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Synthesis and Crystal Structure of 4-(3,4,5-Trimethoxyphenyl)-N3,N5-BIS(3-Chloro-4-Fluoro-Phenyl)-2,6-Dimethyl-Pyridine

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The title compound, $C_{30}H_{29}Cl_2F_2N_3O_7$, crystallizes in the triclinic crystal system and space group P-1 with cell parameters a = *7.0250(18) Å,* b = *14.311(5) Å,* c = *15.841(6) Å,* $\alpha = 107.437(7)^\circ$, $\beta = 91.69(2)^\circ$, $\gamma = 100.36(2)^\circ$, V = *1488.7(9) Å^3 for* Z = 2. *The structure exhibits inter-molecular hydrogen bonds of the type N-H… O.*

Keywords Pyridine; crystal structure; hydrogen bond

Introduction

Pyridine is a simple aromatic heterocyclic organic compound used as a precursor to agrochemicals and pharmaceutical. It is structurally related to benzene, wherein one CH group in the aromatic six-membered ring is replaced by a nitrogen atom. The pyridine ring occurs in many important compounds, including nicotinamides. Pyridines and some pyridine fused ring systems have attracted great attention as potential chemotherapeutic agents [1–7]. Pyridine acts as reagent for detection of acid on paper chromatograms [8]. It is also used as a solvent or intermediary in numerous industries including producing piperdine, rubber products, polycarbonate resins, medicines, vitamins, food flavorings, herbicides, pesticides, explosives, paints, dyes, adhesives and waterproofing for fabrics, antihistamine steroids, sulfa antibiotics. In addition it is a denaturant for antifreeze mixtures and is sometimes used as a ligand in coordination chemistry.

The compound was synthesized and crystallized as dihydropyridine, but due to aromatiztion, dihydropyridine loses the proton and converts into pyridine structure. In continuation with our research activities on pyridine, we herein report the synthesis and characterization of a pyridine possessing dicarbomoyl functionality at C-3 and C-5 position by NMR, IR, Mass and X-ray crystallographic studies [9–10]. The title compound was synthesized

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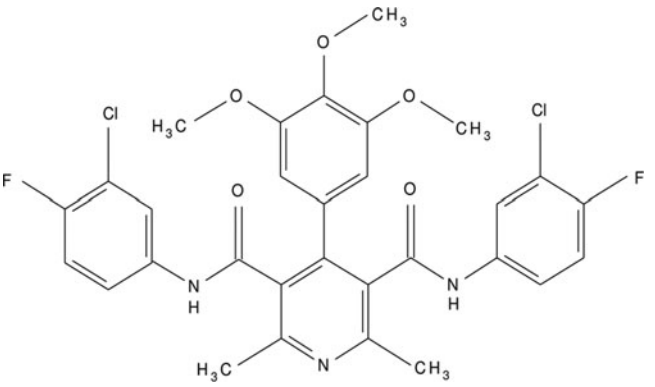

Figure 1. Schematic diagram.

through multi-component reaction (MCR) by Hantzsch method which also bears halogens, both chlorine andfluorine, as a part of phenyl carbamoyl moieties.

Synthesis and Method of Crystallization

To a stirred solution of 3-chloro-4-fluoro-acetoacetanilide (0.02 mol, 2 eq) and 3,4,5-trimethoxy benzaldehyde (0.01 mol, 1 eq) in 25 mL of ethanol, ammonia was added. The

