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Crystal Structure Analysis of a Bioactive Piperazine Analog: 1-[Bis-(4-fluorophenyl)-methyl]-4-methane Sulfonyl Piperazine

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Crystal Structure Analysis of a Bioactive Piperazine Analog: 1-[Bis-(4-fluorophenyl)-methyl]-4-methane Sulfonyl Piperazine

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The title compound, $C_{18}H_{20}F_2N_2O_2S$, was synthesized, and the structure was investigated by X-ray crystallography. The compound crystallizes in the monoclinic space group $P2_1/n$ with cell parameters $a = 9.905(6)$ Å, $b = 16.907(15)$ Å, $c = 10.778(9)$ Å, $\beta = 98.831(5)^\circ$ for $Z = 4$. The structure has been solved by direct methods and refined to $R_1 = 0.0408$ for 2905 observed reflections with $I > 2\sigma(I)$. The piperazine ring is in a chair conformation. The geometry around the S atom is a distorted tetrahedron. The structure exhibits a weak intermolecular hydrogen bond of the type C–H...F.

Keywords: chair conformation; piperazine; tetrahedron geometry

INTRODUCTION

The piperazine moiety serves as a building block for the synthesis of biologically active molecules. Compounds possessing a piperazine moiety also have a wide range of biological applications. Also, the piperazine ring occurs in many physiologically active compounds, and it is a building block of pharmaceuticals [1]. Piperazine and some of its

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derivatives are commonly used as drugs with anti-arthritic, anthelmintic, spasmolytic activities and nonspecific bacteriostatic effects [2]. 1-[Bis(4-fluorophenyl)-methyl]piperazine and related compounds destroy internal worms, making these chemicals useful in both medical and veterinary preparation. Diphenyl piperazine derivatives possess broad pharmacological action on the central nervous system (CNS), especially on dopaminergic neurotransmission [3]. Piperazine sulfonamides exhibit diverse pharmacological activities such as MMP-3 inhibition, antibacterial activity, and carbonic anhydrase inhibition [4]. Recently, we have reported the synthesis and *in vitro* antimicrobial studies of medicinally important novel N-alkyl and N-sulfonyl derivatives of 1-[bis(4-fluorophenyl)-methyl]piperazine [5]. *In vitro* antimicrobial studies of the title compound showed potent antimicrobial activity against various bacteria and fungi. This compound may serve as a new class of antimicrobial agent. This prompted us to study the molecular structure of the compound 1-[bis-(4-fluorophenyl)-methyl]-4-methane sulfonyl piperazine.

METHOD OF CRYSTALLIZATION

After synthesis [5] and purification, the resultant product was allowed to crystallize in methanol for 2 days and was left undisturbed. The resultant product was washed with hexane. Colorless single crystals grew because of the slow evaporation of methanol. A schematic diagram of the molecule is shown in Fig. 1.

CRYSTAL STRUCTURE DETERMINATION

A single crystal of the title compound with dimensions $0.3 \times 0.27 \times 0.25$ mm was chosen for an X-ray diffraction study. The data were

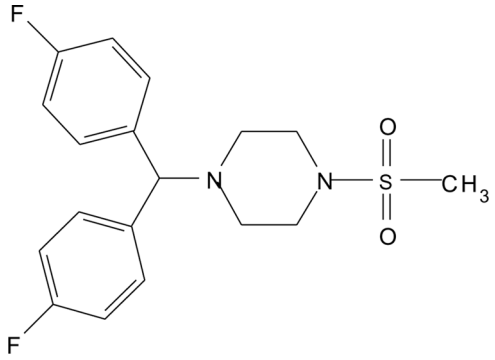

FIGURE 1 Schematic diagram.

collected on a DIPLabo Image Plate system equipped with a normal focus, 3-kW sealed X-ray source (graphite monochromated MoK_α). The crystal-to-detector distance is fixed at 120 mm with a detector area of $441 \times 240\,mm^2$. Thirty-six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 400 s. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5°. Image processing and data reduction were done using Denzo [6]. The reflections were merged with Scalepack [7]. All of the frames could be indexed using a primitive monoclinic lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97 [8]. All the nonhydrogen atoms were revealed in the first

