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Synthesis, study of the structure, and modification of the products of the reaction of 4-aryl-4-oxobut-2-enoic acids with thiourea

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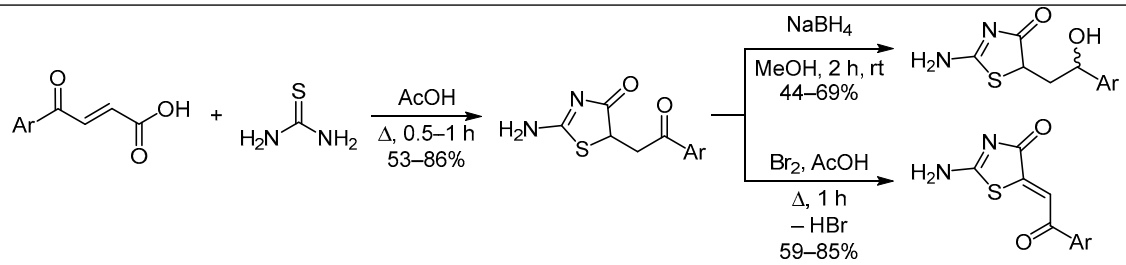


A number of previously undescribed derivatives of 2-amino-5-(2-aryl-2-oxoethyl)thiazol-4(5*H*)-one containing electron-donating substituents in the aromatic ring were synthesized by the reaction of (*E*)-4-aryl-4-oxobut-2-enoic acids with thiourea. Reduction of the reaction products with $NaBH_4$ yielded diastereomeric alcohols, whereas bromination in AcOH was accompanied by elimination of HBr and the formation of (*Z*)-2-amino-5-(2-aryl-2-oxoethylidene)thiazol-4(5*H*)-ones.

Keywords: 2-amino-5-(2-aryl-2-oxoethyl)thiazol-4(5*H*)-ones, 4-aryl-4-oxobut-2-enoic acids, thiourea, cyclocondensation, oxidative bromination, reduction.

Derivatives of thiazolidin-4-ones exhibit various physiological activity:[1–3] analgesic and anti-inflammatory drugs,[4–6] fungicides,[7] inhibitors of cyclooxygenase-2,[8] anticancer and antiviral agents[2,9,10] were found among them. Synthetic approaches to 2-amino(imino)thiazolidin-4-ones are based, as a rule, on the reactions of thiourea and its derivatives with bielectrophilic reagents.[4,7,11–14] Thus, the reaction of 4-aryl-4-oxobut-2-enoic acids with thioureas is a very convenient method for the formation of the thiazolidine ring.[15–20]

Despite the fact that cyclocondensation of 3-benzoylacrylic acid with thiourea was first carried out as early as in 1947,[15] the structure of the molecules of the resulting compounds has been a subject of discussion until recently. Thus, the authors of studies describing the formation of thiazol-4(5*H*)-ones **A** in the reactions of 3-aroylacrylic acids with thioureas by heating under reflux in EtOH with additions of catalytic amounts of AcOH (Fig. 1)[16,17] postulate the existence of the keto-enol equilibrium with the participation of the endocyclic carbonyl group. The formation of imino form **B** has been described elsewhere,[18–20] and the imino form becomes the only one possible when *N*,*N*'-disubstituted thioureas are used in such condensations.[21] At the same time, heating the starting reagents in AcOH under reflux leads to tetrahydropyrimidine-2-thione[22] or, when the reaction is carried out in MeOH in the presence of EtONa, to its aromatized analog **C**.[23] Data from early studies,[24,25] the authors of which postulated the formation of thiohydantoins **D**, have been convincingly refuted in later studies.

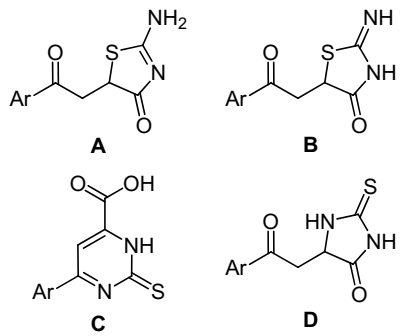
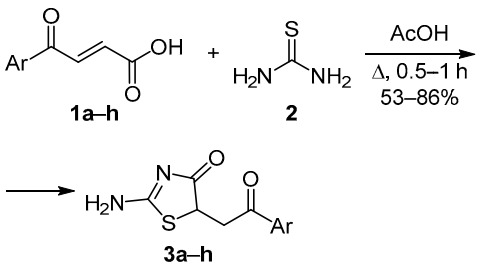


Figure 1. Structures of cyclocondensation products of 3-aroylacrylic acids with thiourea proposed in the literature.

It is known that the first step of the reaction of 3-aroylacrylic acids with nucleophiles is the attack at the α-position to the activated double bond with the formation of Michael adducts, which is due to the higher electron-withdrawing properties of the carbonyl group as compared to the carboxy group.[26–30] A similar mechanism follows from the ease of formation of α-adducts in the reactions with thiols and amines. For example, when 3-aroylacrylic acids react with 1,3-diazine-2(1*H*)-thione derivatives, which are formally cyclic thiourea derivatives, a Michael adduct is always formed at the sulfur atom[31] and not at the endocyclic nitrogen atom, which is logically consistent with the scale of nucleophilicity.

The aim of this work was to synthesize novel derivatives of thiazol-4(5*H*)-ones **3c**–**h** as well as previously described products **3a**,**b** based on 4-aryl-4-oxobut-2-enoic acids **1a**–**h** and thiourea (**2**) and reliably establish their structures (Scheme 1). The use in the reaction of 3-aroylacrylic acids **1a**–**h** containing donor groups in the aromatic ring is due to their higher synthetic availability. The target compounds **3a**–**h** were obtained in good yields according to the well-known literature methods: by heating the starting reagents in glacial AcOH under reflux.[14–18]

Scheme 1



a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 2,4-$Me_2C_6H_3$, **d** Ar = 3,4-$Me_2C_6H_3$, **e** Ar = 2,5-$Me_2C_6H_3$, **f** Ar = 4-EtC_6H_4, **g** Ar = 4-$EtOC_6H_4$, **h** Ar = 4-$MeSC_6H_4$

