Crystal Structure Analysis of Methyl 8-bromo-3-phenyl-5a,9a-dihydro-3H-chromen [4,3-c][1,2] isoxazole-3a(4H)-carboxylate

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Abstract

The crystal structure of the potential active Methyl 8-bromo-3-phenyl-5a,9a-dihydro-3H-chromen [4,3-c][1,2] isoxazole-3a(4H)- carboxylate ($C_{18}H_{15}BrNO_4$) has been determined from single crystal X-ray diffraction technique. The title compound crystallizes in the triclinic space group P$\bar{1}$ with unit cell dimension a=8.3129 (3) Å, b=9.5847 (4) Å and c= 11.1463(4) Å [α= 98.457(3)°, β= 102.806(2)° and γ= 105.033(5)°]. Single crystals suitable for X-ray diffraction were obtained by slow evaporation method, the isoxazole and six membered pyran rings adopts envelope conformation. In the crystal, molecules are linked via pairs of inter molecular C-H…O hydrogen bonds to form dimmers.

Keywords: Chromen, Pyran, Isoxazole, Single Crystal Structure, X-ray Diffraction

1. Introduction

The title compound consists of biologically active function group like Isoxazole and chromen moieties. 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. Chromenes constitute one of the main class of naturally occurring oxygen heterocycles, which posses several biological and pharmacological properties such as anti-coagulant, anti-sterility, anti-viral, anti-fungal, antiinflammatory, cardionthonic, anti-diabetic, spasmolytic, diuretic, anti-anaphylactic, anti-cancer activities[1-10] and also useful in treatment of Schizophrenia and Alzheimer's diseases[11,12]. The literature survey reveals that Isoxazoles and chromen moieties are important pharmacophores and exhibit outstanding biological properties.

In view of the growing medicinal importance of Isoxazole-chromen and its derivatives, the single crystal X-ray diffraction study was carried out for one such compound. The IUPAC name and chemical diagram of the compound is given in Fig. 1.
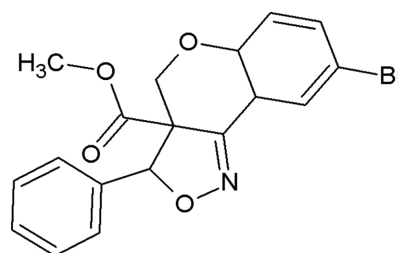
Fig. 1. Chemical structure of Methyl 8-bromo-3-phenyl-5a,9a-dihydro-3H-chromen [4,3-c][1,2] isoxazole-3a(4H)-carboxylate

2. Material and Methods

The title compound is crystallized by ethyl acetate solvent using slow evaporation method. Three rounds of crystallization trials to obtain qualified crystals were achieved. The diffraction quality crystals after screening its size and stability, X-ray diffraction data collection was done at IIT-Madras. The data was reduced with appropriate corrections at the facility and the error free data was taken for structure determination. Using WinGx suite, structure determination was done using SHELXS97 with Direct Methods protocols. After manual inspections and corrections, Isotropic refinements followed by anisotropic refinements were carried out. With the satisfied model (agreeable R factor, Goodness of Fit and other) hydrogen atoms were geometrically fixed and after the final refinement the R factor is 4.0%.

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3. Experimental Section

3.1. Synthesis of the Title Compound

At 283 - 293 K, NCS (4 mmol) was added pinch wise over 3 h to a solution of ((E)-methyl2-((2ethoxy-6-((E)-(hydroxyimino) methyl)phenoxy)methyl) -3-phenylacrylate (2 mmol) in CCl_4. After Et_3N (4 mmol) was added to the reaction mixture which was stirred at room temperature for 2 hrs. After completion of the reaction, the 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 combined organic layers were 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 title product as a colourless solid. Single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a solution in ethyl acetate at room temperature.

