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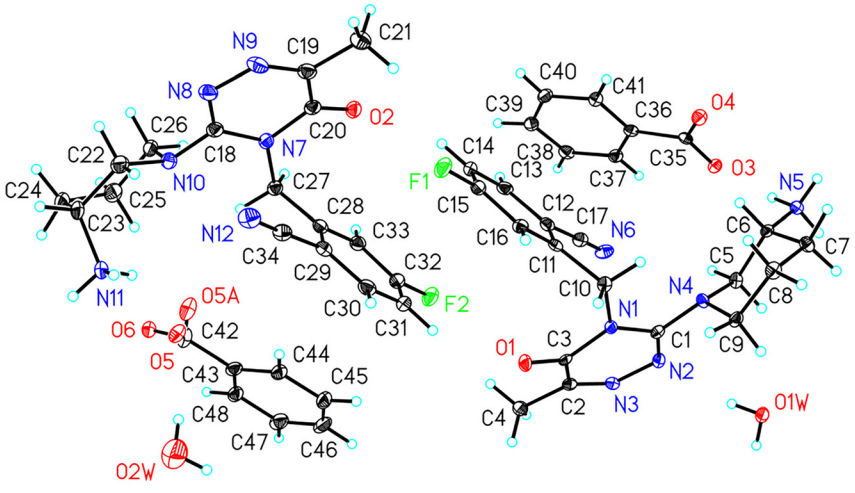
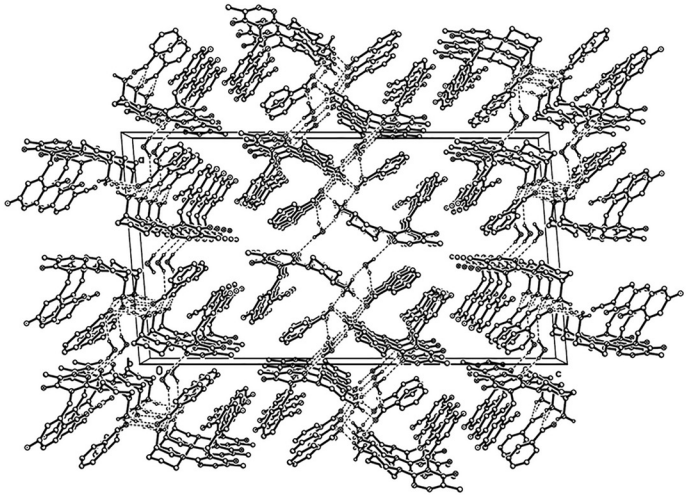
Crystal structure of (*R*)-2-((3-(3-aminopiperidin-1-yl)-6-methyl-5-oxo-1,2,4-triazin-4(5*H*)-yl) methyl)-4-fluorobenzonitrile benzoate monohydrate, $C_{24}H_{27}FN_6O_4$





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Abstract

$C_{24}H_{27}FN_6O_4$, monoclinic, $C2$ (no. 5), a = 19.7270(4) Å, b = 6.4057(2) Å, c = 36.3058(8) Å, β = 94.602(2)°, V = 4573.0(2) Å^3, Z = 8, $R_{gt}(F)$ = 0.0625, $wR_{ref}(F^2)$ = 0.1565, T = 100 K.

CCDC no.: 2375470

A part of 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.

Table 1: Data collection and handling.

Crystal:	Colourless prism
Size:	0.15 × 0.05 × 0.04 mm
Wavelength:	Cu *K*α radiation (1.54178 Å)
μ:	0.86 mm^{-1}
Diffractometer, scan mode:	SuperNova, ω
θ_{max}, completeness:	65.0°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	20198, 7780, 0.097
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 6,155
$N(param)_{refined}$:	644
Programs:	SHELX[1,2]

