Molecular Crystals and Liquid Crystals

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

Synthesis and Crystal Structure of 1-(2-Nitro-benzenesulfonyl)-piperidin-4-yl-diphenyl-methanol

S. B. Benaka Prasad [a], S. Naveen [b], C. S. Anandakumar [a], K. Vinaya [a], N. S. Linge Gowda [a], M. A. Sridhar [b], J. Shashidhara Prasad [b] & K. S. Rangappa [a]

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

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

Version of record first published: 22 Sep 2010

To cite this article: S. B. Benaka Prasad, S. Naveen, C. S. Anandakumar, K. Vinaya, N. S. Linge Gowda, M. A. Sridhar, J. Shashidhara Prasad & K. S. Rangappa (2008): Synthesis and Crystal Structure of 1-(2-Nitro-benzenesulfonyl)-piperidin-4-yl-diphenyl-methanol, Molecular Crystals and Liquid Crystals, 482:1, 145-154

To link to this article: http://dx.doi.org/10.1080/15421400801914988

Mol. Cryst. Liq. Cryst., Vol. 482, pp. 145–154, 2008

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/15421400801914988

Synthesis and Crystal Structure of 1-(2-Nitro-benzenesulfonyl)-piperidin-4-yl-diphenyl-methanol

S. B. Benaka Prasad[1], S. Naveen[2], C. S. Anandakumar[1], K. Vinaya[1], N. S. Linge Gowda[1], M. A. Sridhar[2], J. Shashidhara Prasad[2], and K. S. Rangappa[1]
[1]Department of Studies in Chemistry, University of Mysore, Mysore, India
[2]Department of Studies in Physics, University of Mysore, Mysore, India

The title compound 1-(2-nitro-benzenesulfonyl)-piperidin-4-yl-diphenyl-methanol was synthesized by the condensation of [piperidin-4-yl]-diphenyl-methanol with 2-nitro benzene sulfonylchloride in methylene dichloride as solvent and triethylamine as the base. 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 Pc with cell parameters $a = 9.2360(4)$ Å, $b = 10.7750(8)$ Å, $c = 13.4110(8)$ Å, $\beta = 124.162(4)^\circ$, $V = 1104.35(12)$Å^3 *for* $Z = 2$. *The structure reveals that the piperidine ring is in a chair conformation. There is a large discrepancy around the bond angles of the piperidine N atom. The geometry around the S atom is distorted tetrahedron.*

Keywords: conformation; distorted tetrahedron; hydrogen bond; nitrobenzene sulfonyl piperidine

INTRODUCTION

In the last decade, combinational chemistry has represented the most promising approach to allow entry to a great number of biological targets arising from molecular biology and genomic studies [1]. In fact, the possibility of synthesizing libraries of hundreds of compounds in a suitable scalable fashion has determined an epochal change in medicinal chemistry, especially in the fundamental processes of lead

Received October 4, 2007; accepted November 8, 2008.
Address correspondence to Dr. K. S. Rangappa, Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore 570 006, India. E-mail: rangappaks@gmail.com

discovery and optimization [2]. The importance of synthesizing the organic compounds nitrogen heterocycles, especially of the piperidine type as subunits of bioactive molecular stimulate the chemist for the development of new synthetic methods [3]. Piperidine is among the most important heterocyclic compounds, which exhibits its therapeutic activity due to its conformationally flexible nature. The accentuated interest in the piperidine class of opiate analgesics continues to be expressed in the pharmaceutical community and biological properties of these agents have been the subject of on-going investigations [4].

Piperidine derivatives possess broad pharmacological action on central nervous system (CNS), especially on dopaminergic neurotransmission and HIV transcriptase and protease inhibitors [5]. Piperidine is a key structural component of successful anti-Parkinsons drugs [6] and displays antipsychotic, antiviral [7], metabolic [8], antimicrobial [9], antidepresants [10], acetylcholinesterase inhibitors [11], anticonvulsants [12], and antimalarial activity [13]. In continuation of our work on the synthesis of bioactive heterocycles and their biological evaluation [14], the title compound was synthesized. The compound obtained was characterized spectroscopically and finally confirmed by X-ray crystallography.

