Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl20

Crystal and Molecular Structure Studies of a Novel 1-Benzhydryl-piperazine Derivative: 1-Benzhydryl-4-(4-chloro-2-fluoro-benzene-sulfonyl)-piperazine

S. Naveen [a], C. S. Ananda Kumar [b], H. R. Manjunath [a], K. Vinaya [b], S. B. Benaka Prasad [b], M. A. Sridhar [a], K. S. Rangappa [b] & J. Shashidhara Prasad [a]

[a] Department of Studies in Physics, University of Mysore, Mysore, India

[b] Department of Studies in Chemistry, University of Mysore, Mysore, India

Version of record first published: 03 Jun 2009

To cite this article: S. Naveen, C. S. Ananda Kumar, H. R. Manjunath, K. Vinaya, S. B. Benaka Prasad, M. A. Sridhar, K. S. Rangappa & J. Shashidhara Prasad (2009): Crystal and Molecular Structure Studies of a Novel 1-Benzhydryl-piperazine Derivative: 1-Benzhydryl-4-(4-chloro-2-fluoro-benzene-sulfonyl)-piperazine, Molecular Crystals and Liquid Crystals, 503:1, 151-158

To link to this article: http://dx.doi.org/10.1080/15421400902841585

Mol. Cryst. Liq. Cryst., Vol. 503, 151–158, 2009

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/15421400902841585

Crystal and Molecular Structure Studies of a Novel 1-Benzhydryl-piperazine Derivative: 1-Benzhydryl-4-(4-chloro-2-fluoro-benzene-sulfonyl)-piperazine

S. Naveen[1], C. S. Ananda Kumar[2], H. R. Manjunath[1], K. Vinaya[2], S. B. Benaka Prasad[2], M. A. Sridhar[1]†, K. S. Rangappa[2], and J. Shashidhara Prasad[1]
[1]Department of Studies in Physics, University of Mysore, Mysore, India
[2]Department of Studies in Chemistry, University of Mysore, Mysore, India

The title compound 1-benzhydryl-4-(4-chloro-2-fluoro-benzenesulfonyl)-piperazine was synthesized, and structure of the product obtained was confirmed by the X-ray diffraction study. The compound $C_{23}H_{22}ClFN_2O_2S$ crystallizes in the monoclinic crystal class in the space group $P2_1/c$ with cell parameters a = 9.6180(7) Å, b = 12.9670(10) Å, c = 19.4020(12) Å, β = 114.716(3)°, and Z = 4. The structure has been solved by direct methods and refined to $R_1 = 0.0440$ for 3877 observed reflections with $I > 2\sigma(I)$. The structure reveals that the piperazine ring is in a chair conformation. The geometry around the S atom is distorted tetrahedral.

Keywords: chair conformation; distorted tetrahedron; piperazine; sulfonamide; X-ray crystallography

INTRODUCTION

Piperazine is a versatile heterocycle which contains four carbon atoms and two nitrogens at the first and the fourth positions (also called 1,4-hexahydropyrazine) [1]. Piperazine exists as small alkaline deliquescent crystals with a saline taste and is soluble in water, alcohol, glycerol, and glycols [2]. It is formed by the action of sodium glycol on ethylenediamine hydrochloride [3]. Piperazines have paved their way to become the most important blocks in modern day drug discovery. Owing to the number of positive hits encountered in biological screening with this class of heterocycles and its congeners, the

Address correspondence to M. A. Sridhar, Department of Studies in Physics, University of Mysore, Mysore 570 006, India. E-mail: mas@physics.uni-mysore.ac.in

piperazine scaffold certainly deserves to be the molecular backbone with versatile binding properties representing a frequently occurring binding motif. They provide potent and selective ligands for a range of different biological targets in medicinal chemistry, and thus piperazines are considered as privileged scaffolds [4].

The nitrogen atoms in the piperazine ring play an important role in biological research and drug manufacturing industry including the preparation of antihelminthic, antiallergic, antibacterial, antiasthmatic, and antimigraine agents. The piperazine ring and its derivatives are important cyclic components in the field of industry as raw materials for hardening of epoxy resins, corrosion inhibitors, insecticides, accelerators for rubber, urethane catalysts and antioxidants [1]. It is also reported that piperazine derivatives are important pharmacophores across a number of different therapeutic areas such as antibacterial [5], antifungal [6], antimalarial [7], antipsychotic agents [8], HIV protease inhibitors [9], antidepressant [10], and antitumour activities [11]. Some of the piperazine derivatives are used to treat psychosis and bipolar disorders [12], while others are neurokinin antagonists [13].

