Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2018, 7 (3): 513-520

(International Peer Reviewed Journal)

Synthesis, Characterization, Crystal Structure and Hirshfeld Surface Analysis of 4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole-2-yl) Phenyl Carboxylic acid Monohydrate

M. K. Ravindra[1], Karthik Kumara[2], K. M. Mahadevan[1], H. S. Bhojya Naik[3], Kakarla Raghava Reddy[4], N. K. Lokanath[2] and S. Naveen[5]*

1. Department of Chemistry, Kuvempu University, P. G. Center, Kadur 577 548, **INDIA**
2. Department of Studies in Physics, University of Mysore, Manasagangotri, Mysuru 570 006, **INDIA**
3. Department of Industrial Chemistry, Kuvempu University, Shankaraghatta 577451, **INDIA**
4. The School of Chemical and Biomolecular Engineering, The University of Sydney, NSW 2006, **AUSTRALIA**
5. Department of Physics, School of Engineering and Technology, Jain University, Bangalore 562112, **INDIA**

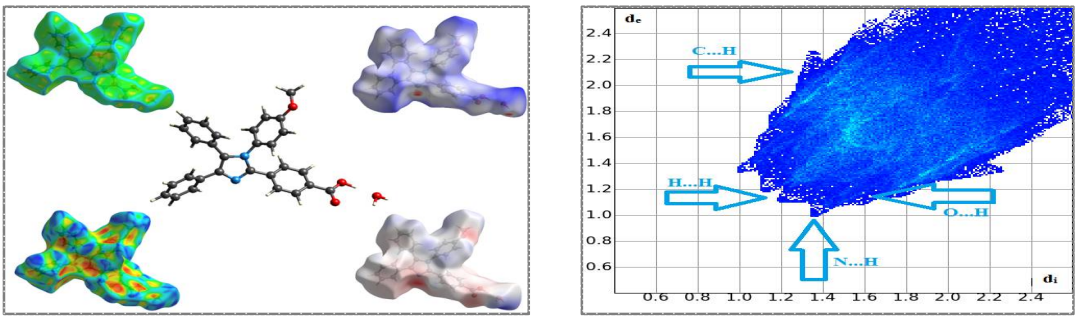
Email: s.naveen@jainuniversity.ac.in

Accepted on 21st April, 2018

ABSTRACT

A novel and rapid procedure for the synthesis of 4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole-2-yl)phenyl carboxylic acid through a multi-component reaction of 4-methoxyaniline, Benzil, Ammonium acetate and 4-formyl-benzoic acid in glacial acetic acid and catalytic amount of concentrated H_2SO_4 has been reported. The product obtained was characterized by IR, ^{1}H-NMR, ^{13}C NMR, SEM and EDAX spectroscopic techniques and finally the structure was confirmed by X-ray diffraction studies. The crystal structure reveals π electron delocalization in the molecule. Inter- and intra-molecular hydrogen bonds of the type O-H…O and C-H…O interactions help in the stability of the structure.

Graphical Abstract



Fingerprint plot of the title compound (Atom $_{inside}$…Atom $_{outside}$).

Keywords: 4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole-2-yl)phenyl carboxylic acid, Synthesis, X-ray diffraction, SEM, EDAX, Hirshfeld Surface, C-H... π interactions.

INTRODUCTION

Imidazole derivatives are biologically and pharmaceutically more significant compounds as they possess antidiabetic, antihypertensive, and anti-inflammatory activities [**1**]. Imidazolines are also known as very important synthons for the preparation of various bio active compounds [**2, 3**]. Literature survey reveals that synthetically produced imidazole compounds offer enormous scope in the field of medicinal chemistry due to their anti-antihelmintic [**4**], cardiovascular [**5, 6**], analgesic and anti-inflammatory [**7-10**], anti-neoplastic, anti- fungal [**11, 12**], anti-filarial, anti-viral and anti- ulcer activities [**13-15**]. Hence, due to their wide range of biological applications and in continuation of our work on such novel heterocyclic compounds [**16-19**], hereby we report the synthesis, characterization and crystal structure analysis of 4-(1-(4-methoxyphenyl)-4,5-diphenyl-*1H*-imidazole-2-yl)phenyl carboxylic acid.

