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Synthesis and crystal structure of 6-(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(2-methoxyphenyl)-3,4-dihydropyrimidine-2(1H)-thione

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The structure of 6-(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(2- methyoxyphenyl)-3,4-dihydropyrimidine-2(1H)-thione was determined by X-ray crystallography. The compound crystallizes as colourless needles shaped in the triclinic system, space group Pī with cell constants: a = 10.0624(5) Å, b = 10.3668(6) Å, c = 11.8773(9) Å, α = 91.865 (4)˚, β = 114.838 (2)˚, γ = 99.304 (3)˚, V = 1102.58(12) Å3 , Z = 2. The crystal structure was solved by direct methods and refined by full-matrix least-squares on F2 to final values of R1 = 0.0583 and wR2 = 0.1930. In the crystal structure, supramolecular chains mediated by C–H…O contacts along the a-axis are linked into a double layer *via* N-H…S hydrogen bonds and π–π [ring centroid (pyrimidine)…ring centroid (triazole) distance = (3.508(1) Å] interactions. The resulting double layer stacks along the b-axis without any specific interactions.

Keywords: 1, 2, 3-triazole, Single-crystal X-ray diffraction, Crystal structure, Hydrogen bonding

INTRODUCTION

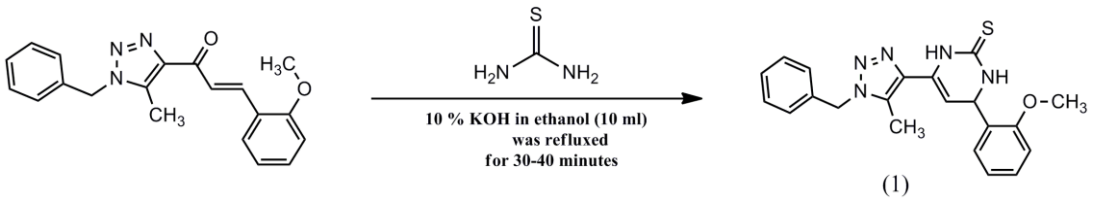
1,2,3-triazoles have found a wide range of important applications in pharmaceutical, polymer, and material fields [1]. In addition, they have shown a broad spectrum of biological properties such as antibacterial [2] anti-allergic [3], anti-HIV activity [4] and also serve as potential chemotherapeutic agents for various diseases [5]. On the other hand, substituted pyrimidine nuclei are found antiviral [6], anti-tubercular, antineoplastic, anti-inflammatory, diuretic, antimalarial and cardiovascular [7]. In view of these bioactivities of the individual heterocycles, it was envisaged that the synthesis of novel hybrid molecules containing two of the above said moieties in a single frame is worth attempting. Several similar structures related to the title compound have been synthesized and antibacterial activities are reported by our coauthors [8]. Here we present the crystal structure of 6-(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-4-(o-tolyl)-3,4-dihydropyrimidine-2(1H)-thione (**1**), $C_{21}H_{21}N_5OS$.

EXPERIMENTAL

Synthesis and characterization

The title compound (**1**) was obtained according to the reaction scheme 1.

A mixture of (*E*)-1-(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-3-(2-methoxyphenyl)prop-2-en-1-one (0.2 g, 0.58 mmol), thiourea (0.067 g, 0.88 mmol) and 10 % aq. KOH in ethanol (10 ml) was refluxed for 30-40 minutes and poured onto excess of crushed ice and neutralized with dilute hydrochloric acid. The precipitated 6-(1-benzyl-5-methyl-1H-1, 2,3-triazol-4-yl)-4-(2-methoxyphenyl)-3,4-dihydro pyrimidine-2(1H)-thione were filtered and recrystallized from ethanol. Needle-like colourless single crystals of the title compound **1**, suitable for single crystal X-ray diffraction analyses, grown in ethanolic solution by slow evaporation of the solvent at room temperature were collected (yield 2.58 g (93 %) , m.p. 175-177 ºC).



Scheme 1. Reaction scheme and chemical diagram of the title compound (1)

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X-ray – single crystal analyses

A crystal of the title compound having approximate dimensions of 0.30×0.24×0.10 mm^3 was mounted on a glass fiber using cyanoacrylate adhesive. All measurements were made on a Bruker AXS Kappa Apex II single crystal X-ray diffractometer using graphite mono-chromated MoKα (λ = 0.71071 Å) radiation and CCD (Charge coupled device) detector. Diffraction data were collected at room temperature by the *ω*-scan technique. Accurate unit cell parameters and orientation matrix were obtained by a least-squares fit of several high angle reflections in the ranges $1.9^o < \theta < 26.3^o$ for the title compound.

