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Crystal Structure Analysis of 6-Ethoxy-3-phenyl-5a,9a-dihydro-3H-chromen[4,3-c][1,2]oxazole-3a(4H)-carbonitrile

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Abstract

The crystal structure of the potential active 6-ethoxy-3-phenyl-5a,9a-dihydro-3H-chromen[4,3-c][1,2]oxazole-3a(4H)-carbonitrile ($C_{19}H_{15}N_2O_3$) has been determined from single crystal X-ray diffraction technique. The title compound crystallizes in the monoclinic space group C2/c with unit cell dimension a= 29.3026(9) Å, b= 6.7695(2) Å and c= 19.7597(6) Å [α= 90°, β= 125.709 (10)° and γ= 90°]. Single crystals suitable for X-ray diffraction were obtained by slow evaporation method, the isoxazole and six membered pyran rings adopts envelope conformation. The crystal packing of the molecules is stabilized by the weak C-H…N hydrogen bond interaction.

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.

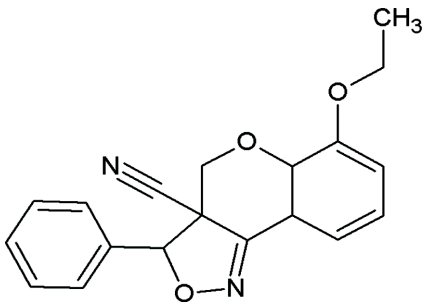

Fig. 1. Chemical structure of 6-ethoxy-3-phenyl-5a,9a-dihydro-3H-chromen[4,3-c][1,2]oxazole-3a(4H)-carbonitrile

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

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of Fit and other) hydrogen atoms were geometrically fixed and after the final refinement the R factor is 5.0%.

3. Experimental Section

3.1. Synthesis of the Title Compound

To a solution of (*E*)-2-((4-bromo-2-((*E*)-(hydroxyimino) methyl)phenoxy)methyl)-3-phenyl acrylonitrile (2 mmol) in CCl_4 at 273-283 K was added pinch wise NCS (4 mmol) over 3 hours. 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 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 title product as a colourless solid. Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a solution of the title compound in ethyl acetate at room temperature.

3.2. X-Ray Crystallography

For the crystal structure determination, the single crystal of the compound $C_{19}H_{15}N_2O_3$ was used for data collection on a Bruker Kappa APEXII CCD diffractometer[13]. The MoKα radiation of wavelength, (# = 0.71073 Å) and multi-scan technique for absorption

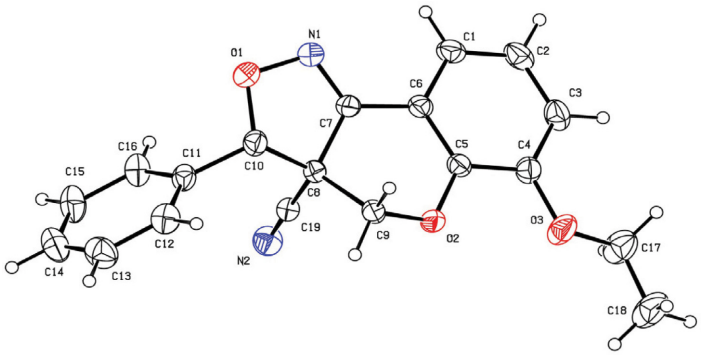

Fig. 2. The ORTEP plot of compound with the atom numbering scheme. Displacement ellipsoids are drawn at 30% probability level.

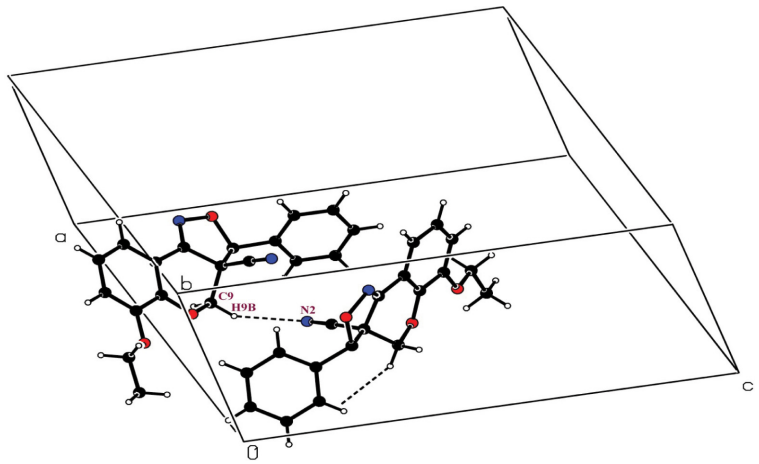

Fig. 3. Crystal packing of the title compound viewed down *b*-axis, dashed line indicate the inter molecular interaction in the unit cell.

