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N,*N*′-Diphenyldithiomalonodiamide: Structural Features, Acidic Properties, and In Silico Estimation of Biological Activity

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Abstract—The spectral characteristics of dithiomalondianilide (*N*,*N*′-diphenyldithiomalonodiamide) were studied, and the dissociation constant was determined by potentiometric titration. Quantum-chemical methods at the B3LYP-D3BJ/6-311+G (2d,p) level were used to calculate the molecular geometry and vibrational spectra of the most stable tautomeric forms of dithiomalondianilide. The bioavailability parameters were calculated, and possible protein targets were predicted by the protein ligand docking method.

Keywords: methylene active thioamides, dithiomalondianilide, tautomerism, potentiometric determination of the dissociation constant, calculated biological activity

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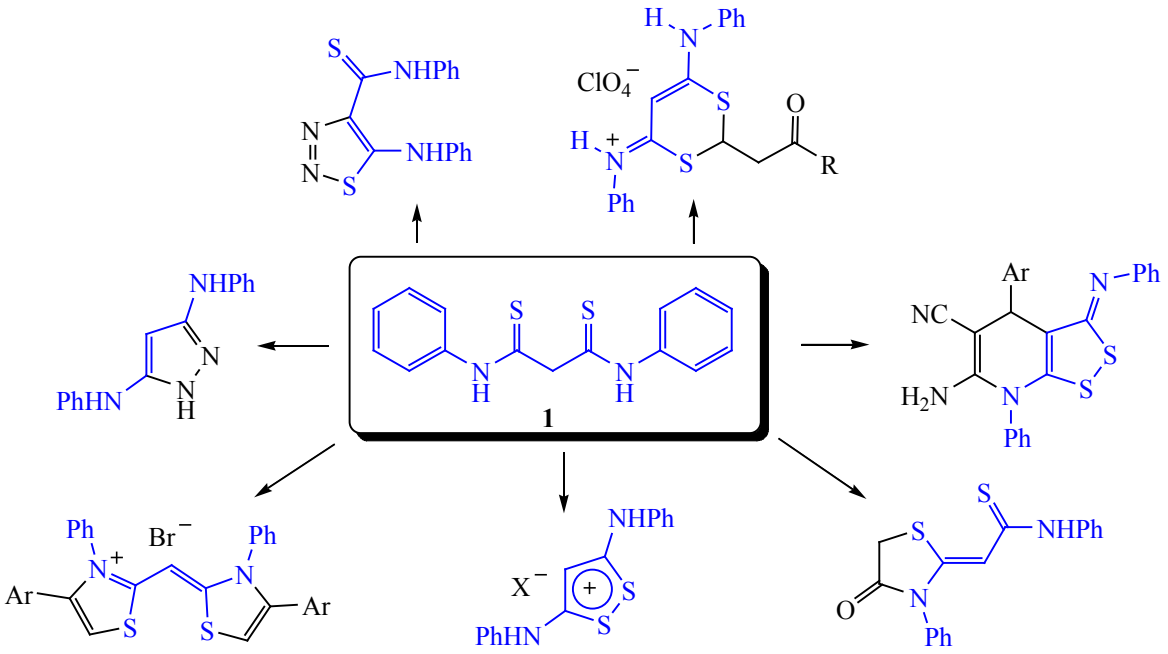
Dithiomalonodiamides and, in particular, *N,N*′-diphenyldithiomalonodiamide **1** are actively used in various chemistry fields as bidentate complexing agents [1–6], steel corrosion inhibitors [7], reagents for the Ag^+ extraction from chloride-containing aqueous solutions [8], and also as starting reagents for the synthesis of a number of sulfur-containing heterocyclic systems—derivatives of 1,2-dithiol [9–14], thiazole [15, 16], 1,3-dithiine [17–22], [1,2]dithiolo[3,4-*b*]pyridine [23], 1,2,3-thiadiazole [24], thiophene [25, 26], 3,5-diaminopyrazole [11, 26, 27], etc. (Scheme 1).

At the same time, when comparing *N,N*′-diphenyldithiomalonodiamide **1** with other methylene active thioamides (see reviews [28–32]), it can be noted that the potential of thioamide **1** as a methylene active compound is practically not disclosed—scarce information is available on the interaction of dithiomalondianilide **1** with Michael acceptors [23] or active carbonyl compounds [26]. Continuing research in the field of the methylene active thioamides chemistry, we focused on *N,N*′-diphenyldithiomalonodiamide **1** as a promising available methylene active compound for the preparation of a number of heterocyclic systems.

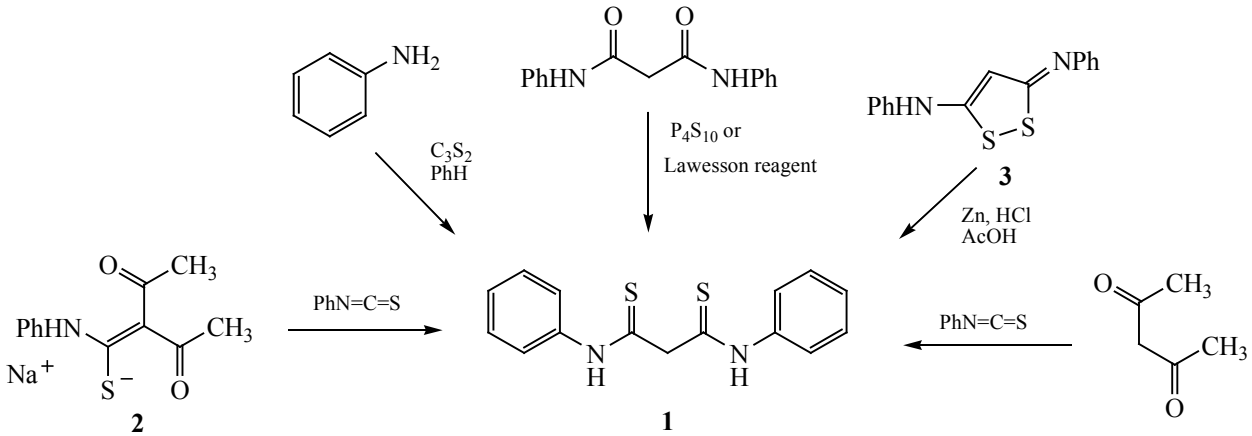
In this work, using experimental and theoretical methods, the tautomerism and geometry of dithiomalondianilide molecule have been studied, the experimental and calculated vibrational spectra have been correlated, the pK_a value of dithiomalondianilide has been experimentally determined for the first time by potentiometric titration, as well as the bioavailability parameters have been calculated and possible protein targets for molecule **1** have been predicted.

