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Crystal Structure of 3-phenyl-3a,4-dihydro-3H-chromeno[4,3-c] isoxazole-3a-carbonitrile

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ABSTRACT

Single crystals of 3-phenyl-3a,4-dihydro-3H-chromeno[4,3-c]isoxazole-3a-carbonitrile were grown by slow evaporation method at room temperature. Single crystal x-ray diffraction analysis reveals that the title compound crystallizes in Monoclinic system with space group $P2_1/c$ and the calculated lattice parameters are a=10.4380(7)Å, b=6.5517(4)Å, c=19.9654(13)Å, α=90°, β=102.308(2)° and γ= 90°. In the title compound the five membered ring isoxazole adopts envelope conformation. The crystal packing of the compound is through weak C-H...N and C-H…π intermolecular interactions in addition to van der Waals forces.

INTRODUCTION

Isoxazole is an azole compound with an oxygen atom next to the nitrogen. Isoxazolyl is the univalent radical derived from isoxazole. Isoxazole rings are found in some natural products, such as ibotenic acid. Isoxazoles also form the basis for a number of drugs, including the COX-2 inhibitor valdecoxib (Bextra). A derivative, furoxan, is a nitric oxide donor. An isoxazolyl group is found in many beta-lactamase-resistant antibiotics, such as cloxacillin, dicloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also has an isoxazole ring. Using Baylis-Hillman derivatives through *in situ* formation of nitrones followed by an intramolecular [3+2] dipolar cycloaddition reaction sequence is a novel and simple method of synthesizing tricyclic chromenoisoxozolidine frameworks. The new [3+2] cycloaddition reaction leads to a novel class of angularly substituted fused tricyclic chromenoisoxazolidines, creating two rings and three contiguous stereocenters, one of them being a tetrasubstituted carbon center [1].

Isoxazole derivative is used for the treatment of rheumatoid arthritis[2]. Isoxazoles are molecules of great interest in chemistry because these compounds has also exhibit diverse biological activities such as antiprotozoal activities[3], Hsp90 superchaperone complex inhibitors[4], tau aggregation inhibitors for treatment of Alzheimer's disease[5], Mycobacterium tuberculosis pantothenate synthetase inhibitors[6]. Chromenopyrrole compounds are used in the treatment of impulsive disorders[7], in the treatment of Parkinsons disease[8] and memory disorders[9]. Isoxazole and its derivatives are key intermediates for the preparation of products which mimic natural compounds[10]. They have been shown to possess anticonvulsant activity[11]. It is well known that benzopyran and isoxazolidine derivatives possess interesting biologicaland pharmacological activities[12][13]. Benzopyran and isoxazolidine derivatives are well known for their biological activity and proven medicinal utility. For example, benzopyran derivatives possess antipsychotic and antidepressant activities[14]. Isoxazolidine and isoxazole sulfonamide are found to inhibit *HIV*-1 infection in human *CD*4+ lymphocytic *T* cells[15].

Isoxazoline derivatives have been shown to be efficient precursors for many synthetic intermediates including γ-amino alcohols and β-hydroxy ketones[16]. Spiroisoxazolines display interesting biological properties such as herbicidal, plant growth regulators and antitumour activities[17]. Isoxazole compounds have also attracted much

interest because of their fungicidal activity, plant-growth regulating activity and antibacterial activity[18]. Isoxazole derivative exhibit anti-fungal activities[19].

4*H*-Chromenes are biologically important compounds used as synthetic ligands for drug designing and discovery process. They exhibit numerous biological and pharmacological properties such as anti-viral, anti-fungal, anti-inflammatory, antidiabetic, cardionthonic, anti anaphylactic and anti-cancer activity[20-27]. In view of the importance of Isoxazole derivatives, in the present communication we have report the synthesis and crystal structure of 3-phenyl-3a,4-dihydro-3H-chromeno[4,3-c]isoxazole-3a-carbonitrile.

