X-ray powder diffraction data for 5, 6-dihydro-3-(4-morpholinyl)-1-[4-(2-oxo-1-piperidinyl)phenyl]-2(1H)-pyridinone, $C_{20}H_{25}N_3O_3$

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X-ray powder diffraction data for 5,6-dihydro-3-(4-morpholinyl)-1-[4-(2-oxo-1-piperidinyl)phenyl]-2(1H)-pyridinone, $C_{20}H_{25}N_3O_3$, are reported [$a = 5.989(2)$, $b = 6.669(3)$, $c = 24.605(5)$Å, $\alpha = 84.466(7)°$, $\beta = 89.859(6)°$, $\gamma = 69.074(4)°$, unit-cell volume $V = 913.11$ Å^3, $Z = 2$, and space group $P-1$]. No detectable impurities were observed. © *2016 International Centre for Diffraction Data*.
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Key words: pharmaceutical intermediate, anticoagulant, apixaban, single crystal

I. INTRODUCTION

Apixaban (Eliquis®) is a novel oral pyrazole-based direct FXa inhibitor; this drug was developed by Bristol-Myers Squibb and Pfizer to treat and prevent thrombotic disorder (Watson *et al*., 2011). Since May 2011, Apixaban has been approved for VTE prevention in adult elective hip or knee replacement patients in various countries, such as the USA, China, Brazil, Australia, New Zealand, and some European countries (Deeks, 2012). The title compound is an intermediate in the synthesis of the anticoagulant, Apixaban (Jiang and Ji, 2013). Presently, the crystal structure of the title compound has not been reported.

II. EXPERIMENTAL

A. Sample preparation

The sample (Figure 1) was prepared using 5-chloro-N-[4-(5,6-dihydro-3-(4-morpholinyl)-2-oxo-1(2H)-pyridinyl)phenyl]-pentanamide (CAS: 1643330-62-4) (Wang *et al*., 2015). The melting point and measured density of the title compound are 203–205 °C and 1.274 g cm^{-3}, respectively. Crystallization of the title compound at room temperature was successful using methanol as solvent. Then, parts of crystals were dried and ground into powder and mounted on a flat zero background plate.

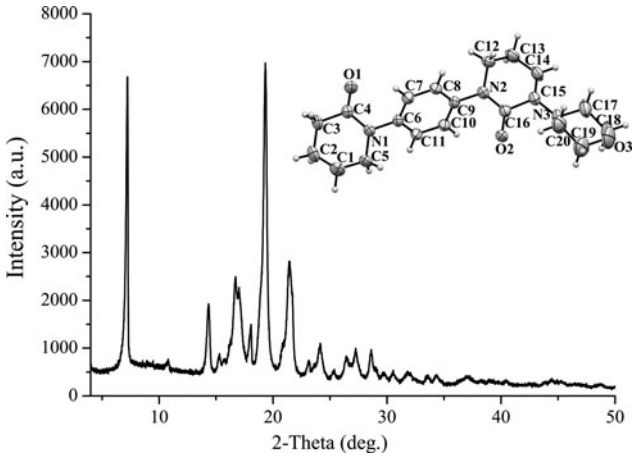

Figure 2. X-ray powder diffraction pattern of title compound using Cu$K\alpha$ radiation. The inset is the ORTEP drawing of molecular structure of title compound with the labeling of non-H atoms.

B. Diffraction data collection and reduction

X-ray powder diffraction measurement was performed at room temperature using an X'Pert PRO diffractometer (PANalytical Co., Ltd., Netherlands) with a PIXcel one-dimensional (1D) detector and Cu$K\alpha$ radiation (generator setting: 40 kV and 40 mA). The sample was mounted on a flat

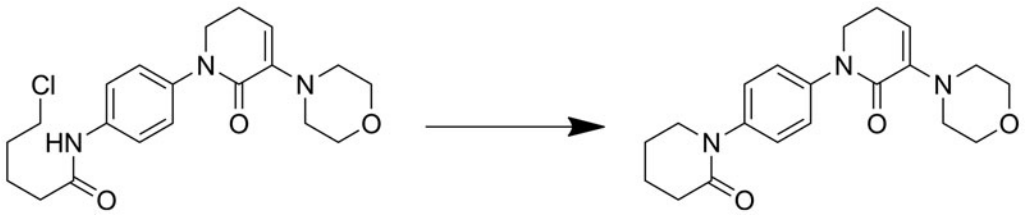

Figure 1. Synthesis of the title compound.

