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SYNTHESIS AND CRYSTAL STRUCTURE OF 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile

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Abstract
A new symmetric dihydropyridine possessing cyano group at C_3 and C_5 has been synthesized using a modified Hantzsch method. The title compound $C_{24}H_{18}C_lN_5$ was characterized spectroscopically by Mass, IR and ^{1}H NMR methods and finally confirmed by X- ray diffraction study. The compound crystallizes in the monoclinic crystal class in the space group P 21/c with cell parameters a = 6.9484(5)Å, b = 22.1710(16) Å, c = 13.9101(9) Å, β = 103.717(7)°, Z = 4 and V=2081.8(3) Å^3.

Keywords: Pyrazole, crystal structure, biological activities, pyridine, planar.

Introduction
In recent years, very significant attention has been given to the synthesis of 1,4-dihydropyridines owing to their good biological activity.[1] 1,4-Dihydropyridine (DHP) containing drugs like Nifedipine, Amlodipine, Felodipine and others have been used as calcium channel blockers,[2-4] and are widely used as cardiovascular agents for the treatment of hypertension.[5] Second generation calcium antagonists include dihydropyrdine derivatives with improved bioavailability, tissue selectivity, and/or stability such as the antihypertensive, antianginal drugs like Elgodipine,[6] Furnidipine,[7-8] Darodipine,[9] Pranidipine,[10] Lemildipine,[11] Dexniguldipine,[12] Lacidipine[13] and Benidipine.[14] Number of DHP calcium agonists has been introduced as potential drug candidates for treatment of congestive heart failure.[15-16] The majority of 1,4-dihydropyridines synthesized possess (acetyl or ester) at C_3 and C_5. However, very few symmetric 1,4-dihydropyridines having cyano group at both C_3 and C_5 positions, have been reported.

In continuation of the search of such potent molecules,[17] the title compound was synthesized using the modified Hantzsch method. The structure of the compound was established on the basis of (FT-IR), NMR, Mass and Elemental Analysis and finally confirmed by X-ray crystallography.

Experimental section
Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/DMSO solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Synthesis of 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile

Pyrazole aldehyde has been synthesized by reported procedure using phenyl hydrazine and 4-Chloro acetophenone followed by Vilsmeier-Haack reaction.[18] A mixture of pyrazole aldehyde (0.01 mol), 3-amino crotononitrile (0.02 mol) in glacial CH_3COOH was stirred for 10-15 min at 60-70^{O}C in a stoppered flask. The reaction mixture was kept at room temperature for half an hour. During the reaction the

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progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3: 2) as a mobile phase. After the reaction to be completed, the reaction mixture was kept to room temperature for 1 hours and the crystalline product was separated by filtration. The solid product was obtained after cooling and then filtered and washed first with acetic acid and then with hexane.

Method of Crystallization:

The pure single spot compound (0.5 gm) was taken in a beaker and dissolved in minimum quantity of methanol (25 ml) at room temperature. To the solution, 0.5 gm of activated charcoal was added and heated on water bath for 15 min. The solution was filtered, while hot through wattmann filter paper no. 42. The solution was kept in a slightly opened stoppered conical flask and the solvent was allowed to evaporate by thin layer evaporation and the single crystals were observed after 16 days. The crystals were filtered and washed with chilled methanol. The method employed for synthesis is shown in Fig. 1.

