X-ray powder diffraction data for piperaquine, $C_{29}H_{32}Cl_2N_6$

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X-ray powder diffraction data for piperaquine, $C_{29}H_{32}Cl_2N_6$, are reported [$a = 15.8865(1)$ Å, $b = 12.5975(3)$ Å, $c = 13.2647(3)$ Å, $\beta = 91.2890(1)°$, unit-cell volume $V = 2654.02$ Å^3, $Z = 4$, and space group $P2_1/n$]. All measured lines were indexed and are consistent with the $P2_1/n$ space group. No detectable impurities were observed. © *2015 International Centre for Diffraction Data*.
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Key words: X-ray powder diffraction, piperaquine

I. INTRODUCTION

The title compound piperaquine (Figure 1), systematic name quinoline, 4,4′-(1,3-propanediyldi-4,1-piperazinediyl)bis (7-chloroquinoline), is bisquinoline anti-malarial drug which shows good activity against chloroquine-resistant *Plasmodium* strains (Divya *et al*., 2014). Evidence suggesting the inhibition of the heme-digestion pathway in the parasite food vacuole is most convincing (Laskhmi and Mohan Gandhi, 2014). Piperaquine's bulky bisquinoline structure may be important for activity against chloroquine resistant strains and may act by inhibition of the transporters that efflux chloroquine from the parasite food vacuole (Reddy and Reddy, 2014).

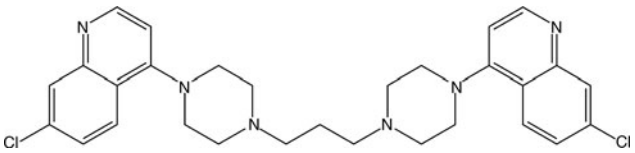


Figure 1. Structural formula of piperaquine.

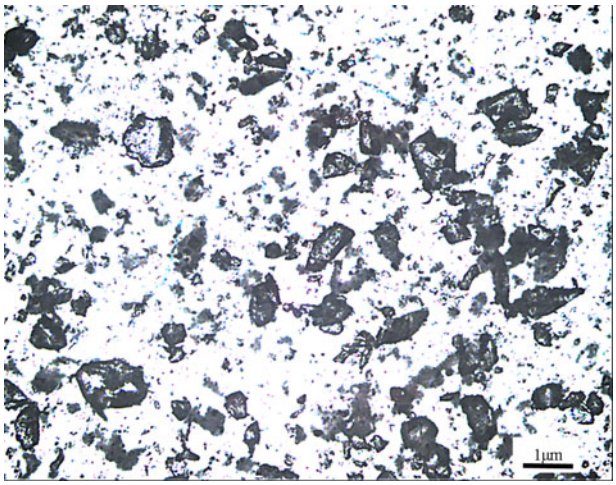


Figure 2. (Color online) Optical microscopy image of piperaquine powder.

II. EXPERIMENTAL

A. Sample preparation

The title compound was purchased from Tianjin Heowns Biochemical Technology Co., Ltd., China, with 98% purity and characterized by Ultraviolet Visible (UV) and Fourier Transform Infrared Spectroscopy (FT-IR). The melting point and measured density of piperaquine are 199–200 °C and 1.346 g cm^{-3}, respectively. Crystallization of piperaquine at room temperature was successful using chloroform as solvent. Then, part of crystals were dried and ground into powder (Figure 2).

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 1D detector and Cu$K\alpha$ radiation (generator setting: 40 kV and 40 mA). 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 4.2 (Accelrys Co. Ltd., CA, USA) was used to process the data in the State Key Laboratory of Polymer Materials Engineering (Sichuan University, China). The X-ray powder diffraction pattern was pre-treated by subtracting the background, smoothing, and stripping off the $K\alpha_2$ component (Li *et al*., 2014). Automatic indexing results were obtained by the DICVOL91 method. The indexing results were then refined with the type of Pawley, which involves assigning the Miller indices (*h, k, l*) to each observed peak in the experimental powder X-ray diffraction (XRD) pattern (Wang *et al*., 2013).

C. Single-crystal XRD

XRD data for piperaquine were collected on a 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 the ShelXL (Sheldrick, 2008) refinement package using least-squares minimization.