3.2. X-Ray Crystallography

For the crystal structure determination, the single crystal of the compound $C_{18}H_{15}BrNO_4$ was used for data collection on a Bruker Kappa APEXII CCD diffractometer[13]. The MoKα radiation of wavelength, (#
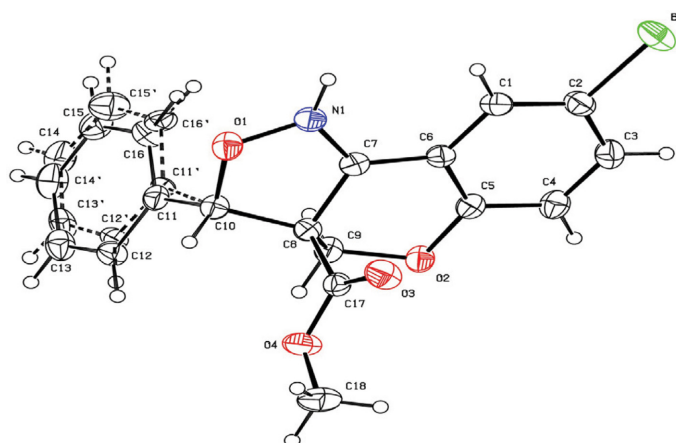
Fig. 2. The ORTEP plot of compound with the atom numbering scheme. Displacement ellipsoids are drawn at 30% probability level.
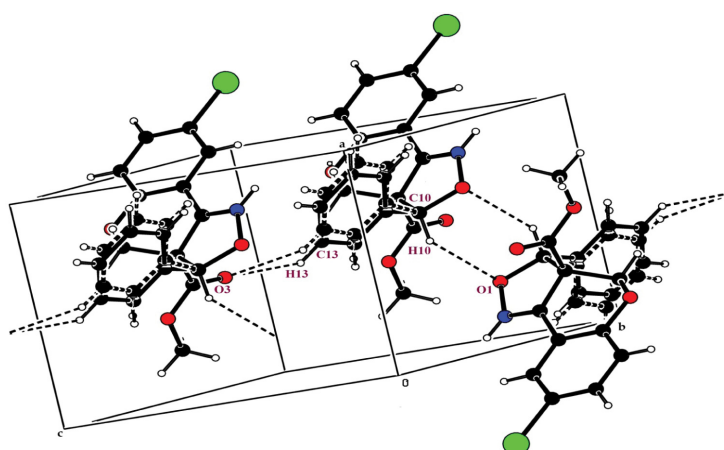
Fig. 3. Crystal packing of the title compound viewed down *c* axis, dashed line indicate the inter molecular interaction in the unit cell.
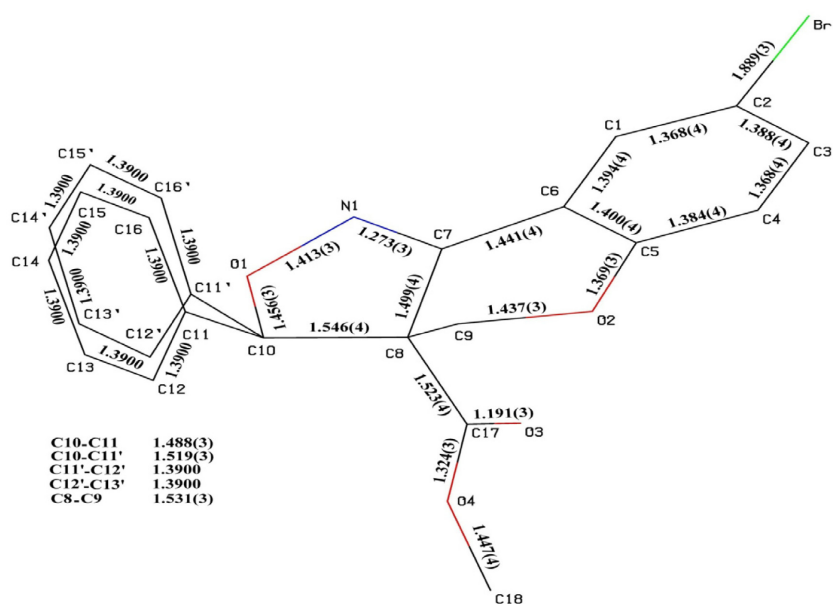
C10-C11	1.488(3)
C10-C11'	1.519(3)
C11'-C12'	1.3900
C12'-C13'	1.3900
C8-C9	1.531(3)