MATERIALS AND METHODS

Chemical reagents used for the synthesis and analysis were procured commercially from Sigma Aldrich, India. Analytical grade solvents were purchased from Loba Chem Pvt Ltd., Mangalore. The melting point was measured on a Boetius-Mikroheiztisch the company "VEB" weighing Rapido Radebeul / VEB NAGEMA "measured and are uncorrected. TLC was performed by using aluminium foil fluorescent indicator from Merck KGaA (silica gel 60 F254, layer thickness 0.2 mm). Rf -values (run level relative to the solvent front). ^{1}H-NMR spectrum was recorded on a Jeol 400 MHz. using dimethyl sulfoxide (DMSO) solvent, "Gemini 2000" (400/100 MHz). The ATR spectrum was recorded on a FT-IR spectrometer "IFS 28" by "Bruker". Crystal structure was recorded on a RIGAKU Single-crystal X-ray diffractometer. SEM (Scanning Electron Microscope) and EDAX (Energy Dispersion X-ray Analyzer) were analyzed by using Hitachi (Table top, Model TM 3000).

Synthesis of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole (5): A mixture of mole equivalent of 4-methoxy aniline (1 mmol, 0.123 g), benzyl (1 mmol, 0.210 g), ammonium acetate (1 mmol, 0.75 g) and 4-formylbenzoic acid (1mmol, 0.150 g) were taken in glacial acetic acid (20 mL).The reaction mixture was then subjected to ultrasonication for 10 to 20 min and the reaction mixture was refluxed for 4-5 h on heating mantle. The progress of the reaction was monitored by TLC [2:8 (v:v) ethyl acetate-pet ether mixture]. After the completion of the reaction, the mixture was cooled to room temperature and poured into crushed ice. The reaction mixture was quenched by aqueous sodium bicarbonate solution and the product was extracted with ethyl acetate. The crude product was then recrystallized in hot ethanol to get fine crystals of analytically pure 4-(1-(4-methoxyphenyl)-4, 5-diphenyl-*1H*-imidazole-2-yl)phenyl carboxylic acid with good yield (70%). M. P. 150^0-154^0 C. The reaction scheme is shown in figure 1.

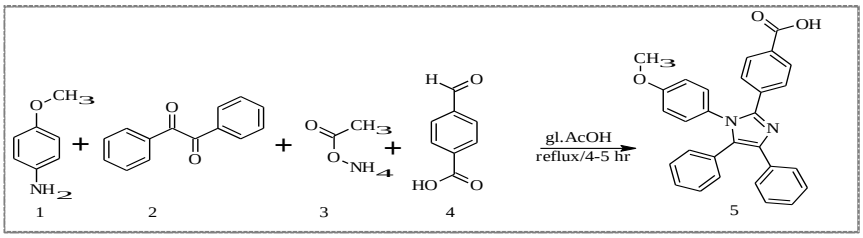


Figure 1. Reaction scheme

Spectral Analysis data: IR (KBr) (ν_{max} cm^{-1}): 1478.77 (C=C), 1514.04 (C=N), 1596.99 (acidic C=O), 2958.52(-C-H), 3051.58(Ar C-H), 3440.45 (acid-OH). ^{1}H NMR (400MHz, DMSO, δ (ppm)):3.710 (s 3H), 6.86(d J=8.8 2H Ar-H), 7.150-7.275(m 7H Ar-H), 7.311 (t J=6.4 3H Ar-H), 7.499-7.518 (m 4H Ar-H), 7.83(d J=8.4 2H Ar-H), 12.969 (brs 1H, COOH). ^{13}C NMR (400MHz, $CDCl_3$, δ (ppm)): 55.7, 114.6, 127.0, 127.6, 128.2, 128.6, 128.8, 129.2, 129.4, 129.6, 130.0, 130.1, 131.3, 131.96, 133.6, 134.6, 138.4, 146.02, 159.68, 170.50.

