Research Article

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A comparative study of the crystal structures of 2-(4-(2-(4-(3-chlorophenyl)piperazine-1-yl)ethyl)benzyl)isoindoline-1,3-dione by synchrotron radiation X-ray powder diffraction and single-crystal X-ray diffraction

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Abstract: The crystal structures of the title compound, $C_{27}H_{26}ClN_3O_2$, were established by single-crystal X-ray diffraction and synchrotron radiation X-ray powder diffraction. The simulated annealing approach and rigid-body Rietveld refinement were applied to the structure solution from powder data. Direct methods and full-matrix least-squares techniques were used to solve and refine the crystal structure from single-crystal data. The title compound crystallized in space group $P\bar{1}$ with lattice parameters $a=17.396(7)$ Å, $b=10.010(4)$ Å, $c=6.833(3)$ Å, $\alpha=77.345(12)^\circ$, $\beta=93.534(6)^\circ$, $\gamma=97.210(9)^\circ$, unit-cell volume $V=1151.0(2)$ Å³, $Z=2$ from powder data, and in space group $P\bar{1}$ with lattice parameters $a=82.485(2)^\circ$, $\beta=86.5110(10)^\circ$, $\gamma=77.518(2)^\circ$, $a=6.8159(6)$ Å, $b=10.0003(9)$ Å, $c=17.4140(15)$ Å, unit-cell volume $V=1148.3(2)$ Å³, $Z=2$ from single-crystal data. No detectable impurities were observed.

Keywords: Crystal structure; Synchrotron radiation X-ray powder diffraction; Rietveld refinement; Single-crystal X-ray diffraction.

1 Introduction

As a vital pharmacophore, the structure of arylpiperazine motifs could produce extensive pharmacological activities [1,2]. Arylpiperazine moieties containing compounds have shown their application in anti-proliferative [3,4]. Specifically, naftopidil is an arylpiperazine ether derivative, which is widely used as an adrenergic receptor antagonist [5,6]. This compound is a popular drug

in Japan to treat the benign prostatic hyperplasia (BPH) [7, 8]. Recently, naftopidil had also proven to arrest the G1 cell cycle phase [9,10] and induce apoptosis in malignant mesothelioma cell lines [11], which could be potentially used as an anticancer drug. Moreover, the arylpiperazine derivative studied in this research possessed an antitumor capability [12].

Despite having a variety of known functions, the crystal structure of the title compound, 2-(4-(2-(4-(3-chlorophenyl)-piperazine-1-yl)ethyl)benzyl)isoindoline-1,3-dione, was still unknown. Therefore, in this paper, we presented the crystal structure of compound **1** that were analyzed by both single-crystal X-ray diffraction (SXRD) and synchrotron radiation X-ray powder diffraction (PXRD), while the powder diffraction data were solved by the simulated annealing method and was further verified by rigid-body Rietveld refinement, and the single-crystal diffraction data were solved by direct methods and refined with full-matrix least-squares techniques [13-16]. Very little work had been done in comparing the crystal structure data, such as bond length and bond angle, obtained from these two approaches. Li and his co-workers reported a comparative study of the crystal structure data of griseofulvin obtained from SXRD and PXRD [17]. In this research, we showed an improved result with a sub-1% deviation between most of the crystal

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structure data of compound 1 obtained from PXRD and SXRD. The PXRD and SXRD structure data of compound 1 were already deposited in the Cambridge Crystallographic Data Centre (CCDC) with CCDC numbers of 1535586 and 1892781 by the authors, respectively. The molecular structure of compound 1 was shown in **Figure 1**.

Figure 1: Molecular structure of compound 1.

