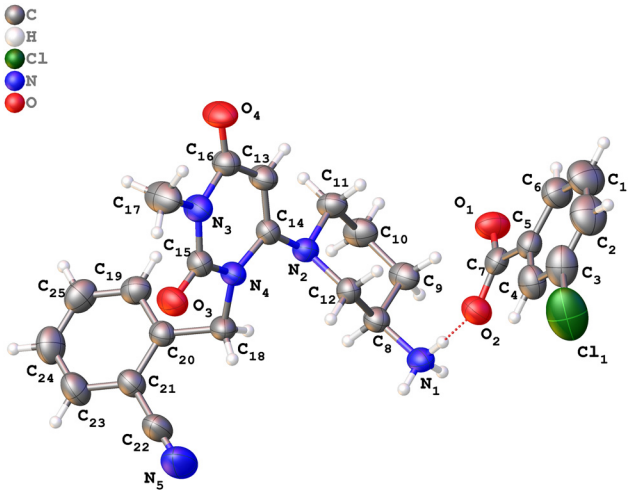
Yu-Heng Ma, Wen-Jing Ma, Kang Yang, Kai-Yue Zhang, Qiao Zhang, Qing Hu, Wu-Guang Shan and Yi-Hong Wang*

The crystal structure of alogliptinium *meta*-chlorobenzoate



https://doi.org/10.1515/ncrs-2024-0283
Received July 5, 2024; accepted September 16, 2024;
published online September 30, 2024

Abstract

$C_{18}H_{22}N_5O_2{\cdot}C_7H_4ClO_2$, orthorhombic, $P2_12_12_1$ (no. 19), a = 8.9188(2) Å, b = 10.8391(2) Å, c = 25.9295(5) Å, V = 2506.65(9) Å^3, Z = 4, $R_{gt}(F)$ = 0.0357, $wR_{ref}(F^2)$ = 0.1085, T = 293(2) K.

CCDC No.: 2239925

The asymmetric unit of the title crystal 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.

***Corresponding author: Yi-Hong Wang**, School of Chemistry and Chemical Engineering, Southeast University, Nanjing, Jiangsu, 211189, P.R. China, E-mail: yihongwang@seu.edu.cn
Yu-Heng Ma, School of Chemistry and Chemical Engineering, Southeast University, Nanjing, Jiangsu, 211189, P.R. China; and School of Materials Science and Chemical Engineering, Chuzhou University, Chuzhou, Anhui, 239000, P.R. China
Wen-Jing Ma, Kang Yang, Kai-Yue Zhang, Qiao Zhang, Qing Hu and Wu-Guang Shan, School of Materials Science and Chemical Engineering, Chuzhou University, Chuzhou, Anhui, 239000, P.R. China. https://orcid.org/0000-0002-8704-4190 (W.-J. Ma)

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.40 × 0.37 × 0.34 mm
Wavelength:	Cu *K*α radiation (1.54184 Å)
μ:	1.69 mm^{-1}
Diffractometer, scan mode:	XtaLAB Synergy, ω
θ_{max}, completeness:	66.6°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	9419, 4279, 0.030
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 3,898
$N(param)_{refined}$:	345
Programs:	Olex2,[1] SHELX[2,3]

1 Source of material

All chemicals were purchased from commercial sources and used as received. The alogliptin (33.9 mg, 0.1 mol) and ^{m}chlorobenzoic acid (15.6 mg, 0.1 mol) were dissolved in MeOH (10 mL). The mixture was refluxed for 0.5 h and then filtered and placed in a sample vial, covered with membrane and punctured. The filtrate was slowly evaporated at room temperature to obtain crystals of the title compound.

2 Experimental details

X-ray intensity data of the crystal of dimensions 0.40 × 0.37 × 0.34 mm were collected on Rigaku HyPix detector diffractometer. Using Olex2,[1] the structure was solved with the XT[2] structure solution program and refined with the ShelXL[3] refinement package. All H atoms were positioned geometrically and treated as riding on their parent atoms, with the d(C–H) = 0.93 Å and d(N–H) = 0.89 Å, U_{iso}(H) = 1.2 times U_{iso}(C) and U_{iso}(H) = 1.5 times U_{iso}(O).

3 Comment

Alogliptin is a novel dipeptide peptidase-4 inhibitor approved for the treatment of type 2 diabetic mellitus.[4] Because of its low water solubility, alogliptin was commercialized orally in its benzoate salt form (Nesina), which was developed by Takeda Pharmaceutical Co., LTD. and has been approved for

Open Access. © 2024 the author(s), published by De Gruyter. This work is licensed under the Creative Commons Attribution 4.0 International License.

