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A Novel Crystal and Molecular Structure of 7-(4-Chloro-Phenyl)-5-Phenyl-4-Pyrrolidin-1-yl-7H-Pyrrolo[2,3-d]Pyrimidine

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ABSTRACT

In the title compound, $C_{22}H_{19}ClN_4$, the pyrrole and pyrimidine rings form a dihetrocyclic fused pyrrolo-pyrimidine ring system which is almost co-planar; dihedral angle between two ring planes is 6.2º, to which five membered pyrrolidine ring is substituted, which is puckered to attain half chair conformation. Two other rings chloro-phenyl and phenyl are substituted at the 7 and 9 positions respectively in the fused ring system. Chloro-phenyl ring also shares the plane of fused ring system. (Dihedral angle between two ring system is 12.4º.) Crystal packing is stabilized due to π-π interaction observed between pyrrole and chloro-phenyl ring of its symmetry related molecules (centroid-centroid distance: 3.8641 Å). Intramolecular C-H…N hydrogen bond is also observed in the molecular structure.

Introduction

Pyrrolo[2,3-d]pyrimidine belongs to an important class of biologically active heterocyclic compounds. These groups of compounds are very well recognized for their biological activities like anti-tumor, anti-allergic, anti viral and anti inflammatory [1-5] and are structurally very much related to nucleosides and some anti-biotics [6-7]. As a part of interest in studying such heterocyclic compounds [8-9], we have synthesized the title compound, 7-(4-Chloro-phenyl)-5-phenyl-4-pyrrolodin-1-yl-7H-pyrrolo[2,3-d] pyrimidine, ($C_{22}H_{19}ClN_4$) and report its three dimensional structure. The chemical structure of the title compound is shown in Fig. 1.

Experimental

The title compound is synthesized by nucleophilic displacement reaction method. It is well-known that single crystals are pre-requisite for the three dimensional study employing the X-Ray diffraction technique. So using slow evaporation method, transparent rectangular needle shaped diffraction quality single crystals (Fig. 2) of the title compound are grown in worm ethanol as the solvent at room temperature. A crystal of 0.35 x 0.20 x 0.15 mm size has been used to collect the intensity data on CCD Diffractometer (Smart Apex-II) at CSMCRI, Bhavnagar with graphite monochromated MoK_α radiation by ω-2θ scan mode [10]. The intensity data collection detail is tabulated in Table. 1. In addition, the density is measured by flotation method using potassium iodide solution. Measured density confirmed number of molecules per unit cell is 4. Structure solution and Refinement

The structure is solved by Direct methods using WinGX programme [11]. The structure is refined with full-matrix least squares procedure in which H atoms have been located from difference Fourier map and refined isotropically using SHELXS programme [12] and the data are tabulated in Table. 2. The fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$) of all atoms are tabulated in Table. 3. The Atomic displacement parameters ($Å^2$) of non-hydrogen atoms are listed in Table. 4. The final residual index R is converged to 0.0522 and ωR(F2) = 0.0696 for 2924 reflections ($I > 2\sigma(I)$) and 320 parameters. The goodness of fit S has the value 1.053. The title compound is crystallized into orthorhombic system with $Pca2_1$ space group with lattice parameters a = 7.8104 (13), b = 13.1789 (21) and c = 17.7368 (28) Å. In Table. 5, the preliminary crystallographic data are listed. The ORTEP diagram of the molecule showing 50% probability of the displacement ellipsoids is depicted in Fig. 3. The intermolecular hydrogen bonding interactions and the molecular graphics are prepared using PARST [13] and PLATON software programmes [14]. The selected bond lengths and bond angles are listed in Table. 6 and Table. 7 respectively.

