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Synthesis, Characterization and Crystal Structure Analysis of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

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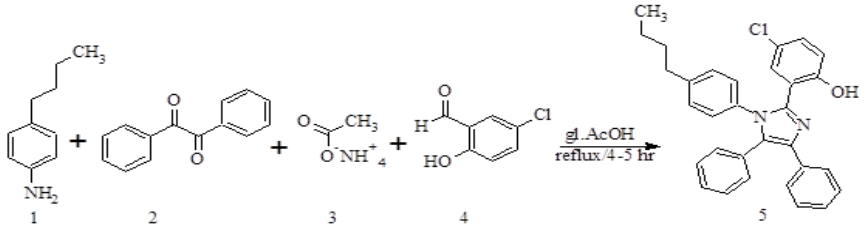
ABSTRACT

High efficiency process for the synthesis of 2-(1-(4-ethylphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-4-chlorophenol (5) through a four-component condensation reaction of 4-butylaniline (1), Benzyl (2), Ammonium Acetate (3) and 4-chloro-salycylaldehyde (4) in a acetic acid media with 2-3 drops of con H_2SO_4 has been reported. The compound obtained was characterized spectroscopically by IR, ^{1}H-NMR, ^{13}C NMR, SEM and EDAX techniques and finally the structure of 2-(1-(4-ethylphenyl)-4,5-diphenyl-1H-imidazol-2-yl)-4-chlorophenol (5) was established by X-ray diffraction studies. The compound crystallizes in the triclinic p-1 space group with cell parameters a = 10.253(15) Å, b = 11.107(16) Å, c = 12.481(19) Å, α = 99.560(16)°, β = 130.254(8)°, γ = 93.785(3)° and Z = 2. The imidazole ring in the structure is planar. The structure exhibits intramolecular hydrogen bonds of the type O—H…N and C—H…N hydrogen bonds which contribute for the stability of the compound. Further, the Hirshfeld surface analysis reveals the nature of intermolecular contacts; the fingerprint plot provides the information about the percentage contribution from the intermolecular contacts to the surface.

Graphical Abstract:



Synthesis of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

Keywords: Antiaging, Imidazole, O—H…N and C—H…N hydrogen bonds, Hirshfeld surface.

INTRODUCTION

In biomedical research, nitrogen heterocycles have a long history and still they have pacemaker for bioactive applications [1]. In particular, imidazole moieties have the ability to bond with metals as a ligand hence, they act as bioactive molecules [2-6]. Further, azole antifungal agents contain an imidazole groups inhibit the accumulation of methylated sterols and destroy the composition of the lipid bilayer of membranes. Presence of high concentration of some imidazole group directly inhibits the action on membranes without interference with sterols and sterol esters [7-8]. Thus, medicinal properties of imidazole broadly include anticancer, α-lactamase inhibitors, carboxypeptidase inhibitors, hemoxygenase inhibitors, antiviral, antitubercular, antiaging agents, anticoagulants, antiinflammatory, antibacterial, antifungal, antidiabetic and antimalarial agents [9-15]. Hence due to their wide range of biological applications and in continuation of our work on novel bioactive heterocyclic compounds [16-19], herein we report the synthesis, characterization and crystal structure studies of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5).

MATERIALS AND METHODS

Chemicals and reagents used for the synthesis and analysis were procured from commercially supplier, Sigma Aldrich, India. Analytical grade solvents were purchased from Loba chemie 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). Commercially available chemicals were used directly as received. ^{1}H-NMR and ^{13}C NMR spectra were recorded on a Joel 400 MHz using ($CDCl_3$) solvent, and an IR spectrum was recorded on a Nicolet 5700 FT-IR instrument as KBr discs. Crystal structure was recorded by Single-crystal X-ray diffractometer. SEM (Scanning Electron Microscope) and EDAX (Energy Dispersion X-ray Analyser) were analysed by using Hitachi (Table top, Model TM 3000) Scanning Electron Microscope (SEM).