SEM and EDAX Analysis: The exterior morphology, an important characteristic of chemical compound, of the 4-(1-(4-methoxyphenyl)-4, 5-diphenyl-*1H*-imidazole-2-yl)phenyl carboxylic acid was studied with Scanning Electron Microscope (Fig. 2).

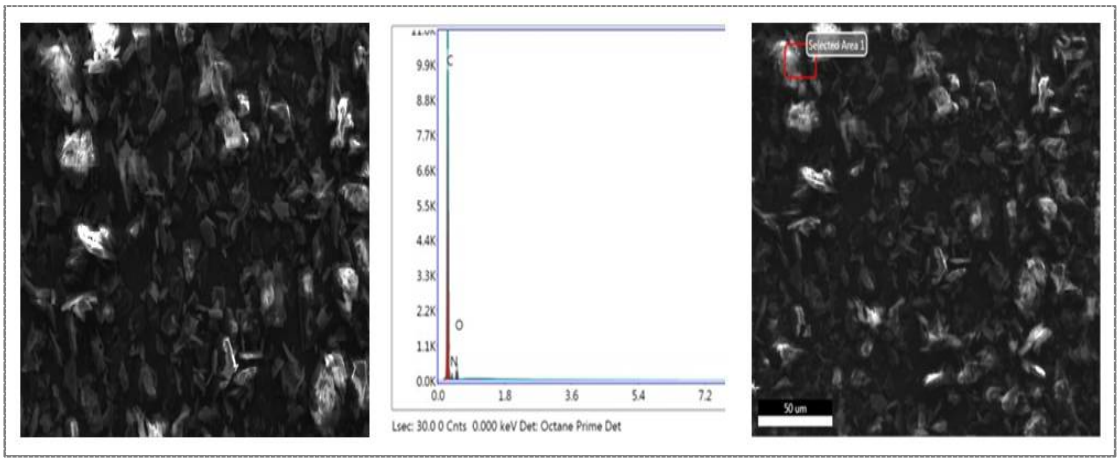


Figure 2. SEM image and EDAX spectra of 4-(1-(4-methoxyphenyl)-4,5-diphenyl-*1H*-imidazole-2-yl)phenyl carboxylic acid

The SEM micrograph exhibits the soft surface morphology and cutting edges having rod like shape for 4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole-2-yl)phenyl carboxylic acid compound. The width and length of the rods were observed to be 50 µm. Further, it was confirmed that the rod like structures are not distributed uniformly. Elemental composition of the title compound was studied using EDAX (Fig. 2). The CNO composition of compound from EDAX spectrum of 4-(1-(4-methoxyphenyl)-4, 5-diphenyl-1H-imidazole-2-yl)phenyl carboxylic acidic carbon (81.23%), nitrogen (10.07%), and oxygen(8.69%) atoms.

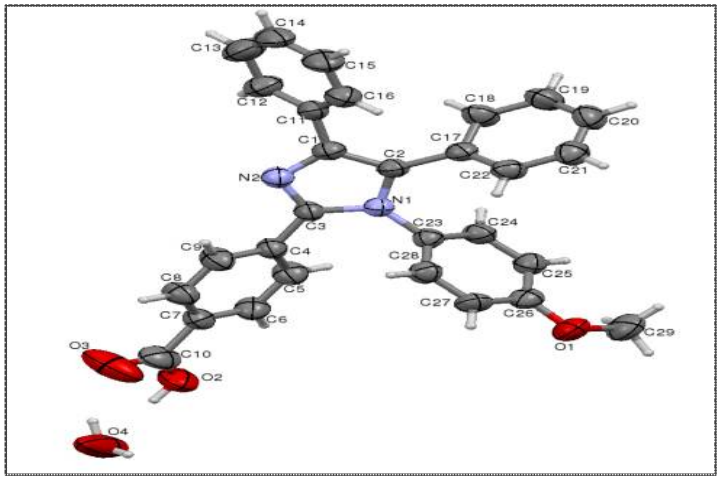


Figure 3: ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability. The typical data of crystal structure and data refinement are given in table 1. The list of selected bond lengths and bond angles are given in tables 2.