Sulfonamides are among the most widely used antibacterial agents in the world, chiefly because of their low cost, low toxicity, and excellent activity against common bacterial disease. Sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial, anticarbonic anhydrase, diuretic hypoglycaemic, antithyroid, and anticancer activities. From a structural point of view, sulfonamides are interesting because of their tendency to form different hydrogen-bond systems in the solid state by introducing various hydrogen-bond donors and acceptors as substituents into simple sulfonamide molecules. Piperazine sulfonamides exhibit diverse therapeutic activity such as antibacterial activity, MMP-3 inhibition, and carbonic anhydrase inhibition [14].

Recently, we have reported the synthesis and in vitro antiproliferative studies of medicinally important novel 1-benzhydrylpiperazine derivatives against human cancer cell lines [15]. This compound may serve as a new class of antiproliferative agent. This prompted us to study the molecular structure of the compound 1-benzhydryl-4-(4-chloro-2-fluoro-benzene-sulfonyl)-piperazine.

METHOD OF CRYSTALLIZATION

After synthesis [15] and purification, the pure product obtained was dissolved in ethyl acetate. Due to the slow evaporation of the solvent, white rectangular crystals grew after three days. A schematic diagram of the molecule is shown in Fig. 1.

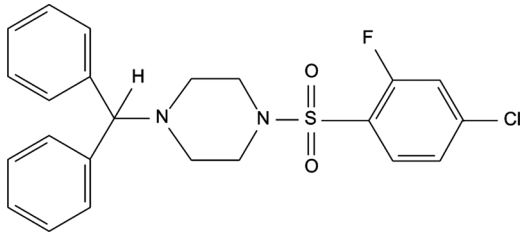

FIGURE 1 Schematic diagram.

CRYSTAL STRUCTURE DETERMINATION

A single crystal of the title compound with dimensions of $0.3 \times 0.27 \times 0.25$ mm was chosen carefully and glued to a thin glass fiber for X-ray diffraction study. The data were 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 [16]. The reflections were merged with Scalepack [17]. All of the frames could be indexed using a primitive monoclinic lattice. No absorption corrections were applied. The structure was solved by direct methods using SHELXS-97 [18]. All the non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement using SHELXL-97 [18] with isotropic temperature factors for all the atoms converged the residuals to $R_1 = 0.1769$. Refinement of the non-hydrogen atoms with anisotropic parameters was started at this stage. The hydrogen atoms were placed at chemically acceptable positions and were allowed to ride on the parent atoms. 271 parameters were refined with 3877 unique reflections which saturated the residuals to $R_1 = 0.0440$.

The ORTEP [19] diagram of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2. The details of the crystal data and refinement are given in Table 1.[1] Table 2 gives the list of

[1]"CCDC 705749 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 Crystal-lographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44(0)1223-336033. E-mail: de-posit@ccdc.cam.ac.uk"

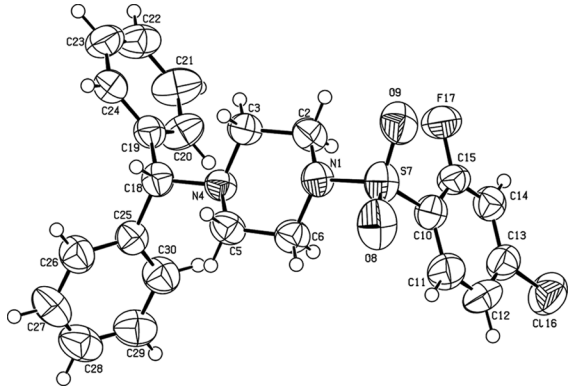

FIGURE 2 ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

TABLE 1 Crystal Data and Structure Refinement Table

Empirical formula	$C_{23}H_{22}ClFN_2O_2S$
Formula weight	444.94
Crystal color, habit	White, Rectangle
Temperature	293(2)K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell dimensions	$a = 9.6180(7)$ Å
	$b = 12.9670(10)$ Å
	c = 19.4020(12) Å
	$\beta = 114.716(3)^\circ$
Volume	2198.1(3) Å^3
Z	4
Density (calculated)	1.345 Mg/m^3
Absorption coefficient	0.299 mm^{-1}
F_{000}	928
Crystal size	$0.3 \times 0.3 \times 0.3$ mm
Theta range for data collection	2.33° to 25.02°
Index ranges	$-11 \le h \le 11$
	$-15 \le k \le 15$
	$-23 \le l \le 23$
Reflections collected	6994
Independent reflections	3877 [R(int) = 0.0266]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3877/0/271
Goodness-of-fit on F^2	1.035
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0440$, $wR2 = 0.1374$
R indices (all data)	$R1 = 0.0587$, $wR2 = 0.1602$
Largest diff. peak and hole	0.194 and -0.333 e · Å^{-3}

