Hong Chen* and Hui-Xia Jia

Crystal structure of 2-(4-(2-(4-(2-fluorophenyl)piperazin-1-yl)ethyl) benzyl)benzo[*d*]isothiazol-3(2H)-one 1,1-dioxide, $C_{26}H_{26}FN_3O_3S$ – a saccharin dervative

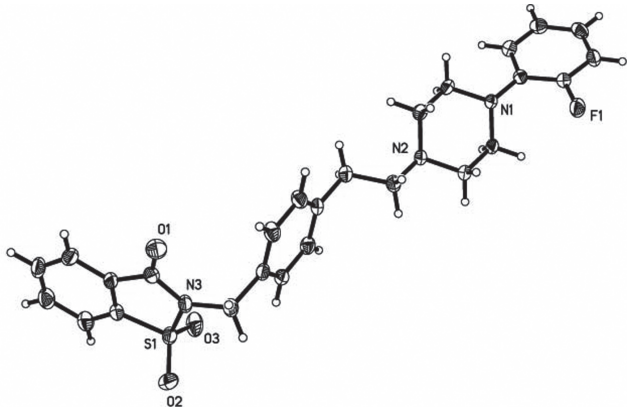

Table 1: Data collection and handling.

Crystal:	Block, clear light yellow
Size:	0.16 × 0.12 × 0.12 mm
Wavelength:	Mo *Kα* radiation (0.71073 Å)
μ:	90.18 mm^{-1}
Diffractometer, scan mode:	Bruker P4, ω-scans
$2\theta_{max}$, completeness:	25.3°, 98%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	19521, 4252, 0.149
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 3291
$N(param)_{refined}$:	307
Programs:	Bruker programs [1], SHELX [2], OLEX2 [3]

https://doi.org/10.1515/ncrs-2017-0197
Received July 11, 2017; accepted October 10, 2017; available online November 8, 2017

Abstract

$C_{26}H_{26}F_1N_3O_3S_1$, triclinic, $P\bar{1}$ (no. 2), $a = 7.0252(14)$ Å, $b = 9.3017(19)$ Å, $c = 19.388(4)$ Å, $\alpha = 97.80(3)°$, $\beta = 97.77(3)°$, $\gamma = 106.84(3)°$, $V = 1180.9(5)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0729$, $wR_{ref}(F^2) = 0.1854$, $T = 296.15$ K.

CCDC no.: 1578933

The crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

The title compound was synthesized starting with saccharin *N*-(4-(methyl)phenethyl 4-methylbenzenesulfonate). To a solution of saccharin *N*-(4-(methyl)phenethyl 4-methylbenzenesulfonate) (100 mg, 0.21 mmol) in acetonitrile (CH_3CN, 10 mL) was added 1-(2-fluorophenyl)piperazine (45.36 mg, 0.25 mmol) and potassium carbonate (173 mg, 1.26 mmol). The reaction mixture was stirred at reflux for 16 h. After cooling to ambient temperature, the reaction mixture was filtered through a Buchner funnel. After filtration the filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1/4, v/v) as eluent to afford the title compound [4].

Experimental details

The hydrogen atoms were assigned with isotropic displacement factors $U_{iso}(H) = 1.2U_{eq}$ (N and imidazol C), or $U_{iso}(H) = 1.5U_{eq}$ (methyl C) and included in the final refinement by using geometrical restraints, with C—H = 0.93 Å (imidazol) or C—H = 0.96 Å (methyl), and N—H = 0.86 Å.

Discussion

The saccharin moiety has been identified as an important molecular component in various classes of 5HT1a antagonists [5], human leukocyte elastase (HLE) inhibitors [6–10], analgesics [11], human mast cell tryptase inhibitors [12], α1a adrenergic receptor antagonists [13] and aldehyde dehydrogenase inhibitors [14]. Moreover, compounds with arylpiperazine moieties have anti-proliferative properties [15, 16]. For these reasons, the efficient synthesis of arylpiperazine derivatives containing the saccharin moiety attract the interest of synthetic chemists. In this context, we report the synthesis of the title compound.