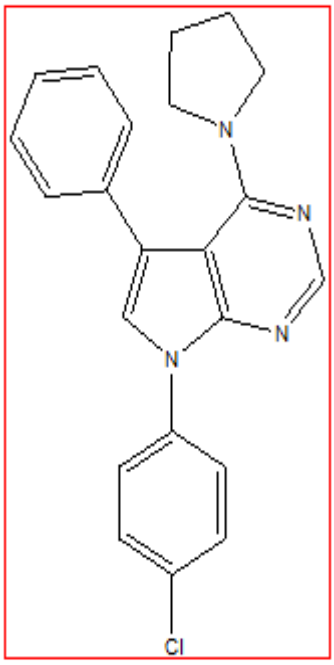

Fig 1. The chemical structure of the title compound

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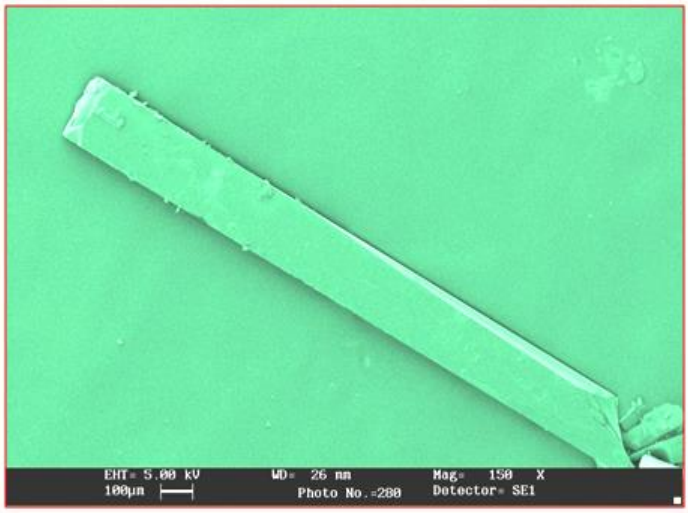