2 Experimental

2.1 Synthesis

2-(4-(2-(4-(3-chlorophenyl)piperazin-1-yl)ethyl)benzyl)isoindoline-1,3-dione. 2-(4-((1,3-dioxoiso-indolin-2-yl)methyl)phenyl)ethyl-4-methylbenzene sulfonate (217.8 mg, 0.5 mmol) and KOH (112.2 mg, 2.0 mmol) were dissolved in 50 mL of ethanol and then 1-(3-chlorophenyl) piperazine (108.2 mg, 0.55 mmol) was added at room temperature. This reaction mixture refluxed for 2-3 hours under stirring. The end of the reaction was determined by thin layer chromatography (TLC). The solvent was later removed by a rotary evaporator and compound 1 was extracted by three sequential CH_2Cl_2 extractions (100 mL per time). The combined organic layer was washed with water and brine in turn, dried with anhydrous Na_2SO_4 , and concentrated by rotary evaporation. Silica gel column chromatography was used to further purify the obtained compound 1 which was a white solid. The eluent was a mixture of ethyl acetate and petroleum ether with a volume ratio of 1:8. ^1H NMR(400MHz, CDCl_3) d in ppm: 7.828 (dd, $J=5.5, 3.0$ Hz, 2H), 7.687 (dd, $J=5.5, 3.0$ Hz, 2H), 7.364 (d, $J=8.0$ Hz, 2H), 7.161 (dd, $J=8.0, 5.0$ Hz, 2H), 7.124 (s, 1H), 6.862 (t, $J=2.0$ Hz, 1H), 6.790 (dd, $J=8.0, 1.6$ Hz, 2H), 4.815 (s, 2H), 3.206 (t, $J=5.0, 4$ Hz), 2.801 (t, $J=8.0, 2$ Hz), 2.633 (dd, $J=10.0, 5.0$ Hz, 4H) 2.591 (d, $J=8.0$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) d in ppm: 168.04, 152.31, 139.81, 134.95, 133.96, 132.16, 130.01, 129.01, 123.32, 119.24, 115.72, 113.84, 77.37, 77.05, 76.74, 60.24, 52.99, 48.64, 41.33, 33.22; HRMS (ESI) m/z $[\text{M}+1]^+$: calculated for $\text{C}_{27}\text{H}_{26}\text{N}_3\text{O}_2\text{Cl}$, 460.1786, found, 460.1778.

2.2 X-ray diffraction

2.2.1 Sample preparation and crystallization

The crude product was recrystallized from ethanol. Colorless powders with enhanced crystallinity were obtained which were suitable for synchrotron X-ray powder diffraction. Rod-like single crystals were obtained

by slow evaporation of the ethanolic mixture solution of the title compound at ambient temperature.

2.2.2 Synchrotron radiation X-ray powder diffraction

PXRD patterns were obtained at the BLO1C2 beamline at the National Synchrotron Radiation Research Center (NSRRC) TLS light source in Taiwan at 295 K. The wavelength was 0.77491 Å, and the 2θ range was from 3.00 ° to 52.00 ° with 0.01 ° interval, and a counting time of 0.1 s per step. The synchrotron energy and current were maintained at 1.5 GeV and 360 mA, respectively, in the TOP-UP mode. A Mar345 imaging plate detector with a pixel size of 100 μm was employed to collect the diffraction data. The GSAS-II and cake-type integration were utilized to convert a 2D diffraction spectrum to a 1D diffraction profile according to the reference [18]. LaB_6 was used to calibrate diffraction angles. The powder sample was rotated at 600 revolutions per minute (rpm) to avoid any preferred orientation.

2.2.3 Single-crystal X-ray diffraction

SXRD data were collected on Bruker SMART [19] using Mo $K\alpha$ ($\lambda=0.71073$ Å) with a CCD area detector at 298 K and the θ range of 2.361 - 25.026 °. Then the data were reduced by Bruker SAINT, and the structure model was solved by direct methods using SHELXS-97 [20,21] program and refined by (SHELXL) [22] embedded in Olex2-1.2 [23] software. The positions of hydrogen atoms were first calculated according to the geometry of the molecule and then refined with a riding model.

Ethical approval: The conducted research is not related to either human or animal use.