The molecule of the title compound consists of a 1,4-piperazine moitey, a benzo[b]thiophene moiety (saccharin), the ethyl bezyl moiety as well as a 2-fluorophenyl group (cf. the figure). The best planes of the piperazine moiety, the 2-fluorophenyl group and the central arene unit are not in the same plane. The whole molecule is in a twisty conformation. C7—N1—C6—C1 torsion angles between 1,4-piperazine ring

***Corresponding author: Hong Chen,** College of Food and Drug, Luoyang Normal University, Luoyang, Henan 471934, P.R. China, e-mail: chenwexpo@sina.com
Hui-Xia Jia: College of Food and Drug, Luoyang Normal University, Luoyang, Henan 471934, P.R. China

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
S1	1.12276(11)	0.18097(7)	0.92905(3)	0.0463(2)
F1	−0.0029(2)	0.13890(19)	0.24270(8)	0.0577(4)
O1	1.3174(3)	0.5703(2)	0.88626(10)	0.0589(5)
O2	1.2623(3)	0.0968(2)	0.93180(11)	0.0710(6)
O3	0.9126(3)	0.0962(2)	0.90818(11)	0.0687(6)
N1	0.0003(3)	0.2318(2)	0.38308(10)	0.0345(5)
N2	0.2411(3)	0.1984(2)	0.50894(10)	0.0357(5)
N3	1.1891(3)	0.3122(2)	0.87851(10)	0.0410(5)
C1	−0.1682(4)	0.1746(3)	0.25980(13)	0.0389(6)
C2	−0.3220(4)	0.1643(3)	0.20618(14)	0.0505(7)
H2	−0.3166	0.1294	0.1594	0.061*
C3	−0.4855(4)	0.2068(3)	0.22270(15)	0.0525(7)
H3	−0.5924	0.2000	0.1871	0.063*
C4	−0.4891(4)	0.2593(3)	0.29206(15)	0.0491(7)
H4	−0.5978	0.2902	0.3031	0.059*
C5	−0.3335(4)	0.2669(3)	0.34581(13)	0.0429(6)
H5	−0.3403	0.3013	0.3925	0.051*
C6	−0.1664(3)	0.2237(2)	0.33124(12)	0.0353(5)
C7	0.0161(4)	0.0815(2)	0.39356(12)	0.0390(6)
H7A	0.0067	0.0194	0.3480	0.047*
H7B	−0.0953	0.0298	0.4150	0.047*
C8	0.2145(4)	0.0991(3)	0.44063(12)	0.0408(6)
H8A	0.2189	−0.0007	0.4486	0.049*
H8B	0.3252	0.1417	0.4169	0.049*
C9	0.2222(4)	0.3456(3)	0.49653(13)	0.0465(7)
H9A	0.3299	0.3948	0.4729	0.056*
H9B	0.2367	0.4111	0.5416	0.056*
C10	0.0206(4)	0.3265(3)	0.45172(13)	0.0466(6)
H10A	−0.0877	0.2788	0.4754	0.056*
H10B	0.0106	0.4258	0.4452	0.056*
C11	0.4338(4)	0.2146(3)	0.55249(12)	0.0429(6)
H11A	0.5420	0.2706	0.5309	0.051*
H11B	0.4467	0.1137	0.5534	0.051*
C12	0.4600(4)	0.2967(3)	0.62846(13)	0.0466(6)
H12A	0.4675	0.4025	0.6285	0.056*
H12B	0.3433	0.2493	0.6485	0.056*
C13	0.6492(4)	0.2908(3)	0.67369(12)	0.0396(6)
C14	0.6484(4)	0.1641(3)	0.70453(13)	0.0446(6)
H14	0.5292	0.0830	0.6977	0.053*
C15	0.8211(4)	0.1563(3)	0.74506(13)	0.0425(6)
H15	0.8166	0.0705	0.7653	0.051*
C16	1.0018(4)	0.2753(3)	0.75603(12)	0.0389(6)
C17	1.0044(4)	0.4013(3)	0.72511(13)	0.0472(6)
H17	1.1242	0.4816	0.7313	0.057*
C18	0.8300(4)	0.4089(3)	0.68496(13)	0.0483(7)
H18	0.8345	0.4951	0.6651	0.058*
C19	1.1901(4)	0.2701(3)	0.80278(12)	0.0453(6)
H19A	1.2002	0.1677	0.7934	0.054*
H19B	1.3083	0.3394	0.7909	0.054*
C20	1.2566(3)	0.4619(3)	0.91420(13)	0.0411(6)
C21	1.2405(3)	0.4644(3)	0.98975(13)	0.0408(6)
C22	1.2841(4)	0.5915(3)	1.04280(15)	0.0520(7)
H22	1.3319	0.6900	1.0337	0.062*
C23	1.2536(4)	0.5658(4)	1.11023(15)	0.0618(8)
H23	1.2831	0.6493	1.1467	0.074*
C24	1.1816(5)	0.4221(4)	1.12440(15)	0.0647(8)
H24	1.1625	0.4099	1.1700	0.078*
C25	1.1367(4)	0.2942(4)	1.07184(14)	0.0581(8)
H25	1.0871	0.1958	1.0809	0.070*
C26	1.1695(4)	0.3201(3)	1.00528(13)	0.0430(6)