The unit cell parameters were determined for 36 frames measured (0.5° phi-scan) from three different crystallographic zones and using the method of difference vectors. The intensity data were collected with an average four-fold redundancy per reflection and optimum resolution (0.75 Å). The intensity data collection, frames integration, Lorentz-polarization correction and decay correction were done using SAINT-NT (version 7.06a) software. Empirical absorption correction (multi-scan) was performed using SADABS [9] program. The structure was solved by direct methods using ShelxS [10] and refined by full-matrix least-square procedures on F^2 with ShelxL-97 [10]. All H atoms were positioned geometrically and constrained to ride on their parent atom with C—H = 0.93–0.97 Å and N—H = 0.86 Å, and with $U_{iso}(H) = 1.5\ U_{eq}$ for methyl H atoms and $1.2U_{eq}(C)$ for other H atoms. The investigated crystal was found to be a two-component rotational twin. The data for both components were integrated using SAINT and scaled with TWINABS. Final refinement was performed using a HKLF5 file generated by TWINABS with a BASF parameter (0.1666(1)). The crystal structure contained solvent accessible voids of 148 $Å^3$, showed no electrons in the voids. This might indicate that the crystal lost its solvent during crystallization without collapsing the structure.

NMR

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker Advance 300 MHz spectrometer and the chemical shifts are reported as *δ* values in parts per million (ppm) relative to tetramethylsilane, with *J* values in Hertz. The splitting patterns in the ^{1}H NMR spectra are reported as follows: s = singlet; d = doublet; br s = broad singlet; br d = broad doublet; m = multiplet. ^{13}C NMR data are reported with the solvent peak ($CDCl_3$ = 77.0 MHz) as the internal standard.

White solid; m.p. 175-177 °C; Yield:93%; **^{1}H NMR (300 MHz, $CDCl_3$)**: 8.51 (br s, 1H, NH), 7.35-6.84 (m, 9H, ArH), 6.84 (br s, 1H, NH), 5.63 (br s, 1H, -CH), 5.55 (m, 2H, -CH2), 5.18 (br s, 1H, olefinic -CH), 3.86 (s, 3H, -OCH_3), 2.27 (s, 3H, -CH_3); **^{13}C NMR (75 MHz, $CDCl_3$):** 175.45, 156.09, 137.61, 134.16, 130.25, 129.54, 129.08, 128.51, 127.46, 127.09, 121.08, 110.59, 97.88, 55.41, 52.11, 50.48, 29.60, 9.47.

RESULTS AND DISCUSSION

The chemical diagram of the studied compound (**1)** is illustrated in Scheme 1 and experimental conditions are summarized in Table 1.

Selected bond distances and bond angles are listed in Table 2.

Table 1.. Crystal data and structure refinement for 1

Crystal Data	
Empirical formula	$C_{21}H_{21}N_5OS$
Formula weight	391.49 g mol^{-1}
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	Pī
Hall Symbol	– P 1
Unit cell dimensions	a = 10.0624(5) Å, b = 10.3668(6) Å, c = 11.8773(9) Å, α= 91.865 (4)°, β= 114.838 (2)° , γ = 99.304 (3)°
Volume	1102.58(12) $Å^3$
Z	2
Calculated Density	1.179 Mg/m^3
Absorption coefficient	0.166 mm^{-1}
F(000)	412
Crystal Color, habit	colourless, needle
Crystal size	0.30 ×0.24 ×0.10 mm^3
Data Collection	
Diffractometer	Bruker APEX II CCD area detector
θ range for data collection	1.9 to 26.3°.
Index ranges	–12≤h≤12, –12≤k≤12, –14≤l≤14
Reflections collected	20070
Independent reflections	20070 [R(int) = 0.0000]
Completeness to theta = 26.28°	99.1 %
Refinement	
Refinement method	Full-matrix least-squares on F^2
Absorption correction	Multi-scan
Data / restraints / parameters	20070 / 0 / 256
Goodness-of-fit on F^2	1.143
Final R indices [I>2σ(I)]	R1 = 0.0583, wR2 = 0.1778
R indices (all data)	R1 = 0.0717, wR2 = 0.1930
Largest diff. peak and hole	0.314 and -0.261 e.$Å^{-3}$
CCDC Deposition number	974620

A diagram of the molecular structure with 50% probability and the atom numbering scheme are shown in Fig. 1.

