Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(2):286-291
(http://derpharmachemica.com/archive.html)

Synthesis, characterization, Hirshfeld analysis, crystal and molecular structure studies of 2,6-difluoro phenoxy acetic acid

Yasser Hussein Issa Mohammed[1#], S. Naveen[2#], Hamid Hussein Issa[3], H. R. Manjunath[4], N. K. Lokanath[5] and Shaukath Ara Khanum[1*]

[1]*Department of Chemistry, Yuvaraja's College, University of Mysore, Mysuru, India*
[2]*Institution of Excellence, Vijnana Bhavana, Manasagangotri, University of Mysore, Mysuru, India*
[3]*Department of Chemistry, Education and Applied Science College, University of Hajah, Yemen*
[4]*Department of Physics, Acharya Institute of Technology, Soldevanahalli, Bengaluru, India*
[5]*Department of Studies in Physics, Manasagangotri, University of Mysore, Mysuru, India*

ABSTRACT

The title compound, 2,6-difluoro phenoxy acetic acid was synthesized by refluxing 2,6-difluorophenol with ethyl chloroacetate to achieve 2,6-difluoro phenoxy ethyl acetate, followed by the hydrolysis with sodium hydroxide in presence of ethanol. The product obtained was characterized by spectroscopic techniques and finally the structure was confirmed by X-ray diffraction studies. The compound crystallizes in the monoclinic crystal system with the space group $P2_1/n$ with unit cell parameters a = 4.2443(3) Å, b = 20.0337(14) Å, c = 9.2243(8) Å, β = 96.258(5)° and Z=4. The structure exhibits both inter and intra-molecular hydrogen bonds of the type C—H...O, O—H...O and C—H...F respectively. In the crystal, adjacent molecules form inversion-related dimers *through strong O-H...O hydrogen bonds, generating* $R_2^2(8)$ *ring motif. Hirshfeld analysis was carried out in order to understand the packing pattern and intermolecular interactions.*

Keywords: Phenoxy acetic acid, Crystal structure, Inversion related dimer, Hirshfeld Surfaces, C-H…O interaction**.**

INTRODUCTION

Phenoxyacetic acids are interesting to study by various chemical and physical methods. Also, it is very useful in the treatment of insulin resistance and hyperglycemia which has been investigated by various researchers [1-3]. Analogues of phenoxy ethanoic acid are considered to be very important compounds in the field of medicinal chemistry and the compounds were found to have good antifungal activity against pathogenic fungi and possess moderate activity against gram negative bacteria in comparison to standard ciprofloxacin [9]. Phenoxyacetic acid and substituted phenoxyacetic acids have potential biological properties and are widely used in herbicides [4] and pesticide [5] formulations. Anti-micro bioactivities [6], anticancer, antitumour, analgesic, antiinflammatory, plant growth regulation, inhibition of tillage [7, 8] are some of their other reported properties. The phenoxy acetic acid analogues show very good anti ulcerogenic activity, cyclooxygenase activity, anti-convulsant activity [10,12] and also exhibits the antitumor activity on Ehrlich ascites tumor cells [11]. In view of their broad spectrum of medicinal properties and as a part of our ongoing work on synthesis and characterization of novel compounds, the title compound was synthesized. The compound obtained was characterized spectroscopically and finally the structure was confirmed by X-ray diffraction studies.

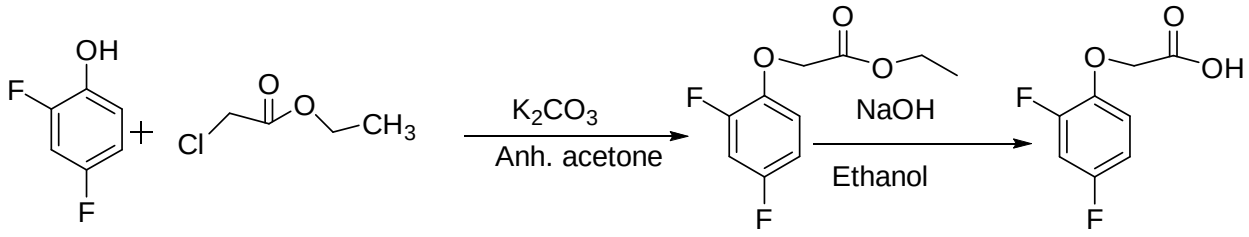
MATERIALS AND METHODS

All the chemicals were purchased from Sigma Aldrich Chemical Co. ^{1}H NMR spectra was recorded on a Bruker 400 MHz in $CDCl_3$ and the chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass

spectra were obtained with a VG70-70H spectrophotometer. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyzer. The results of elemental analyses were within ±0.4% of the theoretical values.

