318 cm^{-1} can be attributed to NH and NH_2 groups of **5e** and **5f**, respectively. In all the compounds, the absorptions in the 3,091–3,054 cm^{-1} range are due to CH stretching of aromatic groups, and the peaks due to O=S=O stretching appeared at 1,169 and 1,161 cm^{-1}. Further, the peaks owing to the O=S=O group appeared at 1,160 and 1,168 cm^{-1} for **5e** and **5f**, respectively. The absorption bands in the 3,071 cm^{-1} and 2,991 cm^{-1} range are due to CH stretching of aromatic rings in **5g** and **5h**, respectively. The OH groups of **5b**, **5c**, **5j**, and **5k** are confirmed by the absorptions between 3,531 and 3,411 cm^{-1}. In the products **5n**, **5o**, and **5p** the transitions at 1,519, 1,527, and 1,524 cm^{-1} are attributed correspondingly to the presence of NO_2 group.

Single-crystal X-ray analysis

Single crystals of **3**, **5e**, **5f**, and **5k** suitable for X-ray diffraction were obtained by slow evaporation of their solutions in methanol. Crystal data and structure refinement of all the products are presented in Table 2, while Table 3 presents selected bond lengths and angles.

The ORTEP diagram for **3** is shown in Fig. 1. It was found in monoclinic form with eight molecules in the unit cell arrangement, as shown in Fig. 2. Compound **3** has a basal plane which involves the benzene ring, S atom, and C7 atom of the carbonyl group. The carbon and oxygen atoms of the carbonyl group along with the two N atoms of the hydrazino group lie in another plane [mean deviation 0.051(2) Å] with dihedral angle of 57.5(2)° to the basal plane. The intramolecular N1–H1···O3 hydrogen bond forces the O atom of carbonyl group and the N atom of sulfamoyl group to lie on the same side of the basal plane, and thus the molecule adopts a chiral conformation. The structure is further stabilized by intermolecular hydrogen bonds and π–π stacking interactions between the phenyl rings. Due to the repulsion among the lone pairs of electrons at S1 atom in **3**, the bond angle O1–S1–O2 increases to 118.63(7)° while the angles O1–S1–N1 and O2–S1–N1 have to narrow down to 107.18(9)° and 107.15(8)°, respectively.

ORTEP diagrams for compounds **5e**, **5f**, and **5k** are depicted in Fig. 3. In the unit cell of **5e**, there are eight molecules and intermolecular H-bond was observed

Table 2 Crystal data and structure refinement of crystals **3**, **5e**, **5f**, and **5k**

Compound	**3**	**5e**	**5f**	**5k**
Net formula	$C_7H_9N_3O_3S$	$C_{16}H_{17}N_3O_5S$	$C_{16}H_{17}N_3O_5S$	$C_{14}H_{13}N_3O_4S$
Mol. weight (M_r) (g/mol)	215.231	363.389	363.389	319.337
Crystal size (mm)	0.46 × 0.40 × 0.25	0.35 × 0.23 × 0.19	0.25 × 0.19 × 0.11	0.35 × 0.28 × 0.20
Temperature (K)	173(2)	173(2)	173(2)	173(2)
Radiation	Mo K_α	Mo K_α	Mo K_α	Mo K_α
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	*C*2/*c*	$P2_1/n$	$P2_1/c$	$P2_12_12_1$
Unit cell dimensions				
a (Å)	11.8661(8)	18.8205(18)	16.3030(2)	8.0359(9)
b (Å)	11.5910(6)	9.6272(7)	12.6915(2)	11.6060(12)
c (Å)	14.5859(15)	19.6232(19)	8.2361(1)	15.0251(19)
α (°)	90	90	90	90
β (°)	117.650(6)	110.675(11)	90.1813(9)	90
γ (°)	90	90	90	90
Volume ($Å^3$)	1,777.0(2)	3,326.5(5)	1,704.12(4)	1,401.3(3)
Z (molecules/cell)	8	8	4	4
D (calc) (g/cm^3)	1.60902(18)	1.4512(2)	1.41640(3)	1.5137(3)
μ (mm^{-1})	0.349	0.228	0.222	0.254
Absorption correction	Multiscan	Multiscan	None	Multiscan
Transmission factor range	0.83183–1.00000	0.67716–1.00000	–	0.60102–1.00000
Refls. measured	4,764	17,571	14,444	7,731
R_{int}	0.0166	0.0705	0.0238	0.0424
Mean $\sigma(I)/I$	0.0206	0.0623	0.0212	0.0442
θ range for data collection	4.55–26.37	4.22–26.30	3.20–27.54	4.33-26.37
Observed refls.	1,667	5,049	3,360	2,608
Refls. in refinement	1,815	6,710	3,901	2,845
Parameters	142	473	237	211
Restraints	0	6	3	4
$R(F_{obs})$	0.0323	0.0479	0.0356	0.0434
$R_w(F^2)$	0.0881	0.1289	0.0922	0.1133
S	1.034	1.043	1.042	1.077
Shift/error_{max}	0.001	0.001	0.001	0.001
Max. electron density ($e/Å^3$)	0.333	0.269	0.265	0.730
Min. electron density ($e/Å^3$)	−0.503	−0.571	−0.450	−0.351

Table 3 Selected bond lengths and angles of crystals **3**, **5e**, **5f**, and **5k**

Atoms	**3**	**5e**	**5f**	**5k**
Bond length (Å)				
N2–N3	1.417(2)	1.378(2)	1.3831(16)	1.385(3)
N3–C8	–	1.278(3)	1.2875(18)	1.277(3)
S1–N1	1.6119(17)	1.610(3)	1.6139(14)	1.595(3)
C1–C6	1.409(2)	1.409(3)	1.4014(19)	1.400(3)
O3–C7	1.229(2)	1.215(3)	1.2328(16)	1.253(3)
C10–C11	–	1.390(3)	1.3856(18)	1.383(4)
C11–C12	–	1.405(3)	1.389(2)	1.387(3)
C3–C4	1.374(3)	1.375(3)	1.377(2)	1.378(5)
S1–O1	1.4324(13)	1.425(2)	1.4302(11)	1.430(2)
S1–O2	1.4344(12)	1.429(2)	1.4317(11)	1.439(2)
C6–C7	1.504(2)	1.503(3)	1.5034(18)	1.493(4)
C8–C9	–	1.466(3)	1.4533(18)	1.452(4)
Bond angle (°)				
C2–C3–C4	120.01(15)	120.4(2)	119.63(14)	120.0(3)
N2–C7–O3	123.89(15)	122.7(2)	125.56(12)	122.0(2)
N2–N3–C8	–	114.9(2)	113.19(11)	115.6(2)
C7–N2–N3	123.11(15)	119.91(17)	121.79(11)	118.5(15)
C10–C9–C14	–	121.1(2)	117.95(12)	118.5(2)
O1–S1–C1	108.12(8)	107.1(1)	107.76(7)	107.20(12)
O2–S1–C1	107.15(8)	106.8(1)	107.30(6)	107.58(13)
C1–C6–C7	122.74(15)	123.0(2)	124.16(12)	123.3(2)
C11–C12–C13	–	120.1(2)	121.13(14)	120.5(2)
O1–S1–O2	118.63(7)	119.70(12)	119.35(6)	119.38(14)
O1–S1–N1	107.18(9)	108.74(13)	108.07(7)	106.87(14)
O2–S1–N1	107.15(8)	105.91(12)	106.48(7)	106.54(13)

