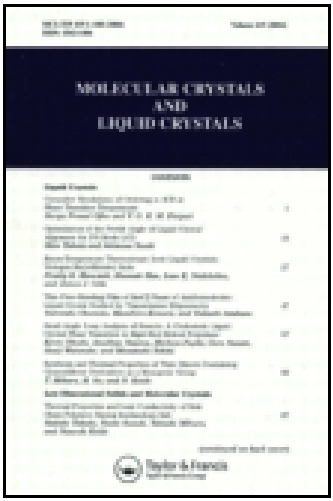

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Synthesis and Crystal Structure of 1-Benzhydryl-4-Methane-Sulfonyl-Piperazine

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Synthesis and Crystal Structure of 1-Benzhydryl-4-Methane-Sulfonyl-Piperazine

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The title compound, 1-benzhydryl-4-methanesulfonyl-piperazine, was synthesized by the nucleophilic substitution of 1-benzhydryl-piperazine with methyl sulfonyl chloride. The product obtained was characterized by spectroscopic techniques, and the structure was investigated by X-ray crystallography. The compound crystallizes in the monoclinic crystal class in the space group $P2_1/c$ with cell parameters $a = 9.5820(4)$ Å, $b = 16.8150(12)$ Å, $c = 13.5280(8)$ Å, $\beta = 127.270(5)^\circ$, and $V = 1734.5(2)$Å^3 for $Z = 4$. The structure reveals that the piperazine ring is in a chair conformation. There is a large discrepancy around the bond angles of the piperazine N atoms. The geometry around the S atom is distorted tetrahedral.

Keywords: 1-benzhydryl piperazine; chair conformation; distorted tetrahedron; nucleophilic substitution

INTRODUCTION

In today's drug discovery environment, piperazines are one of the most important building blocks. The epoxide-containing piperazines are protease inhibitors, which are of use in cardiovascular diseases [1–3]. Protease inhibitors such as NCO-700 have been used in cancer

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therapy, mainly as antimetastatic agents [4–6]. Unfused aromatic systems containing piperazine as the terminal substituent have shown excellent anticancer activity and DNA interaction [7]. They are also found in antitumor drugs used against colon, prostate, breast, and lung cancer and leukemia [8]. Chloroalkyl piperazines have shown potent bioactivity and increased anticancer activity [9]. Bisdioxopiperazines have been reported for their antitumor effects against two experimental lung cancer models *in vivo* [10]. The piperazine analogs have been shown to have potent antiproliferative activity against colon, prostate, breast, and lung tumors and leukemia in cell-based assays. Mechanistic evaluations have shown that the piperazines inhibit microtubule synthesis by a unique mechanism, inhibit cell cycle progression, and inhibit angiogenesis, which is critical to a tumor cell's ability to grow and metastasize.

A literature survey revealed that piperazine derivatives are important pharmacophores across a number of different therapeutic areas [11] and act as antifungal [12], antibacterial, antimalarial, antipsychotic [13], anti-HIV protease [14–16], antidepressant [17], and antitumour agents [8]. Piperazine sulfonamides are among the most widely used antibacterial [18] agents in the world, chiefly because of their low cost, low toxicity, and excellent activity against common bacterial disease. In continuation of our work on the synthesis of bioactive heterocycles and their biological evaluation [19–21], the title compound was sythesized. The compound obtained was characterized spectroscopically and finally confirmed by X-ray crystallography.

EXPERIMENTAL

Melting points were determined using a Selaco650 hot-stage melting-point apparatus and were uncorrected. The infrared (IR) spectra were recorded using a Jasco FTIR-4100 series instrument. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Shimadzu AMX 400 Bruker, 400-MHz spectrometer using dimethylsulfoxide (DMSO) as a solvent and TMS as internal standard (chemical shift in δ ppm). Spin multiplets are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), and m (multiplet). Mass and purity were recorded on a LC-MSD-Trap-XCT. Elemental (CHNS) analyses were obtained on Vario EL III Elementar. Silica-gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck thin-layer chromatography (TLC) plates. The reaction scheme is shown in Fig. 1.