MATERIALS AND METHODS

A solution of (E)-2-((2-((E)-(hydroxyimino)methyl)phenoxy)methyl)-3-phenylacrylonitrile (2 mmol) in CCl_4 at 0-10 ˚C was added pinch wise NCS (4 mmol) over 3h. After Et_3N (4 mmol) was added the reaction mixture was stirred at room temperature for 2h. After completion of the reaction, reaction mixture was evaporated under reduced pressure and the resulting crude mass was diluted with water (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combining organic layer was washed with brine (2 × 10 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated and purified by column chromatography (silica gel 60-120 mesh 7% EtOAc in hexanes) to provide the desired pure product 3-phenyl-3a,4-dihydro-3H-chromeno[4,3-c]isoxazole-3a-carbonitrile a as colorless solid. The compound was crystallized by slow evaporation technique using methanol as solvent at room temperature. The sample was taken and it was recrystallized using solvent combination of chloroform and methanol and good quality crystal was selected for X-ray diffraction.

RESULTS AND DISCUSSION

Crystal structure analysis

X-ray diffraction intensity data were collected for the title compound on Bruker SMART APEX II CCD diffractometer with graphite mono- chromate MoKα (λ=0.71073Å) radiation. Crystals were cut to suitable size and mounted on a glass fibre using cyanoacrylate adhesive. The data collection was covered over a hemisphere of reciprocal space by combination of three sets of exposure each having different Φ angles (0˚, 120˚ and 240˚) for the crystal and each exposure of 15 seconds covered 0.3˚ in ω. The crystal to detector distance was 5 cm and detector swing angle was -35˚. Coverage of the unit set was over 98.2% complete.

Crystal decay was monitored by repeating 30 initial frames at the end of the data collection and analyzing duplicate reflections and was found to be negligible. The intensity data collection, frames integration, Lorentz and polarization correction and decay correction were done using SAINT-NT(version7.06a)software. Empirical absorption correction (multi-scan) was performed using SADABS [28] program. A total of 18001 reflections were collected and among them 4987 reflections were found to be unique. With the criterion $I > 2\sigma$ (I), 4987 reflections were considered as observed. Crystal structures were solved by direct methods using SHELXS-97[29]. The structures were then refined by full matrix least- squares method using SHELXL-97[29]. The computer programme XCAD4 reduced the data and the space group was deduced to be $P2_1/c$ with lattice parameter a=10.4380(7)Å, b=6.5517(4)Å, c=19.9654(13)Å, α=90°, β =102.308(2)° and γ=90°.

The crystal data and structure refinement parameters are given in table 1. The atomic coordinates and their isotropic displacement parameters for non hydrogen atoms are given in Table 2. The anisotropic displacement parameters are listed in Table 3. Selected bond distances and bond angles are given in table 4 and 5. The torsion angles involving non-hydrogen atoms are listed in Table 6. The various hydrogen bond geometrical parameters are presented in table 7 with symmetry codes. The chemical diagram of the title compound is shown in Fig.1. The molecular structure (ORTEP diagram) of the compound is shown in Fig.2. The packing diagram of the compound is shown in Fig.3 and the C-H…π interaction is shown in Fig.4 respectively.

The geometric parameters of the title compound agree well with those reported for closely related structures[30][31]. The five membered isoxazole ring adopts envelope conformation and the two phenyl rings(C_1–C_6 and C_{12}–C_{17}) are in planar conformation. The dihedral angle between the isoxazole ring and pyran ring is 17.2(4)˚. The dihedral angle between the isoxazole ring and the chromeno ring system is 15.21(5)˚. The dihedral angle between the isoxazole ring and the phenyl rings (C_1–C_6 and C_{12}–C_{17}) are 12.96(3)˚ and 74.25(4)˚ respectively. The dihedral angle between the two phenyl rings is 61.35(5)˚. In the pyran ring, the variation of C-C bond distances could be attributed to the presence of heteroatom O_1 in the cyclic system and also to the fusion of pyran and isoxazole ring system[32].

