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Synthesis and crystal structure of di-*tert*-butyl 1''-acetyl-2,2'',9'-trioxo-4*a*',9*a*'-dihydro-1'*H*,3'*H*,9'*H*-dispiro[indoline-3,2'-xanthene-4',3''-indoline]-1,3'-dicarboxylate, C₃₉H₃₈N₂O₉

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.16 × 0.13 × 0.11 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.10 mm ⁻¹
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
$\theta_{\max}$, completeness:	29.6°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	20424, 8056, 0.051
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 5688
$N(\text{param})_{\text{refined}}$:	458
Programs:	Bruker [1], SHELX [2]

The molecular structure is shown in the figure (hydrogen atoms were omitted for clarity). Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

The mixture of *tert*-butyl 2-oxo-3-((4-oxo-4*H*-chromen-3-yl)methyl)indoline-1-carboxylate (0.2 mmol), *tert*-butyl (*E*)-2-(1-acetyl-2-oxoindolin-3-ylidene)acetate (0.3 mmol), 5 Å molecular sieves 125 mg, catalyst (3,5-bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl))((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methylthiourea (10 mol %) and 6.0 mL of freshly distilled Et₂O was maintained at room temperature for 84 h. Then concentration by evaporation under reduced pressure gave a crude product, which was purified by column chromatography on a silica gel column using hexane/EtOAc (8/1, v/v) to give the corresponding pure products [3].

Experimental details

All hydrogen atoms were placed in geometrically idealized positions. The U_{iso} values of the hydrogen atoms of methyl

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Abstract

C₃₉H₃₈N₂O₉, monoclinic, $P2_1/c$ (no. 14), $a = 9.9846(6)$ Å, $b = 31.4308(13)$ Å, $c = 11.5739(6)$ Å, $\beta = 110.712(7)^\circ$, $V = 3397.4(3)$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.0596$, $wR_{\text{ref}}(F^2) = 0.1221$, $T = 293$ K.

