

## Crystal Structure Analysis of Methyl-3-phenyl-3H-chromeno[4,3-c]isoxazole-3a(4H)-carboxylate

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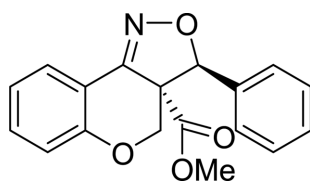
### Abstract

The crystal structure of the potential active methyl-3-phenyl-3H-chromeno[4,3-c]isoxazole-3a(4H)-carboxylate (C<sub>18</sub>H<sub>15</sub>NO<sub>4</sub>) has been determined from single crystal X-ray diffraction data. In the title compound crystallizes in the orthorhombic space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> with unit cell dimension a=9.8320 (17) Å, b=9.9890 (18) Å and c= 15.588 (3)Å [ $\alpha=90^\circ$ ,  $\beta=90^\circ$  and  $\gamma=90^\circ$ ]. In the structure chromene, isoxazole and carboxylate are almost coplanar each other. All geometrical parameters revealed that chromene ring of pyran ring adopt sofa conformation. The crystal packing is stabilized by intermolecular C-H...O and C-H...N hydrogen bond interaction.

**Keywords:** Chromene, Pyran, Single Crystal Structure, X-ray diffraction

### 1. Introduction

Chromenes constitute one of the main class of naturally occurring oxygen heterocycles, which possess 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<sup>[1-10]</sup> and also useful in treatment of Schizophrenia and Alzheimer's diseases<sup>[11,12]</sup>. 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).



**Fig. 1.** Chemical structure of methyl-3-phenyl-3H-chromeno[4,3-c]isoxazole-3a(4H)-carboxylate.

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.

### 2. Material and Methods

The title compound is crystallized by simple solvent slow evaporation method. Three rounds of crystallization trials to obtain a qualified crystal 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%.

### 3. Experimental Section

#### 3.1. Synthesis of the Title Compound

To a solution of aldoxime **4a** (0.63 g, 2 mmol) in 10

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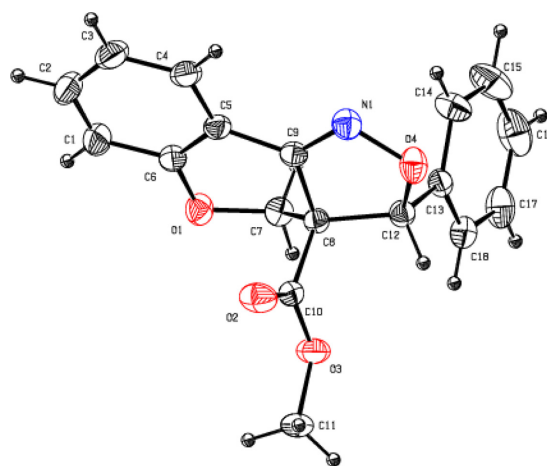
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mL  $\text{CCl}_4$  at 0-10°C was added NCS (0.54 g, 4 mmol, pinch wise) over 3 h. After this period  $\text{Et}_3\text{N}$  (0.57 mL, 4 mmol) was added to the reaction mixture and stirred well at room temperature for 2 h. After completion of the reaction, 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  $\text{Na}_2\text{SO}_4$ . The organic layer was evaporated and the crude mass was purified by column chromatography (silica gel 60-120 mesh 5% EtOAc in hexanes) to provide the desired pure product **5a** (0.43 g, 70%) as a colorless solid; mp: 130-132°C. Since the compound has not yield the diffraction quality crystals initially, the compound has been recrystallized with ethyl acetate by slow

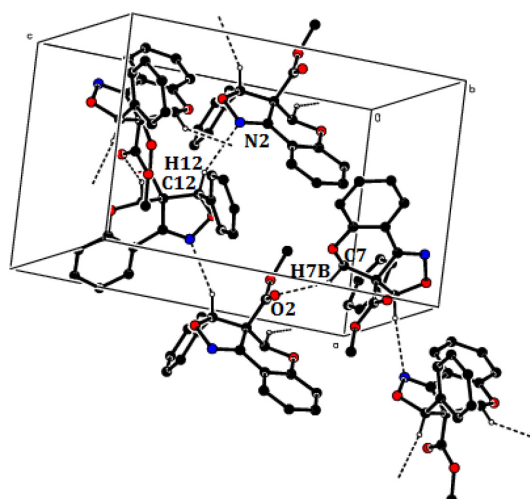
evaporation method to get better quality single crystals.

