Jinhui Zhou*, Cuicui Huang, Maojian Shi, Jing Liu and Lin Ding

Crystal structure of 2-[[4-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]phenyl]methyl]-1*H*-isoindole-1,3(2*H*)-dione, C₂₈H₂₉N₃O₃

Abstract

C₂₈H₂₉N₃O₃, triclinic, $P\bar{1}$ (no. 2), $a = 8.2887(3)$ Å, $b = 14.1977(5)$ Å, $c = 21.3385(7)$ Å, $\alpha = 107.142(3)^\circ$, $\beta = 92.773(3)^\circ$, $\gamma = 104.240(3)^\circ$, $V = 2305.97(15)$ Å³, $Z = 4$, $R_g(F^2) = 0.0555$, $wR_{ref}(F^2) = 0.1620$, $T = 100(1)$ K.

CCDC no.: 1813333

Only one of the two crystallographically independent molecules of the title crystal structure is shown in the figure. Tables 1 and 2 contain details of the measurement method and a list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colorless block
Size:	0.3 × 0.2 × 0.2 mm
Wavelength:	Mo K α radiation (1.54184 Å)
μ :	0.69 mm ⁻¹
Diffraction, scan mode:	SuperNova, φ and ω -scans
$2\theta_{\max}$, completeness:	74°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	15990, 8992, 0.034
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 7757
$N(\text{param})_{\text{refined}}$:	688
Programs:	CrysAlis ^{PRO} [1], SHELX [2]

<https://doi.org/10.1515/ncrs-2018-0034>

Received January 26, 2018; accepted May 9, 2018; available online May 29, 2018

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Source of material

In the mixture of 2-(4-((1,3-dioxoisindolin-2-yl)methyl)phenyl)ethyl-4-methylbenzenesulfonate (217.8 mg, 0.5 mmol), 50 mL EtOH and KOH (112.2 mg, 2.0 mmol), 1-(4-methoxyphenyl)piperazine (105.7 mg, 0.55 mmol) was added at ambient temperature. The reaction mixture was stirred and refluxed for 4 h, until TLC indicated the end of reaction. Then, the solvent was removed under reduced pressure, and the residue was extracted with CH₂Cl₂ (100 mL, 3 times). The combined organic layer was successively washed with water, brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:8, v/v) as the eluent, finally the title compound (a white solid) was afforded.