Fig. 4. Bond lengths (Å) of compound

C14'-C13'-C12'	120.0	C15-C16-C11	120.0	C12'-C11'- C10	116.0(1)
C13'-C12'-C11'	120.0	C12'-C11'-C16'	120.0	C16'-C11'- C10	123.8(1)
C12-C11-C10	120.2(1)	C9-C8- C10	118.2(2)	C16-C15- C14	120.0
C16-C11-C10	119.6(1)	C7-C8-C17	110.2(2)	C13'- C14'- C15'	120.0
C11-C12-C13	120.0	O1-C10-C11	114.60(1)	C16'- C15'- C14'	120.0
C12-C13-C14	120.0	O1-C10-C11'	107.71(1)	C15'- C16'- C11'	120.0
C13-C14-C15	120.0	C11-C10-C11'	9.7	C11'- C10- C8	113.3(1)
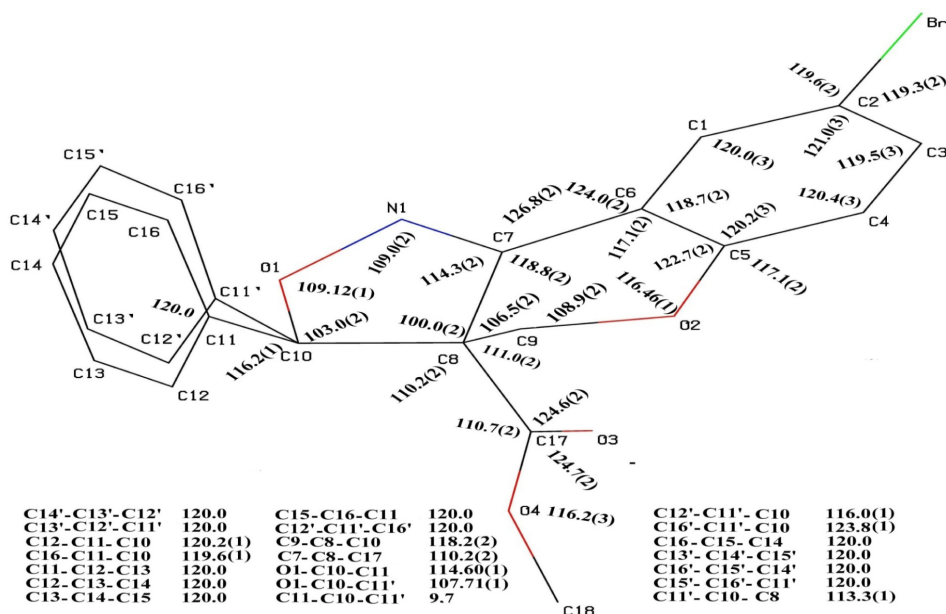
Fig. 5. Bond angles (°) of compound

= 0.71073 Å) and multi-scan technique for absorption correction were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with F2>2$ (F2). The structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97[14,15]. H atoms were positioned geometrically and refined using a riding model, fixing the aromatic C-H distances at 0.93 Å [Uiso(H) = 1.2 Ueq (C)]. The softwares used for

