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X-ray crystal structure analysis of 5-bromospiro[indoline-3,7'-pyrano[3,2-*C*:5,6-*C*']dichromene]-2,6',8'-trione

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RESEARCH ARTICLE

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ABSTRACT

An analog of spirooxindole[pyrano-*bis*-2*H*-l-benzopyran] derivatives namely 5-bromospiro [indoline-3,7'-pyrano[3,2-*c*:5,6-*c*']dichromene]-2,6',8'-trione was synthesized *via* one-pot pseudo three-component reaction of one equivalent of 5-bromoisatin and two equivalents of 4-hydroxycoumarin using mandelic acid as a naturally occurring organo catalyst in aqueous ethanol under reflux conditions. The synthesized compound was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS data. Crystal structure was determined by using single X-ray crystallography technique. It was found that the crystals are triclinic with space group *P*-1, $C_{108}H_{60}Br_4N_4O_{29}S_2$: a = 11.8333(6) Å, b = 12.8151(6) Å, c = 17.1798(8) Å, α = 77.317(4)°, β = 74.147(4)°, γ = 66.493(5)°, V = 2280.0(2) Å^3, Z = 1, T = 149.99(10) K, μ(MoKα) = 1.902 mm^{-1}, *Dcalc* = 1.647 g/cm^3, 11545 reflections measured (3.836° ≤ 2Θ ≤ 50.998°), 8310 unique (R_{int} = 0.0488, R_{sigma} = 0.0875) which were used in all calculations. The final R_1 was 0.0622 (I > 2σ(I)) and wR_2 was 0.1994 (all data). The crystal structure was solved by direct methods and refined by full-matrix least-squares procedure to a final *R*-value of 0.0622 for 6264 observed reflections. The crystal structure was stabilized by an elaborate system of N-H···O, O-H···O, C-H···π, and π···π interactions involving solvent molecules to form supramolecular structure.

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1. Introduction

Heterocyclic skeletons are very common in naturally occurring bioactive compounds as well as in commercially available drug molecules [1-3]. Spiro-oxindoles and 4-hydroxy-coumarin both moieties are very common in naturally occurring bioactive compounds [4,5]. Various synthetic benzopyran derivatives are found to possess a wide range of biological activities [6-8]. Recently, in 2016, Parthasarathy et al. [9] showed that spirooxindole[pyrano-*bis*-2*H*-l-benzopyran] derivatives can be used as an antimicrobial agent. On the other hand, mandelic acid is an inexpensive, commercially available, environmentally benign, naturally occurring organo-catalyst. In recent past, our group, for the first time, has investigated the catalytic activities of mandelic acid for various reactions [10-11]. The title compound, i.e., 5-bromospiro[indoline-3,7'-pyrano[3,2-*c*:5,6-*c*']dichromene]-2,6',8'-trione (**I**) was also synthesized with 69% yield by using 20 mol% mandelic acid as catalyst from the one-pot pseudo three-component reaction of one equivalent of 5-bromoisatin and two equivalents of 4-hydroxycoumarin in aqueous ethanol under reflux conditions at 110 °C. The biological significance of these heterocycles prompted us to synthesize this molecule. We were also able to form single crystals of the title compound. In this communication we wish to report the mandelic acid catalyzed a novel synthetic method and crystal structure of the title compound **I**.

2. Experimental

2.1. Synthesis

To an oven-dried screw cap round bottom flask, a magnetic stir bar, 5-bromoisatin (0.225 g, 1 mmol) and 4-hydroxy-coumarin (0.324 g, 2 mmol), mandelic acid (0.031 g, 20 mol % as an organo-catalyst) and 5 mL aqueous ethanol [EtOH:H_2O (1:1, *v:v*)] were added in a sequential manner. The reaction mixture was then refluxed for four hours at 110 °C. In between, the progress of the reaction was monitored by TLC. The reaction mixture was then allowed to cool. At room temperature, a solid mass precipitated out that was filtered off followed by subsequent washing with aqueous ethanol. Crude product was further purified by column chromatography.

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Table 1. Crystallographic characteristics, details of X-ray data collection and structure refinement parameters for compound **I**.

