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Synthesis, Crystal Structure and DFT Studies of 4-(1-Benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-6-(*o*-tolyl)pyrimidin-2-amine

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The compound (**I**), 4-(1-benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-6-(*o*-tolyl)pyrimidin-2-amine ($C_{21}H_{20}N_6$), was synthesized and structurally characterized by elemental analysis, ^{1}H NMR and ^{13}C NMR and single crystal X-ray diffraction. The compound crystallizes as a colourless needle shaped in the monoclinic system, space group $P2_1/n$ with cell constants: a = 11.2942(16) Å, b = 16.1209(18) Å, c = 10.6253(14) Å, $\alpha = \gamma = 90°$, $\beta = 106.898\ (5)°$, V = 1851 (4) Å^3, Z = 4. In the compound, the triazole and the pyrimidine rings are essentially planar. The molecular conformation is stabilized by an intramolecular C-H…N hydrogen bond, which generates an S(6) ring motif. The crystal packing is stabilized by intermolecular N-H…N and C-H… π hydrogen bonds thereby generating a three-dimensional supramolecular network. The molecular geometry was also optimized using density functional theory using (DFT/B3LYP) method with the 6-311G (d, p) basis set and compared with the experimental data.

Keywords: X-ray structure determination, Hydrogen bonds, DFT calculations.

INTRODUCTION

1,2,3-Triazoles have found a wide range of important applications in the pharmaceutical, polymer and material fields[1]. In addition, they have shown a broad spectrum of biological properties such as anti-bacterial[2] anti-allergic[3], anti-HIV activities[4] and also serve as potential chemotherapeutic agents for various diseases[5]. On the other hand, substituted pyrimidine nuclei were found antiviral[6], anti-tubercular, antineoplastic, anti-inflammatory, diuretic, antimalarial and cardiovascular[7]. In view of these bioactivities of the individual heterocycles, it was envisaged that the synthesis of novel hybrid molecules containing two of the above said moieties in a single frame is worth to attempt. The compound has been synthesized and antibacterial activities were carried out by our co-authors[8]. Here we present the crystal structure of 4-(1-benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-6-(*o*-tolyl)pyrimidin-2-amine (**I**), ($C_{21}H_{20}N_6$). In recent years, density functional theory (DFT) has become an increasingly useful tool for theoretical studies. The success of DFT is mainly due to the fact that it describes small molecules more reliably than Hartree-Fock theory. It is also comput-ationally less demanding than wave function based methods with inclusion of electron correlation[9,10]. Thus, in order to characterize the correlation between molecular structure and macroscopic properties in the studied compound, it seems to be essential to undertake a comparative study of the isolated molecule and the solid state unit. In this paper, a concerted approach by X-ray crystallography and DFT calculation was used, which takes advantage of both the high interpretative power of the theoretical studies and the precision and reliability of the experimental method.

In this paper, we report the synthesis, crystal structure of 4-(1-benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-6-(*o*-tolyl)-pyrimidin-2-amine ($C_{21}H_{20}N_6$), as well as theoretical studies using the DFT(B3LYP) method and 6-311G(d, p) basis set. The aim of the present work was to describe and characterize the molecular structure both experimentally and theoretically.

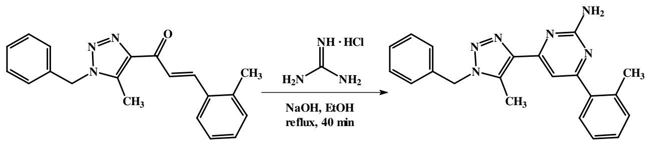
EXPERIMENTAL

Synthesis of (I): The title compound (**I**) was obtained according to the reaction **Scheme-I**. A mixture of (E)-1-(1-benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-(*o*-tolyl)prop-2-en-1-one (0.2 g, 0.63 mmol), guanidine hydrochloride (0.18 g, 1.88 mmol) and NaOH (0.05 g, 1.25 mmol) in ethanol (10 mL) was refluxed for 40 min. Then, the reaction mixture was poured onto excess crushed ice and neutralized with dilute hydrochloric acid. The precipitated 4-(1-benzyl-5-methyl-1*H*-

1,2,3-triazol-4-yl)-6-(*o*-tolyl)pyrimidin-2-amine was filtered and recrystallized from ethanol[8]. Needle like colourless single crystals of the title compound **I**, suitable for single crystal X-ray diffraction studies have been grown in an ethanolic solution by slow evaporation of the solvent at room temperature and collected [yield (78 %) , m.p. 149 °C].

Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded in $CDCl_3$ and DMSO-d_6 on Bruker Advance 300 MHz spectrometer and the chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane, with J values in Hertz. ^{13}C NMR data are reported with the solvent peak ($CDCl_3$ = 77 MHz) as the internal standard.

White solid; m.p.: 149 °C; Yield: 78 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, s, =CH), 7.44-7.15 (9H, m, ArH), 5.53 (2H, s, C_6H_5-CH_2), 5.24 (2H, brs, NH_2), 2.59 (3H, s, CH_3), 2.42 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.05, 162.73, 160.00, 142.19, 138.78, 135.76, 134.54, 133.94, 130.83, 129.03, 128.99, 128.93, 128.34, 127.28, 127.14, 125.85, 108.22, 51.73, 20.22, 9.73.



Scheme-I: Reaction scheme and chemical diagram of the title compound **1**

X-ray crystallography: Crystal of the title compound having approximate dimension 0.30 mm × 0.25 mm × 0.11 mm was mounted on a glass fiber using cyanoacrylate adhesive. All measurement were made on a Bruker AXS Kapppa Apex II single crystal X-ray diffractometer using graphite monochromated MoK_α (λ = 0.71071 Å) radiation and CCD detector. Diffraction data were collected at room temperature by the ω-scan technique. Accurate unit cell parameters and orientation matrix were obtained by a least-squares fit of several high angle reflections in the ranges 1.88° < θ < 28.34° for the title compound. The unit cell parameters were determined for 36 frames measured (0.5° phi-scan) from three different crystallographic zones and using the method of difference vectors. The intensity data were collected with an average four-fold redundancy per reflection and optimum resolution (0.75 Å). The intensity data collection, frames integration, Lorentz-polarization correction and decay correction were done using SAINT-NT (version 7.06a) software. Empirical absorption correction (multi-scan) was performed using SADABS[11] program. The structure was solved by direct methods using SHELXS-97[12] implemented in WinGX[13] program suit. The refinement was carried out by full-matrix least-square method on the positional and anisotropic temperature parameters of the non-hydrogen atoms, using SHELXL-97[14]. All the H atoms were positioned geometrically and constrained to ride on their parent atom with C-H = 0.93-0.97 Å and N-H = 0.86 Å and with $U_{iso}(H) = 1.5\, U_{eq}$ for methyl H atoms and $1.2U_{eq}(C)$ for other H atoms. Owing to poor agreement, the reflection [110], was omitted from the final cycles of refinement. The general-purpose crystallography tool PLATON[15], ORTEP[16] and MERCURY[17] were used for structure analysis and presentation of the results.

Computational details: The molecular structure of the compound in ground state (*in vacuo*) was optimized using density functional theory DFT (B3LYP)[18,19] method with the 6-311G (d, p)[20] basis sets. All the calculations were performed without specifying any symmetry for the title molecule by using GaussView molecular visualization program[21] and Gaussian 03 program package[22]. The optimized geometrical parameters were calculated using Gaussian 03 W package and Gaussview 03 program has been used to construct optimized molecular geometry.

RESULTS AND DISCUSSION

Description of crystal structure: The displacement ellipsoid plot and theoretical geometry structure with the atom-numbering scheme for compound (**I**) is shown in Fig. 1. The compound (**I**) crystallizes as a colourless needle shaped in the monoclinic system, space group $P2_1/n$ with cell constants: a = 11.2942(16) Å, b = 16.1209(18) Å, c = 10.6253(14) Å, $\alpha = \gamma$ = 90°, β = 106.898 (5)°, V = 1851.0(4) Å^3, Z = 4. Details of the data collection, crystal parameters and refinement process of compound **I** are given in Table-1.