Packing Features

The packing of the molecules of the title compound is viewed down b-axis is shown in Fig.3. The crystal packing of the title compound is stabilized through weak C-H...N and C-H…π intermolecular interactions (Table 7) in addition to van der Waals forces. The C-H…π interaction is observed between C_{11} and the centroid (cg1) of the phenyl ring separated by a distance of 3.6700(5) Å. 'cg' is the centroid of the C1-C6 ring.

Computational detail

Data collection: SMART [28]; cell refinement: SAINT [28]; data reduction: SAINT; program(s) used to solve structure: SHELXS97 [29]; program(s) used to refine structure: SHELXL97 [29]; molecular graphics: PLATON [37]; software used to prepare material for publication: SHELXL97 and PARST [38].

Table1 : Crystal Data Table for the title compound

Parameters	Title Compound
Empirical formula	$C_{17}H_{12}N_2O_2$
Formula weight	276.29
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.4380(7)Å b = 6.5517(4)Å c = 19.9654(13)Å α = 90° β = 102.308(2)° γ = 90°
Volume	1333.98(6)Å^3
Z, Calculated density	4, 1.376 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	576
Crystal size (mm)	0.20 x 0.20 x 0.20
θ range	2.0 to 33.2°
Index range	-14 ≤ h ≤ 15 -5 ≤ k ≤ 10 -27 ≤ l ≤ 30
Reflections collected / unique	18001/ 4987 [R(int) = 0.0271]
Completeness	98.2%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4987 / 0 / 194
Goodness-of-fit on F^2	1.02
Final R indices [I>2σ(I)]	R1 = 0.047 wR2 = 0.118
R indices (all data)	R1 = 0.085 wR2 = 0.143
Largest diff.peak and hole	0.30 and -0.22 e.Å^{-3}

Table 2 : Atomic coordinates(x10^4) and equivalent isotropic displacement parameters (Å^2 x10^3) for the non-hydrogen atoms

Atom	X	Y	Z	*U(eq)
C(1)	2362(2)	-29(2)	975(1)	36(1)
C(2)	3652(2)	-37(2)	893(1)	49(1)
C(3)	4161(2)	-1760(3)	655(2)	53(1)
C(4)	3397(2)	-3493(2)	491(1)	50(1)
C(5)	2120(2)	-3503(2)	567(1)	40(1)
C(6)	1584(2)	-1774(2)	816(1)	33(1)
C(7)	251(2)	-1667(2)	922(1)	33(1)
C(8)	-146(1)	139(2)	1302(1)	30(1)
C(9)	248(1)	-151(2)	2050(1)	32(1)
C(10)	535(2)	2025(2)	1094(1)	37(1)
C(11)	-1644(2)	9(2)	1031(1)	36(1)
C(12)	-2492(2)	672(2)	1508(1)	36(1)
C(13)	-3024(2)	2618(2)	1439(1)	44(1)
C(14)	-3710(2)	3340(3)	1915(1)	54(1)
C(15)	-3853(2)	2133(3)	2457(1)	55(1)
C(16)	-3342(2)	196(3)	2523(1)	53(1)
C(17)	-2666(2)	-548(2)	2050(1)	44(1)
N(1)	-688(2)	-2891(2)	682(1)	43(1)
N(2)	527(2)	-310(2)	2631(1)	47(1)
O(1)	1922(1)	1721(2)	1226(1)	43(1)
O(2)	-1846(1)	-2140(2)	857(1)	48(1)