Empirical formula	$C_{108}H_{60}Br_4N_4O_{29}S_2$
Formula weight	2261.36
Temperature(K)	149.99(10)
Crystal system	Triclinic
Space group	*P*-1
a (Å)	11.8333(6)
b (Å)	12.8151(6)
c (Å)	17.1798(8)
α (°)	77.317(4)
β (°)	74.147(4)
γ (°)	66.493(5)
Volume(Å^3)	2280.0(2)
Z	1
ρ_{calc} (g/cm^3)	1.647
μ/mm^{-1}	1.902
F(000)	1140.0
Crystal size (mm^3)	0.3 × 0.2 × 0.2
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection (°)	3.836 to 50.998
Index ranges	-14 ≤ *h* ≤ 12, -15 ≤ *k* ≤ 14, -20 ≤ *l* ≤ 18
Reflections collected	11545
Independent reflections	8310 [R_{int} = 0.0488, R_{sigma} = 0.0875]
Data/restraints/parameters	8310/217/734
Goodness-of-fit on F^2	1.044
Final R indexes [I≥2σ (I)]	R_1 = 0.0622, wR_2 = 0.1671
Final R indexes [all data]	R_1 = 0.0906, wR_2 = 0.1994
Largest diff. peak/hole (e Å^{-3})	0.87/-0.95

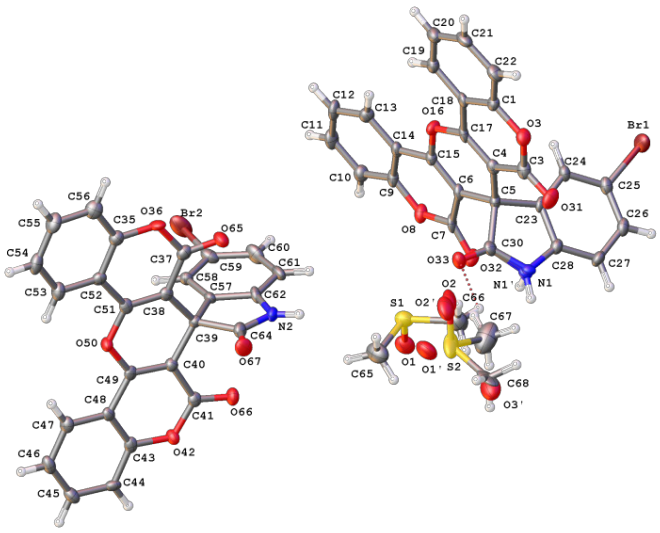

Figure 1. The structure of compound **I**, displacement ellipsoids are drawn at 40% probability level.

Single crystal was obtained from ethanol as solvent. For crystallization, 0.025 g of the purified compound was dissolved in 3 mL DMSO and left at room temperature. Orange block shaped crystals were obtained after few days.

5-Bromospiro[indoline-3, 7'-pyrano[3, 2-*c*:5, 6-*c*']dechromene]-2,6',8'-trione (**I**): Color: Brownish. Yield: 69%. M.p.: 190-191 °C. FT-IR (KBr, ν, cm^{-1}): 3389 (NH), 1709 (C=O) (ester), 1656(C=O) (ester), 1618 (C=O) (amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 11.02 (brs, 1H, -NH), 8.42 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.81-7.89 (m, 2H, Ar-H), 7.55-7.61 (m, 3H, Ar-H), 7.49 (d, 2H, *J* = 8.4 Hz, Ar-H),7.38 (d, 1H, *J* = 8.4 Hz, Ar-H), 6.79(d, 1H, *J* = 7.4 Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 176.12, 156.17, 156.06, 153.89, 152.08, 143.54, 134.04, 131.73, 127.36, 124.97, 123.74, 116.57, 113.12, 113.03, 110.74, 103.09, 46.52. HRMS (ESI-TOF, *m/z*) calcd. for $C_{26}H_{12}BrNO_6$, 512.9848; found 512.9826.