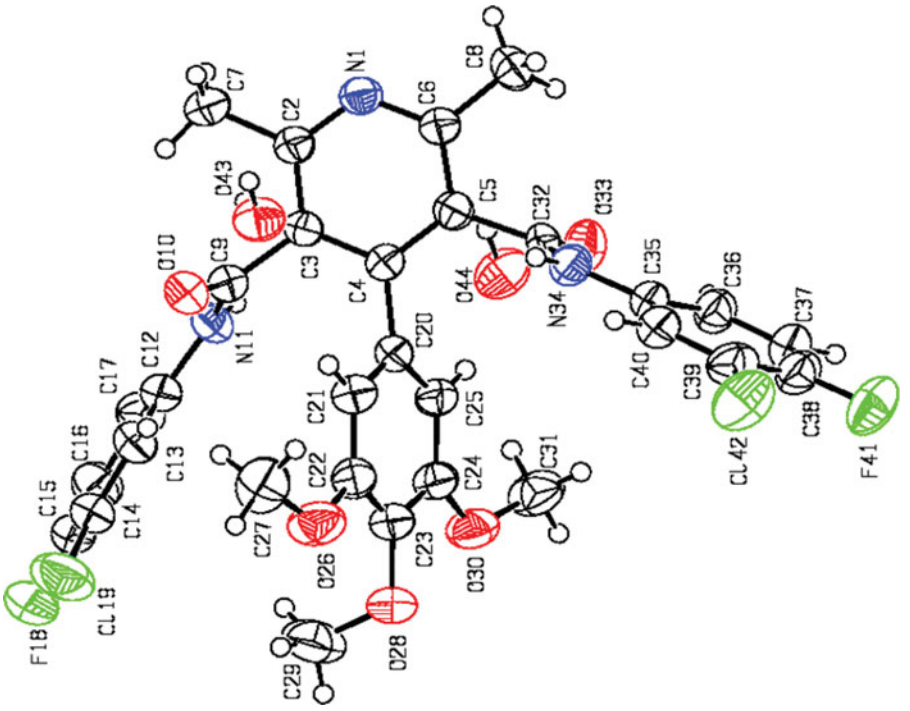

Figure 2. ORTEP of the molecule at 50% probability.

Table 1. Crystal data and structure refinement table

CCDC	691262
Empirical formula	$C_{30}H_{29}Cl_2F_2N_3O_7$
Formula weight	652.46
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Spacegroup	P-1
Cell dimensions	$a = 7.0250$ (18)Å
	$b = 14.311(5)$Å
	$c = 15.841(6)$Å
	$\alpha = 107.437(7)^\circ$
	$\beta = 91.69(2)^\circ$
	$\gamma = 100.36(2)^\circ$
Volume	1488.7(9)Å^3
Z	2
Density (calculated)	1.458 mg/m^3
Absorption coefficient	0.283 mm^{-1}
F_{000}	678
Crystal size	0.3 mm × 0.25 mm × 0.25 mm
θ range for data collection	2.71° to 24.99
Index ranges	$-7 \leq h \leq 7$
	$-16 \leq k \leq 17$
	$-18 \leq l \leq 18$
Reflections collected	5151
Independent reflections	3835 [$R_{\text{int}} = 0.0363$]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3835 / 0 / 403
Goodness-of-fit on F^2	1.053
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0864, wR2 = 0.2368
R indices (all data)	R1 = 0.1226, wR2 = 0.2942
Extinction coefficient	0.020(6)
Largest diff. peak and hole	0.645 and −0.466 e.Å^{-3}

reaction mass was refluxed. The reaction was monitored by TLC. After the completion of reaction as in-dicated by TLC (ethylacetate:hexane :: 30:70, Rf = 0.52), the reaction mixture was cooled to room temperature and then poured into water. It was extracted in ethyl acetate (3 × 15 mL), washed with water and brine and dried on anhydrous Na_2SO_4. The combined ethylac-etate extract was removed in vacuo to leave a crude product. Finally it was purified by silica gel column chromatography (60–100 mesh) using ethylacetate and hexane (20:30) as eluent (mp 246–248 °C). The reaction scheme is shown in Fig. 1. And 2 g of the title compound was dissolved in ethanol (20 mL), charcoal was added and heated at elevated temperature for about 15 min. Hot solution was filtered through Whatman filter paper and the resulting solution was kept in dark. The crystals grown to a suitable size was filtered through Whatman filter paper and washed with chilled diethyl ether. C,H,N analysis: Calculated %: C: (58.21), H: (4.67), N: (6.72). Found %: C: (58.07), H: (4.71),