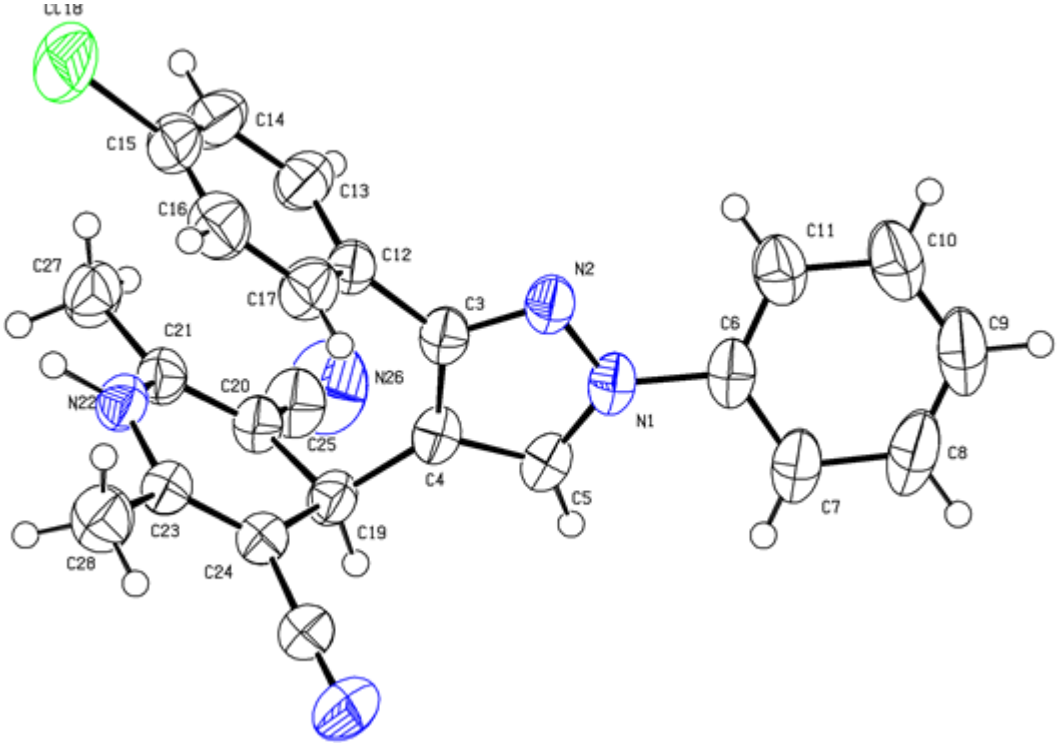


Figure 1: ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

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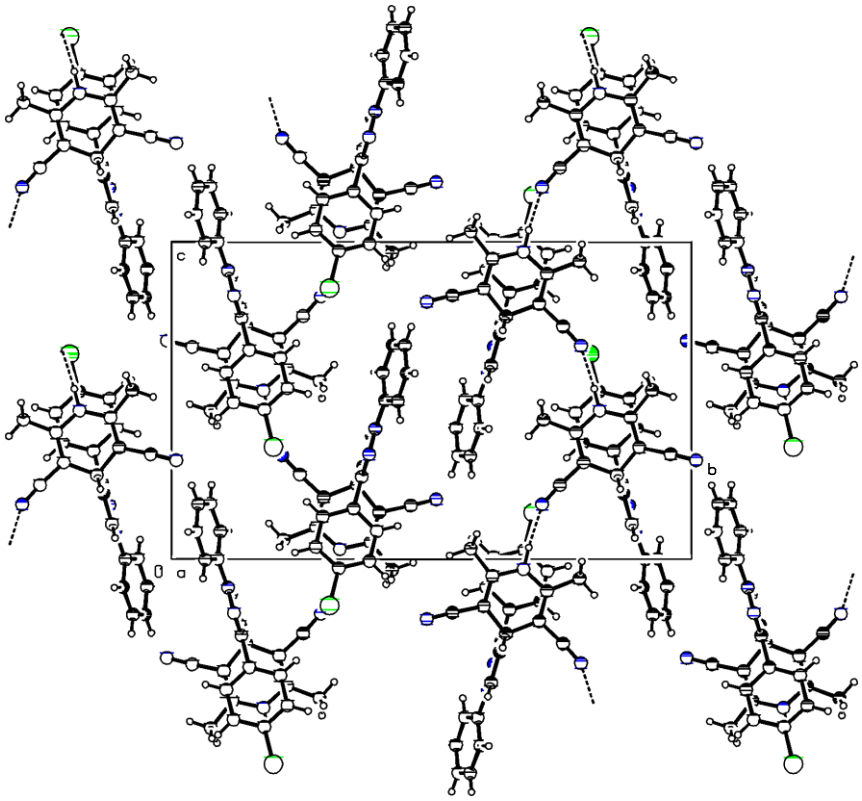
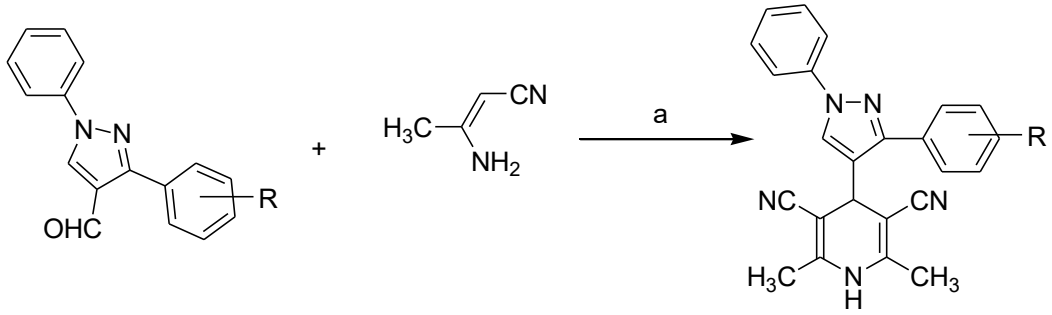


Figure 2 : Packing of the molecules when viewed down the axis.



