Rui Li, Yang Liu, Yue-Yao Jiang and Dong-Li Jiang*

# Crystal structure of 2-(5-ethylpyridin-2-yl)ethyl 2-(6-methoxynaphthalen-2-yl)propanoate, $C_{23}H_{25}NO_3$

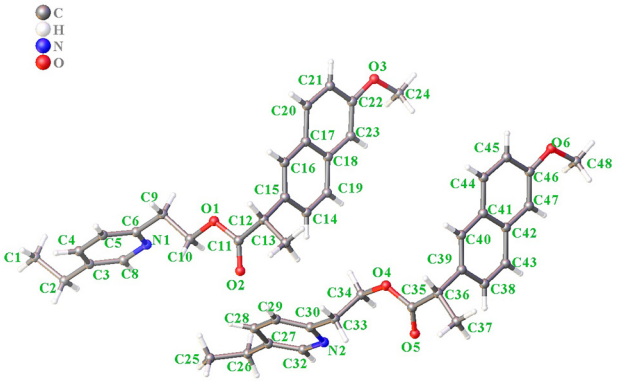


**Table 1:** Data collection and handling.

| | |
|---|---|
| Crystal: | Colourless block |
| Size: | 0.12 × 0.11 × 0.10 mm |
| Wavelength: | MoKα radiation (0.71073 Å) |
| $\mu$: | 0.08 $mm^{-1}$ |
| Diffractometer, scan mode: | Bruker APEX-II, $\varphi$ and $\omega$ |
| $\theta_{max}$, completeness: | 27.7°, >99 % |
| $N(hkl)_{measured}$, $N(hkl)_{unique}$, $R_{int}$: | 71,927, 8918, 0.046 |
| Criterion for $I_{obs}$, $N(hkl)_{gt}$: | $I_{obs} > 2\ \sigma(I_{obs})$, 8051 |
| $N(param)_{refined}$: | 493 |
| Programs: | Bruker [1], Olex2 [2], Shelx [3] |

https://doi.org/10.1515/ncrs-2024-0077
Received February 21, 2024; accepted March 27, 2024;
published online April 15, 2024

**Abstract**

$C_{23}H_{25}NO_3$, monoclinic, $P2_1$ (no. 4), $a$ = 15.2433(7) Å, $b$ = 5.8687(3) Å, $c$ = 22.3558(11) Å, $\beta$ = 105.461(2)°, $V$ = 1927.54(16) $Å^3$, $Z$ = 4, $R_{gt}(F)$ = 0.0413, $wR_{ref}(F^2)$ = 0.1055, $T$ = 100(2) K.

**CCDC no.:** 2343307

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.

## 1 Source of materials

Naproxen acylchloride was synthesized according to the literature method [4]. 5-Ethyl-2-pyridineethanol (0.01 mol, 1.51 g) and 4-(dimethylamino)-pyridin (DMAP, 0.0015 mol, 0.18 g) were dissolved in dry tetrahydrofuran (20 mL) and triethylamine (0.015 mol, 2 mL). The solution of naproxen acylchloride in dry tetrahydrofuran was dropwise added at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtrated to remove the solid and the filtrate was concentrated under vacuum to remove the solvent. The residue was dissolved in dichloromethane, successively washed with 5 % NaOH solution and water to pH = 7, and dried with anhydrous $Na_2SO_4$. The solution was filtrated, and concentrated under vacuum to obtain crude product. The crude product was purified by recrystallization in ethanol. The single crystals were obtained from tetrahydrofuran solution.

## 2 Experimental details

H atoms were set to calculated positions. The $U_{iso}$ values were set to be $1.5U_{eq}$ of the carrier atom for methyl H atoms and $1.2U_{eq}$ for the remaining H atoms.