and the 2-fluoro-benzene ring is −70°, which clearly deviate from planarity. The angle is 34° between the central arene ring and the benzo[b]thiophene. In the molecule, the N(1)—C(6), N(1)—C(7), N(1)—C(10), N(2)—C(8), N(2)—C(9), N(2)—N(11) bond lengths are found to be 1.413(3) Å, 1.472(3) Å, 1.458(3) Å, 1.464(3) Å, 1.461(3) Å and 1.452(3) Å, respectively, which are nearly equal to other typical single bonds. The bond lengths of C(20)—O(3) is found to be 1.206(4) Å, which is in accordance with a typical double bond. S(1)—O(2) and S(1)—O(3) are 1.421(2) and 1.429(9) Å, respectively, which is in accordance with the expectations [17]. The bond angles C6—N1—C7, C6—N1—C10, C10—N1—C7, C11—N2—C8, C11—N2—C9 and C9—N2—C8 are 113.86(18), 116.07(19), 109.36(18), 111.44(18)°, 112.20(19) and 109.01(18)°, respectively. Furthermore, the angles C20—N3—S1, C20—C3—C19, C19—N3—S1 are 115.06(17), 122.8(2), 121.97(17), respectively.

Acknowledgements: This work was supported by the Natural Science Foundation of China (No. 81401462), Henan Province Science and Technology Attack Plan Foundation (No. 162102310477), the Key Scientific Research Project of Higher Education of Henan Province (Nos. 16A350008, 17A150039 and 17B350001) and National Scientific Research Foundation of Luoyang Normal University (No. 2015-PYJJ-005).

References

1. Bruker: APEX2, SAINT and SADABS. Brucker AXS Inc., Madison, WI, USA (2009).
2. Sheldrick, G. M.: A short history of SHELX. Acta. Crystallogr. **A64** (2008) 112–122.
3. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H.: OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. **42** (2009), 339–341.
4. Chen, H.; Liang, X.; Xu, F.; Xu, B.-B.; He, X.-L.; Huang, B.-Y.; Yuan, M.: Synthesis and cytotoxic activity evaluation of novel arylpiperazine derivatives on human prostate cancer cell lines. Molecules **9** (2014) 12048–12064.
5. Romero, A. G.; Darlington, W. H.; Piercey, M. F.; Lahti, R. A.: Synthesis of metabolically stable arylpiperazine 5-HT1A receptor agonists. Bioorg. Med. Chem. Lett. **9** (1992) 1703–1706.