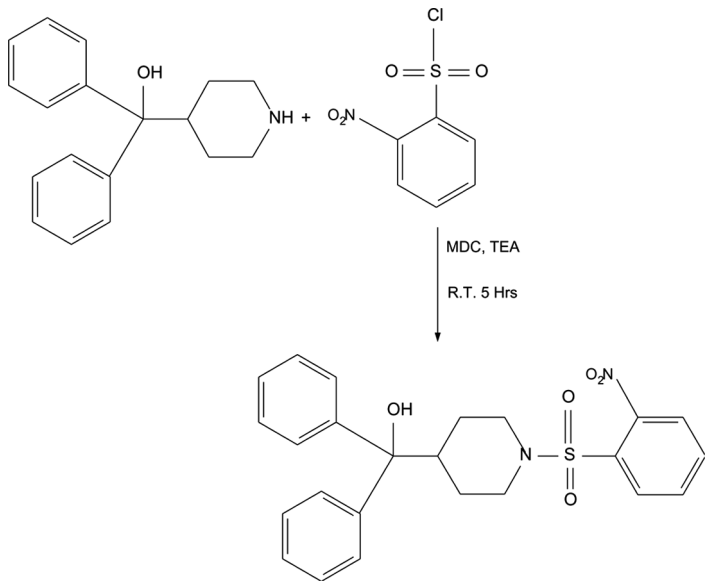

FIGURE 1 Reaction scheme.

EXPERIMENTAL

Melting points were determined using SELACO-650 hot stage melting point apparatus and were uncorrected. The Infrared (IR) spectra were recorded using a Jasco FTIR-4100 series. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Shimadzu AMX 400-Bruker, 400 MHz spectrometer using $CDCl_3$ 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 made TLC plates. The reaction scheme is shown in Figure 1.

TABLE 1 Crystal Data and Structure Refinement Table

CCDC Deposition Number	CCDC 660794
Empirical formula	$C_{24}H_{24}N_2O_5S$
Formula weight	452.51
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*Pc*
Cell dimensions	$a = 9.2360(4)$ Å $b = 10.7750(8)$ Å $c = 13.4110(8)$ Å $\beta = 124.162(4)^\circ$
Volume	1104.35(12) Å^3
Z	2
Density (calculated)	1.361 Mg/m^3
Absorption coefficient	0.186 mm^{-1}
F_{000}	476
Crystal size	0.27 × 0.25 × 0.2 mm
Theta range for data collection	2.63° to 25.03°
Index ranges	$-10 \le h \le 10$ $-12 \le k \le 11$ $-15 \le l \le 15$
Reflections collected	3102
Independent reflections	3102 [R(int) = 0.0000]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3102/2/290
Goodness-of-fit on F^2	1.195
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0367$, $wR2 = 0.1000$
R indices (all data)	$R1 = 0.0379$, $wR2 = 0.1015$
Extinction coefficient	0.105(9)
Largest diff. peak and hole	0.356 and -0.254 e·Å^{-3}

Synthesis of [1-(2-Nitro-benzenesulfonyl)-piperidin-4-yl]-diphenylmethanol

The compound [1-(2-nitro-benzenesulfonyl)-piperidin-4-yl]-diphenyl-methanol was obtained by the condensation of [piperidin-4-yl]-diphenyl-methanol (1.0 g, 3.74 mmol). First [piperidin-4-yl]-diphenyl-methanol was dissolved in dichloromethane (10 ml) and cooled to 0–5°C in an ice bath. Then triethylamine (1.136 g, 11.22 mmol) was added to the cold reaction mixture and stirred for 10 minutes and then