Synthesis of 2,6-difluoro phenoxy acetic acid

A mixture of 2,6-difluorophenol (0.05 mol), ethyl chloroacetate (0.075 mol) and anhydrous potassium carbonate (0.075 mol) in dry acetone (50 ml) was refluxed for 14 hrs. The reaction mixture was cooled and the solvent was removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate, and extracted with ether (3 × 30 ml). The ether layer was washed with 10% sodium hydroxide solution (3 × 30 ml) followed by water (3 × 30 ml) and then dried over anhydrous sodium sulfate and evaporated to afford 2,6-difluoro phenoxy ethyl acetate. Then 2,6-difluoro phenoxy ethyl acetate (0.02 mol) was dissolved in ethanol (15 mL) and sodium hydroxide (0.035 mol) solution in water (5 mL) was added. The mixture was refluxed for 12 hrs and the reaction mixture was cooled and acidified with 5 N hydrochloric acid. The precipitate was filtered, washed with water, and finally recrystallized from ethanol to get the title compound. Yield (82%), M.P = 60-62º C



Scheme(1): synthesis of 2,4- difluoro phenoxy acetic acid

^{1}H NMR ($CDCl_3$): σ: 4.79 (s, 2H, OCH_2), 6.86-7.01 (M, 3H, Ar-H), 8.77 (s, IH, OH); LC–MS m/z 189 (M+1). Anal. Calcd. for $C_8H_6F_2O_2$: C, 51.07; H, 3.21; F, 20.20; O, 25.51 Found: C, 51.38; H, 2.97; F, 20.11; O, 25.26 %.

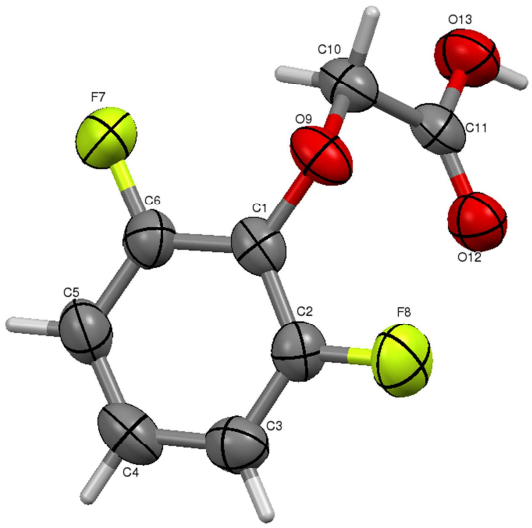


Figure 1: ORTEP of the molecule with thermal ellipsoids drawn at 50% probability

2.2 Crystal Structure Determination

A white coloured rectangle shaped single crystal of dimensions 0.3×0.27×0.25 mm of the title compound was chosen for an X-ray diffraction study. The X-ray intensity data were collected at a temperature of 296 K on a Bruker Proteum2 CCD diffractometer equipped with an X-ray generator operating at 45 kV and 10 mA, using CuK_α radiation of wavelength 1.54178 Å. Data were collected for 24 frames per set with different settings of φ (0° and 90°), keeping the scan width of 0.5°, exposure time of 2 s, the sample to detector distance of 45.10 mm and 2θ value at 46.6°. A complete data set was processed using *SAINT PLUS* [15]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs [16]. All the non-hydrogen atoms were revealed in the first difference Fourier map itself. All the hydrogen atoms were positioned geometrically (C–H = 0.93 Å, O–H = 0.82 Å) and refined using a riding model with U_{iso}(H) = 1.2 U_{eq} and 1.5 U_{eq} (O). After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residuals saturated to 0.0326. The geometrical calculations were carried out using the program *PLATON*

[17]. The molecular and packing diagrams were generated using the software *MERCURY* [18]. The details of the crystal structure and data refinement are given in **Table 1**. **Figure 1** represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

Hirshfeld surface calculations

Hirshfeld surface analyses were carried out and finger print plots were plotted using the software CrystalExplorer 3.0 [19]. The d_{norm} plots were mapped with colour scale in between −0.18 au (blue) and 1.4 au (red). The 2D fingerprint plots [20, 21] were displayed by using the expanded 0.6–2.8 Å view with the d_e and d_i distance scales displayed on the graph axes. When the cif file was uploaded into the CrystalExplorer software, all bond lengths to hydrogen were automatically modified to typical standard neutron values i.e., C–H = 1.083Å.