The synthesized products **3a**–**h** are white powders with low solubility in organic solvents. Their structure was confirmed by IR, ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry. Noteworthy is the absence in the IR spectra of absorption bands of stretching vibrations of the primary amino group in the range of 3200–3500 cm^{-1}, although a band of variable intensity is observed in the 3200 cm^{-1} region. This absorption pattern may be due to the ability of the molecules of cyclic amidines (2-aminoazolines and 2-aminoazines) to dimerize as a result of the formation of short hydrogen contacts N–H···N between amidine fragments.[32] Mass spectra of compounds **3a**–**h** are characterized by the presence of a peak of the molecular ion with low or medium intensity. The main direction of fragmentation involves the elimination of the aroyl radical, followed by the destruction of the thiazoline ring. In the ^{1}H NMR spectra of products **3a**–**h**, two broadened signals of the amino group protons are observed at 8.72–8.78 and 8.93–9.01 ppm, which indicates hindered rotation of the amino group. The ^{13}C NMR spectra of compounds **3a**–**h** contain signals of the carbon atoms of the imine, C=O

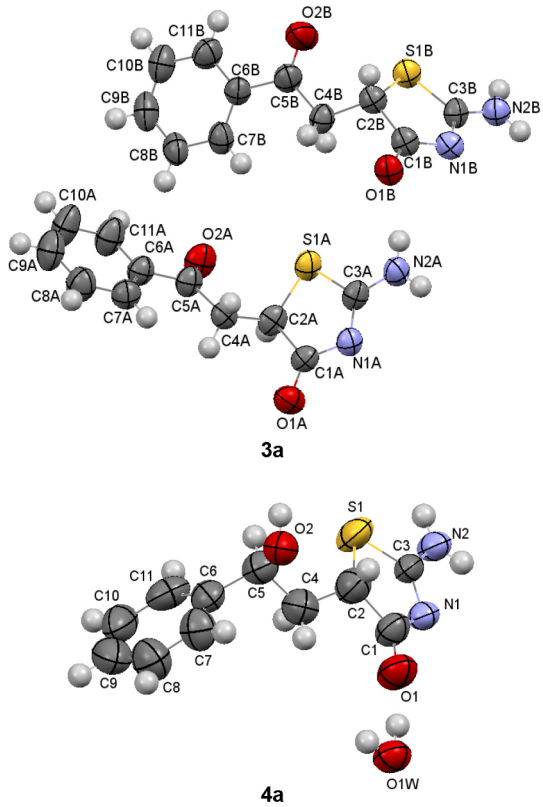


Figure 2. Molecular structure of compounds **3a** and **4a** according to X-ray structural analysis data. Atoms are represented as thermal vibration ellipsoids with 50% probability.

(amide), and C=O (ketone) groups. Thus, thiazol-4(5*H*)-ones **3a**–**h**, exist in the 2-amine tautomeric form according to the obtained spectral data.

The X-ray structural study of compound **3a** and its reduced form **4a**, the synthesis of which is described below, was an additional confirmation of this fact (Fig. 2). Two molecules of compound **3a** (**3aA** and **3aB**) were found in the symmetrically independent part of the unit cell. The reduced form of alcohol **4a** exists in the solid state as a monohydrate. An analysis of the bond lengths in these molecules revealed a significant delocalization of the electron density in the conjugated O(1)–C(1)–N(1)=C(3)–N(2) fragment. The coordinates of the hydrogen atoms of the amino group were revealed from the difference electron density synthesis; their presence confirms the existence of compounds **3a** and **4a** in the solid state in the amine tautomeric form. At the same time, the formally single exocyclic bond C(3)–N(2) turned out to be shorter than the formally double bond N(1)–C(3) (Table 1) in molecules **3aB** and **4a**, in contrast to molecule **3aA**, in which conjugation in the O(1)–C(1)–N(1)=C(3)–N(2) fragment is less pronounced. Based on such redistribution of electron density, the structure of molecules **3aB** and **4a** can be described as a superposition of two resonance structures, neutral and zwitterionic (Scheme 2).

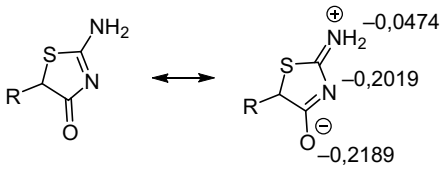
The electron density distribution in the partially hydrogenated aminothiazolone fragment of a molecule of type 3 simulated by the density functional theory (DFT) method fully corresponds to the resonance structure shown

Table 1. Selected bond lengths (Å) in molecules **3a** and **4a** according to X-ray structural analysis data

Bond	Molecule			Mean
	3aA	**3aB**	**4a**	
C(1)–O(1)	1.213(6)	1.227(6)	1.225(8)	1.210
C(1)–N(1)	1.355(7)	1.337(7)	1.337(8)	1.376
N(1)–C(3)	1.307(6)	1.342(6)	1.325(7)	1.313
C(3)–N(2)	1.320(8)	1.298(8)	1.292(7)	1.336

in Scheme 2: the negative charge on the amino nitrogen atom is significantly decreased in absolute value, whereas it is increased on the nitrogen atom of the thiazole ring and carbonyl oxygen atom (see the calculated Mulliken charges on the corresponding atoms in Scheme 2).

Scheme 2



In the solid state, compound **3a** exists in the form of centrosymmetric dimers of the A–A and B–B types due to N(2A)–H···N(1A) and N(2B)–H···N(1B) intermolecular hydrogen bonds (Fig. 3). The dimers, in turn, are linked by intermolecular hydrogen bonds N(2A)–H···O(1B) and N(2B)–H···O(1A), forming chains along the crystallographic direction [0 1 0].

In the solid state, the molecules of compound **4a** form zigzag chains along the crystallographic direction [0 1 0] due to the intermolecular hydrogen bond N(2)–H···N(1) (Table 2). H_2O molecules included in the crystal cell of compound **4a** are located between the chains and form hydrogen bonds N(2)–H···O(1W), O(2)–H···O(1W), O(1W)–H···O(1), and O(1W)–H···O(2) (Table 2).

As noted earlier, the synthesized products **3a**–**h** have limited solubility in polar organic solvents, so we decided to increase their solubility by modifying the structure for further biological screening. For this purpose, the reduction of the carbonyl group was carried out. The reduction of the carbonyl group of compounds **3a**–**c** with $NaBH_4$ in MeOH gave the corresponding alcohols **4a**–**c** in the form of mixtures of two diastereomers with different relative spatial orientations of the hydroxy group and the 5-CH proton of the heterocycle (Scheme 3). According to the data of ^{1}H NMR spectroscopy, they are present in a 2:1 ratio, which may be due to different solubility during recrystallization from a MeOH – H_2O mixture.