There are several methods for preparation of dithiomalondianilide **1**: the compound is obtained by condensation of the sodium salt of diacetylthioacetanilide **2** with PhNCS [33], the reaction of carbon subsulfide C_3S_2 with aniline in an inert solvent [34–36], the interaction of malonanilide with P_4S_{10} [24, 37, 38] or Lawesson reagent [24,37,38] 39], the reduction of 3-phenylamino-5-phenylimino-1,2-dithiol **3** with the Zn–HCl–AcOH system [9], or by the reaction of acetylacetone with PhN=C=S in the presence of sodium alcoholate in EtOH, MeOH or Et_2O [1, 3, 27, 40–43] (Scheme 2). The latter method is the most simple in the preparative relation and gives the largest yields.

Scheme 1.

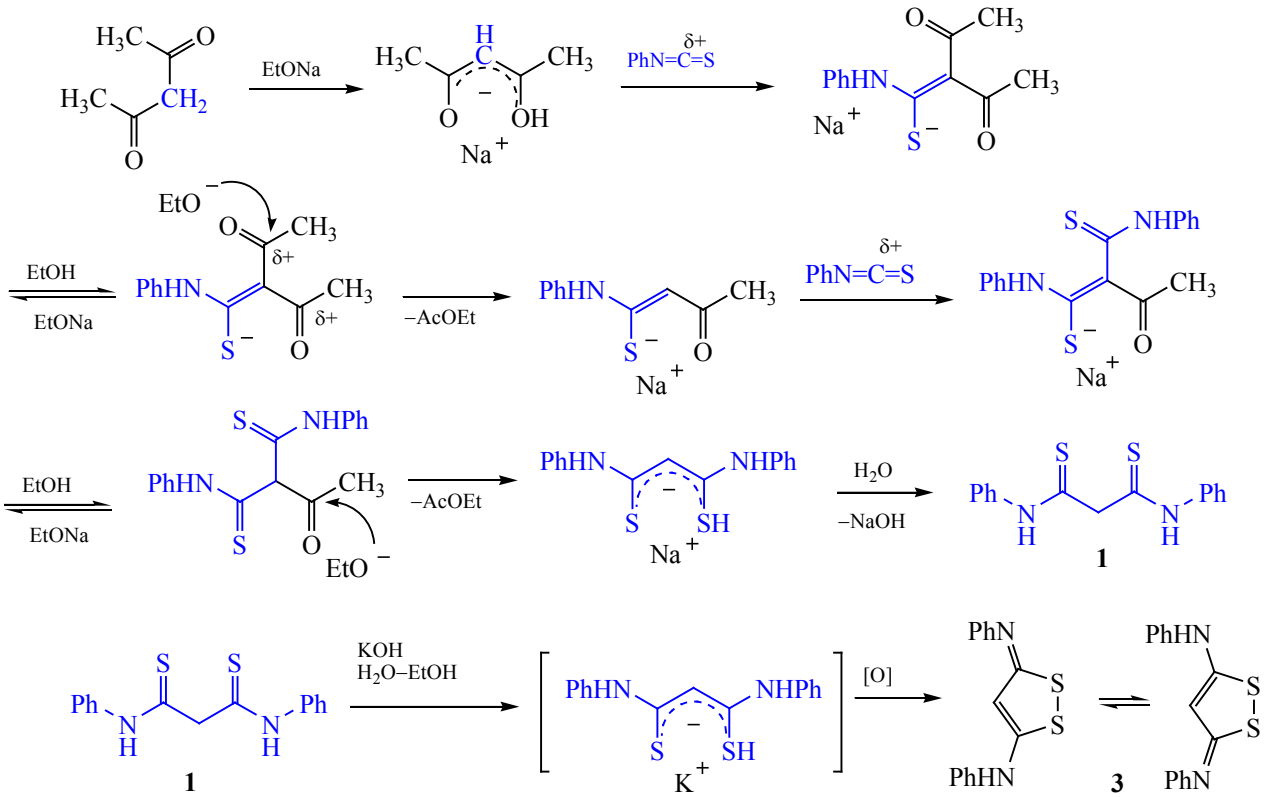


Scheme 2.



Dithiomalondianilide **1** was prepared by us according to a modified procedure [43] in 97% yield. The reaction apparently proceeds as a sequence of tandem processes of thiocarbamoylation–ketone cleavage (Scheme 3). It was found that the using of isopropanol or *n*-butanol as solvents sharply reduced the yield of dithioamide **1**: for example, in the case of *n*-butanol, the yield was only 43%. In our opinion, this may be due to steric hindrances in the course of ketone cleavage with a more bulky nucleophile (*i*-PrO$^-$ or BuO$^-$), as well as to the limited miscibility of these alcohols with water, which prevents the product precipitation during the work up of the reaction mixture of the reaction mixture. It is interesting to note that an attempt to purify dithiomalondianilide by treatment with KOH followed by precipitation with acid led to the formation of a new compound identified by NMR spectroscopy as 3-phenylamino-5-phenylimino-1,2-dithiol **3**.

Scheme 3.



The structure of compounds **1** and **3** was confirmed by IR and NMR spectroscopy data, including two-dimensional NMR spectroscopy (^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC) for dithiomalondianilide **1** (see Supplementary Information). The observed correlations are presented in Table 1.

According to NMR data, in DMSO-d_6 and $CDCl_3$ solutions, compound **1** exists in the dithione form: the spectrum does not show signals of enthiol tautomers in noticeable amounts, which generally correlates with the literature data [44]. It should be noted that the questions about tautomerism and conformational analysis of dithiomalonoamides have practically not been studied up to date. Thus, in the only work [45] that we found, studies of the conformations of *N,N′*-dialkyldithiomalonodiamides based on the analysis of IR spectra in solution were presented. To clarify the details of the dithiomalondianilide structure, we calculated the energies of the most stable tautomers and carried out a comparative analysis of experimental and calculated vibrational spectra using quantum-chemical methods.