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TABLE I. X-ray powder diffraction data for 5,6-dihydro-3-(4-morpholinyl)-1-[4-(2-oxo-1-piperidinyl)phenyl]-2(1H)-pyridinone, $C_{20}H_{25}N_3O_3$. The *d*-values were calculated using Cu$K\alpha_1$ radiation ($\lambda = 1.54056$ Å).

$2\theta_{obs}$ (°)	d_{obs} (Å)	I_{obs}	*h*	*k*	*l*	$2\theta_{cal}$ (°)	d_{cal} (Å)	$\Delta 2\theta$
7.2235	12.2276	96	0	0	2	7.2173	12.2380	0.0061
10.8474	8.1493	10	0	0	3	10.8350	8.1587	0.0124
14.2876	6.1940	25	0	1	0	14.2816	6.1965	0.0060
14.3532	6.1658	28	0	1	1	14.3695	6.1588	−0.0163
15.3117	5.7819	13	0	1	2	15.3398	5.7714	−0.0281
15.8369	5.5913	11	1	0	0	15.8390	5.5906	−0.0021
16.1258	5.4918	15	1	0	−1	16.1270	5.4914	−0.0011
16.3753	5.4087	18	1	0	1	16.3714	5.4099	0.0039
16.6773	5.3114	35	0	1	−2	16.6707	5.3135	0.0066
17.0449	5.1977	31	0	1	3	17.0458	5.1974	−0.0009
17.3075	5.1194	19	1	1	1	17.3082	5.1192	−0.0007
17.7014	5.0063	12	1	1	−1	17.6909	5.0093	0.0106
18.0822	4.9018	21	0	0	5	18.1067	4.8952	−0.0245
18.8569	4.7021	30	0	1	−3	18.8328	4.7081	0.0241
19.3296	4.5882	100	0	1	4	19.2991	4.5954	0.0305
19.5397	4.5393	37	1	0	3	19.5390	4.5395	0.0007
19.8023	4.4797	13	1	1	3	19.8002	4.4802	0.0021
20.8133	4.2643	16	1	1	−3	20.7952	4.2680	0.0181
21.1416	4.1988	20	1	0	−4	21.1360	4.1999	0.0056
21.4173	4.1454	40	0	1	−4	21.4092	4.1470	0.0082
21.7718	4.0787	21	0	0	6	21.7684	4.0793	0.0034
23.0717	3.8518	10	1	1	−4	23.0761	3.8510	−0.0043
23.7151	3.7487	9	1	0	−5	23.7236	3.7474	−0.0085
24.2797	3.6628	12	0	1	−5	24.2769	3.6632	0.0028
25.4483	3.4972	7	1	−1	−2	25.4404	3.4983	0.0079
26.4462	3.3674	12	1	−1	−3	26.4496	3.3670	−0.0034
26.5775	3.3511	11	1	−1	2	26.5890	3.3497	−0.0114
27.0896	3.2889	11	1	1	6	27.0752	3.2906	0.0144
27.3653	3.2564	12	1	2	1	27.3556	3.2575	0.0097
27.7592	3.2111	6	1	2	2	27.7689	3.2100	−0.0096
27.9299	3.1918	6	1	−1	−4	27.9131	3.1937	0.0169
28.5471	3.1242	13	1	1	−6	28.5548	3.1234	−0.0077
28.6652	3.1116	13	0	2	1	28.6457	3.1137	0.0196
29.0460	3.0717	9	1	2	−2	29.0243	3.0739	0.0217
29.6237	3.0131	7	1	0	−7	29.6399	3.0115	−0.0161
29.9651	2.9795	6	2	1	0	29.9617	2.9799	0.0035
30.4772	2.9306	7M	0	2	−2	30.4522	2.9330	0.0250
30.4772	2.9306	M	1	2	−3	30.4689	2.9314	0.0083
30.7661	2.9038	5	2	1	2	30.7675	2.9036	−0.0014
30.9499	2.8869	5	2	1	−2	30.9494	2.8870	0.0005
31.2388	2.8609	5	0	1	8	31.2258	2.8620	0.0129
31.6064	2.8284	7	1	1	−7	31.6132	2.8278	−0.0068
31.9084	2.8024	7	0	2	−3	31.9028	2.8028	0.0056
31.9872	2.7956	7	2	0	0	31.9912	2.7953	−0.0040
32.3286	2.7669	5	2	0	1	32.3329	2.7665	−0.0043
32.5518	2.7484	5	0	2	5	32.5556	2.7481	−0.0038
32.8669	2.7228	5	1	0	−8	32.8561	2.7237	0.0108
33.5103	2.6720	6	2	0	−3	33.5002	2.6727	0.0101
33.5891	2.6659	6	2	1	−4	33.5879	2.6660	0.0012
34.2456	2.6163	6	2	0	3	34.2367	2.6169	0.0089
34.4163	2.6037	6	1	2	−5	34.4114	2.6040	0.0049
34.5870	2.5912	5	0	1	9	34.6079	2.5897	−0.0209
34.6920	2.5836	5	1	−1	6	34.7083	2.5824	−0.0162
35.0334	2.5592	4	2	1	5	35.0277	2.5596	0.0057
35.4273	2.5316	4	2	1	−5	35.4321	2.5313	−0.0047
35.8212	2.5047	4	0	2	−5	35.8211	2.5047	0.0002
36.2151	2.4784	5	1	0	−9	36.2002	2.4794	0.0150
36.4646	2.4620	5	1	1	9	36.4588	2.4624	0.0059
36.8191	2.4391	5	1	2	−6	36.8119	2.4395	0.0072
36.9898	2.4282	6	2	2	−3	36.9722	2.4293	0.0176
37.1080	2.4208	6	2	1	6	37.1087	2.4207	−0.0007
37.4231	2.4011	5	1	−1	7	37.4284	2.4008	−0.0053
38.2110	2.3534	5	0	2	−6	38.1999	2.3540	0.0110
39.1957	2.2965	5	0	2	8	39.1746	2.2977	0.0211
40.3512	2.2334	5	1	−1	8	40.3412	2.2339	0.0100

