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Crystal Structure Analysis of 3-(4-ethylphenyl)-3H-chromeno[4,3-c]isoxazole-3a(4H)-carbonitrile

P. Malathy[1†], Jagadeesan Ganapathy[2], J. Srinivasan[3], and Bakthadoss Manickam[3]

Abstract

The crystal structure of the potential active **3-(4-ethylphenyl)-3H-chromeno[4,3-c]isoxazole-3a(4H)-carbonitrile** ($C_{19}H_{16}N_2O_2$) has been determined from single crystal X-ray diffraction data. In the title compound crystallizes in the monoclinic space group $P2_1/c$ with unit cell dimension a=6.6869 (8) Å, b=15.8326 (19) Å and c= 15.237 (2) Å [α=90°, β= 100.663° and γ= 90°]. In the structure chromene, isoxazole and carboxylate are almost coplanar each other. All geometrical parameters revelled that chromene ring of pyran ring adopt sofa conformation. The crystal packing is stabilized by intermolecular C-H...N and C-H...O hydrogen bond interaction.

Keywords: Chromene, Nitrile, Pyran, Single Crystal Structure, X-ray Diffraction

1. Introduction

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, anti-inflammatory, 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]. Recently, the structural modification of chromene scaffold with the addition of heterocyclic substituents at either the second or third position has attracted extensive interest in the field of structure based drug designing (SBDD).

In view of the growing medicinal importance of chromene 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.

IUPAC name of the compound: **3-(4-ethylphenyl)-3H-chromeno[4,3-c]isoxazole-3a(4H)-carbonitrile**

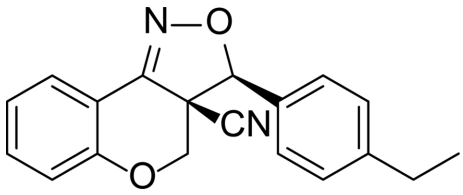

Fig. 1. Chemical structure.

2. Materials and Methods

The title compound is crystallized by simple solvent slow evaporation method. Three rounds of crystallization trials, diffraction crystals. 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 6.0%.

[1]CAS in Crystallography and Biophysics, University of Madras, Chennai 600025, India
[2]Department of Physics, Presidency College, Chennai 600005, India
[3]Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai-600025, India

[†]Corresponding author : bioinfomalathi@gmail.com
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3. Experimental Section

3.1. Synthesis of the Title Compound

To a solution of aldoxime **8a** (0.56 g, 2 mmol) in 10 mL CCl_4 at 0-10°C was added NCS (0.54 g, 4 mmol, pinch wise) over 3 h. After this period Et_3N (0.57 mL, 4 mmol) was added to the reaction mixture and stirred well at room temperature for 2 h. 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 combined organic layer was washed with brine (2×10 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated and the residue was purified by column chromatography (silica gel 60-120 mesh 7% EtOAc in hexanes) to provide the desired pure product **9a** (0.34 g, 62%) as a colorless solid; mp: 136-138°C. Since the compound has not yield the diffraction quality crystals initially, the compound has been recrystallized with ethyl acetate by slow evaporation method to get better quality single crystals.

3.2. X-Ray Crystallography

For the crystal structure determination, the single crystal of the compound $C_{18}H_{15}NO_4$ 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 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

Table 1. Crystal Data and Structure Refinement

Parameters	COMPOUND
Empirical formula	$C_{19}H_{16}N_2O_2$
Formula weight	304.34
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, $P2_1/c$
Unit cell dimensions	a = 6.6869 (8) Å b = 15.8326 (19) Å c = 15.237 (2) Å α = γ =90° and β =100.663 (7)
Volume	1585.3 (3) $Å^3$
Z, Calculated density	4, 1.275 Mg/m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	640
Crystal size (mm)	0.25×0.20×0.20
θ range for data collection	1.87 to 28.32°
Limiting indices	-8 ≤ h ≤ 8 -21 ≤ k ≤ 18 -18 ≤ l ≤ 19
Reflections collected/unique	14998/3889 [Rint = 0.037]
Completeness to theta	100%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3761/1/210
Goodness-of-fit on F^2	1.05
Final R indices [I>2σ(I)]	R1 = 0.0636, wR2 = 0.1836
R indices (all data)	R1 = 0.1303, wR2 = 0.2258
Largest diff. peak and hole	0.441 and -0.403 $e.Å^{-3}$