Reagents / Reaction Condition (a): Glacial Acetic acid / 60-70°C, 1 hours. Where, R = 4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2

Spectral data of 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile

IR: 3290 (N-H stretching), 3126, 3016 (Aromatic C-H stretching), 2993 (Aliphatic -CH3 stretching), 2839 (Aliphatic -CH2 stretching), 2200 (C-N Stretching), 1662-1599 (N-H bending), 1545, 1446, 1357 (C-H bending), 1294(C-N bending), 754 (disubstituted), 690 (monosubstituted)

1H NMR: 1.86 (s, 6H), 4.48 (s, 1H), 7.18-7.22 (t, 1H), 7.31-7.33 (d, 2H), 7.34-7.38 (t, 2H), 7.48-7.51 (d, 2H, J=8.0Hz), 7.66-7.68 (d, 2H), 7.95 (s, 1H) , 8.90 (s, 1H)

Mass: m/z = 411 (M+), 413 (M+2)

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Elemental analysis: Anal. Calcd. for $C_{24}H_{18}ClN_5$: C, 69.98; H, 4.40; Cl,8.61; N, 17.00; Found: C, 69.89; H, 4.40; Cl, 8.59; N, 16.98.

Table 1: Crystal data and structure refinement table

Empirical formula	$C_{24}H_{18}ClN_5$
Formula weight	411.88
Temperature	293(2)K
Wavelength	0.71073Å Crystal
system	Monoclinic Space
group	$P2_1/c$
Cell dimensions	a = 6.9484(5) Å
	b = 22.1710(16) Å
	c = 13.9101(9) Å
	β = 103.717(7)°
Volume	2081.8(3)Å^3
Z	4
Density(calculated)	1.314 Mg/m^3
Absorption coefficient	0.204 mm^{-1}
F ooo	856
Crystal size	0.30 × 0.20 × 0.10 mm
Theta range for data collection	3.53 ° to 25.00°
Index ranges	−8 ≤ h ≤ 8
	−26 ≤ k ≤ 26
	−16 ≤ l ≤ 16
Reflections collected/Unique	18771/3684 [R_{int} =0.0639] Absorption
correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3684/0/279
Goodness-of-fit on F^2	1.011
Final R indices	R_1 = 0.0785, wR_2 = 0.2471
R indices (all data)	R_1 = 0.0963, wR_2 = 0.2812
Extinction coefficient	0.006(3)
Largest diff. peak and hole	0.406 and −0.347 e.Å^{-3}

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Table 2: Bond Length

Atoms	Length	Atoms	Length
N1-C5	1.345(5)	C14-C15	1.369(7)
N1-N2	1.360(5)	C15-C16	1.348(8)
N1-C6	1.426(5)	C15-Cl18	1.740(4)
N2-C3	1.321(5)	C16-C17	1.392(6)
C3-C4	1.415(6)	C19-C24	1.518(5)
C3-C12	1.487(5)	C19-C20	1.519(5)
C4-C5	1.367(5)	C20-C21	1.349(5)
C4-C19	1.516(5)	C20-C25	1.415(6)
C6-C11	1.374(7)	C21-N22	1.376(5)
C6-C7	1.373(7)	C21-C27	1.490(5)
C7-C8	1.398(7)	N22-C23	1.377(5)
C8-C9	1.361(10)	C23-C24	1.345(5)
C9-C10	1.366(8)	C23-C28	1.491(5)
C10-C11	1.387(6)	C24-C29	1.422(5)
C12-C13	1.387(6)	C25-N26	1.151(6)
C12-C17	1.388(6)	C29-N30	1.148(6)
C13-C14	1.375(6)		

Crystal structure determination

A single crystal of the title compound with dimensions of 0.10 × 0.20 × 0.30 mm was chosen for an X-ray diffraction study. The data were collected on a Xcalibur, Sapphire3 system equipped with a normal focus, sealed X-ray source graphite monochromated Mo Kα radiation. The structure was solved by direct methods using SHELXS-97.[19] All the non-hydrogen atoms were revealed in the first Fourier map it-self. Least-squares refinement using SHELXL-97 with isotropic temperature factors was done for all the non-hydrogen atoms. Subsequent refinements were carried out with anisotropic thermal parameters for the non-hydrogen atoms. After refinement, the residuals converged to 0.0785. Details of the crystal data and refinement are given in Table 1. Figure 1 represents the ORTEP[20] diagram of the molecule with thermal ellipsoids drawn at 50% probability. Details of the Crystal data and refinement are given in Table1.