*Ueq=(1/3) Σ i Σ jUij ai*aj***ai.aj**

Table 3 : Anisotropic displacement parameters ($Å^2x10^3$) for the non-hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	43(1)	37(1)	30(1)	-3(1)	10(1)	-6(1)
C(2)	44(1)	58(1)	46(1)	-5(1)	12(1)	-13(1)
C(3)	42(1)	70(1)	50(1)	0(1)	15(1)	3(1)
C(4)	56(1)	50(1)	46(1)	2(1)	17(1)	12(1)
C(5)	53(1)	33(1)	36(1)	0(1)	14(1)	2(1)
C(6)	42(1)	31(1)	26(1)	0(1)	8(1)	-3(1)
C(7)	42(1)	28(1)	28(1)	-2(1)	9(1)	-5(1)
C(8)	38(1)	27(1)	26(1)	0(1)	8(1)	-3(1)
C(9)	37(1)	30(1)	30(1)	0(1)	8(1)	-3(1)
C(10)	51(1)	28(1)	34(1)	0(1)	16(1)	-4(1)
C(11)	39(1)	39(1)	30(1)	0(1)	5(1)	-2(1)
C(12)	32(1)	43(1)	33(1)	0(1)	4(1)	-2(1)
C(13)	41(1)	45(1)	46(1)	3(1)	8(1)	0(1)
C(14)	43(1)	53(1)	67(1)	-11(1)	11(1)	2(1)
C(15)	42(1)	80(1)	48(1)	-14(1)	14(1)	-3(1)
C(16)	40(1)	81(1)	42(1)	10(1)	12(1)	-2(1)
C(17)	38(1)	52(1)	45(1)	9(1)	11(1)	0(1)
N(1)	47(1)	42(1)	44(1)	-12(1)	13(1)	-9(1)
N(2)	52(1)	55(1)	33(1)	5(1)	6(1)	0(1)
O(1)	49(1)	35(1)	49(1)	-12(1)	17(1)	-14(1)
O(2)	43(1)	48v	55(1)	-16(1)	13(1)	-13

The anisotropic displacement factor takes the form: $\exp\{-2\pi^2[h^2 a^{*2}U11 +...+2hka^*b^*U12]\}$

Table 4 : Bond Distance for the non hydrogen atoms of the title compound

Atoms	Distance (Å)
O(1)-C(1)	1.3698(1)
O(1)-C(10)	1.4292(1)
O(2)-N(1)	1.4173(1)
O(2)-C(11)	1.4553(2)
N(1)-C(7)	1.2783(1)
N(2)-C(9)	1.1372(1)
C(1)-C(2)	1.391(2)
C(1)-C(6)	1.3990(1)
C(2)-C(3)	1.374(2)
C(3)-C(4)	1.385(2)
C(4)-C(5)	1.373(2)
C(5)-C(6)	1.4009(2)
C(6)-C(7)	1.4519(2)
C(7)-C(8)	1.5116(2)
C(8)-C(9)	1.4745(1)
C(8)-C(10)	1.5267(2)
C(8)-C(11)	1.5445(1)
C(11)-C(12)	1.4954(2)
C(12)-C(13)	1.3857(2)
C(12)-C(17)	1.3879(2)
C(13)-C(14)	1.388(2)
C(14)-C(15)	1.373(2)
C(15)-C(16)	1.372(3)
C(16)-C(17)	1.384(2)