### 3.2. X-Ray Crystallography

For the crystal structure determination, the single crystal of the compound  $\text{C}_{18}\text{H}_{15}\text{NO}_4$  was used for data collection on a Bruker Kappa APEXII CCD diffractometer<sup>[13]</sup>. The  $\text{MoK}\alpha$  radiation of wavelength, ( $\lambda = 0.71073 \text{ \AA}$ ) 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  $F_2 > 2\sigma(F_2)$ . The



**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.

**Table 1.** Crystal data and structure refinement

Parameters	Compound
Empirical formula	$\text{C}_{18}\text{H}_{15}\text{NO}_4$
Formula weight	309.31
Temperature	293(2) K
Wavelength	0.71073 $\text{Å}$
Crystal system,	Orthorhombic,
space group	$P2_12_12_1$
Unit cell dimensions	$a = 9.832 (17) \text{ Å}$ $b = 9.989 (18) \text{ Å}$ $c = 15.588 (3) \text{ Å}$ $\alpha = \beta = \gamma = 90^\circ$
Volume	$1530.9 (5) \text{ Å}^3$
Z, Calculated density	4, 1.342 $\text{Mg/m}^3$
Absorption coefficient	$0.104 \text{ mm}^{-1}$
$F(000)$	684
Crystal size (mm)	$0.25 \times 0.20 \times 0.20$
$\theta$ range for data collection	$2.42$ to $28.3^\circ$
Limiting indices	$-9 \leq h \leq 13$ $-12 \leq k \leq 13$ $-20 \leq l \leq 16$
Reflections	8382/3761
collected/unique	[ $R_{\text{int}} = 0.022$ ]
Completeness to theta	100%
Refinement method	Full-matrix least-squares on $F^2$
Data/restraints/parameters	3761/0/209
Goodness-of-fit on $F^2$	1.03
Final R indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0414$ , $wR_2 = 0.1054$
R indices (all data)	$R_1 = 0.0499$ , $wR_2 = 0.1117$
Largest diff. peak and hole	0.138 and $-0.217 \text{ e.Å}^{-3}$

structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97<sup>[14,15]</sup>. H atoms were positioned geometrically and refined using a riding model, fixing the aromatic C-H distances at

0.93 Å [ $U_{iso}(H) = 1.2 U_{eq}(C)$ ]. The softwares used for Molecular graphics are ORTEP-3 for Windows<sup>[16]</sup> and PLATON<sup>[17]</sup>. The software used to prepare material for publication is WinGX publication routines<sup>[18]</sup>. Experimental data are listed in Table 1. Fig. 1 shows schematic

**Table 2.** Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å<sup>2</sup>)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{iso}^*/U_{eq}$
C15	0.7170 (3)	0.3871 (2)	0.02410 (18)	0.0885 (8)
H15	0.6326	0.3608	0.0031	0.106*
O3	1.11601 (12)	0.80271 (12)	0.18420 (9)	0.0550 (3)
O1	0.80063 (12)	0.80751 (12)	0.27848 (7)	0.0494 (3)
C10	1.01274 (15)	0.87692 (15)	0.15798 (10)	0.0379 (3)
O4	0.85940 (14)	0.78040 (12)	-0.01379 (7)	0.0529 (3)
C8	0.89258 (14)	0.78681 (14)	0.13534 (9)	0.0345 (3)
O2	1.01362 (12)	0.99504 (11)	0.15118 (10)	0.0611 (4)
N1	0.75646 (15)	0.86306 (14)	0.02254 (9)	0.0486 (3)
C12	0.92527 (16)	0.70425 (14)	0.05431 (9)	0.0388 (3)
H12	1.0238	0.7064	0.0448	0.047*
C6	0.70761 (15)	0.90170 (15)	0.25214 (10)	0.0430 (3)
C7	0.84395 (16)	0.71217 (15)	0.21507 (9)	0.0414 (3)
H7A	0.7690	0.6535	0.2002	0.050*
H7B	0.9172	0.6578	0.2379	0.050*
C13	0.87935 (15)	0.56032 (15)	0.05508 (9)	0.0393 (3)
C5	0.68673 (14)	0.93267 (15)	0.16604 (10)	0.0400 (3)
C9	0.77408 (15)	0.86712 (15)	0.10356 (9)	0.0375 (3)
C18	0.96689 (19)	0.46419 (17)	0.08648 (11)	0.0493 (4)
H18	1.0513	0.4897	0.1078	0.059*
C4	0.58712 (16)	1.02751 (18)	0.14485 (13)	0.0504 (4)
H4	0.5699	1.0472	0.0876	0.061*
C1	0.63491 (18)	0.9676 (2)	0.31638 (12)	0.0583 (5)
H1	0.6503	0.9480	0.3739	0.070*
C11	1.24148 (17)	0.8703 (2)	0.20549 (15)	0.0632 (5)
H11A	1.2524	0.9471	0.1692	0.095*
H11B	1.3166	0.8102	0.1971	0.095*
H11C	1.2389	0.8983	0.2644	0.095*
C14	0.7525 (2)	0.5218 (2)	0.02478 (14)	0.0617 (5)
H14	0.6914	0.5859	0.0050	0.074*
C2	0.54026 (18)	1.0620 (2)	0.29310 (15)	0.0675 (6)
H2	0.4922	1.1071	0.3356	0.081*
C3	0.51473 (18)	1.0916 (2)	0.20805 (15)	0.0632 (5)
H3	0.4489	1.1545	0.1937	0.076*
C17	0.9310 (3)	0.33064 (18)	0.08664 (12)	0.0635 (5)
H17	0.9906	0.2668	0.1083	0.076*
C16	0.8070 (3)	0.2925 (2)	0.05466 (16)	0.0835 (8)
H16	0.7835	0.2024	0.0536	0.100*