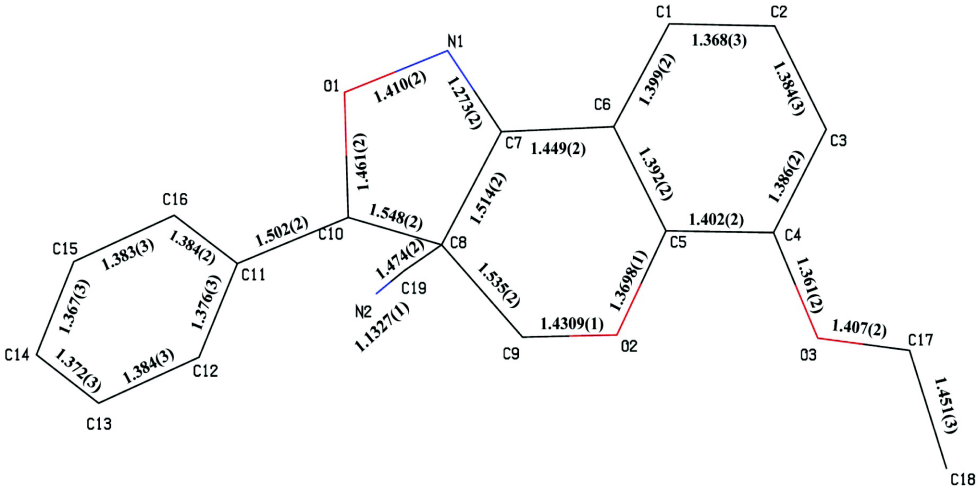

Fig. 4. Bond lengths (Å) of compound

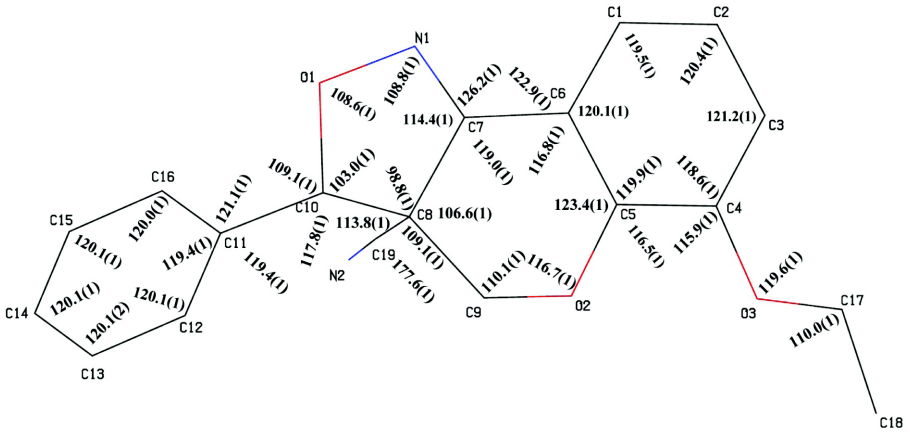

Fig. 5. Bond angles (°) of compound

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 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 1. Crystal Data and Structure refinement statistics

Parameters	Compound
Empirical formula	$C_{19}H_{15}N_2O_3$
Formula weight	319.33
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 29.3026(9) Å
	b = 6.7695(2) Å
	c = 19.7597(6) Å
	β = 125.709(10)°
Volume	3182.69(17) $Å^3$
Z, Calculated density	8, 1.333 Mg/m^3
Absorption coefficient	0.09 mm^{-1}
F(000)	1336
Crystal size(mm)	0.22×0.20×0.20
θ range	1.71 to 28.48º
Limiting indices	-39 ≤ h ≤ 36,
	-9 ≤ k ≤ 7,
	-24 ≤ l ≤ 26
Reflections collected /	14360/ 4005
unique	[R(int) = 0.0305]
Completeness to theta	99.50%
Refinement method	Full-matrix
	least-squares on F^2
Data / restraints / parameters	4005/0/ 218
Goodness-of-fit on F^2	0.99
Final R indices [I>2σ(I)]	R1 = 0.0498
R indices (all data)	wR2 = 0.1323
	R1 = 0.0672
	wR2 = 0.1451
Largest diff. peak and hole	0.68 and -0.26 e.$Å^{-3}$