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
F1	0.79470 (17)	0.2212 (7)	0.74527 (10)	0.0353 (9)
O1	0.56100 (19)	0.6276 (7)	0.71070 (10)	0.0235 (9)
N1	0.5764 (2)	0.6425 (8)	0.64925 (12)	0.0174 (9)
N2	0.5285 (2)	0.9239 (8)	0.61357 (12)	0.0204 (10)
N3	0.5184 (2)	1.0313 (8)	0.64570 (13)	0.0209 (10)
N4	0.5785 (2)	0.6434 (8)	0.58474 (12)	0.0182 (9)
N5	0.6666 (2)	0.7837 (8)	0.50136 (12)	0.0187 (9)
H5A	0.6923	0.8896	0.5117	0.022*
H5B	0.6303	0.8375	0.4875	0.022*
H5C	0.6922	0.7061	0.4867	0.022*
N6	0.6855 (2)	0.9966 (9)	0.63322 (15)	0.0278 (11)
C1	0.5587 (2)	0.7429 (8)	0.61588 (15)	0.0168 (11)
C2	0.5296 (3)	0.9392 (9)	0.67750 (15)	0.0202 (11)
C3	0.5547 (2)	0.7259 (10)	0.68174 (14)	0.0187 (11)
C4	0.5191 (3)	1.0581 (10)	0.71241 (16)	0.0250 (12)
H4A	0.5121	1.2063	0.7065	0.037*
H4B	0.5593	1.0423	0.7299	0.037*
H4C	0.4791	1.0031	0.7235	0.037*
C5	0.5969 (3)	0.7770 (8)	0.55431 (14)	0.0186 (11)
H5D	0.6215	0.9026	0.5641	0.022*
H5E	0.5556	0.8225	0.5392	0.022*
C6	0.6422 (3)	0.6487 (9)	0.53112 (14)	0.0194 (11)
H6	0.6827	0.6018	0.5474	0.023*
C7	0.6058 (3)	0.4578 (9)	0.51555 (15)	0.0221 (12)
H7A	0.6369	0.3737	0.5014	0.026*
H7B	0.5665	0.5002	0.4985	0.026*
C8	0.5810 (3)	0.3271 (9)	0.54709 (16)	0.0229 (12)
H8A	0.5525	0.2111	0.5366	0.028*
H8B	0.6208	0.2654	0.5615	0.028*
C9	0.5401 (3)	0.4553 (9)	0.57274 (15)	0.0208 (12)
H9A	0.4961	0.4959	0.5597	0.025*
H9B	0.5307	0.3706	0.5946	0.025*
C10	0.6225 (3)	0.4613 (9)	0.65253 (15)	0.0191 (11)
H10A	0.6359	0.4232	0.6277	0.023*
H10B	0.5981	0.3409	0.6623	0.023*
C11	0.6861 (3)	0.5060 (10)	0.67793 (15)	0.0199 (11)
C12	0.7231 (3)	0.6900 (9)	0.67631 (15)	0.0211 (12)
C13	0.7829 (3)	0.7186 (10)	0.69921 (16)	0.0255 (13)
H13	0.8066	0.8474	0.6987	0.031*
C14	0.8077 (3)	0.5613 (10)	0.72258 (16)	0.0265 (14)
H14	0.8487	0.5785	0.7379	0.032*
C15	0.7711 (3)	0.3799 (11)	0.72299 (16)	0.0255 (13)
C16	0.7111 (3)	0.3477 (9)	0.70156 (15)	0.0205 (12)
H16	0.6872	0.2196	0.7029	0.025*
C17	0.7023 (3)	0.8581 (9)	0.65194 (16)	0.0225 (12)
F2	0.68405 (18)	0.9308 (7)	0.76107 (10)	0.0382 (9)
O2	0.9152 (2)	0.5351 (7)	0.79227 (11)	0.0283 (10)
N7	0.8999 (2)	0.4828 (8)	0.85317 (13)	0.0233 (10)
N8	0.9496 (2)	0.1857 (9)	0.88328 (15)	0.0314 (12)
N9	0.9585 (3)	0.0978 (9)	0.84931 (16)	0.0332 (13)
N10	0.9030 (2)	0.4457 (9)	0.91788 (14)	0.0269 (11)
N11	0.7908 (2)	0.3944 (9)	0.97124 (13)	0.0270 (11)
H11A	0.7708	0.4255	0.9923	0.032*
H11B	0.7736	0.2721	0.9618	0.032*
H11C	0.7822	0.4984	0.9544	0.032*
N12	0.7893 (3)	0.1421 (9)	0.87114 (17)	0.0350 (13)
C18	0.9197 (3)	0.3667 (10)	0.88432 (17)	0.0259 (13)
C19	0.9466 (3)	0.2060 (11)	0.81929 (17)	0.0288 (13)
C20	0.9210 (3)	0.4204 (10)	0.81928 (16)	0.0237 (12)
C21	0.9579 (3)	0.1079 (11)	0.78277 (19)	0.0322 (14)
H21A	0.9973	0.1729	0.7726	0.048*
H21B	0.9175	0.1287	0.7656	0.048*
H21C	0.9662	−0.0419	0.7862	0.048*
C22	0.9005 (3)	0.2874 (12)	0.94707 (18)	0.0331 (14)
H22A	0.9473	0.2422	0.9552	0.040*
H22B	0.8750	0.1639	0.9371	0.040*
C23	0.8663 (3)	0.3731 (12)	0.97984 (16)	0.0319 (15)
H23	0.8739	0.2703	1.0005	0.038*
C24	0.8973 (3)	0.5792 (13)	0.99318 (18)	0.0381 (17)
H24A	0.9427	0.5523	1.0060	0.046*
H24B	0.8684	0.6415	1.0114	0.046*
C25	0.9048 (3)	0.7360 (12)	0.96192 (19)	0.0366 (16)
H25A	0.8593	0.7862	0.9524	0.044*
H25B	0.9315	0.8578	0.9716	0.044*
C26	0.9401 (3)	0.6368 (12)	0.93080 (17)	0.0311 (14)
H26A	0.9415	0.7368	0.9101	0.037*
H26B	0.9875	0.6006	0.9396	0.037*
C27	0.8534 (3)	0.6642 (10)	0.85332 (16)	0.0231 (12)
H27A	0.8774	0.7904	0.8455	0.028*
H27B	0.8404	0.6878	0.8788	0.028*
C28	0.7902 (3)	0.6312 (10)	0.82787 (16)	0.0234 (12)
C29	0.7512 (3)	0.4517 (10)	0.82854 (16)	0.0243 (12)
C30	0.6911 (3)	0.4291 (11)	0.80562 (17)	0.0282 (13)
H30	0.6660	0.3025	0.8057	0.034*
C31	0.6684 (3)	0.5917 (11)	0.78286 (17)	0.0306 (15)
H31	0.6272	0.5803	0.7675	0.037*
C32	0.7067 (3)	0.7688 (11)	0.78297 (17)	0.0284 (14)
C33	0.7672 (3)	0.7938 (10)	0.80455 (16)	0.0250 (12)
H33	0.7927	0.9192	0.8035	0.030*
C34	0.7724 (3)	0.2812 (10)	0.85291 (17)	0.0267 (13)
O5A[a]	0.7356 (8)	0.697 (2)	0.9246 (4)	0.037 (3)
O5[a]	0.7092 (6)	0.689 (3)	0.9343 (4)	0.031 (3)
O6	0.7394 (2)	0.9971 (7)	0.95724 (11)	0.0270 (9)
C42	0.7115 (3)	0.8809 (11)	0.93235 (17)	0.0324 (15)
C43	0.6614 (3)	0.9792 (11)	0.90366 (17)	0.0276 (13)
C44	0.6378 (3)	0.8635 (12)	0.87290 (17)	0.0307 (15)

