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ORIGINAL PAPER

Structure of a New Bioactive Agent Containing Combined Antibacterial and Antifungal Pharmacophore Sites: 4-{[(*E*)-(5-Bromo-2-hydroxyphenyl)methylidene]amino}-*N*-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide

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Abstract The title compound (**3**), $C_{17}H_{14}BrN_3O_4S$, is a Schiff base compound of 5-bromosalicylaldehyde (**1**) and sulfamethoxazole (**2**). The structure of (**3**) was determined by spectral (IR, ^1H and ^{13}C NMR), elemental analyses and X-ray diffraction data. Compound (**3**) crystallizes in the monoclinic space group C2/c, with $a = 31.936(3)$, $b = 6.2571(5)$, $c = 16.903(1)$ Å, $\beta = 94.867(8)$, $V = 3365.5(5)$ Å^3, $Z = 8$. In the molecule of compound (**3**), the molecule is bent at the S atom with a C–SO_2–NH–C torsion angle of −86.3(3)°. Pairs of molecules, related by inversion centres, form intermolecular N–H···N hydrogen bonds to produce a dimer. An intramolecular phenolic O–H···N hydrogen bond is also formed. Intermolecular hydrogen bonding and π–π stacking hold the molecules together. The average distance between stacked benzene ring planes is 3.625(2) Å.

Keywords Sulfonamide · Bidentate · Antibacterial · Antifungal

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Introduction

Sulfonamide derived Schiff bases are potential class of compounds, which have been found to possess a wide range of medicinal properties [1]. These compounds have also been found to possess a variety of pharmacological properties including antibacterial, antifungal, anti-neoplastic, antiulcer, antiviral and enzymatic inhibition [2–5]. As a result, there is an increasing interest in exploring novel methodologies for the synthesis and biological screening of more such compounds [6–8]. Motivated by this idea and in continuation of our previous work [9–16], we wish to report here, the title compound 4-{[(*E*)-(5-bromo-2-hydroxyphenyl)methylidene]amino}-*N*-(5-methyl-1,2-oxazol-3-yl)-benzene sulfonamide, synthesized from the reaction of sulfamethoxazole with 5-bromosalicylaldehyde (Fig. 1).

Results and Discussion

Chemistry

4-{[(*E*)-(5-Bromo-2-hydroxyphenyl)methylidene]amino}-*N*-(5-methyl-1,2-oxazolyl)-benzenesulfonamide was formed by an equimolar reaction of 5-bromosalicylaldehyde and sulfamethoxazole (Scheme 1). It was stable to air and moisture and soluble in Dioxane, DMF and DMSO. It sharply melts at 216 °C. The spectral and analytical data, agreed well with the structure.

X-Ray Structure Determination of O,N-Ligand (**3**)

Suitable single crystal of malonate derivative (**3**) was obtained by recrystallization from ethanol. A white-transparent

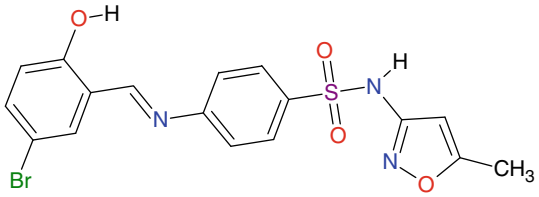

Fig. 1 Proposed structure of antimicrobial agent (**3**)

crystal of $C_{17}H_{14}BrN_3O_4S$ having approximate dimensions of 0.23 × 0.21 × 0.17 mm was mounted on a glass fibre. All measurements were made in the ω-scan technique on a CCD Saphire 3 Xcalibur diffractometer (Oxford Diffraction) with graphite monochromatized MoKα radiation. The structure was solved by direct methods using the program SIR-97 [17]. The non-hydrogen atoms were refined anisotropically by the full-matrix least-square techniques using the program SHELXL97 [18]. All H atoms were located geometrically and treated using a riding model, with O–H = 0.84 Å, N–H = 0.88 Å, C–H = 0.95–0.98 Å and U_{iso} (H) = 1.2 U_{eq} ($C_{aromatic}$, N_{amine}) and U_{iso} (H) = 1.5 U_{eq} (C_{methyl}, $O_{hydroxyl}$).

