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Synthesis and Crystal Structure of (Z)-3-Benzyl-5-[4-(benzyloxy)-3-methoxybenzylidene]thiazolidine-2,4-dione

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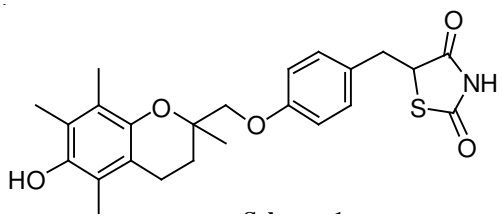
The synthesis and crystal structure of the (Z)-3-benzyl-5-(4-(benzyloxy)-3-methoxybenzylidene)thiazolidine-2,4-dione has been determined by single crystal X-ray diffraction method. The crystal belongs to triclinic, space group P1, with a = 9.098(4), b = 10585(5), c = 11.609(5)Å, α = 80.549(6), β = 88.159(6), γ = 71.587(4)°, V = 1046.2(8)Å^3, Z = 2, Dx = 1.370 Mg/m^3, λ(MoK$_\alpha$) = 0.71073, F(000) = 452, μ(MoK$_\alpha$) = 0.188 mm^{-1}, R = 0.0815 and wR = 0.2507 for 2038 reflections with I > 2σ(I). The C(6)-C(7) bond (1.506 Å) confirm the delocalization of the p electrons between thiazolidine-2,4-dione ring and benzene ring in the title compound, but the thiazolidine-2,4-dione ring and benzene C(7)-C(12) planes are not in the same plane and make a dihedral angle of 16.69(0.20)° with each other.

Key Words: Synthesis, Crystal structure, (Z)-3-Benzyl-5-(4-(benzyloxy)-3-methoxybenzylidene)thiazolidine-2,4-dione.

INTRODUCTION

Thiazolidinediones (TZDs) are known to sensitize tissues to insulin, have been developed and clinically used as antidiabetic agents. They have been shown to reduce plasma glucose, lipid and insulin levels and used for the treatment of type 2 diabetes[1,2]. Within a short time after the launch of the thiazolidinediones, several reports of treatment-related toxicity have been published[3]. Troglitazone (**Scheme-I**), the first thiazolidinedione marketed, had been associated with severe drug-induced liver failure which resulted in its withdrawal from the market in 2000[4].



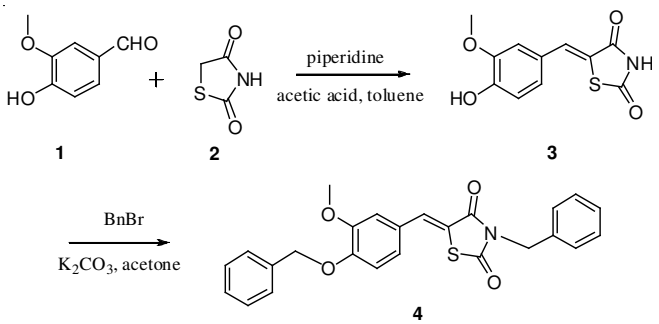
Scheme-I: Structure of troglitazone

In order to synthesis, characteristics and biological activity of novel thiazolidinedione derivatives with with better safety and efficacy, we introduced different groups substitution on the benzene ring moiety[5]. As part of our search for bioactive compounds, here we report the synthesis and crystal structure of (Z)-3-benzyl-5-(4-(benzyloxy)-3-methoxybenzylidene) thiazolidine-2,4-dione.

EXPERIMENTAL

The melting point was determined on a Yamato MP-21 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-300P Instrument (300 MHz) with $CDCl_3$ as the solvent. ESI mass spectra were performed on an API-3000 LC-MS spectrometer. The single-crystal structure was determined on a Rigaku Saturn CCD area detector. All the reagents were of analytical reagent grade.

Synthesis and characterization: The (Z)-3-benzyl-5-(4-(benzyloxy)-3-methoxybenzylidene) thiazolidine-2,4-dione (4) was prepared following **Scheme-II**.