Results and discussion

The pyrazole ring is almost planar with rms deviation from least squares plane 0.004˚A. A study of the torsion angles, asymmetric parameters, and least-square plane calcu- lations reveals that the pyridine ring in the structure is in a flattened boat conform-mation with the atoms C19 and N2 lying at 0.130(4)4)o and 0.093(44)˚from the least squares plane defined by the a atoms C0/C21/C23/C24. This is confirmed by the puckering parameters21 Q = 0.203(44)˚, θ=107.6(11)◦, and φ=1.213)◦◦. The ring puckering analysis revealed that the pyridine ring has weighted rage ring bond distance 1.4162, ˚329)˚d a weighted averages ion angle of 12.13(25,2425,247) ◦ bond angle of C20-C25-N26 = 178.22◦ is slightly larger than bond angle of C24- C29-N30= 175.99◦. The bond length of N1-C6=1.426(5) ˚A is comparable with bond length of for compound22. The chlorine atom substituted for phenyl ring is in +antiperiplanar conformation as reported angle about the atoms C13-C14-C15-Cl18 is 177.4(4) ˚A. The structure exhibits

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intermolecular H-bonds of the type N-H· · · N, C-H· · · N and C-H· · · cl. The intermolecular hydrogen bonds are N22-H22· · · N30, C14-H14· · · N26, C17-H17· · · Cl18 has a bond length of 2.960(6) ˚A, 3.479(7) ˚A, 3.672(5)˚A and an angle of 174(3)◦, 174◦, 164◦ with Symmetry code (x, 1/2 − y, −1/2 + z), (−x, −y, 1 − z) and (x, 1/2 − y, 1/2 + z) respectively. Fig 3 shows packing of the molecule when viewed down the a-axis. The dotted line represents intermolecular hydrogen bonds, which indicates that the molecules are stacked in pairs. The stability of the crystal structure can be accounted for by these hydrogen bonds. Table 2 and Table 3 gives list of bond lengths and bond angles.

Table 3: Bond Angles (^{0})

Atoms	Angle	Atoms	Angle
C5-N1-N2	111.7(3)	C16-C15-C14	121.9(4)
C5-N1-C6	128.8(3)	C16-C15-Cl18	119.0(4)
N2-N1-C6	119.5(3)	C14-C15-Cl18	119.1(4)
C3-N2-N1	104.6(3)	C15-C16-C17	119.7(4)
N2-C3-C4	112.0(3)	C16-C17-C12	119.9(4)
N2-C3-C12	119.9(3)	C24-C19-C4	112.1(3)
C4-C3-C12	128.2(3)	C24-C19-C20	107.9(3)
C5-C4-C3	103.8(3)	C4-C19-C20	111.1(3)
C5-C4-C19	127.3(4)	C21-C20-C25	119.7(4)
C3-C4-C19	128.8(3)	C21-C20-C19	123.1(3)
N1-C5-C4	107.9(4)	C25-C20-C19	117.2(3)
C11-C6-C7	121.1(4)	C20-C21-N22	119.8(3)
C11-C6-N1	119.3(4)	C20-C21-C27	125.1(4)
C7-C6-N1	119.6(4)	N22-C21-C27	115.0(3)
C6-C7-C8	118.2(5)	C21-N22-C23	122.1(3)
C9-C8-C7	121.4(5)	C24-C23-N22	119.4(3)
C8-C9-C10	119.4(5)	C24-C23-C28	125.1(4)
C9-C10-C11	120.8(5)	N22-C23-C28	115.5(3)
C6-C11-C10	119.1(5)	C23-C24-C29	120.5(4)
C13-C12-C17	118.6(4)	C23-C24-C19	123.7(3)
C13-C12-C3	120.4(4)	C29-C24-C19	115.7(3)
C17-C12-C3	121.1(4)	N26-C25-C20	178.2(5)
C14-C13-C12	121.1(4)	N30-C29-C24	176.0(5)
C15-C14-C13	118.9(4)		

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