The details of the crystal and experimental data was listed in Table 1. Selected bond distances and bond angles are given in Table 2. The molecular structure of the title O,N-ligand (**3**) is shown in Fig. 2. Packing and hydrogen bonding interactions are illustrated in Fig. 3.

The structure of the same compound but without the bromine atom, 4-[(2-hydroxy-benzylidene)-amino]-*N*-(5-methyl-isoxazol-3-yl)-benzenesulfonamide, has been recently reported by Subashini et al. [19]. The S1–C11 distance [1.759(3) Å] has a normal single-bond value and agree well with those reported for other sulfonamides [19]. The atoms around the S1 atom exhibit a slightly distorted tetrahedral configuration with the largest angle O3–S1–O2 of 121.50(12) (Table 2). As shown in Fig. 2, the two benzene rings C1–C6 and C8–C13 are tilted by 1.24(14)° relative to each other. Therefore, they are almost coplanar. The isoxazole ring N3/O4/C14–C16 with the benzene rings C1–C6 and C8–C13 is oriented at dihedral angles of 79.38(15) and 80.16(16)°, respectively. The molecule is bent at the S atom with a C–SO_2–NH–C torsion angle of −86.3(3)° (Table 3).

Table 1 Crystal data and structure refinement for (**3**)

Empirical formula	$C_{17}H_{14}BrN_3O_4S$
Formula weight	436.28
Temperature	150(2) K
Wavelength	0.71069 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	
a = 31.936(3) Å	α = 90°
b = 6.2571(5) Å	β = 94.867(8)°
c = 16.903(1) Å	γ = 90°
Volume	3365.5(5) Å^3
Z	8
Calculated density	1.722 Mg/m^3
F(000)	1760.0
Absorption coefficient	2.597 mm^{-1}
θ range for data collection	2.64–26.99°
Limiting indices	$-40 \le h \le 40$, $-7 \le k \le 7$, $-21 \le l \le 21$
Reflections collected/unique	20752/3554 (R_{int} = 0.098)
Completeness to θ = 26.990	97%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3554/0/236
Goodness-of-fit on F^2	0.83
Final R indices [1937 reflections with $I > 2\sigma(I)$]	R_1 = 0.0371, wR_2 = 0.0407
Largest diff. peak and hole	0.72 and −0.56 e Å^{-3}

In the molecule, an intramolecular O–H···N (O1–N1 = 2.597(3) Å) hydrogen bond forms a six-membered ring of graph-set notation S(6) (Fig. 2; Table 4). Therefore, the benzene ring and the azomethine group of the molecule are almost coplanar as in the crystal structure of similar compound 4-[(2-hydroxy-benzylidene)-amino]-*N*-(5-methyl-isoxazol-3-yl)-benzenesulfonamide [19].

An C–H···Br interaction is observed (Fig. 2; Table 4). Pair of molecules are centrosymmetrically linked via N–H···N hydrogen bonds [N2–(H2)···N3] as shown in Fig. 3 (Table 4). Further the crystal structure of the title compound is stabilized by intermolecular C–H···Br interactions

Scheme 1 Preparation and structure of antimicrobial agent (**3**)