Synthesis of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5): In a 250mL round-bottom flask, 4-butyl aniline (1 mmol, 0.14g), benzyl (1 mmol, 0.210g), ammonium acetate (1 mmol, 0.75g) and 4-chloro-salycylaldehyde (1mmol, 0.157g) were taken in glacial acetic acid (20mL). The reaction mixture was then subjected to ultra-sonication for 30 min and kept it for reflux 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 ice cold water. The reaction mixture was quenched in water, neutralized by aqueous sodium bicarbonate solution and the product was extracted with ethyl acetate. The crude product was then recrystallized by hot chloroform and ethyl acetate (2:6) to get fine crystals of analytically pure 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) with good yield (70-80%).M.P.140^{o}-142^{o}C. The reaction scheme is shown in Figure 1.

Physical and Spectral Data of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5): Figure 2 gives the IR spectrum of the title compound whereas figures 3-6 depicts the ^{1}H NMR and ^{13}C NMR spectrum of the title compound.

IR (KBr) (ν_{max}/cm^{-1})): 1443 (C-C), 1575.04 (C=C), 1600.64 (C=N), 2958(alkyl C-H), 3028.09(Ar C-H), 3444.11 (O-H).

^{1}H NMR(400MHz, $CDCl_3$, δ (ppm)): 0.90 (t, J=14.4Hz, 3H), 1.26-1.36 (m, 2H), 1.56-1.63(m, 2H), 2.64(t, J=14.83Hz, 2H), 6.39 (d, J=2.4Hz, 1H, Ar-H), 6.98 (d, J=8.4Hz, 1H, Ar-H), 7.05-7.08 (m, 2H, Ar-H), 7.15 (m, 1H, Ar-H), 7.19-7.27 (m, 11H, Ar-H), 7.50-7.53 (m, 1H, Ar-H), 11.23 (brs, 1H, OH).

^{13}C NMR (400MHz, $CDCl_3$, δ (ppm)): 13.30, 21.90, 33.06, 34.34, 113.92, 119.0, 122.52, 127.76, 127.98, 128.16, 128.38, 128.86, 129.76, 130.0, 131.06, 131.50, 133.04, 134.16, 135.50, 144.22, 144.80, 157.50.