Table 2. Atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms

Atom	*x*	*y*	*Z*	U_{eq}
N1	0.2384 (6)	1.5049 (3)	0.4460 (3)	0.0450 (1)
C2	0.2236 (8)	1.4191 (4)	0.4639 (3)	0.0431 (1)
C3	0.1836 (7)	1.3274 (3)	0.3968 (3)	0.0400 (1)
C4	0.1595 (8)	1.3250 (3)	0.3082 (3)	0.0425 (1)
C5	0.1734 (7)	1.4146 (3)	0.2907 (3)	0.0440 (1)
C6	0.2163 (8)	1.5051 (3)	0.3615 (3)	0.0457 (1)
C7	0.2459 (9)	1.4242 (4)	0.5604 (3)	0.0557 (1)
C8	0.2404 (1)	1.6035 (4)	0.3449 (4)	0.0612 (2)
C9	0.1661 (8)	1.2311 (4)	0.4180 (3)	0.0450 (1)
O10	0.3096 (6)	1.1985 (3)	0.4348 (2)	0.0564 (1)
N11	−0.0196 (6)	1.1833 (3)	0.4141 (3)	0.0457 (1)
C12	−0.0876 (8)	1.0821 (4)	0.4080 (3)	0.0472 (1)
C13	−0.2785 (9)	1.0530 (4)	0.4212 (4)	0.0578 (2)
C14	−0.3585 (1)	0.9538 (5)	0.4088 (4)	0.0682 (2)
C15	−0.2415 (1)	0.8843 (4)	0.3838 (4)	0.0647 (2)
C16	−0.0516 (1)	0.9117 (4)	0.3711 (4)	0.0616 (2)
C17	0.0281 (1)	1.0106 (4)	0.3840 (4)	0.0576 (2)
F18	−0.3204 (7)	0.7878 (3)	0.3714 (2)	0.0886 (1)
Cl19	0.0882 (3)	0.82177 (1)	0.3384 (1)	0.0938 (7)
C20	0.1131 (8)	1.2250 (3)	0.2363 (3)	0.0443 (1)
C21	0.2358 (9)	1.1579 (4)	0.2301 (3)	0.0505 (1)
C22	0.1800 (9)	1.0618 (4)	0.1719 (3)	0.0542 (1)
C23	0.0073 (9)	1.0326 (4)	0.1203 (3)	0.0554 (2)
C24	−0.1135 (8)	1.1022 (4)	0.1238 (3)	0.0512 (1)
C25	−0.0601 (8)	1.1976 (4)	0.1817 (3)	0.0480 (1)
O26	0.2922 (7)	0.9903 (3)	0.1603 (3)	0.0745 (1)
C27	0.4533 (1)	1.0070 (5)	0.2214 (4)	0.0754 (2)
O28	−0.0519 (7)	0.9374 (3)	0.0624 (3)	0.0738 (1)
C29	−0.1109 (1)	0.8629 (5)	0.1023 (5)	0.093 (2)
O30	−0.2812 (6)	1.0674 (3)	0.0700 (3)	0.0650 (1)
C31	−0.3795 (1)	1.1388 (5)	0.0521 (4)	0.0733 (2)
C32	0.1395 (8)	1.4182 (3)	0.1968 (3)	0.0450 (1)
O33	−0.0122 (6)	1.4354 (3)	0.1711 (2)	0.0601 (1)
N34	0.2926 (6)	1.4002 (3)	0.1482 (3)	0.0470 (1)
C35	0.3053 (8)	1.3941 (4)	0.0577 (3)	0.0456 (1)
C36	0.1649 (9)	1.4141 (4)	0.0065 (3)	0.0533 (1)
C37	0.1915 (9)	1.4049 (4)	−0.0822 (4)	0.0597 (2)
C38	0.3533 (9)	1.3755 (4)	−0.1182 (3)	0.0572 (2)
C39	0.4931 (9)	1.3530 (4)	−0.0686 (4)	0.0599 (2)
C40	0.4703 (9)	1.3630 (4)	0.0194 (3)	0.0552 (1)
F41	0.3794 (6)	1.3697 (3)	−0.2039 (2)	0.0845 (1)
Cl42	0.6905 (3)	1.3111 (2)	−0.11712 (1)	0.0882 (7)
O43	0.6774 (6)	1.3064 (3)	0.4064 (2)	0.0608 (1)
O44	−0.3651 (6)	1.3766 (3)	0.2412 (3)	0.0696 (1)

