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Synthesis, Structure, and Conformational Analysis of *N*-(2,4-Dichlorophenyl)-2-[6-methyl-2,4-dioxo-3-(thietan-3-yl)-1,2,3,4-tetrahydropyrimidine-1-yl]acetamide

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Abstract—The reaction of 6-methyluracil with 2-chloromethyltiiran affords 6-methyl-3-(thietan-3-yl)uracil. Its subsequent reaction with *N*-(2,6-dichlorophenyl)-2-chloroacetamide resulted in *N*-(2,4-dichlorophenyl)-2-[6-methyl-2,4-dioxo-3-(thietan-3-yl)-1,2,3,4-tetrahydropyrimidin-1-yl]acetamide, proved by X-ray analysis, NMR and IR spectroscopy. Computer modeling at the PBE/3ζ, PBE/cc-pVDZ and PBE/SV(P) levels showed that its conformational behavior is determined by internal rotation of the thietanyl group both in the gas phase and in chloroform or dimethyl sulfoxide solutions.

Keywords: 6-methyl-3-(thietan-3-yl)uracil, 6-methyluracil derivatives, thietanes, computer simulation, cluster model

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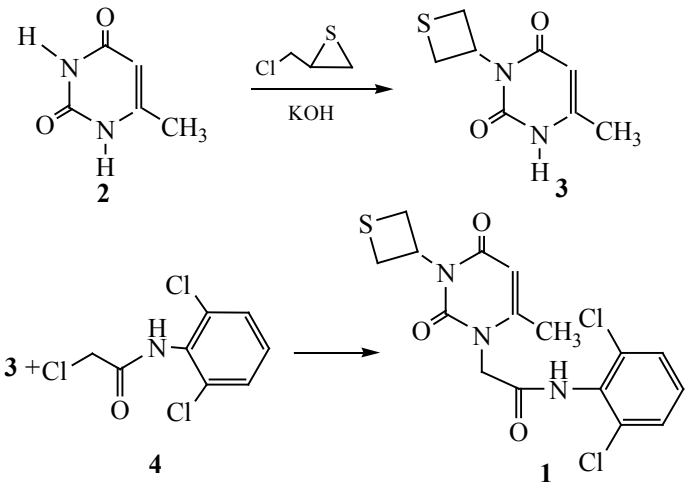
6-Methyluracil derivatives are widespread in nature [1]; they are used in organic synthesis [2] and serve as the basis for obtaining a number of new medicinal compounds [3]. Thietane derivatives are widely used in organic synthesis, and their anti-inflammatory, sedative, and insecticidal properties make this class of compounds promising objects for research in pharmaceutics [4, 5]. In addition, amides of 1,2,3,4-tetrahydropyrimidinecarboxylic acids have antioxidant and anti-metastatic activity with an overall low toxicity [6, 7]. Thus, the introduction of thietane and amide groups as substituents into the 6-methyluracil molecule should lead to an increasing of the spectrum of biological activity of the obtained derivatives. In view of the foregoing, the purpose of this study is to synthesize a previously unknown amide derivative of 6-methyl-3-(thietan-3-yl) uracil, investigate its structure, as well as carry out a conformational analysis within the DFT approximations PBE/3ζ, PBE/cc-pVDZ, PBE/SV(P) (software package PRIRODA [8]).

The target *N*-(2,4-dichlorophenyl)-2-[6-methyl-2,4-dioxo-3-(thietan-3-yl)-1,2,3,4-tetrahydropyrimidin-1-yl] acetamide **1** was synthesized in two steps (Scheme 1). Initially, the intermediate 6-methyl-3-(thietan-3-yl) pyrimidine-2,4(1*H*,3*H*)-dione **3** was obtained by the reaction of 6-methyluracil **2** with chloromethylthiiran, as described previously [9]; the structure of compound **3** was proved in [10]. The reaction of derivative **3** with *N*-(2,6-dichlorophenyl)-2-chloroacetamide **4** gave the final acetamide **1**. Its structure was confirmed by ^{1}H NMR and IR spectroscopy and clearly proved by X-ray diffraction analysis.

According to X-ray diffraction analysis, molecules of acetamide **1** form orthorhombic crystals with the space group $Pna2_1$ (Table 1). The thietanyl substituent is located at the N^3 atom [10]. The acetamide part is raised above the plane of the uracil ring, and the angle between the planes of the dichlorophenyl and uracil fragments is 58.7(3)° (Fig. 1). The individual bond lengths, as well as

Scheme 1.



valence and torsion angles in the molecule of compound **1** are shown in Table 2.

