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Crystal structure of (*E*)-7-methoxy-2-((5-methoxypyridin-3-yl)methylene)-3,4-dihydronaphthalen-1(2*H*)-one, C₁₈H₁₇NO₃

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.14 × 0.13 × 0.11 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.09 mm ⁻¹
Diffractometer, scan mode:	SuperNova,
$\theta_{\max}$, completeness:	25.5°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	4628, 2684, 0.032
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 2178
$N(\text{param})_{\text{refined}}$:	202
Programs:	CrysAlis ^{PRO} [1], SHELX [2, 3]

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Abstract

C₁₈H₁₇NO₃, triclinic, $P\bar{1}$ (no. 2), $a = 7.3950(5)$ Å, $b = 8.6697(5)$ Å, $c = 11.6813(9)$ Å, $\alpha = 85.457(6)^\circ$, $\beta = 76.712(6)^\circ$, $\gamma = 82.759(5)^\circ$, $V = 722.07(9)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0502$, $wR_{\text{ref}}(F^2) = 0.1342$, $T = 99.9(3)$ K.

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The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

5 mL (25%) of a sodium hydroxide aqueous solution was added dropwise to the mixture of 7-methoxy-3,4-dihydronaphthalen-

1(2*H*)-one and 5-methoxy-3-pyridinecarboxaldehyde in 10 mL methanol and stirred at room temperature for 3 h (monitored by TLC, 254 nm). The mixture was filtered and subsequently dissolved with ethyl acetate, and the organic solution was washed with water and brine, and finally dried over anhydrous sodium sulfate. After filtration, the ethyl acetate was condensed in vacuo to yield a white solid, which was purified by silica-gel column chromatography (petroleum ether: ethyl acetate = 2:1, v/v). The title compound was recrystallized from dichloromethane and methanol (1:1, v/v) system to attain suitable crystals.

Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with $d(\text{C-H}) = 0.97$ Å (methylene), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$, $d(\text{C-H}) = 0.93$ Å (aromatic), $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$, and $d(\text{C-H}) = 0.96$ Å (methyl), $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$.

Comment

Neuroinflammation mediated by overactivated microglia (pro-inflammatory M1 phenotype) plays a key role in many inflammatory neurodegenerative diseases in the central nervous system (CNS) [4–6]. Studies have shown that the activation of NF- κ B is the result of potential inflammation and the expression of pro-inflammatory cytokines nitric

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

Atom	x	y	z	<i>U</i> _{iso} */ <i>U</i> _{eq}
C1	0.2881 (2)	0.25272 (19)	0.07345 (14)	0.0208 (4)
C2	0.2992 (2)	0.18244 (18)	0.19352 (14)	0.0198 (4)
C3	0.2340 (2)	0.28930 (18)	0.29461 (14)	0.0227 (4)
H3A	0.270553	0.239693	0.364486	0.027*
H3B	0.098742	0.310015	0.311771	0.027*
C4	0.3209 (3)	0.44212 (19)	0.26202 (15)	0.0244 (4)
H4A	0.273227	0.512734	0.325177	0.029*
H4B	0.455397	0.422068	0.252654	0.029*
C5	0.2496 (2)	0.67721 (19)	0.13078 (15)	0.0256 (4)
H5	0.255905	0.739861	0.190477	0.031*
C6	0.2135 (2)	0.74763 (19)	0.02628 (16)	0.0262 (4)
H6	0.197058	0.855566	0.016120	0.031*
C7	0.2021 (2)	0.65511 (19)	−0.06287 (14)	0.0223 (4)
C8	0.2267 (2)	0.49447 (19)	−0.04637 (15)	0.0219 (4)
H8	0.218229	0.432477	−0.105955	0.026*
C9	0.2639 (2)	0.42506 (18)	0.05856 (14)	0.0194 (4)
C10	0.2766 (2)	0.51708 (19)	0.14944 (15)	0.0219 (4)
C11	0.3701 (2)	0.03352 (19)	0.20258 (15)	0.0208 (4)
H11	0.420132	−0.015397	0.132393	0.025*
C12	0.3774 (2)	−0.06131 (18)	0.31234 (15)	0.0212 (4)
C13	0.2249 (2)	−0.0550 (2)	0.40799 (15)	0.0261 (4)
H13	0.120697	0.014993	0.402483	0.031*
C14	0.3712 (3)	−0.2411 (2)	0.51501 (16)	0.0314 (5)
H14	0.370778	−0.301574	0.584473	0.038*
C15	0.5304 (2)	−0.25706 (19)	0.42443 (15)	0.0249 (4)
C16	0.5327 (2)	−0.16791 (18)	0.32063 (15)	0.0220 (4)
H16	0.635593	−0.178714	0.257618	0.026*
C17	0.8485 (3)	−0.3635 (3)	0.36896 (19)	0.0473 (6)
H17A	0.841206	−0.399577	0.294723	0.071*
H17B	0.939487	−0.431523	0.401059	0.071*
H17C	0.884841	−0.259922	0.357587	0.071*
C18	0.1466 (3)	0.87790 (19)	−0.18855 (17)	0.0292 (5)
H18A	0.041879	0.923116	−0.131760	0.044*
H18B	0.127134	0.904731	−0.266476	0.044*
H18C	0.258528	0.917046	−0.180440	0.044*
N1	0.2198 (2)	−0.14418 (18)	0.50756 (13)	0.0325 (4)
O1	0.16465 (17)	0.71244 (13)	−0.16914 (10)	0.0289 (3)
O2	0.29442 (17)	0.17020 (13)	−0.00849 (10)	0.0271 (3)
O3	0.67215 (18)	−0.36274 (15)	0.44767 (11)	0.0355 (4)

