Communication

Synthesis and Crystal Structure of 3-(4-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one

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Abstract: Synthesis of the title compound from 4-methoxyaniline was accomplished in three steps. The structure was supported by spectroscopic data and unambiguously confirmed by single crystal X-ray diffraction data. It crystallizes in the monoclinic space group P2$_1$ with unit cell dimensions $a = 9.9349(8)$, $b = 6.3377(5)$, $c = 10.5783(10)$ Å, $\beta = 97.752(3)°$, $V = 659.97(10)$ Å^3, Z = 2.
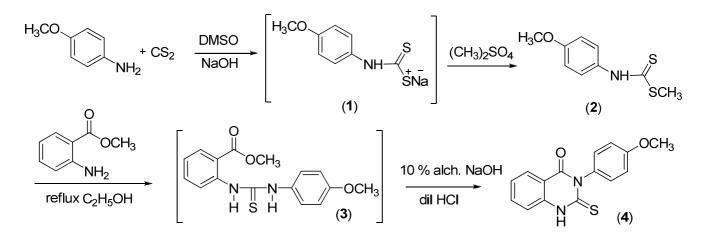
1. Introduction

Quinazolinone is the building unit of approximately 150 naturally occurring alkaloids isolated from microorganisms, plants and animals [1]. It is a very important heterocycle exhibiting excellent pharmacological activities such as antimicrobial [2], antifungal [3], antitumor [4], anticancer [5], antiinflammatory [6], antidepressant [7], and anticonvulsant [8] activities. 3-Aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one are derivatives of quinazolinones have a wide range of pharmacological and biological activities such as anticonvulsant and antitumor [9]. Altanserin (3-(2-(4-(4-fluorobenzoyl)-l-piperidinyl)-ethyl)-2,3-dihydro-2-thioxo-1*H*-quinazolin-4-one) and nitro altanserin are used as drugs for 5-HT2A receptor antagonists [10].

2. Results and Discussion

The title compound was synthesized by slight modification of a reported method [11] according to the route depicted in Figure 1. 4-Methoxyaniline in DMSO was treated with carbon disulfide and aqueous sodium hydroxide to afford sodium 4-methoxyphenylcarbamodithioate (**1**) followed by reaction with dimethyl sulfate to furnish the methyl 4-methoxyphenylcarbamodithioate (**2**). A solution of (**2**) in ethanol (20 mL) was treated with methyl anthranilate in presence of anhydrous potassium carbonate to provide the methyl 2-(3-(4-methoxyphenyl)thioureido)benzoate as intermediate (**3**), which on basic hydrolysis yielded the title compound (**4**) which was recrystallized from ethanol as colorless crystals.

Figure 1. Synthetic route to 3-(4-methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one.

Formation of (**4**) was confirmed by IR which showed peaks at 3187.6 cm^{-1} for NH, 1706.6 cm^{-1} for C=O and 1224.9 cm^{-1} for C=S, respectively. In the ^{1}H-NMR spectrum a singlet at δ 3.88 ppm due to OCH$_3$ group, a multiplet at δ 7–8.1 ppm for aromatic (8H) protons and a singlet at d 10.36 ppm indicated the presence of NH.

The molecular structure of (**4**) is shown in Figure 2. The dihydroquinazoline N1/C1/N2/C2-C8 ring system essentially planar with an r.m.s. deviation of 0.052(1) Å. The molecule is twisted around the C9-N2 bond with a dihedral angle of 79.84(4)° between the dihydroquinazoline ring system and the substituted phenyl C9-C14 ring. The C1=S1 and C2=O1 bond lengths are 1.6799(10) and 1.2119(14) Å, respectively, which are comparable with the reported double bond lengths [12]. Packing diagrams of (**4**) are shown in Figures 3 and 4. The molecules are linked by an N-H...S hydrogen bond (N1-H1...S1^{i} N1-H1 = 0.796(17) Å, H1...S1 = 2.656(18) Å, N1...S1 = 3.4181(10) Å, <H1-N1...S1 = 160.9(16)°; symmetry code: (i) 1–x, –1/2+y, –z) forming a zig-zag chain structure along the b axis (Figure 3). The molecular chains are further connected by a C-H...O hydrogen bond (C11-H11...O1^{ii} C11-H11 = 0.95 Å, H11...O1 = 2.36 Å, C11...O1 = 3.2543(15) Å, C11-H11...O1 = 157°; symmetry code: (ii) 1–x, –1/2+y, 1–z), forming a layer parallel to the bc plane (Figure 4).

Figure 2. The molecular structure of (**4**). Anisotropic displacement ellipsoids are drawn at the 50% probability level.
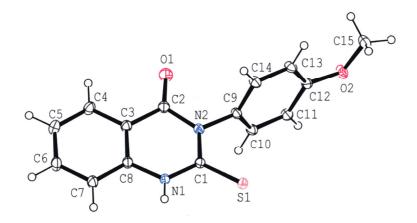

Figure 3. A packing diagram of (**4**), showing a zig-zag chain structure running along the b axis. N-H...S hydrogen bonds are indicated by dashed lines. H atoms not involved in the hydrogen bonds have been omitted.
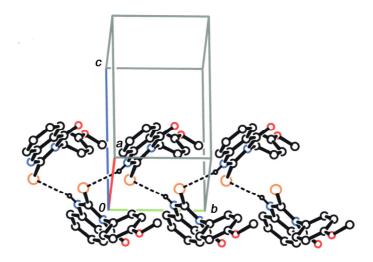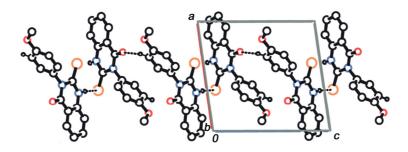

Figure 4. A packing diagram of (**4**) viewed along the b axis, showing a layer structure formed by N-H..S and C-H...O hydrogen bonds. The hydrogen bonds are indicated by dashed lines. H atoms not involved in the interactions have been omitted.