Continued

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TABLE I. Continued

$2\theta_{obs}$ (°)	d_{obs} (Å)	I_{obs}	h	k	l	$2\theta_{cal}$ (°)	d_{cal} (Å)	$\Delta 2\theta$
40.5219	2.2243	4	0	0	11	40.5076	2.2251	0.0143
40.9814	2.2004	3	0	1	−10	40.9745	2.2008	0.0070
41.3622	2.1811	4	1	2	9	41.3622	2.1811	0.0000
41.8874	2.1549	3	0	2	9	41.8622	2.1562	0.0252
42.2945	2.1351	4	2	2	7	42.2876	2.1355	0.0068
42.5833	2.1213	4	2	1	−8	42.5803	2.1215	0.0031
43.0298	2.1003	4	2	0	−8	43.0374	2.1000	−0.0076
43.6731	2.0709	4	0	3	2	43.6527	2.0718	0.0205
43.8045	2.0650	4	0	3	0	43.7922	2.0655	0.0123
44.3822	2.0394	5	0	0	12	44.3764	2.0397	0.0058
45.2094	2.0040	5	1	1	−11	45.1729	2.0055	0.0365
45.4851	1.9925	4	3	1	0	45.4855	1.9925	−0.0004
46.8507	1.9375	3	1	0	−12	46.8463	1.9377	0.0044
47.4021	1.9163	3	3	2	2	47.3922	1.9167	0.0099
48.7152	1.8677	4	3	2	−3	48.6989	1.8682	0.0162
49.4767	1.8407	3	2	3	−5	49.4718	1.8409	0.0050
49.8181	1.8289	2	2	3	7	49.7898	1.8298	0.0283

TABLE II. Crystal and experimental data of title compound.