among NH group with the carbonyl and sulfonyl O atom of a neighboring molecule as well as intramolecular H-bond with NH_2 group and carbonyl O atom (Fig. 4). Crystals **5f** and **5k** encompass four molecules of the compounds, as shown in Figs. 5 and 6. In **5f**, the NH group of a molecule is intermolecularly H-bonded with the oxygen of the carbonyl group and sulfonamide H atom of adjacent molecule, which is extended further. Intermolecular H-bond was also observed in **5k** between NH group and the carbonyl O atom of a neighboring molecule. The crystal system of **5k** is orthorhombic, while **5e** and **5f** occurred in monoclinic form. The N2–N3 bond distance [1.417(2) Å] in **3** is longer than the corresponding lengths in **5e**, **5f**, and **5k** (avg. 1.3835 Å). This may be due to the existence of active $NHNH_2$ group in compound **3**. The S1–N1 bond lengths in **3** (1.6119 Å) and in **5e**, **5f**, and **5k** (avg. 1.6067 Å) are almost similar, which may be a reason for the presence of stable SO_2NH_2 group.

The N2–N3–C8 bond angles observed in **5e** [113.3(2)°] and **5f** [113.19(11)°] encompass nearly the same values, although being lesser than in **5k** [115.6(2)°].

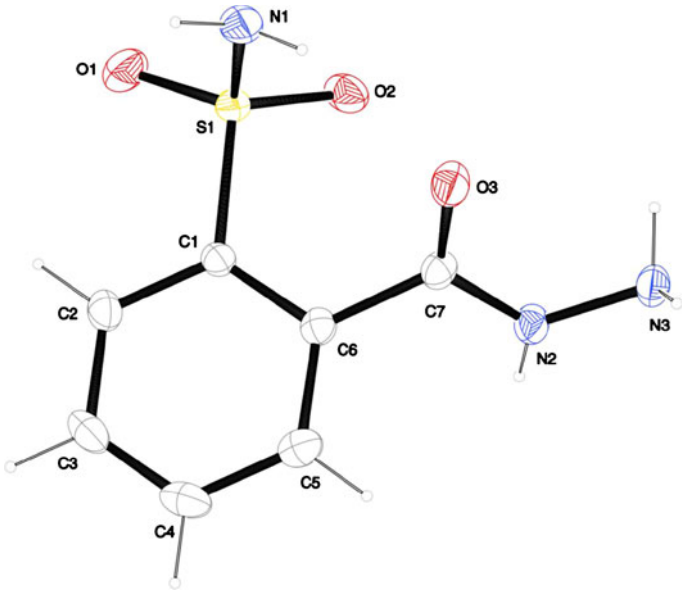


Fig. 1 ORTEP diagram of single-crystal **3**

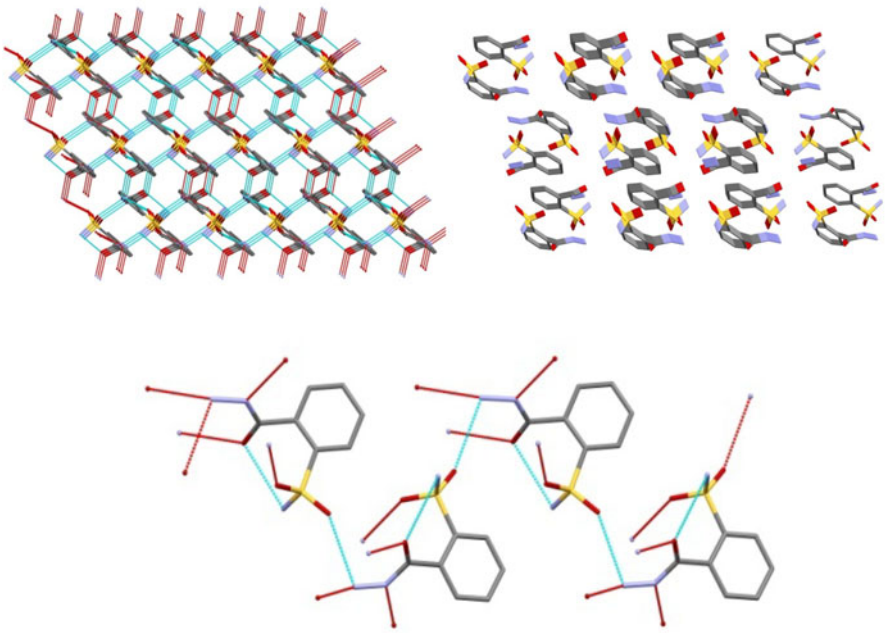


Fig. 2 Crystal packing of **3** showing inter- and intramolecular hydrogen bonding