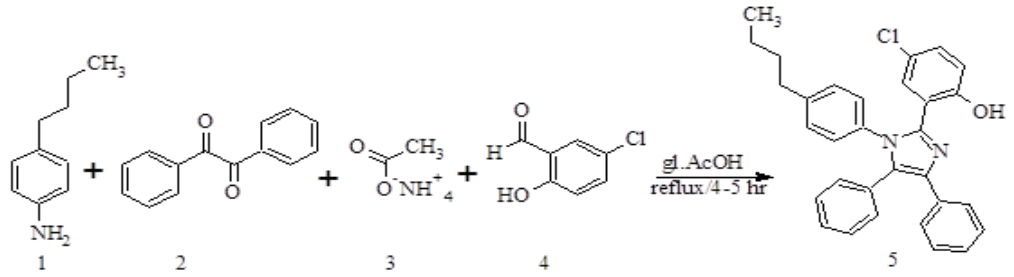


Figure 1. Synthesis of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

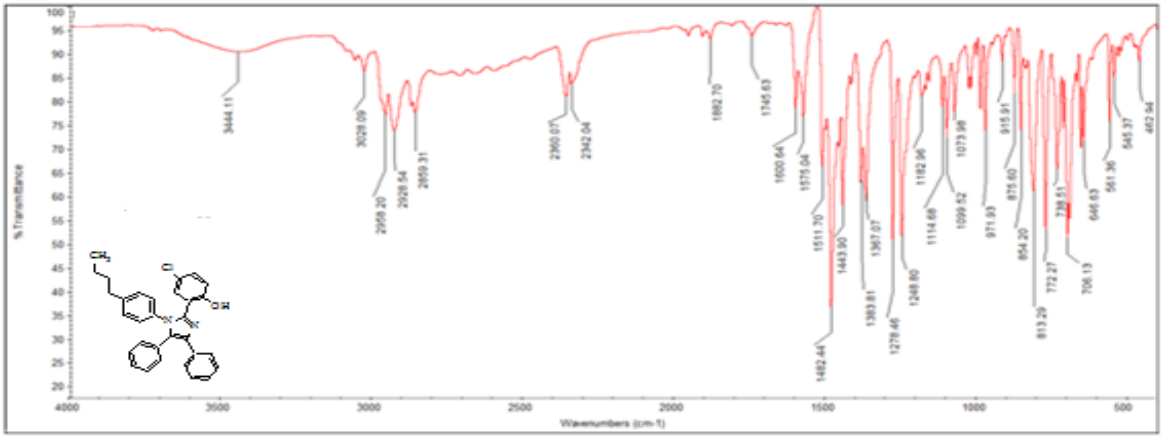


Figure 2. IR spectrum of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

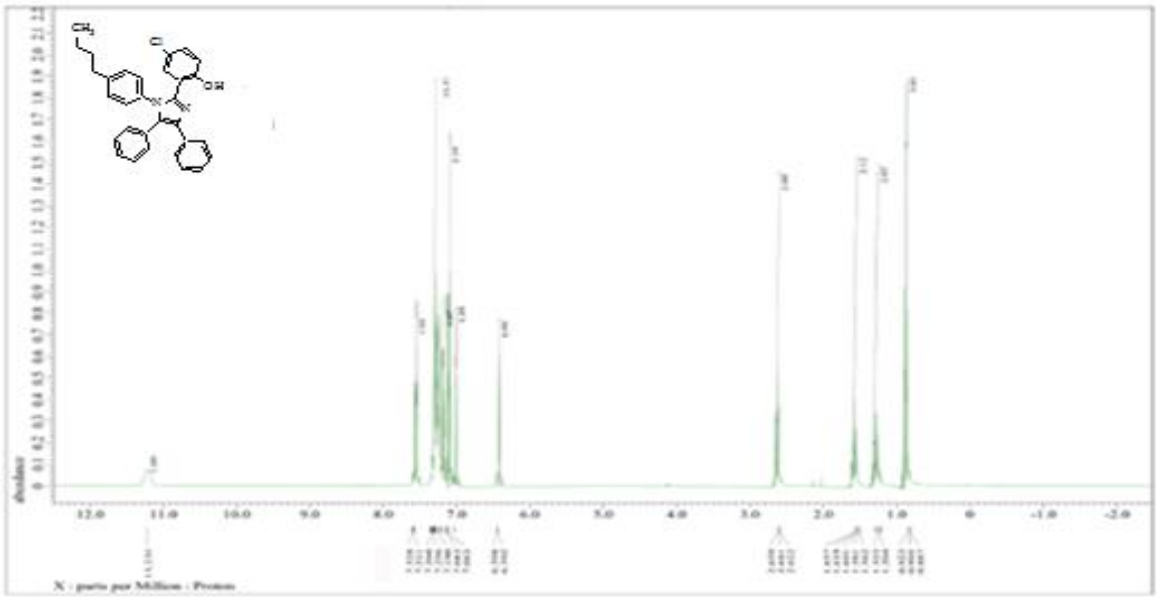


Figure 3. ^{1}H NMR spectrum of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