Table 5 : Bond Angles for non hydrogen atoms of the title compound

Atoms	Angles(°)
C(1)-O(1)-C(10)	117.09(2)
N(1)-O(2)-C(11)	107.91(2)
O(2)-N(1)-C(7)	108.46(1)
O(1)-C(1)-C(2)	117.05(1)
O(1)-C(1)-C(6)	122.89(2)
C(2)-C(1)-C(6)	120.05(2)
C(1)-C(2)-C(3)	119.86(3)
C(2)-C(3)-C(4)	120.71(5)
C(3)-C(4)-C(5)	120.01(3)
C(4)-C(5)-C(6)	120.39(2)
C(1)-C(6)-C(5)	118.97(2)
C(1)-C(6)-C(7)	117.12(1)
C(5)-C(6)-C(7)	123.91(1)
N(1)-C(7)-C(6)	126.67(1)
N(1)-C(7)-C(8)	114.12(1)
C(6)-C(7)-C(8)	119.03(2)
C(7)-C(8)-C(9)	111.09(2)
C(7)-C(8)-C(10)	107.67(2)
C(7)-C(8)-C(11)	98.47(2)
C(9)-C(8)-C(10)	109.52(2)
C(9)-C(8)-C(11)	113.03(2)
C(10)-C(8)-C(11)	116.47(2)
N(2)-C(9)-C(8)	177.35(3)
O(1)-C(10)-C(8)	110.49(2)
O(2)-C(11)-C(8)	102.82(2)
O(2)-C(11)-C(12)	110.99(2)
C(8)-C(11)-C(12)	117.01(2)
C(11)-C(12)-C(13)	118.92(1)
C(11)-C(12)-C(17)	121.47(2)
C(13)-C(12)-C(17)	121.47(2)
C(12)-C(13)-C(14)	120.01(3)
C(13)-C(14)-C(15)	120.08(2)
C(14)-C(15)-C(16)	120.25(5)
C(15)-C(16)-C(17)	120.26(5)
C(12)-C(17)-C(16)	120.02(3)

Table 6 : Torsion angles for the non hydrogen atoms of the title compound

Atoms	Torsion Angle
C(10)-O(1)-C(1)-C(2)	158.99(1)
C(10)-O(1)-C(1)-C(6)	-22.32(2)
C(1)-O(1)-C(10)-C(8)	50.95(3)
C(11)-O(2)-N(1)-C(7)	18.72(3)
N(1)-O(2)-C(11)-C(8)	-28.32(1)
N(1)-O(2)-C(11)-C(12)	-154.18(1)
O(1)-C(1)-C(2)-C(3)	178.80(2)
C(6)-C(1)-C(2)-C(3)	0.1(2)
O(1)-C(1)-C(6)-C(5)	-179.47(1)
O(1)-C(1)-C(6)-C(7)	0.60(7)
C(2)-C(1)-C(6)-C(5)	-0.82(2)
C(2)-C(1)-C(6)-C(7)	179.27(1)
C(1)-C(2)-C(3)-C(4)	0.5(2)
C(2)-C(3)-C(4)-C(5)	-0.2(2)
C(3)-C(4)-C(5)-C(6)	-0.6(2)
C(4)-C(5)-C(6)-C(1)	1.08(2)
C(4)-C(5)-C(6)-C(7)	-179.02(3)
C(1)-C(6)-C(7)-N(1)	164.36(2)
C(1)-C(6)-C(7)-C(8)	-10.24(6)
C(5)-C(6)-C(7)-N(1)	-15.6(2)
C(5)-C(6)-C(7)-C(8)	169.84(1)
C(6)-C(7)-N(1)-O(2)	-174.97(2)
C(8)-C(7)-N(1)-O(2)	-0.13(4)
N(1)-C(7)-C(8)-C(9)	102.03(2)
N(1)-C(7)-C(8)-C(10)	-138.07(1)
N(1)-C(7)-C(8)-C(11)	-16.72(3)
C(6)-C(7)-C(8)-C(9)	-82.71(3)
C(6)-C(7)-C(8)-C(10)	37.19(3)
C(6)-C(7)-C(8)-C(11)	158.54(2)
C(7)-C(8)-C(10)-O(1)	-56.00(2)
C(9)-C(8)-C(10)-O(1)	64.90(2)
C(11)-C(8)-C(10)-O(1)	-165.34(2)
C(7)-C(8)-C(11)-O(2)	25.66(1)
C(7)-C(8)-C(11)-C(12)	147.54(2)
C(9)-C(8)-C(11)-O(2)	-91.62(1)
C(9)-C(8)-C(11)-C(12)	30.24(4)
C(10)-C(8)-C(11)-O(2)	140.29(2)
C(10)-C(8)-C(11)-C(12)	-97.84(2)
O(2)-C(11)-C(12)-C(13)	-143.76(2)
O(2)-C(11)-C(12)-C(17)	41.76(6)
C(8)-C(11)-C(12)-C(13)	98.73(4)
C(8)-C(11)-C(12)-C(17)	-75.74(6)
C(11)-C(12)-C(13)-C(14)	-173.83(3)
C(17)-C(12)-C(13)-C(14)	0.8(2)
C(11)-C(12)-C(17)-C(16)	173.16(3)
C(13)-C(12)-C(17)-C(16)	-1.3(2)
C(12)-C(13)-C(14)-C(15)	0.5(2)
C(13)-C(14)-C(15)-C(16)	-1.2(2)
C(14)-C(15)-C(16)-C(17)	0.7(2)
C(15)-C(16)-C(17)-C(12)	0.6(2)