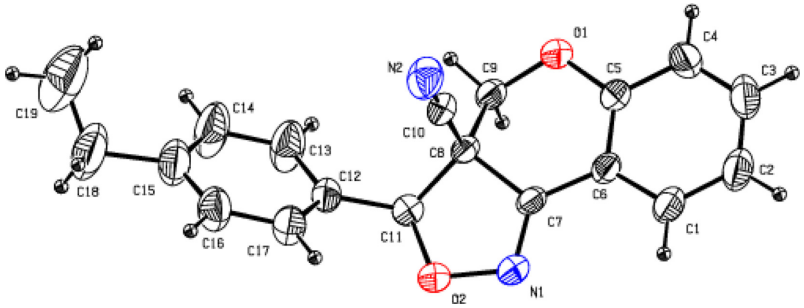

Fig. 2. Displacement ellipsoids are drawn at the 30% probability level.

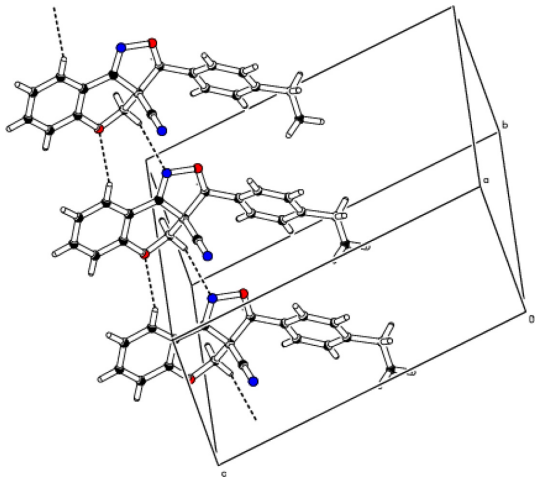

Fig. 3. Crystal packing of the title compound, dashed line indicate the inter molecular interaction in the unit cell.

publication is WinGX publication routines[18]. Experimental data are listed in Table 1. Fig. 1 shows schematic 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. Table 1 shows the crystal data and crystal refinement statistics. the title compound structure has been deposited in Cambridge structural data base with the CCDC reference number: 791957. Table 2 gives the atomic coordinates, Table 3 describes the bond lengths and angles; Table 4 shows anisotropic displacement parameters, Table 5 shows the torsion angles and Table 6 shows hydrogen-bond geometry.

4. Results and Discussion

Title compound crystallizes in the monoclinic system

Table 2. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C13	0.9896 (5)	0.4607 (3)	0.7062 (2)	0.1082 (14)
H1	0.9491	0.4945	0.7496	0.130*
C18	0.7773 (7)	0.3861 (4)	0.4672 (3)	0.160 (2)
H18A	0.7964	0.4344	0.4305	0.193*
H18B	0.8222	0.3363	0.4392	0.193*
C19	0.5718 (8)	0.3780 (4)	0.4688 (4)	0.184 (3)
H19A	0.5530	0.3359	0.5119	0.276*
H19B	0.5008	0.3613	0.4108	0.276*
H19C	0.5194	0.4311	0.4849	0.276*
O1	1.1707 (2)	0.38791 (12)	1.03275 (11)	0.0656 (6)
O2	1.5266 (3)	0.41989 (14)	0.80430 (12)	0.0740 (6)
C7	1.4942 (3)	0.38162 (14)	0.93879 (16)	0.0493 (6)
C8	1.2767 (3)	0.38921 (14)	0.88883 (15)	0.0470 (6)
C6	1.5280 (3)	0.36073 (14)	1.03245 (16)	0.0525 (6)
C9	1.1547 (3)	0.43241 (17)	0.95048 (15)	0.0566 (7)
H00A	1.2040	0.4897	0.9622	0.068*
H00B	1.0129	0.4353	0.9215	0.068*
C5	1.3625 (4)	0.36516 (16)	1.07563 (17)	0.0568 (7)
C10	1.1969 (3)	0.30462 (17)	0.86360 (16)	0.0562 (7)
C11	1.3166 (3)	0.44079 (17)	0.80853 (16)	0.0563 (6)
H009	1.3099	0.5009	0.8230	0.068*
N1	1.6265 (3)	0.39896 (15)	0.89154 (15)	0.0667 (7)
N2	1.1378 (4)	0.23839 (16)	0.84523 (16)	0.0831 (8)
C12	1.1799 (4)	0.42530 (17)	0.72106 (17)	0.0598 (7)
C1	1.7162 (4)	0.33486 (16)	1.08127 (19)	0.0668 (7)
H013	1.8287	0.3321	1.0535	0.080*