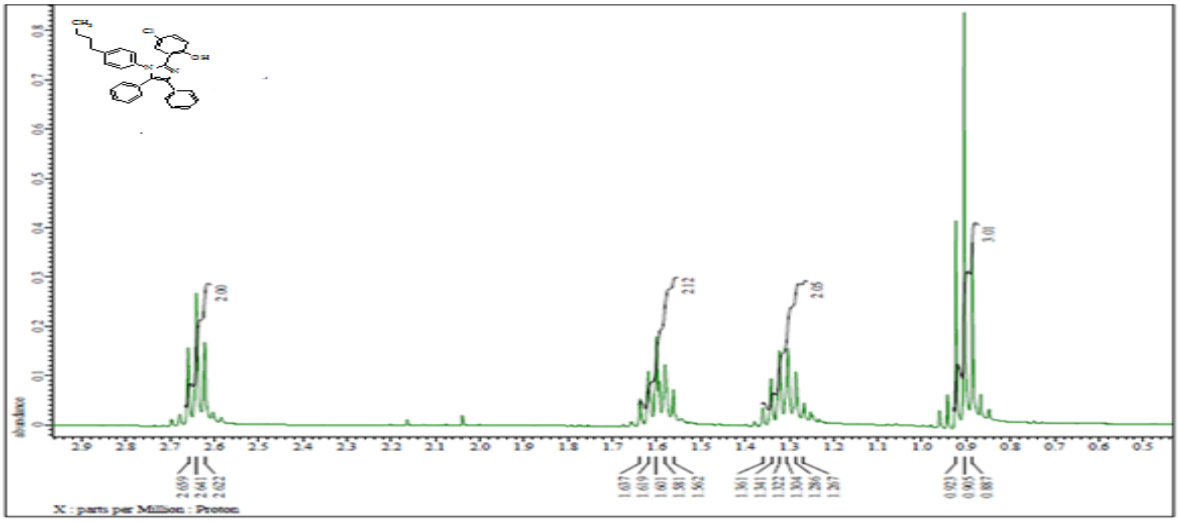


Figure 4. Aliphatic enlarged region of ^{1}H NMR spectrum of 2-(1-(4-butylphenyl)-4,5-diphenyl -*1H*-imidazol-2-yl)-4-chlorophenol

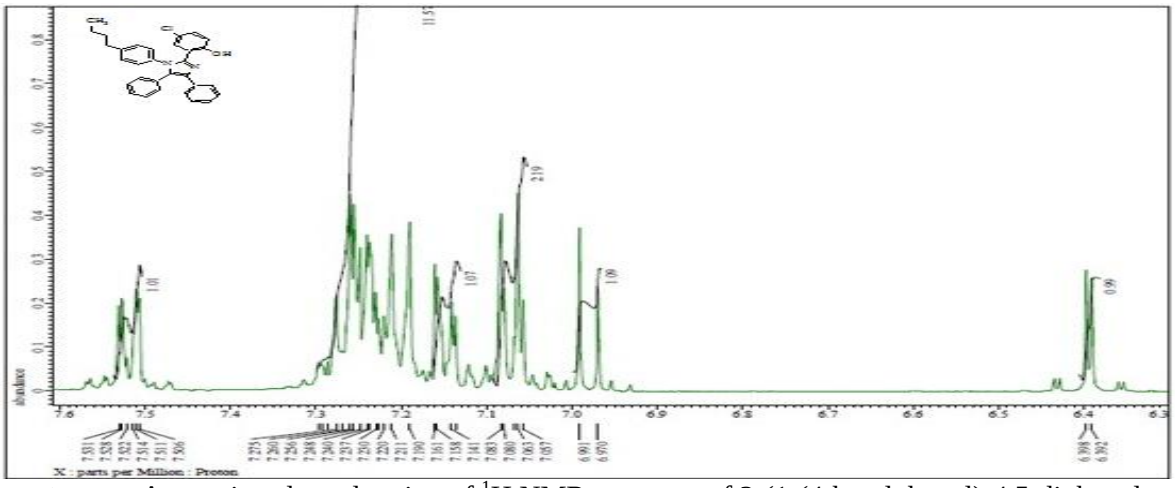


Figure 5. Aromatic enlarged region of ^{1}H NMR spectrum of 2-(1-(4-butylphenyl)-4,5-diphenyl -*1H*-imidazol-2-yl)-4-chlorophenol