Table 7 : Hydrogen bond interactions [Å and º]

D-H…A	D-H	H…A	D…A	D-H…A
C10-H10B…N2i	0.97	2.59	3.4582	150
C11-H11…Cg1[ii]	0.93	2.74	3.6700	160

Symmetry code:
(i) –x,1/2+y,1/2-z
(ii) –x,-y,-z

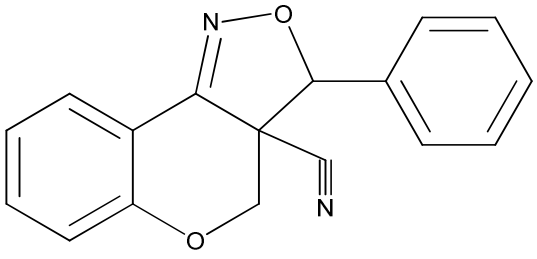

Figure 1 : Schematic Diagram of the title compound

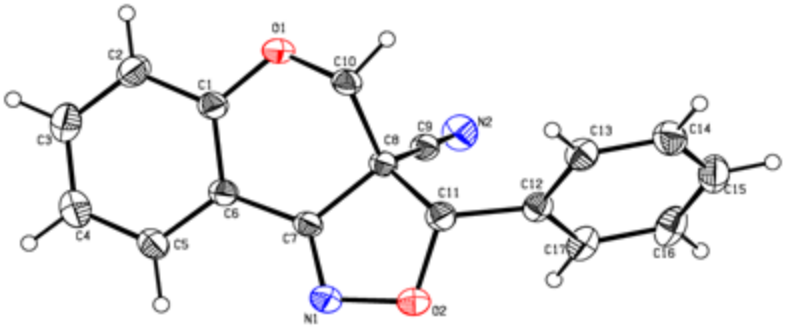