Synthesis of 1-Benzhydryl-4-Bethanesulfonyl-Piperazine

A solution of 1-benzhydryl-piperazine (0.5 g, 1.98 mmol) in dry dichloromethane was taken and cooled to 0–5°C in an ice bath. Then

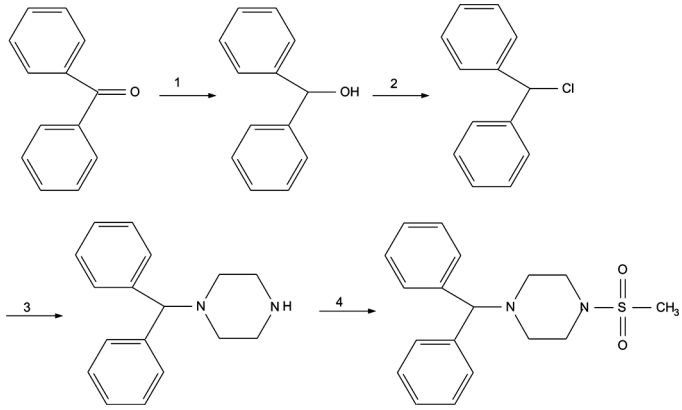

FIGURE 1 Reaction scheme. Reagents and conditions: 1) $NaBH_4$, methanol, rt, 5 h 2) thionyl chloride, MDC, 0–5°C, 4 h 3) piperazine, K_2CO_3, DMF, 80°C, 8 h 4) methane sulfonyl chloride, MDC, triethylamine, rt, 5–6 h.

triethylamine (0.601 g, 5.94 mmol) was added to the cold reaction mixture and stirred for 10 min. Then methyl sulfonyl chloride (0.226 g, 1.98 mmol) was added. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was monitored by TLC. On completion of the reaction, the solvent was removed under reduced pressure, and the residue was taken in water and extracted with ethyl acetate. Finally a water wash was given to the organic layer and dried with anhydrous sodium sulphate. The solvent was evaporated to get the crude product, which was purified by column chromatography over silica gel using hexane–ethyl acetate (8:2) as an eluent. The pure product obtained (0.556 g, 85%) was dissolved in ethyl acetate. White crystals developed after 3 days, due to the slow evaporation of the solvent. Mp: 192–194°C.

Anal. calcd. for $C_{18}H_{22}N_2O_2S$ (in %): C, 65.43; H, 6.71; N, 8.48; S, 9.70. Found: C, 65.40; H, 6.68; N, 8.45; S, 9.66. ^{1}H NMR (DMSO, 400 MHz): δ 7.38 (d, 4H, Ar−H), 7.27 (t, 4H, Ar−H), 7.15 (t, 2H, Ar−H), 4.25 (s, 1H, −CH−), 2.92 (bs, 4H, $-CH_2-$), 2.50 (bs, 4H, $-CH_2-$), 2.7 (s, 3H, $-CH_3-$). IR (KBr, cm^{-1}): 3029, 2959, 2850, 1346, 1285. MS: 331.56. Purity: 99.21.

Crystal Structure Determination

A single crystal of the title compound with dimensions $0.27 \times 0.25 \times 0.2$ mm was chosen for an X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with

TABLE 1 Crystal Data and Structure Refinement

Parameter	Value
CCDC deposition number	CCDC 650181
Empirical formula	$C_{18}H_{22}N_2O_2S$
Formula weight	330.44
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell dimensions	$a = 9.5820(4)$ Å $b = 16.8150(12)$ Å $c = 13.5280(8)$ Å $\beta = 127.270(5)^\circ$
Volume	1734.5(2) Å^3
Z	4
Density (calculated)	1.265 Mg/m^3
Absorption coefficient	0.198 mm^{-1}
F_{000}	704
Crystal size	$0.27 \times 0.25 \times 0.2$ mm
Theta range for data collection	2.25° to 25.02°
Index ranges	$-10 \le h \le 10$ $-20 \le k \le 20$ $-15 \le l \le 16$
Reflections collected	5314
Independent reflections	2805 [$R_{\text{int}} = 0.0224$]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2805/0/210
Goodness of fit on F^2	1.172
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0395$, $wR_2 = 0.1129$
R indices (all data)	$R_1 = 0.0484$, $wR_2 = 0.1357$
Extinction coefficient	0.023(3)
Largest diff. peak and hole	0.260 and −0.260 e.Å^{-3}

a normal focus, 3-kW sealed X-ray source (graphite monochromated MoK_α). The crystal-to-detector distance was fixed at 120 mm with a detector area of 441×240 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 [22]. The reflections were merged with Scalepack [23]. All of the frames could be indexed using a primitive orthorhombic lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97 [24]. Least-squares refinement using SHELXL-97 [25]