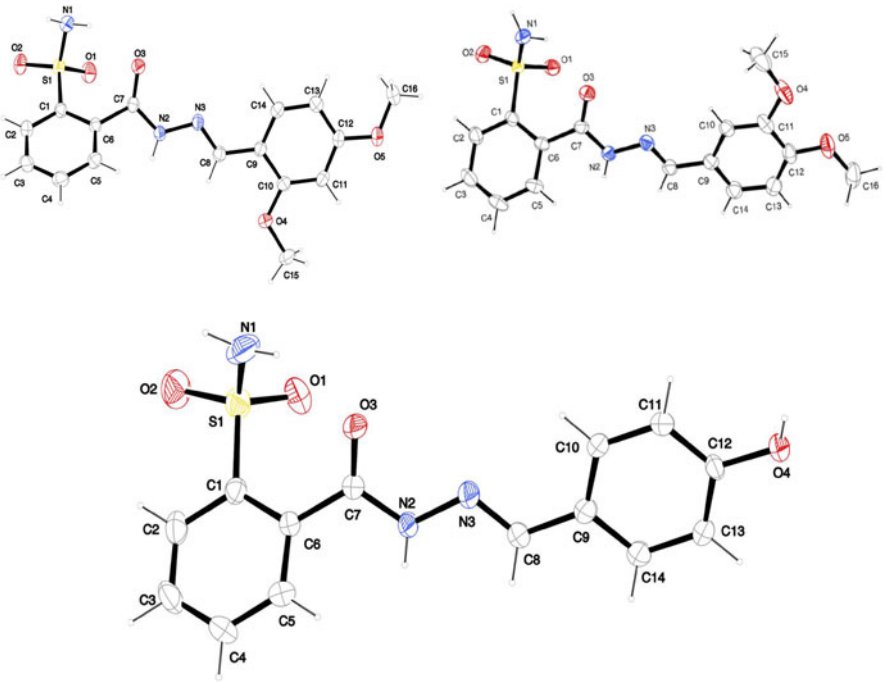


Fig. 3 ORTEP views of **5e**, **5f**, and **5k**

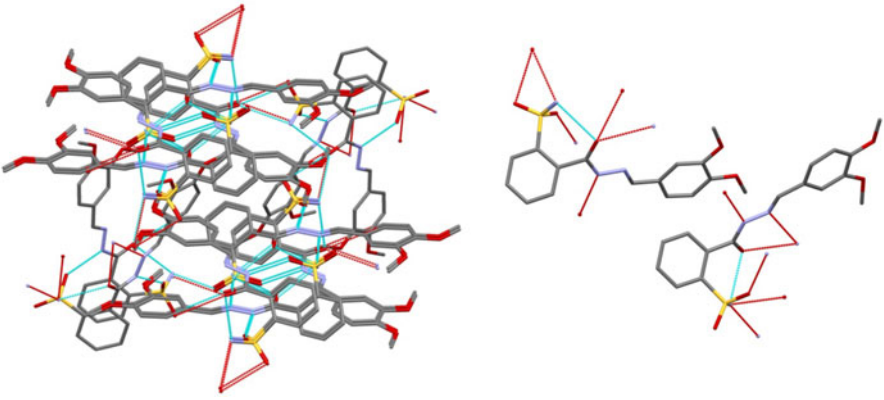


Fig. 4 Inter- and intramolecular hydrogen bonding in crystal packing of **5e**

This may be a result of the respective positions of the functional groups in **5e**, **5f**, and **5k**. The O1–S1–C1 bond angle was found to be less in **5e** (105.56°) in comparison with compounds **5k** and **5f** (avg. 107.35°). The C2–C3–C4 bond angle in all the compounds (~120°) shows the planarity of the aromatic rings. A similar pattern is also noticed around C12 atom in molecules of **5e**, **5f**, and **5k**. In all the compounds, N3–C8 bond distances (avg. 1.2826 Å) indicate the double-bond nature

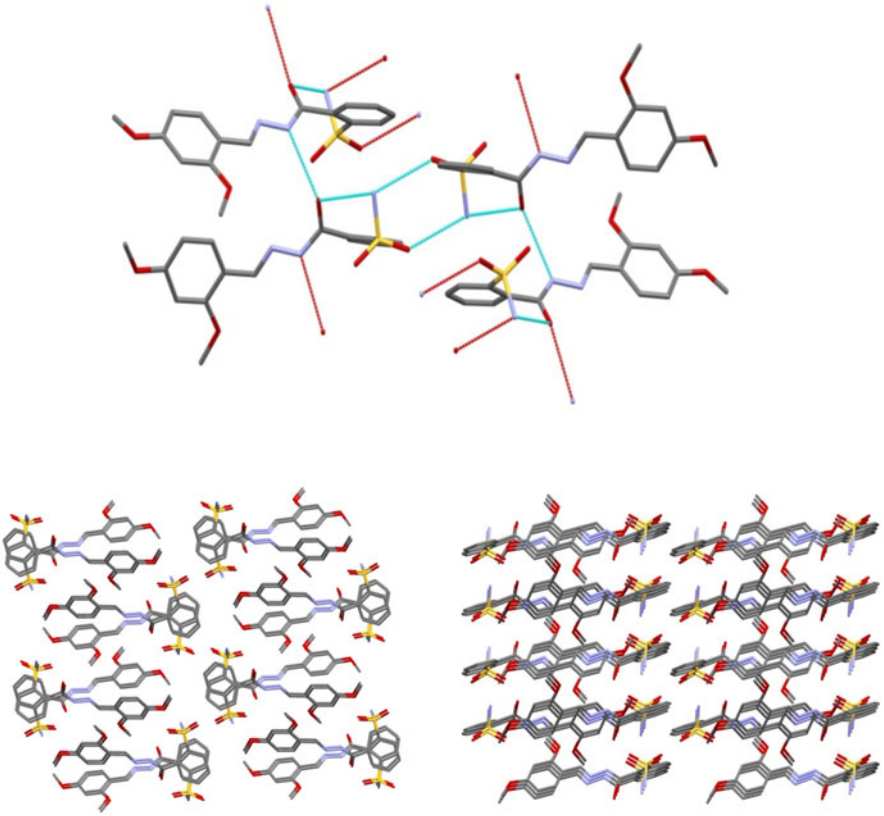


Fig. 5 Molecular packing structure of **5f** showing inter- (N2H···O3···1H···O2) and intramolecular (NH2···O=C) hydrogen bonding

of the N=CH group, in accordance with reported values [29]. Furthermore, the observed C7=O3 bond length (avg. 1.2313 Å) also falls in the range of a double bond. The C10–C9–C14 bond angle in **5f** [117.95(12)°] is smaller than the angle in **5e** [119.8(2)°], which may be due to the difference in positions of the two methoxy groups. In **5k** the O4–H bond length [0.82(3) Å] and the C12–O4–H angle [115(2)°] are slightly different from reported values [29]. The two phenyl rings connected with hydrazone and benzenesulfonamide of **5e**, **5f**, and **5k** have boat-like conformation. Moreover, the hydrazide group displays a *trans* configuration about the C=N double bond in all the studied crystals.

Antibacterial activity

The in vitro antibacterial activity of the aforementioned compounds against Gram-positive *S. aureus* and *B. firmus* and Gram-negative *E. coli* was tested at four different doses, viz. 200, 100, 50, and 25 μg/mL, prepared in dimethyl sulfoxide (DMSO). There was no inhibition of growth in DMSO. The results for all the tested compounds were compared with the well-known marketable antibacterial drug

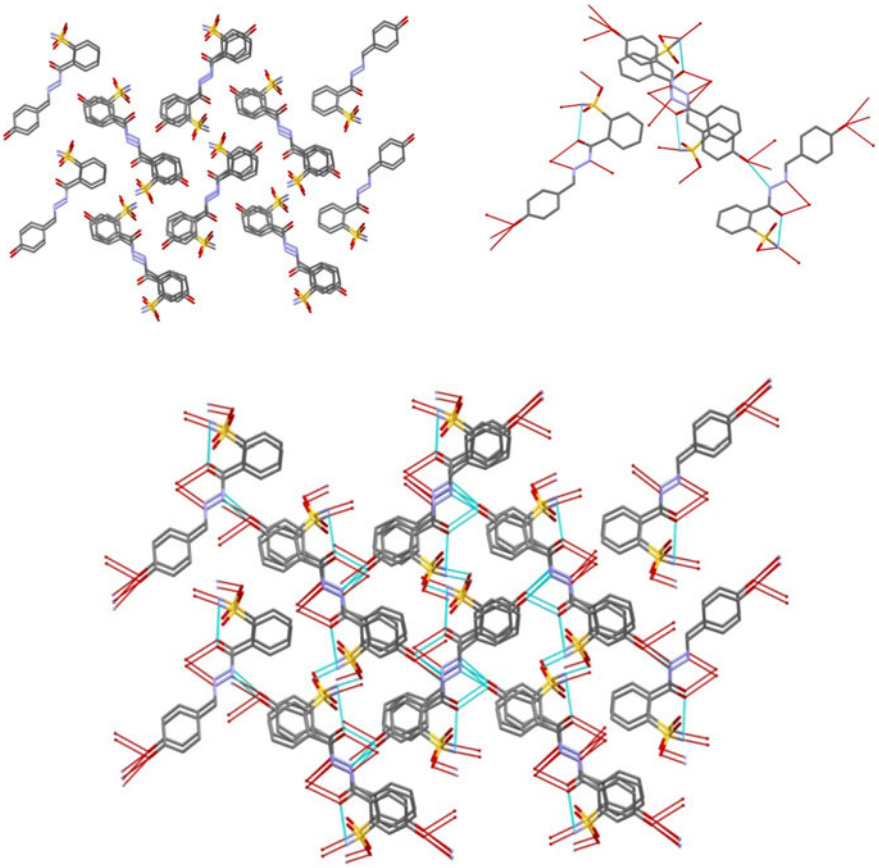


Fig. 6 Molecular packing structure of **5k** showing inter- (NH···O=C) and intramolecular (NH2···O=C) hydrogen bonding