Table 2. Continued

	x	*y*	*z*	U_{iso}*/U_{eq}
C17	1.2317 (4)	0.37481 (19)	0.65602 (19)	0.0712 (8)
H014	1.3587	0.3489	0.6654	0.085*
C4	1.3852 (5)	0.34356 (19)	1.16524 (18)	0.0768 (9)
H015	1.2745	0.3467	1.1942	0.092*
C16	1.0986 (5)	0.3619 (2)	0.5770 (2)	0.0867 (10)
H016	1.1385	0.3275	0.5338	0.104*
C2	1.7360 (5)	0.3137 (2)	1.1695 (2)	0.0827 (9)
H017	1.8613	0.2965	1.2017	0.099*
C3	1.5688 (6)	0.3179 (2)	1.2104 (2)	0.0881 (10)
H018	1.5824	0.3029	1.2702	0.106*
C14	0.8567 (6)	0.4457 (3)	0.6256 (3)	0.1312 (17)
H019	0.7270	0.4692	0.6165	0.157*
C15	0.9123 (5)	0.3974 (3)	0.5599 (2)	0.0984 (12)

Table 3. Bond lengths [Å] and angles [°]

Bond Length	(Å)	**Bond Length**	(Å)
C13—C12	1.370 (4)	C6—C1	1.399 (3)
C13—C14	1.397 (5)	C9—H00A	0.9700
C13—H1	0.9300	C9—H00B	0.9700
C18—C19	1.385 (6)	C5—C4	1.388 (4)
C18—C15	1.539 (5)	C10—N2	1.137 (3)
C18—H18A	0.9700	C11—C12	1.490 (3)
C18—H18B	0.9700	C11—H009	0.9800
C19—H19A	0.9600	C12—C17	1.367 (4)
C19—H19B	0.9600	C1—C2	1.368 (4)
C19—H19C	0.9600	C1—H013	0.9300
O1—C5	1.375 (3)	C17—C16	1.374 (4)
O1—C9	1.425 (3)	C17—H014	0.9300
O2—N1	1.412 (3)	C4—C3	1.354 (4)
O2—C11	1.456 (3)	C4—H015	0.9300
C7—N1	1.269 (3)	C16—C15	1.347 (5)
C7—C6	1.441 (3)	C16—H016	0.9300
C7—C8	1.516 (3)	C2—C3	1.378 (5)
C8—C10	1.466 (3)	C2—H017	0.9300
C8—C9	1.516 (3)	C3—H018	0.9300
C8—C11	1.535 (3)	C14—C15	1.365 (5)
C6—C5	1.390 (4)	C14—H019	0.9300
C12—C13—C14	119.8 (3)	C4—C5—C6	120.1 (2)
C12—C13—H1	120.1	N2—C10—C8	178.7 (3)
C14—C13—H1	120.1	O2—C11—C12	111.1 (2)
C19—C18—C15	114.2 (5)	O2—C11—C8	103.03 (18)
C19—C18—H18A	108.7	C12—C11—C8	117.2 (2)
C15—C18—H18A	108.7	O2—C11—H009	108.4
C19—C18—H18B	108.7	C12—C11—H009	108.4
C15—C18—H18B	108.7	C8—C11—H009	108.4