To explain the violation of the expected equimolar ratio of diastereomeric pairs, we performed quantum-chemical modeling of the structure of the *R*,*R*- and *R*,*S*-isomers of compound **4a** which are formed upon reduction of the carbonyl group of the *R*-enantiomer of compound **3a**. Another diastereomeric pair, *S*,*R* and *S*,*S*, have similar characteristics. Both structures are characterized by the presence of a strong intramolecular hydrogen bond OH···O=C which is facilitated by the excess electron density on the carbonyl oxygen atom (see above). The energy of the discussed hydrogen bond, estimated within the framework of R. Bader's theory of atoms in molecules according to the recommendations,[33] was 10–11 kcal/mol.

Table 2. Geometric characteristics of intermolecular hydrogen bonds in the solid state of compounds **3a** and **4a**

Hydrogen bond	Symmetry operation	Length of bond H···A, Å	Angle D–H···A, deg
Structure **3a**			
N(2A)–H···O(1B)	*x*, *y*, *z*	1.95	163
N(2A)–H···N(1B)	3 – *x*, 1 – *y*, 1 – *z*	2.09	169
N(2B)–H···N(1B)	2 – *x*, –*y*, 1 – *z*	2.08	173
N(2B)–H···O(1A)	*x* – 1, *y* – 1, *z*	1.96	166
Structure **4a**			
N(2)–H···O(1W)	0.5 + *x*, 1.5 – *y*, 1 – *z*	2.17	157
N(2)–H···N(1)	1.5 – *x*, –0.5 + *y*, *z*	2.03	170
O(2)–H···O(1W)	*x*, *y* – 1, *z*	1.97	162
O(1W)–H···O(1)	*x*, *y*, *z*	1.87	162
O(1W)–H···O(2)	0.5 – *x*, 0.5 + *y*, *z*	1.92	170

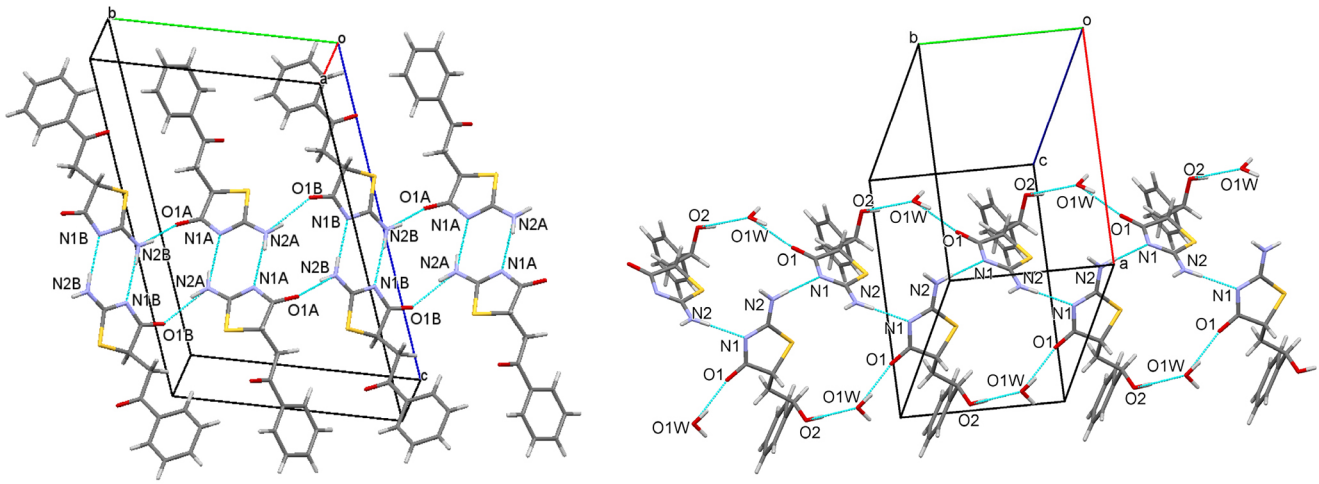
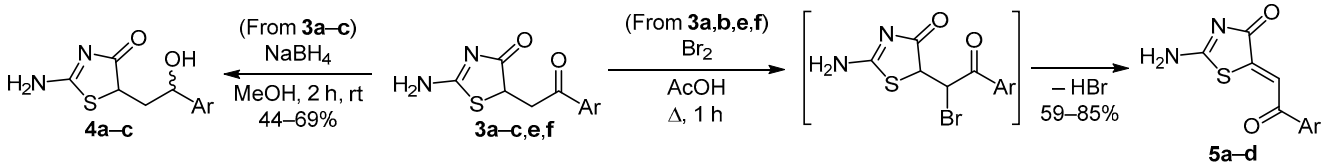


Figure 3. Packing of molecules of compounds **3a** (left) and **4a** (right) in the solid state.

Scheme 3



4 a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 2,4-$Me_2C_6H_3$; **5 a** Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 2,5-$Me_2C_6H_3$, **d** Ar = 4-EtC_6H_4

It should be noted that the *R*,*S*-isomer turned out to be somewhat more sterically hindered in comparison with the *R*,*R*-isomer (Fig. 4) which led to a slightly higher energy advantage of the latter, especially in solvents of higher polarity. According to our DFT calculations in the PCM approximation, the difference in the energies of the *R*,*R*- and *R*,*S*-isomers in MeOH (in which the reduction of compound **3a** was carried out) is only 0.175 kcal/mol, which nevertheless leads to the ratio of *R*,*R*/*R*,*S* ≈ 57:43 (according to Arrhenius). The deviation of the calculated value from the value determined experimentally from the ^{1}H NMR spectrum can be caused both by the disregard in computer modeling of specific intermolecular interactions, which play an important role for solutions in proton-donor methanol, and by the different solubility of diastereomers.