## 3 Comment

Naproxen is one of the strongest non-steroidal anti-inflammatory drugs (NSAIDs), inhibits the cyclooxygenase (COX) enzymes both COX-1 and COX-2. Inhibits both COX-1 and

***Corresponding author: Dong-Li Jiang**, China-Japan Union Hospital of Jilin University, Changchun 130021, China, E-mail: jiangdi@jlu.edu.cn. https://orcid.org/0000-0001-6083-1648
**Rui Li, Yang Liu and Yue-Yao Jiang,** China-Japan Union Hospital of Jilin University, Changchun 130021, China, E-mail: l_r@jlu.edu.cn (R. Li), 10334776@qq.com (Y. Liu), jyy0705@jlu.edu.cn (Y.-Y. Jiang). https://orcid.org/0000-0002-1971-5909 (R. Li)

**Table 2:** Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$).

| Atom | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| C1 | 0.06837 (18) | 1.6084 (5) | 0.95343 (12) | 0.0324 (6) |
| H1A | 0.033347 | 1.621226 | 0.909913 | 0.049* |
| H1B | 0.113271 | 1.731650 | 0.963496 | 0.049* |
| H1C | 0.027089 | 1.619531 | 0.980240 | 0.049* |
| C2 | 0.11720 (17) | 1.3793 (5) | 0.96378 (11) | 0.0276 (6) |
| H2A | 0.151955 | 1.367209 | 1.007907 | 0.033* |
| H2B | 0.071278 | 1.255867 | 0.955131 | 0.033* |
| C3 | 0.18175 (15) | 1.3453 (4) | 0.92336 (10) | 0.0215 (5) |
| C4 | 0.25403 (16) | 1.4931 (4) | 0.92606 (10) | 0.0225 (5) |
| H4 | 0.264981 | 1.616978 | 0.954451 | 0.027* |
| C5 | 0.31011 (16) | 1.4588 (4) | 0.88706 (10) | 0.0208 (5) |
| H5 | 0.360209 | 1.557485 | 0.889012 | 0.025* |
| C6 | 0.29215 (15) | 1.2781 (4) | 0.84498 (10) | 0.0200 (5) |
| C8 | 0.17068 (16) | 1.1671 (5) | 0.88081 (11) | 0.0244 (5) |
| H8 | 0.122346 | 1.062963 | 0.879048 | 0.029* |
| C9 | 0.34953 (17) | 1.2356 (4) | 0.80041 (11) | 0.0229 (5) |
| H9A | 0.310253 | 1.235428 | 0.757287 | 0.027* |
| H9B | 0.394876 | 1.359263 | 0.804209 | 0.027* |
| C10 | 0.39778 (16) | 1.0095 (4) | 0.81446 (10) | 0.0213 (5) |
| H10A | 0.435649 | 1.006307 | 0.857962 | 0.026* |
| H10B | 0.352880 | 0.884018 | 0.808619 | 0.026* |
| C11 | 0.50806 (15) | 0.7960 (4) | 0.78198 (10) | 0.0193 (5) |
| C12 | 0.56224 (15) | 0.7744 (4) | 0.73406 (10) | 0.0193 (5) |
| H12 | 0.590414 | 0.925765 | 0.730292 | 0.023* |
| C13 | 0.63886 (16) | 0.5999 (5) | 0.75534 (11) | 0.0274 (5) |
| H13A | 0.681518 | 0.652910 | 0.793793 | 0.041* |
| H13B | 0.671098 | 0.582179 | 0.723104 | 0.041* |