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Non-Hydrogen Atoms

Atom	x	y	z	U_{eq}
Nl	0.1029(2)	0.5218(2)	0.2694(1)	0.0585(5)
C2	0.0895(3)	0.5037(2)	0.3410(2)	0.0632(6)
C3	0.1333(3)	0.6008(2)	0.3881(1)	0.0606(6)
N4	0.2899(2)	0.6320(1)	0.4039(1)	0.0530(4)
C5	0.2970(3)	0.6522(2)	0.3315(2)	0.0619(6)
C6	0.2578(3)	0.5560(2)	0.2826(1)	0.0629(6)
S7	0.02472(8)	0.43692(5)	0.20161(3)	0.0689(2)
O8	0.0394(3)	0.4751(2)	0.13641(9)	0.0920(6)
O9	−0.1232(2)	0.4129(2)	0.1980(1)	0.0833(6)
C10	0.1418(3)	0.3260(2)	0.2308(1)	0.0601(6)
C11	0.2485(3)	0.3063(2)	0.2013(2)	0.0773(7)
C12	0.3452(4)	0.2229(2)	0.2256(2)	0.0841(8)
C13	0.3385(3)	0.1585(2)	0.2806(1)	0.0680(6)
C14	0.2346(3)	0.1747(2)	0.3112(1)	0.0614(6)
C15	0.1379(2)	0.2579(2)	0.2854(1)	0.0570(5)
C116	0.46205(9)	0.05505(6)	0.31254(5)	0.0958(3)
F17	0.0358(2)	0.2720(2)	0.31459(9)	0.0775(4)
C18	0.3353(2)	0.7251(2)	0.4526(1)	0.0566(5)
C19	0.3166(2)	0.7069(2)	0.5254(1)	0.0568(5)
C20	0.3804(3)	0.6217(2)	0.5707(2)	0.0773(7)
C21	0.3570(3)	0.6033(3)	0.6352(2)	0.0906(9)
C22	0.2702(3)	0.6705(3)	0.6558(2)	0.0869(9)
C23	0.2083(3)	0.7553(3)	0.6122(2)	0.0845(8)
C24	0.2310(3)	0.7737(2)	0.5473(2)	0.0708(7)
C25	0.4966(2)	0.7590(2)	0.4681(1)	0.0569(5)
C26	0.5265(3)	0.8624(2)	0.4641(2)	0.0735(7)
C27	0.6713(4)	0.8965(2)	0.4788(2)	0.0878(8)
C28	0.7880(3)	0.8284(3)	0.4968(2)	0.0862(9)
C29	0.7619(3)	0.7255(3)	0.5009(2)	0.0808(8)
C30	0.6164(3)	0.6902(2)	0.4871(2)	0.0720(7)

atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms. Tables 3 and 4 give the list of bond lengths and bond angles, respectively, which are in good agreement with the standard values.

The piperazine ring in the structure adopts almost a perfect chair configuration. This is confirmed by the puckering parameters [19] $Q = 0.5913(32)$ Å, $\theta = 177.50(28)^\circ$, and $\phi = 5(6)^\circ$, and the intraring torsion angles having positive and negative values ranging from $-56.6(2)^\circ$ to $61.0(2)^\circ$ for the atom sequence N1/C2/C3/N4/C5/C6. The conformation of the attached diphenylmethyl and the sulfonyl groups to the nitrogen atom of the piperazine ring are well described by the torsion angle values of $165.6(2)^\circ$ and $-177.9(3)^\circ$ for S7-N1-C6-C5 and C18-N4-C3-C2,

TABLE 3 Bond Lengths (Å)