Bromination of compounds **3a**,**b**,**e**,**f** was carried out in AcOH. It was assumed that the bromination of products of type 3 would lead to the formation of the corresponding α-bromocarbonyl derivatives, convenient two-carbon synthons in the synthesis of five- and six-membered heterocycles. It turned out that the reaction practically cannot be stopped at the step of the formation of the α-bromo derivative, since dehydrobromination is a competing process in the reaction mixture. To obtain individual compounds, the reaction mixture, after the addition of a Br_2 solution, was additionally heated under reflux in AcOH, which made it possible to obtain yellow 5-arylethylidenediazol-4(5*H*)-ones **5a**–**d** in good yields (Scheme 3). Note that even under the conditions of an excess of Br_2, no further bromination of the double bond in products **5a**–**d** under the described experimental conditions was observed. The process of oxidative bromination was previously described by us for 3-(2-aryl-2-oxoethyl)-3,4-dihydroquinoxalin-2(1*H*)-ones, the products of the reaction of 3-aroylacrylic acids with *o*-phenylenediamine.[34]

The structure of ketones **5a**–**d** is convincingly confirmed by spectral characteristics. In the ^{1}H NMR spectra of these products, the typical ABX system of signals for the protons of the thiazoline fragment disappears, but a signal for the vinylene proton appears in the 7.65–7.90 ppm range, whereas the signals of the protons of amino groups are shifted downfield. In the ^{13}C NMR spectra, the signals of the carbon atoms of the double bond in the sp^2-hybridized state are recorded. The signals of the carbon atoms of the imine, amide, and carbonyl groups are shifted upfield, which indicates the presence of π-conjugation in the system. The fragmentation pattern in the mass spectra of ketones **5a**–**d** is similar to that for thiazol-4(5*H*)-ones **3a**–**h**.

The question of the spatial configuration of 2-amino-5-(2-aryl-2-oxoethylidene)thiazol-4(5*H*)-ones **5a**–**d** was difficult to solve using available physical research methods. The use of NOE is impossible due to the absence of spatially close hydrogen atoms in the studied molecule: the distance between the vinylidene proton and the protons of the amino group in position 2 of the thiazole ring is ~5 Å and more.

This problem was solved using the methods of computer simulation of molecule **5a** by optimizing its molecular geometry by the DFT method (B3LYP/cc-pVDZ, vacuum). The initial approximation for both calculations was set flat, the optimization was carried out without imposing restrictions on the admissible ranges of bond lengths, bond and torsion angles. In the initial planar *E*-configuration, the oxygen atoms of the exo- and endocyclic carbonyl groups turned out to be close to each other at a distance less than the sum of their van der Waals radii; as a result, the increased steric hindrances were eliminated by turning the benzoyl fragment around the C–C single bond connecting it with the methylidene group. Thus, the calculations predicted a substantially nonplanar structure for the *E*-isomer, making it energetically unfavorable compared to the *Z*-isomeric form, which has a planar structure. The calculated energy difference was about 11 kcal/mol, which made it possible to exclude with a high probability the formation of the *E*-configuration under the reaction conditions.

Similar conclusions were reached somewhat earlier by other researchers who studied the benzylidene derivative of

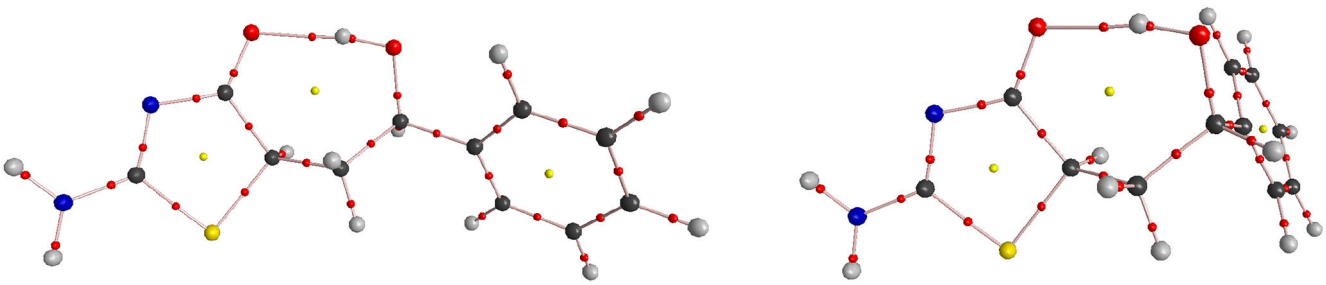


Figure 4. The structure of the molecules of *R*,*R*- (left) and *R*,*S*-isomers (right) of compound **4a** as calculated according to the B3LYP/cc-pVDZ method. Shown are the critical points (–3, 1) of chemical bonds, estimated within the framework of R. Bader's atoms in molecules theory.

thiazolidin-4-one.[10] Despite the absence of an exocyclic carbonyl group, the *Z*-configuration turned out to be more preferable.

Thus, we have established that 5-substituted thiazol-4(5*H*)-ones obtained from 3-aroylacrylic acids and thiourea exist mainly in the 2-amine tautomeric form in solutions and in the solid state. It was shown that the reduction of the starting thiazol-4(5*H*)-ones with sodium borohydride forms a mixture of diastereomeric alcohols in a 2:1 ratio, and bromination in AcOH leads to 2-amino-5-(2-aryl-2-oxoethylidene)thiazol-4(5*H*)-ones existing in the *Z*-configuration, according to quantum-chemical modeling.

Experimental

IR spectra were registered on an Agilent Technologies Cary 630 FT-IR spectrometer by the diffuse reflectance technique in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Varian MR-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. The assignment of signals of carbon atoms in the ^{13}C NMR spectra was carried out according to a published method.[35] Mass spectra of compounds were recorded on a Finnigan MAT INCOS-50 mass spectrometer (EI ionization, 70 eV). Elemental analysis was performed on a EuroVector EA 3000 CHNS-analyzer. Melting points were determined on a Kofler bench and are uncorrected. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates, eluent $CHCl_3$–MeOH, 9:1, visualization with a phosphomolybdic acid solution in 2-PrOH.

3-Aroylacrylic acids **1a**–**h** were synthesized according to literature methods.[36]

Synthesis of 2-amino-5-(2-aryl-2-oxoethyl)thiazol-4(5*H*)-ones 3a–h (General method). A mixture of acid **1a**–**h** (0.01 mol) and thiourea (**2**) (0.01 mol) in glacial AcOH (10–15 ml) was heated under reflux for 0.5–1 h (the reaction mixture became turbid, TLC control). After cooling to room temperature, the formed precipitate was filtered, washed with AcOH, then with MeOH (2×10 ml), and dried.