| H13C | 0.613038 | 0.453038 | 0.762742 | 0.041* |
| C14 | 0.44808 (15) | 0.5073 (4) | 0.66278 (10) | 0.0182 (4) |
| H14 | 0.452165 | 0.410014 | 0.697370 | 0.022* |
| C15 | 0.49834 (14) | 0.7139 (4) | 0.67096 (10) | 0.0167 (4) |
| C16 | 0.49061 (14) | 0.8549 (4) | 0.62069 (10) | 0.0159 (4) |
| H16 | 0.522608 | 0.995595 | 0.626147 | 0.019* |
| C17 | 0.43597 (14) | 0.7951 (4) | 0.56094 (10) | 0.0145 (4) |
| C18 | 0.38717 (14) | 0.5859 (4) | 0.55250(9) | 0.0142 (4) |
| C19 | 0.39357 (15) | 0.4460 (4) | 0.60554 (10) | 0.0172 (4) |
| H19 | 0.359700 | 0.308296 | 0.601310 | 0.021* |
| C20 | 0.43177 (14) | 0.9341 (4) | 0.50789 (10) | 0.0165 (4) |
| H20 | 0.461538 | 1.077825 | 0.512993 | 0.020* |
| C21 | 0.38556 (14) | 0.8633 (4) | 0.44995 (10) | 0.0174 (4) |
| H21 | 0.385423 | 0.954999 | 0.414903 | 0.021* |
| C22 | 0.33760 (14) | 0.6529 (4) | 0.44177 (10) | 0.0162 (4) |
| C23 | 0.33622 (14) | 0.5186 (4) | 0.49179 (10) | 0.0160 (4) |
| H23 | 0.301621 | 0.381838 | 0.486067 | 0.019* |
| C24 | 0.25315 (16) | 0.3843 (4) | 0.36967 (10) | 0.0210 (5) |
| H24A | 0.228742 | 0.361848 | 0.324867 | 0.032* |
| H24B | 0.203353 | 0.377706 | 0.389741 | 0.032* |
| H24C | 0.297506 | 0.264282 | 0.386623 | 0.032* |
| C25 | 0.5923 (2) | 0.5174 (6) | 0.99068 (14) | 0.0382 (7) |
| H25A | 0.593639 | 0.664498 | 0.970208 | 0.057* |
| H25B | 0.647422 | 0.500637 | 1.024981 | 0.057* |
| H25C | 0.538591 | 0.510260 | 1.006852 | 0.057* |
| C26 | 0.58800 (15) | 0.3270 (5) | 0.94433 (11) | 0.0236 (5) |
| H26A | 0.534892 | 0.353873 | 0.908352 | 0.028* |
| H26B | 0.577264 | 0.181905 | 0.963850 | 0.028* |
| C27 | 0.67177 (15) | 0.2991 (4) | 0.92058 (10) | 0.0180 (5) |
| C28 | 0.73496 (15) | 0.4704 (4) | 0.92229 (11) | 0.0214 (5) |
| H28 | 0.727781 | 0.614643 | 0.939669 | 0.026* |
| C29 | 0.80912 (15) | 0.4299 (4) | 0.89837 (11) | 0.0202 (4) |
| H29 | 0.851670 | 0.547687 | 0.897868 | 0.024* |
| C30 | 0.81998 (15) | 0.2148 (4) | 0.87526 (10) | 0.0194 (5) |
| C32 | 0.68804 (16) | 0.0924 (4) | 0.89557 (11) | 0.0236 (5) |
| H32 | 0.644793 | −0.025816 | 0.893681 | 0.028* |
| C33 | 0.89934 (16) | 0.1575 (4) | 0.84941 (11) | 0.0228 (5) |
| H33A | 0.940216 | 0.290927 | 0.853307 | 0.027* |
| H33B | 0.934565 | 0.029625 | 0.873092 | 0.027* |
