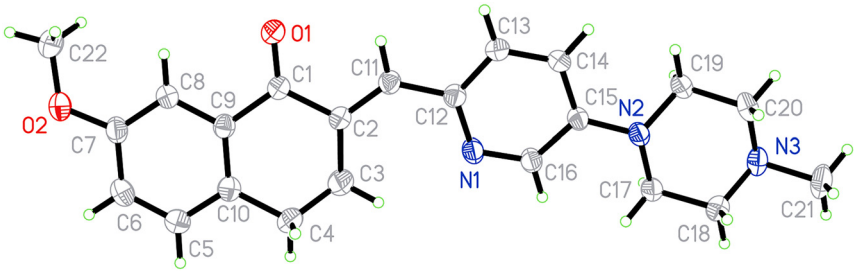
Wen-Wen Li, Yu Chen, Gui-Ge Hou and Feng Zhao*

# Crystal structure of (*E*)-7-methoxy-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)methylene)-3,4-dihydronaphthalen-1(2*H*)-one, $C_{22}H_{25}N_3O_2$




https://doi.org/10.1515/ncrs-2025-0261
Received June 4, 2025; accepted July 16, 2025;
published online July 31, 2025

**Abstract**

$C_{22}H_{25}N_3O_2$, triclinic, $P2_1$ (no. 4), $a$ = 11.0885(2) Å, $b$ = 5.9571(1) Å, $c$ = 14.7361(3) Å, $\beta$ = 99.633(2)°, $V$ = 959.67(3) Å$^3$, $Z$ = 2, $R_{gt}(F)$ = 0.0506, $wR_{ref}(F^2)$ = 0.1503, T = 293 K.

**CCDC no.:** 2473121

The molecular structure is shown in the figure. 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.

## 1 Source of material

Synthesis method based on literature reports.[4,5] In a 500 mL spherical backside flask, (*N*)-methylpiperazine (16.03 g, 0.16 mol) and potassium carbonate (27.64 g, 0.2 mol) were reacted with *N*,*N*-dimethylformamide (20.0 mL) at 313 K for 12 h. Then 5-fluoropicolinaldehyde (1.76 g, 0.01 mol) is added to the system and the temperature is raised to 393 K for reflux reaction. Thin-Layer Chromatography (TLC, dichloromethane:methyl alcohol = 25:1, *v*:*v*) was used for detection, the reaction was stopped after 7 h. After cooling to room temperature, perform solid-liquid separation and wash the precipitate with dichloromethane (25.0 mL) until it turns white. After drying the solid, use a mixture of dichloromethane and methanol (50:1, *v*:*v*) as the eluent for purification by silica gel column chromatography to obtain the intermediate 5-(4-methylpiperazin-1-yl)picolinaldehyde. The intermediate (2.04 g, 0.01 mol) and 7-methoxy-3,4 dihydronaphthalen-1(2*H*)-one (1.76 g, 0.01 mol) were dissolved in methanol (15.0 mL), and 25 % NaOH (10.0 mL) was added as a catalyst. The reaction was carried out at room temperature for 5 h. The product was obtained by filtration under suction, washing the precipitate with 20 % methanol, followed by recrystallization with 10 mL of dichloromethane/methanol solution (1:1, *v*:*v*) to yield yellow crystals of the title compound.

## 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

**Table 1:** Data collection and handling.

| | |
|---|---|
| Crystal: | Clear light yellow block |
| Size: | 0.16 × 0.14 × 0.12 mm |
| Wavelength: | Cu$K\alpha$ radiation (1.54178 Å) |
| $\mu$: | 0.65 mm$^{-1}$ |
| Diffractometer, scan mode: | Rigaku Synergy, $\omega$ scan |
| $\theta_{max}$, completeness: | 74.0°, 99 % |
| $N(hkl)_{measured}$, $N(hkl)_{unique}$, $R_{int}$: | 5458, 3037, 0.013 |
| Criterion for $I_{obs}$, $N(hkl)_{gt}$: | $I_{obs} > 2\sigma(I_{obs})$, 2,942 |
| $N(param)_{refined}$: | 246 |
| Programs: | Bruker,[1] SHELX[2,3] |