Table 1. Crystal Data and Structure refinement statistics

Parameters	Compound
Empirical formula	$C_{18}H_{15}BrNO_4$
Formula weight	389.22
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P$\bar{1}$
Unit cell dimensions	a = 8.3129(3) Å
	b = 9.5847(4) Å
	c = 11.1463(4) Å
	α = 98.457(3)°
	β = 102.806(2)°
	γ = 105.033(5)°
Volume	816.40 (5) Å^3
Z, Calculated density	2, 1.583 Mg/m^3
Absorption coefficient	2.539 mm^{-1}
F(000)	394
Crystal size(mm)	0.25×0.20×0.20
θ range	1.9 to 26.9°
Limiting indices	-10 ≤ h ≤ 10
	-11 ≤ k ≤ 12
	-14 ≤ l ≤ 14
Reflections collected /	11704/ 3396
unique	[R(int)= 0.038]
Completeness to theta	96.80%
Refinement method	Full-matrix
	least-squares on F^2
Data / restraints / parameters	3396 / 0 / 237
Goodness-of-fit on F^2	1.03
Final R indices [I>2σ(I)]	R1 = 0.0421
R indices (all data)	wR2 = 0.1120
	R1 = 0.0632
	wR2 = 0.1255
Largest diff. peak and hole	0.62 and -0.94 e.Å^{-3}

Molecular graphics are ORTEP-3 for Windows[16] and PLATON[17]. The software used to prepare material for publication is WinGX publication routines[18]. Fig. 1 shows chemical diagram of the molecule and molecular structure of the title compound along with the atom numbering scheme is depicted in Fig. 2 and a packing diagram is shown in Fig. 3 and The bond lengths of compound involving the non-hydrogen atoms are shown in Fig. 4. The bond angles of compound involving the non-hydrogen atoms are shown in Fig. 5. Table 1 shows the crystal data and crystal refinement statistics. Table 2 gives the atomic coordinates of non hydrogen atom, Table 3 shows anisotropic displacement parameters, Table 4 shows atomic coordinates of the hydrogen atoms, Table 5 shows the torsion angles, The least-squares planes calculated for various groups of atoms in the molecules of compound are presented in Table 6 and Table 7 Shows Hydrogen-bond geometry.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for the non-hydrogen atoms of compound

Atom	x	y	z	*U(eq)
C1	8990(3)	1281(3)	6966(3)	41(1)
C2	7930(3)	262(3)	5910(3)	45(1)
C3	8014(4)	465(3)	4715(3)	47(1)
C4	9163(4)	1710(3)	4591(3)	44(1)
C5	10255(3)	2751(3)	5647(2)	36(1)
C6	10193(3)	2539(3)	6854(2)	34(1)
C7	11457(3)	3609(3)	7909(2)	34(1)
C8	12910(3)	4729(3)	7664(2)	33(1)
C9	12126(4)	5222(3)	6483(2)	38(1)
C10	13552(3)	5857(3)	8940(2)	36(1)
C11	13131(1)	7274(1)	8941(1)	38(2)
C12	14193(1)	8438(1)	8600(1)	43(2)
C13	13751(1)	9735(1)	8547(1)	49(2)
C14	12247(1)	9868(1)	8835(1)	54(2)
C15	11184(1)	8703(1)	9176(1)	55(2)
C16	11626(1)	7407(1)	9229(1)	49(2)
C17	14316(3)	4043(3)	7463(2)	35(1)
C18	17013(4)	4505(5)	7006(4)	70(1)
C11'	12814(1)	7149(1)	8926(1)	24(2)
C12'	13807(1)	8400(1)	8642(1)	33(2)
C13'	13260(1)	9653(1)	8650(1)	44(2)
C14'	11720(1)	9656(1)	8943(1)	58(3)
C15'	10727(1)	8406(1)	9227(1)	60(3)
C16'	11274(1)	7153(1)	9219(1)	41(2)
O1	12854(3)	4996(2)	9783(2)	44(1)
O2	11389(3)	3957(2)	5449(2)	41(1)
O3	14344(3)	2846(2)	7619(2)	55(1)
O4	15529(3)	4979(2)	7130(2)	53(1)
N1	11446(3)	3766(3)	9061(2)	41(1)
Br	6395(1)	-1489(1)	6078(1)	80(1)

*Ueq= (1/3)$\sum_i \sum_j$Uij ai*aj*ai.aj

Table 3. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for the non-hydrogen atoms of compound