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

Atom	x	y	z	*U(eq)
C1	1664(1)	11046(2)	-377(1)	47(1)
C2	1116(1)	11129(3)	-1056(1)	54(1)
C3	762(1)	9529(3)	-1264(1)	55(1)
C4	955(1)	7803(2)	-801(1)	46(1)
C5	1518(1)	7702(2)	-109(1)	38(1)
C6	1868(1)	9329(2)	108(1)	39(1)
C7	2440(1)	9141(2)	848(1)	40(1)
C8	2591(1)	7400(2)	1424(1)	36(1)

Table 2. Continued

Atom	x	y	z	*U(eq)
C9	2280(1)	5603(2)	865(1)	38(1)
C10	3236(1)	7432(3)	1886(1)	45(1)
C11	3597(1)	6953(3)	2800(1)	42(1)
C12	3847(1)	5126(3)	3060(1)	55(1)
C13	4165(1)	4635(3)	3897(1)	67(1)
C14	4238(1)	5981(4)	4472(1)	67(1)
C15	3991(1)	7800(4)	4219(1)	64(1)
C16	3671(1)	8301(3)	3383(1)	53(1)
C17	53(1)	6283(4)	-1460(2)	75(1)
C19	2410(1)	7720(2)	1972(1)	37(1)
N1	2854(1)	10228(3)	1043(1)	57(1)
N2	2271(1)	7898(2)	2396(1)	54(1)
O1	3346(1)	9463(2)	1769(1)	64(1)
O2	1688(1)	5973(2)	334(1)	43(1)
O3	643(1)	6148(2)	-963(1)	66(1)

*Ueq= (1/3)∑i∑jUij ai*aj*ai.aj

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

Atom	U11	U22	U33	U23	U13	U12
C1	62(1)	36(1)	47(1)	2(1)	34(1)	-2(1)
C2	69(1)	43(1)	46(1)	12(1)	31(1)	13(1)
C3	52(1)	52(1)	40(1)	6(1)	16(1)	11(1)
C4	43(1)	43(1)	41(1)	-1(1)	19(1)	1(1)
C5	42(1)	35(1)	34(1)	3(1)	21(1)	2(1)
C6	46(1)	37(1)	34(1)	0(1)	24(1)	-2(1)
C7	47(1)	38(1)	35(1)	-2(1)	24(1)	-8(1)
C8	36(1)	40(1)	30(1)	-1(1)	19(1)	-3(1)
C9	40(1)	38(1)	32(1)	1(1)	18(1)	1(1)
C10	36(1)	60(1)	37(1)	-2(1)	20(1)	-6(1)
C11	32(1)	57(1)	37(1)	-4(1)	19(1)	-2(1)
C12	49(1)	60(1)	54(1)	-5(1)	30(1)	3(1)
C13	60(1)	69(1)	67(1)	16(1)	33(1)	16(1)
C14	52(1)	100(2)	42(1)	11(1)	24(1)	12(1)
C15	51(1)	93(2)	40(1)	-12(1)	22(1)	6(1)
C16	43(1)	64(1)	42(1)	-7(1)	19(1)	6(1)
C17	46(1)	71(1)	91(2)	0(1)	32(1)	0(1)
C18	44(1)	78(2)	115(2)	2(1)	26(1)	-9(1)
C19	36(1)	39(1)	33(1)	-2(1)	18(1)	-3(1)
N1	54(1)	65(1)	42(1)	4(1)	22(1)	-20(1)
N2	56(1)	64(1)	50(1)	-7(1)	36(1)	-2(1)
O1	46(1)	80(1)	49(1)	7(1)	19(1)	-23(1)
O2	38(1)	37(1)	42(1)	6(1)	16(1)	-4(1)
O3	37(1)	51(1)	74(1)	5(1)	13(1)	-4(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 ($Å^2 \times 10^3$) for hydrogen atoms of compound

Atom	x	y	z	*U(eq)
H1	1900	12125	-239	56
H2	979	12267	-1380	65
H3	389	9615	-1724	65
H9A	2415	5331	528	46
H9B	2355	4452	1208	46
H12	3803	4217	2673	65
H13	4330	3392	4070	81
H14	4456	5654	5035	80
H15	4038	8704	4610	77
H16	3506	9543	3213	63
H17A	-80	6874	-1992	89
H17B	-63	7121	-1187	89
H18A	-594	4440	-1929	137
H18B	-61	3755	-1064	137
H18C	-82	3514	-1871	137

