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ORIGINAL PAPER

Synthesis, Crystal Structure and Spectroscopic Characterization of {6-[2-(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazol-3(2*H*)-yl}acetic acid

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Abstract The title compound {6-[2-(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazol-3(2*H*)-yl}acetic acid was prepared and characterized by elemental analyses, FT-IR, ^{1}H NMR spectroscopy, X-ray diffraction. A quantum-chemical calculation was performed using the CNDO method. In the title compound, $C_{18}H_{11}ClN_2O_3S_2$, the crystal structure is stabilized by intermolecular hydrogen bonds (C–H···O=C) to form centrosymmetric $R_2^2(16)$ dimers and the C–H···O, O–H···N, and C–H···N interactions generating the graph set motifs $R_2^2(9)$ and $R_2^2(22)$.

Keywords Crystal structure · Acetic acid · X-ray · CNDO method

Introduction

2-Benzothiazolinone (2-benzoxazolinone) derivatives exhibit a variety of pharmacological effects, including analgesic and anti-inflammatory activity [1, 2].

Small and simple heterocyclic molecules such as benzothiazole and its derivatives represent the types of compounds of versatility for their utilization. They contain extended π-delocalized systems which are capable of binding to DNA molecules via π–π interactions and therefore exhibit complex biological properties, as antitumor, anti-infective, antifungal or antihelmintic activities [3].

This title compound, $C_{18}H_{11}ClN_2O_3S_2$, was synthesized to serve as an inhibitor for the cyclooxygenase (COX) enzyme. However, certain inhibitor activity was seen neither on COX-1 nor on COX-2 [4]. The COX enzyme has two forms: COX-1 and COX-2. The measure of COX-1 and COX-2 inhibitions of the active compounds was also investigated by using in vitro human whole blood assay [4].

Results and Discussion

Chemistry

The 1,3-benzothiazol-2(3*H*)-one was prepared via condensation of 2-aminothiophenol with the urea under microwave irradiation (MWI). The 1,3-benzothiazol-2(3*H*)-one was converted to 6-(2-bromoacetyl)-2-oxo-1,3-benzothiazole by bromoacetic acid exchange reaction followed under MWI. After, to synthesize 6-[(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazole, the 6-(2-bromoacetyl)-2-oxo-1,3-benzothiazole was condensed with 2-chlorothiobenzamide in diglyme. Acetic acid derivative was synthesized by the acid hydrolysis of the corresponding ethyl ester which was prepared by the reaction of 6-[(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazole with ethyl bromoacetate in the presence of metallic sodium [4] (Scheme 1).

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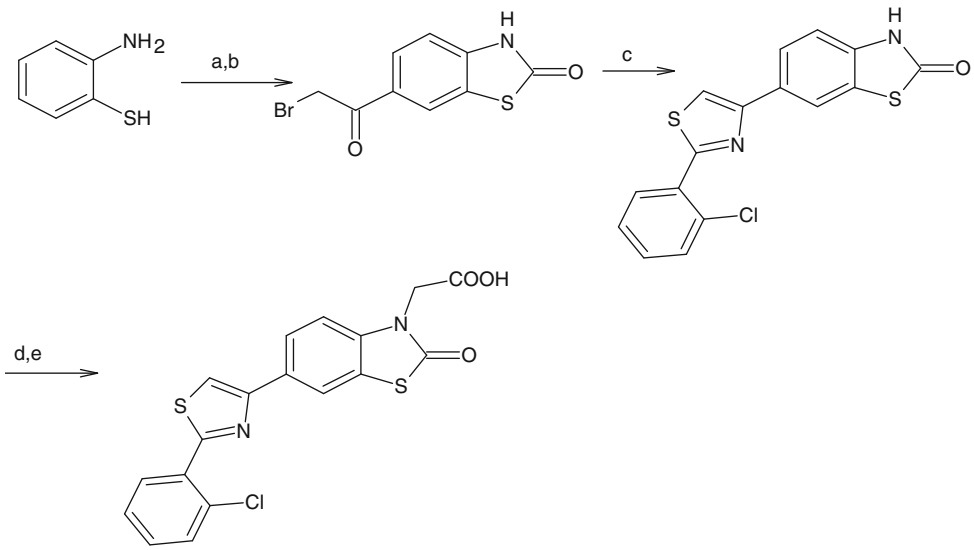
Scheme 1 Synthetic route of title compound



a: Urea, MWI; b: PPA, $BrCH_2COOH$, MWI; c: 2-Chlorothiobenzamide, diglyme; d: NaOEt, $BrCH_2COOC_2H_5$; e: HCI

