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Crystal Structure Analysis of 4-Chloro-2{[(2-hydroxy-5-methylphenyl)amino]methyl}5-methylphenol

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Abstract

The crystal structure of the saliciline derivatives 4-chloro-2{[(2-hydroxy-5-methylphenyl)amino]methyl}5-methylphenol ($C_{15}H_{15}ClNO_2$) has been determined from single crystal X-ray diffraction data. In the title compound crystallizes in the monoclinic space group $P2_1/c$ with unit cell dimension a= 11.5241(2) Å, b=8.733(2) Å and c= 13.649(2) Å [α=90°, β= 130.876(2)° and γ= 90°]. the title compound are essentially planar conformation. The compound lies across a crystallographic inversion centre and adopts E configurations with respect to the C-N bonds. The crystal packing of the molecules of compound is stabilized through weak O-H...O inter molecular interactions

Keywords: Chromene, Schiff Base Ligand, Single Crystal Structure, X-ray Diffraction

1. Introduction

Salicylidene is a Schiff base ligand. A Schiff base named after Hugo Schiff, is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group . Schiff bases in a broad sense have the general formula $R_1R_2C=NR_3$, where R is an organic side chain. The chain on the nitrogen makes the Schiff base a stable imine.

The electrophilic carbon atoms of aldehydes and ketones can be targets of nucleophilic attack by amines. The end result of this reaction is a compound in which the C=O double bond is replaced by a C=N double bond. This type of compound is known as an Imine or Schiff base. Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilizers.

Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties[1,2]. Imine or azomethine groups are present in various natural (Ancistrocladidine), natural-derived (Chitosan), and non-natural (N-Salicylidene-2-hydroxyaniline) compounds. The imine group present in such compounds has been shown to be critical to their biological activities like anti malarial, antifungal and anti bacterial[3,4].

Salicylidene acylhydrazides are promising compounds for the treatment of infections caused by Gram-negative pathogens. They are inhibitors of bacterial type III secretion (T3S) in Yersinia, Salmonella, Shigella and enterohemorrhagic Escherichia coli. Salicylideneamino-2-thiophenol (SAL-2) can be a potent anti-inflammatory agent for treatment of inflammatory-related diseases[5].

Chloro-salicylidene aniline with Co(II) and Cu(II) were screened for antibacterial activity against several bacterial strains, namely Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa[6]. Salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate are a good platform for the design of new antiviral agents[7].

In view of these biological and medicinal importance of the Salicylidene derivatives, X-ray crystallographic studies of the following one compound have been carried out to obtain detailed information on the molecular conformation in the solid state. The IUPAC name and chemical diagram of the compounds are given in Fig 1.

IUPAC name of the compound: **4-chloro-2{[(2-hydroxy-5-methylphenyl)amino]methyl}5-methylphenol**

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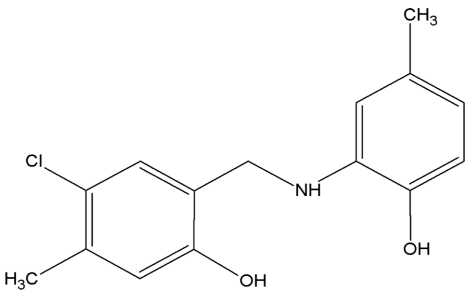

Fig. 1. shows schematic diagram.

2. Material and Methods

The title compound is crystallized by simple solvent slow evaporation method. Three round of crystallization trials, diffraction crystals were obtained.

The diffraction quality crystals after screening its size and stability, X-ray diffraction data collection was done at Department of chemistry- Pondicherry University. The data was reduced with appropriate corrections at the facility and the error free data was taken for structure determination.

Using WinGx suite, structure determination was done using SHELXS97 with Direct Methods protocols. After manual inspections and corrections, Isotropic refinements followed by anisotropic refinements were carried out. With the satisfied model (agreeable R factor, Goodness of Fit and other) hydrogen atoms were geometrically fixed and after the final refinement the R factor is 6.0%.