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

Atoms	Angle	Atoms	Angle
C(9)-O(2)-C(5)-C(6)	-20.7 (2)	C(6)-C(5)-C(4)-C(3)	1.3 (2)
C(9)-O(2)-C(5)-C(4)	161.19 (13)	N(1)-O(1)-C(10)-C(11)	-150.88 (13)
O(2)-C(5)-C(6)-C(1)	-179.98 (14)	N(1)-O(1)-C(10)-C(8)	-24.88 (16)
C(4)-C(5)-C(6)-C(1)	-2.0 (2)	C(12)-C(11)-C(10)-O(1)	-139.55 (16)
O(2)-C(5)-C(6)-C(7)	-0.4 (2)	C(16)-C(11)-C(10)-O(1)	42.1 (2)
C(4)-C(5)-C(6)-C(7)	177.67 (14)	C(12)-C(11)-C(10)-C(8)	103.48 (18)
C(5)-C(6)-C(7)-N(1)	162.37 (17)	C(16)-C(11)-C(10)-C(8)	-74.9 (2)
C(1)-C(6)-C(7)-N(1)	-18.0 (3)	C(19)-C(8)-C(10)-O(1)	-96.05 (15)
C(5)-C(6)-C(7)-C(8)	-11.5 (2)	C(7)-C(8)-C(10)-O(1)	22.12 (14)
C(1)-C(6)-C(7)-C(8)	168.16 (14)	C(9)-C(8)-C(10)-O(1)	135.68 (13)
C(5)-O(2)-C(9)-C(8)	50.73 (16)	C(19)-C(8)-C(10)-C(11)	24.2 (2)
N(2)-C(19)-C(8)-C(7)	157 (4)	C(7)-C(8)-C(10)-C(11)	142.34 (15)
N(2)-C(19)-C(8)-C(9)	40 (4)	C(9)-C(8)-C(10)-C(11)	-104.09 (16)
N(2)-C(19)-C(8)-C(10)	-92 (4)	C(12)-C(11)-C(16)-C(15)	-0.5 (3)
N(1)-C(7)-C(8)-C(19)	105.88 (17)	C(10)-C(11)-C(16)-C(15)	177.93 (16)
C(6)-C(7)-C(8)-C(19)	-79.59 (16)	O(3)-C(4)-C(3)-C(2)	-179.01 (18)
N(1)-C(7)-C(8)-C(9)	-135.11 (15)	C(5)-C(4)-C(3)-C(2)	0.1 (3)
C(6)-C(7)-C(8)-C(9)	39.43 (18)	C(6)-C(7)-N(1)-O(1)	-174.81 (15)
N(1)-C(7)-C(8)-C(10)	-14.14 (18)	C(8)-C(7)-N(1)-O(1)	-0.7 (2)
C(6)-C(7)-C(8)-C(10)	160.39 (14)	C(10)-O(1)-N(1)-C(7)	16.9 (2)
O(2)-C(9)-C(8)-C(19)	62.95 (15)	C(6)-C(1)-C(2)-C(3)	0.1 (3)
O(2)-C(9)-C(8)-C(7)	-57.50 (15)	C(4)-C(3)-C(2)-C(1)	-0.8 (3)
O(2)-C(9)-C(8)-C(10)	-166.53 (12)	C(16)-C(11)-C(12)-C(13)	0.6 (3)
C(5)-C(6)-C(1)-C(2)	1.3 (2)	C(10)-C(11)-C(12)-C(13)	-177.78 (16)
C(7)-C(6)-C(1)-C(2)	-178.33 (16)	C(15)-C(14)-C(13)-C(12)	0.8 (3)
C(17)-O(3)-C(4)-C(3)	-20.6 (3)	C(11)-C(12)-C(13)-C(14)	-0.8 (3)
C(17)-O(3)-C(4)-C(5)	160.27 (19)	C(13)-C(14)-C(15)-C(16)	-0.6 (3)
O(2)-C(5)-C(4)-O(3)	-1.4 (2)	C(11)-C(16)-C(15)-C(14)	0.5 (3)
C(6)-C(5)-C(4)-O(3)	-179.54 (15)	C(4)-O(3)-C(17)-C(18)	176.5 (2)
O(2)-C(5)-C(4)-C(3)	179.42 (15)		