Crystal Structure Analysis

In this study, the crystal structure of the title compound, {6-[2-(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazol-3(2*H*)-yl}acetic acid, was determined by X-ray analysis. The data were collected on an Enraf–Nonius Turbo CAD-4 [5] diffractometer with a scintillation detector. Diffraction measurements were made at 293 K. The cell was refined on a CAD-4 Express and the data were reducted on a XCAD-4 [6]. The structure was solved by direct methods using SIR-97 [7] and refined by a full-matrix least-squares procedure using the program SHELXL-97 [8]. The H atoms were positioned geometrically and refined by riding rigid body approximation, with C–H distances in the range 0.93 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$. The isotropic displacement parameter of the H15 atom bounded to the C15 atom was fixed at the value of 0.5 $Å^2$ during the refinement procedure. The 24 disagreeable reflections were omitted in the refinement. The software used to prepare material for publication: WinGX publication routines [9]. Empirical absorption corrections were applied by the ψ-scan method [10].

An ORTEP drawing [11] of the title molecule with 30% probability displacement thermal ellipsoids and atom-labeling scheme are shown in Fig. 1. The crystal data and structure refinement details for the compound are given in Table 1. The selected bond lengths and angles are given in Table 2.

The bond lengths and angles are in the normal range [12–14]. The benzothiazole ring is essentially planar

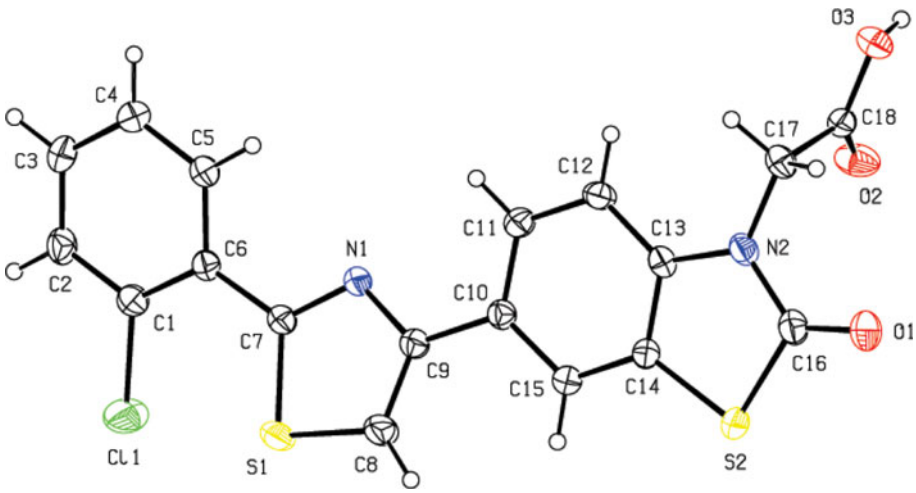


Fig. 1 An ORTEP view of the title compound with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level

Table 1 Crystal data and details for structure determination of $C_{18}H_{11}ClN_2O_3S_2$