Fig 2. The SEM photograph of the title compound

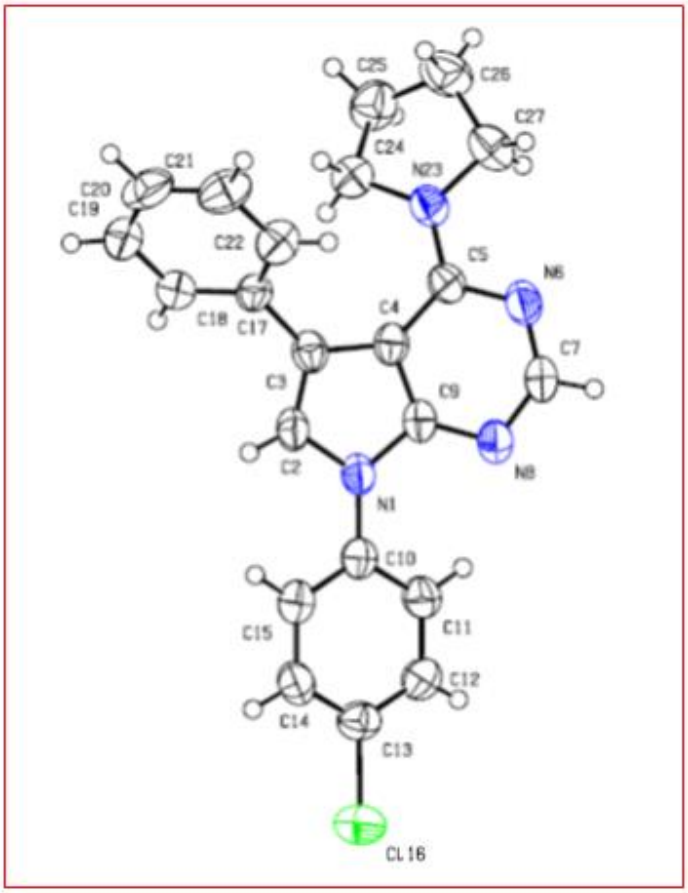

Fig 3. ORTEP view of the molecule with the numbering scheme of atoms

Result and Discussion

In the crystal structure, a five membered pyrrole ring fused to a six membered pyrimidine ring with varied substituents Chloro-phenyl at pyrrole N_1 and phenyl ring at atom C_3 of pyrrole and a five membered pyrrolidine ring at C_5 of pyrimidine ring. Molecular dimension of the central fused ring system is comparable with those reported in other pyrrolo-pyrimidine derivatives reported [15]. As expected, fusion of the two rings affects the neighbouring bond lengths and angles. The N-C bond lengths varies over a wide range 1.317(4) Å to 1.427(4) Å and accordingly the length of C-C bond ranges from 1.347(4) Å to 1.439(4) Å. The endocyclic angles at C_7 and C_9 open up to 130.3(3) (N_8-C_7-N_6) and 126.4(3)^0 (N_8-C_9-C_4) and the effect is also observed at exocyclic angle viz C_3-C_4-C_5 is 138.7(3)^0 and N_1-C_9-C_8 = 124.4(3)^0. The weighted average C-C bond length in the substituted phenyl rings C_{10} …C_{15} and C_{17}…C_{22} lie in the range and 1.383(2) Å respectively and the range of these values agree reasonably well with the literature values [16]. Bond angles in the two benzene rings vary from 118.1(3)° to 121.0(3)° with an average value at 120.0(3)° which coincides exactly with the theoretical values of Sp^2 hybridization.

The weighted average absolute intra-ring torsional angles of the five membered pyrrole ring is 2.80(2)° and that of for six membered pyrimidine ring is 7.2(2)° confirming an almost planar configuration of the rings which is further supported by dihedral angle of 6.21(2)° between the least-square planes of pyrroles and pyrimidine rings. Six membered pyrimidine ring is distorted to adopt screw boat conformation. The puckering parameter of the pyrimidine ring is puckering amplitude Q = 0.098(3), q2 = 0.091 Å, θ = 68.7(18)°, q3 = 0.036(3) Å and ϕ = 146(2)°.

Distortion of the pyrimidine ring results in the non-planar configuration of the central ring system. Interestingly in most of the analogous derivatives pyrimidine adopts a planar configuration. Five membered pyrrolidine, as commonly observed is highly puckered to adopt a half-chair conformation. The puckering parameters are puckering amplitude Q = 0.405(5), ϕ = 273.7(5) and the pseudo rotation parameters are ρ = 76.0(3), τm = 42.0(3) for reference bond N23 - C24.

Both the phenyl rings substituted at pyrrole N1, and at carbon C3 are planar with maximum deviation of 0.010(3) Å for C11 and 0.006(5) Å for C20 atom respectively.

Torsional angle C4 - C5 - N23 - C27 (-179.1(3)°) confirms a very much extended conformation for the pyrrolidine ring which is rotated out by 37.63(19)˚ to the central system whereas Chloro-phenyl ring shares the plane of central ring (dihedral angle is 14.91(13)°(Table. 8)) thereby making feasible an intramolecular interaction involving C11-H11 with N8 of pyrimidine ring of 2.926(4) Å. Chlorine shares the plane of respective phenyl ring (deviation 0.048(1) Å). The phenyl ring substituted at C3 of the pyrrole twisted out maximum 50.50(15)° of the plane of the fused ring system thereby keeping away itself from taking part in any kind of intermolecular interactions.

There is a lack of even non-conventional hydrogen bond interactions in the molecular structure. However, only one intermolecular interactions responding to the structure stability is a direction specific π…π interaction (Fig. 4) involving centroids of pyrimidine and symmetry related pyrrole ring. Intramolecular and comparatively weak C-H…N hydrogen bond (Fig. 5) exist with C11-H11, acting as donor to pyrimidine nitrogen N8, a pseudo six membered ring of graph set motif S(6) [17]. The molecules are arranged in a zigzag chain along c axis. The chains are cross-linked through π…π stacking interactions along b axis between two symmetry related pyrimidine and pyrrole ring with Cg3-Cg1(i) distance of 3.8641(9) Å with a slippage of 1.09 Å. Cg3 is the centroid of C4 - C5 - N6 - C7 - N8 - C9 ring and Cg1 is N1 - C2 - C3 - C4 - C9 ring centroid. The symmetry code is (-½+x, 1-y, z). π…π stacked molecules led to formation of layer parallel to plane. The molecule arranged sinusoidally along c axis, where inactive halogen Chloride positioned itself at the boundary and the centre of the unit cell forming a column along b axis. Chlorine-Chlorine distance is 5.3119(14) Å. Only two significant van der Waal distances < 3.6 Å could be observed in the structure indicating a very weak molecular packing (Table. 9).