X-ray diffraction studies: A white colored rectangle shaped single crystal of dimensions 0.29×0.26×0.24 mm of the title compound was chosen for an X-ray diffraction study. X-ray intensity data for the title compound was collected at temperature 293 K on Rigaku XtaLAB Mini Mercury 3 diffractometer with X-ray generator operating at 50 kV and 12 mA, using MoK_{α} radiation of

wavelength 0.71073 Å.Data were collected with χ fixed at 54^0 and for different settings of φ (0^0 and 360^0), keeping the scan width of 0.5^0, exposure time of 4 s, the sample to detector distance of 50 mm. The complete intensity data sets were processed using *CRYSTAL CLEAR* [20]. The crystal structure was solved by direct method and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* [21]. All the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were positioned geometrically, with C-H = 0.93–0.98 Å and refined using a riding model with U_{iso}(H) = 1.2 U_{eq}(C, N), U_{iso}(H) = 1.5 U_{eq}(C_{methyl}). A total of 320 parameters are refined with 5598 unique reflections. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residuals saturated to 0.0952. The geometrical calculations were carried out using the program *PLATON* [22]. The molecular and packing diagrams were generated using the software *MERCURY* [23]. Figure 3 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

Table 1. Crystal data and structure refinement details.

Empirical formula	$C_{29}H_{24}N_2O_4$
Formula weight	464.50
Temperature	293(2) K
Wavelength	0.71073 Å
Reflections for cell determination	3774
θ range for above	3.74^o to 27.5^o
Crystal System	Monoclinic
Space Group	*P2*
Cell dimensions	*A* = 10.216(9) Å
	b = 9.845(9) Å
	c = 13.241(12) Å
	$\beta = 98.243(10)^o$
Volume	1318(2) $Å^3$
Z	2
Density (calculated)	1.170 mgm^{-3}
Absorption coefficient	0.079 mm^{-1}
F_{000}	488
Crystal size	0.29 x 0.26 x 0.24 mm
Index ranges	$-13 \le h \le 8$
	$-12 \le k \le 10$
	$-17 \le l \le 16$
Reflections collected	7742
Independent reflections	5598 [R_{int} = 0.0458]
Absorption correction	Multi-scan
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5598 / 1 / 320
Goodness of fit on	1.027
R indices [I > 2s(I)]	*R1* = 0.0952, *ωR2* = 0.2603
Largest diff. Peak and hole	1.183 and -0.563 e $Å^{-3}$

Crystal structure studies: The imidazole ring is planar with a maximum deviation of 0.010(4) Å for the atom N2. The rings C11-C16 and C17-C22 are twisted by the angles $49.2(2)^0$ and $55.2(2)^0$ respectively with respect to the imidazole ring, which are different from the values of $15.2(3)^0$ and $68.(3)^0$ reported earlier [24]. The methoxyphenyl ring and the phenyl ring containing the carboxylic acid group bisects the plane of the imidazole ring which is confirmed by the dihedral angle values of $58.9(2)^0$ and $43.8(2)^0$ respectively about the least squares plane of the imidazole ring. The bond values of 1.394(5) Å and 1.367(5) Å for N1-C2 and N1-C3 have a partial double bond character as they are significantly shorter than Csp^2 *-N* bond distance. The molecules exhibits both inter and intramolecular hydrogen bonds of the type C-H...O and O-H...O which helps in stabilizing the crystal structure. Further the molecule also exhibits C-H... π interactions and packing of the molecules indicate that the molecules exhibit layered stacking and run in to chains in a zig-zag pattern when viewed down along the *c* axis (Figure 4).

