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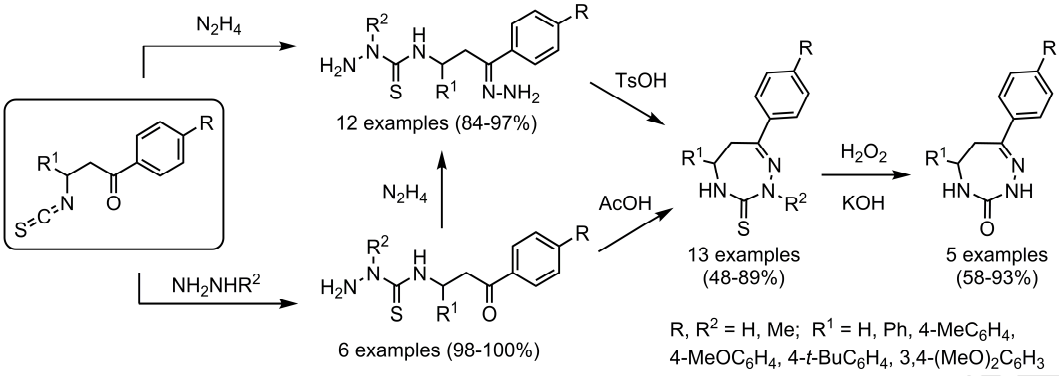

Synthesis of aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones starting from chalcone-derived β-isothiocyanato ketones

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Abstract: A general two-step synthesis of 7-aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones from 1-aryl-3-isothiocyanatopropan-1-ones has been developed. The synthesis involved reaction of these isothiocyanato ketones with hydrazines followed by acid-catalyzed heterocyclization of the prepared 4-(3-oxopropyl)thiosemicarbazides or their hydrazones. Triazepine-3-thiones were converted into their 3-oxo analogs by oxidation with H_2O_2 under basic conditions. Conformations of the obtained triazepine-3-thiones/ones in DMSO solution and in solid state were established using ^{1}H NMR spectroscopy and single crystal X-ray diffraction.

Keywords: Isothiocyanato ketones; Thiosemicarbazides; Hydrazones; 1,2,4-Triazepine-3-thiones/ones

1. Introduction

1,2,4-Triazepines,[1] particularly 1,2,4-triazepin-2-ones/thiones are the subject of intensive studies due to their diverse pharmacological properties. These compounds are effective antagonists of parathyroid hormone 1 (PTH1R)[2] and holecystokinin hormone 2 (CCK_2)[3] receptors. They possess antioxidant,[4] antipsychotic,[5] and HIV protease inhibitory activities.[6] The reported approaches to 1,2,4-triazepin-2-one/thione backbone include reaction of β-isocyanato or β-isothiocyanato ketones with hydrazines,[7,8] condensation of (thio)semicarbazides with various 1,3-dicarbonyl compounds or their derivatives,[4,9] reaction of arylidene ketones with $N_2H_4 \cdot 2HNCS$,[10] addition of (thio)semicarbazides to α,β-unsaturated carbonyl compounds or their synthetic equivalents,[11] reaction of γ-hydrazino-substituted amines with phosgene equivalents,[3a,6,12] intramolecular cyclization of 4-(γ-oxoalkyl)(thio)semicarbazides and their derivatives.[7b,8d,13]

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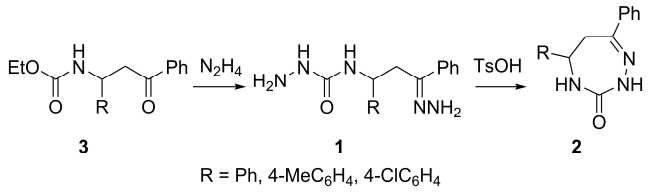
Various benzo- and hetero-fused 1,2,4-triazepin-2-ones/thiones were prepared using the above methods. In contrast, only a few specific types of monocyclic triazepin-2-ones/thiones were described. Besides, some of the reported results on the triazepine formation from acyclic precursors were proved to be incorrect. For example, it was demonstrated that the reaction of 2-substituted thiosemicarbazides with malonyl chlorides provided four-membered imides[9i] instead of triazepines,[14] and condensation of acetylacetone with 2-methylsemicarbazides did not afford any triazepines (ref. 15 vs ref. 9d). Thus, the development of reliable and practical approaches to monocyclic triazepines remains a challenge.

Previously, we showed that aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **2** can be obtained by acid-catalyzed cyclization of hydrazones of 4-[(1,3-diaryl-3-oxo)prop-1-yl]semicarbazides **1** (Scheme 1).[13]



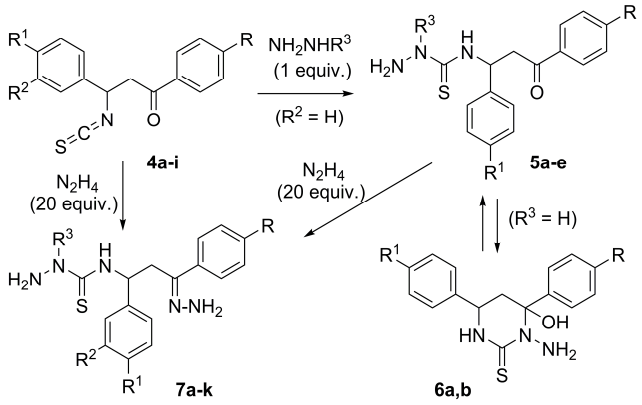
Scheme 1. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **2**.

We studied this cyclization under various conditions and found that the reaction temperature and concentration of the starting material **1** had a dramatic effect on the yield of triazepines **2**. However, under all conditions tested, the yield of the products did not exceed 45%. Besides, synthesis of semicarbazides **1** involved substitution of the ethoxy group in the corresponding ethyl *N*-(3-oxopropyl)carbamates **3** under the action of refluxing anhydrous hydrazine for 20–24 h. Because of the harsh reaction conditions the starting carbamates partially decomposed, and therefore semicarbazides **1** were obtained in only 28–46% yield. Thus, the low availability of starting material remained the principal limitation of 1,2,4-triazepine synthesis by the cyclization of 4-[(1,3-diaryl-3-oxo)prop-1-yl]semicarbazide hydrazones. We hypothesized that triazepines could be obtained from thioxo analogs of **1** whose simple synthesis could be based on the reaction of readily available 1,3-diaryl-3-isothiocyanatopropan-1-ones[16] with hydrazines. Here, we report synthesis of aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones and their oxidative transformation into the corresponding 3-oxo derivatives starting from 1,3-diaryl-3-isothiocyanatopropan-1-ones.

2. Results and discussion

2.1. Synthesis of 4-(3-aryl-3-oxopropyl)thiosemicarbazides and their hydrazones

4-(3-Aryl-3-oxopropyl)thiosemicarbazides and their hydrazones were obtained from 1,3-diaryl-3-isothiocyanatopropan-1-ones **4a-i** (Scheme 2). Isothiocyanates **4a-i** were synthesized by the addition of HNCS to the corresponding chalcones following our previously reported procedure.[16]



Scheme 2. Synthesis of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **5a-e** and their hydrazones **7a-k**.

The reaction of isothiocyanates **4a,g** with 1 equivalent of hydrazine hydrate readily proceeded in EtOH at room temperature for 1 h to give 4-(3-oxopropyl)thiosemicarbazides **5a,b** in excellent yields (Scheme 2, Table 1).

Table 1. Reaction of isothiocyanato ketones **4a,b,g** with hydrazine hydrate or methyl hydrazine.[a]
Table 1. Reaction of isothiocyanato ketones **4a,b,g** with hydrazine hydrate or methyl hydrazine.[a]

Entry	**4**	R	R^1	R^3	Product(s)	**5**/**6** ratio[b]	Yield (%)[c]
1	**4a**	H	H	H	**5a** + **6a**	89:11[d]	99
2	**4g**	Me	Me	H	**5b** + **6b**	95:5[e]	98
3	**4a**	H	H	Me	**5c**	-	99
4	**4b**	H	Me	Me	**5d**	-	98
5	**4g**	Me	Me	Me	**5e**	-	98

[a] 1:1 molar ratio of reagents, EtOH, rt, 1 h.
[b] According to ^{1}H NMR spectroscopic data for the crude products.
[c] Isolated yields.
[d] Diastereomeric ratio for **6a** was 69:31.
[e] Diastereomeric ratio for **6b** was 67:33.

It should be noted that preparation of oxo-analogs of **5a,b**, namely 4-(3-oxopropyl)semicarbazides, by the reaction of ethyl *N*-(3-oxopropyl)carbamates with hydrazine (see Scheme 1) did not work since substitution of the ethoxy group by hydrazine proceeded much slower than formation of hydrazone moiety.[13]

According to ^{1}H NMR data, initially formed thiosemicarbazides **5a,b** partly cyclized into 1-amino-6-hydroxypyrimidines **6a,b** (11 and 5 mol%, respectively). Pyrimidines **6a,b** were obtained as mixtures

of two diastereomers (69:31 for **6a**, 67:33 for **6b**). The major diastereomer of **6a,b** had (4*R**,6*R**)-configuration with equatorial orientations of the aryl groups and axial position of the hydroxyl group ($^3J_{H\text{-}4,H\text{-}5}$ = 11.8–12.1, $^3J_{N(3)H,H\text{-}4}$ = 0, $^4J_{H\text{-}5,OH}$ = 1.5 Hz)[17,18] in DMSO-d_6 solution. The minor diastereomer had (4*R**,6*S**)-configuration with equatorial orientations of the hydroxyl group and 4-aryl substituent ($^3J_{H\text{-}4,H\text{-}5}$ = 11.6–12.0, $^3J_{N(3)H,H\text{-}4}$ = 0, $^4J_{H\text{-}5,OH}$ = 0 Hz). Since the ratios of acyclic and two cyclic isomers did not change after crystallization we suppose that these three isomers were formed under thermodynamic control.

Isothiocyanates **4a,b,g** reacted with methyl hydrazine (EtOH, rt, 1 h) with complete regioselectivity to give 2-methyl-substituted thiosemicarbazides **6c-e** in 98–99% yields (Scheme 2, Table 1).

Hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **7a-i** were obtained by the reaction of isothiocyanates **4a-i** with excess hydrazine hydrate (20 equiv.) in refluxing EtOH for 3 h in 89–94% yields (Scheme 2; Table 2, entries 1, 3–10). The crude thiosemicarbazides **7a-i** were isolated as mixtures of *E*- and *Z*-isomers with significant predominance of one of them (83–97%). At room temperature isothiocyanate **4a** reacted with $N_2H_4 \cdot H_2O$ (20 equiv.) in EtOH for 24 h to give hydrazone **7a** as a single isomer (entry 2).

Table 2. Synthesis of 4-(3-aryl-3-oxopropyl)thiosemicarbazide hydrazones **7a-k** by reaction of isothiocyanates **4a-i** or thiosemicarbazides **5c,d** with excess hydrazine.[a]

Entry	Starting compd	R	R^1	R^2	R^3	Product	Isomer ratio[b]	Yield (%)[c]
1	**4a**	H	H	H	H	**7a**	87:13	92
2[d]	**4a**	H	H	H	H	**7a**	100:0	84
3	**4b**	H	Me	H	H	**7b**	83:17	91
4	**4c**	H	OMe	H	H	**7c**	84:16	94
5	**4d**	H	OMe	OMe	H	**7d**	84:16	89
6	**4e**	H	*t*-Bu	H	H	**7e**	90:10	89
7	**4f**	Me	H	H	H	**7f**	97:3	93
8	**4g**	Me	Me	H	H	**7g**	83:17	89
9	**4h**	Me	OMe	H	H	**7h**	88:12	89
10	**4i**	Me	OMe	OMe	H	**7i**	83:17	92
11	**5c**	H	H	H	Me	**7j**[e]	78:22	94
12	**5d**	H	Me	H	Me	**7k**[f]	78:22	97

[a] 20 equiv. of $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 h.
[b] According to ^{1}H NMR spectra of the crude products.
[c] Isolated yields.
[d] 20 equiv. of $N_2H_4 \cdot H_2O$, EtOH, rt, 24 h.
[e] Along with 5 mol% of **7a**.
[f] Along with 5 mol% of **7b**.

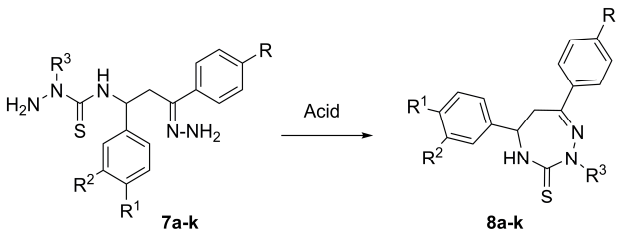
Treatment of 2-methyl thiosemicarbazides **5c,d** with hydrazine hydrate (20 equiv.) in refluxing EtOH for 3 h led to formation of hydrazones **7j,k** (two geometric isomers, 78:22) along with small amounts of the corresponding thiosemicarbazides **7a,b** (5%) (entries 11, 12). Crystallization of the crude products from EtOH afforded pure **7j,k**. The formation of **7a** was not observed when **5c** reacted with excess hydrazine hydrate at room temperature, but this reaction proceeded very slowly to give **7j** (80% conversion after 24 h according to ^{1}H NMR spectrum of isolated product).

The C=N double bond geometries in the major and minor isomers of hydrazones **7a-k** were determined as *E* and *Z*, respectively. The assignments were based on ^{1}H and ^{13}C NMR spectroscopic data, ^{1}H,^{1}H NOESY experiment for **7a** in DMSO-d_6, DFT calculations of hydrogen and carbon chemical shifts for both *E*-**7a** and *Z*-**7a**, and comparison of ^{1}H and ^{13}C NMR spectra of **7a-k** with those of structurally similar semicarbazides.[13] For the major isomer of **7a**, NOE was observed between the C=NNH$_2$ and CH$_2$ protons, and no NOE correlation was detected between the *ortho*-phenyl protons of the PhC=N fragment and the C=NNH$_2$ protons, thus confirming the *E*-configuration of the C=N double bond in this isomer.[19] Comparison of the experimental carbon chemical shift for the CH$_2$ group in **7a** (31.5 ppm in DMSO-d_6) with that calculated by the GIAO method at the DFT B3LYP/6-311++G(2df,p) level using the DFT B3LYP/6-311++G(d,p) optimized geometries for *E*-**7a** and *Z*-**7a** in the gas phase (33.7 and 54.0 ppm, respectively) also proved the *E*-configuration of the major isomer of **7a**. The assignment of the stereochemistry of other thiosemicarbazides **7b-k** followed from similarity of the ^{1}H and ^{13}C NMR spectra of the major and minor isomers of **7a** with those of **7b-k**.