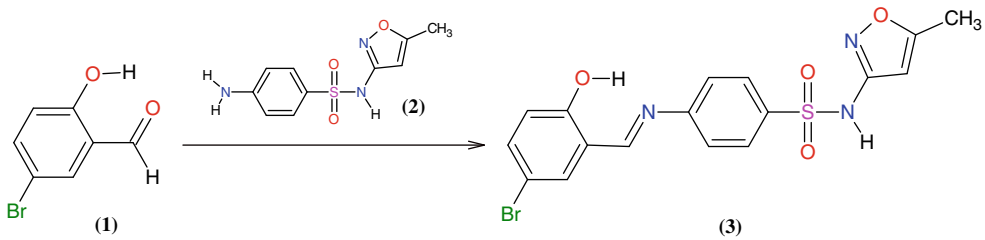

Table 2 Bond lengths (Å) and angles (°) for (**3**)

Br1–C4	1.888(3)	O4–C16	1.342(3)
S1–O3	1.4179(18)	O4–N3	1.409(2)
S1–O2	1.4236(18)	N1–C7	1.272(3)
S1–N2	1.628(2)	N1–C8	1.421(3)
S1–C11	1.759(3)	N2–C14	1.388(3)
O1–C1	1.351(3)	N3—C14	1.316(3)
O3–S1–O2	121.50(12)	C5–C4–Br1	120.6(3)
O3–S1–N2	107.99(12)	C3–C4–Br1	119.2(2)
O2–S1–N2	104.85(11)	N1–C7–C6	122.6(3)
O3–S1–C11	108.51(13)	C9–C8–N1	115.9(3)
O2–S1–C11	107.14(14)	C13–C8–N1	124.8(3)
N2–S1–C11	105.84(12)	C12–C11–S1	118.7(2)
C16–O4–N3	108.2(2)	C10–C11–S1	121.1(2)
C7–N1–C8	121.7(3)	N3–C14–N2	116.7(2)
C14–N2–S1	126.76(19)	N3–C14–C15	112.2(3)
C14–N3–O4	104.6(2)	N2–C14–C15	131.1(3)
O1–C1–C2	118.4(3)	C15–C16–O4	110.8(3)
O1–C1–C6	121.6(3)	O4–C16–C17	115.9(3)

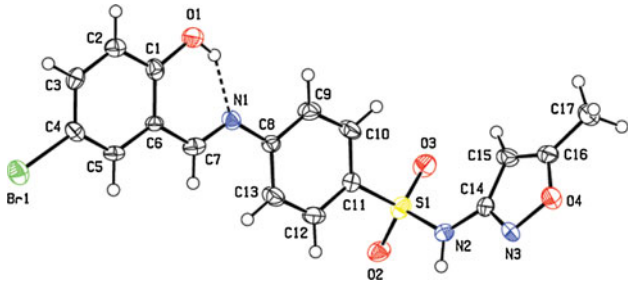

Fig. 2 View of the title compound with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level

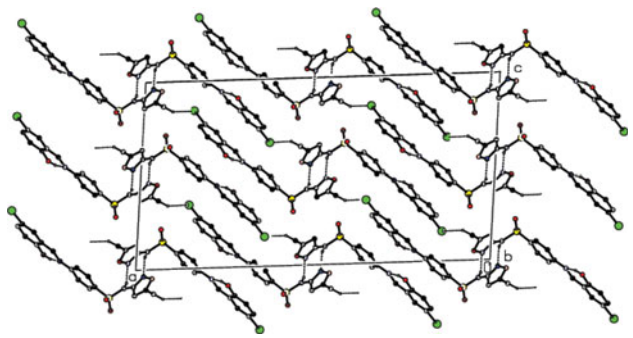

Fig. 3 View of the packing and the intermolecular N–H···N hydrogen bonds (*dashed lines*) of the title compound down the *b* axis

and π–π stacking interactions between stacked benzene ring planes (C1–C6 and C8–C13) with a centroid-to-centroid distance of 3.625(2) Å.