norfloxacin at the same concentrations. There was significant difference in activity between higher and lower doses of compounds. The results, presented in Table 4, indicate that some of the synthesized compounds have efficient antibacterial activity against all three bacterial strains, but were less potent when compared with the standard drug norfloxacin. Among all the tested compounds, **5j** showed the highest activity against *S. aureus* (32 mm), *B. firmus* (28 mm), and *E. coli* (26 mm) at 200 μg/mL, albeit considerably less than that of the standard drug norfloxacin against *S. aureus* (36 mm), *B. firmus* (30 mm), and *E. coli* (34 mm) at 200 μg/mL. Compound **5j** also displayed significant activity against *S. aureus* (10 mm at 25 μg/mL), *B. firmus* (9 mm at 25 μg/mL), and *E. coli* (13 mm at 50 μg/mL). Compounds **5a** and **5p** also showed moderate activity against all the tested bacterial strains, whereas **5r** had significant effect on *S. aureus* (17 mm at 200 μg/mL) and *E. coli* (14 mm at 200 μg/mL) but no effect on *B. firmus*. Compounds **5b** and **5n** showed significant activity (14 and 15 mm at 200 μg/mL, respectively) against *S. aureus*,

while compounds **5k** and **5o** also showed noteworthy effect (16 and 14 mm at 200 μg/mL, respectively) against *E. coli*. Compound **5f** had considerable activity (15 mm at 200 μg/mL) against *B. firmus*. Compounds **5b** and **5e** exhibited significant activity (14 and 10 mm at 200 μg/mL, respectively) against *S. aureus*, but had no effect on *B. firmus* or *E. coli*. Likewise, compound **5k** had no impact on *S. aureus* or *B. firmus* but showed reasonable performance (16 mm at 200 μg/mL) against *E. coli*. In addition, compounds **5d**, **5g**, **5h**, **5i**, **5l**, and **5m** had no activity against all the tested organisms.

The effective antibacterial activity of our final products was also confirmed by their minimum inhibitory concentration (MIC) values (Table 5). The moderate antibacterial activity of compound **5j** was confirmed by its MIC values of 25 μg/mL for *S. aureus* and *B. firmus* and 50 μg/mL for *E. coli*. The MIC value of **5a** and **5p** against all three tested bacterial strains was 50 μg/mL, further indicating the effectiveness of these compounds in medicinal chemistry research. Therefore, it may be concluded that the tested compounds containing hydroxyl group in *o*-position and nitro group in *p*-position of second phenyl ring along with azomethine and benzenesulfonamide group exhibited maximum zones of inhibition. The

Table 4 Antibacterial activity of synthesized compounds

X	*S. aureus*				*B. firmus*				*E. coli*			
	200	100	50	25	200	100	50	25	200	100	50	25
5a	18	14	10	–	12	8	–	–	16	13	7	–
5b	14	12	9	–	–	–	–	–	–	–	–	–
5c	13	10	–	–	12	9	–	–	–	–	–	–
5d	–	–	–	–	–	–	–	–	–	–	–	–
5e	10	–	–	–	–	–	–	–	–	–	–	–
5f	11	–	–	–	15	12	9	–	–	–	–	–
5g	–	–	–	–	–	–	–	–	–	–	–	–
5h	–	–	–	–	–	–	–	–	–	–	–	–
5i	–	–	–	–	–	–	–	–	–	–	–	–
5j	32	26	19	10	28	20	16	9	26	21	13	–
5k	–	–	–	–	–	–	–	–	16	13	8	–
5l	–	–	–	–	–	–	–	–	–	–	–	–
5m	–	–	–	–	–	–	–	–	–	–	–	–
5n	15	12	9	–	–	–	–	–	10	7	–	–
5o	–	–	–	–	–	–	–	–	14	11	8	–
5p	16	14	10	–	14	11	9	–	15	12	9	–
5q	–	–	–	–	–	–	–	–	12	9	–	–
5r	17	15	11	–	8	–	–	–	14	8	–	–
N	36	32	24	16	30	26	18	8	34	31	25	18
DMSO	–	–	–	–	–	–	–	–	–	–	–	–

– No activity, *N* norfloxacin

Table 5 MIC (μg/mL) values of **5a–r**

X	*S. aureus*	*B. firmus*	*E. coli*
5a	50	100	50
5b	50	–	–
5c	100	100	–
5d	–	–	–
5e	200	–	–
5f	200	50	–
5g	–	–	–
5h	–	–	–
5i	–	–	–
5j	25	25	50
5k	–	–	50
5l	–	–	–
5m	–	–	–
5n	50	–	100
5o	–	–	50
5p	50	50	50
5q	–	–	–
5r	50	200	100

decreasing order of activity of our products towards the bacterial strains was found to be: *S. aureus* > *E. coli* > *B. firmus*.

Experimental

Materials and methods

For all the syntheses, the used solvents were of reagent grade and dried by standard procedures [30]. Saccharin **1**, hydrazine hydrate **2**, and various aromatic aldehydes (**4a–r**) were obtained from Sigma-Aldrich Chemicals. MW irradiation was carried out in a modified domestic Samsung microwave oven (model no. GE 83HDT, 2,450 MHz, 850 W). An infrared thermometer was used for recording temperature during the MW reactions. The synthesized products were frequently checked by thin-layer chromatography (TLC) on silica gel GF-254 using hexane/ethyl acetate or else chloroform/methanol as eluents, and the spots were visualized by short exposure to iodine vapor, UV light, and $KMnO_4$ solution. Infrared (IR) spectra were measured from potassium bromide pellets using a Nicolet 6700 spectrophotometer series Fourier-transform infrared (FT-IR) spectrometer. NMR spectra were recorded in DMSO-d_6:CCl_4 (2:3) with tetramethylsilane (TMS) (0 ppm) as internal standard on a Bruker AVANCE-DRX-400 MHz NMR spectrometer. Carbon tetrachloride (CCl_4) was used along with DMSO-d_6 to reduce the cost of expensive deuterated NMR solvent.

Synthesis of 2-hydrazinecarbonyl-benzenesulfonamide **3**

Conventional heating method

To a dry RB flask, hydrazine hydrate **2** (1.36 g, 27.3 mmol) was added to a stirred solution of saccharin **1** (1 g, 5.46 mmol) in 10 mL methanol. The resulting mixture was refluxed at 95 °C for 5 h. The solvent was evaporated under reduced pressure, and this crude upon washing with 5 mL 2-propanol:ethanol (7:3) solvent yielded a white crystalline solid, which was filtered and dried in vacuum. The product **3** was further purified by crystallization from methanol.

Microwave heating method

In a dry sealed tube, saccharin (1 g, 5.46 mmol) was added to hydrazine hydrate (1.36 g, 27.3 mmol) and mixed with methanol (1 mL). The resulting mixture was heated under microwave irradiation at ~95 °C for 4 min to give a waxy yellow liquid. This liquid upon washing with 5 mL 2-propanol:ethanol (7:3) solvent mixture yielded a white crystalline solid, which was filtered and dried in vacuum. Crystallization of this product from methanol gave compound **3**. m.p. 179–81 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 9.87 (s, 1H, NH), 7.95 (m, 1H, Ar–CH), 7.65 (m, 2H, Ar–CH), 7.59 (m, 1H, Ar–CH), 7.09 and 7.02 (ss, 2H, SNH_2), 3.87 (d, 2H, $J = 2.8$ Hz, NNH_2); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 167.5 (C=O), 141.2 (Ar–C–S), 133.2 (Ar–C), 131.7, 129.9, 129.1 and 126.9 (Ar–CH); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 131.7, 129.9, 129.1, 126.9 (Ar–CH); IR (KBr): 3,341.3 (NH, NH_2), 3,068.7 (Ar–CH), 1,662.8 (C=O), 1,170.1 cm^{-1} (O=S=O).