Table 3. Continued

Bond Angle	(°)	Bond Angle	(°)
H18A—C18—H18B	107.6	C7—N1—O2	109.06 (18)
C18—C19—H19A	109.5	C17—C12—C13	118.1 (3)
C18—C19—H19B	109.5	C17—C12—C11	123.3 (2)
H19A—C19—H19B	109.5	C13—C12—C11	118.5 (3)
C18—C19—H19C	109.5	C2—C1—C6	120.5 (3)
H19A—C19—H19C	109.5	C2—C1—H013	119.7
H19B—C19—H19C	109.5	C6—C1—H013	119.7
C5—O1—C9	117.33 (19)	C12—C17—C16	120.8 (3)
N1—O2—C11	107.69 (17)	C12—C17—H014	119.6
N1—C7—C6	127.8 (2)	C16—C17—H014	119.6
N1—C7—C8	113.7 (2)	C3—C4—C5	119.8 (3)
C6—C7—C8	118.4 (2)	C3—C4—H015	120.1
C10—C8—C9	111.3 (2)	C5—C4—H015	120.1
C10—C8—C7	109.15 (18)	C15—C16—C17	122.2 (3)
C9—C8—C7	107.51 (18)	C15—C16—H016	118.9
C10—C8—C11	112.7 (2)	C17—C16—H016	118.9
C9—C8—C11	116.5 (2)	C1—C2—C3	119.5 (3)
C7—C8—C11	98.65 (18)	C1—C2—H017	120.2
C5—C6—C1	118.6 (2)	C3—C2—H017	120.2
C5—C6—C7	117.7 (2)	C4—C3—C2	121.3 (3)
C1—C6—C7	123.7 (2)	C4—C3—H018	119.3
O1—C9—C8	111.1 (2)	C2—C3—H018	119.3
O1—C9—H00A	109.4	C15—C14—C13	121.6 (3)
C8—C9—H00A	109.4	C15—C14—H019	119.2
O1—C9—H00B	109.4	C13—C14—H019	119.2
C8—C9—H00B	109.4	C16—C15—C14	117.3 (3)
H00A—C9—H00B	108.0	C16—C15—C18	119.6 (4)
O1—C5—C4	117.0 (2)	C14—C15—C18	123.0 (4)
O1—C5—C6	122.9 (2)		

Table 4. Anisotropic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C13	0.084 (2)	0.158 (4)	0.075 (2)	0.051 (2)	-0.0066 (17)	-0.026 (2)
C18	0.102 (3)	0.265 (7)	0.095 (3)	0.007 (4)	-0.031 (3)	-0.038 (4)
C19	0.133 (4)	0.226 (6)	0.169 (5)	0.013 (4)	-0.036 (4)	-0.083 (5)
O1	0.0462 (10)	0.0977 (14)	0.0541 (10)	-0.0069 (8)	0.0126 (8)	-0.0013 (9)
O2	0.0472 (10)	0.1195 (17)	0.0564 (11)	-0.0083 (10)	0.0127 (8)	0.0057 (10)
C7	0.0335 (11)	0.0593 (14)	0.0539 (14)	-0.0040 (10)	0.0048 (10)	-0.0044 (11)
C8	0.0362 (11)	0.0559 (13)	0.0475 (12)	-0.0051 (9)	0.0039 (9)	-0.0043 (10)
C6	0.0445 (12)	0.0569 (14)	0.0523 (14)	-0.0070 (10)	-0.0008 (10)	-0.0018 (11)
C9	0.0407 (12)	0.0741 (17)	0.0542 (14)	-0.0002 (11)	0.0061 (10)	-0.0060 (12)
C5	0.0512 (14)	0.0639 (15)	0.0528 (14)	-0.0120 (11)	0.0033 (11)	-0.0026 (12)
C10	0.0475 (13)	0.0669 (17)	0.0507 (14)	-0.0060 (11)	-0.0003 (10)	-0.0034 (12)

Table 4. Continued

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C11	0.0498 (13)	0.0643 (15)	0.0543 (14)	-0.0033 (11)	0.0084 (11)	0.0005 (11)
N1	0.0423 (11)	0.0978 (18)	0.0590 (13)	-0.0067 (11)	0.0065 (10)	0.0002 (12)
N2	0.0940 (18)	0.0712 (17)	0.0762 (17)	-0.0225 (14)	-0.0050 (14)	-0.0061 (13)
C12	0.0549 (14)	0.0723 (17)	0.0497 (14)	0.0041 (12)	0.0032 (11)	0.0031 (12)
C1	0.0536 (14)	0.0706 (17)	0.0694 (17)	-0.0047 (12)	-0.0065 (12)	0.0036 (14)
C17	0.0692 (17)	0.0788 (19)	0.0624 (17)	0.0102 (14)	0.0038 (14)	-0.0057 (14)
C4	0.084 (2)	0.092 (2)	0.0534 (16)	-0.0211 (16)	0.0110 (15)	0.0018 (14)
C16	0.091 (2)	0.105 (2)	0.0592 (18)	0.0065 (18)	0.0009 (16)	-0.0137 (16)
C2	0.078 (2)	0.085 (2)	0.0717 (19)	-0.0097 (16)	-0.0196 (16)	0.0155 (16)
C3	0.107 (3)	0.092 (2)	0.0553 (17)	-0.0232 (19)	-0.0126 (18)	0.0136 (15)
C14	0.085 (2)	0.206 (5)	0.089 (3)	0.059 (3)	-0.019 (2)	-0.024 (3)
C15	0.086 (2)	0.138 (3)	0.063 (2)	0.010 (2)	-0.0082 (17)	-0.009 (2)