Atoms	Length	Atoms	Length
N1-C2	1.466(3)	C14-C15	1.375(3)
N1-C6	1.471(3)	C15-F17	1.335(2)
N1-S7	1.637(2)	C18-C19	1.514(3)
C2-C3	1.508(3)	C18-C25	1.518(3)
C3-N4	1.463(3)	C19-C24	1.379(3)
N4-C5	1.460(3)	C19-C20	1.386(4)
N4-C18	1.482(3)	C20-C21	1.381(4)
C5-C6	1.517(3)	C21-C22	1.377(4)
S7-O8	1.419(2)	C22-C23	1.363(4)
S7-O9	1.429(2)	C23-C24	1.385(4)
S7-C10	1.768(2)	C25-C30	1.380(3)
C10-C15	1.392(3)	C25-C26	1.380(3)
C10-C11	1.392(3)	C26-C27	1.373(4)
C11-C12	1.374(4)	C27-C28	1.354(4)
C12-C13	1.378(4)	C28-C29	1.366(5)
C13-C14	1.374(3)	C29-C30	1.387(3)
C13-C116	1.726(3)		

TABLE 4 Bond Angles (°)

Atoms	Angle	Atoms	Angle
C2-N1-C6	111.6(2)	C13-C14-C15	117.9(2)
C2-N1-S7	117.4(1)	F17-C15-C14	117.3(2)
C6-N1-S7	115.7(1)	F17-C15-C10	119.7(2)
N1-C2-C3	109.1(2)	C14-C15-C10	123.0(2)
N4-C3-C2	111.1(2)	N4-C18-C19	110.5(2)
C5-N4-C3	107.8(2)	N4-C18-C25	111.4(2)
C5-N4-C18	110.4(2)	C19-C18-C25	111.9(2)
C3-N4-C18	111.3(2)	C24-C19-C20	117.9(2)
N4-C5-C6	110.8(2)	C24-C19-C18	120.6(2)
N1-C6-C5	109.0(2)	C20-C19-C18	121.5(2)
O8-S7-O9	120.1(1)	C21-C20-C19	121.1(2)
O8-S7-N1	107.4(1)	C22-C21-C20	120.1(3)
O9-S7-N1	107.4(1)	C23-C22-C21	119.3(3)
O8-S7-C10	106.4(1)	C22-C23-C24	120.7(3)
O9-S7-C10	109.1(1)	C19-C24-C23	120.9(3)
N1-S7-C10	105.8(1)	C30-C25-C26	118.2(2)
C15-C10-C11	117.2(2)	C30-C25-C18	122.4(2)
C15-C10-S7	123.0(2)	C26-C25-C18	119.3(2)
C11-C10-S7	119.8(2)	C27-C26-C25	121.2(3)
C12-C11-C10	120.8(3)	C28-C27-C26	120.2(3)
C11-C12-C13	119.9(2)	C27-C28-C29	119.9(3)
C14-C13-C12	121.3(2)	C28-C29-C30	120.4(3)
C14-C13-C116	118.7(2)	C25-C30-C29	120.0(3)
C12-C13-C116	120.1(2)		

respectively, i.e., they adopt *+antiperiplanar* and *−antiperiplanar* conformations, respectively. The bonds N1−S7 and N4−C18 make an angle 86.26(12)° and 73.20(19)°, respectively, with the Cremer and Pople plane [20] of the piperazine ring and thus are in the equatorial plane of the piperazine ring. The dihedral angle between the least-squares plane of the piperazine ring and the chlorofluorophenyl ring is 81.87(15)°. The piperazine ring makes an angle of 78.30(15)° and 72.59(16)° with the two phenyl rings [C19−C24] and [C25−C30], respectively. The dihedral angle between the two phenyl rings bridged by the carbon atom is 64.70(16)°. These values differ from the corresponding values reported for 1-benzhydryl piperazine [21] and l-benzhydryl-4-(2-nitro-benzenesulfonyl)-piperazine [22]. The geometry around the S atom is distorted from regular tetrahedron, with the largest deviation observed for the O-S-O [O9-S7-O8 = 120.1(l)°] and O-S-N angles [O9-S7-N1 = 107.4(1)°]. This widening of the angles is due to the repulsive interaction between the two short S=O bonds and the nonbonded interactions involving the two S–O bonds, resulting in the structure with less steric interference and the varied steric hindrance of the substituents. 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 105.9(2)° from the ideal tetrahedral value is attributed to the Thorpe-Ingold effect [23]. The sum of the bond angles around the piperazine N atoms (Nl = 329.7(2)° and N4 = 329.7(2)°, respectively) indicate that they adopt a pyramidal geometry and are sp^3 hybridized. The sulfonyl O atoms, O9 and O8, are oriented in *+synclinal* and *−synclinal* conformations, respectively, as indicated by the torsion angle values of 44.2(2)° and −50.2(2)° for C2-N1-S7–O9 and C6-N1-S7-O8. No classic hydrogen bonds were found in the structure.