$U_{eq} = (1/3)\Sigma_i\ \Sigma_j\ U_{ij}\ (a^*_i a^*_j)(a_i a_j)$.

Table 3. Bond lengths **(Å)**

Atoms	Length	Atoms	Length
N1-C2	1.328 (6)	C20-C25	1.395 (7)
N1-C6	1.344 (6)	C21-C22	1.386 (7)
C2-C3	1.395 (6)	C22-C23	1.367 (8)
C2-C7	1.510 (7)	C22-O26	1.374 (7)
C3-C4	1.399 (6)	C23-O28	1.376 (6)
C3-C9	1.499 (7)	C23-C24	1.409 (8)
C4-C5	1.378 (7)	C24-O30	1.356 (6)
C4-C20	1.511 (6)	C24-C25	1.375 (7)
C5-C6	1.412 (6)	O26-C27	1.405 (8)
C5-C32	1.518 (7)	O28-C29	1.403 (8)
C6-C8	1.490 (7)	O30-C31	1.420 (7)
C9-O10	1.237 (6)	C32-O33	1.220 (7)
C9-N11	1.350 (7)	C32-N34	1.359 (7)
N11-C12	1.413 (6)	N34-C35	1.417 (6)
C12-C13	1.372 (8)	C35-C36	1.381 (8)
C12-C17	1.392 (8)	C35-C40	1.405 (8)
C13-C14	1.382 (8)	C36-C37	1.393 (7)
C14-C15	1.379 (1)	C37-C38	1.363 (8)
C15-F18	1.344 (6)	C38-F41	1.355 (6)
C15-C16	1.360 (9)	C38-C39	1.380 (9)
C16-C17	1.376 (8)	C39-C40	1.376 (8)
C16-Cl19	1.725 (7)	C39-Cl42	1.720 (6)
C20-C21	1.386 (8)		

N: (6.77). ^{1}H NMR ($CDCl_3$, Bruker, 300 MHz): δ 9.65 (s, 2H, Ar-NH), 2.07 (s, 6H, 2xCH3), 5.07(s, 1H, Ar-H), 3.62(s, 9H, 3x-OCH3), 6.69(d, 2H, Ar-H, J = 4), 7.90 (d, 4H, Ar-H, J = 8.5), 7.13 (d, 2H, Ar-H, J = 3.5). IR (KBr, cm^1 : 3288(−NH str.), 3078 (−CH str. Symm.), 2939 (−CH str. Asymm.), 1668 (C = O str.), 1604 (C-N str.), 1625 (−C = C str.), 686 (C−Cl str), 1128 (C-F str.), 1090 (C−O str.).