oxide (NO), tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β and IL-6 can be down-regulated by inhibiting the activation of NF- κ B, and play antineuroinflammatory effects on activated microglial cells [7–11]. Therefore, the development of a NF- κ B inhibitor with anti-neuroinflammatory activities and low toxicity is an effective therapeutic strategy for treating inflammatory neurodegenerative CNS diseases, which is of great significance [12, 13].

3,4-Dihydronaphthalen-1(2H)-one (DHN) derivatives with anti-tumor and anti-inflammatory activities have been studied as new allergic and inflammatory responses

modifiers for the treatment of skin diseases and cancers, and have been developed as anti-inflammatory drugs to stabilize mast cells [14, 15]. However, the development of DHN derivatives as anti-neuroinflammatory drugs is rare. Our group synthesized some of these compounds and studied their anti-neuroinflammatory activity. The results showed that the fluorine-substituted compounds had better activity [16, 17]. In this study, a new benzylidene-substituted DHN derivative, which may have anti-neuroinflammatory activity was designed and synthesized by Claisen–Schmidt condensation reaction (see the figure).

Single-crystal structure analysis revealed that the title compound crystallized in the triclinic space group $P\bar{1}$. The ORTEP diagram is presented in the Figure. Bond lengths and angles are all in the expected ranges [18, 19]. There is only one drug molecule in the asymmetric unit. The structure shows that the constitution at the C(2)=C(11) olefinic bond adopts the *E* stereochemistry [20]. Because of the distorting effect of 3,4-dihydronaphthalen-1(2H)-one, the 7-methoxyphenyl and 5-methoxy-3-pyridinyl groups are not coplanar to each other, with a dihedral angle of approximately 67.7(2)°. This twisted configuration may increase interactions with bioactive molecules with the aim of creating more potent anti-neuroinflammatory activity [21].

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References

1. Rigaku OD. *CrysAlis^{PRO}*; Rigaku Oxford Diffraction Ltd.: Yarnton, Oxfordshire, England, 2017.
2. Sheldrick G. M. A short history of *SHELX*. *Acta Crystallogr.* 2008, *A64*, 112–122.
3. Sheldrick G. M. Crystal structure refinement with *SHELXL*. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Goldmann T., Prinz M. Role of microglia in CNS autoimmunity. *Clin. Dev. Immunol.* 2013, 2013, 208093.
5. Lee D. S., Kwon K. H., Cheong S. H. Taurine chloramine suppresses LPS-induced neuroinflammatory responses through Nrf2-mediated heme oxygenase-1 expression in mouse BV2 microglial cells. *Adv. Exp. Med. Biol.* 2017, 975, 131–143.