General procedure for syntheses of **5a**–**r**

Conventional heating

The appropriate aromatic aldehydes (12 mmol) were added to solution of compound **3** (10 mmol) in 10 mL methanol/acetic acid (9:1 mL). The resulting mixtures were refluxed at 85 °C in a sealed tube for 8 h. The crude products were concentrated under reduced pressure and poured into ice-cold distilled water (10 mL). The resulting precipitates were filtered and dried in vacuum. After that, all the derivatives (**5a**–**r**) were purified by crystallization from methanol.

Microwave heating

In a dry sealed tube, the appropriate aromatic aldehydes (12 mmol) were added to a mixture of compound **3** (10 mmol) and 1 mL methanol:acetic acid (9:1). The resulting mixture was subjected to microwave irradiation for 2–4 min at ~85 °C. At the end of this period, the crude products were cooled to RT and poured into ice-cold distilled water (10 mL). The resulting products (**5a**–**r**) were filtered and dried in vacuum. After that, all the derived products were purified by crystallization from methanol.

2-({(2E)-2-[Benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5a***

M.p. 158–160 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.03 and 12.00 (ss, 1H, NH), 8.64 and 8.31 (ss, 1H, N=CH), 8.07–7.30 (m, 9H, Ar–CH), 7.02 and 6.87 (ss, 2H, SNH_2); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.5 (C=O), 148.4 (N=CH), 144.2, 141.5 (Ar–C–S), 134.0 and 133.3 (Ar–C), 131.7, 130.1, 129.9 and 129.0 (4C, Ar–CH), 128.4, 128.4, 127.1 and 126.7 (5C, Ar–CH); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 148.4 (N=CH), 144.3, 131.7, 130.1, 129.9, 129.0, 128.4, 127.1 and 126.7 (9C, Ar–CH); IR (KBr): 3,247.9 (NH, NH_2), 3,053.3 (Ar–CH), 1,660.8 (C=O), 1,573 (C=N), 1,162.7 (O=S=O) cm^{-1}.

2-({(2E)-2-[(4-Hydroxy-3-methoxy)benzylidene]hydrazine}carbonyl) benzenesulfonamide ***5b***

M.p. 188–190 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.92 and 11.87 (ss, 1H, NH), 9.32 (br s, 1H, OH), 8.17 (s, 1H, N=CH), 7.98–6.67 (m, 7H, Ar–CH), 7.06 and 7.04 (ss, 2H, SNH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.2 (C=O), 149.2 (N=CH), 147.8 (Ar–C–O), 141.4 (Ar–C–S), 133.4 (Ar–C), 131.6, 129.0, 127.0, 125.2, 122.3, 115.1 and 108.9 (Ar–CH), 55.4 (OCH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): 149.3 (N=CH), 131.6, 130.1, 129.0, 127.0, 122.3, 115.1 and 108.8, 55.5 (OCH_3); IR (KBr): 3,531.5 (OH), 3,271.3 (NH, NH_2), 3,091.3 (Ar–CH), 1,643.1 (C=O), 1,597.6 (C=N), 1,164.8 (O=S=O) cm^{-1}.

2-({(2E)-2-[(3-Ethoxy-4-hydroxy)benzylidene]hydrazine}carbonyl) benzenesulfonamide ***5c***

M.p. 163–164 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.83 and 11.81 (ss, 1H, NH), 9.19 (br s, 1H, OH), 8.15 (s, 1H, N=CH), 7.99–6.68 (7H, Ar–CH), 7.04 and 7.01 (ss, 2H, SNH_2), 4.14 (q, 2H, J = 8.0 Hz, CH_2), 1.44–1.41 (m, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.1 (C=O), 149.4 and 149.0 (2C, Ar–C–O), 147.0 (N=CH), 141.5, 133.5, 131.6, 130.0, 129.0, 127.0, 125.2, 122.2, 115.1, 110.3, 63.8 (CH_2), 14.6 (CH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 147.0 (N=CH), 131.6, 130.0, 129.0, 127.1, 122.2, 115.2 and 110.3 (Ar–CH), 63.8 (CH_2), 14.6 (CH_3); IR (KBr): 3,530.3 (OH), 3,268.8 (NH, NH_2), 3,065.6 (Ar–CH), 1,648.3 (C=O), 1,595.2 (C=N), 1,168.5 (O=S=O) cm^{-1}.

2-({(2E)-2-[(4-Methoxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5d***

M.p. 182–184 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.89 and 11.87 (ss, 1H, NH), 8.35 and 8.24 (ss, 1H, N=CH), 8.0–7.98 (m, 2H, Ar–CH), 7.70–7.63 (m, 4H, Ar–CH), 7.02 and 6.97 (ss, 2H, S-NH_2), 6.97–6.8 (m, 2H, Ar–H), 3.83 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.3 (C=O), 160.9 (Ar–C–O), 148.3 (N=CH), 141.5 (Ar–C–S), 133.4 (Ar–C), 130.6, 129.0, 128.7, 128.2, 127.1, 126.5, 113.7, 54.9 (OCH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 148.3 (N=CH), 130.5, 129.0, 128.8, 128.2, 127.1, 115.5, 54.8 (OCH_3); IR (KBr): 3,263.9 (NH), 3,067.4 (Ar–CH), 1,647.3 (C=O), 1,604.9 (C=N), 1,169.2 (O=S=O) cm^{-1}.

2-({(2E)-2-[(3,4-Dimethoxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5e***

M.p. 168–170 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.93 and 11.89 (ss, 1H, NH), 8.34 and 8.21 (ss, 1H, N=CH), 7.99–7.95 (m, 1H, Ar–CH), 7.72–7.60 (m, 3H, Ar–CH), 7.50–7.15 (m, 2H, Ar–CH), 7.03 and 7.01 (ss, 2H, SNH_2), 6.95–6.81 (m, 2H, Ar–CH), 3.88 (s, 6H, OCH_3); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.3 (C=O), 150.9 (Ar–C–O), 149.1 (Ar–C–O), 148.7 (N=CH), 141.5 (Ar–C–S), 133.4 (Ar–C), 131.7, 130.1, 129.0, 127.1, 126.6, 122.1, 111.0, 108.3, 55.3 (2C, OCH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): 148.6 (N=CH), 131.7, 130.1, 129.0, 127.1, 122.1, 111.0 and 108.2 (Ar–CH), 55.3 (OCH_3); IR (KBr):υ_{max} 3,245.7 (NH, NH_2), 3,082 (Ar–CH), 1,661.5 (C=O), 1,603 (C=N), 1,160.9 (O=S=O) cm^{-1}.