2.2. Crystal structure determination and refinement

The molecular structure solution was obtained by direct method procedure as using SHELXT [12]. The structure was solved by direct methods. Six cycles of full-matrix least-squares refinement was carried out and it brought the final R-factor to 0.0622. All non-hydrogen atoms of the molecule were located in the best E-map and refined in anisotropic approximation using SHELXS [12]. The Crystallographic data are summarized in Table 1. All hydrogen atoms were geometrically fixed and a riding model was used for them (N-H = 0.86, C-H = 0.93-0.98 Å), U_{iso}(H) = 1.5U_{eq} for the attached C atoms of methyl groups and 1.2U_{eq}(N,C) for other H atoms except for H2, H1 and H1' atoms attached to N2, N1 and N1' of pyrrole group in molecule. They were localized from the difference Fourier map, and their parameters were refined in the isotropic approximation of atomic displacements. The geometry of the molecule was calculated using the WinGX [13], PARST [14], and PLATON [15] programs.

3. Results and discussion

The molecular structure containing atomic labeling of the asymmetric unit of crystals (**I**), '4($C_{26}H_{12}BrNO_6$), 2(C_2H_6OS), 3(O)' is shown in Figure 1 (ORTEP program) [16] and the packing diagram as generated using PLATON [15] is shown in Figure 2.

Table 2. Selected bond lengths and angles for compound **I**.

Bond	*d*, Å	Bond	*d*, Å
C1-O3	1.375(6)	C35-O36	1.372(7)
C3-O3	1.383(7)	C37-O36	1.379(6)
C3-O31	1.205(7)	C37-O65	1.213(7)
C7-O32	1.218(7)	C41-O66	1.210(6)
C7-O8	1.380(6)	C41-O42	1.359(6)
C9-O8	1.381(7)	C43-O42	1.383(6)
C15-O16	1.366(6)	C49-O50	1.367(6)
C17-O16	1.364(6)	C51-O50	1.353(7)
C25-Br1	1.900(6)	C59-Br2	1.884(6)
C28-N1'	1.402(10)	C62-N2	1.384(7)
C28-N1	1.410(16)	N2-C64	1.361(7)
N1-C30	1.344(16)	C64-O67	1.203(7)
N1'-C30	1.347(10)		
C30-O33	1.218(6)		
Angle	**∠, deg**	**Angle**	**∠, deg**
C1-O3-C3	121.9(4)	C35-O36-C37	122.2(4)
C7-O8-C9	122.5(4)	C41-O42-C43	122.2(4)
C17-O16-C15	118.0(4)	C51-O50-C49	117.5(4)
C4-C5-C6	108.7(4)	C38-C39-C40	107.6(4)
C23-C5-C30	100.8(4)	C57-C39-C64	101.6(4)

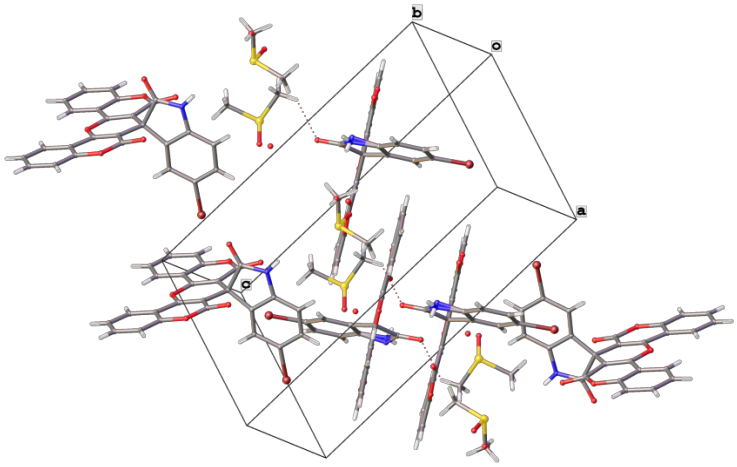

Figure 2. View of molecules packing down the *a*-axis in the unit cell (**I**).

The asymmetric unit consists of two molecules of the title compound **I**, one molecule of solvent DMSO and 1.5 molecules of partial water who's H-atoms could not be located. Molecules *A* and *B* of the compound are built up from a fused pyrrole and pyran ring system through a spiro junction at common carbon atoms C5 and C39, respectively. The nitrogen atom of molecule **I** is disordered over two sites with an occupancy ratio of N1:N1' = 0.296:0.703. All the atoms of DMSO solvent molecule and partial oxygen atoms are refined to site of occupancy of 0.5000. The structural parameters, including bond distances and angles show a normal geometry, and are close to their normal geometry [17] and show a fair amount of agreement with those observed in the related molecule ($C_{26}H_{12}FNO_6$) [8].