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

<b>Bond Length</b>	<b>(Å)</b>	<b>Bond Length</b>	<b>(Å)</b>
C15—C16	1.380 (4)	C13—C18	1.379 (2)
C15—C14	1.390 (3)	C13—C14	1.388 (2)
C15—H15	0.9300	C5—C4	1.402 (2)
O3—C10	1.3219 (18)	C5—C9	1.454 (2)
O3—C11	1.445 (2)	C18—C17	1.380 (3)
O1—C6	1.3748 (19)	C18—H18	0.9300
O1—C7	1.4371 (19)	C4—C3	1.374 (3)
C10—O2	1.1847 (18)	C4—H4	0.9300
C10—C8	1.5265 (19)	C1—C2	1.373 (3)
O4—N1	1.4237 (18)	C1—H1	0.9300
O4—C12	1.4577 (19)	C11—H11A	0.9600
C8—C9	1.499 (2)	C11—H11B	0.9600
C8—C7	1.5262 (19)	C11—H11C	0.9600
C8—C12	1.542 (2)	C14—H14	0.9300
N1—C9	1.275 (2)	C2—C3	1.381 (3)
C12—C13	1.507 (2)	C2—H2	0.9300
C12—H12	0.9800	C3—H3	0.9300
C6—C5	1.393 (2)	C17—C16	1.371 (4)
C6—C1	1.395 (2)	C17—H17	0.9300
C7—H7A	0.9700	C16—H16	0.9300
C7—H7B	0.9700		
<b>Bond Angle</b>	<b>(°)</b>	<b>Bond Angle</b>	<b>(°)</b>
C16—C15—C14	119.9 (2)	C6—C5—C9	117.28 (13)
C16—C15—H15	120.0	C4—C5—C9	123.99 (15)
C14—C15—H15	120.0	N1—C9—C5	126.67 (14)
C10—O3—C11	117.70 (14)	N1—C9—C8	114.57 (14)
C6—O1—C7	116.44 (12)	C5—C9—C8	118.61 (13)
O2—C10—O3	125.49 (15)	C13—C18—C17	120.94 (18)
O2—C10—C8	124.91 (14)	C13—C18—H18	119.5
O3—C10—C8	109.59 (12)	C17—C18—H18	119.5
N1—O4—C12	109.19 (11)	C3—C4—C5	120.52 (18)
C9—C8—C7	106.68 (12)	C3—C4—H4	119.7
C9—C8—C10	111.25 (12)	C5—C4—H4	119.7
C7—C8—C10	110.01 (12)	C2—C1—C6	118.78 (19)
C9—C8—C12	100.23 (11)	C2—C1—H1	120.6
C7—C8—C12	118.09 (12)	C6—C1—H1	120.6
C10—C8—C12	110.08 (11)	O3—C11—H11A	109.5
C9—N1—O4	108.41 (13)	O3—C11—H11B	109.5
O4—C12—C13	111.75 (12)	H11A—C11—H11B	109.5
O4—C12—C8	102.99 (11)	O3—C11—H11C	109.5
C13—C12—C8	116.18 (12)	H11A—C11—H11C	109.5
O4—C12—H12	108.5	H11B—C11—H11C	109.5
C13—C12—H12	108.5	C13—C14—C15	119.8 (2)