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Nonhydrogen Atoms

Atom	x	y	z	U_{eq}
N1	0.7336(2)	0.3808(2)	0.2085(2)	0.0510(5)
C2	0.5826(3)	0.3462(2)	0.2125(2)	0.0529(5)
C3	0.6487(3)	0.2871(2)	0.3344(2)	0.0514(5)
C4	0.7636(3)	0.1742(2)	0.3578(2)	0.0458(5)
C5	0.9136(3)	0.2143(2)	0.3464(2)	0.0543(5)
C6	0.8447(3)	0.2736(3)	0.2249(2)	0.0551(6)
S7	0.70581(7)	0.49136(5)	0.11771(6)	0.0525(2)
O8	0.8719(3)	0.5160(2)	0.5160(2)	0.0709(6)
O9	0.6152(3)	0.5895(2)	0.1306(2)	0.0681(5)
C10	0.5688(3)	0.4350(2)	−0.0324(2)	0.0493(5)
C11	0.6452(3)	0.3610(2)	−0.0761(2)	0.0575(6)
C12	0.5474(4)	0.3137(3)	−0.1908(3)	0.0676(7)
C13	0.3701(4)	0.3381(3)	−0.2648(3)	0.0749(8)
C14	0.2924(4)	0.4112(3)	−0.2247(3)	0.0720(8)
C15	0.3913(3)	0.4593(3)	−0.1089(2)	0.0547(6)
N16	0.2986(3)	0.5421(3)	−0.0751(2)	0.0693(6)
O17	0.2408(4)	0.4963(3)	−0.0204(3)	0.0986(9)
O18	0.2788(4)	0.6483(2)	−0.1077(3)	0.0957(8)
C19	0.8296(3)	0.1114(2)	0.4801(2)	0.0487(5)
O20	0.9426(2)	0.1955(2)	0.5766(1)	0.0634(5)
C21	0.6735(3)	0.0731(2)	0.4862(2)	0.0467(5)
C22	0.6455(4)	0.1234(3)	0.5682(3)	0.0708(8)
C23	0.5051(5)	0.0854(4)	0.5719(3)	0.0882(1)
C24	0.3929(4)	−0.0033(3)	0.4975(3)	0.0684(7)
C25	0.4193(4)	−0.0558(3)	0.4156(3)	0.0761(8)
C26	0.5577(4)	−0.0175(3)	0.4106(3)	0.0695(7)
C27	0.9379(3)	−0.0055(2)	0.5030(3)	0.0569(6)
C28	1.0542(4)	−0.0443(3)	0.6229(3)	0.0773(9)
C29	1.1429(5)	−0.1551(4)	0.6479(5)	0.0985(1)
C30	1.1200(5)	−0.2290(4)	0.5587(5)	0.1010(1)
C31	1.0069(4)	−0.1928(3)	0.4410(5)	0.0874(1)
C32	0.9155(4)	−0.0810(3)	0.4125(3)	0.0686(7)

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

2-Nitrobenzenesulfonyl chloride (0.830 g, 3.74 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 5 hours. The reaction mass was monitored by thin-layer chromatography (TLC). After the completion of the reaction, the solvent was removed under reduced pressure and the residue was taken in water and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulphate. White crystalline solid was obtained and was kept in ethyl acetate:methanol (3:1) for three days. Pure light yellow crystals were obtained after three days due to the slow evaporation of the solvent. MP: 226°C. Yield: 15.2 g, 90%.

Anal. Calcd. for $C_{24}H_{24}N_2O_5S$ (in %): C: 63.65, H: 5.32, N: 6.19, S: 7.06. Found C: 63.61, H: 5.29, N: 6.15, S: 7.02.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (d, 1H, Ar-H), 8.11 (d, 1H, Ar-H), 7.81 (m, 1H, Ar-H), 7.62 (m, 1H, Ar-H), 7.2–7.4 (m,10H, Ar-H), 2.8 (t, 4H, piperidine-CH_2–), 2.15 (s, –OH), 1.5–1.7 (m, 5H, piperidine-CH).

IR (KBr, cm^1): $-SO_2$ str 1350 (asymmetric str), $-SO_2$ 1279 str (symmetric str), –OH. FAB Ms m/z (%) 453.14.

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

TABLE 3 Bond Lengths (Å)

Atoms	Length	Atoms	Length
N1-C2	1.473(3)	N16-O18	1.202(4)
N1-C6	1.478(3)	N16-O17	1.227(4)
N1-S7	1.618(2)	C19-O20	1.438(3)
C2-C3	1.526(3)	C19-C27	1.529(3)
C3-C4	1.526(3)	C19-C21	1.545(3)
C4-C5	1.538(3)	C21-C22	1.374(4)
C4-C19	1.548(3)	C21-C26	1.381(4)
C5-C6	1.518(3)	C22-C23	1.387(5)
S7-O9	1.418(2)	C23-C24	1.350(5)
S7-O8	1.435(2)	C24-C25	1.373(5)
S7-C10	1.778(2)	C25-C26	1.381(4)
C10-C15	1.385(3)	C27-C32	1.377(5)
C10-C11	1.395(4)	C27-C28	1.405(4)
C11-C12	1.372(4)	C28-C29	1.379(5)
C12-C13	1.383(5)	C29-C30	1.351(7)
C13-C14	1.363(5)	C30-C31	1.373(7)
C14-C15	1.385(4)	C31-C32	1.396(4)
C15-N16	1.474(4)		