Empirical formula	$C_{20}H_{25}N_3O_3$
Formula weight	355.43
Temperature (K)	293.15
Crystal system	Triclinic
Space group	$P-1$
a (Å)	6.0164(5)
b (Å)	6.6483(8)
c (Å)	24.700(3)
α (°)	83.957(10)
β (°)	89.451(9)
γ (°)	69.222(10)
Volume (Å^3)	918.17(18)
Z	2
ρ_{calc} (g cm^{-3})	1.286
μ (mm^{-1})	0.088
$F(000)$	380.0
Crystal size (mm^3)	0.3 × 0.2 × 0.2
Radiation	Mo$K\alpha$ (λ = 0.710 73)
2θ range for data collection (°)	6.6–52.74
Index ranges	$-7 \le h \le 7$, $-5 \le k \le 8$, $-22 \le l \le 30$
Reflections collected	6996
Independent reflections	3732 [R_{int} = 0.0343, R_{sigma} = 0.0723]
Data/restraints/parameters	3732/0/235
Goodness-of-fit on F^2	1.078
Final R indexes [$I \geqq 2\sigma(I)$]	R_1 = 0.0947, wR_2 = 0.1745
Final R indexes (all data)	R_1 = 0.1462, wR_2 = 0.2002
Largest diff. peak/hole (e Å^{-3})	0.26/−0.24

TABLE III. Fractional atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3).

Atom	X	y	z	U(eq)
O1	1476(5)	9078(5)	4211.2(13)	56.6(9)
O2	10 302(5)	5503(5)	2063.9(12)	51.6(8)
O3	14 014(8)	2799(8)	291.8(17)	102.4(15)
N1	4228(5)	10 438(5)	3879.3(12)	37.0(7)
N2	7453(6)	4232(5)	2380.5(13)	40.6(8)
N3	11 738(6)	2605(6)	1294.9(14)	49.6(9)
C1	4423(9)	13 768(8)	4194(2)	68.3(15)
C2	3106(9)	13 416(8)	4677(2)	64.0(14)

Continued

TABLE III. Continued

Atom	X	y	z	U(eq)
C3	1500(8)	12 214(7)	4573.2(18)	51.8(11)
C4	2396(7)	10 428(6)	4208.7(16)	39.8(9)
C5	5629(8)	11 816(7)	3923.7(19)	54.5(12)
C6	5052(6)	8827(6)	3507.5(15)	35.0(8)
C7	3488(7)	8631(6)	3126.6(16)	42.1(9)
C8	4264(7)	7128(6)	2759.9(16)	41.7(9)
C9	6646(7)	5806(6)	2761.2(15)	36.5(9)
C10	8205(7)	5999(6)	3141.2(15)	38.5(9)
C11	7407(6)	7521(6)	3510.0(15)	37.5(9)
C12	5967(7)	2962(6)	2275.3(17)	46(1)
C13	7535(8)	701(6)	2187.2(19)	54.3(12)
C14	9306(8)	761(7)	1774.8(18)	50.0(11)
C15	10 032(7)	2441(6)	1682.5(16)	42.2(10)
C16	9267(7)	4209(6)	2055.1(16)	38.3(9)
C17	12 881(9)	674(8)	1025(2)	68.0(14)
C18	14 842(10)	964(12)	681(3)	94(2)
C19	12 965(12)	4701(11)	564(2)	99(2)
C20	10 940(10)	4516(8)	901(2)	70.6(15)
H1A	5602	14 347	4302	82
H1B	3324	14 849	3934	82
H2A	2166	14 806	4795	77
H2B	4232	12 608	4970	77
H3A	15	13 253	4415	62
H3B	1145	11 594	4922	62
H5A	6039	12 253	3561	65
H5B	7100	10 973	4124	65
H7	1897	9527	3119	51
H8	3192	6995	2510	50
H10	9797	5105	3150	46
H11	8474	7658	3761	45
H12A	4949	3635	1955	55
H12B	4963	2922	2583	55
H13A	8342	−56	2527	65
H13B	6572	−77	2066	65
H14	9937	−407	1573	60
H17A	11 722	421	797	82
H17B	13 528	−572	1294	82
H18A	16 049	1109	916	112
H18B	15 576	−315	495	112
H19A	12 388	5963	297	119
H19B	14 155	4880	797	119
H20A	10 270	5795	1090	85
H20B	9704	4436	664	85