3. Experimental Section

3.1. Synthesis of the Title Compound

To a stirred solution of 2-amino-4-methylphenol (0.061 g, 0.5 mmol) in EtOH as solvent was refluxed with 5-chloro-2-hydroxy-4-methylbenzaldehyde (0.085 g, 0.5 mmol) for 12 hrs. The yellow precipitate was filtered off and recrystallized twice from EtOH. The purity of the product was checked by thin layer chromatography [Yield: 0.11 g (85%)].

3.2. X-Ray Crystallography

For the crystal structure determination, the single crystal of the compound $C_{15}H_{15}ClNO_2$ was used for data collection on a Oxford diffractometer[8]. The MoKα radiation of wavelength, (# = 0.71073 Å) and multi-scan technique for absorption correction were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with F2>2$ (F2). The structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97[9,10]. H atoms were positioned geometrically and refined using a riding model, fixing the aromatic C-H distances at 0.93 Å [Uiso(H) = 1.2 Ueq (C)]. The softwares used for Molecular graphics are ORTEP-3 for Windows[11] and PLATON[12]. The software used to prepare material for publication is

Table 1. Crystal Data and Structure Refinement

Parameters	Compound II
Empirical formula	$C_{15}H_{15}ClNO_2$
Formula weight	276.73
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.5241(19) Å
	b = 8.7233(11) Å
	c = 13.649(2) Å
	β = 130.876(15)°
Volume	1332.0(3) Å^3
Z, Calculated density	4, 1.380 Mg/m^3
Absorption coefficient	0.284 mm^{-1}
F(000)	580
Crystal size(mm)	0.25×0.20×0.18
θ range	2.8 to 25.00°
Limiting indices	-10 ≤ h ≤ 13
	-10 ≤ k ≤ 9
	-13 ≤ l ≤ 16
Reflections collected /	5100/ 2350
unique	[R(int) = 0.07]
Completeness to theta	100%
Refinement method	Full-matrix
	least-squares on F^2
Data / Restraints / Parameters	2350/0/ 179
Goodness-of-fit on F^2	1.016
Final R indices [I>2σ(I)]	R1 = 0.0674
R indices (all data)	wR2 = 0.0918
	R1 = 0.1894
	wR2 = 0.1292
Largest diff. peak and hole	0.28 and -0.21 e.Å^{-3}

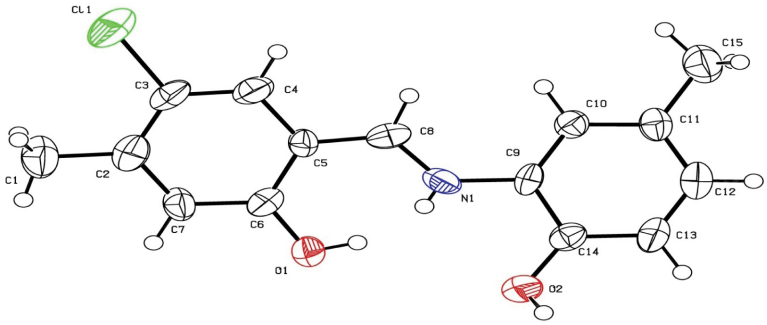

Fig. 2. Displacement ellipsoids are drawn at the 30% probability level.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for the non-hydrogen atoms of compound

Atom	x	y	z	*U(eq)
C1	4948(5)	7451(5)	256(4)	67(2)
C2	3953(4)	8526(5)	268(4)	45(1)
C3	3849(5)	9203(5)	1178(4)	47(2)
C4	2957(4)	10198(5)	1207(4)	46(1)
C5	2068(4)	10539(5)	330(4)	32(1)
C6	2135(4)	9848(5)	-599(4)	40(1)
C7	3114(4)	8884(5)	-585(4)	45(1)
C8	1148(4)	11548(4)	396(3)	38(1)
C9	-635(4)	13077(4)	-386(4)	32(1)
C10	-913(4)	13586(4)	479(4)	36(1)
C11	-1810(4)	14630(5)	427(4)	40(1)
C12	-2421(4)	15172(5)	-504(4)	48(2)
C13	-2138(4)	14656(5)	-1361(4)	47(2)
C14	-1225(4)	13605(5)	-1339(4)	38(1)
C15	-2102(4)	15209(5)	1380(4)	61(2)
Cl1	4895(1)	8781(2)	2296(1)	88(1)
N1	291(5)	11996(6)	-362(4)	39(1)
O1	1327(3)	10094(3)	-1420(2)	55(1)
O2	-876(3)	13100(3)	-2154(2)	53(1)