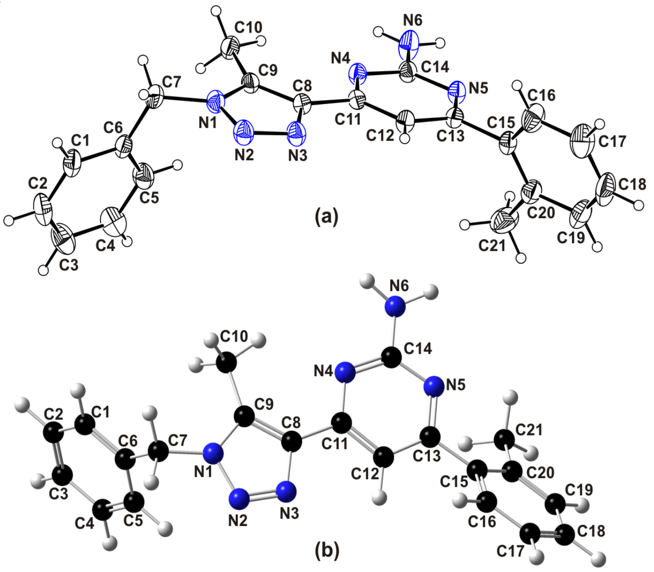


Fig. 1. (a) View of title compound showing the atom-numbering scheme. Displacement ellipsoids for the non-H atoms are drawn at the 30 % probability level. The H atoms are presented with spheres with arbitrary radii. (b) The theoretical geometric structure of the title compound (B3LYP/6-311G(d,p) level)

In the title compound with m.f. $C_{21}H_{20}N_6$, the triazole (N1/N2/N3/C8/C9) and the pyrimidine (N4/N5/C11-C14) rings are essentially planar [maximum deviation = 0.005(2) Å for the N2 atom and 0.009(2) Å for the atom C12] and forms dihedral angle of 5.5 (1)° between them. The methyl phenyl ring attached to the pyrimidine ring is in equatorial position. The dihedral angle between the benzene rings is 61.1 (1)°. The bond distances N3-C8, C8-C9, C9-N1, N1-N2 and N2-N3 are 1.365(2), 1.374(2), 1.352(2), 1.347(2) and 1.301(2) Å respectively, which agrees with C-C, N-N, C-N distances found in literature for compound having triazole heterocycles[23,24].

TABLE-1
CRYSTAL AND EXPERIMENTAL
DATA FOR THE COMPOUND **I**

Empirical formula	$C_{21}H_{20}N_6$
Formula weight	356.43
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions (Å, °)	
a	11.2942(16)
b	16.1209(18)
c	10.6253(14)
β	106.898 (5)
Volume ($Å^3$)	1851.0(4)
Z	4
Calculated density (Mg/m^3)	1.279
Absorption coefficient (mm^{-1})	0.080
F(000)	752
Crystal size (mm^3)	0.30 × 0.25 × 0.11
Theta range for data collection (°)	1.88 to 28.34.
Index ranges	$-14 <= h <= 15, -21 <= k <= 13, -13 <= l <= 14$
Reflections collected	15750
Independent reflections	4559 [R(int) = 0.0306]
Completeness to θ = 28.34°	98.6 %
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4559/0/247
Goodness-of-fit on F^2	1.024
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0466, wR2 = 0.1128
R indices (all data)	R1 = 0.0734, wR2 = 0.1286
Largest diff. peak and hole (e. $Å^{-3}$)	0.211 and -0.165

The hydrogen bond geometry for compound **1** is presented in Table-2. The molecular conformation is stabilized by an intramolecular C10-H10B…N4 hydrogen bond, which generates an S(6) ring motif[25]. In the crystal, molecules are linked by N6-H6B…N5 hydrogen bonds into cylic centrosymmetric $R_2^2(8)$ dimers. These dimers are linked *via* N6-H6A···N3 hydrogen bonds, forming a two-dimensional network lying parallel to the [1 0 0] plane (Fig. 2 and Table-2). These two dimensional networks are connected by C18-H18B···Cg^{iii} (Table-2 and Fig. 3; Symmetry code: (iii) = -x, 1/2 + y, -1/2-z, Cg is the centroid of the C1-C6 benzene ring) hydrogen bonds, forming a three-dimensional supramolecular network.