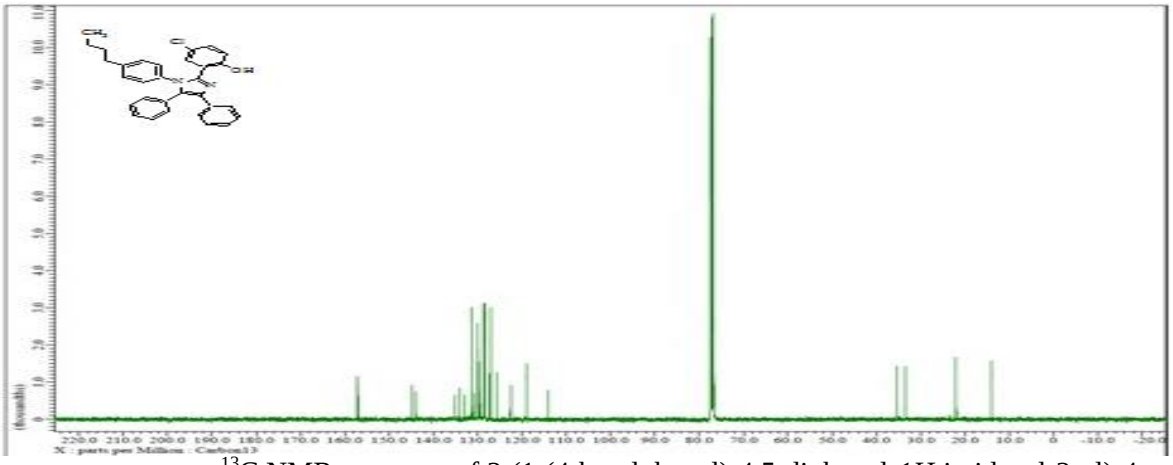


Figure 6. ^{13}C NMR spectrum of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

SEM and EDAX Analysis: As illustrated in figure 7, the particle size and morphology of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) was shown to be hard surface morphology and having 500 µm in size of the particle. However, the width, length and size of the particle structures were not distributed uniformly.

Further the EDAX spectrum in figure 8 of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) reveals that the composition from the micro graph the large peak confirms the abundance of carbon atom and the remaining peaks shows the existence of oxygen, nitrogen, chlorine, with respective percentage of composition for carbon, nitrogen, oxygen and chlorine are as shown Table 1.

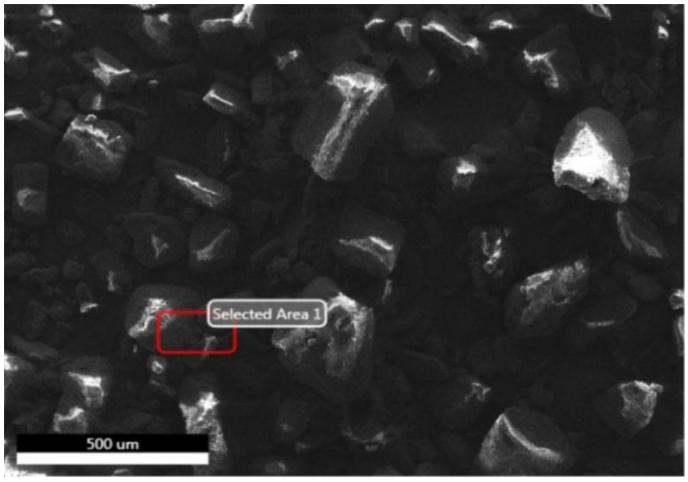


Figure 7. SEM image of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

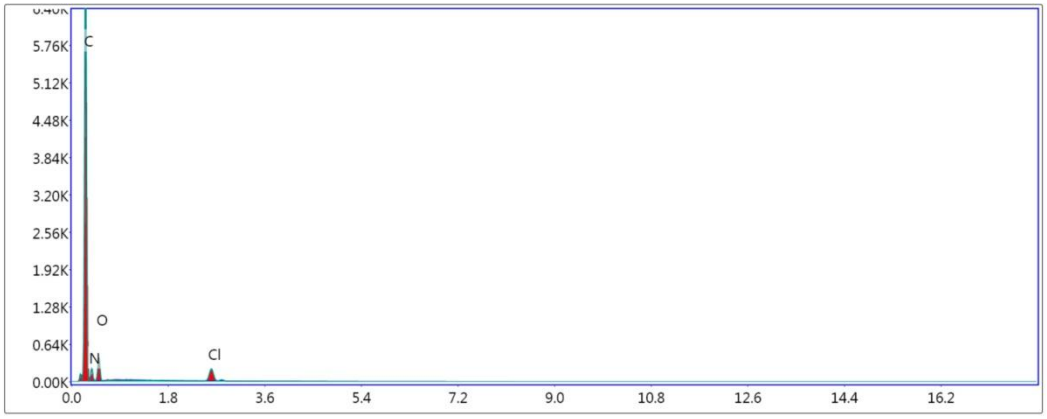


Figure 8. EDAX spectrum of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol

.