For central pyran skeleton of the molecule *A*, bond distances are O16-C17 = 1.364(6) Å, O16-C15 = 1.366(6) Å and bond angle C15-O16-C17= 118.0(4)°. For the molecule *B*, O50-C49 = 1.367(6) Å, O50-C51 = 1.353(7) Å and bond angle C52-O50-C49 =117.5(4)° are quite similar to related structure (1.3712 (16) Å, 1.3685 (16) Å, 117.29 (10)°). For hetero O atom of chromene rings attached adjacent to central pyran ring for molecule *A* and *B*, the bond distances and bond angles vary from 1.359(6) to 1.383(6) Å and 121.9(4) to 122.5(4)° indicating hetero π-electron delocalization over carbonyl groups attached to these rings. Whereas the C=O bond lengths vary from 1.203(7) to 1.218(7) Å, which are very close to the standard value for carbonyl group (1.210 Å; [10]). The N1-C28, N1'-C28, N2-C62; and N1-C30, N1'-C30, N2-C64 bond lengths (1.410(16), 1.402(10), 1.384(7) Å; and 1.344(16), 1.347(10), 1.361(7) Å, respectively) differ from the corresponding mean values of 1.419 and 1.331 Å, respectively, as reported for γ-lactams [10], which may reflect the delocalization of electrons in this ring. Moreover, around C5 and C39 in pyrrole ring, C23-C5-C30 and C57-C39-C64 (100.8(4)°, 101.6(4)°) deviate significantly from the ideal tetrahedral value of 109.4°. Whereas in pyran ring, the angles (C4-C5-C6= 108.7(4)°, C40-C39-C38 = 107.6(4)°) differ from similar angle of 101.17(10)° of the related structure. The Bromine atom substituted at C25 and C59 are at 1.900(6) Å, 1.884(6) Å of bond lengths, respectively. In ^{1}H NMR, all the hydrogen atoms expected N*H* are appeared in the aromatic region.

In the benzene rings of the oxindole ring system, the endocyclic angles at C24, C27, C58, and C61 are narrowed while those at C23, C25, C28, C60 and C62 are expanded from 120° respectively. This would appear to be a real effect caused by the fusion of the smaller pyrrole ring to the six-membered benzene ring and the strain is taken up by the angular distortion rather than by bond-length distortions. All rings of molecules *A* and *B* show planar conformation. The dihedral angle of 87.52(8)° shows that the oxindole ring is almost perpendicular to the fused pyrano-bis-2*H*-l-benzopyran moiety in molecule *B*. Table 2. contains the selected bond lengths and angles for compound **I**.

The crystal structure is assembled from the title molecules with solvent molecules via hydrogen bonding. Hydrogen bonded interactions between the title molecule and solvent molecules are also observed. Analysis of the crystal packing showed that there exist N-H···O and O-H···O types of intra- and inter-molecular hydrogen bonds.

Table 3. Geometry of intermolecular and intramolecular interactions for compound **I** *.

D–H···*A*	*D*–H, Å	H···*A*, Å	*D*···*A*, Å	∠(*D*–H···*A*), deg
N1'-H1'···O1'^{i}	0.84(4)	2.14(5)	2.8400(2)	140(6)
N1'-H1'···O1^{ii}	0.84(4)	2.01(5)	2.8017(2)	155(6)
N2-H2···O2	0.84(2)	2.11(3)	2.879(10)	152(5)
N2-H2···O2'	0.84(2)	2.18(3)	2.902(10)	143(3)
C67-H67B···S1	0.96	2.22	2.8378	121
C10-H10···Cg8^{ii}	0.96	2.75	3.5973	152
C27-H27···Cg14^{iii}	0.96	2.80	3.3689	120
C44-H44···Cg15^{iv}	0.96	2.72	3.5742	153
C60-H60···Cg3	0.96	2.75	3.6349	159

* Symmetry codes: (i) *x*, 1+*y*, z; (ii) 1-*x*, 1-*y*, 1-*z*; (iii) 1-*x*, 1-*y*, -*z*; (iv) 1-*x*, -*y*, 1-*z*; Cg3, Cg8, Cg14, and Cg15 present the center of gravity of the rings (O3/C1/C18/C17/C4/C3), (C23/C24/C25/C26/C27/C28), (C43/C44/C45/C46/C47/C48) and (C57/C58/C59/C60/C61/C62), respectively.