Table 1. Correlations in the ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC NMR spectra of dithiomalondianilide **1**

δ_H, ppm	δ_C, ppm	
	^{1}H–^{13}C HSQC	^{1}H–^{13}C HMBC
4.27 s (2H, CH_2)	62.8 (CH_2)	195.4 (C=S)
7.23–7.27 m (2H, H^4-Ph)	126.2* (2C^4-Ph)	123.0* (2C^2, 2C^6-Ph)
7.40–7.43 m (4H, H^3, H^5-Ph)	128.5* (2C^3, 2C^5-Ph)	123.0* (2C^2, 2C^6-Ph), 128.5* (2C^3, 2C^5-Ph), 139.4 (2C^1-Ph)
7.86 d (4H, H^2, H^6-Ph, ^3J 7.6 Hz)	123.0* (2C^2, 2C^6-Ph)	123.0* (2C^2, 2C^6-Ph), 126.2* (2C^4-Ph), 139.4 (2C^1-Ph)
11.86 s (2H, NH)	–	62.8 (CH_2), 123.0* (2C^2, 2C^6-Ph)

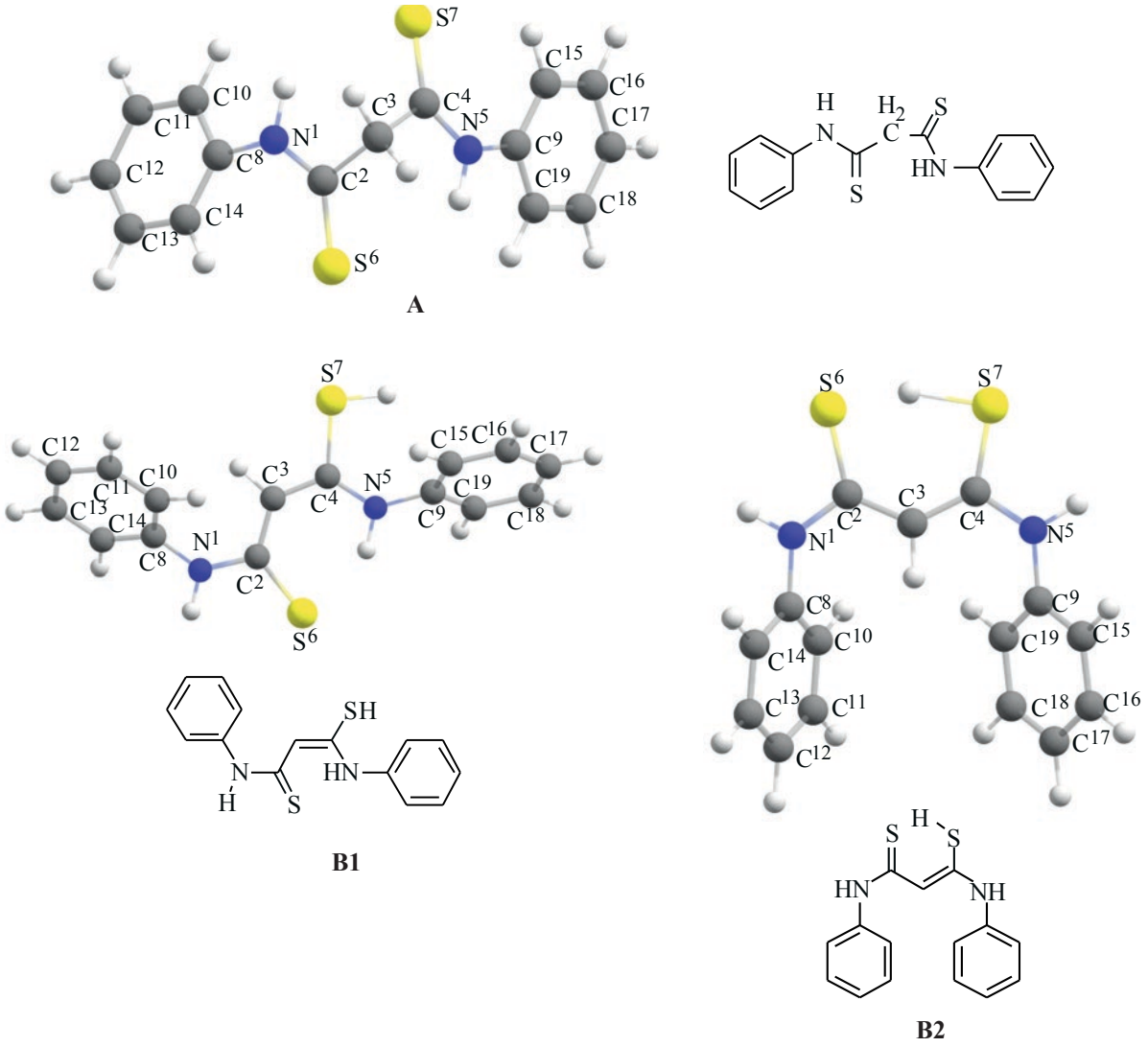


Fig. 1. Molecular structures of the tautomeric forms of dithiomalondianilide optimized at the B3LYP-D3BJ/6-311+G(2d,p) level: (**A**) *trans*-dithione form, (**B1**) *trans*-isomer of the enthiol form, and (**B2**) *cis*-isomer of the enthiol form.

The molecular geometry and vibrational spectra of dithiomalondianilide tautomers were calculated using the ORCA 4.2 software package [46, 47] using the B3LYP hybrid functional [48, 49] with the D3BJ dispersion correction [50] in the split valence basis set 6-311+G(2d,p). The calculated vibrational frequencies were compared with the experimental ones taking into account the correction factors [0.9679 for high-frequency (>1000 cm^{-1}) and 1.0100 for low-frequency vibrations (<1000 cm^{-1})] [51]. To determine the energy of solvation of the studied compounds, a calculation was carried out taking into account nonspecific solvation within the framework of the CPCM model [52]. All calculations were performed after a preliminary search for the most stable conformations. To generate Input-files, we used the Gabedit 2.5 program [53]. The ChemCraft 1.8 software was used to visualize the molecular geometry and vibrational frequencies.