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	0.574(0)	-0.489(0)	-0.655(0)	-0.427(8)	C10*	0.179(1)
					O1*	-0.107(1)
					N1*	0.056(1)
					C7*	0.052(1)
					C8*	-0.103(1)
					N2	-2.475(1)
					C11	-0.621(1)
2	0.779(0)	-0.284(0)	-0.558(0)	2.198(4)	C7*	0.086(2)
					C6*	0.075(1)
					C5*	-0.020(1)
					O2*	-0.095(1)
					C9*	0.374(1)
					C8*	-0.265(1)
					N2	-2.837(1)
3	0.736(0)	-0.351(0)	-0.577(0)	1.630(6)	C1*	0.003(2)
					C2*	0.060(2)
					C3*	-0.005(2)
					C4*	-0.003(2)
					C5*	0.008(1)
					C6*	-0.008(1)
					O3	0.005(1)
4	-0.927(0)	-0.357(1)	-0.106(0)	-8.946(5)	C11*	0.001(2)
					C12*	-0.002(2)
					C13*	0.003(2)
					C14*	-0.002(2)
					C15*	0.001(2)
					C16*	-0.001(2)
					C10	0.045(2)

*Atoms are included in the plane calculations

Dihedral angles (°) formed by LSQ-planes

Plane	Plane	Angle
1	2	17.55(5)
1	3	13.00(6)
1	4	73.23(7)
2	3	4.67(5)
2	4	55.83(6)
3	4	60.25(7)

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

D-H…A	D-H (Å)	H…A (Å)	D…A (Å)	D-H…A (º)
C9-H9B…N2^{i}	0.97	2.53	3.408(4)	151

Symmetry Code: (i) 1/2 - x, -1/2 + y, -z + ½

4. Results and Discussion

Title compound crystallizes in the monoclinic system with C2/c space group and total number molecule found in the unit cell is Z = 8. The similar type of structure has been published[19,20]. The chromene and isoxazole rings are coplanar one another. The isoxazole ring adopts envelope conformation. The puckering parameters[21] q2 = 0.242(1) Å, φ2 = 0.94(7)° for isoxazole, strongly indicate that the isoxazole ring adopts envelope conformation with atom C10 deviating by 0.179(1) Å respectively from the planes formed by the remaining atoms of the ring. The six membered pyran ring (C5-C9/O2) also adopts envelope conformation with atom C9 deviating by 0.374(1) Å from the planes formed by the remaining atoms of the ring. The puckering parameter for pyran ring are q2 = 0.372(1) Å, and φ2 = -141.97(2)° strongly indicate that the pyran ring adopts envelope conformation. In the chromeno ring system, the dihedral angle between the mean plane of the pyran ring and the benzene ring is 4.67(5)°. The dihedral angle between the mean planes of the pyran ring system and the isoxazole ring is 17.55(5)°. Atom O3 of Compound deviate by 0.005(1) Å from the Benzene ring (C1-C6) of chromeno moiety and also the atom N2 deviates from the pyran ring by -2.837(1) Å. In the compound, crystal packing of the molecules is stabilized by the weak C9-H9B…N2 hydrogen bond interaction.

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 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.

References

[1] W. Kemnitzer, S. Jiang, Y. Wang, S. Kasibhatla, C. Crogan-Grundy, M. Bubenik, D. Labrecque, R. Denis, S. Lamothe, G. Attardo, H. Gourdeau, B. Tseng, J. Drewe, and S. X. Cai, "Discovery of 4-aryl-4H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based HTS assay. Part 5: Modifications of the 2- and 3-positions", Bioorg. Med. Chem. Lett., Vol. 18, pp. 603-607, 2008.

[2] P. Valenti, P. Da Re, A. Rampa, P. Montanari, M. Carrara, and L. Cima, "Benzo-gamma-pyrone analogues of geiparvarin: synthesis and biological evaluation against B16 melanoma cells", Anti-cancer Drug Design, Vol. 8, pp. 349-360, 1993.