6. Martyn, D. C.; Moore, M. J.; Abell, A. D.: Succinimide and saccharinbased enzyme-activated inhibitors of serine proteases. Curr. Pharm. Des. **9** (1999) 405–415.
7. Groutas, W. C.; Epp, J. B.; Venkataraman, R.; Kuang, K.; Truong, T. M.; McClenahan, J. J.; Prakash, O.: Design, synthesis, and in vitro inhibitory activity toward human leukocyte elastase, cathepsin G, and proteinase 3 of saccharin-derived sulfones and congeners. Bioorg. Med. Chem. **9** (1996) 1393–1400.
8. Hlasta, D. J.; Bell, M. R.; Boaz, N. W.; Court, J. J.; Desai, R. C.; Franke, C. A.; Mura, A. J.; Subramanyam, C.; Dunlap, R. P.: A benzisothiazolone class of potent, selective mechanism-based inhibitors of human leukocyte elastase. Bioorg. Med. Chem. Lett. **9** (1994) 1801–1806.
9. Hlasta, D. J.; Bell, M. R.; Court, J. J.; Cundy, K. C.; Desai, R. C.; Ferguson, E. W.; Gordon, R. J.; Kumar, V.; Maycock, A. L.; Subramanyam, C.: The design of potent and stable benzisothiazolone inhibitors of human leukocyte elastase. Bioorg. Med. Chem. Lett. **9** (1995) 331–336.
10. Hlasta, D. J.; Subramanyam, C.; Bell, M. R.; Carabateas, P. M.; Court, J. J.; Desai, R. C.; Drozd, M. L.; Eickhoff, W. M.; Ferguson, E. W.; Gordon, R. J.; Johnson, J. A.; Kumar, V.; Maycock, A. L.; Mueller, K. R.; Pagani, E. D.; Robinson, D. T.; Saindane, M. T.; Silver, P. J.; Subramanian, S.; Dunlap, R. P.; Franke, C. A.; Mura, A. J.; Rowlands, A. G.: Orally bioavailable benzisothiazolone inhibitors of human leukocyte elastase. J. Med. Chem. **9** (1995) 739–744.
11. Gonzalez-Martin, G.; Lyndon, C.; Sunkel, C.: Hepatic kinetics of SCP-1(*N*-[α-(1,2-benzisothiazol-3(2*H*)-ona-1,1-dioxide-2-yl)-acetyl]-*p*-aminophenol) compared with acetaminophen in isolated rat liver. Eur. J. Pharm. Biopharm. **9** (1998) 293–297.
12. Combrink, K. D.; Gulgeze, H. B.; Meanwell, N. A.; Pearce, B. C.; Zulan, P.; Bissacci, G. S.; Roberts, D. G. M.; Stanley, P.; Seiler, S. M.: 1,2-Benzisothiazol-3-one 1,1-dioxide inhibitors of human mast cell tryptase. J. Med. Chem. **9** (1998) 4854–4860.
13. Patane, M. A.; Dipardo, R. M.; Price, R. P.; Chang, R. S. L.; Ransom, R. W.; OMalley, S. S.; De-Salvo, J.; Bock, M. G.: Selective α-1A adrenergic receptor antagonists. Effects of pharmacophore regio- and stereochemistry on potency and selectivity. Bioorg. Med. Chem. Lett. **9** (1998) 2495–2500.
14. Nagasawa, H. T.; Kawle, S. P.; Elberling, J. A.; DeMaster, E. G.; Fukuto, J. M.: Prodrugs of nitroxyl as potential aldehyde dehydrogenase inhibitors vis-a-vis vascular smooth muscle relaxants. J. Med. Chem. **9** (1995) 1865–1871.
15. Berardi, F.; Abate, C.; Ferorelli, S.; De Robertis, A. F.; Leopoldo, M.; Colabufo, N. A.; Niso, M.; Perrone, R.: Novel 4-(4-aryl)cyclohexyl-1-(2-pyridyl)piperazines as delta(8)-delta(7) sterol isomerase (emopamil binding protein) selective ligands with antiproliferative activity. J. Med. Chem. **9** (2008) 7523–7531.
16. Liu, W.-H.; Chang, J.-X.; Liu, Y.; Luo, J.-W.; Zhang, J.-W.: Design, synthesis and activities of novel benzothiazole derivatives containing arylpiperazine. Acta Pharmaceutica Sinica **9** (2013) 1259–1265.
17. Lu, N.; Chiang, H.-F.; Wei, R.-J.; Wen, Y.-S.; Liu, L.-K.: Molecular structures of 3-[(2,2,3,3-tetrafluoropropoxy)methyl]- and 3-[(2,2,3,3,3-pentafluoropropoxy)methyl]pyridinium saccharinates. Acta Crystallogr. **C73** (2017) 593–599.