Table 2: (continued)

Atom	x	y	z	U_{iso}*/U_{eq}
H44	0.6532	0.7243	0.8701	0.037*
C45	0.5918 (3)	0.9495 (13)	0.84621 (18)	0.0385 (18)
H45	0.5771	0.8709	0.8249	0.046*
C46	0.5676 (3)	1.1466 (13)	0.8506 (2)	0.0409 (18)
H46	0.5352	1.2039	0.8326	0.049*
C47	0.5902 (3)	1.2619 (13)	0.8809 (2)	0.0383 (17)
H47	0.5733	1.3993	0.8839	0.046*
C48	0.6374 (3)	1.1799 (12)	0.90740 (18)	0.0321 (15)
H48	0.6533	1.2619	0.9281	0.039*
O3	0.75915 (18)	1.0244 (6)	0.54135 (10)	0.0210 (8)
O4	0.80815 (19)	0.7205 (7)	0.55702 (11)	0.0255 (9)
C35	0.7981 (3)	0.9073 (9)	0.56232 (14)	0.0177 (11)
C36	0.8332 (3)	1.0138 (9)	0.59578 (15)	0.0181 (11)
C37	0.8180 (3)	1.2164 (10)	0.60424 (16)	0.0243 (12)
H37	0.7881	1.2950	0.5878	0.029*
C38	0.8462 (3)	1.3079 (10)	0.63690 (17)	0.0260 (13)
H38	0.8360	1.4490	0.6424	0.031*
C39	0.8888 (3)	1.1930 (11)	0.66130 (16)	0.0269 (13)
H39	0.9058	1.2521	0.6842	0.032*
C40	0.9066 (3)	0.9917 (11)	0.65223 (16)	0.0269 (13)
H40	0.9381	0.9153	0.6682	0.032*
C41	0.8782 (3)	0.9008 (9)	0.61963 (15)	0.0203 (11)
H41	0.8895	0.7614	0.6137	0.024*
O1W	0.42813 (19)	1.0158 (7)	0.54708 (11)	0.0254 (9)
H1C	0.4521	0.9960	0.5673	0.038*
H1D	0.3931	1.0801	0.5533	0.038*
O2W	0.5643 (4)	0.5946 (14)	0.9474 (2)	0.084 (2)
H2C	0.6042	0.6243	0.9418	0.125*
H2D	0.5363	0.6221	0.9290	0.125*