Table1: Elemental composition from EDAX spectrum analysis

Element	Weight %	Atomic %
C	74.61	80.04
N	12.78	11.76
O	08.19	06.59
Cl	04.42	01.61

X-ray diffraction studies: A white colored rectangle shaped single crystal of dimensions 0.29×0.26×0.25 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 2θvalue at 46.6°. A complete data set was processed using *SAINT PLUS* [20]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs [21]. All the non-hydrogen atoms were revealed in the first difference Fourier map itself. All the hydrogen atoms were positioned geometrically and refined using a riding model. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residuals saturated to 0.0861. The geometrical calculations were carried out using the program *PLATON* [22]. The molecular and packing diagrams were generated using the software *MERCURY* [23]. The details of the crystal structure and data refinement are given in Table 2. The list of selected bond lengths and bond angles are given in Tables 3 and 4. Figure 7 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

Table 2. Crystal data and structure and refinement details

CCDC Number	
Empirical formula	$C_{31}H_{28}ClN_2O$
Formula weight	480.00
Temperature	293(2) K
Wavelength	1.54178 Å
Reflections for cell determination	2620
□ range for above	4.82^o to 64.22^o
Crystal System	Triclinic
Space Group	*P-1*
Cell dimensions	a = 10.253(15) Å b = 11.107(16) Å c = 12.481(19) Å $\alpha = 99.560(16)^o$ $\beta = 130.254(8)^o$ $\gamma = 93.785(3)^o$
Volume	1265(3) $Å^3$
Z	2
Density (calculated)	1.258 Mgm^{-3}
Absorption coefficient	0.178 mm^{-1}
F_{000}	506
Crystal size	0.29 x 0.26 x 0.25 mm
Index ranges	$-13 \leq h \leq 13$ $-13 \leq k \leq 14$ $-11 \leq l \leq 16$
Reflections collected	7382
Independent reflections	5675 [R_{int} = 0.060]
Absorption correction	Multi-scan
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5675 / 0 / 318
Goodness of fit on	0.93
R indices [I > 2s(I)]	*R1* = 0.0780, □ *R2*= 0.3027
Extinction coefficient	0.0050(7)
Largest diff. Peak and hole	0.61 and -0.43 e $Å^{-3}$

Table 3. Bond lengths (Å)

Atoms	Length	Atoms	Length
Cl1-C15	1.726(4)	C3-C4	1.382(5)
O1-C18	1.354(4)	C1-C2	1.382(5)
N2-C12	1.368(4)	C2-C3	1.390(5)
N2-C19	1.397(5)	C1-C6	1.381(4)
N1-C1	1.443(4)	C5-C6	1.388(5)
N1-C26	1.397(4)	C4-C5	1.371(6)
C5-C6	1.388(5)	C6-C1	1.381(6)
C7-C8	1.434(7)	C8-C9	1.554(8)

C17-C16	1.351(6)	C4-C7	1.518(5)
C22-C23	1.343(6)	C8-C7	1.434(7)