WinGX publication routines[13]. Experimental data are listed in Table 1. Fig. 1 shows schematic diagram of the molecule and molecular structure of the title compound along with the atom numbering scheme is depicted in Fig. 2 and a packing diagram is shown in Fig. 3. Table 1 shows the crystal data and crystal refinement statistics. Table 2 gives the atomic coordinates, Fig. 3 and Fig. 4 describes the bond lengths and angles respectively; Table 3 shows anisotropic displacement parameters, Table 4 shows the torsion angles, Table 5 shows Mean planes through various groups of atoms in the structure of Compound and Table 6 shows Hydrogen-bond geometry.

4. Results and Discussion

Title compound crystallizes in the monoclinic system with $P2_1/c$ space group and total number molecule found in the unit cell is $Z = 4$. The title compound is essentially planar. The atoms C1, O1 and Cl1 are deviated by -0.061(3) Å, -0.030(4) Å and -0.048(1) Å respectively from the least-squares plane of the chloro

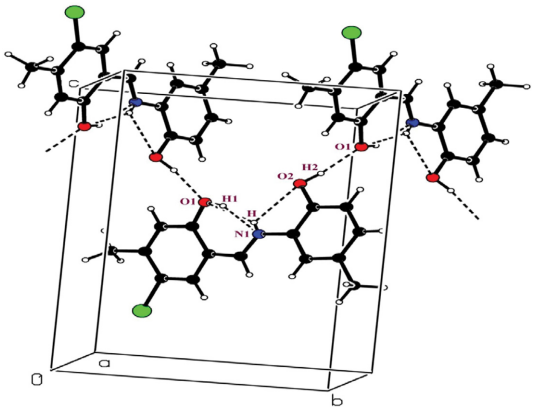

Fig. 3. Crystal packing of the title compound viewed down the *a*-axis, dashed line indicate the inter molecular interaction in the unit cell.

phenyl ring (C2-C7). The torsion angle C5-C8-N1-C9 is -175.7(5)º adopt anti-periplanar conformation. The compound lies across a crystallographic inversion centre and adopts E configurations with respect to the C-N bonds. The imino group is coplanar with the benzene ring. Within the molecule, the planar units are parallel but extend in opposite directions from the methylene bridge. In the molecule, the O1-C6 (1.351(2) Å) bond has single-bond character, whereas the N1-C8 (1.308(6) Å) bond has a high degree of double-bond character as in related structure[14]. Also, the N1-C8 (1.308(6) Å) bond is a partial double bond showing phenol-imine and ketoamine tautomersism[15]. The atoms O2 and C15 are deviated from the methyl cyclohexanone ring by -0.051(3) Å and -0.030(4) Å

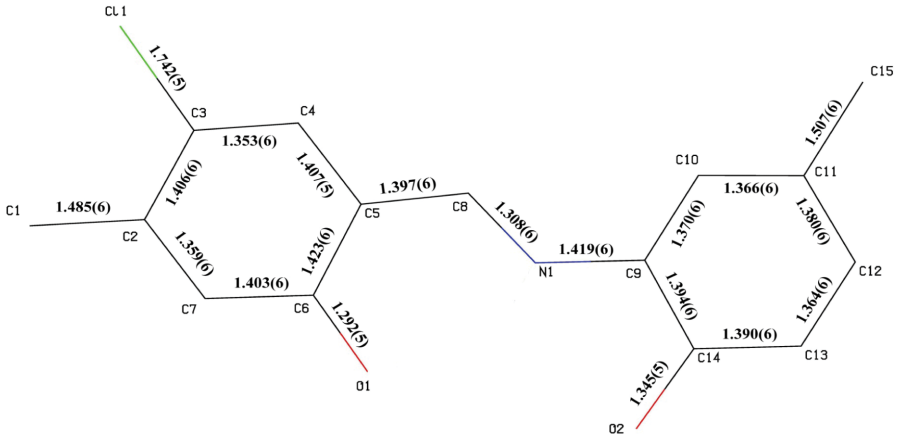

Fig. 4. Bond lengths [Å] of the compound.