Scheme-II: Procedure of preparing the title compound (**4**)

Preparation of compound 3: A mixture of 2,4-thiazolidinedione (3.51 g, 0.03 mol), 4-hydroxy-3-methoxybenzaldehyde

(4.56 g, 0.03 mol), acetic acid (0.18 g, 0.003 mol) and piperidine (0.26 g, 0.003 mol) in toluene (60 mL) was refluxed for 5 h with continuous removal of water. The reaction mixture was cooled to room temperature and the resultant crystalline compound was filtered and washed with water and dried to afford the (Z)-5-(4-hydroxy-3-methoxybenzylidene)-thiazolidine-2,4-dione (**3**). Yield 7.33 g, 97.3 %, yellow powder[6]. m.p. 224.3-225.6 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.92 (w, 1H, NH), 7.72 (s, 1H, 6-H), 6.97-6.71 (m, 3H, 8-H, 11-H, 12-H), 3.83 (s, 3H, OCH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 167.53, 165.59, 149.05, 147.24, 143.44, 128.94, 123.79, 116.54, 115.37, 55.82. MS(ESI) m/z calcd. (%) for $C_{11}H_{19}NO_4S$ 251.25, found (%) $[M-H]^+$ 250.13.

Synthesis of compound 4: (Z)-5-(4-Hydroxy-3-methoxy-benzylidene)thiazolidine-2,4-dione (**3**) (0.5 g, 2 mmol) in anhydrous acetone (20 mL) was added benzyl bromide (0.4 mL, 3.4 mmol) and K_2CO_3 (0.4 g, 3 mmol) with stirring. The resulting mixture was refluxed for 6 h. the mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was added water (100 mL) and extracted with EtOAc (40 mL × 3). The extract was washed with saturated brine (20 mL) succesively. The organic layer was dried over Na_2SO_4, after removal of the solvent, the product was purified by flash column chromatography eluted with a mixture of hexane/EtOAc (3:1 v/v) as eluent to provide the compound (Z)-3-benzyl-5-(4-(benzyloxy)-3-methoxybenzylidene)-thiazolidine-2,4-dione **4** (0.42 g). Yield: 48.95 %, yellow powder[7]. m.p. 157-158 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 (s, 1H, 6-H), 7.46-7.26 (m, 10H, Ar-H), 7.03-6.96 (m, 3H, 8-H, 11-H, 12-H), 5.22 (s, 2H, OCH_2Ph), 4.90 (s, 2H, NCH_2Ph), 3.94 (s, 3H, OCH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 167.80, 166.20, 150.36, 149.82, 136.22, 135.22, 134.09, 128.81, 128.69, 128.18, 128.13, 127.18, 126.40, 124.49, 118.76, 113.53, 112.84, 70.84, 56.01, 45.18. MS(ESI) m/z calcd. (%) for $C_{10}H_{12}O_5$ 431.49, found (%) $[M-H]^+$ 430.25.

Crystallography studies: The title compound was dissolved in butanone and yellow crystals suitable for X-ray analysis grew over a period of 2 weeks when the solution was exposed to air at room temperature. The crystal having approximate dimensions of 0.15 mm × 0.10 mm × 0.08 mm was mounted on the top of a glass fiber in a random orientation. The data were collected by a Bruker SMART 1000 CCD area detector diffractometer equipped with a graphite-monochromatized MoK_αradiation radiation (λ = 0.71073 Å) by using a φ-ω scan mode at 293 K. A total of 4357 reflections were collected in the range of $1.78 < \theta < 25.01$º, of which 3606 were independent (R_{int} = 0.0302) and 2038 were observed with $I > 2\sigma(I)$.

The data collection and procession were performed with program SMART and SHELXTL[8]. The structure was solved by direct methods and refined by fullmatrix least-squares/difference Fourier techniques with SHELXS-97 and SHELXL-97 programs[9]. All non-hydrogen atoms were refined with anisotropic displacement parameters. After that, all hydrogen atoms were located theoretically and refined with riding model position parameters and fixed isotropic thermal parameters. The final R = 0.0815, wR = 0.2507($w = 1/[\sigma^2(F_o^2) + (0.1598P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$), $(\Delta/\sigma)_{max}$ = 0.000, S = 0.978, $(\Delta\rho)_{max}$ =1.447 and $(\Delta\rho)_{min}$ = -0.310 e/Å^{-3}.

RESULTS AND DISCUSSION

Crystal structure description: The title compound was prepared according to **Scheme-II**. The ^{1}H, ^{13}C NMR, MS and m.p. for the product are in good agreement with the title compound. In order to confirm the configuration of the product, a single crystal of the title compound was cultured for X-ray diffraction analysis. The crystal belongs to Triclinic with space group P-1. The molecular structure and perspective view of the crystal packing in a unit cell of the title compound are shown in Figs. 1 and 2, respectively. The selected bond lengths are listed in Table-1 and the bond angles in Table-2.