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 [15]. The reflections were merged with Scalepack [16]. 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 [17]. Least-squares refinement using SHELXL-97 [18] with isotropic temperature factors for all the nonhydrogen atoms converged the residual *R1* to 0.1216. Subsequent refinements were

TABLE 4 Bond Angles (°)

Atoms	Angle	Atoms	Angle
C2-N1-C6	112.9(2)	O18-N16-O17	124.9(3)
C2-N1-S7	117.4(1)	O18-N16-C15	117.4(3)
C6-N1-S7	119.4(2)	O17-N16-C15	117.6(3)
N1-C2-C3	109.1(2)	O20-C19-C27	106.0(2)
C4-C3-C2	111.5(2)	O20-C19-C21	110.4(2)
C3-C4-C5	108.4(2)	C27-C19-C21	107.1(2)
C3-C4-C19	112.4(2)	O20-C19-C4	109.5(2)
C5-C4-C19	112.8(2)	C27-C19-C4	113.4(2)
C6-C5-C4	111.5(2)	C21-C19-C4	110.4(2)
N1-C6-C5	109.0(2)	C22-C21-C26	116.7(3)
O9-S7-O8	119.2(1)	C22-C21-C19	122.5(2)
O9-S7-N1	108.2(1)	C26-C21-C19	120.7(2)
O8-S7-N1	107.7(1)	C21-C22-C23	120.8(3)
O9-S7-C10	107.4(1)	C24-C23-C22	121.8(3)
O8-S7-C10	105.7(1)	C23-C24-C25	118.4(3)
N1-S7-C10	108.2(1)	C24-C25-C26	120.0(3)
C15-C10-C11	117.6(2)	C21-C26-C25	122.1(3)
C15-C10-S7	124.7(2)	C32-C27-C28	118.3(3)
C11-C10-S7	117.7(2)	C32-C27-C19	123.5(2)
C12-C11-C10	121.0(2)	C28-C27-C19	117.9(3)
C11-C12-C13	120.2(3)	C29-C28-C27	120.2(4)
C14-C13-C12	120.1(3)	C30-C29-C28	121.3(4)
C13-C14-C15	119.7(3)	C29-C30-C31	119.4(3)
C10-C15-C14	121.4(3)	C30-C31-C32	120.8(4)
C10-C15-N16	122.4(2)	C27-C32-C31	120.0(3)
C14-C15-N16	116.1(2)		

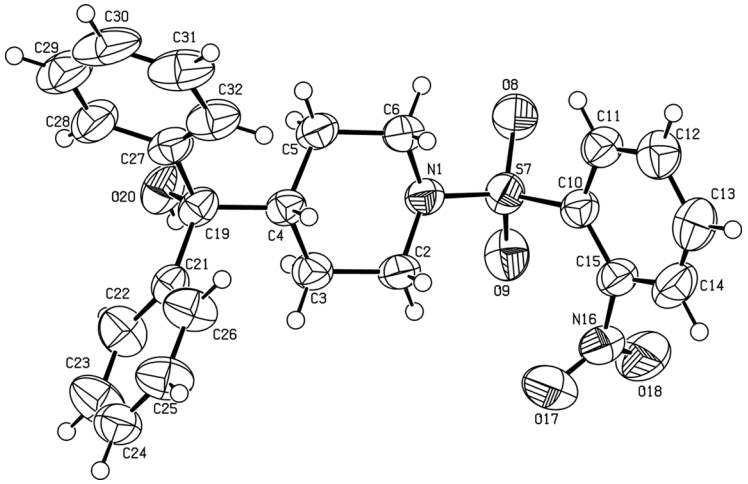

FIGURE 2 ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

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 0.0367. The details of crystal data and refinement are given in Table l.[1] Table 2 gives the atomic coordinates and equivalent thermal parameters of the nonhydrogen atoms. Table 3 and Table 4 give the list of bond lengths and bond angles, respectively, which are in good agreement with the standard values. The ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Figure 2.