***Corresponding author: Feng Zhao**, School of Pharmacy, Binzhou Medical University, Yantai, 264003, P.R. China,
E-mail: zhaofeng2015@163.com
**Wen-Wen Li, Yu Chen and Gui-Ge Hou,** School of Pharmacy, Binzhou Medical University, Yantai, 264003, P.R. China. https://orcid.org/0000-0002-9493-3981 (G.-G. Hou)

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

## 3 Comment

3,4–Dihydronaphthalen-1(2*H*)-one derivatives[4] have been reported in numerous articles. Their key active fragment is the *α*, *β*-unsaturated ketone moiety, which is considered as a novel anti-inflammatory modulator.[5] It can inhibit COX-2 (cyclooxygenase-2) or regulate the NF-*κ*B pathway to reduce the release of inflammatory factors (such as IL-6 and TNF-*α*),[6] and also exhibits antibacterial and anti-tumor activities.[7] 3,4–Dihydronaphthalen-1(2*H*)-one derivatives can bind to P65 and NLRP3 proteins. Molecular docking revealed that the naphthoquinone could fit well into the active pocket.[8] Research has found that nitrogen-containing heterocyclic compounds conjugated with naphthone can form hydrogen bonds with amino acid residues near the active site, further stabilizing the complex conformation and effectively inhibiting the release of inflammatory factors.[8] (*N*)-Methylpiperazine is primarily used as an important chemical intermediate in the pharmaceutical and chemical industries. Its derivatives have shown potential value in antibiotic, antipsychotic drug development, and anti-tumor research.[9] Therefore, introducing (*N*)-methylpiperazine and electron-withdrawing groups into the synthesis is expected to further enhance the activity of 3,4-dihydronaphthalen-1(2*H*)-one derivatives. We synthesized the target compound by starting with (*N*)-methylpiperazine and 5-fluoropicolinaldehyde as raw materials. Through a nucleophilic substitution reaction, we obtained the intermediate, which was then subjected to a Claisen–Schmidt reaction with 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one.

Single-crystal structure analysis reveals that there is only a molecule in the asymmetric unit of the title crystal structure (*cf.* the figure). 3,4-Dihydronaphthalen-1(2*H*)-one is the main pharmacophore, followed by the introduction of 5-(4-methylpiperazin-1-yl)picolinaldehyde at position 2 to form an *α*, *β*-unsaturated ketone. The bond lengths of C(1)=O(1), N(1)=C(12), N(2)–C(17), N(3)–C(21) and O(2)–C(22) are 1.225(4) Å, 1.343(4) Å, 1.456(4) Å, 1.469(4) Å and 1.404(5) Å, respectively. The torsion angles of C(22)–O(2)–C(7)=C(8), O(1)=C(1)–C(2)=C(11) and N(2)–C(19)–C(20)–N(3) are about 4.4(5)°, 1.9(5)° and 56.2(4)°, respectively. Through the Claisen–Schmidt reaction, 5-(4-methylpiperazin-1-yl)picolinaldehyde can be introduced at the C(2) position. The introduction of the double bond allows the parent nucleus and the substituent to be coplanar, with a bond length of 1.351(4) Å between C(2) and C(11). The dihedral angle between the *N*-methylpiperazine ring and the pyridine ring is about 7.71(3)°. Furthermore, the *N*-methylpiperazine ring displays “chair” conformation.[10–13]