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
O1A	0.94578(14)	−0.38365(8)	0.02709(5)	0.0249(3)
O2A	0.7976(2)	0.87148(10)	0.35045(7)	0.0473(4)
O3A	1.18938(14)	0.85538(9)	0.50192(6)	0.0299(3)
N1A	0.94977(16)	0.02636(10)	0.14359(7)	0.0237(3)
N2A ^a	1.0795(5)	0.2456(3)	0.1826(2)	0.0207(8)
N2A ^b	1.0341(6)	0.2445(4)	0.2027(2)	0.0210(9)
N3A	1.01801(18)	0.85778(10)	0.41402(7)	0.0272(3)
C11 ^b	0.9195(10)	0.1917(7)	0.1408(4)	0.0244(14)
H11C ^b	0.9262	0.2382	0.1138	0.029*
H11D ^b	0.8027	0.1732	0.1509	0.029*
C1A	0.8588(2)	−0.43917(12)	−0.03772(8)	0.0303(4)
H1AA	0.9023	−0.4030	−0.0686	0.045*
H1AB	0.7387	−0.4448	−0.0374	0.045*
H1AC	0.8758	−0.5079	−0.0517	0.045*
C9 ^b	1.0179(15)	0.1794(11)	0.2448(6)	0.0255(18)
H9A ^b	0.9020	0.1634	0.2562	0.031*
H9B ^b	1.0964	0.2144	0.2863	0.031*
C2A	0.94081(19)	−0.28391(11)	0.05288(7)	0.0204(3)
C19 ^b	0.9713(15)	0.5926(8)	0.2262(6)	0.0229(17)
H19 ^b	0.9074	0.5688	0.1837	0.027*
C3A	0.8420(2)	−0.23776(11)	0.02391(8)	0.0230(3)
H3A	0.7714	−0.2758	−0.0166	0.028*
C15 ^b	1.1387(16)	0.5655(11)	0.3111(6)	0.0236(18)
H15 ^b	1.1893	0.5215	0.3261	0.028*
C4A	0.8467(2)	−0.13597(12)	0.05431(8)	0.0234(3)
H4A	0.7775	−0.1057	0.0343	0.028*
C5A	0.95057(18)	−0.07668(11)	0.11366(8)	0.0207(3)
C6A	1.0476(2)	−0.12532(12)	0.14237(8)	0.0231(3)
H6A	1.1188	−0.0876	0.1828	0.028*
C7A	1.0411(2)	−0.22761(12)	0.11260(8)	0.0235(3)
H7A	1.1061	−0.2593	0.1333	0.028*
C8A	1.0596(2)	0.08108(12)	0.20599(8)	0.0267(3)
H8AA ^a	1.1775	0.0828	0.1994	0.032*
H8AB ^a	1.0277	0.0459	0.2391	0.032*
H8AC ^b	1.1773	0.0984	0.1968	0.032*
H8AD ^b	1.0504	0.0354	0.2336	0.032*
C9A ^a	1.0418(14)	0.1900(9)	0.2304(5)	0.0226(19)
H9AA ^a	0.9255	0.1872	0.2403	0.027*
H9AB ^a	1.1183	0.2283	0.2721	0.027*
C10A	0.9680(2)	0.08854(12)	0.09916(9)	0.0340(4)
H10A ^a	1.0781	0.0907	0.0828	0.041*
H10B ^a	0.8807	0.0523	0.0604	0.041*
H10C ^b	0.8907	0.0524	0.0574	0.041*
H10D ^b	1.0846	0.1052	0.0887	0.041*
C11A ^a	0.9572(9)	0.1921(6)	0.1245(4)	0.0263(13)
H11A ^a	0.8430	0.1924	0.1360	0.032*
H11B ^a	0.9797	0.2267	0.0905	0.032*
C12A ^a	1.1014(4)	0.3553(2)	0.20940(14)	0.0215(8)
H12A ^a	1.1366	0.3859	0.1744	0.026*
H12B ^a	1.1954	0.3833	0.2460	0.026*
C12 ^b	0.9921(4)	0.3393(3)	0.23905(16)	0.0224(9)
H12C ^b	1.0570	0.3675	0.2838	0.027*
H12D ^b	0.8714	0.3225	0.2443	0.027*
C13A ^a	0.9512(4)	0.3926(3)	0.23565(17)	0.0271(9)
H13A ^a	0.8588	0.3717	0.1990	0.032*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
H13B ^a	0.9100	0.3609	0.2695	0.032*
C13 ^b	1.0291(4)	0.4204(2)	0.20484(16)	0.0218(9)
H13C ^b	1.1355	0.4196	0.1858	0.026*
H13D ^b	0.9388	0.4020	0.1677	0.026*
C14A ^a	1.0034(6)	0.5084(4)	0.2658(3)	0.0235(9)
C14 ^b	1.0435(6)	0.5282(4)	0.2490(3)	0.0193(10)
C15A ^a	1.1130(14)	0.5582(10)	0.3253(5)	0.0237(15)
H15A ^a	1.1545	0.5188	0.3480	0.028*
C16A	1.16131(19)	0.66520(12)	0.35148(8)	0.0252(3)
H16A ^a	1.2436	0.6966	0.3894	0.030*
H16B ^b	1.2192	0.6895	0.3951	0.030*
C17A	1.0946(2)	0.72792(12)	0.32459(8)	0.0254(3)
C18A	0.9932(2)	0.68498(14)	0.26392(8)	0.0299(4)
H18A ^a	0.9539	0.7257	0.2417	0.036*
H18B ^b	0.9363	0.7268	0.2494	0.036*
C19A ^a	0.9496(14)	0.5703(7)	0.2356(5)	0.0267(17)
H19A ^a	0.8805	0.5386	0.1941	0.032*
C20A	1.1281(2)	0.84018(13)	0.36258(9)	0.0313(4)
H20A	1.2466	0.8675	0.3833	0.038*
H20B	1.1107	0.8778	0.3316	0.038*
C21A	1.0573(2)	0.86139(11)	0.47903(8)	0.0246(3)
C22A	0.9060(2)	0.87468(11)	0.51214(9)	0.0265(4)
C23A	0.7877(2)	0.88043(12)	0.46622(9)	0.0323(4)
C24A	0.8588(2)	0.86972(12)	0.40250(9)	0.0328(4)
C25A	0.6336(2)	0.89313(13)	0.48208(11)	0.0395(5)
H25A	0.5535	0.8976	0.4505	0.047*
C26A	0.6000(2)	0.89916(13)	0.54612(11)	0.0412(5)
H26A	0.4947	0.9078	0.5586	0.049*
C27A	0.7182(2)	0.89271(12)	0.59240(10)	0.0365(4)
H27A	0.6919	0.8967	0.6358	0.044*
C28A	0.8743(2)	0.88050(12)	0.57597(9)	0.0297(4)
H28A	0.9554	0.8764	0.6073	0.036*
O1B	0.56914(15)	0.12963(8)	0.02880(6)	0.0291(3)
O2B	0.32758(16)	1.37770(9)	0.35041(6)	0.0342(3)
O3B	0.71048(14)	1.35501(8)	0.50275(6)	0.0266(3)
N1B	0.50624(17)	0.52587(10)	0.14323(6)	0.0230(3)
N2B	0.54660(16)	0.73918(10)	0.20929(6)	0.0236(3)
N3B	0.54339(17)	1.35925(9)	0.41422(6)	0.0227(3)
C1B	0.6537(2)	0.10623(12)	−0.02816(9)	0.0318(4)
H1BA	0.6085	0.1303	−0.0620	0.048*
H1BB	0.6366	0.0320	−0.0457	0.048*
H1BC	0.7740	0.1404	−0.0159	0.048*
C2B	0.5687(2)	0.22982(12)	0.05615(8)	0.0238(3)
C3B	0.4727(2)	0.24935(12)	0.10800(8)	0.0265(3)
H3B	0.4167	0.1947	0.1229	0.032*
C4B	0.4577(2)	0.34620(12)	0.13785(8)	0.0262(3)
H4B	0.3918	0.3574	0.1731	0.031*
C5B	0.53832(19)	0.42921(11)	0.11704(8)	0.0221(3)
C6B	0.6544(2)	0.31085(12)	0.03646(8)	0.0247(3)
H6B	0.7232	0.2996	0.0022	0.030*
C7B	0.6394(2)	0.40946(12)	0.06723(8)	0.0241(3)
H7B	0.7001	0.4646	0.0537	0.029*
C8B	0.5154(2)	0.56668(12)	0.21542(8)	0.0247(3)
H8BA	0.6330	0.5835	0.2358	0.030*
H8BB	0.4463	0.5138	0.2319	0.030*
C9B	0.4535(2)	0.66164(13)	0.23565(8)	0.0272(3)