3 Results and discussion

3.1 Indexing

The powder diffraction pattern was initially indexed on a primitive triclinic unit cell having $a=17.5154\text{ \AA}$, $b=9.9195\text{ \AA}$, $c=6.5992\text{ \AA}$, $\alpha=80.341^\circ$, $\beta=93.238^\circ$, $\gamma=96.838^\circ$, $V=1121.49\text{ \AA}^3$, using DICVOL91 [24] embedded in DASH3.3.5 [25] with figures of merit $M(19)=11.1$, $F(19)=53.7$. The refined lattice parameters of the powder X-ray diffraction data was a triclinic crystal system, $P\bar{1}$ space group and lattice parameters $a=17.396(7)\text{ \AA}$, $b=10.010(4)\text{ \AA}$, $c=6.833(3)\text{ \AA}$, $\alpha=77.345(12)^\circ$, $\beta=93.534(6)^\circ$, $\gamma=97.210(9)^\circ$, $V=1151.0(2)\text{ \AA}^3$.

For SXRD the intensities of the x-ray diffraction were collected at every orientation of the crystal, and the diffraction pattern was indexed by matching the orientation matrix. Following processing the data, the indexing results were obtained as a triclinic crystal system, $P\bar{1}$ space group, and lattice parameters $a=6.8159(6)\text{ \AA}$, $b=10.0003(9)\text{ \AA}$, $c=17.4140(15)\text{ \AA}$, $\alpha=82.485(2)^\circ$, $\beta=86.5110(10)^\circ$, $\gamma=77.518(2)^\circ$, $V=1148.3(2)\text{ \AA}^3$.

3.2 Structure solution

3.2.1 Structure solution from powder diffraction

After indexing the structure-independent Pawley fit was carried out and converged to a χ^2 value of 9.98, which indicated a good fit. The molecule volume of compound 1 was estimated to be $594\text{ \AA}^3$ based on the rule of $18\text{ \AA}^3$ per non-hydrogen atom, so the number of formula units per unit cell could be determined as $Z=2$. This suggested that the most probable space group was $P\bar{1}$ with one molecule in the asymmetric unit. This result was further verified by the Rietveld refinement. The molecule (see **Figure 1**) was built and its geometry optimized using Avogadro1.2.0 [26] and saved as a mol2 file. Standard bond lengths, torsions, and angles were employed to calculate the internal coordinate description of a given molecule. This molecule was used to solve the crystal structure with DASH 3.3.5 using the $3^\circ - 14^\circ$ portion of the diffraction pattern. The trial structure was then subjected to a global optimization procedure that sought to minimize profile χ^2 . The first attempt, in which thirteen variable parameters were adopted in the simulated annealing (SA) runs (three positional coordinates for the center of mass of the molecule, four quaternions representing the molecular orientation in the unit cell and six torsion angles), failed to find a solution. On the second attempt, a total of seven parameters were

varied (three positional coordinates for the center of mass of the molecule, four quaternions) and six torsion angles of the molecule were held fixed during the simulated annealing runs. After about 15 minutes of SA runs, the structure was solved with a profile $\chi^2=17.35$ which was less than two times that of the Pawley profile $\chi^2 9.98$. The ratio of profile χ^2 to Pawley profile χ^2 should generally be less than 5 (the smaller, the better) for a promising solution. The fit was excellent and the difference plot was shown in **Figure 2**.

3.2.2 Structure solution from single crystal diffraction

In this research, Olex2-1.2 platform was used to determine the single-crystal structure. Atomic positions in a unit cell of a given molecule were determined by direct methods implemented SHELXS-97 program embedded in Olex2-1.2 platform. In this approach, the types of diffraction intensities were used to determine the phase information, which was further used to obtain the electron density distribution of a unit cell. Since each atom in a structure was correlated to a specific electron density peak, the crystal structure of compound 1 was determined.