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III. RESULTS

Pawley refinement results confirmed that piperaquine is monoclinic with space group $P2_1/n$ and unit-cell parameters: $a = 15.8865(1)$ Å, $b = 12.5975(3)$ Å, $c = 13.2647(3)$ Å, $\beta = 91.2890(1)°$, unit-cell volume $V = 2654.02$ Å^3, and $Z = 4$. The values of $2\theta_{obs}$, d_{obs}, I_{obs}, h, k, l, $2\theta_{cal}$, d_{cal}, and $\Delta 2\theta$ are listed in Table I.

The single crystallographic data of piperaquine [$a = 13.2585(8)$ Å, $b = 12.5741(7)$ Å, $c = 15.8609(7)$ Å, $\beta = 91.299(4)°$, unit-cell volume $V = 2643.6(2)$ Å^3, and $Z = 4$] and experimental data are listed in Table II. The figures were drawn with ORTEP-3 (Oak Ridge Thermal Ellipsoid Plot) (Figure 3) and Mercury (Figure 4). Piperaquine was arranged without intramolecular and intermolecular H bonding. Crystallographic data for piperaquine were deposited with the Cambridge Crystallographic Data Center (CCDC) with a supplementary publication number of CCDC-1030995.

The comparison of X-ray powder diffraction pattern with the simulated pattern is shown in Figure 5. Results showed that both single-crystal and powder diffraction methods can get similar structure data.

TABLE I. X-ray powder diffraction data for piperaquine, $C_{29}H_{32}Cl_2N_6$. The d-values were calculated using Cu$K\alpha_1$ radiation ($\lambda = 1.540\,56$ Å).

$2\theta_{obs}$ (°)	d_{obs} (Å)	I_{obs}	h	k	l	$2\theta_{cal}$ (°)	d_{cal} (Å)	$\Delta 2\theta$
8.7991	10.0413	13	1	0	1	8.7751	10.0687	0.0240
8.9436	9.8794	12	1	1	0	8.9523	9.8698	−0.0087
9.6657	9.1429	13	0	1	1	9.6757	9.1335	−0.0100
11.1363	7.9386	12	2	0	0	11.1326	7.9412	0.0037
11.2676	7.8464	13	1	1	1	11.2406	7.8652	0.0270
13.1846	6.7095	8	2	1	0	13.1682	6.7179	0.0164
14.8916	5.9441	18	2	1	1	14.8833	5.9474	0.0083
15.1279	5.8517	26	1	2	0	15.1191	5.8551	0.0088
15.5743	5.6850	11	0	2	1	15.5616	5.6896	0.0127
16.2177	5.4609	9	1	1	2	16.1944	5.4687	0.0233
16.4803	5.3744	18	1	2	−1	16.4855	5.3728	−0.0052
16.6248	5.3281	57	1	2	1	16.5875	5.3399	0.0372
17.2419	5.1387	6	2	0	−2	17.2139	5.1470	0.0280
18.1873	4.8737	11	3	1	0	18.1610	4.8807	0.0262
19.0145	4.6635	16	2	1	2	18.9678	4.6749	0.0467
19.2771	4.6006	18	2	2	1	19.2623	4.6041	0.0148
19.4084	4.5697	66	0	2	2	19.4212	4.5667	−0.0128
19.4478	4.5606	69	3	1	1	19.4940	4.5498	−0.0463
20.1699	4.3989	13	1	2	−2	20.1320	4.4071	0.0380
20.3144	4.3679	16	1	2	2	20.3001	4.3710	0.0143
20.7083	4.2857	9	1	0	−3	20.7188	4.2836	−0.0105
20.9578	4.2353	100	1	0	3	20.9637	4.2341	−0.0060
21.3123	4.1656	11	0	1	3	21.2837	4.1711	0.0285
21.9031	4.0545	13	3	2	0	21.9130	4.0528	−0.0098
22.1395	4.0118	22	1	1	3	22.1303	4.0134	0.0092
22.2708	3.9884	8	2	2	−2	22.2869	3.9856	−0.0161
22.8354	3.8911	14	3	1	2	22.8281	3.8923	0.0073
22.9010	3.8801	12	1	3	1	22.9277	3.8756	−0.0267
23.8727	3.7243	6	2	1	−3	23.8654	3.7254	0.0073
24.2797	3.6628	12	4	1	−1	24.2836	3.6622	−0.0039
24.6211	3.6128	39	0	2	3	24.5827	3.6183	0.0384
24.8049	3.5864	6	2	3	−1	24.8181	3.5845	−0.0132
25.1332	3.5403	8	1	2	−3	25.1204	3.5421	0.0128
25.5665	3.4813	7	3	2	−2	25.5403	3.4848	0.0262
25.6321	3.4725	6	1	3	−2	25.6421	3.4712	−0.0099
25.7897	3.4517	6	1	3	2	25.7760	3.4535	0.0137
25.8422	3.4448	7	4	0	−2	25.8722	3.4408	−0.0300
26.8926	3.3125	39	0	0	4	26.8694	3.3154	0.0232
27.0765	3.2905	7	3	3	0	27.0809	3.2899	−0.0045
27.2603	3.2687	18	4	2	−1	27.2411	3.2710	0.0192
27.4179	3.2503	7	2	3	−2	27.3883	3.2537	0.0295
27.5098	3.2396	8	3	1	3	27.4796	3.2431	0.0301
27.6411	3.2245	7	2	3	2	27.6398	3.2247	0.0012
27.8512	3.2007	8	3	3	−1	27.8250	3.2036	0.0261
28.2713	3.1541	7	1	1	−4	28.2524	3.1561	0.0189
28.3238	3.1483	6	0	4	0	28.3142	3.1494	0.0097
28.5208	3.1270	4	1	1	4	28.4969	3.1296	0.0239
29.0591	3.0703	5	5	0	1	29.0285	3.0735	0.0307
29.4268	3.0328	4	2	0	4	29.4023	3.0353	0.0245
29.5844	3.0170	5	5	1	−1	29.6068	3.0148	−0.0225
29.7682	2.9988	5	1	3	−3	29.7694	2.9987	−0.0012