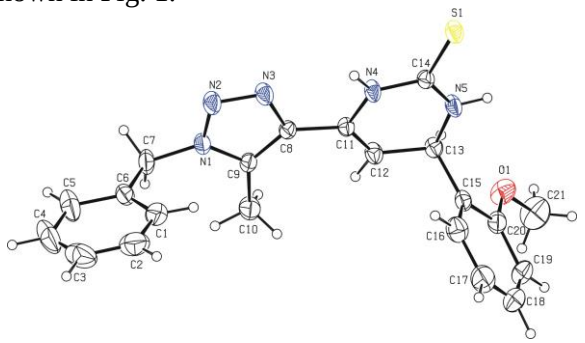

Fig. 1. View of the molecule with an atom-numbering scheme. Displacement ellipsoids for the non-H atoms are drawn at the 50% probability level. The H atoms are presented with spheres with arbitrary radii.

The data for publication were prepared with WinGX [11], *ORTEP* [12], Platon [13] and Mercury [14] program packages.

Hydrogen bonding geometry is presented in Table 3.

In the title compound, $C_{21}H_{21}N_5OS$, the essentially planar triazole (N1/N2/N3/C8/C9) ring [maximum deviation = 0.003(1) Å for the C9 atom] forms dihedral angle of 7.7 (1)º with the pyrimidine (N4/N5/C11-C14) ring [maximum deviation = -0.032(1) Å for the C13 atom]. The methoxy phenyl ring attached to the pyrimidine ring is in equatorial position. The dihedral angle between the benzene rings is 61.9 (1) º. The methoxy group at C20 is almost coplanar with the attached benzene ring as evidenced by the torsion angle of C21–O1–C20–C19 = 1.7 (3)º. The phenyl group and triazole heterocycle are linked by methylene group at carbon atom C7 with C6–C7–N1 angle of 113.1 (1)º distorted from ideal tetrahedral geometry (109.7º). This can be attributed to steric factors of the adjacent cyclic system. The bond distances N3—C8, C8—C9, C9—N1, N1—N2 and N2—N3 are 1.362(2), 1.367(2), 1.358(2), 1.329(2) and 1.308(2) Å respectively, which agrees with C═C, N═N, C—N distances found in literature for compound having triazole heterocycles [15, 16].

The molecular conformation is stabilized by two weak intramolecular C13–H13…O1 and N4–H4A…N3 hydrogen bonds, both forming S(5) ring motifs [17] (Table 3).

Table 2. Bond lengths [Å] and angles [°] for 1

Bond distance			
C7 – N1	1.458(2)	C13 – C15	1.508(2)
C8 – N3	1.362(2)	C14 – N5	1.319(2)
C8 – C9	1.367(2)	C14 – N4	1.348(2)
C9 – N1	1.358(2)	C14 – S1	1.685(2)
C9 – C10	1.482(2)	C20 – O1	1.367(2)
C11 – C12	1.321(2)	C21 – O1	1.403(2)
C11 – N4	1.398(2)	N1 – N2	1.329(2)
C13 – N5	1.469(2)	N2 – N3	1.308(2)
Bond Angle			
N1 – C7 – C6	113.1(1)	N5 – C13 – C12	108.7(1)
N3 – C8 – C9	108.9(1)	N5 – C13 – C15	110.9(1)
N3 – C8 – C11	119.0(1)	C12 – C13 – C15	112.4(1)
C9 – C8 – C11	132.1(1)	N5 – C14 – N4	117.0(1)
N1 – C9 – C8	103.4(1)	N5 – C14 – S1	122.2(1)
N1 – C9 – C10	123.5(1)	N4 – C14 – S1	120.8(1)
C8 – C9 – C10	133.1(1)	O1 – C20 – C15	116.1(1)
C12 – C11– N4	119.8(1)	O1 – C20 – C19	123.7(2)
N4 – C11 – C8	113.5(1)	C15 – C20 – C19	120.1(2)
N2 – N3 – C8	108.7(1)	N2 – N1 – C9	111.7(1)
C14 – N4 – C11	122.9(1)	N2 – N1 – C7	119.1(1)
C14 – N5 – C13	128.0(1)	C9 – N1 – C7	129.2(1)
C20 – O1 – C21	118.2(1)	N3 – N2 – N1	107.3(1)

Table 3. Hydrogen bond for 1(Å, °)

D–H...A	D–H	d(H...A)	d(D...A)	<(DHA)
C13–H13…O1	0.98	2.30	2.786(2)	109.0
N4–H4A…N3	0.86	2.31	2.690(2)	107.0
C7–H7B...S1^{i}	0.97	2.85	3.808(2)	169.8
N5–H5A...S1^{ii}	0.86	2.50	3.343(1)	166.1