Conformational analysis of acetamide **1** was carried out using DFT calculated approximations PBE/3ζ, PBE/cc-pVDZ, and PBE/SV(P) (software package PRIRODA [8]). The PBE method is based on the principle of the generalized gradient approximation (GGA) and has proven itself in the analysis of various organic and inorganic molecular systems [11]. The basis set of the triple valence splitting 3ζ [12] is an all-electron nonrelativistic Gaussian atomic basis, containing a diffuse part and polarization functions. The split valence correlation-consistent basis set cc-pVDZ [13] and the split valence basis set SV(P) [14] are also effectively used for the correct estimation of the thermodynamic parameters in various chemical processes.

Table 1. Crystallographic data and details of the X-ray diffraction experiment

Parameter	Value
Formula	$C_{16}H_{15}Cl_2N_3O_3S$
M	400.27
Temperature, K	293(2)
Crystal system	Orthorhombic
Space group	$Pna2_1$
a, Å	29.6126(17)
b, Å	4.7615(3)
c, Å	12.1663(6)
Volume, Å^3	1715.44(16)
Z	4
d_{calc}, mg/mm^3	1.550
μ, mm^{-1}	0.522
F(000)	824.0
Scan area at θ, deg	$-22 \le h \le 42$, $-6 \le k \le 3$, $-14 \le l \le 16$
Reflection index area	3596 [R_{int} = 0.0149, R_{sigma} = 0.0291]
Number of measured/ independent reflections	3596/1/286
GOOF	1.116
R_1 for $I_{hkl} > 2\sigma(I)$, wR_2	R_1 = 0.0364, wR_2 = 0.0742
R_1 for all I_{hkl}, wR_2	R_1 = 0.0397, wR_2 = 0.0769
$\Delta\rho_{max}/\Delta\rho_{max}$, *e*/Å^3	0.20/–0.22

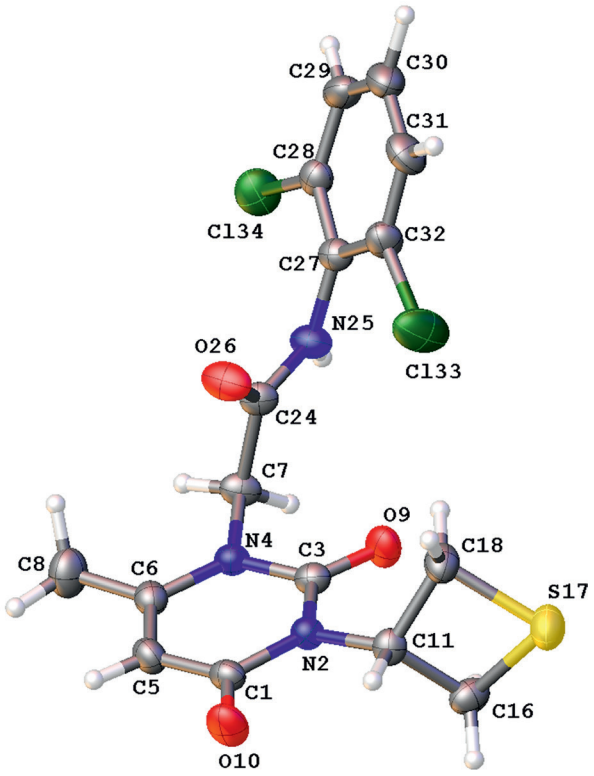


Fig. 1. General view of the molecule of compound **1** in a crystal.