The dithiomalondianilide molecule can exist in two tautomeric forms—dithione **A** and enthiol **B**. In this case, the enthiol form **B**, in turn, can exist in the form of *Z*- and *E*-isomers. To estimate the stability of these forms of dithiomalondianilide, we performed a quantum-chemical DFT calculation of the energy of the most stable

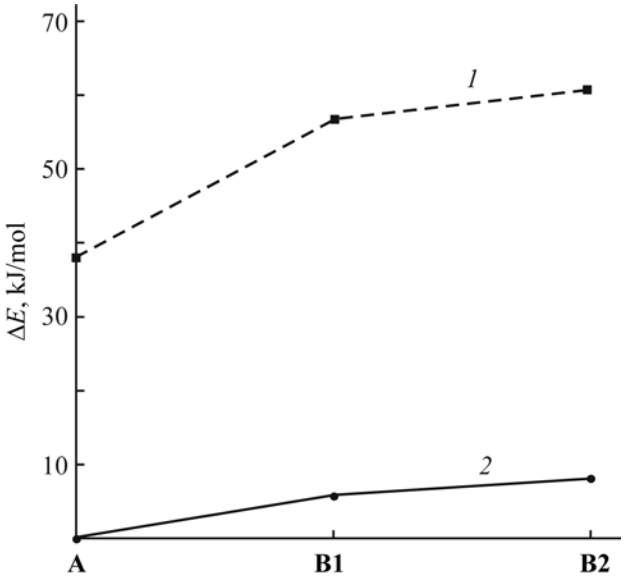


Fig. 2. The energies of the tautomers of dithiomalondianilide **1**, calculated without taking into account the effect of the solvent (*1*) and taking into account the nonspecific solvation in the DMSO medium (*2*), relative to the minimum value of the energy of the tautomer **A** in the DMSO medium.

conformers of molecule **1** both in vacuum and in a DMSO medium (the solvent was taken into account using the CPCM continuum model). The optimized molecular structures of the tautomers are shown in Fig. 1.

The results of calculating the energy of tautomers are shown in Fig. 2. As you can see, according to the calculated data, the dithione form **A** is the most stable both in vacuum and in DMSO, which is confirmed by the NMR spectroscopy data. From the enthiol forms, **B1** *trans*-isomer is somewhat more stable; however, the difference in energy with **B2** *cis*-isomer is small and amounts to 4.1 kJ/mol in vacuum and 2.3 kJ/mol in DMSO. It should be noted that the difference in energy between dithione form **A** and enthiol forms **B1**, **B2** in vacuum (18.7 kJ/mol) significantly exceeds the same value in the DMSO medium (5.8 kJ/mol), which indicates a more efficient solvation of the enthiol forms and the possibility of the existence of tautomeric equilibrium between forms **A**, **B1**, and **B2**. It should be pointed out that the formation of the enthiol forms of dithioamide **1** was recorded in the spectra in a more polar solvent (CD_3COOD) [44].

Thus, according to the quantum-chemical calculations data, dithiomalondianilide **1** in crystalline state should exist in the dithione form **A**, which is the most stable. IR spectroscopic data of dithiomalondianilide in the crystalline state confirm this conclusion. The calculated spectrum of the dithione form **A** agrees with the experimental one much better than the calculated spectra of the enthiol forms **B1** and **B2**. Comparison of the experimental values of the vibrational frequencies of dithiomalondianilide **1** with the quantum-chemical calculations data for tautomer **A** is presented in Table 2. The IR spectra of various tautomers of dithiomalondianilide **1** calculated at the B3LYP-D3BJ/6311+G (2d,p) level are given in Supplementary Information.

In the context of research the reactivity of dithiomalondianilide as a methylene active compound, it seemed appropriate to investigate the acidic properties of this compound. It should be noted that a relatively small number of works have been devoted to the study of the acidity of methylene active thioamides. So, in the literature there is information about the pK values of cyanothioacetamide determined by the method of potentiometric titration (pK_a 10.34 [54], 9.46 [55]), cyanothioacetanilide (pK_a 8.95 [55]), ethyl 3-(*R*-amino)-3-thioxopropanoates (pK_a 14.2–14.5 [56]), a series of β-(*R*-sulfonyl)thioacetamides (pK_a 10.03–13.41 [54, 55]), β-ketothioamides (pK_a 7.04–11.70 [54, 55, 57, 58]). It should be noted that there are no data on the acidic properties of dithiomalonodiamides in the literature.

The protonation constant of *N,N′*-diphenyldithiomalondiamide **1** was determined by potentiometric titration in a aqueous-alcohol (1 : 2 by volume) and aqueous-acetone (1 : 2 by volume) medium. Potentiometric titration curves in aqueous-alcoholic and aqueous-acetone media are given in Supplementary Information. A decrease in the buffer region of the titration curves indicates protolytic equilibrium of *N,N′*-diphenyldithiomalonoamide **1** in aqueous-alcoholic and aqueous-acetone solutions at pH greater than 8 (Scheme 4).

A preliminary estimation of the protonation constant was carried out according to the values of the experimental points of the titration curves by two methods: direct calculation and by the Bjerrum's method. Direct calculation was performed according to Eq. (1).

$$\log K = \log \frac{(1-a)c_{HL} - [H^+] + [OH^-]}{ac_{HL} + [H^+] - [OH^-]} + \text{pH}. \qquad (1)$$

Here a is the degree of neutralization calculated by Eq. (2).