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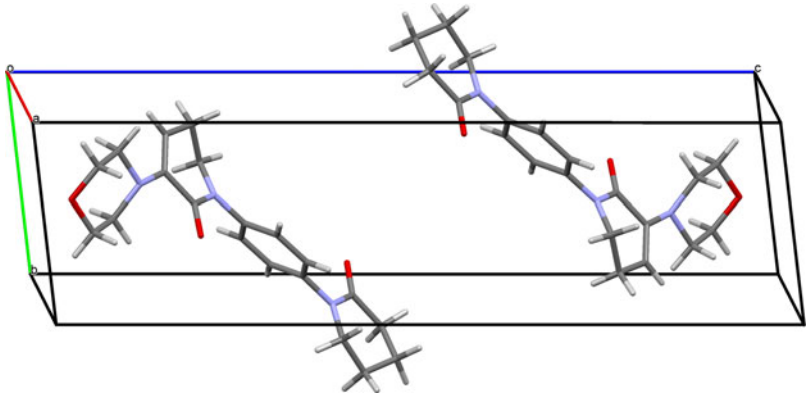

Figure 3. (Color online) Crystal packing of the title compound.

zero background plate. The diffraction data were collected over the angular range from 4 to 50°2θ with a step size of 0.013 13°2θ and a counting time of 30 ms step^{-1}.

The software package Material Studio 8.0 (Accelrys Co., Ltd., CA) was used to process the data in the Analytical & Testing Center (Sichuan University, Chengdu, China). The X-ray powder diffraction pattern (Figure 2) was pre-treated by subtracting the background, smoothing, and stripping off the $K\alpha_2$ component. Automatic indexing results were obtained by the X-cell method (Neumann, 2003). The preliminary cell from indexing was refined using the Pawley method (Pawley, 1981).

C. Single-crystal X-ray diffraction

X-ray diffraction data for the title compound were collected on an Xcalibur, Eos diffractometer. The crystal was kept at 293.15 K during data collection. The structure was solved with olex2 (Dolomanov *et al*., 2009), a structure solution program using charge flipping and refined with ShelXL (Sheldrick, 2008) refinement package using least-squares minimization.

III. RESULTS

Pawley refinement results confirmed that the title compound is triclinic with space group $P-1$ and unit-cell parameters: $a = 5.989(2)$, $b = 6.669(3)$, $c = 24.605(5)$ Å, $\alpha = 84.466(7)°$, $\beta = 89.859(6)°$, $\gamma = 69.074(4)°$, unit-cell volume $V = 913.11$ Å^3, $Z = 2$, and $\rho_{cal} = 1.289$ g cm^{-3} (Table I). The results are in good agreement with the single crystallographic data [$a = 6.0164(5)$, $b = 6.6483(8)$, $c = 24.700(3)$ Å, $\alpha = 83.957(10)°$, $\beta = 89.451(9)°$, $\gamma = 69.222(10)°$, unit-cell volume $V = 918.17(18)$ Å^3, $Z = 2$, and $\rho_{cal} = 1.286$ g cm^{-3}]. The detail single crystallographic data of title compound and the experimental data were listed in Table II and the fractional atomic coordinates were listed in Table III. The title compound is composed of four rings. Two 2-piperidone rings with sofa-half-chair-conformations are connected by phenyl ring, which are respectively twisted by 47.3(5)° (C5–N1–C6–C11) and 136.6(4)° (C12–N2–C9–C10). The morpholine ring with sofa-half-chair-conformation is attached to the piperidone ring twisted by −5.8(6)° (C17–N3–C15–C14). It is arranged without intramolecular and intermolecular H bonding (Figure 3).

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0885715616000385

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