TABLE 1 Crystal Data and Structure Refinement Table

Parameter	Value
CCDC deposition number	CCDC 616413
Empirical formula	$C_{18}H_{20}F_2N_2O_2S$
Formula weight	366.42
Temperature	293(2)K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Cell dimensions	$a = 9.905(6)$Å $b = 16.907(15)$Å c = 10.778(9)Å $\beta = 98.831(5)°$
Volume	1784(2)Å^3
Z	4
Density (calculated)	1.365 Mg/m^3
Absorption coefficient	0.215 mm^{-1}
F_{000}	768
Crystal size	$0.3 \times 0.27 \times 0.25$ mm
Theta range for data collection	2.26° to 25.02°
Index ranges	$-11 \le h \le 11$ $-20 \le k \le 20$ $-12 \le l \le 12$
Reflections collected	5304
Independent reflections	2905 [R(int) = 0.0275]
Absorption correction	None
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	2905/0/227
Goodness of fit on F^2	1.101
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0408$, $wR2 = 0.1197$
R indices (all data)	$R1 = 0.0498$, $wR2 = 0.1398$
Largest diff. peak and hole	0.207 and −0.336 e.Å^{-3}

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Nonhydrogen

Atom	x	y	z	U_{eq}
N1	0.2296(2)	0.0307(2)	0.1166(2)	0.0444(4)
C2	0.3108(2)	0.0894(2)	0.0586(2)	0.0525(5)
C3	0.2184(2)	0.1369(2)	−0.0380(2)	0.0509(5)
N4	0.1122(2)	0.17725(9)	0.01910(2)	0.0411(4)
C5	0.0296(2)	0.1164(2)	0.0686(2)	0.0501(5)
C6	0.1164(2)	0.0679(2)	0.1688(2)	0.0503(5)
S7	0.31620(6)	−0.03618(3)	0.20502(5)	0.0486(2)
O8	0.4170(2)	−0.0676(2)	0.1369(2)	0.0702(5)
O9	0.2194(2)	−0.08864(9)	0.2465(2)	0.0638(5)
C10	0.4019(3)	0.0128(2)	0.3396(2)	0.0599(6)
C11	0.0270(2)	0.2268(2)	−0.0756(2)	0.0433(5)
C12	0.1129(2)	0.2894(2)	−0.1279(2)	0.0436(5)
C13	0.2051(2)	0.3368(2)	−0.0495(2)	0.0527(6)
C14	0.2747(3)	0.3975(2)	−0.0977(3)	0.0618(6)
C15	0.2512(3)	0.4095(2)	−0.2258(3)	0.0630(7)
C16	0.1658(3)	0.3637(2)	−0.3065(2)	0.0621(7)
C17	0.0966(2)	0.3031(2)	−0.2563(2)	0.0508(5)
F18	0.3168(2)	0.4705(2)	−0.2735(2)	0.0922(6)
C19	−0.0895(2)	0.2660(2)	−0.0222(2)	0.0441(5)
C20	−0.2216(2)	0.2630(2)	−0.0878(2)	0.0519(5)
C21	−0.3283(3)	0.3022(2)	−0.0442(2)	0.0619(6)
C22	−0.3010(3)	0.3439(2)	0.0650(3)	0.0598(6)
C23	−0.1730(3)	0.3483(2)	0.1341(2)	0.0588(6)
C24	−0.0685(2)	0.3087(2)	0.0899(2)	0.0515(5)
F25	−0.4061(2)	0.3824(2)	0.1078(2)	0.0903(6)

Note. $U_{eq} = (1/3)\sum_i \sum_j U_{ij}(a_i^* a_i^*)(\mathbf{a_i}.\mathbf{a_j})$.

Fourier map. Least-squares refinement using SHELXL-97 [9] with isotropic temperature factors for all the nonhydrogen atoms converged the residual $R1$ to 0.1681. Subsequent refinements were carried out with anisotropic thermal parameters for nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms, which were placed at chemically acceptable positions. After eight cycles of refinement, the residual converged to 0.0408. The details of crystal data and refinement are given in Table l.[†] Table 2 gives the atomic coordinates and equivalent thermal parameters of the nonhydrogen atoms. Tables 3 and 4 give the list of bond lengths and bond angles, respectively, which

[†]CCDC 616413 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; e-mail: de-posit@ccdc.cam.ac.uk.