3.3 Refinement

3.3.1 Powder diffraction refinement

The initial model used for further refinement in this section was the best result obtained from the SA method. The GSASII program was employed to perform the rigid body Rietveld refinement. Rigid bodies were created for the whole molecule of the title compound, including the hydrogen atoms. An overall isotropic displacement parameter (Uiso) was utilized to refine all the atoms of compound 1. The background function is set to the Cosine Fourier series option with 28 adjustable terms. Although peak overlap in powder diffraction data prevented the final model from being refined freely by the Rietveld method, the excellent fit to the data using rigid-body constraints for the whole molecule demonstrated that the model was very close to the true geometry. At convergence $R_{wp}=15.501\%$, $R-F=9.002\%$, $R-F2=6.387\%$ for 3490 reflections and 65 refined parameters, for a better comparison, the calculated diffraction pattern and the experimental diffraction pattern were all plotted in **Figure 3**. The crystal data, data collection, and refinement details were summarized in **Table 1**.

Figure 2: Fit to the experimental powder pattern of the best-simulated annealing solution for the molecule. The measured pattern (red), calculated pattern (blue), difference profile (magenta).

Figure 3: Observed (+) in blue, calculated (-) in green and difference in cyan X-ray profiles for the final Rietveld refinement of the molecule. Bragg reflection markers in blue were shown (l).

Table 1: Lattice parameters.

List	SXRD	PXRD	Deviation (%)
α (°)	82.485(2)	97.210(9) ($180-\alpha=82.790(9)$)	0.37
β (°)	86.5110(10)	93.534(6) ($180-\beta=86.466(6)$)	-0.05
γ (°)	77.5180(10)	77.345(12)	-0.22
a (Å)	6.8159(6)	6.8328(27)	0.25
b (Å)	10.0003(9)	10.010(4)	0.10
c (Å)	17.4140(15)	17.396(7)	-0.22
V (Å ³)	1148.3(2)	1151.0(2)	0.24
Z	2	2	0

The conventional Rietveld method was not able to refine the final model freely due to peak overlap. Hence, the rigid-body Rietveld refinement was used to refine the model with the powder diffraction data obtained from the synchrotron source. In this approach, only the translation motions of the molecule, **T** matrix, was refined. Refining the **T** matrix while maintaining the **L** and **S** at 0 was identical as refining the overall anisotropic temperature factor of a rigid body. The six parameters of **T** matrix were $T_{11}=0.077(2) \text{ \AA}^2$, $T_{22}=0.089(3) \text{ \AA}^2$, $T_{33}=0.061(2) \text{ \AA}^2$, $T_{12}=0.005(2) \text{ \AA}^2$, $T_{13}=-0.012(2) \text{ \AA}^2$, $T_{23}=-0.024(2) \text{ \AA}^2$ (see **Figure 4**), indicating the isotropic displacement of the molecule.

Figure 4: Crystal structure of compound **1** by single-crystal X-ray diffraction.

3.3.2 Single crystal diffraction refinement

During the SXRD data process, the initial structure model might only represent part of the real crystal structure. Hence, both the difference Fourier techniques and the Rietveld refinement were used to refine the final structure model. Based on the molecule structure of compound **1**, the position of each atom could easily be identified according to the electron density map. The full-matrix least-squares in the SHELXL program was utilized to refine the crystal structure. The final R1 was 5.61%.

3.4 Discussion

The lattice parameters of compound **1** from SXRD and PXRD are listed in **Table 1**, the bond lengths are shown in **Table 2**, while the bond angles are exhibited in **Table 3** and the selected torsion angles are displayed in **Table 4**. Compound **1** crystallizes in space group *Pi* with two molecules per unit cell. Final crystal structure of compound **1** established by the two technologies while crystal structures were presented in **Figure 4** and the asymmetric unit were illustrated in **Figure 5**, where single-crystal R indices of $R_1=5.61\%$, $wR_2=15.57\%$ and powder R indices of $R_p=8.79\%$, $R_{wp}=15.501\%$. As shown in **Table 1**, the deviations between the data obtained from PXRD and SXRD were quite small, which indicate PXRD can achieve good accuracy in determining crystal structure compared to SXRD. **Table 2**, **Table 3** and **Table 4** show the structural geometry difference of compound **1** between powder and single crystal data, resulting in the modulus of deviation ranges of 0%-1.54% for bond length, 0%-2.68% for bond angle and 0%-9.4% for torsion angle. The consistency could be more intuitively observed by the overlay of the PXRD and SXRD structures as shown in **Figure 6**. Converting the 3D single-crystal diffraction data into the 1D powder diffraction data led to the obscure of the diffraction intensities, which was attributed to the slight difference in obtained molecular structures.