Table 2. Bond lengths (Å) and Bond angles (^{0}).

Bond lengths (Å)				Bond angles (^{0}).			
Atoms	**Angle**	**Atoms**	**Angle**	**Atoms**	**Angle**	**Atoms**	**Angle**
O1-C26	1.352(5)	C18-C19	1.378(7)	C26-O1-C29	119.1(4)	O2-C10-C7	115.9(6)
O1-C29	1.426(7)	C4-C9	1.380(6)	C3-N1-C2	107.7(3)	C11-C12-C13	118.7(6)
O2-C10	1.279(8)	C4-C5	1.381(6)	C3-N1-C23	126.5(3)	C16-C11-C12	118.5(4)
O3-C10	1.232(8)	C4-C3	1.482(5)	C2-N1-C23	125.5(3)	C16-C11-C1	120.8(4)
N1-C3	1.367(5)	C6-C5	1.405(6)	C26-C25-C24	119.5(4)	C12-C11-C1	120.5(4)
N1-C2	1.394(5)	C26-C27	1.393(7)	C22-C17-C18	118.0(4)	N2-C3-N1	111.4(3)
N1-C23	1.436(5)	C2-C1	1.395(5)	C22-C17-C2	122.0(4)	N2-C3-C4	123.2(3)
C25-C26	1.397(6)	C12-C11	1.404(6)	C18-C17-C2	119.9(4)	N1-C3-C4	125.3(3)
C25-C24	1.409(6)	C12-C13	1.410(8)	C6-C7-C8	118.7(4)	C24-C23-C28	120.5(4)
C17-C22	1.398(6)	C11-C16	1.394(7)	C6-C7-C10	123.0(5)	C24-C23-N1	120.4(3)
C17-C18	1.400(6)	C11-C1	1.476(5)	C8-C7-C10	118.3(4)	C28-C23-N1	119.0(3)
C17-C2	1.462(5)	C23-C28	1.389(6)	C23-C24-C25	120.2(4)	C20-C21-C22	119.3(4)
C7-C6	1.362(7)	C21-C20	1.378(8)	C3-N2-C1	106.0(3)	C15-C14-C13	119.9(5)
C7-C8	1.398(6)	C14-C15	1.349(9)	C21-C22-C17	121.6(4)	C8-C9-C4	120.7(4)
C7-C10	1.505(7)	C14-C13	1.361(11)	C19-C18-C17	120.9(4)	C21-C20-C19	120.5(4)
C24-C23	1.368(6)	C9-C8	1.366(6)	C9-C4-C5	119.1(4)	C28-C27-C26	120.2(4)
N2-C3	1.325(5)	C20-C19	1.399(8)	C9-C4-C3	117.4(4)	C14-C15-C16	121.6(6)
N2-C1	1.380(5)	C27-C28	1.393(6)	C5-C4-C3	123.5(4)	C9-C8-C7	120.9(4)
C22-C21	1.378(6)	C15-C16	1.369(7)	C7-C6-C5	120.7(4)	C15-C16-C11	120.4(5)
--	--	--	--	O1-C26-C27	116.2(4)	C4-C5-C6	119.9(4)
--	--	--	--	O1-C26-C25	124.2(4)	C18-C19-C20	119.5(5)
--	--	--	--	C27-C26-C25	119.6(4)	N2-C1-C2	110.3(3)
--	--	--	--	C1-C2-N1	104.5(3)	N2-C1-C11	121.1(3)
--	--	--	--	C1-C2-C17	130.0(3)	C2-C1-C11	128.5(4)
--	--	--	--	N1-C2-C17	125.4(3)	C23-C28-C27	119.9(4)
--	--	--	--	O3-C10-O2	123.8(5)	C14-C13-C12	120.9(6)
--	--	--	--	O3-C10-C7	120.4(5)	--	--