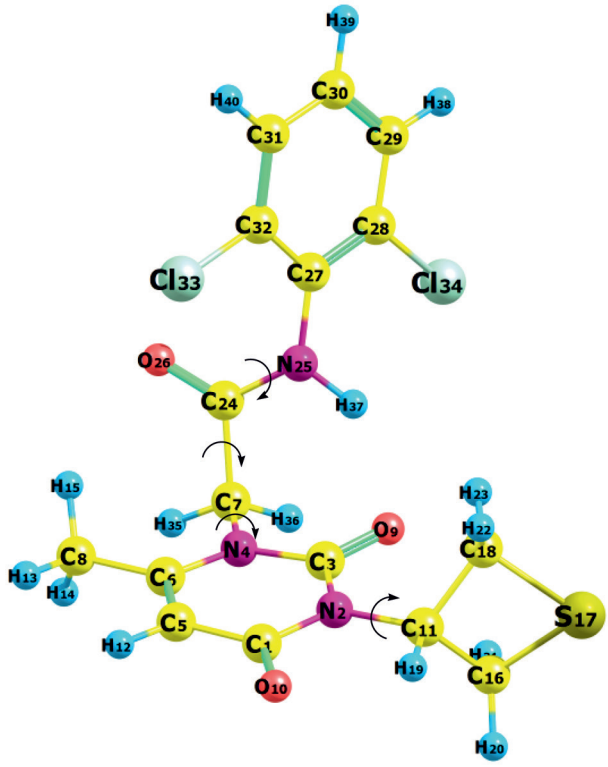


Fig. 2. Conformer **A** corresponding to the minimum potential energy for an isolated molecule of acetamide **1** according to the PBE/3ζ calculation data.

It was established by the PBE/3ζ method that conformer **A** (Fig. 2), which is close to acetamide crystal structure (Fig. 1), corresponds to the global minimum on the potential energy surface of acetamide **1**.

The calculated values of bond lengths, valence and torsion angles in comparison with X-ray diffraction data are presented in Table 2. The main structural differences are associated with the conformation of the amide moiety:

Table 2. Selected bond lengths, valence and torsion angles in the molecule of acetamide **1** (the PBE/3ζ calculation data)

Bond lengths, *r*, Å		Bond angles, φ, deg		Torsion angles, φ, deg	
calculation	experiment	calculation	experiment	calculation	experiment
C^3–N^2		$C^1N^2C^3$		$C^3N^2C^{11}C^{18}$	
1.383	1.383(4)	123.9	123.5(2)	60.01	52.35(2)
N^2–C^{11}		$C^{16}S^{17}C^{18}$		$C^1N^2C^{11}C^{18}$	
1.478	1.473(3)	76.87	77.39(14)	–118.16	–126.81(2)
C^{18}–S^{17}		$C^{11}C^{16}S^{17}$		$N^4C^7C^{24}N^{25}$	
1.863	1.830(3)	89.25	89.94(19)	64.76	147.91(16)
O^9–C^3		$N^2C^1C^5$		$C^7C^{24}N^{25}C^{27}$	
1.239	1.213(3)	114.5	115.0(2)	178.76	179.79(9)
C^5–C^6		$N^2C^3N^4$			
1.361	1.341(4)	116.8	117.1(2)		
N^{25}–C^{24}		$C^3N^4C^6$			
1.377	1.350(4)	122.4	122.0(2)		
C^{32}–Cl^{33}		$C^7C^{24}N^{25}$			
1.748	1.732(3)	112.9	114.8(2)		
C^{24}–O^{26}		$C^{27}C^{32}C^{31}$			
1.224	1.218(3)	121.6	122.0(3)		

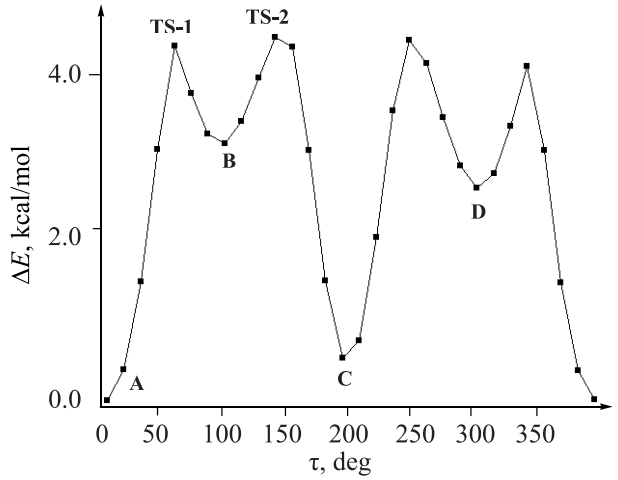


Fig. 3. Dependence of the relative energy of acetamide **1** on the value of the torsion angle $C^1N^2C^{11}H^{19}$ (the relative energy of form **A** is taken as zero).