2-Amino-5-(2-oxo-2-phenylethyl)thiazol-4(5*H*)-one (3a). Yield 1.56 g (67%), white powder, mp 240–241°C (decomp., AcOH) (mp 221°C,[15] mp >300°C[20]). IR spectrum, ν, cm^{-1}: 3242, 2943, 1674 (C=O), 1488, 1387, 1287, 1215, 1141, 755, 685. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.47 (1H, dd, ^2J = 18.8, ^3J = 10.8) and 3.92 (1H, dd, ^2J = 18.8, ^3J = 3.0, CH_2); 4.38 (1H, dd, ^3J = 10.8, ^3J = 3.0, CH); 7.51 (2H, t, *J* = 7.8, H Ph); 7.63 (1H, t, *J* = 7.3, H Ph); 7.95 (2H, d, *J* = 8.0, H Ph); 8.75 (1H, br. s) and 8.97 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 47.9 (CH_2); 55.9 (CH); 133.2, 134.0, 138.8, 141.0 (C Ph); 182.8 (C=N); 190.3 (C=O); 198.0 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 234 $[M]^+$ (24), 129 $[M–PhCO]^+$ (100), 105 $[PhCO]^+$ (64), 87 (22), 77 (50). Found, %: C 56.22; H 4.15; N 11.86. $C_{11}H_{10}N_2O_2S$. Calculated, %: C 56.40; H 4.30; N 11.96.

2-Amino-5-[2-oxo-2-(*p*-tolyl)ethyl]thiazol-4(5*H*)-one (3b). Yield 1.96 g (79%), white powder, mp 243–244°C (decomp., AcOH) (mp 250°C[22]). IR spectrum, ν, cm^{-1}: 3238, 3190, 1668 (C=O), 1607, 1490, 1383, 1356, 1284, 1222, 1175, 1138, 814. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.45 (1H, dd, ^2J = 18.7, ^3J = 10.9) and 3.91 (1H, dd, ^2J = 18.7, ^3J = 3.0, CH_2); 4.40 (1H, dd, ^3J = 10.8, ^3J = 3.0, CH); 7.34 (2H, d, *J* = 8.1, H Ar); 7.88 (2H, d, *J* = 8.1, H Ar); 8.78 (1H, br. s) and 9.00 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.7 (CH_3); 43.1 (CH_2); 51.2 (CH); 128.7, 129.8, 133.8, 144.6 (C Ar); 182.9 (C=N); 189.7 (C=O); 197.7 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 248 $[M]^+$ (31), 129 $[M–ArCO]^+$ (100), 119 $[ArCO]^+$ (64), 91 (47), 87 (23). Found, %: C 58.13; H 4.85; N 11.19. $C_{12}H_{12}N_2O_2S$. Calculated, %: C 58.05; 4.87; N 11.28.

2-Amino-5-[2-(2,4-dimethylphenyl)-2-oxoethyl]thiazol-4(5*H*)-one (3c). Yield 1.39 g (53%), white powder, mp 224–225°C (decomp., AcOH). IR spectrum, ν, cm^{-1}: 3242, 2965, 1668 (C=O), 1609, 1495, 1391, 1269, 1218, 1147, 988, 823, 743. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, CH_3); 2.38 (3H, s, CH_3); 3.37 (1H, dd, ^2J = 18.4, ^3J = 10.7) and 3.79 (1H, dd, ^2J = 18.4, ^3J = 3.2, CH_2); 4.34 (1H, dd, ^3J = 10.7, ^3J = 3.2, CH); 7.09 (1H, s, H Ar); 7.11 (1H, d, *J* = 8.4, H Ar); 7.75 (1H, d, *J* = 8.4, H Ar); 8.74 (1H, br. s) and 8.98 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3); 21.7 (CH_3); 45.4 (CH_2); 51.5 (CH); 127.1, 130.2, 133.0, 133.9, 138.4, 142.6 (C Ar); 182.9 (C=N); 189.7 (C=O); 198.1 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 262 $[M]^+$ (26), 133 $[ArCO]^+$ (100), 129 $[M–ArCO]^+$ (62), 105 (35), 87 (15), 79 (6). Found, %: C 59.41; H 5.30; N 10.43. $C_{13}H_{14}N_2O_2S$. Calculated, %: C 59.52; H 5.38; N 10.68.

2-Amino-5-[2-(3,4-dimethylphenyl)-2-oxoethyl]thiazol-4(5*H*)-one (3d). Yield 1.97 g (75%), white powder, mp 243–244°C (decomp., AcOH). IR spectrum, ν, cm^{-1}: 3250, 2970, 1670 (C=O), 1607, 1504, 1445, 1409, 1373, 1279, 1208, 1117, 824, 751. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (6H, s, $2CH_3$); 3.42 (1H, dd, ^2J = 18.8, ^3J = 11.0) and 3.88 (1H, dd, ^2J = 18.8, ^3J = 3.0, CH_2); 4.37 (1H, dd, ^3J = 11.0, ^3J = 3.0, CH); 7.27 (1H, d, *J* = 7.9, H Ar); 7.69 (1H, d, *J* = 7.8, H Ar); 7.75 (1H, s, H Ar); 8.77 (1H, br. s) and 9.01 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 19.7 (CH_3); 20.1 (CH_3); 43.1 (CH_2); 51.2 (CH); 126.2, 129.5, 130.3, 134.1, 137.3, 143.4 (C Ar); 182.8 (C=N); 189.7 (C=O); 197.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 262 $[M]^+$ (30), 133 $[ArCO]^+$ (100), 129 $[M–ArCO]^+$ (70), 105 (37), 87 (15), 79 (18). Found, %: C 59.38; H 5.21; N 10.55. $C_{13}H_{14}N_2O_2S$. Calculated, %: C 59.52; H 5.38; N 10.68.