Table 1. Intensity Data Collection

Instrument used	**Enraf Nonius CCD Diffractometer**
Temperature of crystal during data collection	293 K
Radiation	MoK_{α}
Wavelength (λ)	0.71073 Å
Mode of data collection	ω-2θ scan mode θ_{min} = 1.55˚, θ_{max} = 28.21˚
Absorption correction	Empirical via ψ-scan
Total number of measured reflections	3681
Total number of independent reflections	2924
h	-10 to 10
k	-16 to 17
l	-22 to 23

Table 2. Refinement Parameters

Refinement method	**Full Matrix Least Square of $\|F\|^2$**
Input data	10325
Number of parameters	320
Goodness of fit (S)	1.053
Final R indices [I > 2σ(I)]	R1 = 0.0524 ωR2 = 0.1128
R indices (all data)	R1 = 0.0697 ωR2 = 0.1212
Largest difference peak and hole	$\Delta\rho_{min}$ = -0.177 eÅ^{-3} $\Delta\rho_{max}$ = 0.189 eÅ^{-3}
Extinction correction	Not applied
Software used to solve the structure	SHELXS-86
Software used to refine the structure	SHELXL-97
Software used for Molecular Graphics	PLATON

Table. 3 Fractional Co-ordinates ($\times 10^{-4}$) of the hydrogen atoms and isotropic displacement parameters ($\times 10^{-3}$)

Atom	**x**	**y**	**z**	**U(iso)**
H2	4240	3920	1380	43
H7	1880	6060	4204	48
H11	2490	6910	2180	55
H12	3060	8220	1420	63
H14	5610	6540	20	44
H15	5250	5170	800	56
H18	2760	1960	1300	60
H19	3800	400	1190	62
H20	5340	-390	2183	49
H21	6150	610	3260	74
H22	4960	2220	3318	36
H241	430	2310	3020	65
H242	1680	1611	3411	22
H251	-890	940	3800	71
H252	-1710	1990	3910	106
H261	850	1300	4790	74
H262	-1000	1690	5050	91
H271	-270	3350	4760	55
H272	1360	2970	5080	63

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^{-4}$) of non-hydrogen atoms with estimated standard deviation in parentheses

Atom	U(1,1)	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
N1	481(15)	446(13)	367(12)	-63(10)	15(11)	53(10)
C2	526(18)	460(16)	376(17)	-97(13)	13(14)	81(13)
C3	435(16)	485(15)	382(14)	-39(13)	-37(13)	71(13)
C4	394(15)	453(14)	408(15)	-75(12)	-59(12)	32(11)
C5	411(15)	499(16)	363(14)	6(12)	-63(12)	3(12)
N6	603(17)	584(15)	406(14)	-80(12)	15(12)	-18(13)
C7	700(02)	520(02)	425(18)	-151(16)	58(15)	1(16)
N8	609(16)	494(14)	426(14)	-85(11)	21(12)	28(12)
C9	421(15)	468(14)	381(16)	-86(12)	-31(12)	34(12)
C10	371(15)	453(15)	417(15)	-45(12)	-48(12)	9(12)
C11	560(02)	508(18)	487(18)	-23(14)	113(16)	60(13)
C12	640(02)	420(17)	580(02)	-19(15)	57(16)	98(15)
C13	457(16)	505(17)	517(18)	53(14)	-53(15)	-79(13)
C14	530(02)	604(18)	410(17)	-71(15)	47(14)	-53(15)
C15	505(18)	478(18)	488(17)	-84(14)	18(14)	35(14)
Cl16	836(06)	631(5)	672(05)	156(04)	77(05)	-109(04)
C17	439(16)	372(14)	446(14)	-21(12)	58(13)	33(12)
C18	630(02)	455(16)	461(17)	11(14)	51(16)	-16(14)
C19	880(03)	473(18)	580(02)	-88(17)	170(02)	-57(18)
C20	690(02)	367(17)	970(03)	61(18)	180(02)	43(16)
C21	560(02)	508(19)	860(03)	100(02)	-130(02)	15(15)
C22	534(19)	510(18)	600(02)	-17(17)	-100(16)	17(14)
N23	471(14)	556(15)	390(13)	-16(11)	-7(11)	-39(11)
C24	610(02)	513(19)	560(02)	-17(16)	19(18)	-40(16)
C25	570(02)	680(2)	800(03)	-110(02)	50(02)	-120(02)
C26	630(02)	870(3)	680(03)	90(02)	160(02)	-140(02)
C27	540(02)	800(2)	448(18)	37(17)	-3(16)	-31(19)