It is noteworthy that the ^{1}H NMR signal of the C=NNH$_2$ group for *E*-**7a-k** (6.45–6.67 ppm) was downfield shifted compared with that for *Z*-**7a-k** (5.59–5.67 ppm) (see also ref. 13). This significant shift (about +1 ppm) could be explained by decrease in electron density on the NH$_2$ nitrogen due to the strong conjugation in the ArC=NNH$_2$ moiety of *E*-**7a-k**. Indeed, DFT B3LYP/6-311++G(d,p) calculations showed that the ArC=NNH$_2$ fragment in *E*-**7a** is almost planar while in *Z*-**7a** the planes of the phenyl ring and C=N bond form an angle of about 65°, resulting in a sharp decrease in the conjugation.

2.2. Acid-catalyzed cyclization of 4-(3-aryl-3-oxopropyl)thiosemicarbazides or their hydrazones into 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones

We found that hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **7a-k** could be readily cyclized in the presence of acid (>1 equiv.) to give the corresponding 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a-k** (Scheme 3).



Scheme 3. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a-k** from hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **7a-k**.

According to the ^{1}H NMR spectroscopic data for isolated crude materials under all studied conditions some amount of unidentified side products always formed along with triazepines **8a-k**. The characteristic feature of these spectra was an increase in the relative integral intensity of the aromatic protons region. The reaction conditions including catalyst, solvent, temperature, substrate concentration, and amount of catalyst were optimized with hydrazone **7a**. The experimental data are summarized in Table 3.

Table 3. Acid-catalyzed cyclization of hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **7a-k** into 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a-k**.

Entry	**7**[a]	R	R^1	R^2	R^3	Solvent	Acid (equiv.)	Conc. of **7** (mol/L)	Reaction conditions	**8**	Purity of **8**[b] (%)	Yield[c] (%)
1	**7a**	H	H	H	H	EtOH	TsOH (1.05)	0.300	rt, 2 h	**8a**	37	–
2	**7a**	H	H	H	H	MeCN	TsOH (1.03)	0.300	rt, 2 h	**8a**	35	–
3	**7a**	H	H	H	H	EtOH	TsOH (1.05)	0.300	reflux, 1.5 h	**8a**	61	–
4	**7a**	H	H	H	H	EtOH	TsOH (1.10)	0.097	reflux, 1.5 h	**8a**	79	–
5	**7a**[d]	H	H	H	H	EtOH	TsOH (1.11)	0.097	reflux, 1.5 h	**8a**	78	76
6	**7a**	H	H	H	H	EtOH	TsOH (1.52)	0.098	reflux, 1.5 h	**8a**	77	–
7	**7a**	H	H	H	H	EtOH	TsOH (1.07)	0.054	reflux, 1.5 h	**8a**	80	–
8	**7a**	H	H	H	H	EtOH	HCl (1.05)	0.107	reflux, 1.5 h	**8a**	72	–
9	**7a**	H	H	H	H	AcOH	AcOH	0.100	reflux, 1.67 h	**8a**	68	–
10	**7b**	H	Me	H	H	EtOH	TsOH (1.10)	0.095	reflux, 1.5 h	**8b**	80	76
11	**7c**	H	OMe	H	H	EtOH	TsOH (1.10)	0.098	reflux, 1.5 h	**8c**	75	75
12	**7d**	H	OMe	OMe	H	EtOH	TsOH (1.15)	0.091	reflux, 1.5 h	**8d**	74	73
13	**7e**	H	*t*-Bu	H	H	EtOH	TsOH (1.12)	0.096	reflux, 1.5 h	**8e**	80	78
14	**7f**	Me	H	H	H	EtOH	TsOH (1.12)	0.098	reflux, 1.5 h	**8f**	84	81
15	**7g**	Me	Me	H	H	EtOH	TsOH (1.11)	0.097	reflux, 1.5 h	**8g**	81	76
16	**7h**	Me	OMe	H	H	EtOH	TsOH (1.12)	0.095	reflux, 1.5 h	**8h**	81	81
17	**7i**	Me	OMe	OMe	H	EtOH	TsOH (1.11)	0.098	reflux, 1.5 h	**8i**	83	82
18	**7j**	H	H	H	Me	MeCN	TsOH (1.12)	0.092	reflux, 1.5 h	**8j**	78	72
19	**7j**	H	H	H	Me	MeOH	TsOH (1.11)	0.095	reflux, 1.5 h	**8j**	75	–
20	**7j**	H	H	H	Me	EtOH	TsOH (1.11)	0.102	reflux, 1.5 h	**8j**	72	–
21	**7k**	H	Me	H	Me	MeCN	TsOH (1.12)	0.092	reflux, 1.5 h	**8k**	71	48

[a] The crude products obtained by the reaction of **4a-i** or **6c,d** with excess N_2H_4 in refluxing EtOH were used. Their *E*/*Z* ratios are presented in Table 2 (enties 2, 3–12).
[b] Purity of the isolated crude product was estimated as ratio of the expected integral intensity of the aromatic protons region (10 H for **8a,j**, 9 H for **8b,c,e,f,k**, 8 H for **8d,g,h**, and 7 H for **8i**) to the observed integral intensity in this region in the ^{1}H NMR spectrum of the crude product multiplied by 100. In all cases complete conversion of the starting material was observed.
[c] Isolated yield (after column chromatography).
[d] The crude product obtained by the reaction of **4a** with excess N_2H_4 in EtOH at rt was used (Table 2, entry 2).

At room temperature in the presence of TsOH (1.03–1.05 equiv.) the reaction of **7a** completed for 2 h. Both in MeCN and in EtOH, considerable amount of side products formed along with **8a** (estimated yields 35–37%) (entries 1 and 2). At reflux the yield of **8a** significantly increased (entry 3 vs entry 1). Decrease in the concentration of the starting material from 0.300 to 0.097 mol/L led to the increase in the amount of **8a** in the crude product from 61 to 78% (entry 3 vs entry 4). Further dilution (up to 0.054 mol/L) of the reaction mixture (entry 4 vs entry 7), use of higher excess of TsOH or other acidic catalysts had no effect on the product yield (entries 6, 8, and 9). It is noteworthy that the yield of

triazepine **8a** did not depend on the configuration of the starting hydrazone **7a** since both *E*/*Z*-**7a** and *E*-**7a** gave **8a** in close estimated yields (column 12 in Table 3, entry 4 vs entry 5).

Thus, under optimal reaction conditions hydrazones **7a-i** cyclized in refluxing EtOH for 1.5 h in the presence of TsOH (1.10–1.15 equiv.) to give triazepines **8a-i** which were isolated in 73–82% yields using column chromatography on aluminium oxide (entries 5, 10–17). Purification of triazepine **8a** by chromatography on silica gel with various eluting systems ($CHCl_3$-petroleum ether, EtOAc-petroleum ether, acetone-petroleum ether) failed to give pure product.

2-Methylthiosemicarbazide **7j** cyclized in the presence of TsOH (1.12 equiv.) to give 2-methyltriazepine **8j**. In this case the yield of the product was slightly higher in refluxing MeCN compared with that in EtOH or MeOH (entries 18, 19, and 20). Thus, compounds **8j** and **8k** were obtained from **7j** and **7k** (MeCN, reflux, 1.5 h) after purification using column chromatography on aluminium oxide in 71% and 48% yield, respectively (entries 18 and 21).

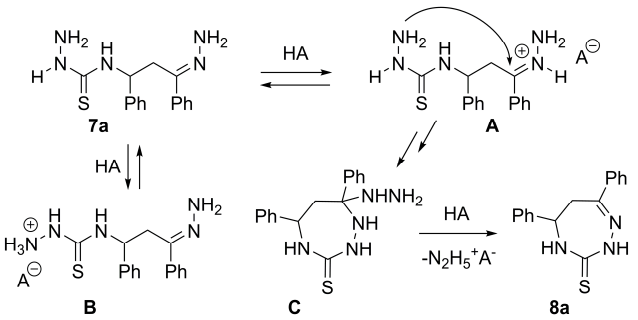
Obviously, acid-catalyzed transformation of **7a-k** into **8a-k** can proceed via two possible pathways with participation of the NH_2 group of either thiosemicarbazide or hydrazone moiety. Formation of **8j,k** from **7j,k** proves that the cyclization of **7a-k** involves nucleophilic attack of the thiosemicarbazide amino group on the electrophilic carbon of the C=N double bond.

The obtained data clearly show that hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides have a stronger tendency to cyclize into triazepines under acidic conditions compared with analogous hydrazones of semicarbazides (see ref. 13). For example, thiosemicarbazide **7a** was converted into triazepine-2-thione **8a** in 76% isolated yield (Table 3, entry 5), while under similar conditions 4-[(3-oxo-1,3-diphenyl)prop-1-yl]semicarbazide hydrazone (**9**) gave 5,7-diphenyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-one (**10**) only in 28% estimated yield.[13] At room temperature, traces of triazepinone **10** formed from semicarbazide **9** under the action of TsOH in EtOH,[13] while compound **7a** gave about 37% of the expected product **8a** (entry 1).

The differences in the reactivity of thiosemicarbazide hydrazones **7** and their oxo-analogs (e.g., **9**) can be explained by different basicities of these compounds. Similar basicities[20] of the semicarbazide NH_2 group and nitrogen atom of the C=N double bond in **9** lead to protonation of the NH_2 group in considerable extent under strong acidic conditions[21] resulting in decrease in cyclization rate. In contrast, significant difference in the basicities[22] of the corresponding nitrogen atoms in **7** provides a greater tendency to give triazepines.

A plausible pathway for the acid-catalyzed cyclization of *E*-**7a** into **8a** is shown in Scheme 4. We suppose that this reaction includes initial protonation of compound **7a** under the action of acid (HA) to give one of two possible cations **A** or **B**. The calculations performed at the DFT B3LYP/6-311++G(d,p) level of theory using the PCM solvation model showed that cation **B** is significantly less stable than cation **A** (ΔG = 8.8 kcal/mol in EtOH, 298 K and 1 atm),[23] therefore its formation can be

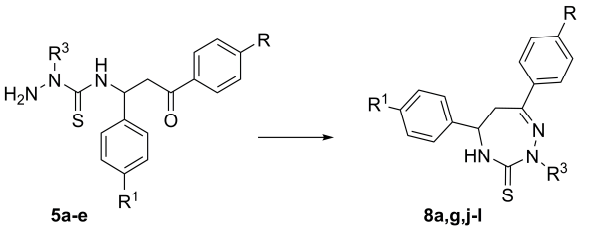
excluded. The initially formed cation **A** cyclizes into **8a** via the intermediate triazepine **C**. Clearly, the acid-catalyzed cyclization of **7b-k** into triazepines **8b-k** proceeds analogously.



Scheme 4. A plausible pathway for the acid-catalyzed (HA) cyclization of *E*-**7a** into **8a**.

Thus, we showed that 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8** can be readily prepared from hydrazones of 4-(1,3-diaryl-3-oxopropyl)thiosemicarbazides **7**. Obviously, thiosemicarbazides **5a-e** could also serve as a precursors for the triazepine synthesis. Reported data indicated that thiosemicarbazide **5a** did not cyclize under acidic or basic conditions.[24] Later, the cyclization of thiosemicarbazides **5a** and **5c** into triazepines **8a** (no yield given) and **8g** (30% yield) by heating in dioxane or isopropyl alcohol in the presence of TsOH was scarcely described without any experimental details.[8d]

We studied transformation of thiosemicarbazides **5a-e** into the corresponding triazepines **8a,g,j-l** (Scheme 5) under different conditions varying solvent, catalyst and its amount, additive, substrate concentration, and reaction time.



Scheme 5. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a,g,j-l** from 4-(3-aryl-3-oxopropyl)thiosemicarbazides **5a-e**.

In initial experiments, we found that triazepine **8a** formed only in 17–23% estimated yields from thiosemicarbazide **5a** along with considerable amounts of unidentified side products in refluxing EtOH or MeCN in the presence of TsOH (0.10–0.11 equiv.) for 1 h (Table 4, entries 1 and 2). One of the

characteristic features of ^{1}H NMR spectra of the isolated crude materials was an increase in the relative integral intensity of the aromatic protons region. The yield of **8a** slightly increased when various TsOH–N_2H_4 combinations were tested (entries 3–5).

Table 4. Acid-catalyzed cyclization of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **5a-e** into 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a,g,j-l**.[a]

Entry	5	R	R[1]	R[3]	Solvent	Acid (equiv.)	Additive (equiv.)	Reaction time (h)	Conv.[b] (%)	8	Purity of 8[c] (%)	Yield[d] (%)
1	**5a**	H	H	H	EtOH	TsOH (0.11)	–	1	100	**8a**	17	–
2	**5a**	H	H	H	MeCN	TsOH (0.10)	–	1	100	**8a**	23	–
3	**5a**	H	H	H	EtOH	TsOH (1.12)	$N_2H_4\cdot H_2O$ (1.01)	1	100	**8a**	32	–
4	**5a**	H	H	H	EtOH	TsOH (1.00)	$N_2H_4\cdot H_2O$ (1.01)	1	100	**8a**	33	–
5	**5a**	H	H	H	MeCN	TsOH (1.04)	$N_2H_4\cdot H_2O$ (1.04)	1	100	**8a**	26	–
6	**5a**	H	H	H	EtOH	AcOH (4.05)	–	1	87	**8a**	68	–
7	**5a**	H	H	H	EtOH	AcOH (4.10)	–	3	100	**8a**	85	83
8	**5a**	H	H	H	MeCN	AcOH (4.14)	–	3	55	**8a**	22	–
9	**5b**	Me	Me	H	EtOH	AcOH (4.13)	–	3	100	**8g**	83	79
10	**5c**	H	H	Me	EtOH	TsOH (0.10)	–	1	85	**8j**	31	–
11	**5c**	H	H	Me	MeCN	TsOH (0.10)	–	1	100	**8j**	58	–
12	**5c**	H	H	Me	EtOH	AcOH (4.01)	–	1	39	**8j**	26	–
13	**5c**	H	H	Me	MeCN	AcOH (4.13)	–	5	21	**8j**	10	–
14	**5c**	H	H	Me	EtOH	AcOH (10.40)	–	8	100	**8j**	89	89
15	**5d**	H	Me	Me	EtOH	AcOH (10.62)	–	8	100	**8k**	89	82
16	**5e**	Me	Me	Me	EtOH	AcOH (10.16)	–	8	100	**8l**	88	81

[a] The reactions were performed at reflux with concentrations of the starting material ranging from 0.091 to 0.136 mol/L.
[b] Level of conversion of the starting material according to ^{1}H NMR of the crude product.
[c] Purity of the isolated crude product was estimated as ratio of the expected integral intensity of the aromatic protons region (10 H for **8a,j**, 9 H for **8k**, 8 H for **8g,l**) to the observed integral intensity in this region in the ^{1}H NMR spectrum of the crude product multiplied by 100.
[d] Isolated yield (after column chromatography).