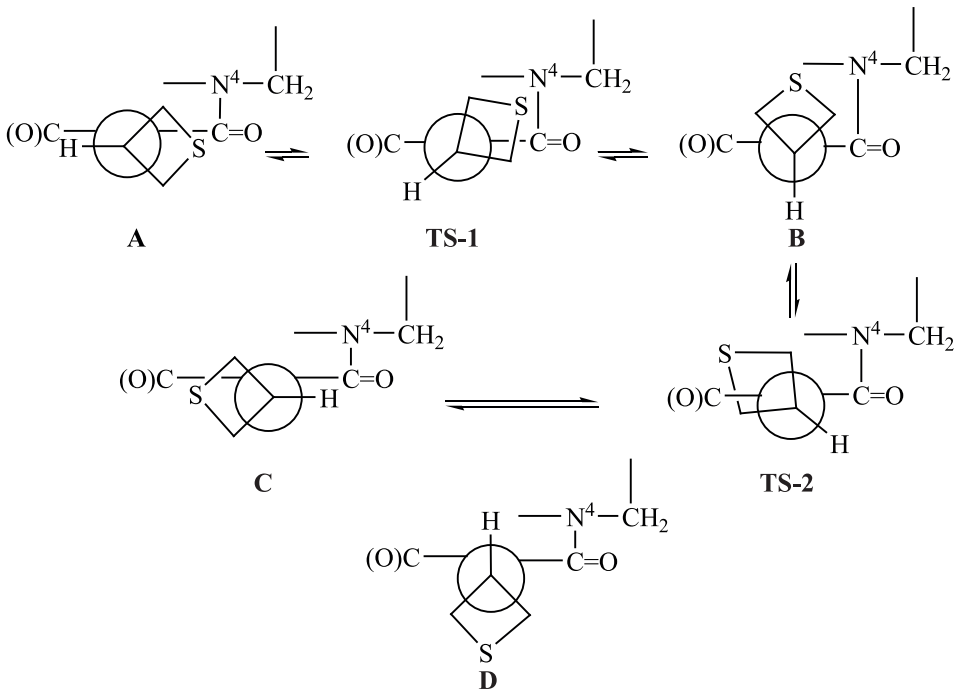
it is more deviated from the uracil moiety in case of isolated molecule; the angle between the planes of the dichlorophenyl and uracil rings is 120°. Changes in the values of some torsion angles are also noticeable.

For estimation of the conformational mobility of the compound **1** molecule, conformational analysis was performed by sequential rotation around the N^4–C^7, C^7–C^{24}, and C^{24}–N^{25} bonds in the amide fragment at 360° (Fig. 2). In each case, the maximum energy of the transition state was assessed relative to the main minimum, which in all cases corresponded to form **A**. In addition, the internal rotation barrier of the thietanyl group around the N^2–C^{11} bond was also calculated. The results, shown in Table 3, indicate the conformational rigidity of the amide part of the molecule: the internal rotation barriers in all used approximations are 10.1–16.5 kcal/mol.

At the same time, the rotation barrier of the thietanyl group is relatively small and does not exceed 4.5–4.8 kcal/mol (Table 3). In this case, in addition to the main one (form **A**), there are several local minima (forms **B**–**D**) on the potential energy surface, as well as almost energy-degenerate transition states **TS-1** and **TS-2** (Fig. 3, Scheme 2).

Conformers **A** and **C** differ in the mutual arrangement of the sulfur atom of the thietane ring and the amide fragment. Their relative energies in all used approximations indicate a marked concentration of the latter form in the conformer mixture at room temperature (Table 3). Within the cluster model [15, 16], we investigated the effect of solvent molecules on the free energy and potential barriers of individual conformers associated with the rotation of the thietanyl substituent in acetamide **1**. Based on the previous results of estimation the medium

Scheme 2.