The molecule contains three benzene and a thiazolidine-dione rings. The five-membered ring of thiazolidine-2,4-dione is nearly planar with maximum atomic deviation of 0.010 (2)Å. As expected, the S(1)-C(2), S(1)-C(5), C(2)-N(3) and N(3)-C(4) bond lengths (Table-1), suggesting the S(1), C(1), C(2), N(3), C(4) and C(5) atoms are sp^2 hybridized. The C(6)-C(7) bond (1.506 Å) confirm the delocalization of the p electrons between thiazolidine-2,4-dione ring and benzene ring in the title compound, but the thiazolidine-2,4-dione ring and benzene C(7)-C(12) planes are not in the same plane and make a dihedral angle of 16.69(0.20)º with each other. The thiazolidine-2,4-dione ring makes dihedral angles of 75.03(0.11)º with the benzene ring C(14)-C(19). The dihedral angle of the two benzene rings C(7)-C(12) and C(22)-C(27) is 14.25(0.23)º.

Conclusion

The compound (Z)-3-benzyl-5-(4-(benzyloxy)-3-methoxybenzylidene)thiazolidine-2,4-dione, was synthesized

TABLE-1
SELECTED BOND LENGTHS (Å) FOR THE TITLE COMPOUND

Bond	Length (Å)	Bond	Length (Å)	Bond	Length (Å)
S(1)-C(5)	1.729(4)	C(5)-C(6)	1.349(6)	C(16)-C(17)	1.371(8)
S(1)-C(2)	1.768(5)	C(6)-C(7)	1.506(6)	C(17)-C(18)	1.354(7)
N(3)-C(4)	1.380(6)	C(7)-C(8)	1.371(6)	C(18)-C(19)	1.366(6)
N(3)-C(2)	1.407(6)	C(7)-C(12)	1.379(6)	C(21)-C(22)	1.507(6)
N(3)-C(13)	1.470(6)	C(8)-C(9)	1.396(6)	C(22)-C(23)	1.370(6)
O(1)-C(2)	1.192(5)	C(9)-C(10)	1.429(6)	C(22)-C(27)	1.381(6)
O(2)-C(4)	1.195(5)	C(10)-C(11)	1.375(6)	C(23)-C(24)	1.397(6)
O(3)-C(9)	1.335(5)	C(11)-C(12)	1.421(6)	C(24)-C(25)	1.350(7)
O(3)-C(20)	1.395(6)	C(13)-C(14)	1.509(6)	C(25)-C(26)	1.350(7)
O(4)-C(10)	1.348(5)	C(14)-C(15)	1.376(6)	C(26)-C(27)	1.379(7)
O(4)-C(21)	1.410(5)	C(14)-C(19)	1.387(6)	–	–
C(4)-C(5)	1.494(6)	C(15)-C(16)	1.384(7)	–	–

TABLE-2
SELECTED BOND ANGLES (°) FOR THE TITLE COMPOUND

Angles	(°)	Angles	(°)	Angles	(°)
C(5)-S(1)-C(2)	92.0(2)	C(8)-C(7)-C(12)	121.6(4)	C(19)-C(14)-C(13)	121.2(4)
C(4)-N(3)-C(2)	116.9(4)	C(8)-C(7)-C(6)	115.9(4)	C(14)-C(15)-C(16)	119.9(5)
C(4)-N(3)-C(13)	123.5(4)	C(12)-C(7)-C(6)	122.5(4)	C(17)-C(16)-C(15)	121.0(5)
C(2)-N(3)-C(13)	119.6(4)	C(7)-C(8)-C(9)	122.5(4)	C(18)-C(17)-C(16)	119.2(5)
C(9)-O(3)-C(20)	118.0(4)	C(7)-C(8)-C(9)	120.4(4)	C(17)-C(18)-C(19)	120.6(5)
C(10)-O(4)-C(21)	120.6(3)	O(3)-C(9)-C(8)	125.0(4)	C(18)-C(19)-C(14)	121.3(4)
O(1)-C(2)-N(3)	125.0(5)	O(3)-C(9)-C(10)	116.5(4)	O(4)-C(21)-C(22)	108.3(3)
O(1)-C(2)-S(1)	125.0(4)	C(8)-C(9)-C(10)	118.4(4)	C(23)-C(22)-C(27)	118.0(4)
N(3)-C(2)-S(1)	110.0(3)	O(4)-C(10)-C(11)	125.6(4)	C(23)-C(22)-C(21)	122.0(4)
O(2)-C(4)-N(3)	122.9(4)	O(4)-C(10)-C(9)	113.6(4)	C(27)-C(22)-C(21)	119.9(4)
O(2)-C(4)-C(5)	127.8(4)	C(11)-C(10)-C(9)	120.8(4)	C(22)-C(23)-C(24)	120.0(5)
N(3)-C(4)-C(5)	109.3(4)	C(10)-C(11)-C(12)	119.2(4)	C(25)-C(24)-C(23)	121.2(5)
C(6)-C(5)-C(4)	118.7(4)	C(7)-C(12)-C(11)	119.4(4)	C(24)-C(25)-C(26)	118.9(4)
C(6)-C(5)-S(1)	129.5(3)	N(3)-C(13)-C(14)	112.4(4)	C(25)-C(26)-C(27)	121.3(5)
C(4)-C(5)-S(1)	111.7(3)	C(15)-C(14)-C(19)	118.1(4)	C(26)-C(27)-C(22)	120.6(5)
C(5)-C(6)-C(7)	129.9(4)	C(15)-C(14)-C(13)	120.7(4)	–	–