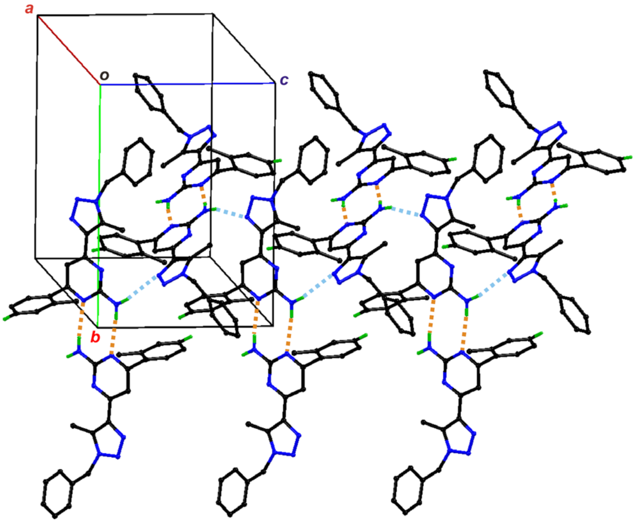


Fig. 2. View of N-H…N hydrogen bonds forming a two-dimensional network lying parallel to the [1 0 0] plane. Hydrogen atoms not included in the hydrogen bonding are omitted for clarity

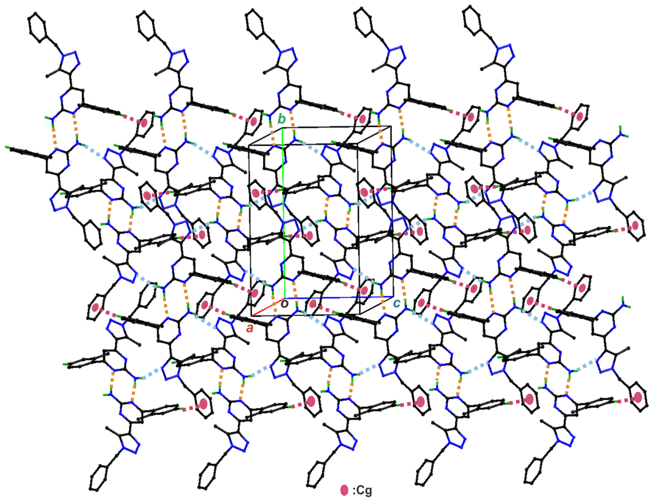


Fig. 3 View of three dimensional supramolecular network. The N-H...N and C-H…π interactions are shown as dashed lines. Cg is the centroid of the (C1-C6) benzene ring. Hydrogen atoms not included in the hydrogen bonding are omitted for clarity.

DFT calculations: The first task of the computational work is to determine the optimized geometry of the title compound. The starting coordinates were obtained from X-ray structure determination. The optimized parameters (bond-lengths, bond angles) of the compound **I** were obtained using (DFT/B3LYP) method with the 6-311G(d,p) basis set. The results are listed in Table-3 and compared with the experimental data for the title compound. As seen from the Table-3, the agreement between the theoretically calculated and the experimentally obtained structure parameters for the title compound are very good. In view of the bond lengths in Table-3, most predicted values are longer than experimental ones. We note that the experimental results are for the solid phase and the theoretical calculations are for the gas phase. In the solid state, the existence of a crystal field along with the intermolecular interactions connect the molecules together, which results in the difference in bond parameters between the calculated and experimental values[26].

TABLE-2
HYDROGEN BONDING GEOMETRY FOR THE COMPOUND **I** (Å, °)

D–H...A	D–H	d(H...A)	d(D...A)	<(DHA)
C10-H10B…N4	0.96	2.44	3.105(2)	127.0
N6-H6A...$N3^{i}$	0.86	2.52	3.348(2)	161.9
N6-H6B...$N5^{ii}$	0.86	2.36	3.214(2)	174.3
C18-H18...Cg^{iii}	0.93	2.59	3.516(2)	172.0

Cg is the centroid of the C1-C6 ring. Symmetry codes : (i) x, -y + 3/2, z + 1/2; (ii) -x, -y + 2, -z ; (iii) -x, y + 1/2, -z-1/2