[3] G. T. Brooks, A. P. Ottridge, and D. W. Mace, "The effect of some furochromene and benzochromene analogues of 2,2-dimethyl-7-methoxychromene (precocene I) and benzofuran precursors on Oncopeltus fasciatus (dallas) and Locusta migratoria migratorioides (R&F)", J. Pestic. Sci., Vol. 22, pp. 41-50, 1988. [4] Q.-G. Tang, W.-Y. Wu, W. He, H.-S. Sun, and C. Guo, "Methyl 2-amino-4-(3-fluoro-phen-yl)-4Hbenzo[h]chromene-3-carboxyl-ate methanol solvate", Acta Crystallographica Section E: Structure Reports Online, Vol. E63, pp. o1437-o1438, 2007.

[5] M. Gábor and F. Kállay, "The pharmacology of benzopyrone derivatives and related compounds", Akademiai Kiado, 1986.

[6] S. X. Cai, "Small molecule vascular disrupting agents: potential new drugs for cancer treatment", Recent Pat. Anti-Canc., Vol. 2, pp. 79-101, 2007.

[7] S. X. Cai, J. Drewe, and S. Kasibhatla, "A chemical genetics approach for the discovery of apoptosis inducers: from phenotypic cell based HTS assay and structure-activity relationship studies, to identification of potential anticancer agents and molecular targets", Curr. Med. Chem., Vol. 13, pp. 2627-2644, 2006.

[8] S. X. Cai, J. Drewe, and W. Kemnitzer, "Discovery

of 4-aryl-4H-chromenes as potent apoptosis inducers using a cell- and caspase-based anti-cancer screening apoptosis program (ASAP): SAR studies and the identification of novel vascular disrupting agents", Anti-Cancer Agent. Me., Vol. 9, pp. 437-456, 2009.

[9] M. Kidwai, S. Saxena, M. K. R. Khan, and S. S. Thukral, "Aqua mediated synthesis of substituted 2-amino-4H-chromenes and in vitro study as antibacterial agents", Bioorg. Med. Chem. Lett., Vol. 15, pp. 4295-4298, 2005.

[10] J.-L. Wang, D. Liu, Z.-J. Zhang, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri, and Z. Huang, "Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells", P. Natl. Acad. Sci. U.S.A., Vol. 97, pp. 7124-7129, 2000.

[11] C. Brühlmann, F. Ooms, P.-A. Carrupt, B. Testa, M. Catto, F. Leonetti, C. Altomare, and A. Carotti, "Coumarins derivatives as dual inhibitors of acetylcholinesterase and monoamine oxidase", J. Med. Chem., Vol. 44, pp. 3195–3198, 2001.

[12] S. R. Kesten, T. G. Heffner, S. J. Johnson, T. A. Pugsley, J. L. Wright, and L. D. Wise, "Design, synthesis, and evaluation of chromen-2-ones as potent and selective human dopamine D4 antagonists", J. Med. Chem., Vol. 42, pp. 3718- 3725, 1999.

[13] Bruker, "APEX2 and SAINT-Plus", Bruker AXS Inc., Madison, 2004.

[14] G. M. Sheldrick, "MSHELXS-97 and SHELXL-97, Program for crystal structure solution and refinement", University of Gottingen, Gottingen, Germany, 1997.

[15] G. M. Sheldrick, "A short history of SHELX", Acta Crystallogr. A, Vol. A64, pp. 112-122, 2008.

[16] L. J. Farrugia, "ORTEP-3 for Windows-A version of ORTEP-III with a graphical user interface (GUI)", J. Appl. Crystallogr., Vol. 30, pp. 565, 1997.

[17] A. L. Spek, "Structure validation in chemical crystallography", Acta Crystallogr. D., Vol. 65, pp. 148-155, 2009.

[18] L. J. Farrugia, "WinGX Suite for small-molecule single-crystal crystallography", J. Appl. Crystallogr., Vol. 32, pp. 837-838, 1999.

[19] P. Malathy, G. Jagadeesan, J. Srinivasan , and M. Bakthadoss, "Crystal structure analysis of 3-(4-ethylphenyl)-3Hchromeno[4,3-c]isoxazole-3a(4H)-carbonitrile", J. Chosun Natural Sci., Vol. 8, pp. 250-257, 2015.

[20] G. Jagadeesan, J. Srinivasan, and M. Bakthadoss "Crystal structure analysis of methyl-3-phenyl-3H-chromeno[4,3-c]isoxazole-3a(4H)-carboxylate", J. Chosun Natural Sci., Vol. 8, pp. 184-191, 2015.

[21] D. Cremer and J. A. Pople, "General definition of ring puckering coordinates". J. Am. Chem. Soc., Vol. 97, pp. 1354-1358, 1975.