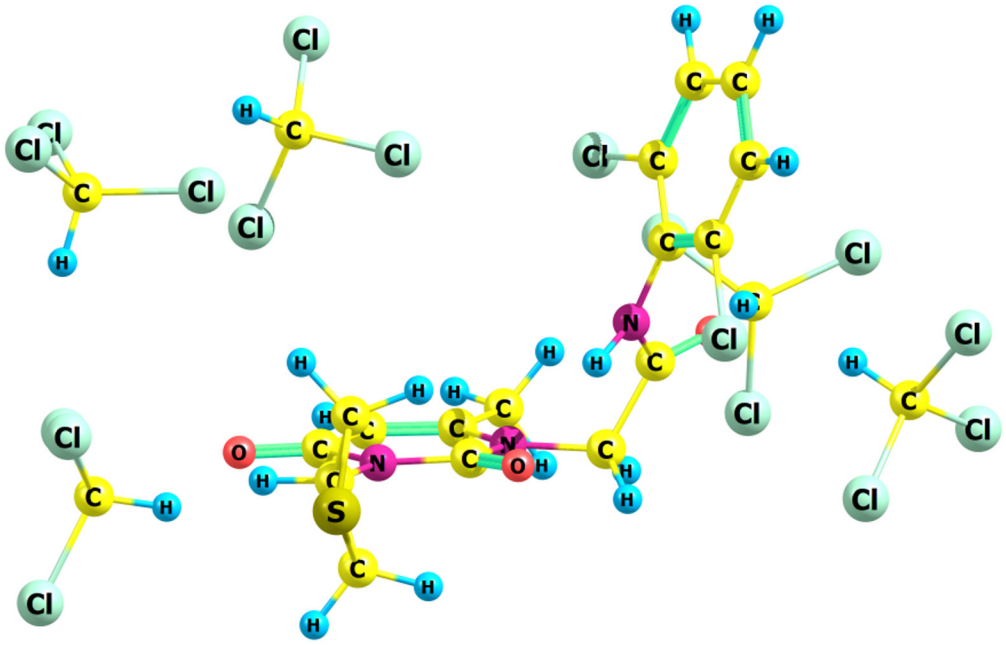


Fig. 4. Cluster **1**@5$CHCl_3$ (conformer **A**).

effect on the conformational equilibrium of heterocyclic compounds [17–19], according to which the optimal number of solvent molecules in the nearest solvation shell should not exceed ten, we considered a model with five molecules (Fig. 4); the low polar chloroform (ε 4.8) and polar dimethyl sulfoxide (ε 46.7) were used as solvents.

Within all used calculated approximations, a high population density of forms **A** and **C** is characteristic for the conformational equilibrium of an isolated molecule (Table 3). In the case of the **1**@5$CHCl_3$ cluster, an additional stabilization of conformer **C** occurs, which becomes the main minimum on the potential energy surface with using the SV(P) basis; the main potential barrier of **TS-2** also decreases. However, in the **1**@5DMSO cluster, form **C** is noticeably destabilized, and the energy of the transition state of **TS-2** increases with the exception of PBE/cc-pVDZ. But in general within the used model, the solvent presence does not change the fundamental character of the conformational behavior of *N*-(2,4-dichlorophenyl)-2-[6-methyl-2,4-dioxo-3- (thietan-3-yl)-1,2,3,4-tetrahydropyrimidin-1-yl] acetamide and indicates only a relatively high population density of form **C** in low-polar chloroform. Taking into account that the calculated dipole moments of conformers **A** and **C** are 3.22 and 3.52 D, respectively, the reason for such a shift in equilibrium is not related to the medium polarity.

EXPERIMENTAL

X-ray diffraction analysis was performed on a XCalibur Eos automatic four-circle diffractometer, (graphite monochromator, MoK_α-radiation, λ 0.71073 Å, ω-scanning, $2\theta_{max}$ 62°). Data collection and processing was carried out using the program CrysAlis^{Pro} Oxford Diffraction Ltd., ver. 1.171.36.20. The structures were solved by a direct method and refined by a full-matrix least-squares method in the anisotropic approximation for non-hydrogen atoms. Hydrogen atoms are localized in the differential Fourier synthesis and are refined isotropically. Calculations were performed using the SHELX97 program [20]. Crystallographic data and details of the X-ray diffraction experiment are given in Table 1. Compound **1** is deposited at the Cambridge Crystallographic Data Center (CCDC 2015447).

The NMR spectra were recorded on a Bruker Avance 400 spectrometer with operating frequency 400.13 (^{1}H) and 100.62 (^{13}C) in DMSO-d_6 relative to the residual nondeuterated solvent signals. The IR spectra were recorded on an Infralum FT-02 device (KBr pellets).

Modeling of the conformational transformations of acetamide **1** was initially carried out using the HyperChem package [21] (PM3), and after that—the PBE/3ζ, PBE/cc-pVDZ, and PBE/SV(P) methods (PRIRODA) [8]. To calculate the transition state, we

Table 3. Energy parameters of conformational transformations of the molecule of acetamide **1** according to the PBE method