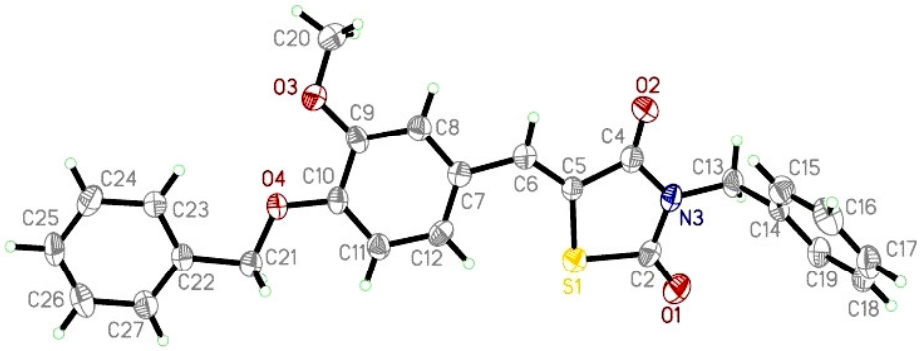


Fig. 1. Molecular structure of the title compound

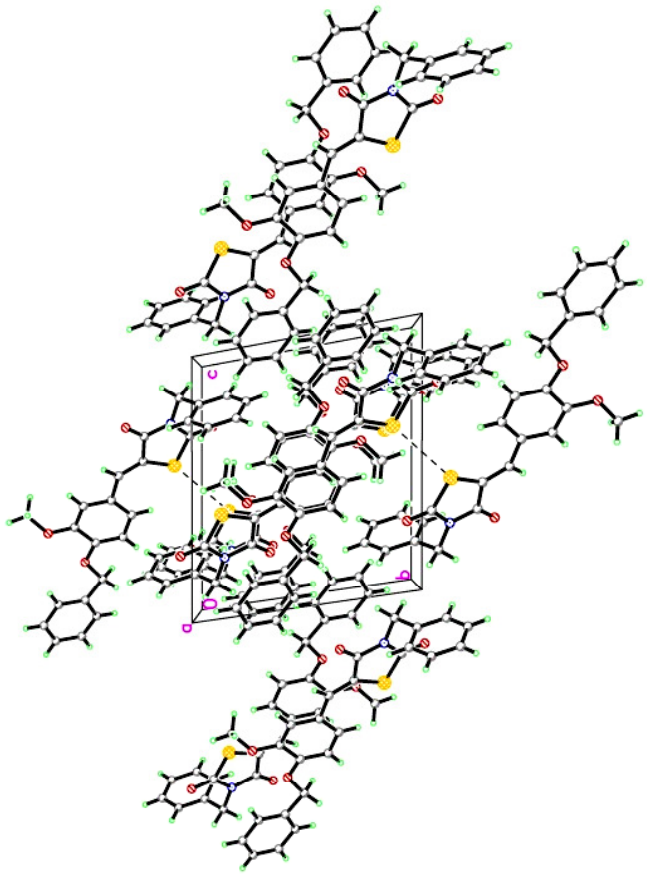


Fig. 2. Crystal packing of the title compound

and characterized by means of ^{1}H, ^{13}C NMR, MS and X-ray diffraction. The crystal belongs to triclinic with space group P-1 and the five-membered ring of thiazolidine-2,4-dione is nearly planar with maximum atomic deviation of 0.010(2) Å. Further biological activities evaluation of this compound on antidiabetic activity is underway in our laboratory.

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