**Table 3.** Continued

Bond Angle	(°)	Bond Angle	(°)
C8—C12—H12	108.5	C13—C14—H14	120.1
O1—C6—C5	122.54 (14)	C15—C14—H14	120.1
O1—C6—C1	116.71 (16)	C1—C2—C3	121.57 (18)
C5—C6—C1	120.74 (16)	C1—C2—H2	119.2
O1—C7—C8	109.22 (12)	C3—C2—H2	119.2
O1—C7—H7A	109.8	C4—C3—C2	119.64 (18)
C8—C7—H7A	109.8	C4—C3—H3	120.2
O1—C7—H7B	109.8	C2—C3—H3	120.2
C8—C7—H7B	109.8	C16—C17—C18	119.7 (2)
H7A—C7—H7B	108.3	C16—C17—H17	120.2
C18—C13—C14	119.23 (15)	C18—C17—H17	120.2
C18—C13—C12	118.69 (14)	C17—C16—C15	120.40 (19)
C14—C13—C12	122.07 (15)	C17—C16—H16	119.8
C6—C5—C4	118.69 (15)	C15—C16—H16	119.8

**Table 4.** Anisotropic displacement parameters ( $\text{\AA}^2$ )

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
C15	0.0923 (17)	0.0775 (15)	0.0956 (17)	-0.0402 (2)	-0.0221 (2)	-0.0103 (13)
O3	0.0391 (6)	0.0486 (6)	0.0774 (8)	0.0022 (5)	-0.0145 (6)	-0.0080 (6)
O1	0.0553 (7)	0.0571 (7)	0.0358 (5)	0.0049 (6)	0.0026 (5)	0.0013 (5)
C10	0.0343 (7)	0.0391 (7)	0.0404 (7)	-0.0007 (6)	0.0010 (6)	-0.0046 (6)
O4	0.0727 (8)	0.0509 (6)	0.0351 (5)	0.0078 (6)	0.0050 (5)	0.0032 (5)
C8	0.0348 (7)	0.0331 (6)	0.0355 (6)	-0.0036 (6)	0.0013 (5)	0.0002 (5)
O2	0.0530 (7)	0.0381 (6)	0.0924 (10)	-0.0076 (5)	-0.0130 (7)	0.0006 (6)
N1	0.0550 (9)	0.0490 (8)	0.0419 (7)	0.0050 (6)	-0.0034 (6)	0.0033 (6)
C12	0.0389 (7)	0.0385 (7)	0.0390 (7)	-0.0024 (6)	0.0033 (6)	-0.0014 (6)
C6	0.0367 (7)	0.0469 (8)	0.0454 (8)	-0.0050 (6)	0.0025 (6)	-0.0049 (6)
C7	0.0449 (8)	0.0399 (7)	0.0393 (7)	-0.0025 (6)	0.0021 (6)	0.0064 (6)
C13	0.0431 (8)	0.0381 (7)	0.0365 (7)	-0.0026 (6)	0.0011 (6)	-0.0051 (6)
C5	0.0320 (7)	0.0405 (7)	0.0474 (8)	-0.0042 (6)	0.0012 (6)	-0.0021 (6)
C9	0.0357 (7)	0.0364 (7)	0.0405 (7)	-0.0034 (6)	-0.0019 (6)	0.0022 (6)
C18	0.0542 (9)	0.0459 (8)	0.0477 (9)	0.0049 (8)	0.0044 (7)	-0.0050 (7)
C4	0.0363 (8)	0.0509 (9)	0.0641 (10)	0.0015 (7)	-0.0046 (7)	-0.0033 (8)
C1	0.0524 (10)	0.0692 (12)	0.0532 (10)	-0.0052 (9)	0.0116 (8)	-0.0117 (9)
C11	0.0341 (8)	0.0772 (13)	0.0783 (13)	-0.0008 (8)	-0.0119 (8)	-0.0217 (11)
C14	0.0567 (11)	0.0595 (11)	0.0688 (12)	-0.0143 (9)	-0.0164 (9)	-0.0017 (9)
C2	0.0470 (10)	0.0715 (13)	0.0840 (15)	0.0014 (9)	0.0184 (10)	-0.0252 (11)
C3	0.0394 (9)	0.0586 (11)	0.0916 (16)	0.0075 (8)	0.0016 (9)	-0.0116 (10)
C17	0.0950 (16)	0.0407 (9)	0.0549 (10)	0.0065 (10)	0.0091 (11)	-0.0002 (8)
C16	0.129 (2)	0.0456 (10)	0.0755 (14)	-0.0249 (2)	0.0079 (15)	-0.0079 (10)