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the NonHydrogen Atoms [$U_{eq} = (1/3)\sum_i \sum_j U_{ij}(a_i^* a_j^*)(\mathbf{a_i} \cdot \mathbf{a_j})$]

Atom	x	y	Z	U_{eq}	
N1	0.1175(2)	0.03334(9)	0.3875(2)	0	.0450(4)
C2	0.2615(3)	0.0916(2)	0.4410(2)	0	.0545(5)
C3	0.2723(3)	0.1400(2)	0.5398(2)	0	.0534(5)
N4	0.1065(2)	0.18145(9)	0.4871(2)	0	.0428(4)
C5	−0.0305(3)	0.1213(2)	0.4410(2)	0	.0523(5)
C6	−0.0496(3)	0.0721(2)	0.3398(2)	0	.0524(5)
S7	0.10797(7)	−0.03449(3)	0.29624(5)	0	.0487(2)
08	−0.0389(2)	−0.08436(9)	0.2564(2)	0	.0645(5)
09	0.2784(2)	−0.0691(1)	0.3612(2)	0	.0709(5)
C10	0.0596(3)	0.01452(2)	0.1631(2)	0	.0559(5)
C11	0.1194(3)	0.2328(2)	0.5809(2)	0	.0471(5)
C12	0.2581(3)	0.2973(1)	0.6271(2)	0	.0496(5)
C13	0.3731(3)	0.3144(2)	0.7532(2)	0	.0657(7)
C14	0.4889(3)	0.3775(2)	0.7967(3)	0	.0880(1)
C15	0.4911(3)	0.4242(2)	0.7146(4)	0	.0930(2)
C16	0.3815(3)	0.4072(2)	0.5889(3)	0	.0780(8)
C17	0.2659(3)	0.3435(2)	0.5452(2)	0	.0601(6)
C18	−0.0569(3)	0.2713(2)	0.5292(2)	0	.0472(5)
C19	−0.1255(3)	0.2662(2)	0.5945(2)	0	.0604(6)
C20	−0.2838(4)	0.3042(2)	0.5494(3)	0	.0729(8)
C21	−0.3710(3)	0.3474(2)	0.4416(3)	0	.0732(7)
C22	−0.3052(3)	0.3521(2)	0.3756(3)	0	.0650(6)
C23	−0.1505(3)	0.3139(1)	0.4183(2)	0	.0535(5)

with isotropic temperature factors for all the nonhydrogen atoms converged the residual *R1* to 0.1674. 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. The hydrogen atoms were allowed to ride on their parent atoms. After eight cycles of refinement, the residual converged to 0.0395. The details of crystal data and refinement are given in Table 1.[†] 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 are in good agreement with the standard values. The

[†]CCDC 650181 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: deposit@ccdc.cam.ac.uk

TABLE 3 Bond Lengths (Å)

Atoms	Length
N1–C6	1.467(2)
N1–C2	1.475(3)
N1–S7	1.642(2)
C2–C3	1.514(3)
C3–N4	1.465(2)
N4–C5	1.466(2)
N4–C11	1.477(2)
C5–C6	1.513(3)
S7–O9	1.429(2)
S7–O8	1.434(2)
S7–C10	1.768(2)
C11–C12	1.526(3)
C11–C18	1.527(3)
C12–C13	1.390(3)
C12–C17	1.390(3)
C13–C14	1.383(4)
C14–C15	1.371(5)
C15–C16	1.383(5)
C16–C17	1.390(3)
C18–C19	1.388(3)
C18–C23	1.393(3)
C19–C20	1.400(3)
C20–C21	1.369(4)
C21–C22	1.373(4)
C22–C23	1.380(3)

ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2.