A study of the torsion angles, asymmetric parameters, and least-squares plane calculations reveals that the piperidine ring in the structure is in a chair conformation with the atoms N1 and C4 deviating $-0.243(2)$ Å and $0.236(3)$ Å from the Cremer and Pople plane [19] defined by the atoms C2/C3/C5/C6. This is confirmed by the puckering parameters $Q = 0.5861(28)$ Å, $\theta = 180.00(26)^\circ$, and $\varphi = 175(27)^\circ$. The bonds N1−S7 and C4−C19 make an angle of $84.15(11)^\circ$ and $72.96(14)^\circ$ with the Cremer and Pople plane of the

[1]"CCDC 660794 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"

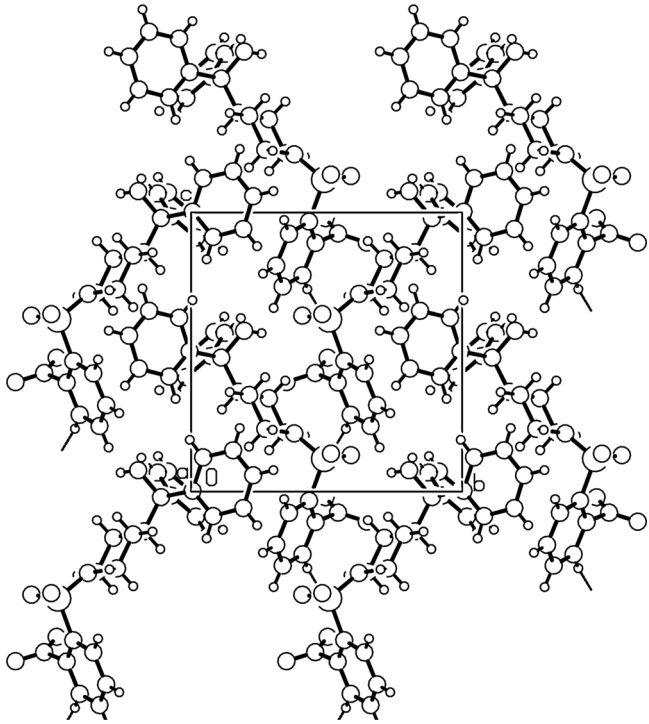

FIGURE 3 Packing of the molecules when viewed down the *a* axis.

piperidine ring and thus lie in the equatorial plane of the piperidine ring. The dihedral angle between the least-squares plane of the piperidine ring and the phenyl ring C21−C26 is 87.40(14)° implying that the phenyl ring is nearly perpendicular to the plane of the piperidine ring. The other phenyl ring C27−C32 makes a dihedral angle of 59.62(18)° with the least-squares plane of the piperidine ring. The dihedral angle between the two phenyl rings bridged by the alcoholic group is 84.74(19)°. The nitrophenyl ring is inclined at an angle of 66.91(13)° to the sulfonyl plane. The nitro group is twisted out of the plane of the adjacent aryl ring as indicated by the torsion angle values of −81.0(4)° and −87.2(4)° for O18-N16-C15-C14 and O17-N16-C15-C10, respectively. The sulfonyl atoms O8 and O9 are oriented in −synclinal and +synclinal conformations as indicated by the torsion angle values of −42.0(2)° and 45.1(2)° for C6-N1-S7-O8 and C2-N1-S7-O9, respectively.

The geometry around the S atom is distorted tetrahedron, with the largest deviations observed for the O-S-O [O8-S7-O9 = 119.2(l)°] and

O-S-N angles [O9 S7N1 = 1O8.2(1)°. This widening of angles is due to the repulsive interaction between the two short S=O bonds. The S-N bond distance lies within the expected range of 1.60–1.69 Å. The reduction of the N1-S7-C10 angle to 108.2(1)° from the ideal tetrahedral value is attributed to the Thorpe-Ingold effect [20]. The structure exhibits an intermolecular hydrogen bond of the type C-H ··· O. The intermolecular hydrogen bond C14-H14 ... O8 between the nitrophenyl ring and the sulfonyl group has a length of 3.323(5)° and an angle of 167° with a symmetry code $-1+x, 1-y, -1+z$. The packing of the molecules when viewed down the a axis indicates that the molecules are stacked in pairs and they form hydrogen bonded dimers (Fig. 3).