TABLE 3 Bond Lengths (Å)

Atoms	Length
N1–C6	1.470(3)
N1–C2	1.475(3)
N1–S7	1.635(2)
C2–C3	1.508(3)
C3–N4	1.467(3)
N4–C5	1.466(3)
N4–C11	1.479(3)
C5–C6	1.514(3)
S7–O9	1.428(2)
S7–O8	1.429(2)
S7–C10	1.769(2)
C11–C12	1.518(3)
C11–C19	1.519(3)
C12–C17	1.388(3)
C12–C13	1.398(3)
C13–C14	1.381(3)
C14–C15	1.380(4)
C15–C16	1.359(4)
C15–F18	1.361(3)
C16–C17	1.388(3)
C19–C20	1.389(3)
C19–C24	1.395(3)
C20–C21	1.389(3)
C21–C22	1.362(4)
C22–F25	1.366(3)
C22–C23	1.370(4)
C23–C24	1.378(3)

are in good agreement with the standard values. The ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2.

The piperazine ring adopts an almost perfect chair conformation, as in the case of 1-benzhydryl piperazine [10]. This is confirmed by the puckering parameters $Q = 0.5865(26)$ Å, $\theta = 4.97(24)^\circ$, and $\phi = 179(3)^\circ$ and the intraring torsion angles for the atom sequence N1/C2/C3/N4/C5/C6. The bonds N1–S7 and N4–C11 make an angle $83.02(14)^\circ$ and $73.48(15)^\circ$, respectively, with the Cremer and Pople plane [11] of the piperazine ring and thus are in the equatorial plane of the piperazine ring. The dihedral angle between the piperazine ring and the fluorophenyl ring plane (C12–C17) is $76.84(13)^\circ$. The piperazine ring makes an angle of $77.55(14)^\circ$ with the other fluorophenyl ring plane consisting of atoms C19–C24. This value is lesser than the corresponding values of $86.32(10)^\circ$ and $88.27(15)^\circ$ reported for 1-benzhydryl

TABLE 4 Bond Angles (°)

Atoms	Angle
C6–N1–C2	111.9(2)
C6–N1–S7	115.8(2)
C2–N1–S7	116.2(2)
N1–C2–C3	109.8(2)
N4–C3–C2	111.0(2)
C5–N4–C3	107.6(2)
C5–N4–C11	111.1(2)
C3–N4–C11	110.2(2)
N4–C5–C6	110.8(2)
N1–C6–C5	110.0(2)
O9–S7–O8	119.1(2)
O9–S7–N1	107.12(9)
O8–S7–N1	107.7(2)
O9–S7–C10	107.2(2)
O8–S7–C10	108.1(2)
N1–S7–C10	107.4(2)
N4–C11–C12	111.0(2)
N4–C11–C19	111.9(2)
C12–C11–C19	109.8(2)
C17–C12–C13	118.1(2)
C17–C12–C11	120.1(2)
C13–C12–C11	121.9(2)
C14–C13–C12	121.1(2)
C15–C14–C13	117.9(2)
C16–C15–F18	118.5(2)
C16–C15–C14	123.3(2)
F18–C15–C14	118.2(3)
C15–C16–C17	117.9(2)
C16–C17–C12	121.6(2)
C20–C19–C24	117.6(2)
C20–C19–C11	120.2(2)
C24–C19–C11	122.2(2)
C21–C20–C19	121.1(2)
C22–C21–C20	118.6(2)
C21–C22–F25	118.5(2)
C21–C22–C23	122.8(2)
F25–C22–C23	118.6(2)
C22–C23–C24	117.8(2)
C23–C24–C19	122.0(2)

piperazine [10]. This might be due to the steric hindrance caused by the bulky sulfonyl substituent at the fourth position [N1] of the piperazine ring. The molecule possesses a chiral center at C11. Because the title compound has crystallized in a centrosymmetric space group,