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

**Table 5.** Torsion angles [°]

Torsion angle	(°)	Torsion angle	(°)
C11—O3—C10—O2	-0.8 (3)	O1—C6—C5—C9	-3.8 (2)
C11—O3—C10—C8	177.68 (14)	C1—C6—C5—C9	175.25 (14)
O2—C10—C8—C9	-0.4 (2)	O4—N1—C9—C5	-175.61 (13)
O3—C10—C8—C9	-178.85 (12)	O4—N1—C9—C8	-0.17 (18)
O2—C10—C8—C7	-118.35 (18)	C6—C5—C9—N1	166.65 (16)
O3—C10—C8—C7	63.15 (16)	C4—C5—C9—N1	-15.6 (2)
O2—C10—C8—C12	109.83 (19)	C6—C5—C9—C8	-8.62 (19)
O3—C10—C8—C12	-68.67 (15)	C4—C5—C9—C8	169.12 (14)
C12—O4—N1—C9	14.20 (16)	C7—C8—C9—N1	-136.21 (14)
N1—O4—C12—C13	104.21 (13)	C10—C8—C9—N1	103.80 (15)
N1—O4—C12—C8	-21.21 (14)	C12—C8—C9—N1	-12.60 (17)
C9—C8—C12—O4	19.27 (14)	C7—C8—C9—C5	39.62 (16)
C7—C8—C12—O4	134.54 (13)	C10—C8—C9—C5	-80.37 (16)
C10—C8—C12—O4	-98.00 (13)	C12—C8—C9—C5	163.23 (12)
C9—C8—C12—C13	-103.22 (14)	C14—C13—C18—C17	1.2 (3)
C7—C8—C12—C13	12.05 (19)	C12—C13—C18—C17	-178.40 (16)
C10—C8—C12—C13	139.51 (13)	C6—C5—C4—C3	2.0 (2)
C7—O1—C6—C5	-19.5 (2)	C9—C5—C4—C3	-175.67 (16)
C7—O1—C6—C1	161.37 (14)	O1—C6—C1—C2	-179.61 (15)
C6—O1—C7—C8	52.42 (17)	C5—C6—C1—C2	1.3 (2)
C9—C8—C7—O1	-60.00 (15)	C18—C13—C14—C15	-1.9 (3)
C10—C8—C7—O1	60.78 (15)	C12—C13—C14—C15	177.7 (2)
C12—C8—C7—O1	-171.72 (12)	C16—C15—C14—C13	1.0 (4)
O4—C12—C13—C18	152.24 (14)	C6—C1—C2—C3	0.7 (3)
C8—C12—C13—C18	-90.00 (17)	C5—C4—C3—C2	-0.1 (3)
O4—C12—C13—C14	-27.4 (2)	C1—C2—C3—C4	-1.3 (3)
C8—C12—C13—C14	90.40 (19)	C13—C18—C17—C16	0.5 (3)
O1—C6—C5—C4	178.30 (14)	C18—C17—C16—C15	-1.4 (4)
C1—C6—C5—C4	-2.6 (2)	C14—C15—C16—C17	0.7 (4)

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

<i>D</i> —H... <i>A</i>	<i>D</i> —H(Å)	H... <i>A</i> (Å)	<i>D</i> ... <i>A</i> (Å)	<i>D</i> —H... <i>A</i> (°)
C7—H7B...O2 <sup>i</sup>	0.97	2.47	3.318 (2)	146
C12—H12...N1 <sup>ii</sup>	0.98	3.53	3.534(2)	157

the CCDC reference number: 791956. 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 orthorhombic sys-

tem with P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> space group and total number molecule found in the unit cell is Z = 2. The chromene and isoxazole rings are coplanar one another. The carboxylate group is attached at the atom C8 of chromene system are almost perpendicular each other. the phenyl ring is attached to the isoxazole ring are tilted with the dihedral angle of 74.37 (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<sup>[19]</sup>. Many of C-H...O and C-H...N type of hydrogen bonds plays a vital role for the stability of crystal packing. In this molecular structure, the C7-H7B...O2 (2-x, 1/2+y, 1/2-z) and C12-H12...N2 (1/2+x, 3/2-y, -z) hydrogen bonds has stabilized the crystal packing of the title compound.

#### Symmetry codes:

- (i) 2-x, -1/2+y, 1/2-z
- (ii) 1/2+x, 3/2-y, -z

### 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 ethonal by slow evaporation technique. The Pyran ring adopt 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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