**Acknowledgments:** This work was supported by 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).

## References

1. Rigaku, O. D. 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. Chen, Y.; Wang, J. P.; Wang, M. D.; Yu, W. X.; Cui, Y. T.; Gao, H. X.; Hou, G. G.; Ren, Y. Crystal Structure of (*E*)-2-(4-(1H-Imidazol-1-yl) benzylidene)-7-fluoro-3,4-dihydronaphthalen-1 (*2H*)-one, $C_{20}H_{15}FN_2O$. *Z. Kristallogr. N. Cryst. Struct.* **2025**, *240*, 19–21.
5. 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(*2H*)-One Derivatives. *J. Enzym. Inhib. Med. Chem.* **2020**, *35*, 1631–1640.
6. 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. C* **2019**, *75* (8), 1157–1165.
7. Balamurugan, K.; Poria, D. K.; Sehareen, S. W.; Krishnamurthy, S.; Tang, W.; McKennett, L.; Padmanaban, V.; Czarra, K.; Ewald, A. J.; Ueno, N. T.; Ambs, S.; Sharan, S.; Sterneck, E. Stabilization of E-cadherin Adhesions by COX-2/GSK3*β* Signaling is a Targetable Pathway in Metastatic Breast Cancer. *JCI Insight* **2023**, *8* (6), e156057.
8. Li, W. X.; Yu, L.; Chi, J. B.; Wang, J. P.; Liu, Y. J.; Wang, C. H.; Zhang, M.; Hou, G. G. Discovery of Anti-Inflammatory Agents from 3,4-Dihydronaphthalene-1(*2H*)-One Derivatives by Inhibiting NLRP3 Inflammasome Activation. *Eur. J. Med. Chem.* **2024**, *268*, 116284.
9. Mo, M.; Zeng, Y.; Zeng, Y. Q.; Li, S. T.; He, X. Y.; Chen, X. W.; Luo, Q. M.; Liu, M.; Luo, G. W.; Dou, X. R.; Peng, F. F.; Long, H. B. N-Methylpiperazine-Diepoxyovatodiolide Ameliorates Peritoneal Fibrosis via Suppressing TGF-*β*/Smad and JAK/STAT Signaling Pathway. *Chem.–Biol. Interact.* **2023**, *382*, 110589.
10. Yu, L.; Wang, J.-P.; Wang, M.-D.; Yu, W.-X.; Cui, Y.-T.; Gao, H.-X.; Liu, Y.-J.; Hou, G.-G. Crystal Structure of (*E*)-6-(4-Ethylpiperazin-1-yl)-2-(3-Fluorobenzylidene)-3,4-Dihydronaphthalen-1(*H*)-One, $C_{23}H_{25}FN_2O$. *Z. Kristallogr. N. Cryst. Struct.* **2024**, *239*, 515–517.
11. Qi, Q. B.; Li, W. X.; Hou, G. G.; Li, C. B. Crystal Structure of (*E*)-7-Bromo-2-(4-(4-methylpiperazin-1-yl)benzylidene)-3,4-dihydronaphthalen-1 (*2H*)-one, $C_{22}H_{23}BrN_2O$. *Z. Kristallogr. N. Cryst. Struct.* **2023**, *238* (2), 235–237.
12. Luo, H. L.; Li, W. X.; Bai, X. Y.; Meng, Q. G.; Hou, Y. Crystal Structure of (*E*)-7-Fluoro-2-(4-morpholinobenzylidene)-3,4-dihydronaphthalen-1(*2H*)-one, $C_{21}H_{20}FNO_2$. *Z. Kristallogr. N. Cryst. Struct.* **2023**, *238* (3), 495–497.
13. Xia, D.-L.; Wang, J. P.; Yu, W. X.; Wang, M. D.; Gao, H. X.; Cui, Y. T.; Hou, G. G. Crystal Structure of (*E*)-6,8-Dimethoxy-4-(4-morpholinobenzylidene)-3,4-dihydro-1-benzoxepin-5(*2H*)-one, $C_{23}H_{25}NO_5$. *Z. Kristallogr. N. Cryst. Struct.* **2024**, *239*, 1133–1136.