| C34 | 0.86379 (16) | 0.0918 (5) | 0.78196 (11) | 0.0247 (5) |
| H34A | 0.822062 | −0.039721 | 0.778441 | 0.030* |
| H34B | 0.828725 | 0.220623 | 0.758657 | 0.030* |
| C35 | 0.96799 (16) | −0.1830 (4) | 0.76251 (10) | 0.0207 (5) |
| C36 | 1.03660 (15) | −0.2296 (4) | 0.72529 (10) | 0.0189 (5) |
| H36 | 1.070573 | −0.085533 | 0.722920 | 0.023* |
| C37 | 1.10484 (17) | −0.4122 (5) | 0.75617 (11) | 0.0301 (6) |
| H37A | 1.140584 | −0.357599 | 0.796789 | 0.045* |
| H37B | 1.145629 | −0.445192 | 0.729996 | 0.045* |
| H37C | 1.072167 | −0.551234 | 0.761573 | 0.045* |
| C38 | 0.93283 (15) | −0.5026 (4) | 0.64924 (10) | 0.0177 (4) |
| H38 | 0.934799 | −0.601855 | 0.683141 | 0.021* |
| C39 | 0.98212 (14) | −0.2945 (4) | 0.65986 (10) | 0.0158 (4) |
| C40 | 0.97825 (14) | −0.1512 (4) | 0.61065 (10) | 0.0150 (4) |
| H40 | 1.010390 | −0.010796 | 0.617538 | 0.018* |
| C41 | 0.92697 (14) | −0.2093 (4) | 0.54953 (10) | 0.0137 (4) |
| C42 | 0.87882 (14) | −0.4190 (4) | 0.53896 (9) | 0.0142 (4) |
| C43 | 0.88241(14) | −0.5627 (4) | 0.59088 (10) | 0.0162 (4) |
| H43 | 0.849478 | −0.702028 | 0.585036 | 0.019* |
| C44 | 0.92538 (14) | −0.0663 (4) | 0.49793 (10) | 0.0158 (4) |
| H44 | 0.955210 | 0.077218 | 0.504460 | 0.019* |
| C45 | 0.88137 (15) | −0.1333 (4) | 0.43903 (10) | 0.0167 (4) |
| H45 | 0.882711 | −0.038329 | 0.404871 | 0.020* |
| C46 | 0.83362 (14) | −0.3437 (4) | 0.42847 (10) | 0.0159 (4) |
| C47 | 0.83042 (14) | −0.4827 (4) | 0.47734 (10) | 0.0156 (4) |
| H47 | 0.796267 | −0.620148 | 0.470178 | 0.019* |
| C48 | 0.74854 (17) | −0.6034 (4) | 0.35303 (11) | 0.0237 (5) |
| H48A | 0.729016 | −0.624616 | 0.307933 | 0.036* |
| H48B | 0.695207 | −0.605776 | 0.369657 | 0.036* |
| H48C | 0.790142 | −0.726629 | 0.371898 | 0.036* |
| N1 | 0.22323 (14) | 1.1317 (4) | 0.84210 (9) | 0.0242 (4) |
| N2 | 0.75986 (15) | 0.0460 (4) | 0.87386 (10) | 0.0263 (5) |
| O1 | 0.45483 (11) | 0.9825 (3) | 0.77199 (7) | 0.0216 (4) |
| O2 | 0.51064 (12) | 0.6639 (3) | 0.82377 (8) | 0.0269 (4) |
| O3 | 0.29660 (10) | 0.6014 (3) | 0.38101 (7) | 0.0194 (3) |
| O4 | 0.93732 (11) | 0.0324 (3) | 0.75463 (7) | 0.0225 (4) |
| O5 | 0.94111 (14) | −0.3212 (3) | 0.79315 (8) | 0.0343 (4) |
| O6 | 0.79413 (10) | −0.3892 (3) | 0.36703 (7) | 0.0204 (3) |