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{iso}^*/U_{eq}
H9BA	0.3327	0.6435	0.2191	0.033*
H9BB	0.4668	0.6895	0.2845	0.033*
C10B	0.5867(2)	0.60463(11)	0.11490(8)	0.0239(3)
H10E	0.5657	0.5763	0.0660	0.029*
H10F	0.7095	0.6250	0.1283	0.029*
C11B	0.5207(2)	0.69801(12)	0.13750(8)	0.0256(3)
H11E	0.5797	0.7509	0.1187	0.031*
H11F	0.3994	0.6790	0.1213	0.031*
C12B	0.5018(2)	0.83553(12)	0.23444(8)	0.0269(4)
H12E	0.5086	0.8552	0.2832	0.032*
H12F	0.3845	0.8260	0.2164	0.032*
C13B	0.6177(2)	0.92125(12)	0.21539(8)	0.0296(4)
H13E	0.7343	0.9162	0.2209	0.035*
H13F	0.5865	0.9109	0.1680	0.035*
C14B	0.6133(2)	1.02780(13)	0.25517(8)	0.0285(4)
C15B	0.6892(2)	1.07132(13)	0.32061(9)	0.0315(4)
H15B	0.7331	1.0308	0.3416	0.038*
C16B	0.7020(2)	1.17229(13)	0.35566(8)	0.0286(4)
H16C	0.7567	1.2007	0.3999	0.034*
C17B	0.6351(2)	1.23266(12)	0.32645(8)	0.0252(3)
C18B	0.5519(2)	1.18875(13)	0.26246(8)	0.0296(4)
H18C	0.5010	1.2280	0.2427	0.036*
C19B	0.5424(2)	1.08763(13)	0.22695(8)	0.0308(4)
H19B	0.4868	1.0590	0.1829	0.037*
C20B	0.6566(2)	1.34422(12)	0.36389(8)	0.0256(3)
H20C	0.7740	1.3756	0.3855	0.031*
H20D	0.6359	1.3800	0.3322	0.031*
C21B	0.58003(19)	1.36151(11)	0.47926(8)	0.0212(3)
C22B	0.42716(19)	1.37450(11)	0.51130(8)	0.0228(3)
C23B	0.3107(2)	1.38106(11)	0.46484(8)	0.0248(3)
C24B	0.3856(2)	1.37274(11)	0.40207(8)	0.0251(3)
C25B	0.1554(2)	1.39275(12)	0.47970(10)	0.0306(4)
H25B	0.0764	1.3975	0.4478	0.037*
C26B	0.1191(2)	1.39735(12)	0.54339(10)	0.0331(4)
H26B	0.0127	1.4047	0.5551	0.040*
C27B	0.2358(2)	1.39136(12)	0.59014(9)	0.0316(4)
H27B	0.2079	1.3951	0.6333	0.038*
C28B	0.3931(2)	1.38002(11)	0.57477(8)	0.0262(3)
H28B	0.4734	1.3763	0.6066	0.031*

^aOccupancies: ^a = 0.524(5), ^b = 0.476(5).