RESULTS AND DISCUSSION

A novel and rapid procedure for the synthesis of 4-(1-(4-methoxyphenyl)-4, 5-diphenyl-1H-imidazole-2-yl)phenyl carboxylic acid through a multi-component reaction of 4-methoxyaniline, Benzil, Ammonium acetate and 4-formyl-benzoic acid in glacial acetic acid and catalytic amount of concentrated H_2SO_4 has been reported. The product obtained was characterized by IR, ^{1}H-NMR, ^{13}C NMR, SEM and EDAX spectroscopic techniques and finally the structure was confirmed by X-ray diffraction studies. The yield is 70%.

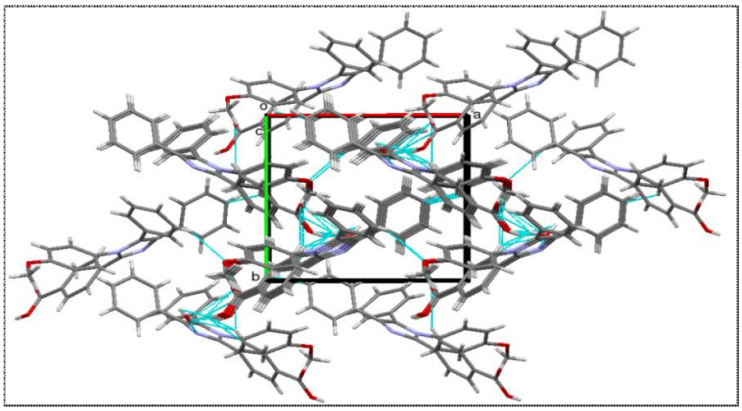


Figure 4. Packing of the molecules when viewed down along the *c* axis. The blue dotted lines represent inter-molecular hydrogen bonds.

Hirshfeld surface analysis: Hirshfeld surface analysis is used for visually analyzing intermolecular interactions in crystal structures employing molecular surface contours and 2D fingerprint plots were used to examine the molecular shapes. It was carried out and fingerprint plots were plotted using Crystal Explorer version 3.0 [**25**]. The d_{norm} plots were mapped with color scale in between -0.224 au (blue, shorter intermolecular contacts) and 2.368 au (red, longer intermolecular contacts) respectively. The expanded 2D fingerprint plots were displayed in the range of 0.6-2.8 Åwith the d_e and d_i distance scales displayed on the graph axes. Shaped-index surfaces are specified on the basis of local curvature of the Hirshfeld surface **[26]** as shown in figure 5.

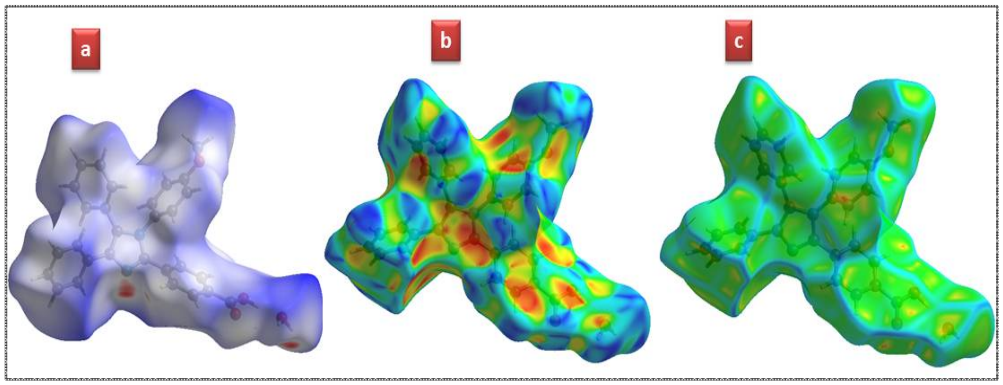


Figure 5. a) d_{norm} mapped with b) shape index, c) curvedness of the title compound.