Compound	Basis set	Conformer	Rotation around bond	ΔG°_{298} ($\Delta G^{\neq}_{298}$), kcal/mol[a]
1	3ζ	**TS**	N^4–C^7	(12.77)
	cc-pVDZ	**TS**		(15.07)
	SV(P)	**TS**		(14.30)
	3ζ	**TS**	C^7–C^{24}	(10.13)
	cc-pVDZ	**TS**		(10.85)
	SV(P)	**TS**		(10.70)
	3ζ	**TS**	C^{24}–N^{25}	(16.61)
	cc-pVDZ	**TS**		(17.01)
	SV(P)	**TS**		(16.50)
	3ζ	**B**	N^2–C^{11}	1.94
		C		0.15
		D		1.97
		TS-1		(4.36)
		TS-2		(4.40)
	cc-pVDZ	**C**		0.66
		TS-2		(4.52)
	SV(P)	**C**		0.30
		TS-2		(4.75)
1@5$CHCl_3$	3ζ	**C**		0.10
		TS-2		(3.94)
	cc-pVDZ	**C**		0.08
		TS-2		(3.98)
	SV(P)	**C**		-0.30
		TS-2		(4.42)
1@5DMSO	3ζ	**C**		0.90
		TS-2		(4.54)
	cc-pVDZ	**C**		0.80
		TS-2		(3.69)
	SV(P)	**C**		1.07
		TS-2		(4.59)

[a] Relative to conformer **A**.

simulated the internal rotation around a specific bond by scanning the corresponding torsion angle within 360°. The conformation corresponding to the top of the obtained energy curve was calculated further in the mode of saddle point search (Fig. 3). The stationary points of the potential energy surface belong to minima in case of the absence of imaginary frequencies, and to transition states—in case of the presence of one imaginary frequency in the corresponding Hessian. Clusters with solvent molecules that were randomly arranged in virtual space near the molecule of acetamide 1, were calculated in a similar way.

***N*-(2,6-Dichlorophenyl)-2-chloroacetamide (4)** was obtained according to the procedure [22]. The solution of 8.1 g (0.05 mol) of 2,6-dichloroaniline in 30 mL of acetone was cooled to 0°C and the solution of 5.65 g (0.05 mol) of chloroacetyl chloride in 7 mL of acetone was added slowly and dropwise with stirring. The reaction mixture was stirred for 2 h at room temperature and and poured in 100 mL of cold water. The precipitate was filtered out, washed with water and dried in desiccator. Yield 7.6 g (64%), mp 173–175°C (EtOH). Found, %: C 40.33; H 2.48; Cl 44.58; N 5.78. $C_8H_6Cl_3NO$. Calculated, %: C 40.25; H 2.52; Cl 44.65; N 5.87.

***N*-(2,6-Dichlorophenyl)-2-[6-methyl-2,4-dioxo-3-(thietan-3-yl)-1,2,3,4-tetrahydropyrimidin-1-yl] acetamide (1).** The suspension of 0.5 g (2.5 mmol) of compound **3**, 0.52 g (3.75 mmol) of powdered and dried potassium carbonate in 12 mL of acetonitrile

was refluxed for 30 min, then 0.72 g (3 mmol) of compound **4** in 3 mL of acetonitrile was added. The obtained mixture was refluxed after that for 7 h, the hot reaction mixture was filtered out, solvent was evaporated under vacuum. The residue was recrystallized. Yield 0.82 g (82%), mp 226–228°C (DMF–water, 1 : 1), R_f (chloroform–ethylacetate, 4:1) 0.85. IR spectrum, ν, cm^{-1}: 1572 s (C=C), 1649 s, 1661 s, 1697 s (C=O), 3209 br (NH). ^{1}H NMR spectrum, (DMSO-d_6), δ, ppm: 2.23 s (3H, C$\underline{CH}_3$), 3.08–3.14 m [2H, S($\underline{CH}$)$_2$], 4.17–4.23 m [2H, S($\underline{CH}$)$_2$], 4.76 s [2H, $\underline{CH}_2$C(O)], 5.70 s (1H, C=C$\underline{H}$), 6.05–6.11 m (1H, NCH), 7.37 t ($1H^4_{Ar}$, $^3J_{HH}$ = 8.1 Hz), 7.56 d ($2H^{3,5}_{Ar}$, $^3J_{HH}$ = 8.0 Hz), 10.30 br. s (1H, NH). Found, %: C 48.11; H 3.70; Cl 17.72; N 11.95; S 7.96. $C_{16}H_{15}Cl_2N_3O_2S$. Calculated, %: C 48.00; H 3.75; Cl 17.75; N 12.00; S 8.00.

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Structural research of *N*-(2,4-dichlorophenyl)-2-[6-methyl-2,4-dioxo-3-(thietan-3-yl)-1,2,3,4-tetrahydropyrimidin-1-yl] acetamide were carried out in the Collective Use Centre "Agidel" at the Institute of Petrochemistry and Catalysis of the Russian Academy of Sciences.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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