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
O1	0.49268 (18)	0.18408 (5)	0.79183 (15)	0.0368 (4)
O2	0.64878 (14)	0.28258 (4)	0.63529 (13)	0.0215 (3)
O3	0.74880 (14)	0.31560 (4)	0.90630 (12)	0.0201 (3)
O4	0.92507 (16)	0.42983 (5)	0.87169 (14)	0.0306 (4)
O5	0.49526 (15)	0.42826 (4)	0.82492 (12)	0.0223 (3)
O6	0.23033 (13)	0.38045 (4)	0.60009 (12)	0.0183 (3)
O7	0.25144 (15)	0.31789 (4)	0.51315 (14)	0.0263 (3)
O8	0.31723 (15)	0.49176 (4)	0.79910 (12)	0.0212 (3)
O9	0.24867 (15)	0.52715 (4)	0.61685 (13)	0.0249 (3)
N1	0.52248 (17)	0.25325 (5)	0.75146 (15)	0.0178 (4)
N2	0.37647 (17)	0.46539 (5)	0.64275 (14)	0.0163 (3)
C1	0.5324 (2)	0.32910 (6)	0.74002 (18)	0.0166 (4)
C2	0.43796 (19)	0.31519 (6)	0.80994 (17)	0.0162 (4)
C3	0.3683 (2)	0.33940 (6)	0.87029 (18)	0.0210 (4)
H3	0.369890	0.368940	0.866324	0.025*
C4	0.2954 (2)	0.31906 (7)	0.93747 (19)	0.0249 (5)
H4	0.246592	0.334953	0.977736	0.030*
C5	0.2960 (2)	0.27518 (7)	0.94391 (19)	0.0250 (5)
H5	0.247062	0.261898	0.988952	0.030*
C6	0.3675 (2)	0.25034 (6)	0.88514 (18)	0.0214 (4)
H6	0.368012	0.220821	0.890802	0.026*
C7	0.4379 (2)	0.27106 (6)	0.81786 (17)	0.0180 (4)
C8	0.5777 (2)	0.28625 (6)	0.69990 (17)	0.0171 (4)
C9	0.6681 (2)	0.35001 (6)	0.83104 (18)	0.0169 (4)
H9	0.639916	0.369778	0.883865	0.020*
C10	0.8779 (2)	0.32722 (6)	0.99111 (18)	0.0202 (4)
C11	0.9436 (2)	0.29799 (7)	1.08407 (19)	0.0257 (5)
H11	0.901493	0.271667	1.085194	0.031*
C12	1.0722 (2)	0.30861 (7)	1.1748 (2)	0.0295 (5)
H12	1.117060	0.289172	1.237076	0.035*
C13	1.1353 (2)	0.34790 (7)	1.1741 (2)	0.0295 (5)
H13	1.220749	0.354919	1.236757	0.035*
C14	1.0714 (2)	0.37641 (7)	1.08101 (19)	0.0250 (5)
H14	1.114289	0.402666	1.080817	0.030*
C15	0.9421 (2)	0.36633 (6)	0.98604 (18)	0.0199 (4)
C16	0.8807 (2)	0.39410 (6)	0.87733 (19)	0.0203 (4)
C17	0.7599 (2)	0.37376 (6)	0.77198 (18)	0.0177 (4)
H17	0.802843	0.352534	0.733661	0.021*
C18	0.6779 (2)	0.40547 (6)	0.67114 (19)	0.0203 (4)
H18A	0.704284	0.400462	0.599278	0.024*
H18B	0.709312	0.433962	0.700578	0.024*
C19	0.5124 (2)	0.40397 (6)	0.62977 (17)	0.0166 (4)
C20	0.4640 (2)	0.35701 (6)	0.62150 (17)	0.0159 (4)
H20	0.498611	0.344297	0.559933	0.019*
C21	0.3025 (2)	0.34942 (6)	0.57068 (17)	0.0168 (4)
C22	0.0706 (2)	0.37942 (6)	0.55657 (19)	0.0222 (4)
C23	0.0371 (2)	0.42098 (7)	0.6058 (2)	0.0357 (6)
H23A	0.084355	0.421828	0.693864	0.054*
H23B	−0.064497	0.423339	0.585978	0.054*
H23C	0.069954	0.444194	0.568963	0.054*
C24	0.0102 (2)	0.37871 (8)	0.4169 (2)	0.0327 (5)
H24A	0.059461	0.399262	0.385260	0.049*
H24B	−0.089981	0.385530	0.388797	0.049*
H24C	0.022641	0.350876	0.388075	0.049*
C25	0.0219 (2)	0.34165 (7)	0.6131 (2)	0.0311 (5)

Table 2: (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
H25A	0.055126	0.315822	0.587999	0.047*
H25B	−0.080747	0.341321	0.585665	0.047*
H25C	0.060573	0.343890	0.701541	0.047*
C26	0.44382 (19)	0.42554 (6)	0.50591 (17)	0.0162 (4)
C27	0.4613 (2)	0.43241 (6)	0.71501 (18)	0.0174 (4)
C28	0.3649 (2)	0.46072 (6)	0.51691 (17)	0.0159 (4)
C29	0.2889 (2)	0.48476 (6)	0.41492 (18)	0.0194 (4)
H29	0.234244	0.507913	0.421966	0.023*
C30	0.2964 (2)	0.47328 (6)	0.30135 (18)	0.0211 (4)
H30	0.245992	0.489034	0.231467	0.025*
C31	0.3774 (2)	0.43895 (6)	0.29027 (18)	0.0209 (4)
H31	0.382392	0.432151	0.213687	0.025*
C32	0.4516 (2)	0.41451 (6)	0.39325 (18)	0.0192 (4)
H32	0.505347	0.391158	0.386180	0.023*
C33	0.2469 (2)	0.52174 (6)	0.85992 (18)	0.0212 (4)
C34	0.3150 (2)	0.56543 (6)	0.8695 (2)	0.0263 (5)
H34A	0.416180	0.563227	0.913497	0.040*
H34B	0.273669	0.584306	0.912976	0.040*
H34C	0.298006	0.576379	0.788123	0.040*
C35	0.0868 (2)	0.52217 (7)	0.7905 (2)	0.0274 (5)
H35A	0.067435	0.532713	0.708333	0.041*
H35B	0.041595	0.540269	0.832701	0.041*
H35C	0.049801	0.493796	0.786470	0.041*
C36	0.2811 (3)	0.50167 (7)	0.9859 (2)	0.0293 (5)
H36A	0.246674	0.472893	0.976435	0.044*
H36B	0.235438	0.517591	1.032424	0.044*
H36C	0.382823	0.501794	1.028791	0.044*
C37	0.5490 (2)	0.20934 (6)	0.74495 (19)	0.0236 (5)
C38	0.6490 (2)	0.19630 (7)	0.6812 (2)	0.0313 (5)
H38A	0.657248	0.165863	0.682714	0.047*
H38B	0.741453	0.208681	0.722864	0.047*
H38C	0.612451	0.205984	0.597151	0.047*
C39	0.3073 (2)	0.49828 (6)	0.68328 (18)	0.0186 (4)