ACKNOWLEDGMENTS

The authors are greatful to DST and Government of India for financial assistance under the projects SP/I2/FOO/93 and UGC-SAP(Phase-I)No.F.540/10/DRS/2004(SAP-I). One of the authors K. Vinaya, would like to thank CSIR, Government of India for the award of Senior Research Fellowship.

REFERENCES

[1] Hobart, A. H. (1992). *A Textbook of Practical Theraupetics*, Lee Brothers and Company.
[2] Elias, H. B. (1984). *A Textbook of Medicinal Chemistry*, Blatkinson Publications, 446.
[3] *Encyclopedia Brittanica*, 11th ed., 1910–1911.
[4] Dinsmore, C. J. (2002). *Tetrahedron*, *58*, 3297.

[5] Berkheij, M. (2005). *Tetrahedron Lett.*, *15*, 2369.
[6] Vacca, J. P., Dorsey, B. D., Schleif, W. A., Levine, R. B., McDaniel, S. L., Darke, P. L., Zugay, J., Quintero, J. C., Blahy, O. M., Sardana, B. B., Schlabach, A. J., Graham, P. I., Condra, J. H., Gotalib, L., Holloway, M. K., Lin, J., Chen, I. W., Vastag, K., Ostovic, D., Anderson, P. S., Emini, E. A., & Hu, J. R. (1994). *J. Med. Chem.*, *37*, 3443.
[7] Castles, T. R., Loth, E., Crawford, C. R., & Lee, C. C. (1970). *J. Pharma. Exper. Thera.*, *172*, 44.
[8] Choudhary, P., Kumar, R., & Verma, K. (2006). *Bioorg. Med. Chem.*, *14*, 1819.
[9] Rossen, K., Weissman, S. A., Sagar, J., Reamer, A., Askin, D. A., Volante, R. P., & Reider, P. J. (1995). *Tetrahedron Lett.*, *36*, 6419.
[10] EGYPT., US-3865828, 1975.
[11] Gordin, F. M. (1984). *Ann. Intern. Med.*, *100*, 495.
[12] Aicher, T. D., Chen, Z., Le Huerou, Y., Martin, G. M., Pineiro-Nunez, M. M., Rocco, V. P., Ruley, K. M., Schaus, J. M., Spinazze, P. G., & Tupper, D. (2004). Patent WO 200401895.
[13] Janssens, F. E., Sommen, F. M., De Boeck, B. C. A. G., Leenaerts, J. E., Ban Roosbroeck, Y. E. M., & Diels, G. S. M. (2004). Patent WO 2004033428.
[14] Ananda Kumar, C. S., Benaka Prasad, S. B., Vinaya, K., Chandrappa, S., Thimmegowda, N. R., Sunil Kumar, Y. C., Swarup, S., & Rangappa, K. S. (2008). *Eur. J. Med. Chem.*, *44*(3), 1223–1229.
[15] Ambrose, A. E., & William, W. J. (2001). *J. Med. Chem.*, *44*, 3849.
[16] Otwinowski, Z., & Minor, W. (1997). In: *Methods in Enzymology: Macromolecular Crystallography*, Carter, C. W. Jr. & Sweet, R. M. (Eds.), Academic Press: New York, Vol. 276, 307.
[17] Mackay, S., Gillmore, C. J., Edwards, C., & Shankland, K. (1999). *maXus, Computer Program for the Solution and Refinement of Crystal Structures*, Bruker Nonius. The Netherlands, MacScience, Japan and the University of Glasgow.
[18] Sheldrick, G. M. (1997). SHELXS-97. Program for Crystal Structure Solution. University of Göottingen, Germany.
[19] Spek, A. L. (1998). *Acta. Cryst.*, *A46*, C34.
[20] Cremer, D., & Pople, J. A.. (1975). *J. Amer. Chem. Soc.*, *97*, 1354.
[21] Naveen, S., Nanjundaswamy, S., Basappa, Prabhuswamy, B., Sridhar, M. A., Prasad, J. S., & Rangappa, K. S. (2006). *Anal. Sci.*, *22*, x41.
[22] Vinaya, K., Naveen, S., Ananda Kumar, C. S., Benakaprasad, S. B., Sridhar, M. A., Shashidhara Prasad, J., & Rangappa, K. S. (2008). *Struct. Chem.*, *19*, 765.
[23] Bassindale, A. (1984). *The Third Dimension in Organic Chemistry*, John Wiley and Sons: New York.