The piperazine ring in the structure adopts a perfect chair conformation with the atoms N1 and N4 deviating 0.216(2) Å and −0.269(2) Å respectively from the least-squares plane defined by the atoms C2/C3/C5/C6. This is confirmed by the puckering parameters [26] Q 0.5896(29) A, θ 175.18(26)°, and ϕ 356(4)°. The ring-puckering analysis revealed that the piperazine ring has a weighted average ring bond distance of 1.4832 (16, 98) Å and a weighted average torsion angle of 58.53 (12,119)°. The conformation of the attachment of the diphenylmethyl and the sulfonyl groups to the piperazine ring are well described by the torsion angle values of 169.4(2)° and −176.4(2)° for S7–N1–C6–C5 and C11–N4–C3–C2 respectively, that is, they adopt +*antiperiplanar* and −*antiperiplanar* conformations with respect to one another. The bonds N1–S7 and N4–C11 connecting the sulfonyl and the diphenylmethyl groups make an angle of 82.71(11)° and

TABLE 4 Bond Angles (°)

Atoms	Angle
C6–N1–C2	111.7(2)
C6–N1–S7	115.4(2)
C2–N1–S7	116.1(1)
N1–C2–C3	109.5(2)
N4–C3–C2	110.6(2)
C3–N4–C5	107.9(2)
C3–N4–C11	111.0(2)
C5–N4–C11	110.9(2)
N4–C5–C6	110.5(2)
N1–C6–C5	110.1(2)
O9–S7–O8	119.3(1)
O9–S7–N1	107.4(1)
O8–S7–N1	106.6(1)
O9–S7–C10	108.2(1)
O8–S7–C10	107.2(1)
N1–S7–C10	107.6(1)
N4–C11–C12	111.5(2)
N4–C11–C18	111.2(2)
C12–C11–C18	109.5(2)
C13–C12–C17	118.6(2)
C13–C12–C11	119.7(2)
C17–C12–C11	121.6(2)
C14–C13–C12	121.1(3)
C15–C14–C13	119.7(3)
C14–C15–C16	120.3(3)
C15–C16–C17	119.9(3)
C16–C17–C12	120.3(2)
C19–C18–C23	118.3(2)
C19–C18–C11	120.2(2)
C23–C18–C11	121.6(2)
C18–C19–C20	120.0(2)
C21–C20–C19	120.5(2)
C20–C21–C22	119.9(2)
C21–C22–C23	120.0(2)
C22–C23–C18	121.2(2)

74.46(18)° respectively with the Cremer and Pople plane [26] of the piperazine ring and thus are in the equatorial plane. The sum of the bond angles around the piperazine N atoms, N1 = 341.3(2)° and N4 = 329.0(2)°, respectively, indicate that they are sp^3 hybridized and that they adopt a pyramidal geometry.

The two phenyl rings bridged by the central carbon atom is planar within the experimental limits, and they make a dihedral angle of 75.65(16)° with each other. The piperazine ring makes an angle of

76.79(15)° and 78.48(14)° with the least-squares plane of the two phenyl rings C12 · · · C17 and C18 · · · C23, respectively. These values are comparable with the reported values of 76.84(13)° and 77.55(14)° reported for 1-[bis-(4-fluorophenyl)-methyl]-4-methane sulfonyl piperazine [27]. The angular disposition of the bonds about the S atom shows significant deviation from that of a regular tetrahedron with the largest deviations being observed for the O–S–O [O8–S7–O9 = 119.3(1)°] and O–S–N [O9–S7–N1 = 107.39(9)°] angles. This widening of the angles is due to the repulsive interactions between the S=O bonds and the nonbonded interactions involving the two S−O bonds and the varied steric hindrance of the substituents. The structure thus has less steric interference. The S–N bond distance [1.642(2) Å] lies within the expected range of 1.63–1.69 Å. The reduction of the N1–S7–C10 angle to 107.62(9)° from the ideal tetrahedral value is attributed to the Thorpe–Ingold effect [28]. The sulfonyl O atoms O8 and O9 are oriented in *+synclinal* and *−synclinal* conformations, respectively, as indicated by the torsion angle values of 50.7(2)° and −47.2(2)° for C2–N1–S7–O9 and C6–N1–S7–O8, respectively. The bond angle