Table 2. Comparison of experimental vibrational frequencies (attenuated total internal reflection spectroscopy) with the data of quantum-chemical calculations for the dithione form (tautomer **A**) of dithiomalondianilide **1**

Assignment	ν, cm^{-1}		
	experiment	calculation	
		without correction factor	with correction factor
N–H	3182.3	3492.9	3380.8
C_{Ar}–H	3012.6	3178.3	3076.3
–[a]	1595.0	1650.1	1597.1
$C–C_{skeleton}$	1595.0	1647.8	1594.9
δ(N–H)	1515.9	1586.1	1535.2
$C–C_{skeleton}$	1492.8	1532.9	1483.7
$δ(CH_2)$	1444.6	1493.7	1445.8
C–N	1392.5	1431.3	1385.3
–[a]	1290.3	1361.8	1318.1
–[a]	1271.0	1282.5	1241.3
C=S	1110.9	1113.5	1077.8
–[a]	1070.4	1103.8	1068.4
–[a]	968.2	996.1	1006.0
–[a]	906.5	915.0	924.1
–[a]	848.6	849.3	857.8
$δ(C_{Ar}–H)_{out-of-plane}$	756.0	770.2	777.9
–[a]	715.5	742.8	750.2
–[a]	682.8	700.2	707.2
–[a]	545.8	557.8	563.4
–[a]	499.5	504.4	509.4

[a] The absorption bands correspond to group vibrations, which are difficult to assign to a specific fragment of the molecule.

$$a = \frac{V_{OH^-} \cdot c_{OH^-}}{V_O \cdot c_{HL}}. \quad (2)$$

Here c_{HL} is the concentration of dithiomalondianilide **1**, mol/L; c_{OH^-} is alkali concentration, mol/L; V_O is the volume of the solution to be titrated, mL.

According to the results of direct calculation, the mean value of the logarithm of the protonation constant of *N,N′*-diphenyldithiomalonoamide **1** is pK_a 10.28±0.02 in an aqueous-alcoholic medium and pK_a 10.25±0.02 in an aqueous acetone medium.

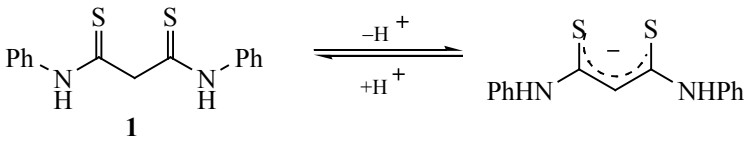
When determining the protonation constant of compound **1** by the Bjerrum's method, the mean ligand number was calculated using Eq. (3).

$$\bar{n} = 1 - \frac{V_{HL} \cdot c_{OH^-}}{(V_O + V_{HL})c_{HL}}. \quad (3)$$

Here $\bar{n}$ is the mean Bjerrum's ligand number.

According to obtained values we plotted the dependences of the mean ligand number $\bar{n}$ on pH in aqueous-alcoholic and aqueous-acetone media (see Supplementary Information). The mean values of the

Scheme 4.



1

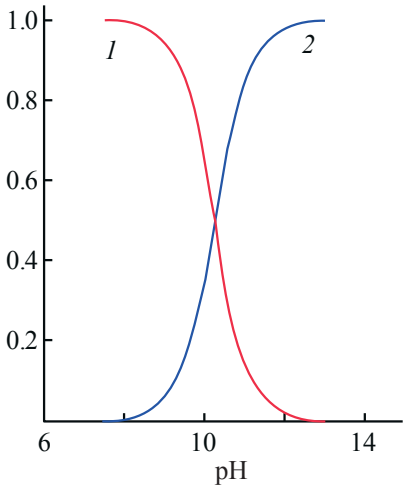


Fig. 3. Distribution curves of protonated (*1*) and deprotonated (*2*) forms of dithiomalondianilide **1** at different pH values of the solution.

protonation constants were pK_a 10.30±0.05 in an aqueous-alcoholic medium and pK_a 10.28±0.07 in an aqueous-acetone medium. The exact values of the protonation constants for *N,N′*-diphenyldithiomalonoamide **1** were pK_a 10.30±0.02 in an aqueous-alcoholic medium and pK_a 10.28±0.04 in an aqueous-acetone medium.

The obtained value of the protonation constant of dithiomalondianilide was used to plot the distribution diagram of the protonated and deprotonated forms of the ligand depending on pH (Fig. 3). From the diagram shown in Fig. 3, it follows that dithiomalondianilide **1** exists in an aqueous-alcoholic solution mainly in a deprotonated form at pH > 8.

The data available in the literature on the biological action of dithiomalonodiamides are fragmentary. Thus, a number of dithiomalonoamides and their complexes exhibit fungicidal activity against *Botrytis cinerea* and the causative agents of grape downy mildew [59]. It has also been reported [60] about the antibacterial effect of a number of malonic acid derivatives, including substituted dithiomalondianilides. 1,2-Dithiol derivatives, including the oxidation products of malondithioamides, are of considerable interest primarily as active anticancer drugs due to their inherent reparative effect on DNA [61–66].

We performed preliminary calculations of possible protein targets, ADMET parameters and bioavailability parameters for dithiomalondianilide **1** and 3-phenylamino-5-phenylimino-1,2-dithiol **3**. The analysis of structures for compliance with the "rule of five" K. Lipinski [molecular weight (MW) ≤ 500, *c*Log*P* ≤ 5.0, TPSA ≤ 140 Å^2, number of hydrogen bond acceptors ≤ 10, donors ≤ 5] [67–69] was carried out using the OSIRIS Property Explorer software service [70]. The parameters were calculated: solubility (log *S*), *c*Log*P* [logarithm of the distribution coefficient between *n*-octanol and water log ($c_{octanol}/c_{water}$)], solubility (log *S*), Topological Polar Surface Area (TPSA), a number of toxicological characteristics—risks side effects (mutagenic, oncogenic, reproductive effects), the parameter of similarity with known drugs (drug-likeness), as well as the overall estimation of the pharmacological potential of the compound (drug score). The obtained calculated data are presented in Table 3. As follows from the Table, compounds **1** and **3** fully correspond to the criteria for oral bioavailability, do not show a predicted risk of toxic effects, and have rather high predicted values of the drug score.

To predict the ADMET parameters, we used the SwissADME [71], admetSAR [72], and GUSAR [73] software packages. The obtained calculated data are presented in Table 4. In general, the estimation of acute toxicity makes it possible to classify compounds **1** and **3** as IV and V hazard classes according to the OECD criteria [74].