Table 5. Preliminary Crystallographic Data

Chemical formula	$C_{22}H_{19}N_4Cl$
Molecular weight	374.9 amu
Crystal system	Orthorhombic
Space group	Pca 2_1
a	7.8104(13) Å
b	13.1789(21) Å
c	17.7368(28) Å
α	90.000(0)°
β	90.000(0)°
γ	90.000(0)°
Volume (V)	1825.69(5) $Å^3$
Z	4
ρ_c	1.363 gm/cm^3
ρ_m	1.354 gm/cm^3
μ	0.224 mm^{-1}
F(000)	784

Table 6. Bond lengths (Å) involving non-hydrogen atoms with estimated standard deviation in parentheses

Atoms	Distance	Atoms	Distance
N1 - C2	1.394(4)	C13 - C14	1.364(5)
N1 - C9	1.390(4)	C14 - C15	1.378(5)
N1 - C10	1.427(4)	Cl16 - C13	1.759 (5)
C2 - C3	1.347(4)	C17 - C18	1.388(4)
C3 - C4	1.439(4)	C17 - C22	1.388(5)
C3 - C17	1.483(4)	C18 - C19	1.384(5)
C4 - C5	1.422(4)	C19 - C20	1.370(6)
C4 - C9	1.400(4)	C20 - C21	1.372(7)
N6 - C5	1.350(4)	C21 - C22	1.380(6)
N6 - C7	1.326(5)	N23 - C24	1.473(6)
N8 - C7	1.317(4)	N23 - C5	1.350(6)
N8 - C9	1.347(4)	N23 - C27	1.473(6)
C10 - C11	1.383(4)	C24 - C25	1.513(6)
C10 - C15	1.381(4)	C25 - C26	1.512(7)
C11 - C12	1.388(5)	C26 - C27	1.497(7)
C12 - C13	1.365(5)		

Table 7. Bond angles (°) involving non-hydrogen atoms with estimated standard deviation in parentheses

Atoms	Angle	Atoms	Angle
C2 - N1 - C9	106.0(2)	C10 - C11 - C12	119.8(3)
C2 - N1 - C10	124.9(2)	C11 - C12 - C13	119.9(3)
C9 - N1 - C10	129.1(2)	C12 - C13 - C14	121.0(3)
N1 - C2 - C3	111.7(3)	Cl16 - C13 - C12	119.6(2)
C2 - C3 - C4	106.6(2)	Cl16 - C13 - C14	119.4(3)
C2 - C3 - C17	122.0(3)	C13 - C14 - C15	119.5(3)
C4 - C3 - C17	130.8(3)	C10 - C15 - C14	120.7(3)
C3 - C4 - C5	138.7(3)	C3 - C17 - C18	121.2(3)
C3 - C4 - C9	106.5(2)	C3 - C17 - C22	120.5(3)
C5 - C4 - C9	114.7(2)	C18 - C17 - C22	118.2(3)
N6 - C5 - C4	118.7(2)	C17 - C18 - C19	120.6(3)
N6 - C5 - N23	116.4(3)	C18 - C19 - C20	120.3(4)
N23 - C5 - C4	124.9(2)	C19 - C20 - C21	119.8(4)
C5 - N6 - C7	117.5(3)	C20 - C21 - C22	120.3(4)
N6 - C7 - N8	130.3(3)	C17 - C22 - C21	120.8(4)
C7 - N8 - C9	111.0(3)	C5 - N23 - C24	123.2(2)
N1 - C9 - C4	109.1(2)	C5 - N23 - C27	120.6(3)
N1 - C9 - N8	124.4(2)	C24 - N23 - C27	110.1(3)
N8 - C9 - C4	126.4(3)	N23 - C24 - C25	103.6(3)
N1 - C10 - C11	120.8(3)	C24 - C25 - C26	102.7(3)
N1 - C10 - C15	120.1(2)	C25 - C26 - C27	102.6(4)
C11 - C10 - C15	119.1(3)	N23 - C27 - C26	103.5(3)