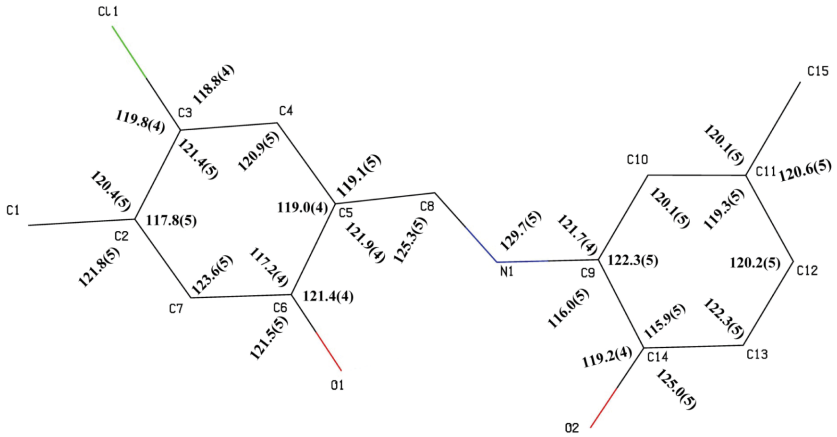

Fig. 5. Bond Angles [º] of the compound.

Table 3. Anisotropic displacement parameters ($Å^2$)

Atom	U11	U22	U33	U23	U13	U12
C1	45(4)	67(3)	86(5)	-7(3)	12(3)	14(3)
C2	29(3)	42(3)	61(4)	9(3)	8(3)	-4(3)
C3	34(4)	59(4)	42(4)	12(3)	-5(3)	4(3)
C4	43(4)	54(3)	35(3)	6(3)	-2(3)	4(3)
C5	25(3)	36(3)	37(3)	0(2)	9(2)	4(2)
C6	36(4)	40(3)	38(3)	6(2)	-1(3)	3(3)
C7	30(3)	49(3)	54(4)	-11(3)	8(3)	7(3)
C8	43(4)	37(3)	30(3)	3(2)	1(3)	-13(3)
C9	24(3)	23(2)	47(3)	8(2)	6(3)	2(2)
C10	29(3)	45(3)	36(3)	7(2)	12(2)	3(2)
C11	30(3)	39(3)	52(4)	-3(3)	12(3)	2(2)
C12	36(3)	43(3)	66(4)	3(3)	14(3)	9(3)
C13	34(3)	45(3)	57(4)	4(3)	3(3)	11(3)
C14	29(3)	44(3)	37(3)	0(3)	1(3)	-2(3)
C15	57(4)	63(3)	69(5)	3(3)	26(3)	14(3)
Cl1	59(1)	122(1)	70(1)	14(1)	-11(1)	29(1)
N1	42(3)	48(3)	32(3)	-9(3)	16(3)	0(2)
O1	56(3)	60(2)	44(2)	-13(2)	1(2)	27(2)
O2	68(3)	54(2)	34(2)	5(2)	9(2)	18(2)

Table 4. Torsion angles [°]