The calculation of the probable antibacterial activity using the Way2Drug AntiBac-Pred service [75, 76] indicates a high potential of dithiomalonanilide **1** as an antimicrobial agent against the causative agent of typhoid fever *Salmonella typhi* (*C* 0.8108), hay bacillus *Bacillus subtilis* (*C* 0.7994), plague bacillus *Yersinia pestis* (*C* 0.5138) [the confidence indicator (*C*) is calculated as the excess of the probability of activity over the probability of inactivity, $P_A > P_I$]. For 1,2-dithiol **3**, the most likely activity is expected against *Yersinia pestis* (*C* 0.3938) and the causative agent of tuberculosis *Mycobacterium bovis*, BCG strain (*C* 0.2291).

Possible protein targets for the obtained compounds were predicted using the new Galaxy Sagittarius protein ligand docking protocol [77] based on the GalaxyWeb web-server [78, 79]. The 3D structures of the compounds were pre-optimized using molecular mechanics in the MM2 force field to select the optimal geometry and minimize energy. Docking with using the GalaxySagittarius protocol was carried out in the Binding compatibility prediction and Re-ranking using

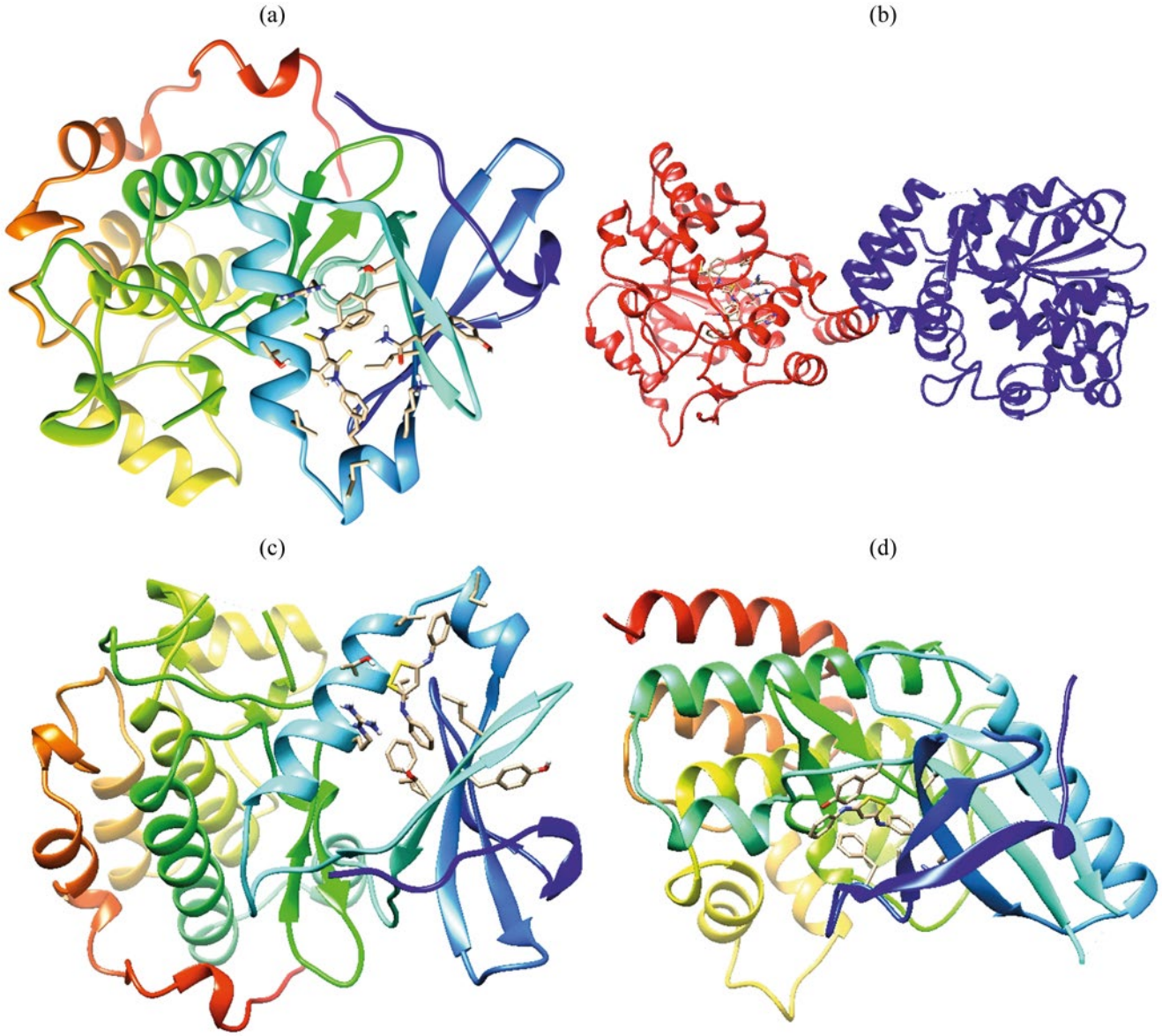


Fig. 4. Predicted structure of protein-ligand complexes for dithiomalondianilide **1** and protein kinase PDK1 (PDB ID 4rqv) (a), dithiomalondianilide **1** and sulfotransferase SULT1C2 (PDB ID 2gwh) (b), 1,2-dithiol **3** and protein kinase PDK1 (PDB ID 4rqv) (c), 1,2-dithiol **3** and tyrosine protein kinase TYK2 (PDB ID 3nyx) (d) (obtained using the GalaxyWeb Sagittarius protocol). Molecular graphics were visualized using the UCSF Chimera software package [95, 96].

docking modes. Table 5 shows the docking results for each of compounds **1**, **3** for 20 protein target–ligand complexes with the minimum free binding energy ΔG_{bind} and the best estimate of the protein–ligand interaction. Predicted protein targets are specified with ID-identifiers in the Protein Data Bank (PDB) and in the UniProt database. Common receptors for compounds **1**, **3** are 3-phosphoinositide-dependent protein kinase PDK1 (PDB ID 4rqv), urokinase plasminogen activator (uPA) (PDB ID 1c5z), PARP14 polymerase (poly(ADP-ribose) polymerase 14 (PDB ID 5o2d), mutant (T315I) Bcr-Abl1 tyrosine kinase (PDB ID 4twp), protein tyrosine kinase TYK2 (PDB ID 3nyx) (Fig. 4).