6. Gao C. L., Hou G. G., Liu J., Ru T., Xu Y. Z., Zhao S. Y., Ye H., Zhang L. Y., Chen K. X., Guo Y. W., Pang T., Li X. W. Synthesis and target identification of benzoxepane derivatives as potential anti-neuroinflammatory agents for ischemic stroke. *Angew. Chem. Int. Ed.* 2020, 59, 2429–2439.
7. Wang J. Z., Wang H. Y., Mou X. D., Luan M. Z., Zhang X. F., He X. T., Zhao F. L., Meng Q. G. The advances on the protective effects of ginsenosides on myocardial ischemia and ischemia-reperfusion injury. *Mini-Rev. Med. Chem.* 2020, 20, 1610–1618.
8. Zhang J. Q., Zhang Q., Xu Y. R., Li H. X., Zhao F. L., Wang C. M., Liu Z., Liu P., Liu Y. N., Meng Q. G., Zhao F. Synthesis and *in vitro* anti-inflammatory activity of C20 epimeric ocotillol-type triterpenes and protopanaxadiol. *Planta Med.* 2019, 85, 292–301.
9. Yang Q. W., Wang N., Zhang J., Chen G., Xu H., Meng Q. G., Du Y., Yang X., Fan H. Y. *In vitro* and *in silico* evaluation of stereoselective effect of ginsenoside isomers on platelet P2Y₁₂ receptor. *Phytomedicine* 2019, 64, 152899.
10. Wang C. M., Liu J., Deng J. Q., Wang J. Z., Weng W. Z., Chu H. X., Meng Q. G. Advances in the chemistry, pharmacological diversity, and metabolism of 20(R)-ginseng saponins. *J. Ginseng Res.* 2020, 44, 14–23.
11. Liu J., Xu Y. R., Yang J. J., Wang W. Z., Zhang J. Q., Zhang R. Z., Meng Q. G. Discovery, semisynthesis, biological activities, and metabolism of ocotillol-type saponins. *J. Ginseng Res.* 2017, 41, 373–378.
12. Li N., Xin W. Y., Yao B. R., Cong W., Wang C. H., Hou G. G. *N*-phenylsulfonyl-3,5-bis(arylidene)-4-piperidone derivatives as activation NF- κ B inhibitors in hepatic carcinoma cell lines. *Eur. J. Med. Chem.* 2018, 155, 531–544.
13. Sun Y., Gao Z. F., Yan W. B., Yao B. R., Xin W. Y., Wang C. H., Meng Q. G., Hou G. G. Discovery of novel NF- κ B inhibitor based on scaffold hopping: 1,4,5,6,7,8-hexahydropyrido[4,3-*d*]pyrimidine. *Eur. J. Med. Chem.* 2020, 198, 112366.
14. Barlow J. W., Zhang T., Woods O., Byrne A. J., Walsh J. J. Novel mast cell-stabilising amine derivatives of 3,4 dihydronaphthalen-1(2*H*)-one and 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one. *Med. Chem.* 2011, 7, 213–223.
15. Kirby A. J., Le L. R., Maharlouie F., Mason P., Nicholls P. J., Smith H. J., Simons C. Inhibition of retinoic acid metabolising enzymes by 2-(4-aminophenylmethyl)-6-hydroxy-3,4-dihydronaphthalen-1(2*H*)-one and related compounds. *J. Enzym. Inhib. Med. Chem.* 2003, 18, 27–33.
16. Sun Y., Zhou Y. Q., Liu Y. K., Zhang H. Q., Hou G. G., Meng Q. G., Hou Y. Potential anti-neuroinflammatory NF- κ B inhibitors based on 3,4-dihydronaphthalen-1(2*H*)-one derivatives. *J. Enzym. Inhib. Med. Chem.* 2020, 35, 1631–1640.
17. Sun Y., Gao Z. F., Wang C. H., Hou G. G. Synthesis, crystal structures and anti-inflammatory activity of fluorine-substituted 1,4,5,6-tetrahydrobenzo[*h*]quinazolin-2-amine derivatives. *Acta Crystallogr.* 2019, C75, 1157–1165.
18. Zingales S. K., Moore M. E., Goetz A. D., Padgett C. W. Crystal structure of (*E*)-2-[(2-bromopyridin-3-yl)methylidene]-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one and 3-[(*E*)-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-ylidene)methyl]pyridin-2(1*H*)-one. *Acta Crystallogr.* 2016, E72, 955–958.
19. Luan M., Wang H., Zhang M., Song J., Xu Y., Zhao F., Meng Q. Crystal structure of (*E*)-2-(4-fluoro-2-(trifluoromethyl)benzylidene)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one, C₁₉H₁₄F₄O₂. *Z. Kristallogr. NCS* 2020, published online ahead of print; <https://doi.org/10.1515/ncrs-2020-0484>.
20. Yao B. R., Sun Y., Chen S. L., Suo H. D., Zhang Y. L., Wei H., Wang C. H., Zhao F., Cong W., Xin W. Y., Hou G. G. Dissymmetric pyridyl-substituted 3,5-bis(arylidene)-4-piperidones as anti-hepatoma agents by inhibiting NF- κ B pathway activation. *Eur. J. Med. Chem.* 2019, 167, 187–199.
21. Li N., Yao B. Y., Wang C. H., Meng Q. G., Hou G. G. Synthesis, crystal structure and activity evaluation of novel 3,4-dihydro-1-benzoxepin-5(2*H*)-one derivatives as protein-tyrosine kinase (PTK) inhibitors. *Acta Crystallogr.* 2017, C73, 1003–1009.