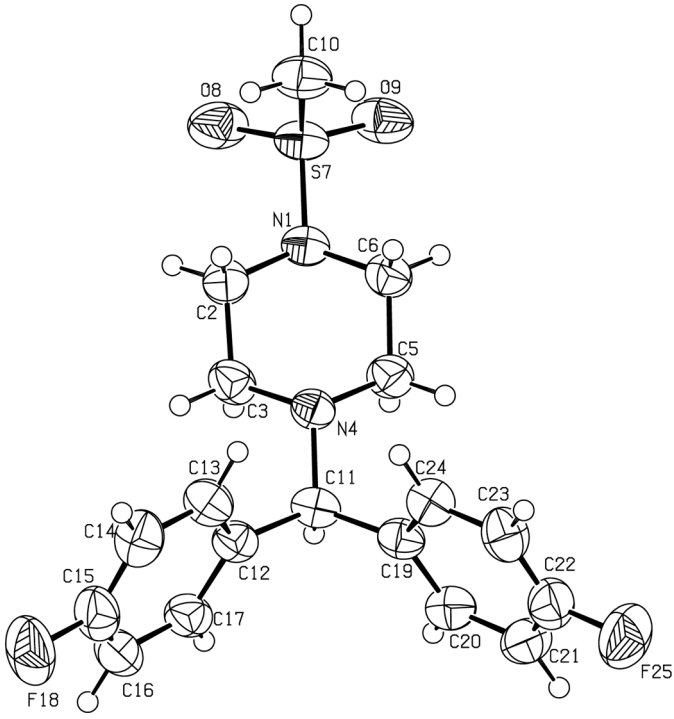

FIGURE 2 ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

we can surmise that the material is a racemic mixture. The geometry around the S atom is distorted from a regular tetrahedron, with the largest deviation observed for the O–S–O [O9–S7–O8 = 119.1(2)°] and O–S–N angles [O9–S7–Nl = 107.12(9)°]. This widening of the angles may be due to the repulsive interaction between the two short S=O bonds. The S–N bond distance lies within the expected range of 1.63– 1.69 Å. The reduction of the N1–S7–C10 angle to 107.4(2)° from the ideal tetrahedral value is attributed to the Thorpe–Ingold effect [12]. The structure exhibits a weak intermolecular hydrogen bond of the type C−H...F. The intermolecular hydrogen bond C6−H6B...F18 between the piperazine ring and the fluorophenyl ring has a length of 3.191(4) Å with an angle of 130(2)° with a symmetry code $-x,1/2+y,1/2-z$. The packing of the molecules as shown in Fig. 3 indicates that the molecules are interlinked by the hydrogen bonds when viewed down the *b* axis. The molecules form hydrogen-bonded dimers.

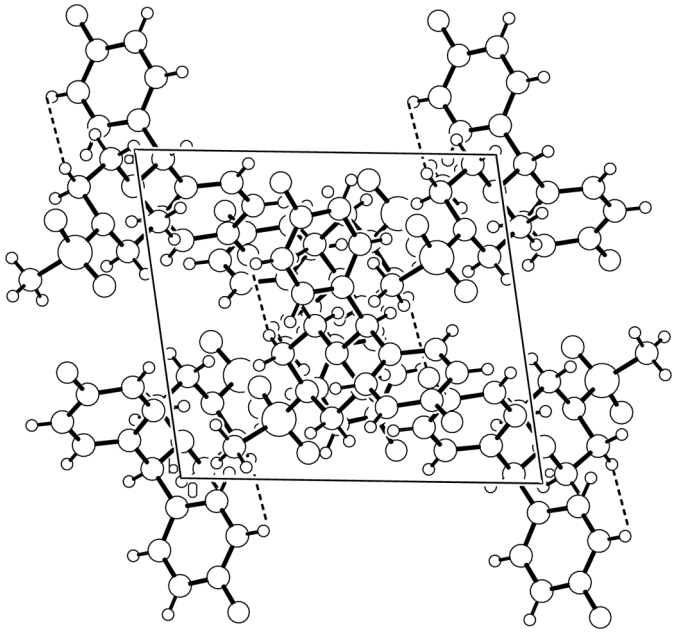

FIGURE 3 Packing of the molecules down the *b* axis. The dashed lines represent the hydrogen bonds.

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