Atom	U11	U22	U33	U23	U13	U12
C1	38(1)	47(2)	42(1)	12(1)	15(1)	12(1)
C2	37(1)	40(2)	56(2)	8(1)	14(1)	9(1)
C3	45(2)	43(2)	45(2)	0(1)	4(1)	11(1)
C4	54(2)	43(2)	35(1)	8(1)	8(1)	17(1)
C5	41(1)	35(2)	37(1)	9(1)	10(1)	18(1)
C6	34(1)	35(1)	36(1)	10(1)	11(1)	14(1)
C7	38(1)	34(1)	35(1)	13(1)	11(1)	17(1)
C8	39(1)	29(1)	33(1)	11(1)	11(1)	12(1)
C9	50(2)	32(1)	34(1)	10(1)	11(1)	13(1)

Table 3. Continued

Atom	U11	U22	U33	U23	U13	U12
N1	49(1)	40(1)	36(1)	14(1)	16(1)	11(1)
C10	41(1)	35(1)	32(1)	9(1)	9(1)	13(1)
C11	40(2)	36(3)	31(3)	-1(3)	7(2)	9(2)
C12	45(2)	39(3)	41(3)	9(3)	14(2)	6(2)
C13	66(3)	36(3)	38(3)	9(2)	7(2)	8(2)
C14	65(4)	40(3)	53(3)	7(3)	0(3)	28(3)
C15	50(3)	49(4)	68(4)	-1(3)	20(3)	25(3)
C16	49(3)	38(3)	55(3)	10(3)	17(2)	4(3)
C11'	23(3)	22(4)	26(4)	9(3)	7(2)	4(3)
C12'	28(3)	35(5)	31(4)	9(3)	8(3)	1(3)
C13'	61(5)	24(4)	37(4)	13(3)	5(3)	0(3)
C14'	65(5)	49(6)	55(5)	1(5)	10(4)	22(4)
C15'	51(4)	67(6)	70(5)	19(5)	21(4)	27(4)
C16'	38(3)	41(4)	53(5)	9(4)	24(3)	19(3)
C17	40(1)	32(2)	35(1)	6(1)	11(1)	10(1)
C18	49(2)	88(3)	83(2)	16(2)	36(2)	25(2)
O1	59(1)	39(1)	31(1)	11(1)	8(1)	12(1)
O2	57(1)	34(1)	31(1)	9(1)	13(1)	9(1)
O3	54(1)	36(1)	86(2)	18(1)	25(1)	21(1)
O4	49(1)	51(1)	71(1)	23(1)	33(1)	17(1)
Br	71(1)	64(1)	85(1)	6(1)	31(1)	-18(1)

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

Table 4. Atomic coordinates ($\times 10^4$) and their isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for hydrogen atoms of compound

Atom	x	y	z	*U(eq)
H1	8907	1134	7760	50
H3	7294	-240	4005	57
H4	9211	1858	3792	53
H9A	11238	5659	6629	46
H9B	13016	5961	6288	46
H10	10701	3212	9352	49
H11	14816	6099	9214	43
H13	15200	8349	8407	51
H14	14462	10514	8319	59
H15	11951	10735	8800	64
H16	10178	8792	9369	66
H17	10915	6628	9457	58
H13'	14838	8397	8447	40
H14'	13925	10489	8460	53
H15'	11354	10495	8948	69
H16'	9696	8408	9422	71
H17'	10609	6316	9409	49
H19A	17588	4355	7801	104
H19B	17799	5251	6748	104
H19C	16636	3596	6385	104