Crystal Structure Determination

A single crystal of the title compound with dimensions 0.30 × 0.25 × 0.25 mm was chosen for the X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with a normal focus, 3 kW sealed X-ray source (graphite monochromated MoK_α). The crystal to detector distance was fixed at 120 mm with the detector area of 441 mm × 240 mm. Thirty-six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to 400 s. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5° . Image processing and data reduction were done using Denzo [11]. The reflections were merged with Scalepack [12]. All the frames could be indexed using a primitive triclinic lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97 [13]. Least-squares refinement using SHELXL-97 [14] with isotropic temperature factors for all the non-hydrogen atoms converged the residual R1 to 0.1678. Subsequent refinements were carried

Table 4. Bond angles (°)

Atoms	Angle	Atoms	Angle
C2-N1-C6	120.1 (4)	C21-C20-C4	119.4 (5)
N1-C2-C3	121.7 (4)	C25-C20-C4	120.0 (4)
N1-C2-C7	117.4 (4)	C22-C21-C20	119.2 (5)
C3-C2-C7	120.9 (4)	C23-C22-O26	115.4 (5)
C2-C3-C4	119.6 (4)	C23-C22-C21	121.1 (5)
C2-C3-C9	121.1 (4)	O26-C22-C21	123.5 (5)
C4-C3-C9	119.3 (4)	C22-C23-O28	122.2 (5)
C5-C4-C3	118.0 (4)	C22-C23-C24	119.7 (5)
C5-C4-C20	123.0 (4)	O28-C23-C24	118.1 (5)
C3-C4-C20	119.0 (4)	O30-C24-C25	124.4 (5)
C4-C5-C6	119.7 (4)	O30-C24-C23	115.9 (5)
C4-C5-C32	121.3 (4)	C25-C24-C23	119.7 (5)
C6-C5-C32	119.0 (4)	C24-C25-C20	119.8 (5)
N1-C6-C5	120.9 (4)	C22-O26-C27	119.1 (5)
N1-C6-C8	118.0 (4)	C23-O28-C29	115.4 (5)
C5-C6-C8	121.2 (4)	C24-O30-C31	117.6 (4)
O10-C9-N11	124.2 (5)	O33-C32-N34	126.2(5)
O10-C9-C3	122.5 (5)	O33-C32-C5	121.2 (4)
N11-C9-C3	113.3 (5)	N34-C32-C5	112.6 (5)
C9-N11-C12	127.8 (4)	C32-N34-C35	127.1 (5)
C13-C12-C17	119.2 (5)	C36-C35-C40	119.8 (5)
C13-C12-N11	118.2 (5)	C36-C35-N34	123.9 (5)
C17-C12-N11	122.5 (5)	C40-C35-N34	116.3 (5)
C12-C13-C14	121.1 (6)	C35-C36-C37	119.2 (6)
C15-C14-C13	118.5 (6)	C38-C37-C36	120.3 (6)
F18-C15-C16	120.5 (6)	F41-C38-C37	119.5 (6)
F18-C15-C14	118.2 (6)	F41-C38-C39	119.1 (5)
C16-C15-C14	121.3 (6)	C37-C38-C39	121.4 (5)
C15-C16-C17	120.1 (6)	C40-C39-C38	119.0 (6)
C15-C16-Cl19	119.6 (5)	C40-C39-Cl42	120.8 (5)
C17-C16-Cl19	120.3 (5)	C38-C39-Cl42	120.2 (4)
C16-C17-C12	119.7 (6)	C39-C40-C35	120.3 (6)
C21-C20-C25	120.4 (4)		

out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms which were placed at chemically acceptable positions. The hydrogen atoms were allowed to ride on their parent atoms. After eight cycles of refinement the residual converged to 0.0864. The details of crystal data and refinement are given in Table 1.† Table 2 gives the atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms. Tables 3 and 4 give the list of bond lengths and bond angles, respectively, which are in good agreement with the standard values. The ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2. The dihedral angles between the least squares planes of pyridine ring and two phenyl rings bridged by C-N group are 83.1(3)° and 70.2(3)°, respectively, while that of pyridine ring and phenyl ring is 57.9(3)°.