Protein kinase PDK1 plays an important role in cellular processes, including activation of the PI3K signaling pathway, which is associated with excessive cell proliferation [80, 81]. Urokinase plasminogen activator

Table 3. Risks of toxicity and physicochemical parameters of compounds **1** and **3**, predicted using the OSIRIS Property Explorer service

Compound	Risk of toxicity[a]				Physicochemical parameters					
	A	B	C	D	*c*Log*P*	log*S*	MW	TPSA	drug-likeness	drug score
1	–	–	–	–	3.15	–5.08	286	88.24	–1.81	0.38
3	–	–	–	–	3.75	–4.04	284	74.99	–0.90	0.48

[a] The "+" sign indicates a high risk of toxicity, "+"—a moderate risk, "–"—no toxicity. A—mutagenicity, B—carcinogenicity, C—irritant effect, D—reproductive effects.

Table 4. Risks of toxicity, ADMET parameters, and bioavailability of compounds **1** and **3**

Compound	Penetration through the BBB[a]	Gastrointestinal absorption[a]	Inhibition of cytochromes P450[a]					Ames test[a]	Acute toxicity (rats), LD_{50}[b]		
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4		IP	IV	Oral‡
1	+	+	+	+	+	–	+	+	0.340	–0.49	0.726
	0.9108	0.8061	0.9691	0.8561	0.5749	0.7075	0.6606	0.5626	627.4	92.7	1524.0
3	+	+	+	+	–	+	–	+	0.009	–0.594	0.565
	0.9397	0.8430	0.8344	0.8049	0.5928	0.5174	0.6330	0.7470	290.3	72.37	1044.0

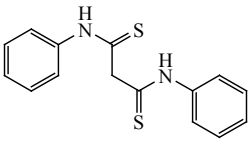
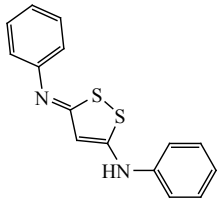
[a] The sign "+" or "–" indicates the presence or absence of the effect, the number means the probability of the effect in fractions of one.
[b] IP (IntraPeritoneal)—intraperitoneal injection, IV (IntraVenous)—intravenous administration, Oral—oral administration.

(uPA)—protease associated with the development of metastases; uPA inhibitors are of interest as promising agents for the therapy of prostate and breast cancer [82–84]. PARP14 polymerase is a promising target for the development of drugs for the treatment of diffuse large B-cell lymphoma, multiple myeloma, prostate cancer and hepatocellular carcinoma, as well as allergic inflammatory processes [85]. At the same time, PARP14 plays an important role in viral replication [86] and regulates the interferon response to SARS-CoV-2 viral infection [87]. Mutant Bcr-Abl^{T315I} tyrosine kinase plays a key role in the pathogenesis of chronic myeloid leukemia [88–90]. Tyrosine kinase TYK2 inhibitors can be used to treat psoriasis, systemic lupus erythematosus, and rheumatoid arthritis [91–93].

The minimum calculated binding energy for dithiomalondianilide **1** (ΔG_{bind} = –21.977 kcal/mol) and one of the lowest values for 1,2-dithiol **3** (ΔG_{bind} = –21.143 kcal/mol) is observed in the case of the protein target SULT1C2 (PDB ID 2gwh)—sulfotransferase regulating the metabolism of phenolic xenobiotics [94]. In general, compounds **1** and **3** are of interest as promising subjects for screening in order to search for new agents, primarily for the treatment of various viral, autoimmune, and oncological diseases.

Thus, in this work, a detailed analysis of the structural features and properties of dithiomalondianilide was carried out: new spectral characteristics were obtained, for the first time the acidity value was experimentally determined, and the most stable tautomeric forms were revealed by calculation methods. For the most stable tautomeric forms, IR spectra were calculated, and their comparative analysis with experimental spectra was carried out. It has been shown that in the crystalline form, dithiomalondianilide exists in the dithione form, while in solution the existence of enthiol tautomers is possible. For dithiomalondianilide and its oxidation product, 3-phenylamino-5-phenylimino-1,2-dithiol, the toxicity

Table 5. Results of prediction of protein-ligand interaction for compounds **1** and **3**

Compound	Protein PDB ID identifier	Protein UniProt ID identifier	Predoking estimation of protein-ligand interaction (Predock score)	Free binding energy, kcal/mol (Docking score)	Overall estimation of protein-ligand interaction
 **1**	4rqv	O15530	0.141	–16.978	0.268
	1c5z	P00749	0.111	–17.425	0.242
	5o2d	Q460N5	0.074	–21.280	0.233
	4twp	P00519	0.081	–18.401	0.219
	2gwh	O75897	0.052	–21.977	0.217
	1q20	O00204	0.058	–20.535	0.212
	1uwj	P15056, P15056	0.068	–18.726	0.209
	3nyx	P29597	0.064	–19.158	0.208
	3rx3	P15121	0.045	–21.513	0.207
	6mom	Q9NWZ3	0.064	–18.916	0.206
	6n8s	Q6P1M3	0.049	–20.850	0.205
	4fmw	Q8TBZ6	0.047	–21.048	0.205
	1ydr	P61925	0.076	–17.220	0.205
	2reo	Q6IMI6	0.044	–21.302	0.204
	5tx5	Q13546	0.047	–20.938	0.204
	4jvl	P49888	0.047	–20.893	0.204
	2onl	P49137, Q16539	0.059	–19.291	0.204
	6e2n	Q99683, Q99683	0.064	–18.560	0.203
	5ek0	Q15858, Q15858, Q15858, Q15858	0.052	–20.089	0.203
	5mwy	P08235	0.061	–18.834	0.202
 **3**	4rqv	O15530	0.147	–15.466	0.263
	4nns	P15090	0.117	–15.670	0.235
	5ewv	P55201	0.102	–17.041	0.229
	5m0c	P61925	0.090	–18.235	0.226
	5d0r	Q96PN6	0.092	–17.629	0.225
	5o2d	Q460N5	0.089	–17.852	0.223
	1c5z	P00749	0.088	–17.586	0.220
	4twp	P00519	0.075	–19.098	0.218
	3nyx	P29597	0.066	–19.765	0.214
	5ngz	Q9NPD8	0.080	–17.410	0.210
	3mdy	O00238	0.058	–20.259	0.210
	5niu	Q9NZQ7, Q9NZQ7	0.050	–21.190	0.209
	2gwh	O75897	0.050	–21.143	0.209
	6c4d	Q13546	0.048	–21.251	0.207
	5dft	P02751, P02751, P02751, P02751, P02751	0.058	–19.680	0.206
	4d83	P56817	0.081	–16.647	0.206
	4y85	P41279, P41279	0.048	–20.967	0.205
	6cnx	Q99986	0.061	–19.162	0.205
	1g3m	P49888	0.052	–20.300	0.204
	6gqo	P35968	0.060	–19.198	0.204