Table 5. Torsion angles (°) involving the non-hydrogen atoms of Compound

Atoms	Angle	Atoms	Angle
C(6)-C(1)-C(2)-C(3)	-0.8 (4)	C(7)-C(8)-C(17)-O(4)	174.2 (2)
C(6)-C(1)-C(2)-Br	176.5 (2)	C(9)-C(8)-C(17)-O(4)	56.4 (3)
C(1)-C(2)-C(3)-C(4)	-0.6 (4)	C(10)-C(8)-C(17)-O(4)	-76.5 (3)
Br-C(2)-C(3)-C(4)	-177.9 (2)	O(3)-C(17)-O(4)-C(18)	-2.7 (4)
C(2)-C(3)-C(4)-C(5)	1.0 (4)	C(8)-C(17)-O(4)-C(18)	175.3 (3)
C(3)-C(4)-C(5)-O(2)	179.0 (2)	C(4)-C(5)-O(2)-C(9)	161.6 (2)
C(3)-C(4)-C(5)-C(6)	0.0 (4)	C(6)-C(5)-O(2)-C(9)	-19.4 (3)
C(2)-C(1)-C(6)-C(5)	1.8 (4)	C(8)-C(9)-O(2)-C(5)	52.2 (3)
C(2)-C(1)-C(6)-C(7)	-174.7 (2)	C(7)-N(1)-O(1)-C(10)	14.0 (3)
O(2)-C(5)-C(6)-C(1)	179.7 (2)	C(11)-C(10)-O(1)-N(1)	106.1 (2)
C(4)-C(5)-C(6)-C(1)	-1.3 (4)	C(11')-C(10)-O(1)-N(1)	98.8 (2)
O(2)-C(5)-C(6)-C(7)	-3.6 (4)	C(8)-C(10)-O(1)-N(1)	-21.2 (2)
C(4)-C(5)-C(6)-C(7)	175.3 (2)	O(1)-C(10)-C(11)-C(12)	155.09 (14)
C(1)-C(6)-C(7)-N(1)	-16.4 (4)	C(11')-C(10)-C(11)-C(12)	-158.96 (6)
C(5)-C(6)-C(7)-N(1)	167.1 (3)	C(8)-C(10)-C(11)-C(12)	-84.8 (2)
C(1)-C(6)-C(7)-C(8)	167.1 (2)	O(1)-C(10)-C(11)-C(16)	-27.8 (2)
C(5)-C(6)-C(7)-C(8)	-9.4 (3)	C(11')-C(10)-C(11)-C(16)	18.14 (5)
N(1)-C(7)-C(8)-C(17)	103.0 (3)	C(8)-C(10)-C(11)-C(16)	92.31 (19)
C(6)-C(7)-C(8)-C(17)	-80.1 (3)	C(10)-C(11)-C(12)-C(13)	177.09 (11)
N(1)-C(7)-C(8)-C(9)	-136.5 (2)	C(10)-C(11)-C(16)-C(15)	-177.11 (11)
C(6)-C(7)-C(8)-C(9)	40.4 (3)	O(1)-C(10)-C(11')-C(12')	153.80 (13)
N(1)-C(7)-C(8)-C(10)	-12.9 (3)	C(11)-C(10)-C(11')-C(12')	17.12 (7)
C(6)-C(7)-C(8)-C(10)	164.0 (2)	C(8)-C(10)-C(11')-C(12')	-92.97 (19)
C(7)-C(8)-C(9)-O(2)	-60.2 (3)	O(1)-C(10)-C(11')-C(16')	-23.9 (2)
C(17)-C(8)-C(9)-O(2)	59.8 (3)	C(11)-C(10)-C(11')-C(16')	-160.6
C(10)-C(8)-C(9)-O(2)	-171.6 (2)	C(8)-C(10)-C(11')-C(16')	89.32 (19)
C(6)-C(7)-N(1)-O(1)	-176.4 (2)	C(10)-C(11')-C(12')-C(13')	-177.81 (10)
C(8)-C(7)-N(1)-O(1)	0.2 (3)	C(10)-C(11')-C(16')-C(15')	177.63 (11)
C(7)-C(8)-C(10)-O(1)	19.4 (2)	C(9)-C(8)-C(10)-C(11)	8.2 (3)
C(17)-C(8)-C(10)-O(1)	-96.6 (2)	C(7)-C(8)-C(10)-C(11')	-96.7 (2)
C(9)-C(8)-C(10)-O(1)	134.4 (2)	C(17)-C(8)-C(10)-C(11')	147.37 (19)
C(7)-C(8)-C(10)-C(11)	-106.8 (2)	C(9)-C(8)-C(10)-C(11')	18.3 (3)
C(17)-C(8)-C(10)-C(11)	137.2 (2)	C(7)-C(8)-C(17)-O(3)	-7.8 (4)
C(9)-C(8)-C(17)-O(3)	-125.6 (3)	C(10)-C(8)-C(17)-O(3)	101.5 (3)