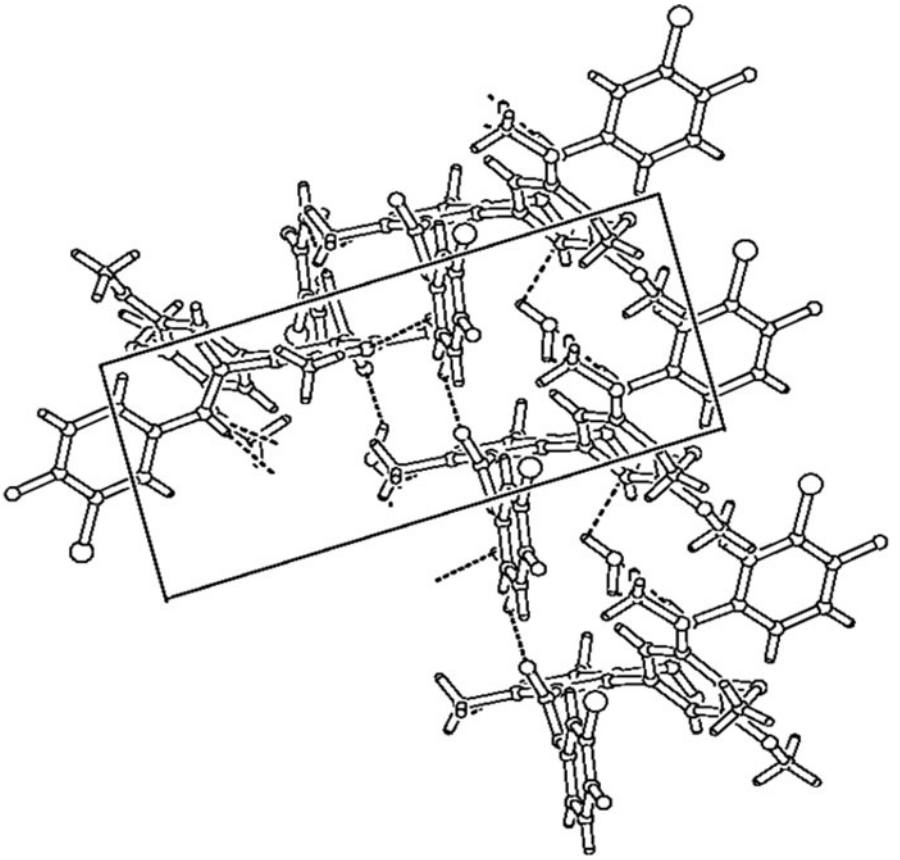

Figure 3. Packing of the molecules down the *b*-axis. The dashed lines represent the hydrogen bonds.

Along with pyridine ring, other three phenyl ring gives planar conformation. The atom C20 deviates from Cremer and Pople plane by −0.020(5), defined by C20-C21-C22-C23-C24-C25. The torsion angles about C35-N34-C32-C5 and C12-N11-C9-C3 are 177.1(5)° and 162.8(5)°, respectively, give anti-periplanar conformation. While C3-C4-C20-C25 give anti-clinal conformation with a value 119.0(6)°. The molecule exhibits both intra and inter-molecular hydrogen bonds of the type O–H· · · O, C–H· · · O and N–H· · · O, O–H· · · N. The intra-molecular hydrogen bonds O43–H43A· · · O10 and C17–H17· · · O10, have lengths of 2.881(6) Å and 2.916(8) Å with both angles 119° , while C36–H36· · · O33, has length of 2.879(6) Å, with an angle of 122° . O43–H43B· · · N34, exhibits inter-molecular hydrogen bonding, which has a length of 2.910(7) Å, with an angle of 115° with symmetry codes $1 - x, 3 - y, 1 - z$ and $-1 + x, y, z$, respectively. The stability of the crystal structure can be accounted for by these hydrogen bonds. Packing of the molecules down *b* axis is shown in Fig. 3.

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*CCDC 691262 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033. E-mail: deposit@ccdc.cam.ac.uk

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