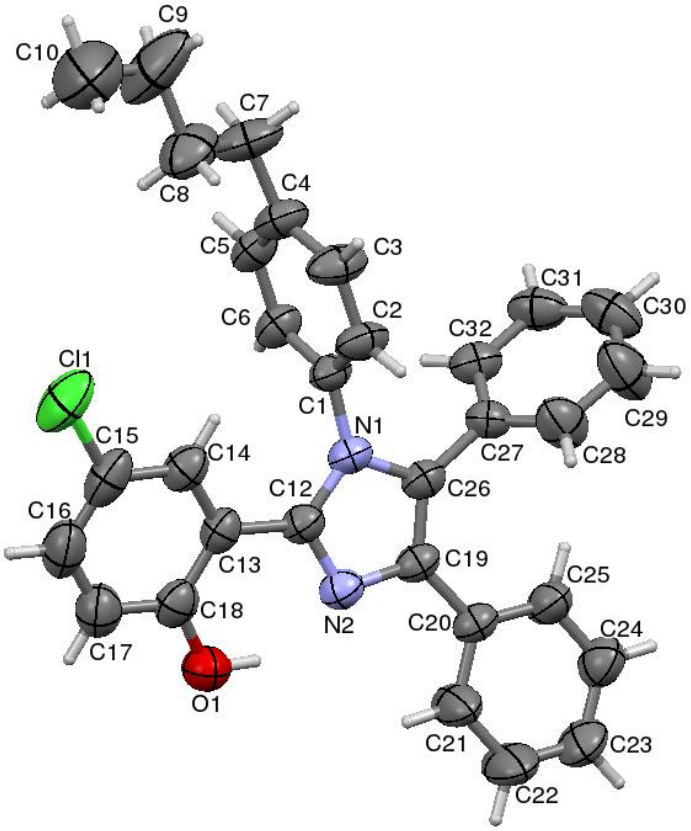


Figure 7: ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability

Table 4. Bond angles (°)

Atoms	Angle	Atoms	Angle
C12-N1-C26	107.9(3)	C13-C14-C15	120.4(4)
C12-N1-C1	126.7(3)	N1-C26-C19	105.8(3)
C26-N1-C1	125.4(3)	N1-C12-C13	128.9(3)
C12-N2-C19	107.0(3)	N2-C12-N1	110.2(3)
C28-C27-C32	119.3(3)	N2-C12-C13	120.9(3)
C1-C2-C3	119.6(3)	C3-C4-C5	118.8(3)
C7-C8-C9	110.2(5)	C8-C7-C4	114.1(4)
C26-C19-N2	109.1(3)	C10-C9-C8	111.2(7)

RESULTS AND DISCUSSION

Synthesis of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) was accomplished by the reaction of mole quantities of 4-butylaniline (1), Benzyl (2), Ammonium acetate (3) and 4-chloro-salycylaldehyde (4) in one pot reaction.Excellent yield (85%) of 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-

imidazol-2-yl)-4-chlorophenol (5) was obtained in a convenient and economical method. The crude product was recrystallized by hot chloroform and ethyl acetate (2:6) which furnished fine crystals of analytically pure 2-(1-(4-butylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) with good yield (70-80%). M.P.140° -142°C.

Crystal structure studies: The imidazole ring is planar with a maximum deviation of 0.008(4)Å for the atom C12. The rings C21-C25 and C27-C32 are twisted by the angles 5.1(2)° and 67.2(2)° respectively with respect to the imidazole ring, which are different from the values of 15.2(3)° and 68.(3)° reported earlier [ali-24]. The butyl phenyl and chlorophenol rings are in equatorial and axial conformation with respect to the imidazole ring. This is confirmed by the dihedral angle values of 79.4(2)° and 14.9(2)° respectively about the least squares plane of the imidazole ring. The bond values of 1.398(5) Å and 1.328(5) Å for N2-C19 and N2-C12 have a partial double bond character as they are significantly shorter than Csp^2-N bond distance. The molecules exhibit intramolecular hydrogen bonds of the type O-H...N and C-H...N which has a length of 2.584 (5) Å and an angle of 147°.

APPLICATIONS

Eco friendly high efficient process for the synthesis of 2-(1-(4-ethylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) through a four-component condensation reaction of 4-butylaniline (1), Benzyl (2), Ammonium Acetate (3), and 4-chloro-salycylaldehyde (4) in acetic acid media with 2-3 drops of conc. H_2SO_4.

CONCLUSIONS

Eco friendly high efficient process for the synthesis of 2-(1-(4-ethylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) through a four-component condensation reaction of 4-butylaniline (1), Benzyl (2), Ammonium Acetate (3) and 4-chloro-salycylaldehyde (4) in acetic acid media with 2-3 drops of conc. H_2SO_4 has been reported. The crystal structure and surface morphology and size of 2-(1-(4-ethylphenyl)-4,5-diphenyl-*1H*-imidazol-2-yl)-4-chlorophenol (5) was studied and established by using ^{1}H-NMR, ^{13}C NMR, SEM and EDAX and X-ray Crystal structure analysis. The structure exhibits the intramolecular hydrogen bonds.

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