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)	$\Delta 2\theta$
29.9651	2.9795	8	1	3	3	29.9445	2.9815	0.0207
30.2671	2.9505	5	2	1	4	30.2635	2.9508	0.0036
30.4641	2.9318	13	3	3	2	30.4747	2.9308	−0.0106
30.7530	2.9050	4	4	1	−3	30.7319	2.9069	0.0211
30.9762	2.8845	5	4	3	0	30.9703	2.8851	0.0059
31.1075	2.8727	5	1	2	4	31.0841	2.8748	0.0234
31.2782	2.8574	4	2	3	−3	31.2758	2.8576	0.0024
31.6064	2.8284	4	4	3	−1	31.6028	2.8287	0.0036
32.7488	2.7323	5	2	2	4	32.7240	2.7343	0.0247
33.5760	2.6669	4	2	4	2	33.5360	2.6700	0.0400
33.6810	2.6588	4	3	4	−1	33.6917	2.6580	−0.0107
33.8517	2.6458	4	3	4	1	33.8484	2.6460	0.0032
34.3769	2.6066	4	1	0	5	34.3771	2.6065	−0.0002
34.4163	2.6037	6	0	3	4	34.4377	2.6021	−0.0214
34.8233	2.5742	6	4	0	−4	34.8324	2.5735	−0.0090
35.0597	2.5573	5	1	3	4	35.0129	2.5607	0.0468
35.9657	2.4950	4	3	4	2	35.9519	2.4959	0.0138
36.1232	2.4845	5	2	1	−5	36.1427	2.4832	−0.0194
36.3990	2.4663	3	4	4	0	36.3809	2.4675	0.0181
36.6353	2.4509	4	2	1	5	36.6323	2.4511	0.0030
36.7272	2.4450	4	0	2	5	36.7359	2.4444	−0.0087
36.9373	2.4315	4	6	1	−2	36.9442	2.4311	−0.0069
37.2918	2.4092	5	1	2	5	37.3042	2.4085	−0.0124
38.0271	2.3643	4	5	2	3	38.0053	2.3656	0.0218
38.2241	2.3526	3	5	3	2	38.2265	2.3525	−0.0024
38.7099	2.3242	4	4	4	−2	38.7276	2.3232	−0.0177
38.9462	2.3106	3	3	1	5	38.9502	2.3104	−0.0039
39.0776	2.3032	4	4	4	2	39.0975	2.3020	−0.0199
39.5765	2.2753	3	3	5	0	39.5810	2.2750	−0.0045
40.1280	2.2453	3	3	5	−1	40.1164	2.2459	0.0116
40.2199	2.2403	3	6	3	0	40.2396	2.2393	−0.0197
40.3381	2.2341	4	7	1	0	40.3579	2.2330	−0.0198
40.5088	2.2250	4	1	3	−5	40.4850	2.2263	0.0238
40.7188	2.2140	4	1	3	5	40.7082	2.2146	0.0107
40.8239	2.2086	5	7	1	−1	40.7960	2.2100	0.0279
41.2440	2.1870	3	0	5	3	41.2070	2.1889	0.0370
41.7167	2.1633	3	1	1	−6	41.7182	2.1633	−0.0015
41.8612	2.1562	4	6	2	−3	41.8777	2.1554	−0.0165
41.9662	2.1511	4	1	1	6	41.9795	2.1504	−0.0132
42.0713	2.1459	4	3	5	2	42.0797	2.1455	−0.0085
42.1894	2.1402	4	4	4	3	42.1558	2.1418	0.0336
42.2945	2.1351	3	7	2	0	42.3042	2.1347	−0.0097
42.4389	2.1282	3	4	5	0	42.4561	2.1274	−0.0172
42.8722	2.1077	3	3	4	−4	42.8529	2.1086	0.0193
43.5287	2.0774	4	3	3	−5	43.4914	2.0791	0.0373
43.8701	2.0620	7	1	2	6	43.8668	2.0622	0.0033
43.9883	2.0568	5	1	6	1	44.0194	2.0554	−0.0311
44.9468	2.0151	3	3	5	3	44.9507	2.0149	−0.0039
45.1043	2.0084	4	5	4	−3	45.1035	2.0085	0.0008
45.1569	2.0062	4	2	2	6	45.1447	2.0067	0.0122
45.3407	1.9985	3	6	4	1	45.3529	1.9980	−0.0122
45.5902	1.9881	3	5	1	5	45.5818	1.9885	0.0084
45.7083	1.9833	3	5	4	3	45.7154	1.9830	−0.0070
46.0891	1.9678	3	7	3	1	46.0785	1.9682	0.0106
46.2204	1.9625	6	8	1	0	46.2549	1.9611	−0.0345
46.3386	1.9578	5	5	2	−5	46.3595	1.9569	−0.0209
46.4830	1.9520	3	3	6	0	46.4907	1.9517	−0.0077
46.9295	1.9345	3	8	1	1	46.9469	1.9338	−0.0175
48.2294	1.8853	3	5	5	2	48.2462	1.8847	−0.0168
48.5839	1.8724	3	6	3	−4	48.5878	1.8723	−0.0039
49.0434	1.8559	3	4	6	0	49.0392	1.8561	0.0042
49.9757	1.8235	3	3	3	6	49.9924	1.8229	−0.0167