Table 4. Geometry of π···π interactions for (**I**)

CgI	CgJ	CgI···CgJ, Å	CgI···P, Å	α, deg	β, deg	Δ, Å
1	3^{i}	3.8192	0.0345	89	51.9	3.80
1	4^{i}	3.8149	0.0342	88	49.6	3.81
2	3^{i}	3.7887	0.0336	89	49.1	3.79
2	4^{i}	3.8434	0.0330	89	52.4	3.84
3	7^{ii}	3.7242	3.3292	3	45.6	1.67
4	6^{ii}	3.4942	3.3746	1	15.0	0.27
6	4^{ii}	3.4942	3.3746	1	14.8	0.91
6	7^{ii}	3.6797	3.3238	3	25.4	1.58
7	3^{ii}	3.7242	3.2980	3	27.7	1.63
7	6^{ii}	3.6797	3.3927	3	22.8	1.42
9	10^{i}	3.7945	0.0080	89	50.6	3.79
9	11^{i}	3.8314	0.0021	87	51.0	3.38
10	14^{iii}	3.8139	3.4404	3	26.8	1.65
11	13^{iii}	3.5908	3.3487	6	20.0	1.29
13	14^{iii}	3.5890	3.3815	4	18.4	1.20
14	10^{iii}	3.8139	3.4035	3	25.6	1.72
14	13^{iii}	3.5890	3.4049	4	19.6	1.13

Symmetric codes:(i) *x*, *y*, *z*; (ii) -*x*, 1-*y*, 1-*z*; (iii) 2-*x*, -*y*, -*z*.

In addition, the molecular packing is also stabilized with the help of weak π···π, C-H···π, and Van der Waal's forces. The geometry of these interactions is presented in Tables 3 and 4, respectively. The 90° angle for stacking rings is observed for 1-3, 1-4, 2-3, 2-4, 9-10, and 9-11 molecular pairs probably indicates that the stacking is missing. The molecular packing in the unit cell is shown in Figure 2.

Cg1, Cg2, Cg3, Cg4, Cg6, Cg7, Cg9, Cg10, Cg11, Cg13 and Cg14 represent the center of gravity of the rings (N1'/C28/C23/C5/C30), (C5/C23/C28/N1/C30), (C1/C18/C17/C4/C3), (C7/C6/C15/C14/C9), (C1/C18/C19/C20/C21/C22), (C10/C11/C12/C13/C14), (C62/C57/C39/C64), (O36/C35/C51/C38/C37), (O42/C41/C40/C49/C48/C43), (C35/C52/C53/C54/C55/C56) and (C44/C45/C46/C47/C48), respectively. Cg*I*···Cg*J* represents the distance between the ring centroids; CgI···P represents the perpendicular distance of the centroid of one ring from the plane of the other; α is the dihedral angle between the planes of rings I and J; β is the angle between the normal to the centroid of ring I and the line joining ring centroids; Δ is the displacement of the centroid of rings *J* relative to the intersection point of the normal to the centroid of ring *I* and the least- squares plane of ring *J*.

The small values of torsion angle of compound **I** indicates that the bicyclic indole ring systems, along with central pyran ring systems are planar in conformation. Whereas the central pyran ring in the related molecule ($C_{26}H_{12}FNO_6$) [9] adopts a boat conformation.

4. Conclusion

A spiro-oxindoles fused pyrano-*bis*-2*H*-l-benzopyran derivative was synthesized due to the recognition that molecules comprised of two or more heterocyclic skeleton often possess heightened pharmacological activities, in this regard a detailed spectral and X-ray crystallographic behavioral study was carried out. The crystal structure was solved by direct methods and refined by full-matrix least-squares procedure. The structural parameters, including bond distances are close to their normal geometry. Different hydrogen bond modes and π···π interactions involving solvent molecules played an incomparable role in the stabilization and formation of supramolecular crystal structure.

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Supporting information

CCDC-2008867 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
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Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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