Atoms	Angle	Atoms	Angle
C(8)-N(1)-C(9)-C(10)	-14.9 (8)	C(8)-C(5)-C(6)-O(1)	-1.8 (7)
C(8)-N(1)-C(9)-C(14)	164.0 (5)	C(4)-C(5)-C(6)-O(1)	178.3 (4)
C(10)-C(9)-C(14)-O(2)	177.5 (4)	C(8)-C(5)-C(6)-C(7)	178.4 (4)
N(1)-C(9)-C(14)-O(2)	-1.4 (6)	C(4)-C(5)-C(6)-C(7)	-1.4 (7)
C(10)-C(9)-C(14)-C(13)	-1.5 (7)	O(1)-C(6)-C(7)-C(2)	-176.5 (5)
N(1)-C(9)-C(14)-C(13)	179.5 (4)	C(5)-C(6)-C(7)-C(2)	3.3 (7)
C(9)-N(1)-C(8)-C(5)	-175.7 (5)	C(6)-C(7)-C(2)-C(3)	-2.1 (8)
N(1)-C(8)-C(5)-C(4)	177.8 (5)	C(6)-C(7)-C(2)-C(1)	177.5 (4)
N(1)-C(8)-C(5)-C(6)	-2.0 (7)	C(14)-C(13)-C(12)-C(11)	-1.2 (8)
C(14)-C(9)-C(10)-C(11)	1.0 (7)	C(10)-C(11)-C(12)-C(13)	0.6 (7)
N(1)-C(9)-C(10)-C(11)	179.9 (4)	C(15)-C(11)-C(12)-C(13)	179.1 (5)
O(2)-C(14)-C(13)-C(12)	-177.3 (5)	C(5)-C(4)-C(3)-C(2)	2.8 (8)
C(9)-C(14)-C(13)-C(12)	1.6 (7)	C(5)-C(4)-C(3)-Cl(1)	-178.0 (4)
C(9)-C(10)-C(11)-C(12)	-0.5 (7)	C(7)-C(2)-C(3)-C(4)	-1.1 (8)
C(9)-C(10)-C(11)-C(15)	-179.0 (4)	C(1)-C(2)-C(3)-C(4)	179.4 (5)
C(8)-C(5)-C(4)-C(3)	178.7 (4)	C(7)-C(2)-C(3)-Cl(1)	179.7 (4)
C(6)-C(5)-C(4)-C(3)	-1.5 (7)	C(1)-C(2)-C(3)-Cl(1)	0.1 (7)

Table 5. Mean planes through various groups of atoms in the structure of compound and deviations from the plane. The equation of the plane is of the form: m1x + m2y + m3z - D = 0. where m1, m2, m3 and D are constants

Plane	m1	m2	m3	D	Atom	Deviation(Å)
1	0.610(1)	0.772(1)	-0.176(2)	8.410(6)	C2*	-0.003(4)
					C3*	-0.015(5)
					C4*	0.014(4)
					C5*	-0.000(4)
					C6*	-0.015(4)
					C7*	0.017(4)
					O1	-0.061(3)
					C1	-0.022(4)
					C8	0.003(4)
					Cl1	-0.048(1)
2	-0.664(1)	-0.744(1)	-0.067(1)	-8.058(2)	C9*	0.004(4)
					C10*	-0.001(4)
					C11*	0.000(4)
					C12*	-0.002(4)
					C13*	0.006(4)
					C14*	-0.007(4)
					N1	0.001(5)
					C15	-0.030(4)
					O2	-0.051(3)

*Atoms are included in the plane calculations

Table 6. Atomic coordinates ($\times 10^4$) and their isotropic displacement parameters ($Å^2 \times 10^3$) for hydrogen atoms of compound

Atom	x	y	z	*Ueq
H1	820	10678	-1303	83
H2	-925	13800	-2562	79
H8	1146	11931	1032	45
H10	-492	13220	1103	43
H13	-2571	15020	-1982	56
H4	2930	10663	1814	55
H5	3193	8466	-1192	53
H1C	4877	6562	652	100
H1B	5697	7949	533	100
H1A	4913	7146	-427	100
H12	-3028	15890	-547	57
H15C	-2875	14836	1416	92
H15B	-2109	16310	1376	92
H15A	-1510	14851	1954	92
H	40040	1179040	-76030	14

respectively. The crystal packing of the molecules of compounds II is stabilized by the weak O1-H1…N1, N1-H…O2 intra molecular and O2-H2…O1 inter molecular hydrogen bond interactions running along c-axis.

5. Conclusion

Crystal structure of a novel saliciline schiff bases derivatives have also been exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic. The title compound is crystallized in ethyl acetate by slow evaporation techinique. The compound lies across a crystallographic inversion centre and adopts E configurations with respect to the C-N bonds. A partial double bond showing phenol-imine and ketoamine tautomersism. Title structure may be important from a medicinal point of view as well as their widespread biological significance. The structure may be useful for further investigation on the mechanism, potential activity, optimal reaction condition etc which will be further characterized as a future prospective of our project.