The red concave region on shape index is the acceptor and the blue region is the donor atoms. The dark-red spots on the d_{norm} surface arise as a result of the short interatomic contacts. The adjacent red-blue indicates the C—H…π staking interactions over the surface. The fingerprint plots reveal the percentage of contribution of intermolecular contacts to the surface which is represented in terms of color codes. H···H contacts has maximum (50.3%) contribution whereas N···H contact has minimum (4.5%) contribution. Similarly, C···H (22.7%) and O···H (14.1%) also contacts contribute to the total area of the surface as shown in figure 6.

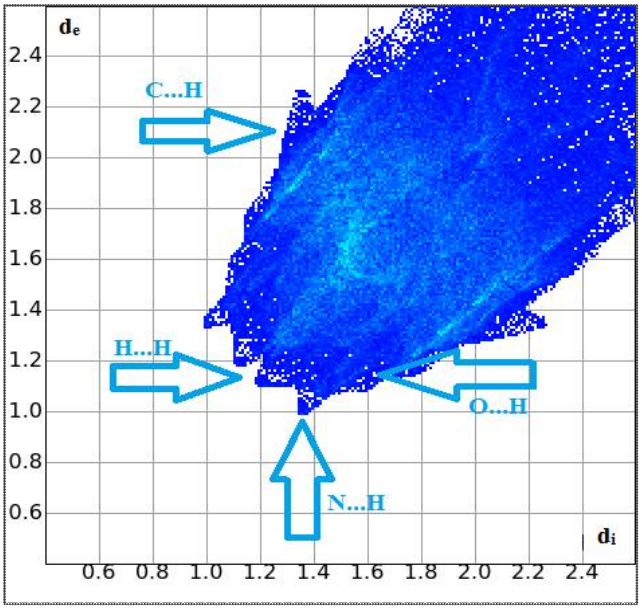


Figure 6. Fingerprint plot of the title compound (Atom $_{inside}$…Atom $_{outside}$).

APPLICATION

Imidazoles exhibit various biological activities and by studying their crystal and molecular structures might provide a deeper insight in understanding their mechanisms in the biological systems.

CONCLUSIONS

The title compound 4-(1-(4-methoxyphenyl)-4, 5-diphenyl-1H-imidazole-2-yl)phenyl carboxylic acid has been synthesized and structure elucidation was carried out by spectroscopic and X-ray diffraction techniques. The SEM images confirmed the width and length of the rods were of the order of 50 µm and EDAX spectrum outputted elemental composition. The methoxyphenyl ring and the phenyl ring containing the carboxylic acid group bisects the plane of the imidazole ring and the structure is stabilized by both inter and intra-molecular hydrogen bonds. Hirshfeld surface analysis for visually analyzing intermolecular interactions in crystal structures employing molecular surface contours and 2D fingerprint plots throw light on molecular shapes.

ACKNOWLEDGEMENTS

The authors are grateful to the National Single Crystal Diffractometer Facility, Department of Studies in Physics, University of Mysore, Manasagangotri, Mysuru for providing X-ray intensity data and DST-FIST for providing financial support under the research grant scheme SR/FST/ETT-378/2014.