Table 3 Torsion angles (°) for (**3**)

O3–S1–N2–C14	29.7(3)	O1–C1–C6–C7	0.0(4)
O2–S1–N2–C14	160.6(2)	C1–C6–C7–N1	−1.0(4)
O1–C1–C2–C3	178.6(2)	O4–N3–C14–N2	177.0(2)
O1–C1–C6–C5	−179.2(2)	S1–N2–C14–N3	168.6(2)

Table 4 Hydrogen-bond parameters (Å, °) for (**3**)

D–H···*A*	*D*–H (Å)	H···*A* (Å)	D···A (Å)	*D*–H···*A* (°)
O1–H1···N1	0.84	1.86	2.597(3)	147
N2–H2···N3^{i}	0.88	2.07	2.876(3)	152
C17–H17C···Br1^{ii}	0.98	2.93	3.686(3)	135

Symmetry codes: (i) $1/2 + x$, $3/2 + y$, z; (ii) $-1/2 + x$, $1/2 - y$, $-3/2 + z$

Experimental Section

All materials and solvents used were of reagent grade as received from commercial sources. ^{1}H NMR spectra were recorded on AC 300 MHz NMR Bruker Spectrometer at ambient temperature and chemical shifts were reference to the internal tetramethylsilane. Infrared spectra were recorded in KBr pellets using a Shimadzu FTIR-8400S spectrophotometer. Mass spectra were determined by JEOL MS Route spectrometer and elemental analyses were performed by Perkin Elmer USA.

4-{[(*E*)-(5-Bromo-2-hydroxyphenyl)methylidene]amino}-*N*-(5-methyl-1, 2-oxazol-3-yl)-benzenesulfonamide (**3**)

An ethanol solution (20 mL) of sulfamethoxazole (0.506 g, 2 mmol) was mixed with 5-bromosalicylaldehyde (0.402 g, 2 mmol) in ethanol (10 mL). The mixture was refluxed for 3 h. The colour of the solution gradually changed from colorless to reddish yellow during refluxing. The completion of reaction was monitored by TLC. After which, the solution was cooled to room temperature, filtered and volume reduced to about one-third on rotary. A solid product thus obtained was filtered, washed with ethanol and recrystallized in a mixture of ethanol: methanol (1:1) by standing at room temperature for 4 days. Crystals of (**3**) have been obtained.

Clear and shinny crystals: 78% of yield, IR (KBr, ν cm^{-1}): 3325 (OH), 1345, 1108 (SO_2N–H), 1605 (CH=N), 1108 (SO_2NH). ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm: 2.31 (s, 3H, methylisoxazole), 6.8 (s, 1H, isoxazole), 6.9–7.6 (m, 3H, Br–Ph), 7.7–8.2 (m, 4H, N–Ph), 8.9 (s, 1H, azomethine), 8.9 (s, 1H, SO_2NH), 12.42 (s, 1H, OH)

^{13}C-NMR (300 MHz, DMSO-D_6) δ ppm: 12.9 (methylisoxazole), 95.1 (C4-isoxazole), 118.4 (C3, Br–Ph), 120.5 (C1, Br–Ph), 122.6 (C2, C6, N–Ph), 116.0 (C5, Br–Ph), 128.6 (C3, C5, N–Ph), 134.0 (C6, Br–Ph), 135.5 (C4, Br–Ph), 138.2 (C4, N–Ph), 150.0 (C3, isoxazole), 156.4 (C1, N–Ph). 160.0 (C2, Br–Ph), 160.9 (C=N, azomethine), 169.6 (C5, isoxazole). MS (IE): Calcd. for $[M]^+$ $C_{17}H_{14}BrN_3O_4S$: 436.28, $[M + H]^+$ $(m/z) = 436.32$ (436.0%). Elemental analysis: Calculated for $C_{17}H_{14}BrN_3O_4S$; C, 46.62; H, 3.49; N, 9.81 found C, 46.80; H, 3.23; N, 9.63%.

Supplementary Information

Crystallographic data for the structural analysis has been deposited with the Cambridge crystallographic Data Centre, CCDC No. 761146 for compound (**3**). Copies of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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