The use of AcOH as the catalyst led to a significant increase in the yield of **8a**. The treatment of **5a** with AcOH (4.05 equiv.) in refluxing EtOH for 1 h resulted in a 87% conversion of the starting material (**8a**/**5a** = 84:16) and 68% purity of **8a** (entry 6). Under these conditions, the reaction completed in 3 h and triazepine **8a** was isolated using column chromatography on silica gel in 83% yield (entry 7). Analogously, triazepine **8g** was obtained from **5b** in 79% isolated yield (entry 9). Though the yields of triazepines **8a,g** prepared from thiosemicarbazides **5a,b** are comparable with those obtained from hydrazones **7a,g** (Table 3, entries 5 and 15), the isolation of compounds **8a,g** when thiosemicarbazides **5a,b** were used as starting materials was much more easy. It is noteworthy that the cyclization of **5a** into **8a** under the action of AcOH proceeded significantly slower in refluxing MeCN compared with that in EtOH (Table 4, entry 7 vs entry 8).

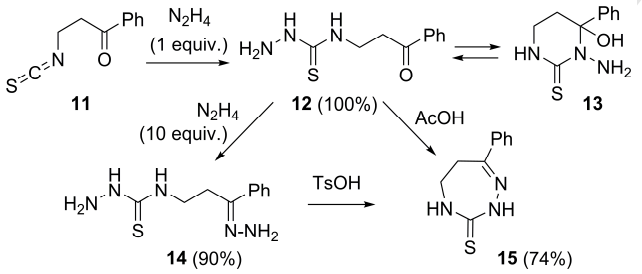
In contrast to **5a**, TsOH-catalyzed cyclization of 2-methylthiosemicarbazide **5c** in refluxing MeCN or EtOH gave the expected triazepine **8j** in higher yields (entry 1 vs entry 10, entry 2 vs entry 11). However, the best results were also achieved with AcOH. In this case, the rate of cyclization of 2-methylthiosemicarbazide **5c** decreased compared with 2-unsubstituted compounds **5a,b** (entry 6 vs entry 12, entry 8 vs entry 13). The use of a 10-fold excess of AcOH and prolongating of the reaction time (8 h) resulted in the smooth formation of 2-methyl-substituted triazepines **8j-l** starting from thiosemicarbazides **5c-e** (entries 14–16). Compounds **8j-l** were isolated in 81–89% yields by column

chromatography on silica gel. The obtained data show that preparation of 2-methyl-substituted triazepines **8j,k** starting from 4-(3-aryl-3-oxopropyl)thiosemicarbazides **5c,d** is more preferable than from their hydrazones **7j,k**.

All attempts to convert compound **5a** into **8a** under basic conditions failed; for example, based on our experience[8a] we tried to cyclize **5a** under the action of KOH (3.02 equiv.) in EtOH at room temperature (2 h). However, a complex mixture of products was obtained containing only 7% of the expected triazepine **8a** (^{1}H NMR spectroscopic data). Low conversion of **5a** into **8a** (< 8%) was observed when compound **5a** was heated at reflux in pyridine for 2 h or in EtOH in the presence of aniline (0.15 equiv.) for 4 h.

2.3. Synthesis of 5-unsubstituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione

Next we studied the effect of substituent at the α-position to nitrogen on the cyclization of 4-(3-aryl-3-oxopropyl)thiosemicarbazides or their hydrazones. Previously, we described regioselective synthesis of β-unsubstituted β-isothiocyanatoketones from α,β-unsaturated ketones by addition of HN_3 followed by reaction of the obtained β-azidoketones with CS_2 and PPh_3.[25] Using this reaction sequence we prepared isothiocyanatoketone **11** from phenylvinylketone and then reacted it with $N_2H_4 \cdot H_2O$. The reaction smoothly proceeded in MeCN (0 °C, 10 min) to give thiosemicarbazide **12** in quantitative yield (Scheme 6).



Scheme 6. Synthesis of 5-unsubstituted triazepine **15** from isothiocyanate **11**.

According to ^{1}H NMR spectroscopic data, thiosemicarbazide **12** was formed along with small amount (2 mol%) of its 6-membered cyclic isomer, 1-amino-6-hydroxypyrimidine **13**. It is noteworthy that the isomeric ratio did not change after crystallization from EtOH indicating that these isomers are in equilibrium.

At room temperature thiosemicarbazide **12** slowly reacted with $N_2H_4 \cdot H_2O$ (10.0 equiv.) in EtOH for 24 h affording a mixture of **14** and **12** in a ratio 25:75 (^{1}H NMR data). In refluxing EtOH the reaction completed in 6 h 20 min to give hydrazone of thiosemicarbazide **14** in 90% yield as a mixture

of *E* and *Z* isomers in a ratio of 92:8, respectively. The stereochemical assignments were based on ^{1}H and ^{13}C NMR spectroscopic data, particularly by comparing these spectra with those of **7a-k** (see above). As for **7a-k**, the ^{1}H NMR signal of the C=NNH$_2$ group for *E*-**14** (6.84 ppm) was significantly downfield shifted compared with that for *Z*-**14** (5.74 ppm).

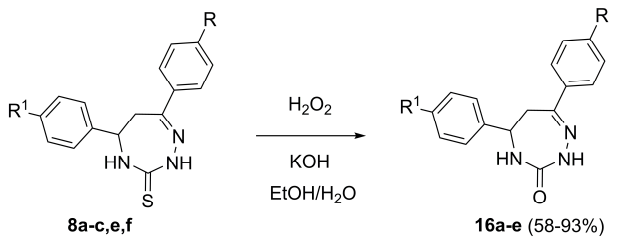
We studied the cyclization of ketone **12** and its hydrazone **14** under the action of TsOH (1.1 equiv.). All reactions were performed with concentrations of the starting material ranging from 0.090–0.150 mol/L which was found to be optimal for the cyclization of **7a-k** and **5a-e** (see Table 3 and Table 4).

At room temperature in EtOH and MeCN in the presence of TsOH the reaction of hydrazone **14** completed for 1 h 45 min. However, besides the expected triazepine **15**, considerable amount of side products formed. According to ^{1}H NMR spectroscopic data, the estimated yield of **15** in isolated crude materials was 24% (in EtOH) and 55% (in MeCN). In contrast to the TsOH-catalyzed cyclization of **7a-k** (Table 3) the estimated yield of **15** significantly decreased (30%) when hydrazone **14** was treated with TsOH in refluxing MeCN for 2 h.

We found that the cyclization of **12** into **15** under the action of TsOH in EtOH at room temperature proceeded quite slowly and gave significant amounts of side products. In refluxing MeCN or EtOH in the presence of TsOH (0.1 equiv.) reaction completed for 1 h to afford triazepine **15** in low yields (27–33%, ^{1}H NMR estimated). Use of AcOH as the catalyst resulted in significant increase in the yield of **15**. Triazepine **15** was obtained by the reaction of thiosemicarbazide **12** with AcOH (4.09 equiv.) in refluxing EtOH for 3 h in 74% yield after column chromatography on silica gel.

2.4. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones

The obtained triazepine-3-thiones **8a-l**, **15**, containing reactive thiosemicarbazone fragment, can serve as versatile starting materials for syntheses of a large variety of triazepines and related compounds. As an example we carried out oxidative transformation of triazepine-3-thiones **8a-c,e,f** into their 3-oxo-analogs **16a-e** (Scheme 7).



8a-c,e,f **16a-e** (58-93%)

Scheme 7. Transformation of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a-c,e,f** into their 3-oxo-analogs **16a-e**.

The oxidation of **8a-c,e,f** proceeded at room temperature for 1.5–2.5 h under the action of excess of H_2O_2 (10 equiv.) in EtOH–H_2O solution in the presence of KOH (5 equiv.) to give the corresponding triazepinones **16a-e** in good yields (Table 5). Compounds **16a-c,e** were isolated with 98% purity (^{1}H NMR spectroscopic data). Column chromatography on silica gel was used only for isolation of compound **16d**.

Table 5. Oxidative transformation of triazepine-3-thiones **8a-c,e,f** into their 3-oxo-analogs **16a-e**.[a]

Entry	**8**	R	R^1	Product	Yield[b] (%)
1	**8a**	H	H	**16a**	89
2	**8b**	H	Me	**16b**	87
3	**8c**	H	OMe	**16c**	88
4	**8e**	H	*t*-Bu	**16d**	58
5	**8f**	Me	H	**16e**	93

[a] Reaction conditions: H_2O_2 (10 equiv.), KOH (5 equiv.), EtOH/H_2O, rt, 1.5–2.5 h.
[b] Isolated yield (for **16d** after column chromatography).

Previously, we prepared triazepinones **16a,b** using carbamate method in overall yields of 11–15% starting from corresponding ethyl *N*-[(aryl)(tosyl)methyl]carbamates.[13] All our attempts to prepare triazepinones **16c** and **16d** by the carbamate method failed. The described above approach to 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones is significantly more effective and flexible. Indeed, triazepinones **16a,b** were obtained in 61–68% overall yields starting from isothiocyanatoketones **4a,b**.

2.5. Structure of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones

The triazepine structure of compounds **8a-l**, **15**, **16a-e** was established by ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectra of **8a-i**, **15**, **16a-e** in DMSO-d_6 show a long-range coupling between the N(2)H and N(4)H protons (^4J = 2.0–2.1 Hz) typical for cyclic (thio)ureas, particularly, 2,3,4,5-tetrahydro- and 2,3-dihydro-1*H*-1,3-diazepin-2-ones,[26] hexahydro- and 1,2,3,4-tetrahydropyrimidine-2-thiones/ones,[25-27] 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones/ones,[8a,13] etc. The proton spin system of the HN(4)-C(5)H-C(6)H(A)H(B) fragment in triazepines **8a-l**, **15**, and **16a-e** is characterized by a long-range coupling between the N(4)H proton and one of the protons of CH_2 group (^4J = 0.7–1.0 Hz), as well as a high geminal coupling constant between the C(6)H(A) and C(6)H(B) protons (^2J = 13.5–14.7 Hz), indicating that these protons are located at α-position to a double bond.[28]

The structures of compounds **8b**, **8i**, and **8j** were independently confirmed by X-ray single-crystal analyses (Fig. 1−3).[29,30] The crystal of **8b** (monoclinic, noncentrosymmetric space group $P2_1$) is a racemic twin. The unit cell contains both enantiomers (Fig. 1). Note, the conformations of these

enantiomers are significantly different; the triazepine ring in both isomers adopts a puckered conformation with a pseudo equatorial position of the *p*-tolyl group for *R*-**8b** (C8–C5–C6–C7 torsion angle is 173.4°) (Fig. 1a) and a pseudo axial orientation of this group for *S*-**8b** (C8–C5–C6–C7 torsion angle is 53.4°) (Fig. 1b), while the C7, N1, N4, and C5 atoms in *R*-**8b** are located in one plane (maximal deviation from the plane is 0.013 Å), and the N2, C3, and C6 atoms deviate from the plane by 0.618, 0.428, and 0.746 Å in the same direction, respectively. Therefore, the triazepine ring in *R*-**8b** has a distorted boat conformation. In contrast to *R*-**8b**, the seven-membered ring in *S*-**8b** adopts a distorted envelope conformation where the C6 and C7 atoms deviate from the mean-square plane formed by the other ring atoms (maximal deviation from the plane is 0.016 Å) by 0.943 and 0.395 Å, respectively.

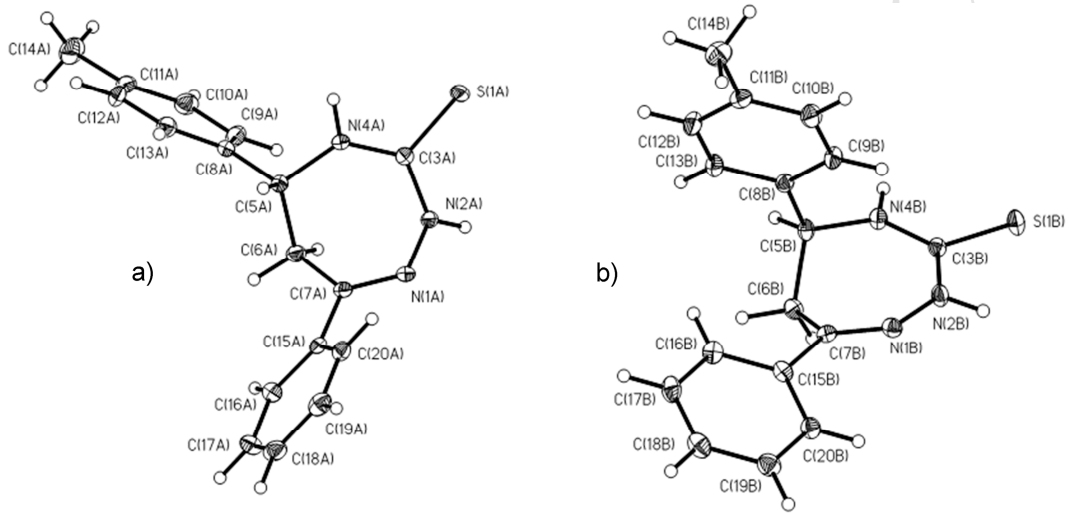


Figure 1. Views of molecular X-ray structures of *R*-**8b** (a) and *S*-**8b** (b) with ellipsoids drawn at the 50% probability level.

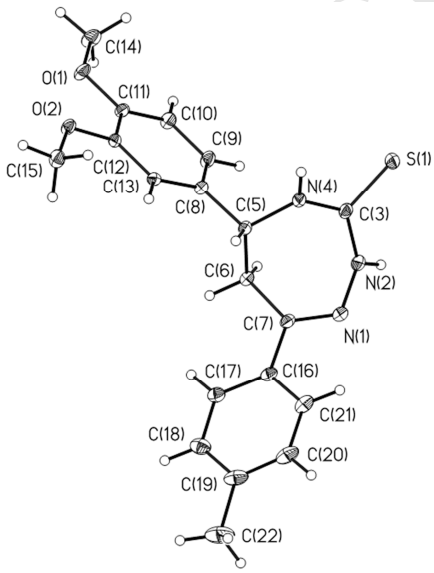


Figure 2. A view of molecular X-ray structure of **8i** with ellipsoids drawn at the 50% probability level.