Figure 5: Displacement ellipsoid plot of the molecule determined by SXRD (a) and PXRD (b) with ellipsoids at the 30% probability level.

Figure 6: Overlay of the SXRD (green) and PXRD (red) structures.

The crystal structure model obtained from the best solution showed that the smallest intermolecular Carbon...Carbon intermolecular distance was 3.294 Å (see **Figure 5**), which was close to the standard value of the

Table 2: Bond lengths (Å) for based on both single-crystal X-ray diffraction (SXRD) and powder X-ray diffraction (PXRD).

List	SXRD	PXRD	Deviation (%)
O1-C1	1.208(4)	1.219	0.91
O2-C2	1.207(4)	1.200	-0.58
N1-C2	1.384(4)	1.401	1.22
N1-C1	1.383(4)	1.382	-0.07
N1-C9	1.456(4)	1.460	0.27
N2-C21	1.437(4)	1.454	1.18
N2-C17	1.449(4)	1.460	0.76
N2-C18	1.446(4)	1.450	0.28
N3-C22	1.393(4)	1.401	0.57
N3-C20	1.449(4)	1.456	0.48
N3-C19	1.453(4)	1.452	-0.07
C3-C4	1.373(4)	1.380	0.51
C2-C3	1.465(4)	1.481	1.09
C3-C8	1.371(4)	1.377	0.44
C1-C4	1.478(5)	1.483	0.34
C4-C5	1.378(4)	1.380	0.15
C10-C11	1.367(4)	1.385	1.32
C10-C9	1.499(4)	1.504	0.33
C10-C15	1.366(4)	1.369	0.22
C11-C12	1.365(4)	1.377	0.87
C13-C12	1.374(4)	1.374	0
C13-C16	1.494(4)	1.510	1.07
C13-C14	1.381(5)	1.382	0.07
C5-C6	1.377(5)	1.386	0.65
C7-C8	1.377(4)	1.386	0.65
C6-C7	1.371(5)	1.379	0.58
C22-C27	1.377(5)	1.379	0.15
C22-C23	1.398(5)	1.388	-0.71
C16-C17	1.507(5)	1.518	0.73
C14-C15	1.376(5)	1.382	0.43
C20-C21	1.495(5)	1.514	1.27
C18-C19	1.491(5)	1.495	0.27
C26-C27	1.374(5)	1.379	0.36
C25-C26	1.364(5)	1.343	-1.54
C24-C25	1.366(5)	1.369	0.22
C23-C24	1.362(5)	1.380	1.32
Cl1-C24	1.738(4)	1.742	0.23

Table 3: Bond angles (°) for based on both single-crystal X-ray diffraction (SXRD) and powder X-ray diffraction (PXRD).