CCDC No	731834
Empirical formula	$C_{18}H_{11}ClN_2O_3S_2$
Formula weight	402.88
Temperature (K)	293
Wavelength (Å)	0.71073 (MoK_α)
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	11.9392(16)
b (Å)	13.693(2)
c (Å)	10.468(6)
α (°)	90
β (°)	91.22(3)
γ (°)	90
Volume (Å^3)	1711.0(10)
Z	4
Color	Light yellow
D_{calc} (g cm^{-3})	1.564
Absorption coefficient (mm^{-1})	0.489
$F(000)$	824
Crystal size (mm)	0.40 × 0.40 × 0.40
θ range for data collection (°)	2.45–26.30
Collected reflections	7152
Independent reflections	3440
Number of data with $I > 2\sigma(I)$	2805
Absorption correction	ψ-scan
T_{min}	0.828
T_{max}	0.828
R_{int}	0.0184
h	−14 → 14
k	−17 → 17
l	0 → 13
Refinement method	Full-matrix least-squares on F^2
Final R indices [$I > 2\sigma(I)$]	0.0330
$wR(F^2)$	0.0919
Goodnes-of-fit on F^2	1.010
Structure determination	SIR-97
$(\Delta/\sigma)_{max}$	<0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.47
$\Delta\rho_{min}$ (e Å^{-3})	−0.33

$w = 1/[\sigma^2(F_0^2) + (0.049P)^2 + 0.6298P]$ where $P = (F_0^2 + 2F_c^2)/3$

($\chi^2 < 5$) [15]. The plane of the benzothiazole ring (S2/N2/C10–C16) makes the dihedral angles of 16.92(6) and 4.20(7)° with the S1/N1/C7–C9 and C1–C6 rings, while the mean planes of these rings form 20.61(8)° with each other. The torsion angles N2–C17–C18–O2 and N2–C17–C18–O3 are −0.5(2) and 179.54(14)°, respectively.

Table 2 Selected bond lengths (Å) and angles (°) for $C_{18}H_{11}ClN_2O_3S_2$

Bond lengths (Å)		Bond angles (°)	
Cl1–C1	1.7333 (18)	C8–S1–C7	89.72 (9)
S1–C8	1.704 (2)	C7–N1–C9	112.05 (14)
O1–C16	1.213 (2)	C16–N2–C17	119.58 (14)
N1–C9	1.375 (2)	C2–C1–C6	122.13 (17)
C1–C2	1.376 (3)	C2–C1–Cl1	116.43 (14)
C2–C3	1.374 (3)	C5–C6–C1	116.58 (15)
C3–C4	1.383 (3)	N1–C7–C6	121.99 (15)
C4–C5	1.379 (2)	N1–C7–S1	113.20 (12)
C5–C6	1.398 (2)	C6–C7–S1	124.58 (12)
C6–C7	1.474 (2)	N1–C9–C10	121.04 (14)
C8–C9	1.356 (2)	N2–C13–C14	112.45 (14)
C9–C10	1.478 (2)	C13–C14–S2	111.15 (12)
C10–C11	1.398 (2)	O1–C16–N2	125.48 (18)
C11–C12	1.385 (2)	O1–C16–S2	124.83 (16)
C12–C13	1.382 (2)	N2–C16–S2	109.69 (12)
C13–C14	1.398 (2)	N2–C17–C18	111.59 (14)
C14–C15	1.377 (2)	O2–C18–O3	125.02 (15)
C17–C18	1.515 (2)	O2–C18–C17	124.05 (15)

Table 3 Hydrogen-bond parameters (Å, °)

D–H···*A*	*D*–H (Å)	H···*A* (Å)	D···A (Å)	*D*–H···*A* (°)
O3–H3···N1^{i}	0.82	1.94	2.713 (2)	158
C2–H2···O1^{ii}	0.93	2.58	3.435 (3)	153
C5–H5···N1	0.93	2.53	2.851 (3)	101
C11–H11···O2^{i}	0.93	2.53	3.291 (3)	140
C15–H15···O2^{iii}	0.93	2.39	3.187 (3)	143

Symmetry codes: (i) 1−*x*, 2−*y*, −*z*; (ii) −1 + *x*, *y*, 1 + *z*; (iii) 1; (iv) *x*, 1/2−*y*, −1/2 + *z*

In the crystal structure, molecules of the title compound are linked by intermolecular hydrogen bonds (C–H···O=C) to form centrosymmetric $R_2^2(16)$ dimers. In addition, the C–H···O, O–H···N, and C–H···N interactions generate rings of graph set motifs $R_2^2(9)$ and $R_2^2(22)$ [16, 17], forming a three-dimensional network (Table 3).