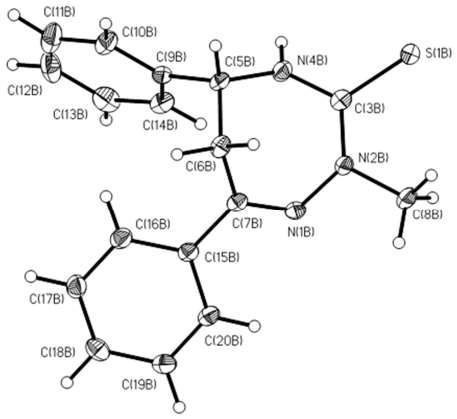


Figure 3. A view of molecular X-ray structure of **8j** with ellipsoids drawn at the 50% probability level. Only *R*-isomer is represented.

The crystal of *R*-**8i** obtained by crystallization of racemic **8i** was triclinic with the space group *P*-1. Conformation of *R*-**8i** is close to that of *R*-**8b** (see above), the triazepine ring adopts a distorted boat conformation where the N2, C3, and C6 atoms deviate from the mean-square plane formed by the other ring atoms (maximal deviation from the plane is 0.017 Å) by 0.681, 0.504, and 0.709 Å, respectively. The dimethoxyphenyl substituent has a pseudo equatorial orientation (C8–N5–C6–C7 dihedral angle is 177.0°) (Fig. 2).

The unit cell of the crystal of **8j** (monoclinic, space group $P2_1/c$) contains both enantiomers (Fig. 3). Conformations of *R*-**8j** and *S*-**8j** are very close. Analogously to *R*-**8b,i**, the seven-membered ring in *R*-**8j** and *S*-**8j** adopts a distorted boat conformation where the C7, N1, N4, and C5 atoms are located in one plane, and the N2, C3, and C6 atoms deviate from this plane. However, in contrast to *R*-**8b,i**, the C5 substituent in **8j** has a pseudo axial position (C8–C5–C6–C7 torsion angles in *R*-**8j** and *S*-**8j** are 70.5° and -72.4°, respectively).

The values of couplings between the N(4)H, C(5)H, C(6)H(A), and C(6)H(B) protons ($^3J_{N(4)H,H-5}$ = 2.2–2.5, $^3J_{H-5,H(A)-6}$ = 4.4–4.6, and $^3J_{H-5,H(B)-6}$ = 9.0–9.3 Hz) in ^{1}H NMR spectra of 2-methyl-substituted triazepinethiones **8j-l** in DMSO-d_6 prove that they exist predominantly in a puckered conformation with a pseudo equatorial orientation of the C5 substituent. It is noteworthy that conformations of **8j** in DMSO solution and in solid state (see above) are different. According to ^{1}H NMR spectroscopic data, 2-unsubstituted triazepinethiones/ones **8a-i**, **16a-e** in DMSO-d_6 have a pseudo axial position of the C5 substituent ($^3J_{N(4)H,H-5}$ = 3.2–5.0, $^3J_{H-5,H(A)-6}$ = 6.2–7.0, and $^3J_{H-5,H(B)-6}$ = 2.6–3.4 Hz).

3. Conclusion

A general synthesis of 7-aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones and their 3-oxo analogs has been developed. The key step of the synthesis includes acid-catalyzed cyclizations of 4-(3-oxopropyl)thiosemicarbazides or their hydrazones to give corresponding 1,2,4-triazepine-3-thiones in high yields. Under optimal reaction conditions 4-(3-oxopropyl)thiosemicarbazide hydrazones are cyclized in refluxing EtOH for 1.5 h in the presence of TsOH (1.10–1.15 equiv.), and 4-(3-oxopropyl)thiosemicarbazides are converted into the target products under reflux in EtOH for 3–8 h using AcOH (4.10–10.62 equiv.) as a catalyst. Both triazepine precursors can be prepared in excellent yields by reaction of readily available 1-aryl-3-isothiocyanatopropan-1-ones with hydrazine or methyl hydrazine in EtOH at room temperature or at reflux. 1,2,4-Triazepin-3-ones are obtained in good yields by oxidation of 3-thioxo derivatives with excess of H_2O_2 in EtOH–H_2O solution in the presence of KOH at room temperature (1.5–2.5 h). Conformational analysis of the obtained triazepine-3-thiones/ones in DMSO solution and solid state based on ^{1}H NMR spectroscopic data and single crystal X-ray diffraction shows that the triazepine ring adopts a puckered conformation (distorted boat or distorted envelope) with a pseudo axial or pseudo equatorial orientation of substituent at the C5 carbon.

4. Experimental section

4.1. General

All solvents were distilled before use. 95% EtOH was used unless otherwise indicated. The petroleum ether had a distillation range of 40–60 °C. 100% hydrazine hydrate was used. Isothiocyanatoketones **4a-i** were prepared as described in ref. 16. Isothiocyanatoketone **11** was prepared as described in ref. 25. All other reagents were purchased from commercial sources and used without additional purification. IR spectra (Nujol) were recorded using a BrukerVector 22 spectrophotometer. Band characteristics in the IR spectra are defined as very strong (vs), strong (s), medium (m), weak (w), and shoulder (sh). ^{1}H NMR and proton decoupled ^{13}C NMR spectra (solutions in DMSO-d_6) were acquired using a Bruker DPX 300 spectrometer at 300.13 MHz (^{1}H) and 75.48 MHz (^{13}C). ^{1}H NMR chemical shifts are referenced to the residual proton signal in DMSO-d_6 (2.50 ppm). In ^{13}C NMR spectra, central signals of DMSO-d_6 (39.50 ppm) were used as references. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), and some combinations of these, multiplet (m). Selective ^{1}H–^{1}H decoupling and DEPT-135 experiments were used to aid in the assignment of ^{1}H and ^{13}C NMR signals. Elemental analyses (CHN) were performed using a Thermo Finnigan Flash EA1112 apparatus. Thin-

layer chromatography was carried out on Aldrich silica gel 60 F254 aluminum backed plates in $CHCl_3$ and $CHCl_3$/MeOH (9:1, v/v) as solvent systems. Spots were visualized with UV light or iodine vapors. Column chromatography was performed with Macherey–Nagel silica gel 60 (0.063–0.200 mm) or Macherey–Nagel aluminium oxide 90 neutral (activity 1). X-ray diffraction experiments were carried out on an automatic four-circle diffractometer with area detector Bruker KAPPA APEX II at 100 K, MoK_α radiation, graphite monochromator. Unit cell parameters were refined over the whole datasets.[31] The structures were solved using direct method (SHELXS97[32]) and refined using full-matrix least-squares method (SHELXL-2014[33]) on F^2 over the whole dataset in the anisotropic approximation for all nonhydrogen atoms. H atoms were introduced in geometrically calculated positions with isotropic temperature factors $U_H = 1.5U_{eq}(C)$ for CH_3 groups and $U_H = 1.2U_{eq}(C,N)$ for CH, NH, CH_2 and NH_2 groups. Suitable single crystals were obtained from slow evaporation of saturated solutions in MeCN (for **8b,i**) and EtOH (for **8j**) at room temperature. All yields refer to isolated, spectroscopically and TLC pure compounds. The color of solid substances was white, if not otherwise mentioned. The geometry optimizations of *R*-**7a** and *S*-**7a**, cations **A** and **B** (Scheme 4) were carried out at the B3LYP level of theory using Gaussian 09 suite[34] of quantum chemical programs. Pople's basis set, 6-311++G(d,p), was employed for geometry optimization. The effect of continuum solvation was incorporated by using the polarizable continuum model (PCM). Enthalpies and Gibbs free energies were obtained by adding unscaled zero-point vibrational energy corrections (ZPVE) and thermal contributions to the energies.

4.2. Synthesis of 4-(3-aryl-3-oxopropyl)thiosemicarbazides 5a-e

*4.2.1. 4-[(3-Oxo-1,3-diphenyl)prop-1-yl]thiosemicarbazide (**5a**).* To a stirred suspension of isothiocyanatoketone **4a** (1.51 g, 5.66 mmol) in EtOH (20 mL) was added a solution of $N_2H_4 \cdot H_2O$ (0.290 g, 5.80 mmol) in EtOH (5 mL) over 1 min. The resulting mixture was stirred at room temperature for 1 h and the solvent was removed in vacuum. The obtained solid residue was triturated with H_2O and the suspension was cooled. The precipitate was filtered, washed with ice-cold H_2O, petroleum ether, and dried to give product (1.68 g, 99%) as a 89:11 mixture of thiosemicarbazide **5a** and 1-amino-6-hydroxy-4,6-diphenylhexahydropyrimidine-2-thione (**6a**) (two diastereomers in a ratio of 69:31). After crystallization from EtOH the isomeric ratio did not change. Mp 151−152 °C (dec, EtOH) (lit.[24] 153 °C); IR (Nujol) ν, cm^{-1}: 3340 (s), 3316 (m), 3293 (br s), 3173 (br s), 3148 (sh) (ν NH), 3085 (w), 3061 (w), 3055 (sh), 3030 (w) (ν CH_{arom}), 1662 (s) (ν C=O), 1632 (m) (δ NH_2), 1597 (m), 1578 (m) (ν CC_{arom}), 1519 (s) (thioamide-II), 1494 (m), 1485 (m) (ν CC_{arom}), 744 (s), 699 (m) (δ CH_{arom}); ^{1}H NMR of thiosemicarbazide **5a** (300.13 MHz, DMSO-d_6) δ: 8.80 (1H, br s, N*H*NH_2), 8.40 (1H, br d, ^3J = 9.5 Hz, N*H*CH), 7.93–7.99 (2H, m, ArH), 7.59–7.66 (1H, m, ArH), 7.47–7.55 (2H, m,

ArH), 7.16–7.43 (5H, m, ArH), 6.02 (1H, ddd, ^3J = 9.5, ^3J = 6.5, ^3J = 6.1 Hz, CHN), 4.55 (2H, br s, NH_2), 3.89 (1H, dd, ^2J = 17.3, ^3J = 6.1 Hz, H_A in CH_2), 3.61 (1H, dd, ^2J = 17.3, ^3J = 6.5 Hz, H_B in CH_2); ^{1}H NMR of the major isomer of pyrimidine **6a** (300.13 MHz, DMSO-d_6) δ: 8.71 (1H, br d, ^4J = 2.0 Hz, $N_{(3)}H$), 6.97 (1H, d, ^4J = 1.5 Hz, OH), 4.73 (2H, br s, NH_2), 4.72 (1H, dd, ^3J = 11.8, ^3J = 4.2 Hz, H-4), 2.18 (1H, ddd, ^2J = 13.6, ^3J = 11.8, ^4J = 1.5 Hz, H_{ax}-5), 2.08 (1H, ddd, ^2J = 13.6, ^3J = 4.2, ^4J = 2.0 Hz, H_{eq}-5), signals of aromatic protons overlap with proton signals of the acyclic isomer; ^{1}H NMR of the minor isomer of pyrimidine **6a** (300.13 MHz, DMSO-d_6) δ: 6.80 (1H, s, OH), 5.14 (2H, br s, NH_2), 3.98 (1H, dd, ^3J = 11.6, ^3J = 4.2 Hz, H-4), 2.46 (1H, dd, ^2J = 13.8, ^3J = 11.6 Hz, H_{ax}-5, signals partly overlap with residual proton signals in DMSO), 2.29 (1H, ddd, ^2J = 13.8, ^3J = 4.2, ^4J = 1.8 Hz, H_{eq}-5), signals of other protons overlap with proton signals of the acyclic isomer; ^{13}C NMR of thiosemicarbazide **5a** (75.48 MHz, DMSO-d_6) δ: 198.0 (C=O), 180.6 (C=S), 142.5 (C), 136.6 (C), 133.4 (CH), 128.7 (2CH), 128.1 (2CH), 128.0 (2CH), 126.8 (2CH), 126.7 (CH), 52.7 (CHN), 43.6 (CH_2). Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04. Found: C, 64.38; H, 5.88; N, 14.17.

*4.2.2. 4-{[1,3-Di(4-methylphenyl)-3-oxo]prop-1-yl}thiosemicarbazide (**5b**).* The reaction of isothiocyanatoketone **4g** (0.989 g, 3.35 mmol) with $N_2H_4 \cdot H_2O$ (0.172 g, 3.43 mmol) in EtOH (25 mL) (rt, 1 h) to give product (1.08 g, 98%) as a 95:5 mixture of thiosemicarbazide **5b** and 1-amino-6-hydroxy-4,6-[di(4-methylphenyl)]hexahydropyrimidine-2-thione (**6b**) (two diastereomers in a ratio of 67:33) was performed as described for the synthesis of **5a**. Crystallization of the crude product from EtOH afforded a 94:6 mixture of thiosemicarbazide **5b** and pyrimidine **6b** (two isomers, 67:33). Mp 162.5–163.5 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3331 (m), 3313 (s), 3249 (br s), 3179 (br s) (ν NH), 3098 (w), 3055 (w), 3024 (w) (ν CH_{arom}), 1669 (s) (ν C=O), 1626 (s) (δ NH_2), 1606 (s), 1571 (sh) (ν CC_{arom}), 1528 (br s) (thioamide-II), 818 (s), 805 (s) (δ CH_{arom}); ^{1}H NMR of thiosemicarbazide **5b** (300.13 MHz, DMSO-d_6) δ: 8.77 (1H, br s, N*H*NH_2), 8.34 (1H, br d, ^3J = 8.7 Hz, N*H*CH), 7.83–7.88 (2H, m, ArH), 7.23–7.34 (4H, m, ArH), 7.05–7.11 (2H, m, ArH), 5.95 (1H, ddd, ^3J = 8.7, ^3J = 6.8, ^3J = 5.8 Hz, CHN), 4.53 (2H, br s, NH_2), 3.81 (1H, dd, ^2J = 17.1, ^3J = 5.8 Hz, H_A in CH_2), 3.54 (1H, dd, ^2J = 17.1, ^3J = 6.8 Hz, H_B in CH_2), 2.36 (3H, s, CH_3), 2.24 (3H, s, CH_3); ^{1}H NMR of the major isomer of pyrimidine **6b** (300.13 MHz, DMSO-d_6) δ: 8.59 (1H, br d, ^4J = 2.0 Hz, $N_{(3)}H$), 6.89 (1H, d, ^4J = 1.5 Hz, OH), 4.70 (2H, br s, NH_2), 4.67 (1H, dd, ^3J = 12.1, ^3J = 3.8 Hz, H-4), 2.16 (1H, ddd, ^2J = 13.4, ^3J = 12.1, ^4J = 1.5 Hz, H_{ax}-5), 2.01 (1H, ddd, ^2J = 13.4, ^3J = 3.8, ^4J = 2.0 Hz, H_{eq}-5), 2.27 (6H, s, two CH_3), signals of aromatic protons overlap with proton signals of the acyclic isomer; ^{1}H NMR of the minor isomer of pyrimidine **6b** (300.13 MHz, DMSO-d_6) δ: 6.71 (1H, s, OH), 5.10 (2H, br s, NH_2), 3.94 (1H, dd, ^3J = 12.0, ^3J = 4.0 Hz, H-4), 2.33 (3H, s, CH_3), 2.26 (3H, s, CH_3), signals of other protons overlap with proton signals of the acyclic isomer; ^{13}C NMR of thiosemicarbazide **5b** (75.48 MHz, DMSO-d_6) δ: 197.5 (C=O), 180.5 (C=S), 143.7 (C), 139.4 (C), 135.8 (C), 134.1 (C), 129.2 (2CH), 128.6 (2CH),

128.1 (2CH), 126.7 (2CH), 52.6 (CHN), 43.4 (CH_2), 21.1 (CH_3), 20.6 (CH_3). Anal. Calcd for $C_{18}H_{21}N_3OS$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.07; H, 6.60; N, 12.93.