Table 1: Crystal data and structure refinement table

Parameter	Value
CCDC deposit No.	CCDC 1450407
Empirical formula	$C_8H_6F_2O_3$
Formula weight	188.13
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 4.2443(3) Å b = 20.0337(14) Å c = 9.2243(8) Å β = 96.258(5)°
Volume	779.66(10) Å^3
Z, Calculated density	4, 1.603 Mg/m^3
Absorption coefficient	1.350 mm^{-1}
$F_{(000)}$	384
Crystal size	0.3 x 0.27 x 0.25 mm
Theta range for data collection	4.41° to 64.30°
Limiting indices	$-4 \leq h \leq 4$, $-22 \leq k \leq 23$, $-10 \leq l \leq 9$
Reflections collected / unique	4535/ 1258 [R(int) = 0.0904]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1258 / 0 / 119
Goodness-of-fit on F^2	1.093
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0544, $wR2$ = 0.1473
R indices (all data)	$R1$ = 0.0862, $wR2$ = 0.1622
Largest diff. peak and hole	0.242 and −0.250 e. Å^{-3}

RESULTS AND DISCUSSION

The molecule is non-planar. The dihedral angle between the difluorophenyl ring and the methanoic acid moiety is 67.57(1)°. The structure exhibits both inter and intra-molecular hydrogen bonds of the type C—H...O, O—H...O. The inter-molecular hydrogen bond C10—H10B...O9 has a length of 3.350(2) Å and an angle of 135° with a symmetry code *-1+x, y, z* and the other hydrogen bond O13—H13...O12, which has a length of 2.652(3) Å and an angle of 168° with symmetry code *-x,1-y,-z* forms *inversion-related dimers* generating $R_2^2(8)$ ring motif **Figure 2**. In the crystal, these dimeric units are connected further *via* weak C—H...O hydrogen bond together with π...π interactions forming a three dimensional structure along [001] **Figure 3**.

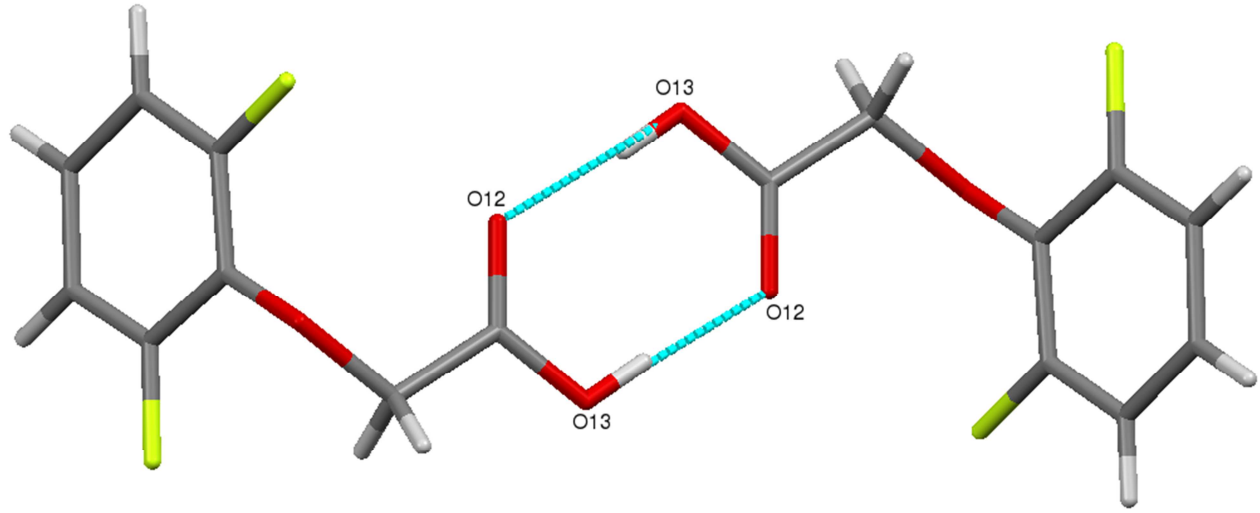


Figure 2: A view of $R_2^2(8)$ ring motif generated by inter-molecular O—H…O hydrogen bond. The dashed lines represent inter-molecular hydrogen bonds