COX-2 which are the enzymes of cyclooxygenase (COX). Naproxen displays analgesic, anti-inflammatory, and antipyretic activity. In addition, the researchers reported

anticancer l activities of naproxen derivatives [5]. In cure of advancing prostate cancer, naproxen was discovered to be reliable and effective with early repetitive disease in a phase II clinical trial [6]. And naproxen and its derivatives have been shown to be effective as well as other NSAIDs to prevent urinary bladder cancer. By inducing apoptosis and cell cycle arrest toward bladder cancer cells, naproxen displayed anticancer influences. Naproxen inhibited protein kinase B (AKT) phosphorylation and induced apoptosis in rat urinary bladder cancers [7]. In order to achieve high efficiency, low toxicity and cost anti-tumor drugs, we chose naproxen as a core compound and modify its structures.

The compound contains two twist 2-(5-ethylpyridin-2-yl) ethyl 2-(6-methoxynaphthalen-2-yl)propanoate molecules in the asymmetric unit (see Figure). The title compound contained one pyridine ring and one naphthyl moiety. The C=O double bond lengths in the independent molecule are 1.207(3) Å (C11=O2) and 1.202(3) Å (C35=O5), respectively, exhibiting the double bond character. The dihedral angles of ring 1 (C3–C4–C5–C6–N1–C8) and ring 2 (C14–C15–C16–C17–C18–C19), ring 1 (C3–C4–C5–C6–N1–C8) and ring 3 (C17–C18–C23–C22–C21–C20), ring 2 (C14–C15–C16–C17–C18–C19) and ring 3 (C17–C18–C23–C22–C21–C20), ring 4 (C27–C28–C29–C30–N2–C32) and ring 5 (C38–C39–C40–C41–C42–C43), ring 4 (C27–C28–C29–C30–N2–C32) and ring 6 (C42–C41–C44–C45–C46–C47), ring 5 (C38–C39–C40–C41–C42–C43) and ring 6 (C42–C41–C44–C45–C46–C47) are 52.2°, 55.0°, 4.6°, 75.6°, 72.1°, 3.5°, respectively. The other bond distances and angles are in their normal ranges according to the previously reported compounds [8, 9].

**Author contributions:** All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

**Research funding:** None declared.

**Conflict of interest statement:** The authors declare no conflicts of interest regarding this article.

## References

1. Bruker. *SAINT and SADABS*; Bruker AXS Inc.: Madison, Wisconsin, USA, 2000.
2. Dolomanov O. V., Bourhis L. J., Gildea R. J., Howard J. A. K., Puschmann H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr* **2015**, *C71*, 3–8.
4. Huang Z., Velázquez C. A., Abdellatif K. R. A., Chowdhury M. A., Reisz J. A., DuMond J. F., King S. B., Knaus E. E. Ethanesulfohydroxamic acid ester prodrugs of nonsteroidal anti-inflammatory drugs (NSAIDs): synthesis, nitric oxide and nitroxyl release, cyclooxygenase inhibition, anti-inflammatory, and ulcerogenicity index studies. *J. Med. Chem.* **2011**, *54*, 1356–1364.
5. Han M. I., Kucukguzel S. G. Anticancer and antimicrobial activities of naproxen and naproxen derivatives. *Mini Rev. Med. Chem.* **2020**, *20*, 1300–1310.
6. Srinivas S., Feldman D. A phase II trial of calcitriol and naproxen in recurrent porstate cancer. *Anticancer Res.* 2009, *29*, 3605–3610.
7. Kim M. S., Kim J. E., Lim D. Y., Huang Z., Chen H., Langfald A., Lubet R. A., Grubbs C. J., Dong Z., Bode A. M. Naproxen induces cell cycle arrest and apoptosis in human urinary bladder cancer cell lines and chemically induced cancers by targeting P13-K. *Canc. Prev. Res.* **2014**, *7*, 236–245.
8. Wang L. L., Xue D. D. Crystal structure of 3-phenylpropyl 2-(6-methoxynaphthalen-2-yl)propanpate, $C_{23}H_{24}O_3$. *Z. Kristallogr. N. Cryst. Struct.* **2022**, *237*, 517–519.
9. Liang D., Yang X. H., Sun W., Wang W. N., Yang J. Z., Liu Y. Y., Wang G. S. Synthesis, crystal structure and biological activities of naproxen-eugenol ester progrug. *Chem. Res. Chinese Univ.* **2013**, *29*, 245–248.