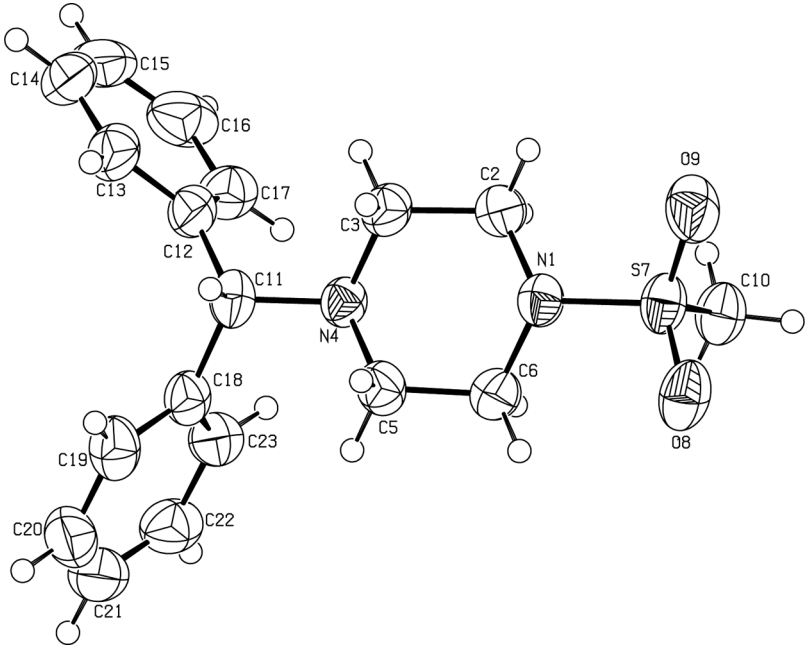

FIGURE 2 ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

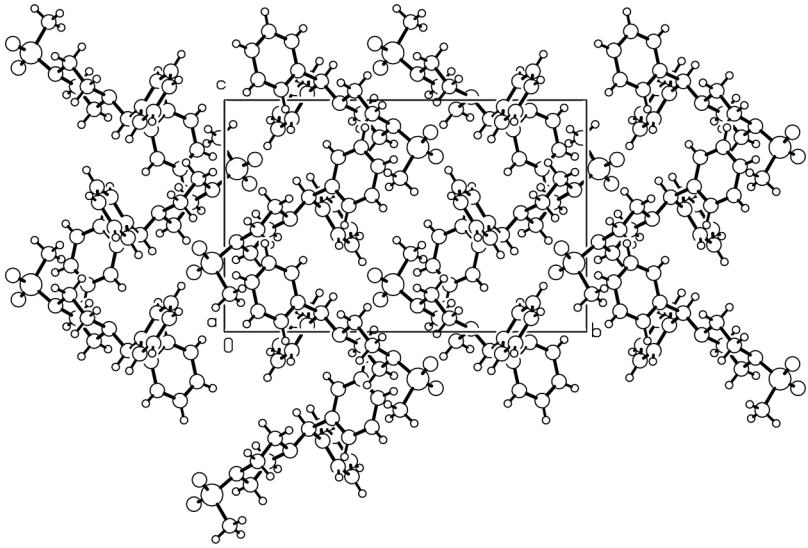

FIGURE 3 Packing of the molecules when viewed down the *a* axis.

C6–N1–C2–111.7(2)° is significantly larger than C3–N4–C5 = 107.9(2)°. This difference seems to result from the steric effects of the sulfonic group attached to the piperazine N atom. The packing of the molecules when viewed down the a axis indicates that the molecules are stacked in pairs (Fig. 3).