TABLE-3
SELECTED STRUCTURAL PARAMETERS BY X-RAY DIFFRACTION AND DFT CALCULATIONS FOR COMPOUND **I**

Parameters	X-ray	DFT
Bond lengths (Å)		
N1-N2	1.347(2)	1.359
N2-N3	1.301(2)	1.291
C7-N1	1.460(2)	1.459
C14-N6	1.341(2)	1.370
C14-N5	1.344(2)	1.340
C14-N4	1.344(2)	1.341
C20-C21	1.488(3)	1.511
C8-C9	1.374(2)	1.390
C8-N3	1.365(2)	1.369
C13-N5	1.336(2)	1.340
C11-N4	1.334(2)	1.341
C17-C18	1.373(3)	1.391
C18-C19	1.355(3)	1.398
Bond angles (°)		
N1-C7-C6	113.6(1)	113.71
C18-C19-C20	121.5(2)	122.10
N3-N2-N1	106.8(1)	107.40
N2-N3-C8	109.2(1)	109.63
N4-C11-C8	116.9(1)	118.15
C11-N4-C14	116.6(1)	116.16
N3-C8-C11	121.2(1)	120.72
N1-C9-C8	102.5(1)	103.39
N1-C9-C10	122.6(1)	123.24
C8-C9-C10	133.9(1)	133.24
N4-C11-C8	116.9(1)	118.15
N6-C14-N4	116.9(1)	116.78
N6-C14-N5	117.2(1)	115.41
N4-C14-N5	126.0(1)	126.40
C19-C18-C17	120.7(2)	119.74
Torsion angles (°)		
N5-C13-C15-C20	-68.3(2)	-43.7
C6-C7-N1-C9	88.1(2)	77.5
C15-C13-N5-C14	179.2(1)	-178.5
N6-C14-N4-C11	-179.4(1)	177.7

When the X-ray structure of the title compound was compared with its optimized counterpart (Fig. 1), conformational discrepancies were observed. The orientation of the phenyl rings of compound **I** proved the most notable discrepancy and is defined with torsion angle N5-C13-C15-C20 = -68.3° and C6-C7-N1-C9 = 88.1°, which is calculated at -43.7° and 77.5°, respectively, for B3LYP/6-311G(d,p) level.

As seen from Table-3, the difference between the X-ray and calculated values for the bond lengths C14-N6 and N2-N3 are 0.029 Å and 0.010 Å, respectively. Similarly, the difference for bond angles C19-C18-C17, N4-C11-N8 and N4-C14-N5 are 0.96°, 1.30° and 0.80°, respectively. This difference is more not only because of intramolecular C10-H10B…N4 hydrogen bond but also due to intermolecular N6-H6A…N3 and N6-H6B…N5 hydrogen bonds.According to experimental and calculated values, the dihedral angles between triazole and pyrimidine rings are 5.5 (1)° and 2.8°, respectively and also between benzene rings are 61.1 (1)° and 59.2°, respectively.

A global comparison was performed by superimposing the molecular skeletons obtained from X-ray diffraction and the theoretical calculations atom by atom (Fig. 4.), obtaining RMSE's values of 0.648 Å for DFT/B3LYP) method with the 6-311G(d,p) basis set. This magnitude of RMSE can be explained by the fact that the intermolecular columbic interaction with the neighboring molecules are absent in gas phase, whereas the experimental result corresponds to interacting molecules in the crystal lattice.

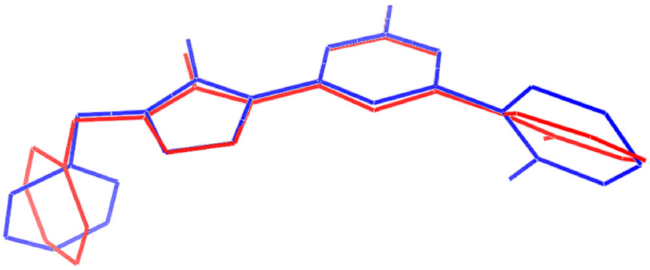


Fig. 4. Atom-by-atom superimposition of the calculated structure (red) on the X-ray structure (blue) for compound I

Conclusion

The compound 4-(1-benzyl-5-methyl-1*H*-1,2,3-triazol-4-yl)-6-(*o*-tolyl)pyrimidin-2-amine was synthesized and has been confirmed by NMR and structural (single-crystal X-ray diffraction) techniques. The molecule forms 3D-supramolecular network by two N-H…N and C-H…π interactions. To support the solid state structure, the geometric parameters of the present compound have been calculated using density functional theory DFT (B3LYP) method with the 6-311G (d,p) basis sets and compared with the experimental findings. It was noted here that the experimental results belong to solid phase and theoretical calculations belong to gaseous phase. In the solid state, the existence of the crystal field along with the intermolecular interactions have connected the molecules together, which result in the differences of bond parameters between the calculated and experimental values.

Supplementary materials: CCDC987427 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge at http://www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(0)1223-336033.