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TABLE II. Crystal and experimental data of piperaquine.

Empirical formula	$C_{29}H_{32}Cl_2N_6$
Formula weight	535.50
Temperature (K)	293.15
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	13.2585(8)
b (Å)	12.5741(7)
c (Å)	15.8609(7)
α (°)	90
β (°)	91.299(4)
γ (°)	90
Volume (Å^3)	2643.6(2)
Z	4
ρ_{calc} (g cm^{-3})	1.346
μ (mm^{-1})	0.276
$F(000)$	1128.0
Crystal size (mm^3)	0.3 × 0.2 × 0.2
Radiation	Mo$K\alpha$ (λ = 0.710 73)
2θ range for data collection (°)	6.074–52.744
Index ranges	$-16 \le h \le 14$, $-14 \le k \le 15$, $-19 \le l \le 19$
Reflections collected	11 701
Independent reflections	5388 [R_{int} = 0.0315, R_{sigma} = 0.0662]
Data/restraints/parameters	5388/0/334
Goodness-of-fit on F^2	1.052
Final R indices [$I \ge 2\sigma(I)$]	R_1 = 0.0647, wR_2 = 0.1067
Final R indices [all data]	R_1 = 0.1132, wR_2 = 0.1270
Largest different peak/hole (e Å^{-3})	0.20/−0.27

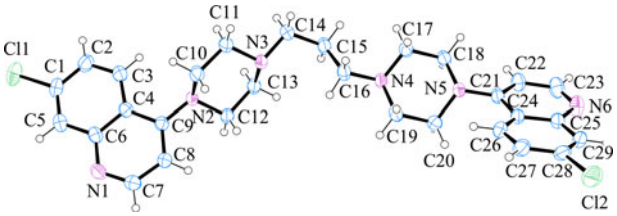


Figure 3. (Color online) ORTEP drawing of molecular structure of piperaquine with the labeling of non-H atoms.

