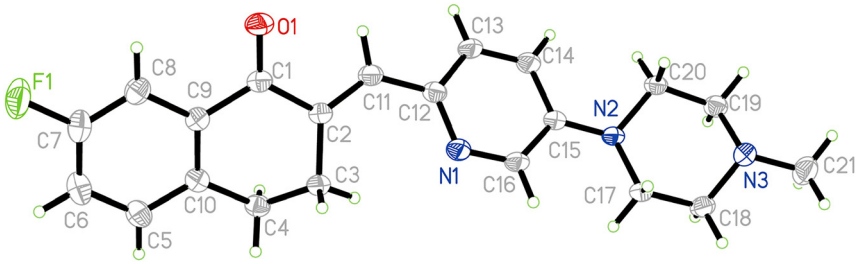
Yu Chen, Wen-Xin Zhu, Wen-Xuan Li, Yan Ren and Gui-Ge Hou*

Crystal structure of (*E*)-7-fluoro-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)methylene)-3,4-dihydronaphthalen-1(2*H*)-one, $C_{21}H_{22}FN_3O$



https://doi.org/10.1515/ncrs-2025-0256
Received June 3, 2025; accepted July 21, 2025;
published online July 28, 2025

Abstract

$C_{21}H_{22}FN_3O$, monoclinic, $P2_1/c$ (no. 14), a = 17.2795(3) Å, b = 6.1659(1) Å, c = 16.7198(3) Å, β = 90.596(1)°, V = 1781.29(5) Å^3, Z = 4, $R_{gt}(F)$ = 0.0408, $wR_{ref}(F^2)$ = 0.1122, T = 293 K.

CCDC no.: 2440890

The crystal structure is shown in the figure. Displacement ellipsoids are drawn at the 30 % probability level.

Table 1 contains the crystallographic data and the list of the atoms including atomic coordinates and displacement parameters can be found in the cif-file attached to this article.

Table 1: Data collection and handling.

Crystal:	Clear light yellow block
Size:	0.14 × 0.13 × 0.10 mm
Wavelength:	Cu*K*α radiation (1.54178 Å)
μ:	0.72 mm^{-1}
Diffractometer, scan mode:	Rigaku Synergy, ω scan
θ_{max}, completeness:	74.9°, 99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	11071, 3489, 0.016
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 3,297
$N(param)_{refined}$:	236
Programs:	Rigaku[1], SHELX[2,3]

1 Source of material

According to the synthesis method described in references, [4–6] *N*-methylpiperazine (16.05 g, 0.16 mol) and potassium carbonate (27.64 g, 0.20 mol) were weighed and added to a 250 mL round bottom reaction flask. *N*,*N*-dimethylformamide (15.0 mL) was used as the reaction solvent. The mixture was stirred at 353 K for about 4 h. 5-Fluorolinaldehyde (2.54 g, 0.02 mol) was added after 4 h and refluxed at 373 K to continue the reaction for about 5 h. The reaction progress is detected by Thin-Layer Chromatography (TLC, dichloromethane: methyl alcohol = 20:1, v:v). After the reaction system droped to room temperature, the precipitate was filtered and washed with dichloromethane to give a light yellow solid (22.0 mL). Spin evaporate the solvent and using dichloromethane: methyl alcohol (50:1, v:v) as the eluent to obtain the intermediate. 7-Fluoro-3,4-dihydronaphthalen-1(2*H*)-one (1.64 g, 0.01 mol) and intermediate (2.1 g, 0.01 mol) were reacted at 293 K for 7 h using methanol (25.0 mL) as the solvent and 25 % sodium hydroxide (20.0 mL) as the catalyst. After completion of the reaction, the precipitate was filtered and washed with 50 % methanol.[7] Finally, recrystallization gave yellow crystals of the title compound from dichloromethane and methanol solutions (1:1, v:v).

2 Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with d(C–H) = 0.96 Å

***Corresponding author: Gui-Ge Hou**, School of Pharmacy, Binzhou Medical University, Yantai, 264003, P.R. China, E-mail: guigehou@163.com. https://orcid.org/0000-0002-9493-3981
Yu Chen, Wen-Xin Zhu, Wen-Xuan Li and Yan Ren, School of Pharmacy, Binzhou Medical University, Yantai, 264003, P.R. China

(methyl), U_{iso}(H) = 1.5U_{eq}(C), and d(C–H) = 0.97 Å (methylene), U_{iso}(H) = 1.2U_{eq}(C), and d(C–H) = 0.93 Å (aromatic), U_{iso}(H) = 1.2U_{eq}(C).

3 Comment

3,4-Dihydronaphthalene-1(2*H*)-one derivatives are of interest because of their wide range of biological activities.[8] There is a large structural modification of space on its right side, and through skeleton assembly strategy, 3,4-dihydronaphthalene-1(2*H*)-one can be assembled with multiple active functional groups, which can endow it with various effects, such as anti rheumatic, anti skin disease, anti-tumor, and anti Alzheimer's disease.[9] Pyridine or dihydropyridine modification is one of the most widely used heterocycles in the field of drug design. Their excellent therapeutic effects have expanded the scope of finding treatments for other diseases.[10] *N*-methylpiperazine, as another nitrogen-containing heterocyclic ring containing two *N* atoms, has been found to have excellent anti-inflammatory, antibacterial, and anti-tumor activities.[11,12] Therefore, we first spliced *N*-methylpiperazine and 5-fluoropicolinaldehyde, two nitrogen-containing heterocycles, into 5-(4-methylpiperazin-1-yl)picolinaldehyde through substitution reaction.[13] Secondly, the fluorine atom has a strong electronegativity, which can improve its lipophilicity and enhance its bioavailability.[14] So we used 7-fluoro-3,4-dihydronaphthalen-1(2*H*)-one and 5-(4-methylpiperazin-1-yl)picolinaldehyde for the Claisen–Schmidt reaction to obtain the title compound.

The single crystal structure analysis revealed that there is only one drug molecule in the asymmetric unit (*cf.* the figure), and the bond lengths and bond angles of the compound are within the normal range. 3,4-Dihydronaphthalene-1(2*H*)-one is the main active site of the title compound.[15,16] In this parent nucleus, the fluorine atom is connected to C(7) position, the bond length of C(7)–F(1) is 1.3585(16) Å. Introducing 5-(4-methylpiperazin-1-yl) picolinaldehyde at C(2) position can form an *α*,*β*-unsaturated ketone structure. The bond length of C(1) =O(1) is 1.2236(15) Å, and the bond length of C(2)=C(11) is 1.3439(17) Å. In addition, the twist angle of O(1)=C(1)–C(2) =C(11) is –17.37(17)°. Through the C(2)=C(11) double bond, the molecule derives a pyridine substituent, with a twist angle of –22.7(2)° for C(2)=C(11)–C(12)=N(1). The bond lengths of C(12)=N(1) is 1.3440(16) Å. The parent nucleus is not coplanar with the pyridine ring, and the dihedral angle is approximately 45.05(4)°. *N*-methylpiperazine is attached to C(15) position, and displays "chair" conformation. The twist angle of N(2)–C(17)–C(18)–N(3) and N(2)–C(20)–C(19)–N(3) are about 54.39(14)° and –53.52(13)°, respectively.

Research funding: This work was supported by Shandong Laboratory Program (No. SYS202205), Shandong Provincial Natural Science Foundation (Nos. ZR2022MH159 and ZR2023MH190) and Shandong Province Science and Technology-based Small and Medium-sized Enterprises Innovation Capacity Enhancement Project (No. 2023TSGC0870).

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