2-Amino-5-[2-(2,5-dimethylphenyl)-2-oxoethyl]thiazol-4(5*H*)-one (3e). Yield 2.04 g (78%), white powder, mp 179–180°C (2-PrOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 2.32 (3H, s, CH_3); 3.37 (1H, dd, ^2J = 18.6, ^3J = 10.6) and 3.78 (1H, dd, ^2J = 18.6, ^3J = 3.2, CH_2); 4.34 (1H, dd, ^3J = 10.6, ^3J = 3.2, CH); 7.15 (1H, d, *J* = 7.8, H Ar); 7.23 (1H, d, *J* = 7.8, H Ar); 7.64 (1H, s, H Ar); 8.74 (1H, br. s) and 8.97 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 20.9 (CH_3); 21.0 (CH_3); 45.7 (CH_2); 51.4 (CH); 130.1, 132.1, 132.9, 134.8, 135.7, 136.8 (C Ar); 182.9 (C=N); 189.7 (C=O); 198.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 262 $[M]^+$ (30), 133 $[ArCO]^+$ (97), 129 $[M–ArCO]^+$ (100), 105 (52), 87 (22), 79 (20). Found, %: C 59.48; H 5.27; N 10.48. $C_{13}H_{14}N_2O_2S$. Calculated, %: C 59.52; H 5.38; N 10.68.

2-Amino-5-[2-(4-ethylphenyl)-2-oxoethyl]thiazol-4(5*H*)-one (3f). Yield 1.38 g (53%), white powder, mp 257–258°C (decomp., AcOH). IR spectrum, ν, cm^{-1}: 3246, 2962, 1670 (C=O), 1607, 1491, 1383, 1308, 1282, 1219, 1175, 1136, 993, 832, 752. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.63 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 3.42 (1H, dd, ^2J = 18.8, ^3J = 11.0) and 3.88 (1H, dd, ^2J = 18.8, ^3J = 3.0, CH_2); 4.36 (1H, dd, ^3J = 11.0, ^3J = 3.0, CH); 7.32 (2H, d, *J* = 8.3, H Ar); 7.86 (2H, d, *J* = 8.3, H Ar); 8.74 (1H, br. s) and 8.96 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 15.7 ($CH_2\underline{C}H_3$); 28.7 ($CH_3\underline{C}H_2$); 43.1 (CH_2); 51.2 (CH); 128.7, 128.8, 134.0, 150.6 (C Ar); 182.9 (C=N); 189.6 (C=O); 197.7 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 262 $[M]^+$ (34), 133 $[ArCO]^+$ (98), 129 $[M–ArCO]^+$ (100), 105 (61), 87 (63), 79 (5). Found, %: C 59.48; H 5.35; N 10.80. $C_{13}H_{14}N_2O_2S$. Calculated, %: C 59.52; H 5.38; N 10.68.

2-Amino-5-[2-(4-ethoxyphenyl)-2-oxoethyl]thiazol-4(5*H*)-one (3g). Yield 1.97 g (71%), white powder, mp 233–235°C (decomp., AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 6.9, $C\underline{H}_3CH_2$); 3.39 (1H, dd, ^2J = 18.6, ^3J = 10.8) and 3.84 (1H, dd, ^2J = 18.6, ^3J = 3.2, CH_2); 4.10 (2H, q, *J* = 6.9, $C\underline{H}_2CH_3$); 4.35 (1H, dd, ^3J = 10.8, ^3J = 3.2, CH); 6.99 (2H, d, *J* = 8.0, H Ar); 7.91 (2H, d, *J* = 8.0, H Ar); 8.72 (1H, br. s) and 8.93 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 15.0 ($CH_2\underline{C}H_3$); 42.9 (CH_2); 51.3 (CH); 64.1 ($O\underline{C}H_2CH_3$); 114.8, 129.0, 130.9, 163.3 (C Ar); 182.9 (C=N); 189.8 (C=O); 196.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 278 $[M]^+$ (45), 149 $[ArCO]^+$ (88), 129 $[M–ArCO]^+$ (100), 121 (90), 93 (24), 87 (24). Found, %: C 56.06; H 5.15; N 9.89. $C_{13}H_{14}N_2O_3S$. Calculated, %: C 56.10; H 5.07; N 10.07.

2-Amino-5-{2-[(4-methylsulfanyl)phenyl]-2-oxoethyl}-thiazol-4(5*H*)-one (3h). Yield 2.40 g (86%), white powder, mp 255–256°C (decomp., AcOH). IR spectrum, ν, cm^{-1}: 3256, 2988, 1674 (C=O), 1591, 1509, 1382, 1275, 1219, 1186, 1129, 1096, 991, 820, 753. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (3H, s, SCH_3); 3.41 (1H, dd, ^2J = 18.7, ^3J = 10.8) and 3.86 (1H, dd, ^2J = 18.7, ^3J = 2.9, CH_2); 4.35 (1H, dd, ^3J = 10.8, ^3J = 2.9, CH); 7.33 (2H, d, *J* = 8.0, H Ar); 7.86 (2H, d, *J* = 8.0, H Ar); 8.73 (1H, br. s) and 8.96 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 14.3 (SCH_3); 42.9 (CH_2); 51.1 (CH); 125.3, 129.0, 132.3, 146.5 (C Ar); 182.8 (C=N); 189.7 (C=O); 197.1 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 280 $[M]^+$ (61), 156 (38), 151 $[ArCO]^+$ (85), 129 $[M–ArCO]^+$ (85), 97 (11), 87 (67). Found, %: C 51.28; H 4.43; N 9.67. $C_{12}H_{12}N_2O_2S_2$. Calculated, %: C 51.41; H 4.31; N 9.99.

Synthesis of 2-amino-5-[2-aryl-2-hydroxyethyl]thiazol-4(5*H*)-ones 4a–c (General method). $NaBH_4$ (1.9 g, 0.05 mol) was added to magnetically stirred and cooled (NaCl–ice) slurry of thiazol-4(5*H*)-one **3a–c** (0.01 mol) in MeOH (15 ml). The mixture was left for 2 h at room temperature. The resulting solution was slowly poured into H_2O (75 ml), the precipitate that formed was filtered, washed with H_2O, and crystallized from 50% aqueous MeOH. The product was obtained as a mixture of diastereomers A and B in a 2:1 ratio.