[a]Occupancy: 0.5.

1 Source of materials

The title compound was added to isopropyl acetate, stirred for half an hour to form a saturated solution, then filtered and allowed to evaporate at room temperature to yield colorless prism crystals. The NMR spectra were acquired on a Bruker Avance III HD 400 MHz spectrometer. X-ray powder diffraction (XRD) intensities were measured at 293 K on a empyrean/Bragg-BrentanoHD diffractometer (CuKα, λ = 1.54056 Å). **^{1}H NMR** (400 MHz, DMSO, ppm): δ 7.96 (m, 1H), 7.36 (br, 1H), 7.29 (d, 1H), 5.23 (s, 2H), 3.15 (m, 3H), 2.72 (m, 2H), 2.23 (s, 3H), 1.78 (d, 1H), 1.64 (d, 1H), 1.47 (m, 1H), 1.12 (m, 1H). PXRD: θ = 8.87, 9.74, 12.58, 14.54, 18.87, 19.51, 20.13, 20.77, 22.13, 23.35, 24.08, 25.36, 26.74, 27.83, 29.53, 30.38, 31.75, 33.25°.

2 Experimental details

The diffraction data obtained were processed using the SHELXT software[1] to solve the crystal structure. This structure was further refined using full-matrix least-squares procedures in SHELXL.[2] Anisotropic refinement was applied to non-hydrogen atoms, while hydrogen atoms were refined isotropically.

3 Comment

Diabetes is a chronic disease where prolonged hyperglycemia can cause damage to various organs of the body, leading to various complications. Therefore, controlling blood glucose levels is the primary goal of diabetes treatment.[3] The title compound belongs to the class of DPP-IV inhibitors, used for the treatment of type II diabetes. Inhibition of DPP-IV in the body can increase the levels of endogenous GLP 1(7–36) and reduce the production of its antagonist GLP 1(9–36). Thus, DPP-IV inhibitors may be effective against diseases associated with DPP-IV activity, such as type II diabetes, diabetic dyslipidemia, impaired glucose tolerance (IGT), impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation, and obesity.[4–6] DPP-IV inhibitors are currently considered a new approach for the treatment of type 2 diabetes.[7,8]

The X-ray structural analysis of the compound reveals that the asymmetric unit contains two ((3-(3-aminopiperidin-1-yl)-6-methyl-5-oxo-1,2,4-triazin-4(5*H*)-yl)methyl)-4-fluorobenzonitrile cations and two benzoic acid anions and two water molecules. This cation can be seen as an aminopiperidinyl group and a 4-fluoro-2-methylbenzonitrile group (with a dihedral angle of approximately 86.6°) connected to the adjacent positions of an oxo-1,2,4-triazinyl group. The pKa value of benzoic acid is 3.9, and another component's pKa value is 8.6, indicating that both are prone to forming salt compound. In the infrared spectrum, the stretching vibrations at 3,056 cm^{-1} and 2,624 cm^{-1}, as well as the deformation vibration at 1,592 cm^{-1}, can be attributed to the $-NH_3^+$ groups. As shown in figure (below), along the crystallographic *b* direction, the two main components of the compound form one-dimensional ribbon-like supramolecule chains relying on the abundant hydrogen bonds between their amino groups and carboxyl groups (N···O = 2.719–2.789 Å). Hydrogen bonds between the carboxyl/triazinyl groups and the surrounding guest water molecules (O···O = 2.755–2.996 Å and O···N = 2.876–3.169 Å) play a role in stabilizing the parallel packing of these one-dimensional chains.

Author contributions: 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.

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