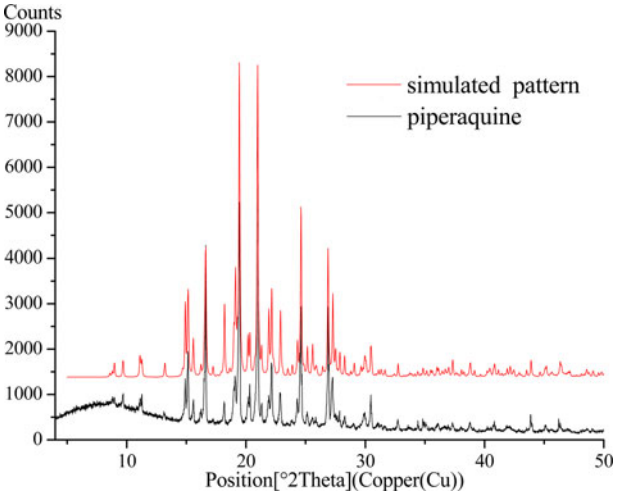


Figure 5. (Color online) X-ray powder diffraction pattern of piperaquine using Cu$K\alpha$ radiation and the simulated pattern of crystal structure.

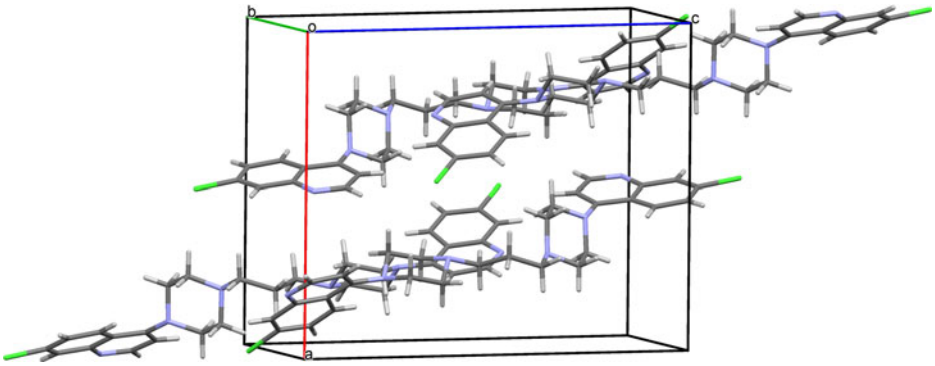


Figure 4. (Color online) Crystal packing of piperaquine.

SUPPLEMENTARY MATERIALS AND METHODS

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0885715615000524

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Divya, M., Vasanth, P., Ramesh, T., and Ramesh, M. (**2014**). "Stability indicating RP-HPLC method development for simultaneous determination of arterolane maleate and piperaquine phosphate in bulk and tablet dosage form," Der Pharm. Lett. **6**, 8–15.

Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K., and Puschmann, H. (**2009**). "OLEX2: a complete structure solution, refinement and analysis program," J. Appl. Crystallogr. **42**, 339–341.

Laskhmi, P. and Mohan Gandhi, B. (**2014**). "Method development and validation for simultaneous estimation of arterolane maleate and piperaquine phosphate by RP-HPLC," Int. J. Pharm. Pharm. Sci. **6**, 441–444.

Li, S. S., Wu, X. Q., Pan, Q. Q., Cheng, Q., and Li, H. (**2014**). "Comparison of the accuracy of powder and single crystal X-ray diffraction techniques in determining organic crystal structure," Chin. Sci. Bull. **59**, 497–501.

Reddy, G. S. and Reddy, S. P. (**2014**). "Development and validation of a stability indicating liquid chromatographic method for simultaneous estimation of arterolane maleate and piperaquine phosphate in combined dosage form," Orient. J. Chem. **29**, 1371–1380.

Sheldrick, G. M. (**2008**). "Foundations of crystallography," Acta Crystallogr. A **64**, 112–122.

Wang, Q., Zhang, L. L., Wu, X. Q., Pan, Q. Q., Su, Y. H., and Li, H. (**2013**). "X-ray powder diffraction data for inclusion complex of β-cyclodextrin with fraxinellone," Powder Diffr. **28**, 234–236.

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