and bioavailability parameters were calculated, and the most probable protein targets were selected by molecular docking. Based on the obtained data, dithiomalondianilide and 3-phenylamino-5-phenylimino-1,2-dithiol are of interest for further research in the search for antibacterial drugs and new therapy for various forms of cancer.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vertex 70 spectrophotometer with an ATR attachment by the method of disturbed total internal reflection on a diamond crystal, the error is ±4 cm^{-1}. NMR spectra were recorded on a Bruker Avance III HD 400 MHz device [400.17 (^{1}H), 100.63 MHz (^{13}C)] in a solution of DMSO-d_6 and $CDCl_3$; residual solvent signals were used as a standard. The individuality of the obtained samples was controlled by TLC method on Sorbfil-A plates (IMID, Krasnodar), eluent—acetone–light petroleum (1 : 1), developer—iodine vapor, UV detector.

Ethanol was dried by boiling with metalic calcium, followed by distillation.

***N,N′*-Diphenyldithiomalonodiamide (1)** was obtained by modified procedure based on patent [43]. To absolute EtOH (50 mL) was added 0.96 g (0.042 mol) of metallic sodium; 4.28 mL (0.042 mol) of freshly distilled acetylacetone was added to a freshly prepared solution of sodium ethylate at 25°C. The solution was stirred for 5 min until the formation of sodium acetylacetonate was completed; and then 10.0 mL (0.084 mol) of phenyl isothiocyanate was added. The mixture was stirred for 2 h and left overnight at 25°C. The obtained yellow-orange solution was poured into 100 mL of ice water and stirred until a lemon-yellow precipitate of dithiomalondianilide **1** was formed. The precipitate was filtered off, washed with EtOH, dried at 50°C, and 8.21 g of thioanilide **1** was obtained. After 24 h, an additional 3.38 g of the product was filtered from the mother solution. Total yield of dithiomalondianilide was 11.59 g (97%), yellow colored powder, mp 150–152°C, R_f 0.42. For analytical purposes, the compound can be purified by recrystallization from hot EtOH or an acetone–heptane mixture, 1 : 1. Dithiomalondianilide is well soluble in acetone, EtOAc, DMSO, and DMF, moderately soluble in hot EtOH, and insoluble in water. IR spectrum, ν, cm^{-1}: 1111 (C=S), 1595 (C–C), 3013 (C_{Ar}–H), 3182 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.27 s (2H, CH_2), 7.23–7.27 m (2H, H^4-Ph), 7.40–7.43 m (4H, H^3, H^5-Ph), 7.86 d (4H, H^2, H^6-Ph, ^3J 7.6 Hz), 11.86 s (2H, NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.22 s (2H, CH_2), 7.26–7.30 m (2H, H^4-Ph), 7.38–7.42 m (4H, H^3, H^5-Ph), 7.72 d (4H, H^2, H^6-Ph, ^3J 7.8 Hz), 10.17 s (2H, NH). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ_C, ppm: 62.8 (CH_2), 123.0* (2C^2, 2C^6-Ph), 126.2* (2C^4-Ph), 128.5* (2C^3, 2C^5-Ph), 139.4 (2C^1-Ph), 195.4 (C=S). Here and below, the *asterisk* marks the signals in antiphase. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 66.7 (CH_2), 123.2 (2C^2, 2C^6-Ph), 127.3 (2C^4-Ph), 129.0 (2C^3, 2C^5-Ph), 138.2 (2C^1-Ph), 193.8 (C=S). Found, %: C 62.87; H 4.99; N 9.75. $C_{15}H_{14}N_2S_2$. Calculated, %: C 62.90; H 4.93; N 9.78. *M* 286.42.

3-Phenylamino-5-phenylimino-1,2-dithiol (3). A mixture of dithiomalondianilide **1** (400 mg, 1.4 mmol), 10 mL of a 10% aqueous solution of KOH and 25 mL of EtOH was stirred and left for 72 h, after which it was neutralized with AcOH. The precipitate was filtered off, washed with aqueous EtOH and light petroleum. 251 mg (63%) of dithiol **3** was obtained as yellow-orange colored powder, R_f 0.52. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.94 br. s (1H, C^{4}H), 6.98–7.02 m (2H, H^4-Ph), 7.24–7.28 m (4H, H^3, H^5-Ph), 7.36–7.50 m (4H, H^2, H^6-Ph), 11.44 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 113.1 (C^4), 121.2 (2C^2, 2C^6-Ph), 122.8 (2C^4-Ph), 128.5 (2C^3, 2C^5-Ph), 145.1 (2C^1-Ph). The C^3 (C^5) signal is not detected, probably due to rapid tautomeric transitions. Found, %: C 63.37; H 4.33; N 9.83. $C_{15}H_{12}N_2S_2$. Calculated, %: C 63.35; H 4.25; N 9.85. *M* 284.40.

pH-Potentiometric titration of aqueous-alcoholic and aqueous-acetone (1 : 2 by volume) solutions of *N,N′*-diphenyldithiomalondiamide **1** was performed using an EXPERT-001-1 ionomer with an ESK-10603 combined glass electrode in a thermostated cell at 25±0.1°C and the ionic strength of the solution is 0.1 M. KCl. A 1 M KOH solution free from carbonates was used as a titrant, the exact concentration of which was established by 1 M HCl solution. To determine the protonation constants, we titrated the mixtures of *N,N′*-diphenyldithiomalondiamide **1** (c_{HL} 0.01 M) and hydrochloric acid (c_{HCl} 0.1 M), an excess of which was required to convert *N,N′*-diphenyldithiomalondiamide **1** into the fully protonated form at the initial moment of titration.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY INFORMATION

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