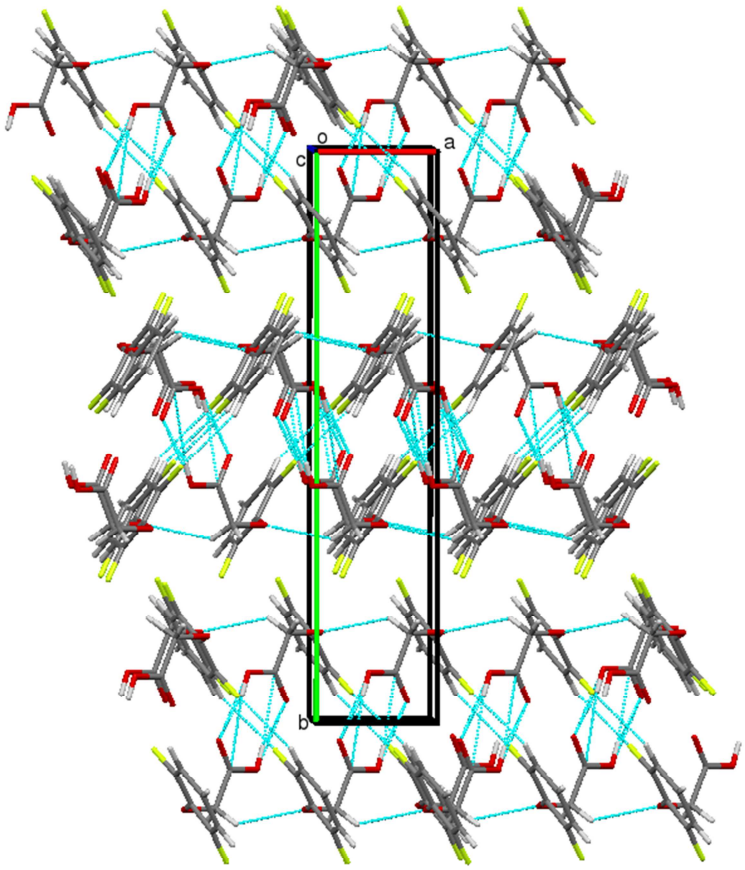


Figure 3: Packing diagram of the molecules when viewed down along the [001] axis

Hirshfeld surface studies

Hirshfeld surface analysis is an effective tool for exploring packing modes and intermolecular interactions in molecular crystals, as they provide a visual picture of intermolecular interactions and of molecular shapes in a crystalline environment. Surface features characteristic of different types of intermolecular interactions can be identified, and these features can be revealed by colour coding distances from the surface to the nearest atom exterior (d_e plots) or interior (d_i plots) to the surface. This gives a visual picture of different types of interactions present and also reflect their relative contributions from molecule to molecule. Further, 2D fingerprint plots (FP), in

particular the breakdown of FP into specific atom…atom contacts in a crystal, provide a quantitative idea of the types of intermolecular contacts experienced by molecules in the bulk and presents this information in a convenient colour plot. Hirshfeld surfaces comprising d_{norm} surface and Finger Print plots were generated and analysed for the title compound in order to explore the packing modes and intermolecular interactions. The two dimensional fingerprint plots from Hirshfeld surface analyses **Figure 4**, illustrates the difference between the intermolecular interaction patterns and the relative contributions to the Hirshfeld surface (in percentage) for the major intermolecular contacts associated with the title compound. Importantly, O...H (26.2%) bonding appears to be a major contributor in the crystal packing, whereas the F...H (25.3%), H...H (19%), C...H(10.6%) plots also reveal the information regarding the intermolecular hydrogen bonds thus supporting for C--H...O intermolecular interactions. This intermolecular contact is highlighted by conventional mapping of d_{norm} on molecular Hirshfeld surfaces and is shown in **Figure 5**. The red spots over the surface indicate the intercontacts involved in hydrogen bond. The dark-red spots on the d_{norm} surface arise as a result of the short interatomic contacts, i.e., strong hydrogen bonds, while the other intermolecular interactions appear as light-red spots.