ACKNOWLEDGMENTS

The authors are grateful to DST and CSIR, New Delhi for financial support under the projects SP/I2/FOO/93 and No. 01(1904)/03/EMR-II 2004. Also, the CHNS, IR data obtained from the instrument granted by DST-FIST and UGC-SAP (phase I) are greatly acknowledged.

REFERENCES

[1] Ganesan, A. (2002). *Drug Discovery Today.*, *7*, 47.
[2] Franzen, R. G. (2000). *J. Comb. Chem.*, *2*, 195.
[3] Cordell, G. A. (Ed.). (2000). *The Alkaloids Chemistry and Biology*, Academic Press: San Diego, vol. 54.
[4] Colapret, J. A., Diamantidis, G., & Spencer, H. K. (1989). *J. Med. Chem.*, *33*, 968.
[5] Pomerantz, R. J. (1999). *J. Am. Med. Assoc.*, *282*(12), 1177.
[6] Klockgether, T., Wullner, J. P., Steinbach, Petersen, V., Turski, L., & Loschmann, P. A. (1996). *Eur. J. Pharmacol.*, *301*, 67.
[7] Willoughby, C. A., Berk, S. C., Rosauer, K. G., Degrado, S., Chapman, K. T., Gould, S. L., Springer, M. S., Malkowitz, L., Schleif, W. A., Hazuda, D., Miller, M., Kessler, J., Danzeisen, R., Holmes, K., Lineberger, J., Carella, A., Carver, G., & Emini, E. A. (2001). *Bioorg. Med. Chem. Lett.*, *11*, 3137.
[8] Lihu Yang, Greg Morriello, Arthur, A. P., Kwan Leung, Tom Jacks, Kang Cheng, Klaus, D. S., William Feeney, Wanda, W. S. C., Shuet-Hing, L. C., & Roy, G. S. (1998). *J. Med. Chem.*, *41*(14), 2439.
[9] Baikenova, G. G., Abdulina, G. A., Gazaliev, A. M., Fazylov, S. D., & Kudaibergenova, S. Z. (2004). *Pharmaceutical Chemistry Journal.*, *38*(1), 19.
[10] Amat, M., Hidalgo, J., & Bosch, J. (1996). *Tet. Asym.*, *7*, 1845.
[11] Contreras, J. M., Parrot, I., Sippl, W., Rival, Y. M., & Wermuth, C. G. (2001). *J. Med. Chem.*, *44*, 2707.
[12] Reddy, P. A., Woodward, K. E., McIlheran, S. M., Hsiang, B. C. H., Latifi, T. N., Hill, M. W., Rothman, S. M., Ferrendelli, J. A., & Covey, D. F. (1998). *J. Med. Chem.*, *40*, 44.

[13] Padmanilayam, M., Scorneaux, B., Dong, Y., Chollet, J., Matile, J., Charman, S. A., Creek, D. J., Charman, W. N., Tomas, J. S., & Scheurer, C. (2006). *Bioorg. Med. Chem. Lett.*, *16*(21), 5542.
[14] Benaka Prasad, S. B., Naveen, S., Anandakumar, C. S., Sunil Kumar, Y. C., Sridhar, M. A., Shashidhara Prasad, J., & Rangappa, K. S. (2007). *Polish J. Chem.*, *81*, 1191–1199.
[15] Otwinowski, Z. & Minor, W. (1997). In *Methods in Enzymology*, Carter Jr., C. W. & Sweet, R. M. (Eds.), Academic Press: New York, 307.
[16] 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: The Netherlands.
[17] Sheldrick, G. M. (1997). SHELXS-97: *Program for Crystal Structure Solution*. University of Göttingen: Germany.
[18] Sheldrick, G. M. (1997). SHELXL-97: *Program for Crystal Structure Solution*. University of Göttingen: Germany.
[19] Cremer, D. & Pople, J. A. (1975). *J. Amer. Chem. Soc.*, *B12*, 13541358.
[20] Bassindale, A. (1984). *The Third Dimension in Organic Chemistry*, John Wiley and Sons: New York.