*4.2.3. 2-Methyl-4-[(3-oxo-1,3-diphenyl)prop-1-yl]thiosemicarbazide (**5c**).* Compound **5c** (1.29 g, 99%) was prepared from isothiocyanatoketone **4a** (1.10 g, 4.13 mmol) and methyl hydrazine (0.197 g, 4.27 mmol) in EtOH (25 mL) (rt, 1 h) as described for **5a**. Mp 167–168 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3346 (s), 3245 (s), 3171 (m), 3142 (m) (ν NH), 3083 (w), 3062 (w), 3052 (w), 3030 (w) (ν CH_{arom}), 1680 (s) (ν C=O), 1642 (m) (δ NH_2), 1599 (w), 1579 (w) (ν CC_{arom}), 1523 (s) (thioamide-II), 1496 (w) (ν CC_{arom}), 744 (m), 697 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.76 (1H, br d, ^3J = 9.0 Hz, NH), 7.93–7.98 (2H, m, ArH), 7.59–7.66 (1H, m, ArH), 7.47–7.54 (2H, m, ArH), 7.35–7.41 (2H, m, ArH), 7.24–7.31 (2H, m, ArH), 7.15–7.22 (1H, m, ArH), 5.93 (1H, ddd, ^3J = 9.0, ^3J = 6.5, ^3J = 6.1 Hz, CHN), 4.95 (2H, br s, NH_2), 3.88 (1H, dd, ^2J = 17.3, ^3J = 6.1 Hz, H_A in CH_2), 3.59 (1H, dd, ^2J = 17.3, ^3J = 6.5 Hz, H_B in CH_2), 3.44 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 198.0 (C=O), 180.2 (C=S), 142.6 (C), 136.6 (C), 133.4 (CH), 128.7 (2CH), 128.1 (2CH), 128.0 (2CH), 126.8 (2CH), 126.7 (CH), 54.2 (CHN), 43.7 (CH_2), 42.5 (CH_3). Anal. Calcd for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11; N, 13.41. Found: C, 65.22; H, 6.31; N, 13.46.

*4.2.4. 2-Methyl-4-{[1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}thiosemicarbazide (**5d**).* Compound **5d** (0.913 g, 98%) was prepared from isothiocyanatoketone **4b** (0.803 g, 2.85 mmol) and methyl hydrazine (0.139 g, 3.01 mmol) in EtOH (20 mL) (rt, 1 h) as described for **5a**. Mp 145–146 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3340 (s), 3287 (m), 3261 (m), 3155 (s), 3127 (s) (ν NH), 3083 (w), 3051 (w), 3026 (w) (ν CH_{arom}), 1682 (s) (ν C=O), 1626 (m) (δ NH_2), 1595 (m), 1579 (w) (ν CC_{arom}), 1512 (br s) (thioamide-II), 822 (m), 746 (s), 686 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.68 (1H, br d, ^3J = 8.9 Hz, NH), 7.92–7.98 (2H, m, ArH), 7.59–7.66 (1H, m, ArH), 7.47–7.54 (2H, m, ArH), 7.23–7.29 (2H, m, ArH), 7.05–7.11 (2H, m, ArH), 5.88 (1H, ddd, ^3J = 8.9, ^3J = 6.8, ^3J = 5.9 Hz, CHN), 4.92 (2H, br s, NH_2), 3.83 (1H, dd, ^2J = 17.1, ^3J = 5.9 Hz, H_A in CH_2), 3.57 (1H, dd, ^2J = 17.1, ^3J = 6.8 Hz, H_B in CH_2), 3.44 (3H, s, NCH_3), 2.24 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 198.0 (C=O), 180.1 (C=S), 139.4 (C), 136.6 (C), 135.7 (C), 133.2 (CH), 128.62 (2CH), 128.58 (2CH), 127.9 (2CH), 126.6 (2CH), 53.9 (CHN), 43.6 (CH_2), 42.4 (NCH_3), 20.5 (CH_3). Anal. Calcd for $C_{18}H_{21}N_3OS$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.00; H, 6.75; N, 12.79.

*4.2.5. 2-Methyl-4-{[1,3-di(4-methylphenyl)-3-oxo]prop-1-yl}thiosemicarbazide (**5e**).* Compound **5e** (1.11 g, 98%) was prepared from isothiocyanatoketone **4g** (0.977 g, 3.31 mmol) and methyl hydrazine (0.157 g, 3.41 mmol) in EtOH (25 mL) (rt, 1 h) as described for **5a**. Mp 166–167.5 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3326 (s), 3294 (s), 3258 (m), 3167 (s), 3131 (w) (ν NH), 3090 (w), 3071 (w), 3050 (w),

3023 (w) (ν CH_{arom}), 1669 (s) (ν C=O), 1630 (s) (δ NH_2), 1605 (s), 1574 (w) (ν CC_{arom}), 1514 (br s) (thioamide-II), 815 (s), 804 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.69 (1H, br d, ^3J = 8.9 Hz, NH), 7.82–7.88 (2H, m, ArH), 7.28–7.33 (2H, m, ArH), 7.22–7.27 (2H, m, ArH), 7.04–7.10 (2H, m, ArH), 5.86 (1H, ddd, ^3J = 8.9, ^3J = 6.9, ^3J = 5.8 Hz, CHN), 4.91 (2H, br s, NH_2), 3.79 (1H, dd, ^2J = 17.0, ^3J = 5.8 Hz, H_A in CH_2), 3.51 (1H, dd, ^2J = 17.0, ^3J = 6.9 Hz, H_B in CH_2), 3.44 (3H, s, NCH_3), 2.36 (3H, s, CH_3), 2.23 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 197.5 (C=O), 180.1 (C=S), 143.6 (C), 139.4 (C), 135.7 (C), 134.1 (C), 129.2 (2CH), 128.6 (2CH), 128.1 (2CH), 126.6 (2CH), 54.0 (CHN), 43.4 (CH_2), 42.4 (NCH_3), 21.1 (CH_3), 20.5 (CH_3). Anal. Calcd for $C_{19}H_{23}N_3OS$: C, 66.83; H 6.79; N, 12.31. Found: C, 66.97; H, 7.02; N, 12.39.

4.3. Synthesis of hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides 7a-k

*4.3.1. Hydrazone of 4-[(3-oxo-1,3-diphenyl)prop-1-yl]thiosemicarbazide (**7a**).* A solution of isothiocyanatoketone **4a** (2.05 g, 7.67 mmol) and $N_2H_4 \cdot H_2O$ (7.69 g, 153.6 mmol) in EtOH (35 mL) was stirred under reflux for 3 h, and the liquids were removed in vacuum (temperature of bath about 50–55 °C). The residue was co-evaporated with toluene (4 × 15 mL), the resulting oily solid was triturated with ether until crystallization was completed. The suspension was cooled (–15 °C). The precipitate was filtered, and washed with cold (–15 °C) ether (3 × 10 mL). Ether was removed from solid by passing the air through the filter, and then the solid was washed with ice-cold H_2O (4 × 10 mL), petroleum ether, and dried to give hydrazone **7a** (2.22 g, 92%) as a 87:13 mixture of geometric isomers. After crystallization from MeCN the isomeric ratio changed to 98:2, respectively. Mp 172.5–173.5 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3433 (m), 3416 (m), 3309 (s), 3258 (sh), 3224 (s), 3192 (br s) (ν NH), 3107 (w), 3084 (w), 3065 (w), 3053 (w), 3027 (w) (ν CH_{arom}), 1629 (s) (ν C=N, δ NH_2), 1588 (m) (ν CC_{arom}), 1529 (br s) (thioamide-II), 1493 (s) (ν CC_{arom}), 756 (s), 695 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.77 (1H, br s, N*H*NH_2), 8.29 (1H, br d, ^3J = 7.9 Hz, N*H*CH), 7.49–7.55 (2H, m, ArH), 7.31–7.37 (2H, m, ArH), 7.12–7.29 (6H, m, ArH), 6.67 (2H, br s, NH_2N=C), 5.72 (1H, ddd, ^3J = 8.0, ^3J = 7.9, ^3J = 7.7 Hz, CHN), 4.49 (2H, br s, NH_2NH), 3.29 (1H, dd, ^2J = 14.3, ^3J = 7.7 Hz, H_A in CH_2), 3.11 (1H, dd, ^2J = 14.3, ^3J = 8.0 Hz, H_B in CH_2); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.68 (1H, br s, N*H*NH_2), 8.20 (1H, br d, ^3J = 8.3 Hz, N*H*CH), 7.39–7.46 (2H, m, ArH), 5.66 (2H, br s, NH_2N=C), 5.49 (1H, ddd, ^3J = 8.3, ^3J = 7.5, ^3J = 6.9 Hz, CHN), 2.99 (1H, dd, ^2J = 14.6, ^3J = 7.5 Hz, H_A in CH_2), 2.96 (1H, dd, ^2J = 14.6, ^3J = 6.9 Hz, H_B in CH_2), signals of other protons overlap with proton signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.6 (C=S), 142.2 (C), 141.7 (C=N), 139.0 (C), 128.1 (2CH), 127.8 (2CH), 127.0 (CH), 126.8 (2CH), 126.7 (CH), 125.0 (2CH), 54.0 (CHN), 31.5 (CH_2). Anal. Calcd for $C_{16}H_{19}N_5S$: C, 61.32; H, 6.11; N, 22.35. Found: C, 61.30; H, 6.17; N, 22.35.

*4.3.2. Hydrazone of 4-{[1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}thiosemicarbazide (**7b**).* Compound **7b** (2.09 g, 91%) as a 83:17 mixture of geometric isomers was prepared from isothiocyanatoketone **4b** (1.96 g, 6.98 mmol) and $N_2H_4 \cdot H_2O$ (7.00 g, 139.8 mmol) in EtOH (30 mL) (reflux, 3 h) as described for **7a**. After crystallization from EtOH the isomeric ratio changed to 90:10, respectively. Mp 163–163.5 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3432 (m), 3419 (sh), 3380 (w), 3312 (s), 3233 (br s), 3191 (br s) (ν NH), 3102 (w), 3079 (w), 3051 (w), 3021 (w) (ν CH_{arom}), 1626 (s) (ν C=N, δ NH_2), 1589 (m) (ν CC_{arom}), 1530 (br s) (thioamide-II), 1492 (s) (ν CC_{arom}), 802 (s), 765 (s), 697 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.75 (1H, br s, N*H*NH_2), 8.22 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.50–7.57 (2H, m, ArH), 7.03–7.27 (7H, m, ArH), 6.45 (2H, br s, NH_2N=C), 5.66 (1H, ddd, ^3J = 8.5, ^3J = 8.2, ^3J = 7.6 Hz, CHN), 4.48 (2H, br s, N*H*$_2$NH), 3.26 (1H, dd, ^2J = 14.3, ^3J = 7.6 Hz, H_A in CH_2), 3.09 (1H, dd, ^2J = 14.3, ^3J = 8.2 Hz, H_B in CH_2), 2.23 (3H, s, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.65 (1H, br s, N*H*NH_2), 8.12 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.32–7.47 (3H, m, ArH), 5.64 (2H, br s, NH_2N=C), 5.42 (1H, ddd, ^3J = 8.5, ^3J = 7.5, ^3J = 6.9 Hz, CHN), 4.46 (2H, br s, N*H*$_2$NH), 2.97 (1H, dd, ^2J = 14.6, ^3J = 7.5 Hz, H_A in CH_2), 2.93 (1H, dd, ^2J = 14.6, ^3J = 6.9 Hz, H_B in CH_2), 2.26 (3H, s, CH_3), signals of six aromatic protons overlap with signals of aromatic protons of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.5 (C=S), 141.7 (C=N), 139.1 (C), 139.0 (C), 136.0 (C), 128.7 (2CH), 127.8 (2CH), 126.7 (3CH), 125.0 (2CH), 53.8 (CHN), 31.5 (CH_2), 20.7 (CH_3). Anal. Calcd for $C_{17}H_{21}N_5S$: C, 62.36; H, 6.46; N, 21.39. Found: C, 62.22; H, 6.64; N, 21.44.

*4.3.3. Hydrazone of 4-{[1-(4-methoxyphenyl)-3-oxo-3-phenyl]prop-1-yl}thiosemicarbazide (**7c**).* Compound **7c** (0.793 g, 94%) as a 84:16 mixture of geometric isomers was prepared from isothiocyanatoketone **4c** (0.730 g, 2.46 mmol) and $N_2H_4 \cdot H_2O$ (2.48 g, 49.5 mmol) in EtOH (12 mL) (reflux, 3 h) as described for **7a**. Crystallization of the crude product from EtOH afforded a 97:3 mixture of isomers, and crystallization from MeCN gave the only major isomer. Mp 90.5–93 °C (dec, EtOH); mp 93–95 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3388 (br m), 3304 (m), 3258 (m), 3195 (br s), 3171 (sh) (ν NH), 3064 (w), 3050 (w), 3033 (w) (ν CH_{arom}), 1651 (m), 1638 (sh) (ν C=N, δ NH_2), 1613 (m), 1586 (w) (ν CC_{arom}), 1542 (s) (thioamide-II), 1516 (s), 1500 (w) (ν CC_{arom}), 1254 (s), 1034 (m) (ν C–O), 828 (m), 766 (m), 702 (m) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.75 (1H, br s, N*H*NH_2), 8.19 (1H, br d, ^3J = 7.9 Hz, N*H*CH), 7.49–7.55 (2H, m, ArH), 7.12–7.29 (5H, m, ArH), 6.77–6.83 (2H, m, ArH), 6.66 (2H, br s, NH_2N=C), 5.64 (1H, ddd, ^3J = 8.4, ^3J = 7.9, ^3J = 7.3 Hz, CHN), 4.48 (2H, br s, N*H*$_2$NH), 3.69 (3H, s, OCH_3), 3.25 (1H, dd, ^2J = 14.2, ^3J = 7.3 Hz, H_A in CH_2), 3.10 (1H, dd, ^2J = 14.2, ^3J = 8.4 Hz, H_B in CH_2); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.59 (1H, br s, N*H*NH_2), 8.07 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.39–7.46 (2H, m, ArH),

7.32–7.39 (1H, m, ArH), 5.62 (2H, br s, NH_2N=C), 5.42 (1H, ddd, ^3J = 8.5, ^3J = 7.5, ^3J = 7.1 Hz, CHN), 4.43 (2H, br s, N*H*$_2$NH), 3.72 (3H, s, OCH_3), 2.99 (1H, dd, ^2J = 14.6, ^3J = 7.5 Hz, H_A in CH_2), 2.93 (1H, dd, ^2J = 14.6, ^3J = 7.1 Hz, H_B in CH_2), signals of other protons overlap with proton signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.4 (C=S), 158.3 (C), 141.7 (C=N), 139.0 (C), 134.0 (C), 128.0 (2CH), 127.8 (2CH), 126.7 (CH), 125.0 (2CH), 113.5 (2CH), 55.0 (OCH_3), 53.5 (CHN), 31.5 (CH_2). Anal. Calcd for $C_{17}H_{21}N_5OS$: C, 59.45; H, 6.16; N, 20.39. Found: C, 59.27; H, 6.30; N, 20.36.