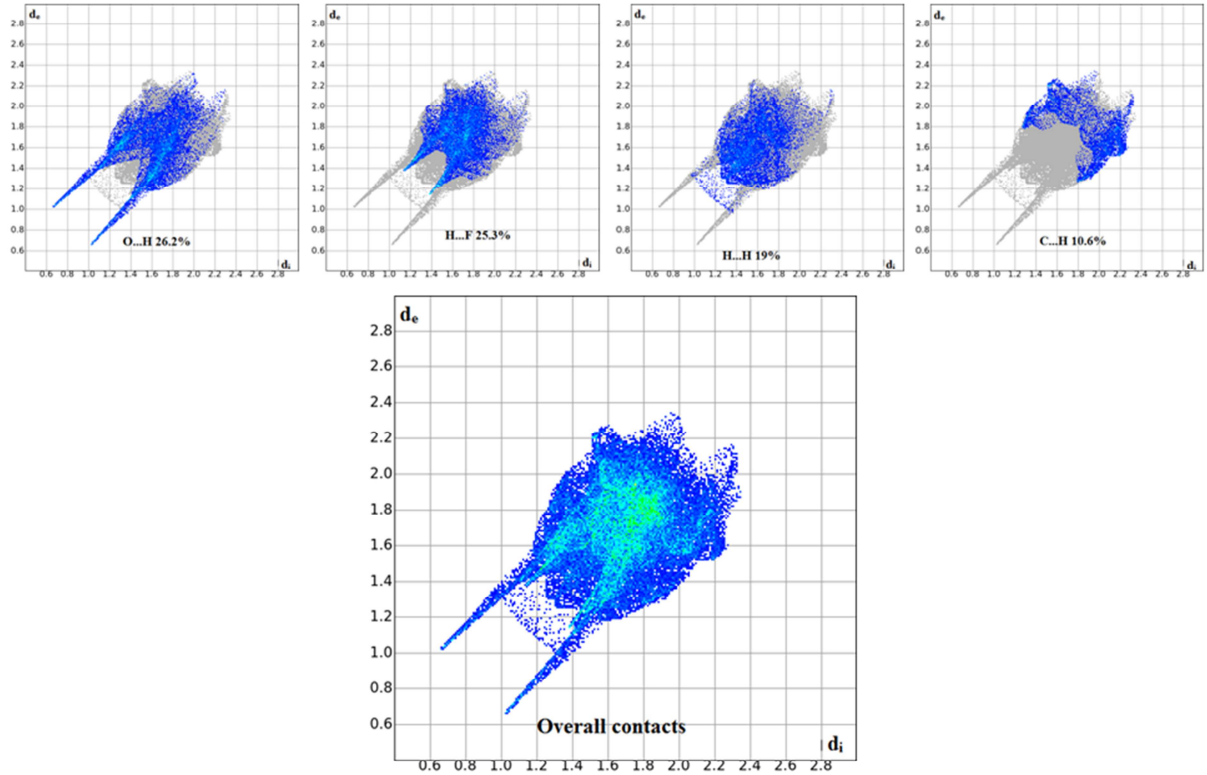


Figure 4: Fingerprint plots of the title compound showing O...H, H…F, H...H and C...H interactions. d_i is the closest internal distance from a given point on the Hirshfeld surface and d_e is the closest external contacts