Table 8. Dihedral angles

Plane	Plane	Angle(^{0})
1 (N_1 - C_2 - C_3 - C_4 - C_9)	3 (C_4 - C_5 - N_6 - C_7 - N_8 - C_9)	6.23(17)
6 (N_1 - C_2 - C_3 - C_4 - C_5 - N_6 - C_7 - N_8 - C_9)	4 (C_{10} - C_{11} - C_{12} - C_{13} - C_{14} - C_{15})	14.91(13)
6 (N_1 - C_2 - C_3 - C_4 - C_5 - N_6 - C_7 - N_8 - C_9)	5 (C_{17} - C_{18} - C_{19} - C_{20} - C_{21} - C_{22})	50.50(15)
6 (N_1 - C_2 - C_3 - C_4 - C_5 - N_6 - C_7 - N_8 - C_9)	2 (N_{23} - C_{24} - C_{25} - C_{26} - C_{27})	37.63(19)

Table 9

(A)π…π stacking interaction

Cg(I) Cg(J)	Cg(I)…Cg(J) Å	Cg(I)…P Å	α	γ	Δ Å
1 3	3.8641(19)	3.650	2.85	19.14	1.26

(B)Intramolecular Hydrogen bonding interactions

D-H…A	D-H Å	D…A Å	H…A Å	∠D-H…A (°)
C_{11} - H_{11}…N_8	0.92	2.926(4)	2.29(3)	126(2)

(C)Short contact distances < 3.6 Å

Atoms	Distance Å	Atoms	Distance Å
C_2 - C_{15}i	3.549(5)	C_7 - C_{14}ii	3.573(5)

(D)Equivalent points

0) x y z

i) ½ + x, 1 - y, z

ii) ½ - x, y, ½ + z

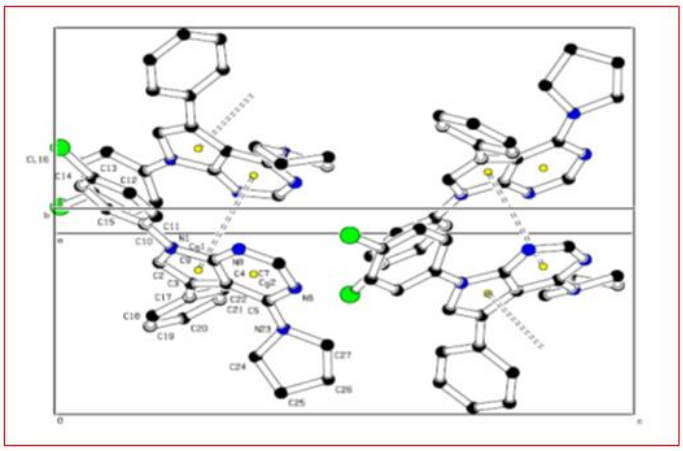

Fig 4. Part of Molecular Packing showing π… π interactions with dash lines

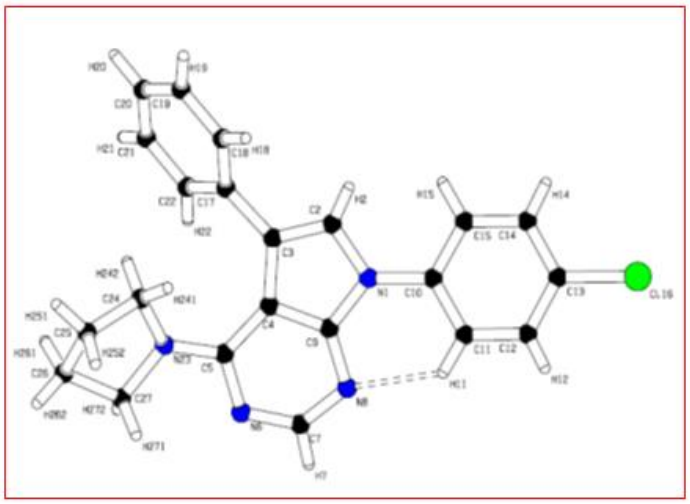

Fig 5. Part of Molecular Packing showing C-H…N intramolecular interactions with dash lines

Supplementary data

The Crystallographic Information File (cif) for the structure reported in this paper has been deposited with Cambridge Crystallographic Data Center CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk) as supplementary publication no. CCDC 897812 ($C_{22}H_{19}ClN_4$). A Copy of the data may be obtained free of charge on application to above address.

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