Theoretical Study

We have carried out CNDO (Complete Neglect of Differential Overlap) [18] quantum mechanical calculations on the title compound. The calculated charge distribution on the molecule of (I) in the gas phase is as at atoms Cl1, S1, S2, N1, N2, O1, O2, and O3 are—0.181,−0.065, −0.172, −0.225, −0.044, −0.408, −0.280, and −0.315e$^-$, respectively. The calculated dipole moment of the title molecule is *ca* 7.798 Debye. The highest occupied and lowest

unoccupied molecular orbital energy levels are −9.7805 and 1.1783 eV, respectively. When the values of the geometric parameters of the title molecule are considered, theoretical calculation results are consistent with experimental results within the error limits.

Experimental

The FT-IR spectra (KBr pellet, 4000–400 cm^{-1}) of the compounds were recorded on a Bruker Vector 22 IR (Opus Spectroscopic Software Version 2.0) spectrometer as KBr discs. Elemental analysis was performed on Leco 932 C, H, N, S instrument (St. Joseph, MI, USA) and the data were within ±0.4% of the theoretical values. The ^{1}H-NMR spectra were recorded with a Varian Mercury-400 FT-NMR spectrometer (Varian Inc., Palo Alto, CA, USA), in DMSO-d_6.

Melting points of the compounds were recorded on an Electrothermal-9200 digital melting points apparatus and were uncorrected.

Synthesis of {6-[2-(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazol-3(2H)-yl}acetic acid, $C_{18}H_{11}ClN_2O_3S_2$

0.002 mol ethyl {6-[(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazol-3-yl}acetate derivative was refluxed in hydrochloric acid for 4 h. The reaction mixture was cooled, and the precipitate was collected by filtration, washed with water, dried, and crystallized from acetic acid–water (4:1). Light yellow crystals of {6-[2-(2-chlorophenyl)-1,3-thiazol-4-yl]-2-oxo-1,3-benzothiazol-3-yl}acetic acid suitable for X-ray measurements were formed by slow evaporation. The yield and m.p. are 0.21 g, 5.2%, 222–227 °C, respectively. Elemental analysis: $C_{18}H_{11}ClN_2O_3S_2$, calculated (%)/found (%): C: 53.66/53.88, H: 2.75/2.54, N: 6.95/7.08.

FT-IR Characterization

The compound, which was expected to show analgesic effect, was synthesized but did not show any activity in experimentals of in vitro enzyme of COX-1 and COX-2. The structure not showing any activity is one of the findings [4].

The significant absorption bands of the compound are given in Table 4. The synthesized compound was in good agreement with elemental and spectral data.

Supplementary Data

Crystallographic data for the structural analysis have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 731834. Data Acquisition—the Cambridge Crystallographic Data Centre deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk/deposit. Telephone: (44) 01223 762910, Facsimile: (44) 01223 336033, Postal Address: CCDC, 12 Union Road, CAMBRIDGE CB2 1EZ, UK.

Table 4 The important IR and ^{1}H-NMR spectral data of the title compound

IR (KBr pelleti) (cm^{-1})	^{1}H-NMR (400 MHz, DMSO-d_6) (δ)
3200–2100 (–OH stretching, carboxylic acid, broad)	8.39 (d, 1H, H^7)
3062 (C–H stretching, aromatic, weak)	8.38–8.34 (m, 1H, phenyl-H^3)
2921 (C–H stretching, alifatic, weak)	8.29 (s, 1H, thiazole-H^4)
1726 (C=O, carbonyl, alifatic carboxylic acid, strong)	8.04 (dd, 1H, H^5)
1602 (C=C, carbonyl, aromatic, weak)	7.68–7.64 (m, 1H, phenyl-H^6)
1677 (C=O, carbonyl, lactam, strong)	7.56–7.50 (m, 2H, phenyl-$H^{4,5}$)
766 (1,2-disubstituted benzene, moderately strong)	7.43 (d, 1H, H^4)
	4.77 (s, 2H, N–CH_2–CO)

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