Table 6. Mean planes through various groups of atoms in the structure of Compound and deviations from the plane. The equation of the plane is of the form: m1x + m2y + m3z − D = 0. where m1, m2, m3 and D are constants

Plane	m1	m2	m3	D	Atom	Deviation(Å)
1	-0.810(0)	0.564(1)	-0.156(1)	-5.928(1)	C10*	0.154(2)
					O1*	-0.084(2)
					N1*	0.048(2)
					C7*	0.040(2)
					C8*	-0.103(2)
					C17	-1.527(2)
2	0.867(0)	-0.490(1)	-0.083(1)	4.444(1)	C7*	-0.077(2)
					C6*	-0.075(2)
					C5*	0.053(2)
					O2*	0.100(2)
					C8*	0.265(3)
					C9*	-0.409(3)
					C17	1.776(2)
3	-0.864(0)	0.502(1)	-0.021(1)	-5.093(8)	C1*	0.008(3)
					C2*	0.000(3)
					C3*	-0.007(3)
					C4*	0.004(3)
					C5*	0.004(2)
					C6*	-0.008(2)
					Br	-0.076(0)

*Atoms are included in the plane calculations

Dihedral angles (°) formed by LSQ-planes

Plane	Plane	Angle
1	2	14.76(9)
1	3	9.02(9)
2	3	6.06(9)

Table 7. Hydrogen bond interactions for Compound [Å and °]

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	D-H...A (°)
C10-H10...O1[i]	0.98	2.56	3.370 (4)	140
C13-H13...O3[ii]	0.93	2.49	3.252(3)	139

Symmetry Codes: (i) 1-x, -y, -z (ii) x, -1 + y, z

4. Results and Discussion

Title compound crystallizes in the triclinic system with P$\bar{1}$ space group and total number molecule found in the unit cell is Z = 2. The similar type of structure has been published[19,20]. The chromene and isoxazole rings are coplanar one another. The five membered isoxazole ring (C10/O1/N1/C7/C8) offers a wide variety of conformational flexibility such as chair, distorted chair, envelope conformation. But in the present study all the geometrical parameters strongly confirm that the isoxazole ring adopts envelope conformation in the compound. The puckering parameters[21] q2 = 0.307 (4) Å, φ2 = -85.59(6) for compound strongly indicate that

the isoxazole ring adopts envelope conformation with atom C10 deviating by 0.154(2) Å from the planes formed by the remaining atoms of the rings in compound. Also, in the six membered pyran ring (C5-C9/O2) adopts envelope conformation with atom C9 deviating by -0.409(3) Å from the planes formed by the remaining atoms of the ring.

In the chromeno ring system, the dihedral angle between the mean plane of the pyran ring and the benzene ring is 6.06(9)°. The dihedral angle between the mean planes of the pyran ring system and the isoxazole ring is 14.76(9)°. In compound, the phenyl ring (C11-C16) are disordered over two sets of sites [site occupancies = 0.610 (8) and 0.390 (8)]. The atom bromine (Br), deviate by -0.076(0) Å, from the Benzene ring (C1-C6) of chromeno moiety.

In the crystal, molecules are linked via pairs of inter molecular C10-H10...O1 hydrogen bonds to form dimers with an [R_2^2(6)] ring motif. These dimers are linked via C13-H13...O3 hydrogen bonds to form chains along with the c-axis of the crystal packing.

5. Conclusion

Crystal structure of a novel isoxazole and chromen based derivatives having a wide range of applications is described. The title compound is soluble in ethyl acetate and it is crystallized in ethyl acetate by slow evaporation technique. The isoxzole and pyran rings adopt a envelop conformation. The title structure may be important from a medicinal point of view as well as their widespread biological significance. The structure may be useful for further investigation on the mechanism, potential activity, optimal reaction condition etc which will be further characterized as a future prospective of our project.

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