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.4242 (5)	0.3274 (4)	0.61808 (18)	0.0819 (12)
H1	0.356699	0.331259	0.645366	0.092 (15)*
C2	0.4866 (6)	0.2165 (5)	0.60452 (18)	0.0834 (13)
H2	0.461870	0.144956	0.622404	0.107 (17)*
C3	0.5853 (5)	0.2126 (4)	0.56450 (16)	0.0734 (11)
C4	0.6237 (5)	0.3166 (3)	0.53667 (13)	0.0596 (8)
H4	0.691428	0.311803	0.509462	0.064 (11)*
C5	0.5591 (3)	0.4282 (3)	0.55022 (12)	0.0480 (7)
C6	0.4610 (4)	0.4332 (4)	0.59151 (14)	0.0623 (9)
H6	0.419743	0.508365	0.601383	0.061 (10)*
C7	0.5989 (3)	0.5440 (3)	0.52018 (11)	0.0457 (7)
C8	0.6868 (3)	0.7879 (3)	0.40523 (11)	0.0438 (6)
H8	0.722457	0.833441	0.374962	0.045 (8)*
C9	0.6339 (3)	0.8781 (3)	0.44572 (12)	0.0507 (7)
H9A	0.713274	0.936255	0.453619	0.073 (12)*
H9B	0.608320	0.834164	0.477108	0.053 (9)*
C10	0.4980 (4)	0.9464 (3)	0.42574 (15)	0.0571 (8)
H10A	0.527196	0.997257	0.396661	0.069 (11)*
H10B	0.460027	1.000352	0.452563	0.077 (12)*
C11	0.3747 (3)	0.8585 (3)	0.40907 (12)	0.0486 (7)
H11A	0.340059	0.811016	0.438441	0.059 (10)*
H11B	0.290492	0.904859	0.395451	0.055 (10)*
C12	0.5605 (3)	0.7018 (3)	0.38933 (11)	0.0406 (6)
H12A	0.595794	0.645176	0.363022	0.050 (9)*
H12B	0.527746	0.653794	0.418827	0.040 (8)*
C13	0.1842 (3)	0.6917 (3)	0.35628 (12)	0.0478 (7)
H13	0.148083	0.733416	0.385056	0.062 (10)*
C14	0.3290 (3)	0.7069 (3)	0.34216 (10)	0.0400 (6)
C15	0.2948 (3)	0.5670 (3)	0.27001 (11)	0.0459 (7)
C16	0.0863 (3)	0.6137 (3)	0.32818 (12)	0.0483 (7)
C17	0.0600 (5)	0.4575 (4)	0.25911 (17)	0.0749 (12)
H17A	0.001306	0.410487	0.283138	0.13 (2)*
H17B	0.125139	0.403179	0.240340	0.111 (18)*
H17C	−0.005501	0.499233	0.235456	0.18 (3)*
C18	0.5177 (3)	0.6949 (3)	0.27054 (11)	0.0472 (7)
H18A	0.585385	0.625800	0.265709	0.057 (10)*
H18B	0.567829	0.755230	0.292111	0.060 (10)*
C19	0.3731 (4)	0.8412 (3)	0.21402 (14)	0.0523 (7)
H19	0.317810	0.864387	0.242845	0.057 (10)*
C20	0.4830 (3)	0.7520 (3)	0.21886 (11)	0.0421 (6)
C21	0.5651 (4)	0.7196 (3)	0.17514 (12)	0.0499 (7)
C22	0.6770 (4)	0.6253 (4)	0.17892 (13)	0.0620 (9)
C23	0.5358 (5)	0.7757 (4)	0.12763 (13)	0.0633 (9)
H23	0.590925	0.753546	0.098627	0.083 (13)*
C24	0.4254 (5)	0.8637 (3)	0.12391 (15)	0.0653 (9)
H24	0.405663	0.901208	0.092371	0.078 (12)*
C25	0.3439 (4)	0.8963 (3)	0.16700 (15)	0.0604 (9)
H25	0.269062	0.955735	0.164427	0.077 (12)*
Cl1	0.6700 (2)	0.07193 (10)	0.54875 (5)	0.1116 (5)
N1	0.8120 (3)	0.7110 (3)	0.42644 (9)	0.0462 (6)
H1A	0.855664	0.669541	0.400878	0.053 (9)*
H1B	0.775610	0.657951	0.449457	0.078 (13)*
H1C	0.879245	0.759691	0.441569	0.085 (14)*
N2	0.4340 (3)	0.7750 (2)	0.36911 (9)	0.0415 (5)
N3	0.1499 (3)	0.5485 (3)	0.28718 (10)	0.0512 (6)
N4	0.3806 (2)	0.6516 (2)	0.29682 (9)	0.0428 (5)
N5	0.7643 (5)	0.5491 (4)	0.18345 (15)	0.0922 (12)
O1	0.5343 (3)	0.6422 (2)	0.53142 (10)	0.0608 (6)
O2	0.6970 (3)	0.5325 (2)	0.48583 (8)	0.0557 (6)
O3	0.3449 (3)	0.5131 (2)	0.23236 (9)	0.0588 (6)
O4	−0.0470 (2)	0.5948 (3)	0.33937 (10)	0.0645 (7)