*4.3.4. Hydrazone of 4-{[1-(3,4-dimethoxyphenyl)-3-oxo-3-phenyl]prop-1-yl}thiosemicarbazide (**7d**).* Compound **7d** (0.964 g, 89%) as a 84:16 mixture of geometric isomers was prepared from isothiocyanatoketone **4d** (0.946 g, 2.89 mmol) and $N_2H_4 \cdot H_2O$ (2.48 g, 57.9 mmol) in EtOH (14 mL) (reflux, 3 h) as described for **7a**. After crystallization from MeCN the isomeric ratio changed to 95:5, respectively. Mp 177.5–178 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3326 (s), 3303 (s), 3193 (br s), 3131 (w) (ν NH), 3085 (w), 3044 (w) (ν CH_{arom}), 1649 (m) (ν C=N, δ NH_2), 1593 (m) (ν CC_{arom}), 1536 (s) (thioamide-II), 1514 (s), 1496 (m) (ν CC_{arom}), 1260 (s), 1020 (s) (ν C–O), 833 (m), 768 (w), 696 (m) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.71 (1H, br s, N*H*NH_2), 8.15 (1H, br d, ^3J = 7.5 Hz, N*H*CH), 7.50–7.56 (2H, m, ArH), 7.12–7.26 (3H, m, ArH), 6.94–6.99 (1H, m, ArH), 6.75–6.84 (2H, m, ArH), 6.64 (2H, br s, NH_2N=C), 5.64 (1H, ddd, ^3J = 8.7, ^3J = 7.5, ^3J = 7.1 Hz, CHN), 4.47 (2H, br s, N*H*$_2$NH), 3.68 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.24 (1H, dd, ^2J = 14.2, ^3J = 7.1 Hz, H_A in CH_2), 3.17 (1H, dd, ^2J = 14.2, ^3J = 8.7 Hz, H_B in CH_2); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.58 (1H, br s, N*H*NH_2), 8.07 (1H, br d, ^3J = 8.9 Hz, N*H*CH), 7.32–7.46 (3H, m, ArH), 6.82–6.88 (2H, m, ArH), 5.63 (2H, br s, NH_2N=C), 5.42 (1H, ddd, ^3J = 8.9, ^3J = 7.4, ^3J = 7.0 Hz, CHN), 4.42 (2H, br s, N*H*$_2$NH), 3.71 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.02 (1H, dd, ^2J = 14.4, ^3J = 7.4 Hz, H_A in CH_2), 2.94 (1H, dd, ^2J = 14.4, ^3J = 7.0 Hz, H_B in CH_2), signals of other aromatic protons overlap with signals of aromatic protons of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.3 (C=S), 148.4 (C), 147.9 (C), 141.8 (C=N), 139.1 (C), 134.2 (C), 127.8 (2CH), 126.6 (CH), 125.1 (2CH), 119.2 (CH), 111.4 (CH), 110.9 (CH), 55.48 (OCH_3), 55.46 (OCH_3), 53.8 (CHN), 31.3 (CH_2). Anal. Calcd for $C_{18}H_{23}N_5O_2S$: C, 57.89; H, 6.21; N, 18.75. Found: C, 57.90; H, 6.42; N, 19.08.

*4.3.5. Hydrazone 4-{[1-(4-tert-butylphenyl)-3-oxo-3-phenyl]prop-1-yl}thiosemicarbazide (**7e**).* Compound **7e** (1.89 g, 89%) as a 90:10 mixture of geometric isomers was prepared from isothiocyanatoketone **4e** (1.86 g, 5.75 mmol) and $N_2H_4 \cdot H_2O$ (5.76 g, 115.1 mmol) in EtOH (28 mL) (reflux, 3 h) as described for **7a**. After crystallization from EtOH the isomeric ratio changed to 95:5, respectively. Mp 157.5–158.5 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3378 (m), 3301 (s), 3199 (br s),

3159 (s) (ν NH), 3089 (w), 3054 (w), 3027 (w) (ν CH_{arom}), 1626 (m) (ν C=N, δ NH_2), 1587 (w) (ν CC_{arom}), 1535 (s) (thioamide-II), 1503 (m) (ν CC_{arom}), 819 (m), 754 (m), 693 (m) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.70 (1H, br s, N*H*NH_2), 8.23 (1H, br d, ^3J = 8.1 Hz, N*H*CH), 7.45–7.50 (2H, m, ArH), 7.24–7.31 (4H, m, ArH), 7.10–7.24 (3H, m, ArH), 6.67 (2H, br s, NH_2N=C), 5.67 (1H, ddd, ^3J = 8.1, ^3J = 7.8, ^3J = 7.7 Hz, CHN), 4.45 (2H, br s, NH_2NH), 3.31 (1H, dd, ^2J = 14.2, ^3J = 7.7 Hz, H_A in CH_2), 3.04 (1H, dd, ^2J = 14.2, ^3J = 7.8 Hz, H_B in CH_2), 1.24 (9H, s, 3×CH_3 in *t*-Bu); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.61 (1H, br s, N*H*NH_2), 8.12 (1H, br d, ^3J = 8.6 Hz, N*H*CH), 7.31–7.45 (3H, m, ArH), 5.64 (2H, br s, NH_2N=C), 5.47 (1H, ddd, ^3J = 8.6, ^3J = 7.6, ^3J = 6.7 Hz, CHN), 2.97 (1H, dd, ^2J = 14.6, ^3J = 7.6 Hz, H_A in CH_2), 2.93 (1H, dd, ^2J = 14.6, ^3J = 6.7 Hz, H_B in CH_2), 1.26 (9H, s, 3×CH_3 in *t*-Bu), signals of other protons overlap with proton signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.6 (C=S), 149.3 (C), 141.9 (C=N), 139.2 (C), 139.0 (C), 127.6 (2CH), 126.5 (CH), 126.4 (2CH), 125.0 (2CH), 124.8 (2CH), 53.7 (CHN), 34.1 (*C*Me_3), 31.7 (CH_2), 31.1 (3×CH_3 in *t*-Bu). Anal. Calcd for $C_{20}H_{27}N_5S$: C, 65.01; H, 7.36; N, 18.95. Found: C, 65.02; H, 7.43; N, 19.20.

*4.3.6. Hydrazone of 4-{[3-(4-methylphenyl)-3-oxo-1-phenyl]prop-1-yl}thiosemicarbazide (**7f**).* Compound **7f** (2.97 g, 93%) as a 97:3 mixture of geometric isomers was prepared from isothiocyanatoketone **4f** (2.76 g, 9.79 mmol) and $N_2H_4 \cdot H_2O$ (9.82 g, 196.2 mmol) in EtOH (55 mL) (reflux, 3 h) as described for **7a**. After crystallization from EtOH the isomeric ratio changed to 98:2, respectively. Mp 156.5–157 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3402 (m), 3349 (m), 3305 (m), 3276 (m), 3191 (br s) (ν NH), 3086 (w), 3061 (w), 3032 (w) (ν CH_{arom}), 1637 (sh), 1608 (m) (ν C=N, δ NH_2), 1583 (w), 1559 (w) (ν CC_{arom}), 1523 (s) (thioamide-II), 1495 (m) (ν CC_{arom}), 815 (m), 755 (m), 702 (m) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.71 (1H, br s, N*H*NH_2), 8.27 (1H, br d, ^3J = 8.4 Hz, N*H*CH), 7.39–7.45 (2H, m, ArH), 7.31–7.37 (2H, m, ArH), 7.22–7.29 (2H, m, ArH), 7.15–7.22 (1H, m, ArH), 7.01–7.06 (2H, m, ArH), 6.52 (2H, br s, NH_2N=C), 5.71 (1H, ddd, ^3J = 8.4, ^3J = 8.1, ^3J = 7.6 Hz, CHN), 4.47 (2H, br s, NH_2NH), 3.26 (1H, dd, ^2J = 14.2, ^3J = 7.6 Hz, H_A in CH_2), 3.09 (1H, dd, ^2J = 14.2, ^3J = 8.1 Hz, H_B in CH_2), 2.25 (3H, s, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.63 (1H, br s, N*H*NH_2), 8.17 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 5.62 (2H, br s, NH_2N=C), 5.47 (1H, ddd, ^3J = 8.5, ^3J = 7.3, ^3J = 6.8 Hz, CHN), 2.96 (1H, dd, ^2J = 14.4, ^3J = 7.3 Hz, H_A in CH_2), 2.93 (1H, dd, ^2J = 14.4, ^3J = 6.8 Hz, H_B in CH_2), 2.32 (3H, s, CH_3), signals of other protons overlap with proton signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.6 (C=S), 142.2 (C), 142.0 (C=N), 136.2 (C), 135.8 (C), 128.4 (2CH), 128.0 (2CH), 126.9 (CH), 126.7 (2CH), 124.9 (2CH), 54.0 (CHN), 31.5 (CH_2), 20.6 (CH_3). Anal. Calcd for $C_{17}H_{21}N_5S$: C, 62.36; H, 6.46; N, 21.39. Found: C, 62.24; H, 6.66; N, 21.48.

*4.3.7. Hydrazone of 4-{[1,3-di(4-methylphenyl)-3-oxo]prop-1-yl}thiosemicarbazide (**7g**).* Compound **7g** (1.30 g, 89%) as a 83:17 mixture of geometric isomers was prepared from isothiocyanatoketone **4g** (1.26 g, 4.27 mmol) and $N_2H_4 \cdot H_2O$ (4.30 g, 85.9 mmol) in EtOH (21 mL) (reflux, 3 h) as described for **7a**. After crystallization from EtOH the isomeric ratio changed to 96:4, respectively. Mp 149–149.5 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3408 (m), 3325 (s), 3195 (br s), 3119 (w) (ν NH), 3050 (w), 3027 (w) (ν CH_{arom}), 1628 (s) (ν C=N, δ NH_2), 1586 (m) (ν CC_{arom}), 1543 (s) (thioamide-II), 1514 (s) (ν CC_{arom}), 818 (s), 797 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.73 (1H, br s, N*H*NH_2), 8.22 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.41–7.47 (2H, m, ArH), 7.19–7.24 (2H, m, ArH), 7.02–7.09 (4H, m, ArH), 6.52 (2H, br s, NH_2N=C), 5.65 (1H, ddd, ^3J = 8.5, ^3J = 8.1, ^3J = 7.6 Hz, CHN), 4.48 (2H, br s, NH_2NH), 3.23 (1H, dd, ^2J = 14.2, ^3J = 7.6 Hz, H_A in CH_2), 3.07 (1H, dd, ^2J = 14.2, ^3J = 8.1 Hz, H_B in CH_2), 2.25 (3H, s, CH_3), 2.24 (3H, s, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.65 (1H, br s, N*H*NH_2), 8.11 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 5.61 (2H, br s, NH_2N=C), 5.39 (1H, ddd, ^3J = 8.5, ^3J = 7.4, ^3J = 7.0 Hz, CHN), 2.95 (1H, dd, ^2J = 14.6, ^3J = 7.4 Hz, H_A in CH_2), 2.91 (1H, dd, ^2J = 14.6, ^3J = 7.0 Hz, H_B in CH_2), 2.32 (3H, s, CH_3), signals of other protons overlap with proton signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.5 (C=S), 142.0 (C=N), 139.2 (C), 136.2 (C), 136.0 (C), 135.8 (C), 128.7 (2CH), 128.5 (2CH), 126.7 (2CH), 125.0 (2CH), 53.8 (CHN), 31.5 (CH_2), 20.67 (CH_3), 20.66 (CH_3). Anal. Calcd for $C_{18}H_{23}N_5S$: C, 63.31; H, 6.79; N, 20.51. Found: C, 63.07; H, 7.13; N, 20.45.