REFERENCES

[1]. A. Chawla, A. Sharma and A. K. Sharma, *Der Pharma Chem.*, **2012**, 4(1), 116-140.
[2]. F. Rondu, G. Le Bihan, X. Wang, A. Lamouri, E. Touboul, G. Dive, T. Bellahsene, B. Pfeiffer, P. Renard, B. Guardiola-Lemaitre, D. Manechez, L. Penicaud, A. Ktorza, J. J. Godfroid, *J. Med. Chem.*,**1997**, 40, 3793.
[3]. A. Davood, E. Alipour, A. Shafiee, Turk. *J. Chem*., **2008**, 32, 389 – 395.
[4]. E. Lunt, C. G. Newton, C. Smith, G. P. Stevens, M. F. Stevens, C. G. Straw, R .J. Walsh, P. J. Warren, C. Fizames, F. Lavelle. *J. Med. Chem.*, **1987**, 30(2), 357- 66.
[5]. D. W. Robertson, E. E. Beedle, J. H. Krushinski, G. D. Pollock, H. Willson, J. S. Wyssvl, Hayes, *J. Med. Chem.*, **1985**, 28(6),717-27.
[6]. P. W. Erhardt , A. A. Hagdon , D. Davey, C. A. Pease, Venepalli, C. W. Griffin, R. P. Gomez, J .R. Wiggins, W. R. Ingebretsen, D. Pang, *J. Med. Chem.*, **1989**, 32(6), 1173-6.
[7]. M. Suzuki, S. Maeda, K. Matsumoto. *Boll Chem. Farm*., l, **1986**, 34(8), 3111-3120.
[8]. F. Suzuki, T. Kuroda, T. Tamura. *J. Med. Chem*., **1992,** 35(15), 2863-2870.
[9]. S. A. El Feky , Z. K. Abdel-Samii, *Pharmazie*., **1995**, 50 (5), 341-343.
[10]. L. Isikdag, A. Meric, *Boll Chem. Farm*., **1999**, 138(1), 24-29.
[11]. R. A. Johnson, S. M. Huong , E. S. Huang, *Anti Viral Research.*, **1999,** 41 (3), 101-111.
[12]. M. D. Brewer, R. J. Dorgan, B. R. Manger, P. Mamalis, R. A. Webster, *J. Med. Chem*., **1987**, 10, 1848- 53.
[13]. J. A. Nathanson, *Mol. Pharmacol*., **1985**, 28(3), 254-68.
[14]. L. I. Kruse , C. Kaiser, J. S. Frazee, E. Garvey, E. L. Hilbert, W. A. Faulkner, K. E. Flaim, J. L. Sawyer , B. W. Berkowitz, *J. Med. Chem.*, **1986**, 29(12),2465-2472.
[15]. H. S. Liyk Hsu, H. Kiyota, M. Segawa, *J. Bio. Chem*., **1998**, 23(3), 416-422.
[16]. K. M. Mahadevan, H. M. Vagdevi and V. P.Vaidya. *Indian J. Chem B.*, **2003**, 42B, 1931.
[17]. A. Srinivasa, K. M. Mahadevan and H. Vijaykumar, *Monatsh. Chem.*,**2008**, 139, 255– 259.
[18]. Siddalingamurthy, K. M. Mahadevan, N. M. Jagadeesh, H. N. Harishkumar, *Tetrahedron Lett.*, **2013**, 54, 5591–5596.
[19]. B. M. Kiran and K. M. Mahadevan. *Heterocycl. Commun.*, **2006**, 12, 481-484.
[20]. Rigaku, **2011**, *CRYSTAL CLEAR*, Rigaku Corporation, Tokyo, Japan.
[21]. G. M. Sheldrick, *Acta Cryst*., **2015**, A71, 3-8.
[22]. A. L. Spek, *Acta. Cryst*., **1990**, A46, C34-C37.

[23]. 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.
[24]. A. Saberi, H.R. Manjunath, S. Naveen, T.N. Mahadeva Prasad, K.S. Rangappa, M.A. Sridhar, J. Shashidhara Prasad, *Mol. Cryst. Liq. Cryst.*, **2009**, 515, 199-206.
[25]. S. Wolff, D. Greenwood, J. McKinnon, M. Turner, D. Jayatilaka, Spackman M. A., *Crystal Explorer*, **2012**.
[26]. K. N. Chetan Prathap, K. Reshma, S. Naveen, Manjunath Bhat, G. K. Nagaraja, N. K. Lokanath, *J. Applicable Chem.*, **2017**, 6(3), 400-409.