2.1. Crystal Structure Determination

Data were collected at 180(1) K on a Rigaku RAPID II IP diffractometer using MoKα radiation. The numerical absorption correction with *NUMABS* were employed [13]. The structure was solved by direct methods [14], and refined by full-matrix least-squares refinement [14] on F² with 185 parameters for 3719 unique intensities. All atoms except H were refined anisotropically. H atoms were found in a difference Fourier map and the N-bound H atom was refined freely. Other H atoms were refined on idealized positions (C-H = 0.95 or 0.98 Å) with $U_{iso}(H) = 1.2 \, U_{eq}(C)$ or $1.5 U_{eq}(Cmethyl)$. Experimental data are listed in Table 1.

Table 1. Crystal data and structure refinement for (**4**).

Empirical formula	$C_{15}H_{12}N_2O_2S$	
Formula weight	284.33	
Temperature	180(1) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.9349(8) Å	α = 90°
	b = 6.3377(5) Å	β = 97.752(3)°
	c = 10.5783(10) Å	γ = 90°
Volume	659.97(10) Å^3	
Z	2	
Density (calculated)	1.431 mg/m^3	
Absorption coefficient	0.247 mm^{-1}	
F(000)	296	
Crystal size	$0.13 \times 0.36 \times 0.38$ mm^3	
Theta range for data collection	3.0 to 30.0°.	
Index ranges	$-13 \leq h \leq 13, -8 \leq k \leq 8, -14 \leq 1 \leq 14$	
Reflections collected	12985	
Independent reflections	3719 [R(int) = 0.014]	
Completeness to theta = 29.97°	99.8%	
Absorption correction	Numerical	
Max. and min. transmission	0.968 and 0.915	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3719/1/185	
Goodness-of-fit on F^2	1.07	
Final R indices [$I > 2\sigma(I_0)$]	R1 = 0.0271, wR2 = 0.0704	
R indices (all data)	R1 = 0.0266, wR2 = 0.0702	
Extinction coefficient	none	
Largest diff. peak and hole	0.347 and -0.150 eÅ^{-3}	
Flack parameter	0.00(4)	
CCDC No.	831309	

3. Experimental Section

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. The FTIR spectra were recorded on FTS 3000 MX, Bio-Rad Merlin (Excalibur Model) spectrophotometer. ^{1}H NMR spectra were determined as CDCl$_3$ solutions at 300 MHz using a Bruker Mass Spectra (EI, 70 eV) on a GC-MS instrument. All compounds were purified by thick layer chromatography using silica gel from Merck.

*Synthesis of 3-(4-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**4**)*

To a solution of 4-methoxyaniline (0.02 mol) in DMSO (10 mL), carbon disulfide (1.6 mL, 0.026 mol) was added followed by an aqueous solution of sodium hydroxide (1.2 mL, 20 M) dropwise with stirring to afford salt (**1**) as an intermediate. After two hours, dimethyl sulfate (0.02 mol) was added gradually while the reaction mixture was kept stirring in a freezing mixture for five hours. After the completion, the reaction mixture was poured into ice water. The solid obtained was filtered, washed and re-crystallized from ethanol to obtain methyl 4-methoxyphenylcarbamodithioate (**2**). To the solution of (**2**) (0.01 mol) in ethanol (20 mL), methyl anthranilate (0.01 mol), anhydrous potassium carbonate (100 mg) was added and the solution was refluxed for 25 hours. The reaction mixture was poured onto cold water. Solid methyl 2-(3-(4-methoxyphenyl)thioureido)benzoate (**3**) obtained, was filtered and refluxed in 10% alcoholic sodium hydroxide solution for two hours. After cooling at room temperature, it was re-precipitated by treatment with dilute hydrochloric acid. The solid obtained was washed with water and recrystallized from ethanol to afford (**4**) as colourless crystals. (80%): m.p. 280 °C; R$_f$: 0.15 (petroleum ether: ethyl acetate,4:1); IR (KBr) υ cm^{-1}: 3187 (N-H),1704 (C=O), 1585 (Ar-C=C), 1196 (C=S); ^{1}H NMR (DMSO, 300 MHz) δ: 13.02 (s, 1H, NH), 7.9 (d, 1H, Ar-H), 7.7 (Pseudo t, 1H, Ar-H), 7.4 (d,1H, Ar-H), 7.3 (pseudo t, 1H, Ar-H), 7.1 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 3.8 (s, 3H, OCH$_3$); ^{13}C NMR (75.4 MHz) δ: 176.8 (C=S), 160.4 (C=O), 159.19 (C-N), 139.9 (Ar), 136.0 (Ar), 132.4 (Ar), 130.4 (Ar), 127 (Ar), 124.7 (Ar), 116.6 (Ar), 116.1 (Ar), 114.5 (Ar), 55.7 (MeO); Anal. Calcd. For C$_{15}$H$_{12}$N$_2$O$_2$S: C, 63.36; H, 4.25; N, 9.85; S, 11.28; Found: C, 63.35; H, 4.24; N, 9.84; S, 11.27; GC-MS *m/z*: 284.06 (M$^{\cdot+}$, 100).

4. Conclusions

Synthesis and molecular structure of a medicinally important compound is described. The dihydroquniazoline ring system is essentially planar; the molecule is twisted around the C9-N2 bond between the dihydroquinazoline ring system and the substituted phenyl C9-C14 ring. The molecules are linked by an N-H...S hydrogen bond forming a zig-zag chain structure along the b axis.

Acknowledgements

References and Notes

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