2-({(2E)-2-[(2,4-Dimethoxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5f***

M.p. 191–193 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.87 and 11.82 (ss, 1H, NH), 8.56 and 8.29 (ss, 1H, N=CH), 7.99–7.87 (m, 2H, Ar–CH), 7.70–7.46 (m, 3H, Ar–CH), 7.02 and 6.84 (ss, 2H, S-NH_2), 6.58–6.35 (m, 2H, Ar–CH), 3.89 and 3.84 (s, 6H, OCH_3); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.2 (C=O), 162.5 (Ar–C–O), 159.1 (Ar–C–O), 144.3 (N=CH), 141.5 (Ar–C–S), 133.4 (Ar–C), 131.6, 130.0, 129.0, 127.1, 126.9, 114.8, 106.0, 97.8, 55.4 (OCH_3), 55.0 (OCH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): 144.3 (N=CH), 131.6, 130.0, 129.0, 127.1, 106.0 and 97.8 (Ar–CH), 55.4 (OCH_3), 55.1 (OCH_3); IR (KBr): 3,318.2 (NH, NH_2), 3,071.7 (Ar–CH), 1,651.6 (C=O), 1,568 (C=N), 1,168.6 (O=S=O) cm^{-1}.

2-({(2E)-2-[(3,4,5-Trimethoxy)benzylidene]hydrazine}carbonyl) benzenesulfonamide ***5g***

M.p. 196–197 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.03 and 11.99 (ss, 1H, NH), 8.20 (s, 1H, N=CH), 8.00–7.92 (m, 1H, Ar–CH), 7.73–7.47 (m, 4H, Ar–CH), 7.02 and 6.92 (ss, 2H, SNH_2), 6.92–6.67 (m, 1H, Ar–CH), 3.86–3.69 (9H, OCH_3); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.5 (C=O), 153.0 and 152.8 (3C, Ar–C–O), 148.5 (N=CH), 141.5 (Ar–C–S), 133.3 (Ar–C), 131.7, 130.2, 129.4, 129.0, 127.2, 104.0 (Ar–CH), 126.8 (Ar–C), 59.9 and 55.8 (3C, OCH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): 148.4 (N=CH), 131.7, 130.2, 129.0, 127.1, 126.8 and 104.4 (Ar–CH), 59.8 and 55.7 (3C, OCH_3); IR (KBr): 3,282.8 (NH, NH_2), 3,073.2 (Ar–CH), 1,676.4 (C=O), 1,579 (C=N), 1,169.5 (O=S=O) cm^{-1}.

2-({(2E)-2-[4-(Dimethylamino)benzylidene]hydrazine}carbonyl) benzenesulfonamide ***5h***

M.p. 191–193 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.78 and 11.76 (ss, 1H, NH), 8.16 (s, 1H, N=CH), 7.99-7.93 (m, 2H, Ar–CH), 7.71–7.48 (m, 6H, Ar–CH), 7.03 and 6.85 (ss, 2H, SNH_2), 6.76–6.71 (m, 2H, Ar–CH), 2.95 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.0 (C=O), 149.2 (N=CH), 141.5 (Ar–

C–S), 133.7 (Ar–C), 131.7, 130.2, 129.0, 128.9, 128.0, 127.1 and 111.8 (Ar–CH), 126.7 (Ar–C), 39.9 (2C, NCH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 149.2, 131.7, 130.02, 129.0, 128.9, 128.0, 127.1, 111.8 (Ar–CH), 39.9 (2C, NCH_3); IR (KBr): 3,359.7 (NH, NH_2), 2,991.6 (Ar–CH), 1,654.2 (C=O), 1,526.8 (N=CH), 1,168.9 (O=S=O) cm^{-1}.

2-({(2E)-2-[(4-Diethylamino)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5i***

M.p. 187–189 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.67 and 11.58 (ss, 1H, NH), 8.34 and 8.16 (ss, 1H, N=CH), 7.86–7.90 (m, 2H, Ar–CH), 7.65–7.39 (m, 6H, Ar–CH), 7.02 and 6.95 (ss, 2H, SNH_2), 6.69–6.63 (m, 2H, Ar–CH), 3.18 (m, 4H, 2-NCH_2), 1.29 (m, 6H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 165.7 (C=O), 148.6 (N=CH), 141.4 (Ar–C–S), 133.9 (Ar–C), 131.2, 130.4, 129.1, 128.8, 128.2, 127.0, 110.9 9 (Ar–CH), 126.5 (Ar–C), 48.6 (CH_2), 40.1 (CH_3); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 148.5 (N=CH), 131.2, 130.4, 129.1, 128.8, 128.2, 127.0, 110.9 (Ar–CH), 48.6 (CH_2), 40.1 (CH_3); IR (KBr): 3,360.1 (NH, NH_2), 2,998.9 (Ar–CH), 1,659.8 (C=O), 1,525.4 (N=CH), 1,166.3 (O=S=O) cm^{-1}.

2-({(2E)-2-[(2-Hydroxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5j***

M.p. 195–197 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.30 and 12.12 (ss, 1H, NH), 9.69 (s, 1H, OH), 8.47 and 8.24 (ss, 1H, N=CH), 8.02–6.70 (m, 8H, Ar–CH), 7.15 and 7.05 (ss, 2H, SNH_2); ^{13}C NMR (400 MHz; DMSO-d_6:CCl_4): δ 164.3 (C=O), 157.9 (Ar–C–O), 149.7 (N=CH), 141.6 (Ar–C–S), 132.8 (Ar–C), 132.0, 131.3, 130.5, 129.3, 128.1, 119.0, 118.0 and 116.4 (Ar–CH), 126.4 (Ar–C); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 149.7 (N=CH), 132.7, 132.1, 131.2, 130.8, 129.7, 128.0,118.9 and 116.3 (Ar–CH); IR (KBr): 3,523.1 (OH), 3,316.9 (NH, NH_2), 2,995.5 (Ar–CH), 1,648.1 (C=O), 1,570 (C=N), 1,162.6 (O=S=O) cm^{-1}.

2-({(2E)-2-[(4-Hydroxy)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5k***

M.p. 186–188 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.82 and 11.78 (ss, 1H, NH), 9.79 (br s, 1H, OH), 8.27 and 8.17 (ss, 1H, N=CH), 7.96 (m, 2H, Ar–CH), 7.67–7.55 (m, 4H, Ar–CH), 7.01 and 6.81 (ss, 2H, SNH_2), 6.81–6.66 (m, 2H, Ar–CH); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.3 (C=O), 159.7 (Ar–C–O), 148.9 (N=CH), 141.5 (Ar–C–S), 133.5 (Ar–C), 131.7, 130.1, 129.1, 128.3, 127.1, 124.7 and 115.5 (Ar–CH), 126.2 (Ar–C); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 148.8 (N=CH), 131.7, 130.0, 129.0, 128.3, 127.1 and 115.5 (Ar–CH); IR (KBr): 3,410.7 (OH), 3,236 (NH, NH_2), 3,068.4 (Ar–CH), 1,638.9 (C=O), 1,600 (C=N), 1,163.6 (O=S=O) cm^{-1}.