Symmetry codes: (i) x-1, y, z; (ii) -x+2, -y+1, -z+1

In the crystal structure, C7–H7B...S1 contacts lead to the formation of a supramolecular chain along the *a*-axis. These chains are linked into a double layer *via* N5–H5A...S1 intermolecular hydrogen bonds forming $R_2^2(8)$ cyclic centrosymmetric dimers and intermolecular π–π interactions occur between inversion related molecules with Cg1…Cg2^{iii} = 3.508(1) Å and Cg2…Cg1^{iii} = 3.508(1) Å [Table 3 and Fig. 2; Cg1 and Cg2 are the centroids of the triazole (N1/N2/N3/C8/C9) ring and pyrimidine (N4/N5/C11–C14) ring, respectively, symmetry code: (iii) *1–x, 1–y, –z*].

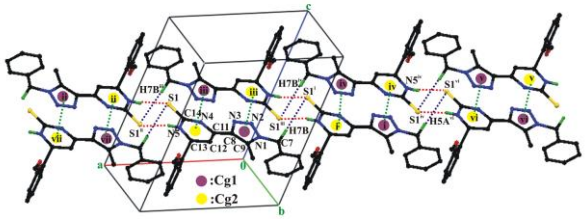

Fig. 2. View of the crystal packing showing supramolecular double layer along the a- axis, which involves the C-H…S (blue dotted lines), N-H…S (red dotted lines) and π-π (green dotted lines) interactions. [Cg1 and Cg2 are the centroids of the triazole (N1/N2/N3/C8/C9) ring and pyrimidine (N4/N5/C11–C14) ring, respectively, symmetry codes: (i) -1+x, y, z, (ii) 2-x, 1-y, 2-z, (iii) 1-x, 1-y, 1-z, (iv) –x, 1-y, 1-z, (v) -1-x, 1-y, 1-z, (vi) -2+x, y, z, (vii) 1+x, y, z].

The resulting double layer stacks along the *b*-axis without any specific interactions (Fig. 3).

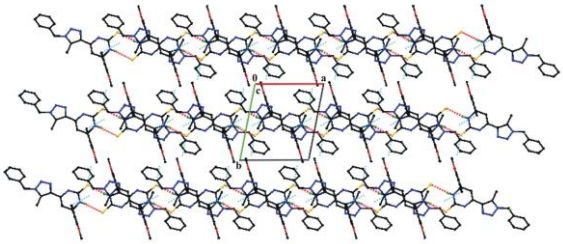

Fig. 3. View of the overall crystal packing highlighting the stacking of double layers along the b-axis.

CONCLUSION

The title compound was synthesized and confirmed by NMR and structural (single-crystal X-ray diffraction) techniques. The molecular conformation is stabilized by two weak intramolecular C–H…O and N–H…N hydrogen bonds. The crystal packing is stabilized by supramolecular chains mediated by C–H…O contacts along the *a*-axis linked into a double layer *via* N-H…S hydrogen bonds and π–π interactions.

SUPPLEMENTARY MATERIALS

CCDC 974620 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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СИНТЕЗ И КРИСТАЛНА СТРУКТУРА НА 6- (1-БЕНЗИЛ-5-МЕТИЛ-1Н-1, 2, 3-ТРИАЗОЛ-4-ИЛ) -4- (2-МЕТОКСИФЕНИЛ) -3,4-ДИХИДРОПИРИМИДИН-2 (1Н) - ТИОН

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(Резюме)

Структурата на 6- (1-бензил-5-метил-1Н-1,2,3-триазол-4-ил) -4- (2- methyoxyphenyl) -3,4-дихидропиримидин-2 (1Н) -тион е определена чрез рентгенова кристалография. Съединението кристализира във вид на безцветни игли, оформени в триклинна система, пространствена група Pi с клетъчните константи: a = 10.0624 (5) Å, b = 10.3668 (6) Å, c = 11.8773(9) Å, α = 91.865 (4)˚ , β = 114,838 (2)˚, γ = 99.304 (3)˚, V = 1102.58(12) Å^3, Z = 2. Кристалната структура бе решена чрез директни методи и уточнена по пълната матрица на най-малките квадрати по F^2 до окончателни стойностите на R_1 = 0.0583 и wR_2 = 0.1930. В кристалната структура, супрамолекулярни вериги с посредничеството на C-H ... O връзки по *a*-оста са свързани в двоен слой чрез NH ... S водородни връзки и π-π [разстоянието пръстенно центроиден (пиримидин) ... пръстенно центроиден (триазол) = (3.508(1) Å] взаимодействия. Получените двойни слоеве се подреждат по оста *b* без конкретни взаимодействия.