*4.3.8. Hydrazone of 4-{[1-(4-methoxyphenyl)-3-(4-methylphenyl)-3-oxo]prop-1-yl}thiosemicarbazide (**7h**).* Compound **7h** (0.582 g, 89%) as a 88:12 mixture of geometric isomers was prepared from isothiocyanatoketone **4h** (0.571 g, 1.83 mmol) and $N_2H_4 \cdot H_2O$ (1.84 g, 36.8 mmol) in EtOH (8 mL) (reflux, 3 h) as described for **7a**. Two crystallization of the crude product from EtOH afforded a 97:3 mixture of isomers, and single crystallization from MeCN gave the only major isomer. Mp 100–103 °C (dec, EtOH); mp 99.5–102.5 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3375 (br m), 3310 (m), 3276 (m), 3197 (br s) (ν NH), 3081 (w), 3065 (w) (ν CH_{arom}), 1650 (m), 1631 (w) (ν C=N, δ NH_2), 1612 (s), 1587 (m) (ν CC_{arom}), 1541 (s) (thioamide-II), 1514 (s) (ν CC_{arom}), 1254 (s), 1034 (s) (ν C–O), 824 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.68 (1H, br s, N*H*NH_2), 8.18 (1H, br d, ^3J = 8.4 Hz, N*H*CH), 7.40–7.45 (2H, m, ArH), 7.22–7.28 (2H, m, ArH), 7.01–7.06 (2H, m, ArH), 6.78–6.84 (2H, m, ArH), 6.50 (2H, br s, NH_2N=C), 5.64 (1H, ddd, ^3J = 8.4, ^3J = 8.4, ^3J = 7.3 Hz, CHN), 4.46 (2H, br s, NH_2NH), 3.70 (3H, s, OCH_3), 3.23 (1H, dd, ^2J = 14.2, ^3J = 7.3 Hz, H_A in CH_2), 3.08 (1H, dd, ^2J = 14.2, ^3J = 8.4 Hz, H_B in CH_2), 2.25 (3H, s, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.58 (1H, br s, N*H*NH_2), 8.06 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.14–7.20 (2H, m, ArH), 7.05–7.10 (2H, m, ArH), 5.59 (2H, br s, NH_2N=C), 5.39 (1H, ddd, ^3J = 8.5, ^3J = 7.4, ^3J = 7.1 Hz, CHN), 3.72 (3H, s, OCH_3), 2.97 (1H, dd, ^2J = 14.5, ^3J = 7.4 Hz, H_A in CH_2), 2.90 (1H, dd, ^2J =

14.5, ^{3}J = 7.1 Hz, H_B in CH_2), 2.32 (3H, s, CH_3), signals of other protons overlap with proton signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.4 (C=S), 158.2 (C), 142.1 (C=N), 136.2 (C), 135.8 (C), 134.0 (C), 128.4 (2CH), 127.9 (2CH), 125.0 (2CH), 113.4 (2CH), 55.0 (OCH_3), 53.5 (CHN), 31.6 (CH_2), 20.6 (CH_3). Anal. Calcd for $C_{18}H_{23}N_5OS\cdot 0.15C_2H_5OH$: C, 60.32; H, 6.61; N, 19.22. Found: C, 59.92; H, 6.67; N, 19.35.[35]

*4.3.9. Hydrazone of 4-{[1-(3,4-dimethoxyphenyl)-3-(4-methylphenyl)-3-oxo]prop-1-yl}thiosemicarbazide (**7i**).* Compound **7i** (1.66 g, 92%) as a 83:17 mixture of geometric isomers was prepared from isothiocyanatoketone **4i** (1.59 g, 4.65 mmol) and $N_2H_4\cdot H_2O$ (4.69 g, 93.7 mmol) in EtOH (24 mL) (reflux, 3 h) as described for **7a**. After crystallization from EtOH the isomeric ratio changed to 88:12, respectively. Mp 131–133 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3332 (s), 3309 (s), 3199 (br s), 3133 (w) (ν NH), 3024 (w) (ν CH_{arom}), 1650 (m), 1626 (w) (ν C=N, δ NH_2), 1604 (w), 1591 (m) (ν CC_{arom}), 1534 (s) (thioamide-II), 1513 (s), 1496 (m) (ν CC_{arom}), 1257 (s), 1021 (s) (ν C–O), 854 (m), 819 (m) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.76 (1H, br s, N*H*NH_2), 8.18 (1H, br d, ^{3}J = 8.5 Hz, N*H*CH), 7.41–7.47 (2H, m, ArH), 7.01–7.07 (2H, m, ArH), 6.98–7.01 (1H, m, ArH), 6.75–6.82 (2H, m, ArH), 6.55 (2H, br s, NH_2N=C), 5.62 (1H, ddd, ^{3}J = 8.6, ^{3}J = 8.5, ^{3}J = 7.2 Hz, CHN), 4.49 (2H, br s, N*H*$_2$NH), 3.683 (3H, s, OCH_3), 3.680 (3H, s, OCH_3), 3.21 (1H, dd, ^{2}J = 14.2, ^{3}J = 7.2 Hz, H_A in CH_2), 3.14 (1H, dd, ^{2}J = 14.2, ^{3}J = 8.6 Hz, H_B in CH_2), 2.25 (3H, s, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.64 (1H, br s, N*H*NH_2), 8.09 (1H, br d, ^{3}J = 8.5 Hz, N*H*CH), 7.21–7.26 (2H, m, ArH), 7.06–7.11 (2H, m, ArH), 6.85–6.87 (1H, m, ArH), 6.81–6.85 (1H, m, ArH), 6.73–6.77 (1H, m, ArH, signals partly overlap with signals of aromatic protons of the major isomer), 5.62 (2H, br s, NH_2N=C), 5.38 (1H, ddd, ^{3}J = 8.5, ^{3}J = 7.4, ^{3}J = 7.2 Hz, CHN), 4.46 (2H, br s, N*H*$_2$NH), 3.71 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 2.99 (1H, dd, ^{2}J = 14.2, ^{3}J = 7.4 Hz, H_A in CH_2), 2.91 (1H, dd, ^{2}J = 14.2, ^{3}J = 7.2 Hz, H_B in CH_2), 2.32 (3H, s, CH_3); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.4 (C=S), 148.4 (C), 147.9 (C), 142.1 (C=N), 136.3 (C), 135.7 (C), 134.3 (C), 128.4 (2CH), 125.0 (2CH), 119.1 (CH), 111.5 (CH), 110.9 (CH), 55.48 (OCH_3), 55.46 (OCH_3), 53.8 (CHN), 31.4 (CH_2), 20.6 (CH_3). Anal. Calcd for $C_{19}H_{25}N_5O_2S$: C, 58.89; H, 6.50; N, 18.07. Found: C, 58.78; H, 6.62; N, 18.19.

*4.3.10. Hydrazone of 2-methyl-4-[(3-oxo-1,3-diphenyl)prop-1-yl]thiosemicarbazide (**7j**).* A solution of thiosemicarbazide **5c** (0.716 g, 2.28 mmol) and $N_2H_4\cdot H_2O$ (2.31 g, 46.2 mmol) in EtOH (18 mL) was stirred under reflux for 3 h, and the liquids were removed in vacuum (temperature of bath about 50–55 °C). The residue was co-evaporated with toluene (4 × 10 mL), the resulting oily solid was triturated upon cooling with H_2O (10 mL) and petroleum ether (10 mL) until crystallization was completed. The suspension was cooled. The precipitate was filtered, and washed with ice-cold H_2O, petroleum ether,

and dried to give product (0.698 g, 94%) as a 95:5 mixture of hydrazone **7j** (two geometric isomers in a ratio of 78:22) and hydrazone **7a**. Crystallization of the crude product from EtOH afforded practically pure hydrazone **7j** (two isomers, 98:2) containing only 1 mol% of hydrazone **7a** as an admixture. Mp 142–143.5 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3415 (m), 3279 (br s), 3171 (m) (ν NH), 3086 (w), 3062 (w), 3033 (w) (ν CH_{arom}), 1626 (s) (ν C=N, δ NH_2), 1584 (w), 1561 (w) (ν CC_{arom}), 1528 (s) (thioamide-II), 1495 (w) (ν CC_{arom}), 764 (m), 754 (m), 691 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.66 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.48–7.54 (2H, m, ArH), 7.29–7.35 (2H, m, ArH), 7.12–7.28 (6H, m, ArH), 6.67 (2H, br s, NH_2N=C), 5.62 (1H, ddd, ^3J = 8.5, ^3J = 8.0, ^3J = 7.7 Hz, CHN), 4.89 (2H, br s, NH_2N), 3.40 (3H, s, NCH_3), 3.27 (1H, dd, ^2J = 14.3, ^3J = 7.7 Hz, H_A in CH_2), 3.08 (1H, dd, ^2J = 14.3, ^3J = 8.0 Hz, H_B in CH_2); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.57 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.39–7.47 (2H, m, ArH), 5.67 (2H, br s, NH_2N=C), 5.38 (1H, ddd, ^3J = 8.5, ^3J = 7.6, ^3J = 6.8 Hz, CHN), 4.88 (2H, br s, NH_2N), 3.41 (3H, s, NCH_3), 2.96 (1H, dd, ^2J = 14.7, ^3J = 7.6 Hz, H_A in CH_2), 2.93 (1H, dd, ^2J = 14.7, ^3J = 6.8 Hz, H_B in CH_2), signals of other protons overlap with proton signals of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.1 (C=S), 142.4 (C), 141.7 (C=N), 139.0 (C), 128.1 (2CH), 127.8 (2CH), 126.9 (CH), 126.74 (2CH), 126.69 (CH), 125.0 (2CH), 55.3 (CHN), 42.4 (NCH_3), 31.6 (CH_2). Anal. Calcd for $C_{17}H_{21}N_5S$: C, 62.36; H, 6.46; N, 21.39. Found: C, 62.56; H, 6.60; N, 21.55.

*4.3.11. Hydrazone of 2-methyl-4-{[1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}thiosemicarbazide (**7k**).* The reaction of thiosemicarbazide **5d** (1.10 g, 3.37 mmol) with $N_2H_4 \cdot H_2O$ (3.41 g, 68.1 mmol) in EtOH (25 mL) (reflux, 3 h) to give product (1.11 g, 97%) as a 95:5 mixture of hydrazone **7k** (two geometric isomers in a ratio of 78:22) and hydrazone **7b** was performed as described for the synthesis of **7j**. Crystallization of the crude product from EtOH afforded practically pure hydrazone **7k** (two isomers, 99:1) containing only 2 mol% of hydrazone **7b** as an admixture. Mp 147.5–149.5 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3420 (m), 3284 (br s), 3175 (m), 3131 (w) (ν NH), 3088 (w), 3060 (w), 3021 (w) (ν CH_{arom}), 1625 (s) (ν C=N, δ NH_2), 1583 (m), 1560 (w) (ν CC_{arom}), 1526 (s) (thioamide-II), 1496 (w) (ν CC_{arom}), 826 (m), 762 (s), 694 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.59 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.50–7.56 (2H, m, ArH), 7.13–7.27 (5H, m, ArH), 7.02–7.08 (2H, m, ArH), 6.65 (2H, br s, NH_2N=C), 5.57 (1H, ddd, ^3J = 8.5, ^3J = 8.2, ^3J = 7.6 Hz, CHN), 4.88 (2H, br s, NH_2N), 3.40 (3H, s, NCH_3), 3.25 (1H, dd, ^2J = 14.2, ^3J = 7.6 Hz, H_A in CH_2), 3.07 (1H, dd, ^2J = 14.2, ^3J = 8.2 Hz, H_B in CH_2), 2.23 (3H, s, CH_3); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.48 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.39–7.47 (2H, m, ArH), 7.32–7.39 (1H, m, ArH), 5.64 (2H, br s, NH_2N=C), 5.32 (1H, ddd, ^3J = 8.5, ^3J = 7.7, ^3J = 6.8 Hz, CHN), 4.85 (2H, br s, NH_2N), 3.40 (3H, s, NCH_3), 2.95 (1H, dd, ^2J = 14.6, ^3J = 7.7 Hz, H_A in CH_2), 2.90 (1H, dd, ^2J = 14.6, ^3J = 6.8 Hz, H_B in CH_2), 2.25 (3H, s, CH_3), signals of other protons overlap with proton signals of

the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.1 (C=S), 141.7 (C=N), 139.3 (C), 139.0 (C), 136.0 (C), 128.6 (2CH), 127.8 (2CH), 126.69 (CH), 126.65 (2CH), 125.0 (2CH), 55.1 (CHN), 42.4 (NCH_3), 31.5 (CH_2), 20.7 (CH_3). Anal. Calcd for $C_{18}H_{23}N_5S$: C, 63.31; H, 6.79; N, 20.51. Found: C, 63.28; H, 7.05; N, 20.80.

4.4. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones 8a-l

*4.4.1. 5,7-Diphenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8a**). Method A*: A solution of hydrazone **7a** (1.18 g, 3.77 mmol) and TsOH·H_2O (0.794 g, 4.17 mmol) in EtOH (39 mL) was stirred under reflux for 1.5 h, and the solvent was removed in vacuum. The residue was triturated with saturated aqueous $NaHCO_3$ (10 mL) upon cooling until crystallization was completed, and the obtained suspension was cooled. The precipitate was filtered, washed with ice-cold H_2O, petroleum ether, and dried. The crude product was purified using column chromatography on aluminium oxide (20.49 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:3). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8a** (0.807 g, 76%) as a very light yellow solid. Analytically pure sample (white crystals) was obtained by crystallization from MeCN. Mp 168.5–170 °C (dec, MeCN) (lit.[8c] 166–168 °C); IR (Nujol) ν, cm^{-1}: 3361 (w), 3181 (br vs), 3089 (m) (ν NH), 3060 (w) (ν CH_{arom}), 1627 (m) (ν C=N), 1555 (s) (thioamide-II), 1180 (vs) (δ NH + ν CN), 766 (s), 697 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.86 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 9.05 (1H, br dd, ^3J = 4.9, ^4J = 2.0 Hz, $N_{(4)}H$), 7.35–7.41 (2H, m, ArH), 7.12–7.32 (8H, m, ArH), 4.96 (1H, ddd, ^3J = 6.2, ^3J = 4.9, ^3J = 2.7 Hz, H-5), 3.54 (1H, ddd, ^2J = 14.7, ^3J = 6.2, ^4J = 1.0 Hz, H_A-6), 3.24 (1H, dd, ^2J = 14.7, ^3J = 2.7 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.1 (C-3), 158.3 (C-7), 142.0 (C), 137.2 (C), 129.2 (CH), 128.1 (2CH), 128.0 (2CH), 127.2 (CH), 125.8 (4CH), 59.0 (C-5), 36.8 (C-6). Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 67.97; H, 5.60; N, 15.08.

Method B: A solution of thiosemicarbazide **5a** (0.594 g, 1.98 mmol) and AcOH (0.47 mL, 8.12 mmol) in EtOH (20 mL) was stirred under reflux for 3 h, and the solvent was removed in vacuum. The residue was triturated with saturated aqueous $NaHCO_3$ (5 mL) upon cooling until crystallization was completed, and the obtained suspension was cooled. The precipitate was filtered, washed with ice-cold H_2O, petroleum ether, and dried. The crude product was purified using column chromatography on silica gel (17.06 g) eluting with petroleum ether–$CHCl_3$ (from 3:2 to 2:3). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with ether, the obtained suspension was cooled (–15 °C), the precipitate was filtered on cold (–15 °C) filter , washed with cold (–15 °C) ether (3 × 5 mL), and dried to give

triazepine **8a** (0.461 g, 83%) as a very light yellow solid. Analytically pure sample (white crystals) was obtained by crystallization from MeCN.