2-Amino-5-(2-hydroxy-2-phenylethyl)thiazol-4(5*H*)-ones (4a). Yield 1.63 g (69%), white powder, mp 207–208°C (MeOH–H_2O, 1:1). IR spectrum, ν, cm^{-1}: 3550 (OH), 3235, 3013, 1647, 1529, 1383, 1273, 1142, 1057, 769, 729, 700. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.76–1.92 (1H, m) and 2.44–2.54 (1H, m, CH_2); 4.03 (0.33H, dd, ^3J = 10.6, ^3J = 2.8, CH B); 4.20 (0.67H, dd, ^3J = 10.6, ^3J = 2.8, CH A); 4.62 (0.65H, dt, *J* = 8.1, *J* = 4.0, C<u>H</u>OH A); 4.74 (0.35H, dt, *J* = 8.2, *J* = 4.0, C<u>H</u>OH B); 5.19 (0.34H, d, *J* = 3.2, OH B); 5.57 (0.66H, d, *J* = 3.2, OH A); 7.25–7.34 (5H, m, H, Ph); 8.71–8.90 (2H, m, NH_2). ^{13}C NMR spectrum, δ, ppm: 44.4 (CH_2 B); 44.1 (CH_2 A); 53.6 (CH); 72.0 (CHOH A); 72.1 (CHOH B); 126.3, 127.6, 128.6, 145.3 (C Ph); 182.5 (C=N B); 183.1 (C=N A); 190.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 236 $[M]^+$ (52), 219 (32), 156 (38), 151 (85), 129 (85), 97 (11), 87 (67). Found, %: C 55.70; H 5.27; N 11.62. $C_{11}H_{12}N_2O_2S$. Calculated, %: C 55.92; H 5.12; N 11.86.

2-Amino-5-[2-hydroxy-2-(*p*-tolyl)ethyl]thiazol-4(5*H*)-ones (4b). Yield 1.22 g (49%), white powder, mp 209–210°C (MeOH–H_2O, 1:1). IR spectrum, ν, cm^{-1}: 3553 (OH), 3239, 3026, 1650, 1489, 1377, 1281, 1138, 1059, 813, 754, 719. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.72–1.90 (1H, m, CH_2); 2.30 (3H, s, CH_3); 2.40–2.50 (1H, m, CH_2); 3.98 (0.34H, d, *J* = 8.4, CH B); 4.18 (0.67H, d, *J* = 8.4, CH A); 4.57–4.62 (0.67H, m, C<u>H</u>OH A); 4.69–4.73 (0.33H, m, C<u>H</u>OH B); 5.42 (0.67H, d, *J* = 3.2, OH A); 5.47 (0.33H, d, *J* = 3.2, OH B); 7.14 (2H, d, *J* = 7.8, H Ar); 7.22 (2H, d, *J* = 7.8, H Ar); 8.66 (1H, br. s) and 8.90 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 44.1 (CH_2 B); 44.5 (CH_2 A); 53.6 (CH); 71.8 (CHOH B); 71.9 (CHOH A); 126.3, 129.2, 136.5, 142.3 (C Ar); 183.0 (C=N B); 182.5 (C=N A); 190.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 250 $[M]^+$ (31), 233 (42), 135 (27), 129 (22), 116 (100), 93 (26), 91 (32). Found, %: C 57.40; H 5.49; N 11.10. $C_{12}H_{14}N_2O_2S$. Calculated, %: C 57.58; 5.64; N 11.19.

2-Amino-5-[2-(4-ethylphenyl)-2-hydroxyethyl]thiazol-4(5*H*)-ones (4c). Yield 1.16 g (44%), white powder, mp 204–205°C (MeOH–H_2O, 1:1). IR spectrum, ν, cm^{-1}: 3554 (OH), 3240, 3024, 2961, 1650, 1491, 1379, 1284, 1138, 1060, 830, 744. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 1.74–1.91 (1H, m) and 2.41–2.51 (1H, m, CH_2); 2.58 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 3.98–4.01 (0.34H, m, CH B); 4.18–4.22 (0.68H, m, CH A); 4.57–4.62 (0.67H, m, C<u>H</u>OH A); 4.67–4.71 (0.33H, m, C<u>H</u>OH B); 5.43 (0.33H, d, *J* = 2.8, OH B); 5.48 (0.67H, d, *J* = 2.8, OH A); 7.17 (2H, d, *J* = 7.8, H Ar); 7.25 (2H, d, *J* = 7.8, H Ar); 8.70 (1H, br. s) and 8.95 (1H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 16.1 ($CH_2\underline{C}H_3$); 28.3 ($\underline{C}H_2CH_3$); 44.0 (CH_2 B); 44.4 (CH_2 A); 53.7 (CH B); 53.8 (CH A); 71.8 (CHOH B); 71.9 (CHOH B); 126.3, 128.0, 142.5, 143.0 (C Ar); 182.5 (C=N B); 183.0 (C=N A); 190.3 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 264 $[M]^+$ (32), 247 (28), 149 (31), 135 (17), 116 (100), 97 (13), 91(12). Found, %: C 59.28; H 6.19; N 10.36. $C_{13}H_{16}N_2O_2S$. Calculated, %: C 59.07; H 6.10; N 10.60

Synthesis of (*Z*)-2-amino-5-(2-aryl-2-oxoethylidene)-thiazol-4(5*H*)-one 5a–d (General method). A solution of Br_2 (0.5 ml, 1 mmol) in AcOH (10 ml) was added in portions to a magnetically stirred solution of 2-amino-

thiazol-4(5*H*)-one **3a**,**b**,**e**,**f** (1 mmol) in AcOH (10 ml). After adding the entire amount of Br_2, the mixture was heated under reflux for 1 h and cooled to room temperature. The formed precipitate was filtered off and crystallized from AcOH.

(*Z*)-2-Amino-5-(2-oxo-2-phenylethylidene)thiazol-4(5*H*)-one (5a). Yield 0.16 g (69%), yellow powder, mp 279–280°C (decomp., AcOH). IR spectrum, ν, cm^{-1}: 3205, 3006, 1683 (C=O), 1643, 1597, 1504, 1447, 1383, 1286, 1225, 1147, 1020, 743, 683. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.54 (2H, t, *J* = 7.6, H Ar); 7.66 (1H, t, *J* = 7.6, H Ar); 7.94 (1H, s, CH); 8.09 (2H, d, *J* = 7.7, H Ar); 9.48 (1H, br. s) и 9.78 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 116.8 (C=CH); 128.3, 129.1, 133.7, 136.4 (C Ph); 147.9 (C=CH); 179.2 (C=N); 179.3 (C=O); 188.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 232 $[M]^+$ (100), 204 (14), 190 (99), 162 (53), 127 (39), 105 $[ArCO]^+$ (94). Found, %: C 56.52; H 3.29; N 12.17. $C_{11}H_8N_2O_2S$. Calculated, %: C 56.89; H 3.47; N 12.06.