marketing in the United States in January 2013.[5,6] Salt formation is one of the most common used methods to improve the solubility and dissolution rates of insoluble drugs.[7]

The asymmetric unit of the title structure contains one alogliptin cation and one ^{m}chlorobenzoic acid anion (see the figure). Bond lengths and angles are all in the expected ranges. The title molecule has an approximately ladder-like structure.[8] It indicates that three types of hydrogen bonds play an important role in maintaining the crystal structure, including, N1–H1A···O4 (1 + *X*, +Y, +*Z*) [length 2.875(3) Å, angle 173.5°], N1–H1B···O2 [length 2.677(3) Å, angle 169.4°], N1–H1C···O1 (1/2 + *X*, 3/2 – Y, 1 – *Z*) [length 2.768(3) Å, angle 174.5°].[9] The carboxylate group forms two hydrogen bonds by interacting with an aminium group of alogliptinium in the unit cell and in an expanded unit cell. Another hydrogen bond comes from the additionally interacting between carbonyl group of alogliptin and an aminium group of another alogliptinium in an expanded unit cell. There are no specific interactions formed by the Cl atoms.

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

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

Research funding: New engineering research and reform practice project (2021xgk10); Chuzhou University college students innovation and entrepreneurship training program (No. 2024CXXL021); Anhui University Natural Science Foundation (No. KJ2021B16).

References

1. 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.
2. Sheldrick, G. M. Crystal Structure Refinement with *SHELXL*. *Acta Crystallogr.* **2015**, *C71*, 3–8.
3. Sheldrick, G. M. A Short History of *SHELX*. *Acta Crystallogr.* **2008**, *A64*, 112–122.

4. Feng, J.; Zhang, Z.; Wallace, M. B.; Stafford, J. A.; Kaldor, S. W.; Kassel, D. B.; Navre, M.; Shi, L.; Skene, R. J.; Asakawa, T.; Takeuchi, K.; Xu, R.; Webb, D. R.; Gwaltney, S. L. Discovery of Alogliptin: A Potent, Selective, Bioavailable, and Efficacious Inhibitor of Dipeptidyl Peptidase IV. *J. Med. Chem.* **2007**, *50*, 2297–2300.
5. Gelbrich, T.; Kahlenberg, V.; Griesser, U. J. Alogliptin and Its Benzoate Salt. *J. Acta Crystallogr.* **2013**, *69*, 674–678.
6. Scott, L. J. Alogliptin: A Review of Its Use in the Management of Type 2 Diabetes Mellitus. *Drugs* **2010**, *70*, 2051–2072.
7. Serajudidin, A. T. M. Salt Formation to Improve Drug Delivery. *Adv. Drug Deliv. Rev.* **2007**, *59*, 613–616.
8. James, T. P. M.; Sebusi, O.; Ofentse, M.; Lebogang, G. J.; Thuto, M.; Florence, N. Synthesis and Crystal Structure of Pyridin-4-Ylmethyl 4-Aminobenzoate, $C_{13}H_{12}N_2O_2$. *Crystallogr. Rep*. **2022**, *67*, 1203–1206.
9. Murthy Bandaru, S. S.; Bhilare, S.; Chrysochos, N.; Gayakhe, V.; Trentin, I.; Schulzke, C.; Kapdi, A. R. Pd/PTABS: Catalyst for Room Temperature Amination of Heteroarenes. *Org. Lett.* **2018**, *20*, 473–476.