Experimental details

All H atoms were placed in geometrically idealized positions and refined using a riding model, with C—H = 0.99 (methylene), 0.95 Å (benzene), and with $U_{iso}(H) = 1.2U_{eq}(C)$ for H atoms on methylene and benzene. The hydrogens on terminal methyls were constrained with C—H = 0.98 Å and $U_{iso}(H) = 1.5U_{eq}(C)$. One of the two crystallographically independent molecules show a disorder of the C_2H_4 moiety.

Discussion

The arylpiperazine structure is an important pharmacophore that has wide pharmacological activities [3, 4]. Naftopidil is a derivative of arylpiperazine ether and a specific antagonist targeted for the adrenergic receptor [5], which has already been regarded as one of the most commonly utilized antagonists targeted for the adrenergic receptor to treat the benign prostatic hyperplasia (BPH) in Japan [6]. The arylpiperazine derivative mentioned in this paper is a subselective antagonist for BPH [7].

The asymmetric unit contains two independent molecules. The title compound contained three benzene rings, one piperazine ring and a pyrrole ring. In molecule A, the link part between the piperazine ring and the benzene ring was refined with a disorder model. The conformations of the two crystallographically independent molecules were similar but not the same. In molecule B, ring (C22B—C28B) and ring (C21B—C22B—C23B—C24B—N3B) are coplanar. The dihedral angles made by the planes of (C21B—C22B—C23B—C24B—N3B) and (C14B—C19B), (C21B—C22B—C23B—C24B—N3B) and (N1B—C8B—C9B—N2B—C11B—N10B), (C21B—C22B—C23B—C24B—N3B) and (C2B—C7B) are 66.81(6)°, 68.36(5)° and 75.76(5)°, respectively. In molecule B, the dihedral angles made by the planes of (C21A—C22A—C23A—C24A—N3A) and (C14A—C19A), (C21A—C22A—C23A—C24A—N3A) and (N1A—C8A—C9A—N2A—C11A—N10A), (C21A—C22A—C23A—C24A—N3A) and (C2A—C7A) are 79.63(12)°, 80.33(14)° and 67.80(5)°, respectively. The packing of the title structure shows no classical hydrogen bonds. π – π interactions were observed between ring (C22A—C28A) and ringⁱ (C22B—C28B) with symmetry code (i) 1 – *x*, 2 – *y*, 1 – *z*.

Acknowledgements: This project was supported by the Natural Science Foundation of Shandong Province, China (No. ZR2011HL003).

References

- Agilent Technologies: CrysAlis^{PRO} Software system, version 1.171.35.15, Agilent Technologies UK Ltd, Oxford, UK (2011).
- Sheldrick, G. M.: Crystal structure refinement with SHELXL. *Acta Cryst.* **C71** (2015) 3–8.
- Shah, S. S.; Rivera, G.; Ashfaq, M.: Recent advances in medicinal chemistry of sulfonamides. Rational design as anti-tumoral, anti/bacterial and anti-inflammatory agents. *Mini-Rev. Med. Chem.* **1** (2013) 70–86.
- Wang, J. H.; Wang, Q. D.; Dun, Y. Y.; Fang, H.: Syntheses and anti-tumor activities of purine-sulfonamides derivatives. *Chem. J. Chin. U.* **6** (2014) 1189–1198.
- Liu, W. H.; Chang, J. X.; Liu, Y.; Luo, J. W.: Design, synthesis and activities of novel benzothiazole derivatives containing arylpiperazine. *Acta Pharmaceut. Sin.* **48** (2013) 1259.

6. Nishino, Y.; Masue, T.; Miwa, K.; Takahashi, Y.; Ishihara, S.; Deguchi, T.: Comparison of two α 1-adrenoceptor antagonists, naftopidil and tamsulosin hydrochloride, in the treatment of lower urinary tract symptoms with benign prostatic hyperplasia: a randomized crossover study. *BJU Int.* **97** (2006) 747–751.
7. Xu, F.; Chen, H.; Xu, J. Y.; Xu, B. B.; Shao, B. H.; Huang, B. Y.; Yuan, M.: Synthesis, structure-activity relationship and biological evaluation of novel arylpiperzines as α 1A/1D-AR sub-selective antagonists for BPH. *Bioorg. Med. Chem.* **24** (2015) 7735–7742.