(*Z*)-2-Amino-5-[2-oxo-2-(*p*-tolyl)ethylidene]thiazol-4(5*H*)-one (5b). Yield 0.21 g (85%), yellow powder, mp >300°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3); 7.35 (2H, d, *J* = 8.1, H Ar); 7.92 (1H, s, CH); 8.00 (2H, d, *J* = 8.1, H Ar); 9.44 (1H, br. s) and 9.73 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.8 (CH_3); 117.5 (C=CH); 129.1, 130.2, 134.6, 145.1 (C Ar); 148.2 (C=CH); 179.6 (C=N); 179.8 (C=O); 188.5 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 246 $[M]^+$ (99), 218 (35), 204 (100), 177 (30), 148 (37), 120 (87), 119 $[ArCO]^+$ (90), 127 (39), 91 (92). Found, %: C 58.40; H 4.14; N 11.32. $C_{12}H_{10}N_2O_2S$. Calculated, %: C 58.52; H 4.09; N 11.37.

(*Z*)-2-Amino-5-[2-(2,5-dimethylphenyl)-2-oxoethylidene]thiazol-4(5*H*)-one (5c). Yield 0.16 g (62%), yellow powder, mp 253–254°C (decomp., AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 2.36 (3H, s, CH_3); 7.19 (1H, d, *J* = 7.8, H Ar); 7.27 (1H, d, *J* = 7.8, H Ar); 7.65 (1H, s, CH); 7.89 (1H, s, H Ar); 9.50 (1H, br. s) and 9.75 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 20.8 (CH_3); 20.9 (CH_3); 121.6 (C=CH); 130.3, 132.3, 133.7, 135.8, 136.0, 136.8 (C Ar); 144.7 (C=CH); 177.7 (C=N); 178.0 (C=O); 187.0 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 260 $[M]^+$ (99), 232 (5), 218 (78), 190 (99), 185 (75), 157 (97), 133 $[ArCO]^+$ (98), 105 (100). Found, %: C 59.49; H 4.49; N 10.60. $C_{13}H_{12}N_2O_2S$. Calculated, %: C 59.98; H 4.65; N 10.76.

(*Z*)-2-Amino-5-[2-(4-ethylphenyl)-2-oxoethylidene]-thiazol-4(5*H*)-one (5d). Yield 0.17 g (65%), yellow powder, mp >300°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.5, $CH_2C\underline{H}_3$); 2.69 (2H, q, *J* = 7.5, $C\underline{H}_2CH_3$); 7.40 (2H, d, *J* = 8.1, H Ar); 7.88 (1H, s, CH); 8.05 (2H, d, *J* = 8.1, H Ar); 9.49 (1H, br. s) and 9.77 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 14.9 ($CH_2C\underline{H}_3$); 28.1 ($C\underline{H}_2CH_3$); 116.9 (C=CH); 128.4, 128.6, 134.3 (C Ar); 147.6 (C=CH); 150.5 (C Ar); 179.3 (C=N); 179.4 (C=O); 187.9 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 260 $[M]^+$ (98), 232 (47), 218 (100), 191 (33), 189 (37), 162 (52), 133 $[ArCO]^+$ (94), 105 (79). Found, %: C 59.86; H 4.57; N 10.55. $C_{13}H_{12}N_2O_2S$. Calculated, %: C 59.98; H 4.65; N 10.76.

Quantum-chemical calculations were carried out within the framework of the DFT theory employing the Gaussian 09 software package[37] using the B3LYP[38] electron density functional in the cc-pVDZ orbital basis.[39] For the analysis of the wave function, elements of R. Bader's atoms in molecules theory were used.[40,41]

X-ray structural analysis of compounds 3a, 4a. Crystals of compound **3a** were obtained by recrystallization from DMSO, triclinic system, $C_{11}H_{10}N_2O_2S$, at 293°C: *a* 5.3108(8), *b* 11.509(2), *c* 18.476(3) Å; α 102.36(1), β 94.34(1), γ 94.39(1)°; *V* 1095.0(3) $Å^3$; M_r 234.27; *Z* 4; $P\bar{1}$ space symmetry group; d_{calc} 1.421 g/cm^3; μ(MoKα) 0.281 mm^{-1}; *F*(000) 488. Unit cell parameters and intensities of 7813 reflections (3874 independent, R_{int} 0.078) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD-detector, graphite monochromator, ω-scanning, $2\theta_{max}$ 50°). The structure was solved by the direct method using the SHELXTL software package.[42] H atom positions were found from difference electron density synthesis and were refined according to the "rider" model with $U_{iso} = 1.2U_{eq}$ for a non-hydrogen atom bonded to given hydrogen atom. The structure was refined against F^2 by the least-squares technique in the full-matrix anisotropic approximation for non-hydrogen atoms to wR_2 0.147 over 3874 reflections (R_1 0.072 over 1789 reflections with $F > 4\sigma(F)$, *S* 0.950). Atomic coordinates, as well as complete tables of bond lengths and bond angles were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2005302).

Crystals of compound **4a** suitable for X-ray structural analysis were obtained by slow evaporation of the solution in 2-PrOH, rhombic system, $C_{11}H_{12}N_2O_2S{\cdot}H_2O$, at 293°C: *a* 12.130(1), *b* 8.1701(5), *c* 25.642(3) Å; *V* 2541.1(4) $Å^3$; M_r 254.30; *Z* 8; *Pbca* space symmetry group; d_{calc} 1.329 g/cm^3; μ(MoKα) 0.253 mm^{-1}; *F*(000) 1072. Unit cell parameters and intensities of 11159 reflections (2235 independent, R_{int} 0.095) were measured on an Xcalibur-3 (MoKα radiation, CCD-detector, graphite monochromator, ω-scanning, $2\theta_{max}$ 50°). The structure was solved by the direct method using the SHELXTL software package. H atom positions were found from difference electron density synthesis and were refined according to the "rider" model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bonded to given hydrogen atom (*n* = 1.5 for the hydroxy group and water molecule and *n* = 1.2 for other hydrogen atoms). The structure was refined against F^2 by the least-squares technique in the full-matrix anisotropic approximation for non-hydrogen atoms to wR_2 0.269 over 2235 reflections (R_1 0.097 over 1386 reflections with $F > 4\sigma(F)$, *S* 1.097). Atomic coordinates, as well as complete tables of bond lengths and bond angles were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2005303).

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