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REFERENCES

[1] Haga, N., Ishibashi, T., Hara, A., & Abiko, Y. (1985). *Pharmacology*, *31*, 208.
[2] Sashida, H. & Abiko, Y. (1985). *Biochempharm.*, *34*, 3875.
[3] Toyo-Oka, T., Kamishiro, T., Masaki, M., & Masaki, T. (1982). *Japanese Jeart J.*, *23*, 829.
[4] Berquin, I. M. & Sloane, B. F. (1994). *Prospectives in Drug Discovery and Design*, *2*, 371.
[5] Dimitroff, C. J., Sharma, A., & Bernacki, R. (1998). *J. Cancer Invest.*, *16*, 279.
[6] Lah, T. T. & Kos, J. (1998). *Biol. Chem.*, *379*, 125.
[7] Wilson, W. D., Henryk, J., Barton, F., Tanious, A., & Kong, S.-B., Strekowski, L. (1990). *Biol. Chem.*, *35*, 227.

[8] Hulme, C. (1999). *Tetrahedron Lett.*, *40*, 5295.
[9] Guo, C. C., Li, H. P., & Zhang, X. B. (2003). *Bioorg. Med. Chem.*, *11*, 1745.
[10] Lu, D.-Y., Xu, B., & Ding, J. (2004). *BMC Pharmacology*, *4*, 32.
[11] Berkheij, M. (2005). *Tetrahedron Lett.*, *15*, 2369.
[12] Upadhayaya, R. S., Sinha, N., Jain, S., Kishore, N., Chandra, R., & Arora, S. K. (2004). *Bioorg. Med. Chem.*, *12*, 2225.
[13] Choudhary, P., Kumar, R., & Verma, K. (2006). *Bioorg. Med. Chem.*, *14*, 1819.
[14] 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.
[15] Askin, D., Eng, K. K., Rossen, K., Purick, R. M., Wells, K. M., Volante, R. P., & Reider, P. J. (1994). *Tetrahedron Lett.*, *35*, 673.
[16] Rossen, K., Weissman, S. A., Sagar, J., Reamer, A., Askin, D. A., Volante, R. P., & Reider, P. J. (1995). *Tetrahedron Lett.*, *36*, 6419.
[17] Korosi, J., Szabo Nee, C., Gabriella, Lay Nee, K., Erdelyi Nee, P., Lujza, Balla Nee, K., Bolya, Kiszelly, & Eniko. (1975). EGYT US-3865828.
[18] Ambrose, A. E. & William, J. W. (2003). *J. Med. Chem.*, *44*, 3849.
[19] Priya, B. S., Basappa, Nanjunda swamy, S., & Rangappa, K. S. (2005). *Bioorg. Med. Chem.*, *13*, 2623.
[20] Nanjunda swamy, S., Basappa, Sarala, G., Priya, B. S., Gaonkar, S. L., Prasad, J. S., & Rangappa, K. S. (2006). *Bioorg. Med. Chem. Lett.*, *15*, 1811.
[21] Narendra Sharath Chandra, J. N., Sadashiva, C. T., Kavitha, C. V., & Rangappa, K. S. (2006). *Bioorg. Med. Chem.*, *14*, 6621.
[22] Otwinowski, Z. & Minor, W. (1997). In: *Methods in Enzymology*, Carter, C. W., Jr. & Sweet, R. M. (Eds.), Academic Press: New York, 276, 307–326.
[23] Mackay, S., Gillmore, C. J., Edwards, C., Stewart, N., & Shankland, K. (1999). *maXus Computer Program for the Solution and Refinement of Crystal Structures*, Bruker Nonius: Delft, The Netherlands.
[24] Sheldrick, G. M. (1997). *SHELXS-97*: *Program for Crystal Structure Solution*, University of Gottingen: Gottingen, Germany.
[25] Sheldrick, G. M. (1997). *SHELXL-97*: *Program for Crystal Structure Solution*, University of Gottingen: Gottingen, Germany.
[26] Cremer, D. & Pople, J. A. (1975). *J. Amer. Chem. Soc.*, *B12*, 1354.
[27] Naveen, S., Sadashiva, C. T., Narendra Sharath Chandra, J. N., Sridhar, M. A., Shashidhara Prasad, J., & Rangappa, K. S. (2007), *Mol. Cryst. Liq. Cryst.*, *469*, 89.
[28] Bassindale, A. (1984). *The Third Dimension in Organic Chemistry*, John Wiley and Sons: New York, ch. 1, 11.