2-({(2E)-2-[(2-Chloro)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5l***

M.p. 185–187 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.24 and 12.22 (ss, 1H, NH), 8.45 and 8.73 (ss, 1H, N=CH), 8.14–7.38 (m, 6H, Ar–CH), 7.01 and 6.90 (ss,

2H, SNH_2), 6.81–6.66 (m, 2H, Ar–CH); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.6 (C=O), 156.4 (Ar–C–Cl), 146.4 (N=CH), 141.6 (Ar–C–S), 133.5 (Ar–C), 133.1, 131.6, 131.1, 130.3, 129.5, 128.9, 127.2 and 127.0 (Ar–CH), 126.6 (Ar–C); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 144.4 (N=CH), 140.4, 131.6, 131.1, 130.3, 129.5, 128.9, 127.2, 127.0; IR (KBr): 3,332.1 (NH, NH_2), 3,056.3 (Ar–CH), 1,657.4 (C=O), 1,555.9 (N=CH), 1,166.1 (O=S=O) cm^{-1}.

2-({(2E)-2-[(4-Chloro)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5m***

M.p. 193–195 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.08 and 12.04 (ss, 1H, NH), 8.28 and 8.04 (ss, 1H, N=CH), 8.0–7.27 (m, 8H, Ar–CH), 7.05 and 7.01 (ss, 2H, SNH_2); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.5 (C=O), 154.2 (Ar–C–Cl), 147.0 (N=CH), 141.5 (Ar–C–S), 134.9 (Ar–C), 132.8, 131.6, 130.8, 130.2, 129.4, 128.9 and 127.2 (Ar–CH), 126.2 (Ar–C); DEPT (400 MHz, DMSO-d_6:CCl_4): δ 147.0 (N=CH), 131.6, 130.8, 130.2, 129.4, 128.9 127.2; IR (KBr): 3,345.9 (NH, NH_2), 3,057.5 (Ar–CH), 1,645.6 (C=O), 1,602.1 (CH=N), 1,166.7 (O=S=O) cm^{-1}.

2-({(2E)-2-[(2-Nitro)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5n***

M.p. 179–80 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.27 and 12.06 (ss, 1H, NH), 8.57 and 8.41 (ss, 1H, N=CH), 8.23–7.46 (m, 8H, Ar–CH), 7.05 and 7.0 (ss, 2H, SNH_2); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.7 (C=O), 148.1 (N=CH), 147.9, 145.8 (Ar–C–N), 141.6 (Ar–C–S), 136.0, 133.0 (Ar–C), 131.7, 130.0, 128.9, 126.9 (Ar–C), 124.0, 123.5, 121.3; DEPT (400 MHz, DMSO-d_6:CCl_4): δ 164.7 (C=O), 148.1 (N=CH), 133.0, 131.7, 130.0, 129.0, 127.1, 123.6, and 121.3 (Ar–CH); IR (KBr): 3,266.7 (NH, NH_2), 3,066.7 (Ar–CH), 1,675.1 (C=O), 1,519.3 (NO_2), 1,558.7 (CH=N), 1,160.2 (O=S=O) cm^{-1}.

2-({(2E)-2-[(3-Nitro)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5o***

M.p. 188–190 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.38 and 11.25 (ss, 1H, NH), 8.23 and 8.20 (ss, 1H, N=CH), 8.18–7.46 (m, 8H, Ar–CH), 7.04 and 7.01 (ss, 2H, SNH_2); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.7 (C=O), 148.1 (N=CH), 145.8 (Ar–C–NO_2), 141.6 (Ar–C–S), 136.0, 133.0 (Ar–C), 132.4, 131.7, 130.3, 129.2, 128.9, 127.2, 124.0, 121.3; DEPT (400 MHz, DMSO-d_6:CCl_4): δ 148.2 (N=CH), 136.0, 131.7, 130.0,129.2, 128.9, 124.1 and 121.2 (Ar–CH); IR (KBr): 3,271.3 (NH), 3,065.4 (Ar–CH), 1,661.4 (C=O), 1,527.9 (NO_2), 1,590.6 (C=N), 1,171.8 (O=S=O) cm^{-1}.

2-({(2E)-2-[(4-Nitro)benzylidene]hydrazine}carbonyl)benzenesulfonamide ***5p***

M.p. 183–184 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.31 and 12.26 (ss, 1H, NH), 8.39 and 8.28 (ss, 1H, N=CH), 8.28–7.45 (m, 8H, Ar–CH), 7.01 and 6.94 (ss, 2H, SNH_2); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.8 (C=O), 147.9 (N=CH), 141.5 (Ar–C–NO_2), 140.3 (Ar–C–S), 133.0 (Ar–C), 131.7, 130.3, 129.2, 128.6, 128.0, 127.2, 123.6; DEPT (400 MHz, DMSO-d_6:CCl_4): δ 147.8 (N=CH), 133.1,

131.6, 130.2, 128.5, 127.2, 123.6; IR (KBr): 3,333.5 (NH, NH_2), 3,065.1 (Ar–CH), 1,659.7 (C=O), 1,524.7 (NO_2), 1,590.2 (C=N), 1,166 (O=S=O) cm^{-1}.

2-({(2E)-2-[(Furan-2-yl)methylene]hydrazine}carbonyl)benzenesulfonamide ***5q***

M.p. 163–65 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 11.98 and 11.92 (ss, 1H, NH), 8.19 (s, 1H, N=CH), 7.99–7.94 (m, 2H, Ar–CH), 7.73–7.45 (m, 3H, Ar–CH), 7.04 and 7.0 (ss, 2H, SNH_2), 6.89–6.46 (m, 2H, Ar–CH); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.5 (C=O), 149.3 (N=CH), 144.7 (Ar–C–O), 141.5 (Ar–C–S), 138.1, 133.2 (Ar–C), 131.7, 130.8, 129.0, 127.2, 113.2, 111.8; DEPT (400 MHz, DMSO-d_6:CCl_4): δ 149.2 (N=CH), 138.1, 131.7, 130.9, 127.2, 113.2, 111.8; IR (KBr): 3,255.6 (NH), 3,060.9 (Ar–CH), 1,653.9 (C=O), 1,589.2 (CH=N), 1,168.8 (O=S=O) cm^{-1}.

2-({(2E)-2-[2-(Anthracen-9-yl)benzylidene]hydrazine}carbonyl) benzenesulfonamide ***5r***

M.p. 157–159 °C, ^{1}H NMR (400 MHz, DMSO-d_6:CCl_4): δ 12.26 and 12.22 (ss, 1H, NH), 8.81 (m, 1H, Ar–H), 8.60 and 8.48 (ss, 1H, N=CH), 8.42 (d, 1H, $J = 8.4$, Ar–CH), 8.09–7.82 (m, 3H, Ar–CH), 7.76–7.39 (m, 7H, Ar–CH), 7.13 and 6.92 (ss, 2H, S-NH_2); ^{13}C NMR (400 MHz, DMSO-d_6:CCl_4): δ 164.5 (C=O), 147.7 (N=CH), 141.7 (Ar–C–S), 140.5, 133.9, 133.3 (Ar–C), 130.8, 129.8, 129.0, 128.5, 126.8, 126.4, 125.1, 124.9; DEPT (400 MHz, DMSO-d_6:CCl_4): δ 147.7 (N=CH), 130.8, 129.8, 129.0, 128.5, 126.8, 126.4, 125.1, 124.8; IR (KBr): 3,302.4 (NH), 3,073.7 (Ar CH), 1,658.8 (C=O), 1,603.6 (C=N), 1,168.7 (O=S=O) cm^{-1}.