Figure 2 : ORTEP of the title compound drawn at 30% probability level

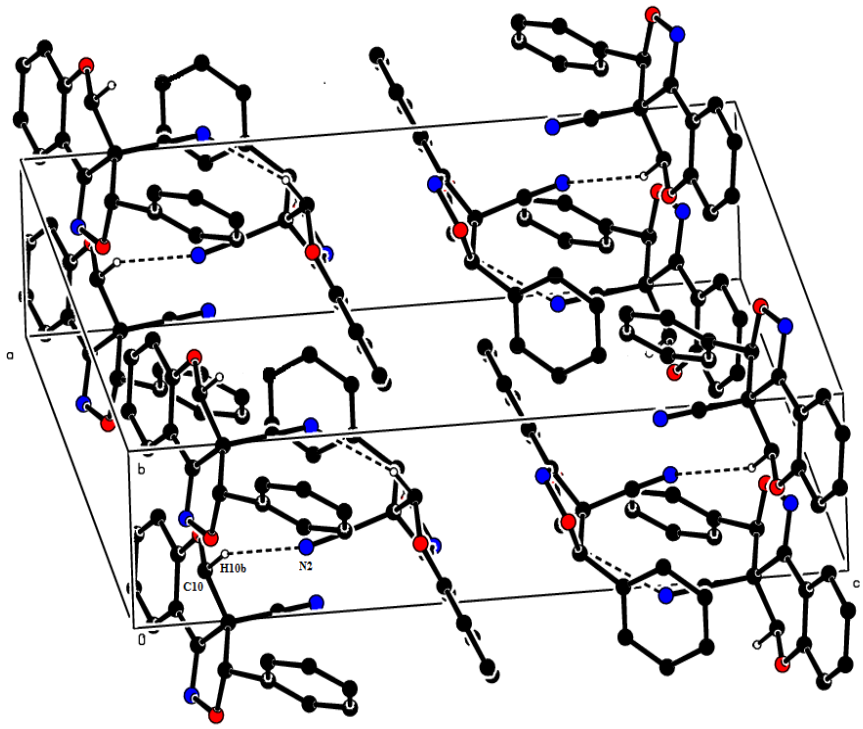

Figure 3 : Packing of the molecules viewed down the *b-axis* for title compound

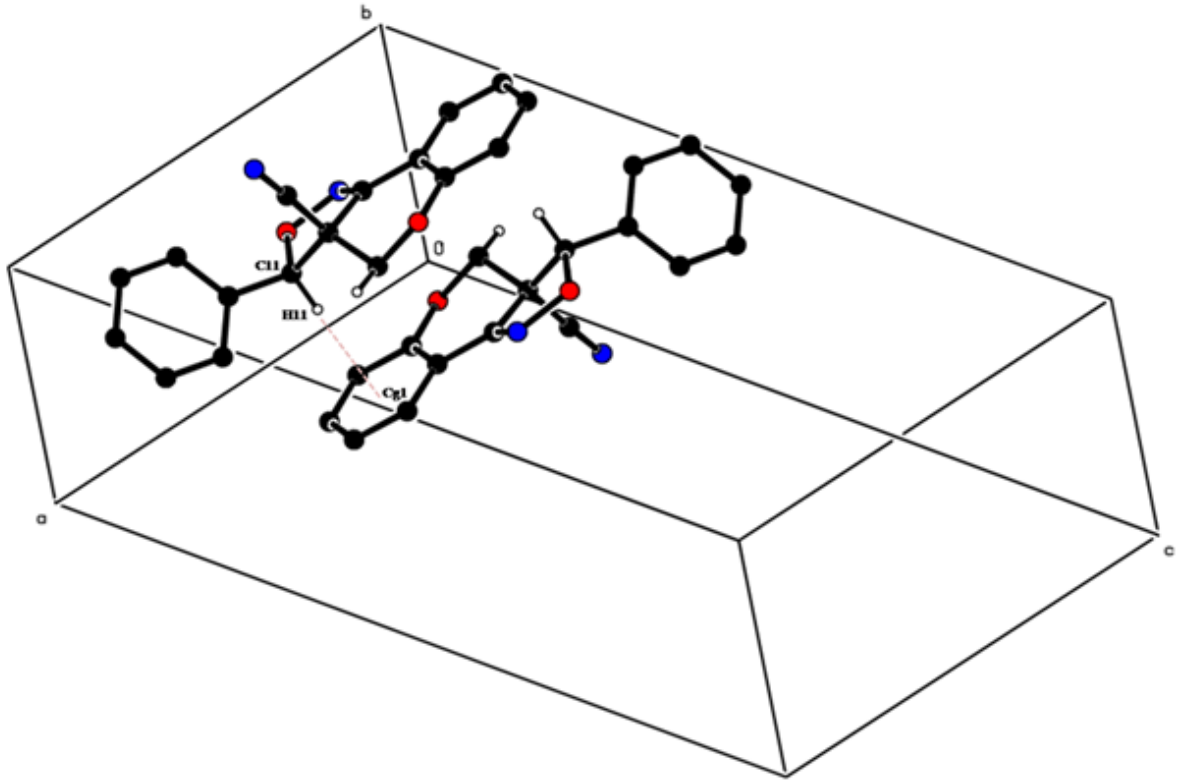

Figure 4 : C-H…π Interaction of the title compound

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