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REFERENCES

1. J. Morales-Sanfrutos, M. Ortega-Munoz, J. Lopez-Jaramillo, F. Hernandez-Mateo and F. Santoyo-Gonzalez, *J. Org. Chem.*, **73**, 7768 (2008).
2. M.J. Genin, D.A. Allwine, D.J. Anderson, M.R. Barbachyn, D.E. Emmert, S.A. Garmon, D.R. Graber, K.C. Grega, J.B. Hester, D.K. Hutchinson, J. Morris, R.J. Reischer, C.W. Ford, G.E. Zurenko, J.C. Hamel, R.D. Schaadt, D. Stapert and B.N. Yagi, *J. Med. Chem.*, **43**, 953 (2000).
3. D.R. Buckle, C.J.M. Rockell, H. Smith and B.A. Spicer, *J. Med. Chem.*, **29**, 2262 (1986).
4. M.J. Giffin, H. Heaslet, A. Brik, Y.C. Lin, G. Cauvi, C.H. Wong, D.E. McRee, J.H. Elder, C.D. Stout and B.E. Torbett, *J. Med. Chem.*, **51**, 6263 (2008).
5. S. Wang, Q. Wang, Y. Wang, L. Liu, X. Weng, G. Li, X. Zhang and X. Zhou, *Bioorg. Med. Chem. Lett.*, **18**, 6505 (2008).
6. H.I. El-Subbagh, S.M. Abu-Zaid, M.A. Mahran, F.A. Badria and A.M. Al-Obaid, *J. Med. Chem.*, **43**, 2915 (2000).

7. A.R. Trivedi, *ARKIVOC*, 131 (2008).
8. S. Nagarajan, P. Shanmugavelan, M. Sathishkumar, R. Selvi, A. Ponnuswamy, H. Harikrishnan and V. Shanmugaiah, *Chin. Chem. Lett.*, **25**, 419 (2014).
9. W. Koch and M.C.A. Holthausen, A Chemistry Guide to Density Functional Theory, Wiley-VCH, Weinheim, New York, Chichester (2000).
10. R.G. Parr and R.G. Yang, Density Functional Theory of Atoms and Molecules, Oxford University Press, New York, USA (1989).
11. APEX-II and SAINT-Plus (Version 7.06a), Bruker AXS Inc. Madison, Wisconsin, USA (2004).
12. G.M. Sheldrick, SHELXS97, A Program for Crystal Structure Solution, University of Göttingen: Germany (1997).
13. L.J. Farrugia, *J. Appl. Cryst.*, **32**, 837 (1999).
14. G.M. Sheldrick, SHELXL97, A Program for Crystal Structure Refinement, University of Göttingen: Germany (1997).
15. A.L. Spek, *J. Appl. Cryst.*, **36**, 7 (2003).
16. L.J. Farrugia, *J. Appl. Cryst.*, **30**, 565 (1997).
17. I.J. Bruno, J.C. Cole, P.R. Edgington, M.K. Kessler, C.F. Macrae, P. McCabe, J. Pearson and R. Taylor, *Acta Crystallogr. B*, **58**, 389 (2002).
18. A.D. Becke, *J. Chem. Phys.*, **98**, 5648 (1993).
19. C.T. Lee, W.T. Yang and R.G. Parr, *Phys. Rev. B*, **37**, 785 (1988).
20. R. Ditchfield, W.J. Hehre and J.A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).
21. R. Dennington II, T. Keith and J. Millam, Gauss View Version 4.1.2, Semichem Inc., Shawnee Mission, KS, (2007).
22. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, T. Vreven Jr., K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Tefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez and J.A. Pople, Gaussian03, Gaussian Inc, Wallingford, CT, USA, (2004).
23. C.C. Huang, R.L. Wu, Y.H. Lo, W.R. Lai and C.H. Lin, *Acta. Cryst.*, **E66**, o1690 (2010).
24. J.I. Sarmiento-Sánchez, G. Aguirre and I.A. Rivero, *Acta. Cryst.*, **E67**, o1856 (2011).
25. J. Bernstein, R.E. Davis, L. Shimoni and N.L. Chang, *Angew. Chem. Int. Ed. Engl.*, **34**, 1555 (1995).
26. F.F. Jian, P.S. Zhao, Z.S. Bai and L. Zhang, *Struct. Chem.*, **16**, 635 (2005).