Antibacterial assay

All the synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) and tested for their antibacterial activity against Gram-positive *S. aureus* and *B. firmus* and Gram-negative *E. coli* bacterial organisms by the hole diffusion method. DMSO was chosen as a control because it has no effect on these bacterial strains. The culture media for the growth of bacterial strains *S. aureus* and *E. coli* were prepared by using peptone (3.0 g), NaCl (1.0 g), yeast (1.5 g), and agar (6.0 g) in 300 mL distilled water at pH 7.0. However, the culture medium intended for *B. firmus* was prepared by the reported procedure [31]. Sterilization of the medium was done by autoclaving at 15 Pa for 20 min, and after keeping at 85 °C for 30 min it was poured into sterilized Petri plates in a laminar flow environment. Solidification of the medium was achieved at 30 °C in 15 min. The bacterial strains were inoculated over the media with the help of a micropipette followed by poking with a 5-mm hollow glass tube to create holes. The four different tested doses, viz. 200, 100, 50, and 25 μg/mL, of each of the synthesized compounds (**5a–r**) and norfloxacin were loaded into these holes separately through bacteria-free micropipettes in different Petri dishes. After 24 h, the antibacterial activity was determined by measuring the zone of inhibition in millimeters (mm) and compared with the results obtained from the standard drug norfloxacin. The lowest

concentration that inhibited the growth of bacteria was noted and considered as the MIC value for each of the tested compounds.

Crystallography

Data collection from crystals of **3** and **5k** was performed on an Oxford Diffraction Xcalibur 3 diffractometer (Mo K_α radiation, graphite monochromator) and on a Nonius Kappa CCD diffractometer for crystals of **5e** and **5f** (Mo K_α radiation, multilayer X-ray optics) at temperature of 173 K. The structures were solved by direct methods with SIR97 [32] and refined by full-matrix least-squares methods on F^2 with SHELXL-97 [33]. All nonhydrogen atoms were refined anisotropically. The C-bound hydrogen atoms were added geometrically and treated as riding on their parent atoms. The O-bound hydrogen atoms for crystal **5k** were refined to a fixed distance of 0.82(1) Å with $U_{iso}(H) = 1.2U_{eq}(N/H)$. The thermal parameters of the N-bound hydrogen atoms were in all cases refined as $U(H) = 1.2U(N)$. The N-bound hydrogen atoms for **3** and **5f** were refined to a fixed distance of 0.86(1) Å, while in **5e** this distance was refined freely. Multiscan absorption corrections were performed with SCALE 3 ABSPACK [34] for the crystals of **3**, **5e**, and **5k**, while the crystal data of **5f** were not corrected for multiscan absorption.

Conclusions

A series of hydrazinecarbonyl benzenesulfonamides (**5a**–**r**) have been synthesized by microwave heating in shorter reaction times and higher yields in small amounts of solvents. A comparison with synthesis of the products by the conventional method has also been undertaken. The obtained products have been characterized by NMR and IR spectral techniques. The crystal and molecular structures of **3**, **5e**, **5f**, and **5k** have also been elucidated by single-crystal X-ray crystallography. The in vitro antibacterial activities of the derived products were evaluated against Gram-positive *S. aureus* and *B. firmus* along with Gram-negative *E. coli* bacterial strains. The zone of inhibition of compounds **5a**, **5j**, **5p**, and **5r** showed that these compounds exhibit moderate bioactivities against all tested organisms.

Supplementary information

The crystallographic information file (CIF) data of **3** (CCDC 853352), **5e** (CCDC 863707), **5f** (CCDC 863710), and **5k** (CCDC 863353) can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

References

1. C. Rooney, A.J. McMichael, R.S. Kovats, M. Coleman, J. Epidemiol. Community Health **52**, 482 (1998)

2. T. Kosatsky, Eurosurveillance **10**, 148 (2005)
3. A. Woodward, S. Hales, P. Weinstein, Clim. Res. **11**, 31 (1998)
4. A. Haines, R.S. Kovats, L.D. Campbell, D. Corvalan, Lancet **367**, 1 (2006)
5. A.S. William, F.B. Aleksel, C. Ron, *Organic Synthesis: The Science Behind Art* (Royal Society of Chemistry, Cambridge, 1998)
6. R.S. Varma, R. Dahiya, R.K. Saini, Tetrahedron Lett. **386**, 7029 (1997)
7. R. Strauss, R.W. Trainor, Aust. J. Chem. **48**, 1665 (1995)
8. N.B. Ondruschka, W. Lautenschlager, Synth. Commun. **31**, 1277 (2001)
9. R.S. Varma, Green. Chem. **1**, 43 (1999)
10. D.R. Baghurst, D.M.P. Mingos, Chem. Soc. Rev. **20**, 1 (1991)
11. C.O. Kappe, Angew. Chem. Int. Ed. **43**, 6250 (2004)
12. K. Rader, P. Stoss, U.S. Patent US4362730, 7 Dec 1982
13. J.W. Rayburn, WO Patent 00/12067, 9 Mar 2000
14. P.M. Bhatt, N.V. Ravindra, R. Banerjee, G.R. Desiraju, Chem. Commun. 1073 (2005)
15. R. Banerjee, P.M. Bhatt, N.V. Ravindra, G.R. Desiraju, Cryst. Growth Des. **5**, 2299 (2005)
16. R. Banerjee, P.M. Bhatt, G.R. Desiraju, Cryst. Growth Des. **6**, 1468 (2006)
17. S.Y. Wang, W.C. Guo, N. Ma, Acta Cryst. E **63**, o3192 (2007)
18. J. Drews, Science **287**, 1960 (2000)
19. A.E. Boyd 3rd, Diabetes **37**, 847 (1988)
20. T.H. Maren, Annu. Rev. Pharmacol. Toxicol. **16**, 309 (1976)
21. C.T. Supuran, A. Scozzafava, Curr. Med. Chem. Immunol. Endocr. Metabol. Agents **1**, 61 (2001)
22. C.W. Thornber, Chem. Soc. Rev. **8**, 563 (1979)
23. L. Yin, L. Yao, Q. Ke-Ming, L. Xiang, F. Jie, Z. Hai-Liang, Bioorg. Med. Chem. **19**, 6069 (2011)
24. S. Rollas, S.G. Kucukguzel, Molecules **12**, 1910 (2007)
25. G. Thiyagarajan, P. Nithiya, A. Pandey, A. Pandey, Int. J. Org. Chem. **1**, 71 (2011)
26. S.K. Sridhar, A. Ramesh, Biol. Pharm. Bull. **24**, 1149 (2001)
27. J.X. Wang, X.Z. Li, L.N. Zhu, J.Y. Wang, H.J. Qu, J. Chem. Crystallogr. **40**, 726 (2010)
28. S. Naskar, R.J. Butcher, S.K. Chattopadhyay, Inorg. Chim. Acta **363**, 3641 (2010)
29. G.N. Lewis, J. Am. Chem. Soc. **38**, 772 (1916)
30. W.L.F. Armarego, L.L.C. Christina, Purification of Laboratory Chemicals, 5th edn. (Elsevier, Amsterdam, 2003)
31. J. Szumigaj, Z. Zakowska, L. Klimek, Pol. J. Microbiol. **57**, 281 (2008)
32. A. Altomare, M.C. Burla, M. Camalli, G.L. Cascarano, C. Giacovazzo, A. Guagliardi, G.G. Moliterni, G. Polidori, R. Spagna, J. Appl. Cryst. **32**, 115 (1999)
33. G.M. Sheldrick, Acta Cryst. A **64**, 112 (2008)
34. L.J. Farrugia, J. Appl. Cryst. **32**, 837 (1999)