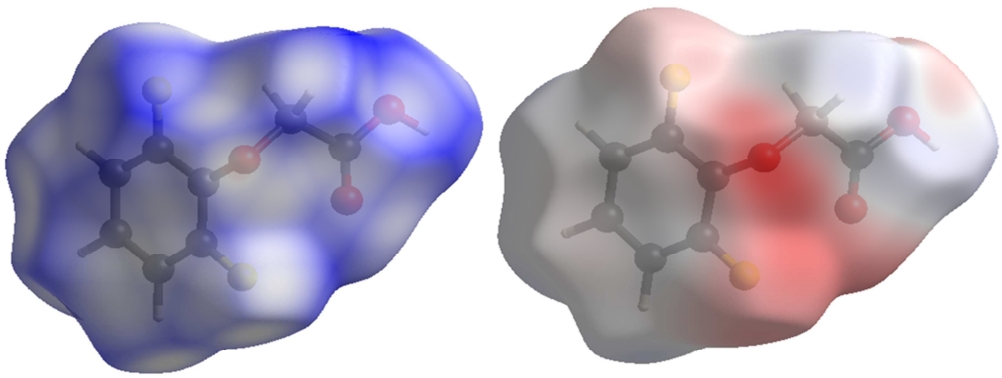


Figure 5: d_{norm} and electrostatic potential mapped on Hirshfeld surface for visualizing the intermolecular contacts

Acknowledgments
The authors are grateful to the Institution of Excellence, Vijnana Bhavana, University of Mysore, India, for providing the single-crystal X-ray diffractometer facility. One of the authors Yasser Hussain Issa Mohammed wants to thank University of Hajah, Yemen for the financial support.

REFERENCES

[1] R. Gurumurthy, K. Sathyanarayana, M. Gopalkrishnan, *Bull. Chem. Soc. Jpn.*, **1992,** 65, 1096-1101.
[2] B. Karthikeyan, R. Gurumurthy, M. Gopalakrishnan, M. Selvaraju, *Asian Chem. Lett.*, **1998,** 2-3 97-101.
[3] C. Timchalk, *Toxicology*, **2004,** 200(1), 1-19.
[4] T. Csrhati, E. Forgacs, *J. Chromatogr. B: Biomed. Sci. Appl.*, **1998,** 717, 157-178.
[5] A.S. Crafts, *Adv. Pest. Control Res.*, **1957,** 1, 39-79.
[6] S. Sarac, C. Safak, H. Erdogan, U. Abbasoglu, Y. Gunay, *Eczacilik Fak. Derg*., **1991,** 11(1), 1. [7] M. Negwar, 7th ed, *Organic Chemical Drugs and their Synonyms*, Vol 1, Academic Verlag, Berlin, **1996**.
[8] H. Marlin, *The Scientific Principles of Crop Protection*, Arnold, London, **1973**.
[9] R. Dahiya, R. Kaur, Aust. *J. Basic Appl. Sci.*, **2007,** 1, 525-532.
[10] B. S. Sudha, S. Shashikanth, S. A. Khanum, S. N. Shriharsha, *Indian J. Pharm. Sci.*, **2003,** 65, 465–470.
[11] M. Al-Ghorbani, V. Vigneshwaran, V. Lakshmi Ranganatha, B.T. Prabhakar, S. A. Khanum, *Bioorg. Chem.*, **2015,** 60, 136–146.
[12] Prashanth T, Prabhu Thirusangu, B.R. Vijay Avin, V. Lakshmi Ranganatha, B.T. Prabhakar and Shaukath Ara Khanum, *Eur. J. Med. Chem.*, **2014,** 87, 274-283.
[13] Naveen S., Benakarpasad S.B., Manjunath H.R., Anandakumar C.S., Rangappa K.S., Lokanath N.K. and Sridhar M.A., *Mol. Cryst. Liq. Cryst.*, **2015,** 616-143-150.
[14] Dinesha, Viveka S., Priya B.K., Ranganatha Pai K.S., Naveen S., Lokanath N.K. and Nagaraja G.K., *Eur. J. Med. Chem.*, **2015,** 104, 25-32.
[15] Bruker, **2004**, APEX2, SAINT-Plus and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.
[16] G. M. Sheldrick, *Acta Cryst*., **2015**, A71, 3-8.
[17] A. L. Spek, *Acta. Cryst*., **1990**, A46, C34-C37.
[18] C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek, P. A. Wood, *J. Appl. Cryst*., **2008**, 41, 466.
[19] S. K. Wolff, D. J. Grimwood, J. J. McKinnon, D. Jayatilaka, M. A. Spackman, Crystal Explorer 3.0, University of Western Australia, Perth, Australia, **2001**.
[20] K. S. Saikat, *CrystEngComm*., **2013**, 9, 1772-1781.
[21] K. S. Saikat, *J. Mol. Structure*., **2014**, 1064, 70-75.