groups were set to 1.5*U*_{eq}(C) and the *U*_{iso} values of all other hydrogen atoms were set to 1.2*U*_{eq}(C).

Comment

The spirooxindole system is the core structure of some natural alkaloids. Moreover, they have momentous medicinal properties including anticancer [4], antioxidant [5], antimicrobial [6], antifungal [7], anti HIV [8] and antitubercular activities [9]. Due to the aforesaid properties a variety of methods using diverse types of catalysts have been reported in the literature for the procurement of these types of compounds [10–13]. On the other hand, 4*H*-chromen-4-ones, a well-known class of oxygenated heterocyclic compounds, play an important role in nature due to their recognized biological, pharmacological and biocidal activities [14–16]. Due to the significance of hybrid systems in

drug discovery [17], there is an urgent need to assemble multiple pharmacophores into a single molecule. According to physiological activity structure combination strategy, spirooxindole skeleton and 4*H*-chromen-4-ones ring were joined together and the title compound was synthesized.

X-ray crystal structural analysis indicates that the molecular structure of the title structure consists of a 1,2,3,4,4*a*,9*a*-hexahydro-9*H*-xanthen-9-one ring, a 1-acetylindoline-2-one ring, a *tert*-butyl 2-oxoindoline-1-carboxylate ring and a *tert*-butyloxycarbonyl moiety (*cf.* the figure). The indoline-2-one rings are essentially planar, with a mean deviation from plane of 0.0168(3) Å for 1-acetylindoline-2-one ring and 0.0120(2) Å for *tert*-butyl 2-oxoindoline-1-carboxylate ring. Xanthen and indoline-2-one rings form spiro structural feature through atom C1 and C19. Because C1 and C19 are sp^3 carbon atoms, the indoline-2-one rings are non-coplanar with the xanthen ring. Bond lengths and angles in the title molecule are all in the expected ranges [18, 19].