List	SXRD	PXRD	Deviation (%)
C1-N1-C2	111.9(3)	111.9	0
C2-N1-C9	123.9(3)	123.1	-0.65
C1-N1-C9	124.1(3)	124.8	0.56
C21-N2-C17	113.7(3)	112.9	-0.66
C21-N2-C18	108.3(3)	108.3	0
C18-N2-C17	109.1(3)	109.1	0
C22-N3-C20	118.1(3)	118.2	0.08
C22-N3-C19	116.3(3)	116.2	-0.08
C20-N3-C19	111.3(3)	110.3	-0.89
C4-C3-C2	108.4(3)	108.7	0.28
C8-C3-C4	121.6(3)	122.0	0.33
C8-C3-C2	129.9(3)	129.2	-0.54
C3-C4-C1	108.0(3)	107.7	-0.28
C3-C4-C5	122.2(3)	121.5	-0.57
C5-C4-C1	129.8(3)	130.7	0.69
O2-C2-N1	124.9(3)	124.7	-0.16
O2-C2-C3	129.1(3)	130.1	0.77
N1-C2-C3	106.0(3)	105.3	-0.66
O1-C1-N1	124.9(3)	124.9	0
O1-C1-C4	129.4(3)	128.7	-0.51
N1-C1-C4	105.7(3)	106.4	0.66
C11-C10-C9	120.4(3)	120.3	-0.08
C15-C10-C11	118.4(3)	117.5	-0.76
C15-C10-C9	121.2(3)	122.2	0.82
C12-C11-C10	121.2(3)	121.5	0.25
C12-C13-C16	120.4(3)	120.4	0
C12-C13-C14	117.6(3)	117.1	-0.43
C14-C13-C16	121.8(3)	122.3	0.41
C6-C5-C4	115.6(3)	116.7	0.95
C3-C8-C7	116.8(3)	116.6	-0.17
C11-C12-C13	121.2(3)	121.2	0
C7-C6-C5	122.6(3)	121.5	-0.90
C6-C7-C8	121.2(3)	121.6	0.33
N1-C9-C10	112.7(2)	112.9	0.18
N3-C22-C27	123.1(3)	122.7	-0.32
N3-C22-C23	119.5(4)	121.1	1.34
C27-C22-C23	117.4(3)	116.1	-1.11

Table 3: Bond angles (°) for based on both single-crystal X-ray diffraction (SXRD) and powder X-ray diffraction (PXRD).

List	SXRD	PXRD	Deviation (%)
C13-C16-C17	109.7(3)	109.5	-0.18
C10-C15-C14	120.8(3)	120.9	0.08
N2-C21-C20	111.3(3)	111.8	0.45
N3-C20-C21	111.4(3)	111.9	0.45
N2-C17-C16	114.6(3)	115.1	0.44
C15-C14-C13	120.8(3)	121.8	0.83
N3-C19-C18	110.3(3)	110.9	0.54
N2-C18-C19	112.0(3)	112.1	0.09
C26-C27-C22	121.9(4)	121.6	-0.25
C26-C25-C24	118.0(4)	119.6	1.35
C25-C26-C27	120.4(4)	121.0	0.50
C24-C23-C22	119.4(4)	122.1	2.26
C23-C24-C25	122.9(4)	119.6	-2.68
C25-C24-Cl1	118.8(3)	120.5	1.43
C23-C24-Cl1	118.3(4)	119.4	0.93

Table 4: Selected Torsion angles (°) for based on both single-crystal X-ray diffraction and powder X-ray diffraction.

List	SXRD	PXRD	Deviation (%)
N1-C9-C10-C11	-77.7(4)	-71.0	-8.6
N1-C9-C10-C1	103.1(4)	110.1	6.8
C1-N1-C9-C10	94.3(4)	92.9	-1.5
C2-N1-C9-C10	-90.2(4)	-91.4	1.3
C12-C13-C16-C17	-93.4(4)	-101.3	8.5
C13-C16-C17-N2	165.7(3)	166.9	0.7
C14-C13-C16-C17	81.6(4)	73.9	-9.4
C18-N2-C17-C16	-177.3(3)	-177.9	0.3
C21-N2-C17-C16	61.6(4)	61.6	0
C22-N3-C19-C18	167.4(3)	166.9	-0.3
C22-N3-C20-C21	-168.1(3)	-169.3	0.7

intermolecular Carbon ••• Carbon distance 3.2 Å [27]. In the crystal, the molecules were linked by C-H...O, C-H...Cl, and π - π (π -stacking) intermolecular interactions into a three-dimensional network. The intermolecular and intramolecular parameters were in agreement with single crystal data reported for other derivatives of this molecule.

All intramolecular and intermolecular bond distances and angles fell within the normal ranges.

4 Conclusion

In this work we have demonstrated that PXRD is a powerful tool for structure analysis for small organic molecule when single crystals are not available. By comparing with the crystal structure data acquired through conventional SXRD, the majority bond length and angle data obtained from our PXRD approach were within 1% difference. Given the wide applicability of this method, this PXRD technique will attract a great deal of attention to elucidate the structures of small organic compounds.

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Conflict of interest: Authors declare no conflict of interest.

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