Table 5. Torsion angles [°]

Torsion Angle	(°)	Torsion Angle	(°)
N1—C7—C8—C10	101.7 (2)	C7—C8—C11—C12	147.3 (2)
C6—C7—C8—C10	-81.5 (3)	C6—C7—N1—O2	-177.0 (2)
N1—C7—C8—C9	-137.5 (2)	C8—C7—N1—O2	-0.5 (3)
C6—C7—C8—C9	39.3 (3)	C11—O2—N1—C7	18.4 (3)
N1—C7—C8—C11	-16.1 (3)	C14—C13—C12—C17	-1.1 (6)
C6—C7—C8—C11	160.8 (2)	C14—C13—C12—C11	-178.6 (4)
N1—C7—C6—C5	163.9 (2)	O2—C11—C12—C17	18.7 (4)
C8—C7—C6—C5	-12.5 (3)	C8—C11—C12—C17	-99.3 (3)
N1—C7—C6—C1	-17.4 (4)	O2—C11—C12—C13	-163.9 (3)
C8—C7—C6—C1	166.2 (2)	C8—C11—C12—C13	78.0 (4)
C5—O1—C9—C8	48.3 (3)	C5—C6—C1—C2	0.6 (4)
C10—C8—C9—O1	63.5 (2)	C7—C6—C1—C2	-178.1 (2)
C7—C8—C9—O1	-55.9 (2)	C13—C12—C17—C16	1.8 (5)
C11—C8—C9—O1	-165.42 (18)	C11—C12—C17—C16	179.2 (3)
C9—O1—C5—C4	162.6 (2)	O1—C5—C4—C3	177.8 (3)
C9—O1—C5—C6	-19.4 (3)	C6—C5—C4—C3	-0.2 (4)
C1—C6—C5—O1	-178.4 (2)	C12—C17—C16—C15	-0.4 (6)
C7—C6—C5—O1	0.4 (4)	C6—C1—C2—C3	0.0 (4)
C1—C6—C5—C4	-0.5 (4)	C5—C4—C3—C2	0.8 (5)
C7—C6—C5—C4	178.3 (2)	C1—C2—C3—C4	-0.7 (5)
N1—O2—C11—C12	-154.0 (2)	C12—C13—C14—C15	-1.1 (7)
N1—O2—C11—C8	-27.7 (2)	C17—C16—C15—C14	-1.7 (6)
C10—C8—C11—O2	-90.1 (2)	C17—C16—C15—C18	175.2 (4)
C9—C8—C11—O2	139.54 (19)	C13—C14—C15—C16	2.4 (7)
C7—C8—C11—O2	25.0 (2)	C13—C14—C15—C18	-174.3 (5)
C10—C8—C11—C12	32.2 (3)	C19—C18—C15—C16	143.8 (5)
C9—C8—C11—C12	-98.2 (3)	C19—C18—C15—C14	-39.5 (8)

Table 6. Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H(Å)	H···*A*(Å)	*D*···*A*(Å)	*D*—H···*A*(°)
C9-H9···N1^{i}	0.97	2.60	3.520 (3)	158
C17-H17···O2^{ii}	0.93	2.47	2.803 (3)	150

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

with $P2_1/C$ space group and total number molecule found in the unit cell is Z = 2. The chromene and isoxazole rings are coplanar one another. The nitrile is attached at the atom C8 of chromene system are almost perpendicular each other. The ethyl phenyl ring is attached to the isoxazole ring are tilted with the dihedral angle of 34.37 (2)°. The six membered ring systems offer a wide variety of conformational flexibility such as chair, distorted chair, half chair, boat and distorted boat conformations. However, the chair or slightly distorted chair conformation is found to be the most favored ones. But in the present study all the geometrical parameters strongly confirm that the six membered pyran ring of chromene moiety adopts sofa conformation[19]. Many of C-H…N and C-H...O type of hydrogen bonds plays a vital role for the stability of crystal packing. In this molecular structure, the C9-H9…N1 (-1+x, y, z) and C17-H17...O2 (1+x, y, z) hydrogen bonds forms a inversion dimer with R_2^2 (8) ring motif, which has stabilized the crystal packing of the title compound.

5. Conclusion

Crystal structure of a novel chromene based derivatives having a wide range of applications is described. The title compound is insoluble in millipore water and it is crystallized in ethanol by slow evaporation techinique. The chromene ring of the pyran ring adopts a sofa 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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