References

[1] D. N. Dhar and C. L. Taploo, “Schiff- bases and their applications”, J. Sci. Ind. Res. India, Vol. 41, pp. 501-506, 1982.

[2] P. Przybylski, A. Huczynski, K. Pyta, B. Brzezinski, and F. Bartl, “Biological properties of Schiff bases and azo derivatives of phenols”, Curr. Org. Chem., Vol. 13, pp. 124-148, 2009.

[3] A. O. D. Souza, F. C. S. Galetti, C. L. Silva, B. Bicalho, M. M. Parma, S. F. Fonseca, A. J. Marsaioli, A. C. L. B. Trindade, R. P. Freitas Gil, F. S. Bezerra, M. Andrade-Neto, and M. C. F. De Oliveira, “Antimycobacterial and cytotoxicity activity of synthetic and natural compounds”, Quim. Nova, Vol. 30, pp. 1563-1566, 2007.

[4] Z. Guo, R. Xing, S. Liu, Z. Zhong, X. Ji, L. Wang, and P. Li, “Antifungal properties of schiff bases of chitosan, nsubstituted chitosan and quaternized chitosan”, Carbohyd. Res., Vol. 342, pp. 1329-1332, 2007.

[5] S. Park, B. Sung, E. J. Jang, D. H. Kim, C. H. Park, Y. J. Choi, Y. M. Ha, M. K. Kim, N. D. Kim, B. P. Yu, and H. Y. Chung, “Inhibitory action of salicylideneamino-2-thiophenol on NF-κB signaling cascade and cyclooxygenase-2 in HNE-treated endothelial cells”, Arch. Pharm. Res., Vol. 36, pp. 880-889, 2013.

[6] J. Iqbal, S. A. Tirmizi, F. H. Wattoo, M Imran, M. H. Sarwar Wattoo, S Sharfuddin, and S. Latif, “Biological properties of chloro-salicylidene aniline and Its complexes with Co(II) and Cu(II)”, Turk J. Biol., Vol. 30, pp. 1-4, 2006.

[7] P. H. Wang, J. G. Keck, E. J. Lien, and M. M. C. Lai, “Design, synthesis, testing, and quantitative structure-activity relationship analysis of substituted salicylaldehyde schiff bases of 1-amino-3-hydroxyguanidine tosylate as new antiviral agents against coronavirus”, J. Med. Chem., Vol. 33, pp. 608-614, 1990.

[8] P. R. O. Crysalis, “Oxford Diffraction Ltd”, Yarnton, England, 2009..

[9] G. M. Sheldrick, “SHELXS-97 and SHELXL-97, Program for crystal structure solution and refinement”, University of Gottingen, Gottingen, Germany, 1997.

[10] G. M. Sheldrick, “A short history of SHELX”, Acta Crystallogr. A., Vol. A64, pp. 112-122, 2008.

[11] L. J. Farrugia, “ORTEP-3 for windows—A version of ORTEP-III with a graphical user interface (GUI)”, J. Appl. Crystallogr., Vol. 30, pp. 565, 1997.

[12] A. L. Spek, “Structure validation in chemical crystallography”, Acta Crystallogr. D., Vol. 65, pp. 148-155, 2009.

[13] L. J. Farrugia, “WinGX suite for small-molecule single-crystal crystallography”, J. Appl. Crystallogr., Vol. 32, pp. 837-838, 1999.

[14] H.-K. Fun, P. S. Patil, S. R. Jebas, K. V. Sujith, and B. Kalluraya, “4-Chloro-N'-[(Z)-4-(dimethyl-amino) benzyl-idene]benzohydrazide mono-hydrate”, Acta Crystallographica Section E: Structure Reports Online, Vol. 64, pp. o1594-o1595, 2008.

[15] G. Özdemir Tari, S. Isik, R. Özkan, and A. Alaman Agar, “3-Methoxy-2-[(E)-(4-Methoxyphenyl)iminomethyl]phenol”, Acta Crystallographica Section E: Structure Reports Online, Vol. 67, pp. o343-o344, 2011.