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References

1. Bruker. *APEX2* and *SAINT*; Bruker AXS Inc.: Madison, Wisconsin, USA, 2012.
2. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, *C71*, 3–8.
3. Liu X. L., Zhou G., Gong Y., Yao Z., Zuo X., Zhang W. H., Zhou Y. Stereocontrolled synthesis of bispirooxindole-based hexahydroxanthenes with five contiguous stereocenters. *Org. Lett.* 2019, *21*, 1428–1431.
4. Ding K., Lu Y., Nikolovska-Coleska Z., Qiu S., Ding Y., Gao W., Stuckey J., Krajewski K., Roller P. P., Tomita Y., Parrish D. A., Deschamps J. R., Wang S. Structure-based design of potent non-peptide MDM2 inhibitors. *J. Am. Chem. Soc.* 2005, *127*, 10130–10131.
5. Mathusalini S., Arasakumar T., Lakshmi K., Lin C. H., Mohan P. S., Ramnath M. G., Thirugnanasampandan R. Synthesis and biological evaluation of new spiro oxindoles with embedded pharmacophores. *New J. Chem.* 2016, *40*, 5164–5169.
6. Ramadoss H., Saravanan D., Sudhan S. P. N., Mansoor S. S. Synthesis and antimicrobial evaluation of diversely substituted spirooxindole derivatives. *Der Pharm. Lett.* 2016, *8*, 25–29.
7. Abdel-Rahman A. H., Keshk E. M., Hanna M. A., El-Bady S. M. Synthesis and evaluation of some new spiro indoline-based heterocycles as potentially active antimicrobial agents. *Bioorg. Med. Chem.* 2004, *12*, 2483–2488.
8. Kumari G., Modi M., Gupta S. K., Singh R. K. Rhodium(II) acetate-catalyzed stereoselective synthesis, SAR and anti-HIV activity of novel oxindoles bearing cyclopropane ring. *Eur. J. Med. Chem.* 2011, *46*, 1181–1188.
9. Vintonyak V. V., Warburg K., Kruse H., Grimme S., Hübel K., Rauh D., Waldmann H. Identification of thiazolidinones spiro-fused to indolin-2-ones as potent and selective inhibitors of the mycobacterium tuberculosis protein tyrosine phosphatase B. *Angew. Chem. Int. Ed. Engl.* 2010, *49*, 5902–5905.
10. Rao B. M., Niranjan Reddy G., Vijaikumar Reddy T., Prabhavathi Devi B. L. A., Prasad R. B. N., Yadav J. S., Reddy B. V. S. Carbon– SO_3H : a novel and recyclable solid acid catalyst for the synthesis of spiro[4*H*-pyran-3,3'-oxindoles]. *Tetrahedron Lett.* 2013, *54*, 2466–2471.
11. Rad-Moghadam K., Youseftabar-Miri L. Ambient synthesis of spiro[4*H*-pyran-oxindole] derivatives under [BMIm]BF₄ catalysis. *Tetrahedron* 2011, *67*, 5693–5699.
12. Wagh Y. B., Tayade Y. A., Padvi S. A., Patil B. S., Patil N. B., Dalal D. S. A cesium fluoride promoted efficient and rapid multicomponent synthesis of functionalized 2-amino-3-cyano-4*H*-pyran and spirooxindole derivatives. *Chin. Chem. Lett.* 2015, *26*, 1273–1277.
13. Li Y., Chen H., Shi C., Shi D., Ji S. Efficient one-pot synthesis of spirooxindole derivatives catalyzed by L-proline in aqueous medium. *J. Comb. Chem.* 2010, *12*, 231–237.
14. Keri R. S., Budagumpi S., Pai R. K., Balakrishna R. G. Chromones as a privileged scaffold in drug discovery: a review. *Eur. J. Med. Chem.* 2014, *78*, 340–374.
15. Gaspar A., Matos M. J., Garrido J., Uriarte E., Chromone B F. A valid scaffold in medicinal chemistry. *Chem. Rev.* 2014, *114*, 4960–4992.
16. Sharma K. S., Kumar S., Chand K., Kathuria A., Gupta A., Jain R. An update on natural occurrence and biological activity of chromones. *Curr. Med. Chem.* 2011, *18*, 3825–3852.
17. Ramprasad J., Nayak N., Dalimba U. Design of new phenothiazine-thiadiazole hybrids via molecular hybridization approach for the development of potent antitubercular agents. *Eur. J. Med. Chem.* 2015, *106*, 75–84.
18. Li W.-W., Gu Y.-Z., Cao L. Synthesis and crystal structure of *tert*-butyl (2'*R*,3*R*,3'*R*,4*a'**R*,9*a'**S*)-1-acetyl-5-chloro-3"-methyl-2,5",9"-trioxo-1"-phenyl-1",4*a'*,5", 9*a'*-tetrahydro-1'*H*,3'*H*,9'*H*-dispiro[indoline-3,4'-xanthen-2',4"-pyrazole]-3'-carboxylate, C₃₆H₃₂ClN₃O₇. *Z. Kristallogr. NCS* 2021, *236*, 77–80.
19. Liu X.-L., Zuo X., Wang J.-X., Chang S.-q., Wei Q.-D., Zhou Y. A bifunctional pyrazolone-chromone synthon directed organocatalytic double Michael cascade reaction: forging five stereocenters in structurally diverse hexahydroxanthenes. *Org. Chem. Front.* 2019, *6*, 1485–1490.