*4.4.2. 5-(4-Methylphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8b**).* Compound **8b** (0.837 g, 76%, very light yellow solid) was obtained from hydrazone **7b** (1.22 g, 3.72 mmol) and TsOH·H_2O (0.781 g, 4.11 mmol) in EtOH (39 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (20.03 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:4). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8b**. The analytically pure sample (very light yellow solid) was obtained by crystallization from MeCN. Mp 200.5–202 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3195 (br vs), 3104 (m) (ν NH), 3057 (w), 3022 (w) (ν CH_{arom}), 1619 (m) (ν C=N), 1573 (m) (ν CC_{arom}), 1548 (s) (thioamide-II), 1513 (m) (ν CC_{arom}), 1178 (vs) (δ NH + ν CN), 816 (m), 766 (s), 702 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.87 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 9.06 (1H, br dd, ^3J = 5.0, ^4J = 2.0 Hz, $N_{(4)}H$), 7.37–7.44 (2H, m, ArH), 7.22–7.34 (3H, m, ArH), 7.03–7.13 (4H, m, ArH), 4.90 (1H, ddd, ^3J = 6.2, ^3J = 5.0, ^3J = 2.6 Hz, H-5), 3.53 (1H, ddd, ^2J = 14.8, ^3J = 6.2, ^4J = 0.9 Hz, H_A-6), 3.20 (1H, dd, ^2J = 14.8, ^3J = 2.6 Hz, H_B-6), 2.19 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.0 (C-3), 158.0 (C-7), 139.1 (C), 137.3 (C), 136.3 (C), 129.3 (CH), 128.7 (2CH), 128.2 (2CH), 125.9 (2CH), 125.8 (2CH), 58.7 (C-5), 36.9 (C-6), 20.6 (CH_3). Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.20; H, 6.13; N, 14.52.

*4.4.3. 5-(4-Methoxyphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8c**).* Compound **8c** (0.855 g, 75%, very light yellow solid) was obtained from hydrazone **7b** (1.26 g, 3.67 mmol) and TsOH·H_2O (0.770 g, 4.05 mmol) in EtOH (37 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (33.26 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:3). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8c**. The analytically pure sample (white solid) was obtained by crystallization from EtOAc. Mp 166–167 °C (dec, AcOEt); IR (Nujol) ν, cm^{-1}: 3183 (br vs), 3101 (m) (ν NH), 1613 (m) (ν C=N), 1578 (s) (thioamide-II), 1511 (s), 1487 (m) (ν CC_{arom}), 1254 (s) (ν C–O), 1177 (s) (δ NH + ν CN), 1034 (m) (ν C–O), 828 (m), 768 (s), 699 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.87 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 9.04 (1H, br dd, ^3J = 5.0, ^4J = 2.0 Hz, $N_{(4)}H$), 7.38–7.44 (2H, m, ArH), 7.22–7.34 (3H, m, ArH), 7.10–7.16 (2H, m, ArH), 6.78–6.85 (2H, m, ArH), 4.89 (1H, ddd, ^3J = 6.3, ^3J = 5.0, ^3J = 2.6

Hz, H-5), 3.66 (3H, s, OCH_3), 3.50 (1H, ddd, ^2J = 14.7, ^3J = 6.3, ^4J = 0.9 Hz, H_A-6), 3.20 (1H, dd, ^2J = 14.7, ^3J = 2.6 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 176.9 (C-3), 158.4 (C), 158.2 (C-7), 137.3 (C), 134.2 (C), 129.3 (CH), 128.2 (2CH), 127.1 (2CH), 126.0 (2CH), 113.6 (2CH), 58.5 (C-5), 55.0 (OCH_3), 37.0 (C-6). Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.58; H, 5.77; N, 13.43.

*4.4.4. 5-(3,4-Dimethoxyphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8d**).* Compound **8d** (0.455 g, 73%, very light yellow solid) was obtained from hydrazone **7d** (0.689 g, 1.82 mmol) and TsOH·H_2O (0.399 g, 2.10 mmol) in EtOH (20 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (20.38 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:2). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8d**. The analytically pure sample (white solid) as a strong solvate with benzene (**8d**/C_6H_6 = 2:1) was obtained after crystallization from C_6H_6.[36] To remove benzene the solid was co-evaporated with $CHCl_3$ (3 × 5 mL), the obtained foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried in high vacuum. Mp 90–91.5 °C; IR (Nujol) ν, cm^{-1}: 3182 (br vs) (ν NH), 3084 (w), 3061 (w) (ν CH_{arom}), 1624 (m) (ν C=N), 1594 (m) (CC_{arom}), 1550 (s) (thioamide-II), 1516 (s) (ν CC_{arom}), 1263 (s) (ν C–O), 1178 (s) (δ NH + ν CN), 1024 (s) (ν C–O), 807 (m), 764 (s), 694 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.86 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 9.04 (1H, br dd, ^3J = 5.0, ^4J = 2.0 Hz, $N_{(4)}H$), 7.43–7.50 (2H, m, ArH), 7.24–7.35 (3H, m, ArH), 6.81–6.87 (2H, m, ArH), 6.65–6.70 (1H, m, ArH), 4.87 (1H, ddd, ^3J = 6.4, ^3J = 5.0, ^3J = 2.6 Hz, H-5), 3.65 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.61 (1H, dd, ^2J = 14.7, ^3J = 6.4 Hz, H_A-6, signals partly overlap with signals of the OCH_3 groups), 3.18 (1H, dd, ^2J = 14.7, ^3J = 2.6 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.0 (C-3), 158.2 (C-7), 148.4 (C), 147.9 (C), 137.3 (C), 134.4 (C), 129.3 (CH), 128.1 (2CH), 125.9 (2CH), 118.1 (CH), 111.5 (CH), 110.2 (CH), 58.6 (C-5), 55.5 (OCH_3), 55.4 (OCH_3), 36.6 (C-6). Anal. Calcd for $C_{18}H_{19}N_3O_2S·0.05CHCl_3$: C, 62.41; H, 5.53; N, 12.10. Found: C, 62.18; H, 5.74; N, 12.21.[37]

*4.4.5. 5-(4-tert-Butylphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8e**).* Compound **8e** (0.882 g, 78%) was obtained from hydrazone **7e** (1.24 g, 3.35 mmol) and TsOH·H_2O (0.711 g, 3.74 mmol) in EtOH (35 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (34.85 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 0:1). The main fraction was concentrated. The residue was dried in vacuum (water pump), triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether,

and dried to give triazepine **8e**. Mp 224–225 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3331 (s), 3206 (br s), 3062 (m) (ν NH), 1625 (m) (ν C=N), 1596 (w), 1575 (w) (ν CC_{arom}), 1552 (s) (thioamide-II), 1511 (w) (ν CC_{arom}), 1182 (vs) (δ NH + ν CN), 832 (m), 763 (m), 693 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.86 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}$H), 9.00 (1H, br dd, ^3J = 4.8, ^4J = 2.0 Hz, $N_{(4)}$H), 7.20–7.38 (7H, m, ArH), 7.10–7.16 (2H, m, ArH), 4.90 (1H, ddd, ^3J = 6.4, ^3J = 4.8, ^3J = 2.7 Hz, H-5), 3.45 (1H, ddd, ^2J = 14.7, ^3J = 6.4, ^4J = 0.9 Hz, H_A-6), 3.23 (1H, dd, ^2J = 14.7, ^3J = 2.7 Hz, H_B-6), 1.19 (9H, s, 3×CH_3 in *t*-Bu); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.1 (C-3), 158.8 (C-7), 149.8 (C), 139.2 (C), 137.3 (C), 129.3 (CH), 128.1 (2CH), 126.0 (2CH), 125.6 (2CH), 124.9 (2CH), 58.9 (C-5), 37.1 (C-6), 34.1 (*C*Me_3), 31.0 (3×CH_3 in *t*-Bu). Anal. Calcd for $C_{20}H_{23}N_3S$: C, 71.18; H, 6.87; N, 12.45. Found: C, 71.12; H, 6.92; N, 12.61.

*4.4.6. 7-(4-Methylphenyl)-5-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8f**).* Compound **8f** (0.994 g, 81%, very light yellow solid) was obtained from hydrazone **7f** (1.36 g, 4.16 mmol) and TsOH·H_2O (0.884 g,4.65 mmol) in EtOH (42 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (42.86 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:5). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8d**. Analytically pure sample (very light yellow solid) was obtained by crystallization from MeCN. Mp 189.5–191 °C (MeCN); IR (Nujol) ν, cm^{-1}: 3407 (s), 3178 (br s), 3103 (br s) (ν NH), 3053 (w) (ν CH_{arom}), 1622 (w) (ν C=N), 1604 (m) (ν CC_{arom}), 1571 (s) (thioamide-II), 1507 (w) (ν CC_{arom}), 1179 (vs) (δ NH + ν CN), 817 (s), 759 (s), 697 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.84 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}$H), 9.02 (1H, br dd, ^3J = 4.9, ^4J = 2.0 Hz, $N_{(4)}$H), 7.12–7.31 (7H, m, ArH), 7.01–7.07 (2H, m, ArH), 4.94 (1H, ddd, ^3J = 6.3, ^3J = 4.9, ^3J = 2.7 Hz, H-5), 3.51 (1H, ddd, ^2J = 14.6, ^3J = 6.3, ^4J = 1.0 Hz, H_A-6), 3.21 (1H, dd, ^2J = 14.6, ^3J = 2.7 Hz, H_B-6), 2.23 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.0 (C-3), 158.5 (C-7), 142.1 (C), 139.0 (C), 134.3 (C), 128.7 (2CH), 128.2 (2CH), 127.2 (CH), 125.9 (2CH), 125.8 (2CH), 59.2 (C-5), 36.6 (C-6), 20.7 (CH_3). Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.01; H, 6.12; N, 14.46.

4.4.7. 5,7-Di(4-methylphenyl)-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione (**8g**). *Method A*: Compound **8g** (0.885 g, 76%, light yellow solid) was obtained from hydrazone **7g** (1.29 g, 3.77 mmol) and TsOH·H_2O (0.794 g, 4.17 mmol) in EtOH (39 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (30.66 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:3). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with

H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8g**. Analytically pure sample (very light yellow solid) was obtained by crystallization from MeCN. Mp 192.5–194 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3388 (s), 3185 (br s), 3097 (br m) (ν NH), 3045 (w) (ν CH_{arom}), 1618 (w) (ν C=N), 1604 (m) (ν CC_{arom}), 1570 (s) (thioamide-II), 1512 (m) (ν CC_{arom}), 1173 (vs) (δ NH + ν CN), 816 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.81 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 9.00 (1H, br dd, ^3J = 5.0, ^4J = 2.0 Hz, $N_{(4)}H$), 7.29–7.34 (2H, m, ArH), 7.03–7.12 (6H, m, ArH), 4.88 (1H, ddd, ^3J = 6.3, ^3J = 5.0, ^3J = 2.7 Hz, H-5), 3.50 (1H, ddd, ^2J = 14.7, ^3J = 6.3, ^4J = 0.9 Hz, H_A-6), 3.17 (1H, dd, ^2J = 14.7, ^3J = 2.7 Hz, H_B-6), 2.24 (3H, s, CH_3), 2.19 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 176.9 (C-3), 158.1 (C-7), 139.2 (C), 139.0 (C), 136.3 (C), 134.5 (C), 128.8 (2CH), 128.7 (2CH), 125.9 (2CH), 125.8 (2CH), 58.8 (C-5), 36.6 (C-6), 20.7 (CH_3 in 7-Ar), 20.6 (CH_3 in 5-Ar). Anal. Calcd for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58. Found: C, 69.75; H, 6.25; N, 13.78.

Method B: Compound **8g** (0.619 g, 79%, very light yellow solid) was obtained from semicarbazide **5b** (0.830 g, 2.54 mmol) and AcOH (0.60 mL, 10.48 mmol) in EtOH (35 mL) (reflux, 3 h) as described for **8a** in Method B. The crude product was purified using column chromatography on silica gel (30.29 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:2). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with ether, the obtained suspension was cooled (–15 °C), the precipitate was filtered on cold (–15 °C) filter , washed with cold (–15 °C) ether (3 × 5 mL), and dried to give triazepine **8g**.

*4.4.8. 7-(4-Methylphenyl)-5-(4-methoxyphenyl)-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8h**).* Compound **8h** (0.851 g, 81%, very light yellow solid) was obtained from hydrazone **7h** (1.16 g, 3.23 mmol) and TsOH·H_2O (0.687 g, 3.61 mmol) in EtOH (34 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (43.21 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:4). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8h**.[38] Mp 88–91 °C; IR (Nujol) ν, cm^{-1}: 3354 (w), 3178 (br s) (ν NH), 3082 (w), 3067 (w) (ν CH_{arom}), 1609 (s) (ν C=N), 1566 (w), 1549 (s) (thioamide-II), 1512 (s) (ν CC_{arom}), 1251 (s) (ν C–O), 1176 (vs) (δ NH + ν CN), 1034 (s) (ν C–O), 822 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.81 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 8.97 (1H, br dd, ^3J = 4.8, ^4J = 2.0 Hz, $N_{(4)}H$), 7.29–7.35 (2H, m, ArH), 7.04–7.16 (4H, m, ArH), 6.78–6.85 (2H, m, ArH), 4.87 (1H, ddd, ^3J = 6.3, ^3J = 4.8, ^3J = 2.6 Hz, H-5), 3.66 (3H, s, OCH_3), 3.47 (1H, ddd, ^2J = 14.7, ^3J = 6.3, ^4J = 0.9 Hz, H_A-6), 3.16 (1H, dd, ^2J = 14.7, ^3J = 2.6 Hz, H_B-6), 2.24 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 176.8 (C-3), 158.3 (C), 158.3 (C-7), 139.0 (C), 134.4 (C), 134.2 (C), 128.8 (2CH), 127.1 (2CH), 125.9 (2CH), 113.6

(2CH), 58.6 (C-5), 55.0 (OCH_3), 36.8 (C-6), 20.7 (CH_3). Anal. Calcd for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.29; H, 5.93; N, 12.83.

*4.4.9. 7-(4-Methylphenyl)-5-(3,4-dimethoxyphenyl)-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8i**).* Compound **8i** (1.01 g, 82%, very light yellow solid) was obtained from hydrazone **7i** (1.34 g, 3.45 mmol) and TsOH·H_2O (0.729 g, 3.83 mmol) in EtOH (35 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on aluminium oxide (43.03 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:4). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The resulting foam was triturated with H_2O, the obtained precipitate was filtered, washed with H_2O, petroleum ether, and dried to give triazepine **8i**. Analytically pure sample (white crystals) was obtained by crystallization from petroleum ether–EtOAc (1:3, v/v). Mp 159–160.5 °C (dec, AcOEt–petroleum ether, 3:1); IR (Nujol) ν, cm^{-1}: 3306 (br vs) (ν NH), 3061 (w), 3022 (w) (ν CH_{arom}), 1600 (m) (ν C=N, ν CC_{arom}), 1564 (w) (ν CC_{arom}), 1531 (sh), 1518 (s) (thioamide-II, ν CC_{arom}), 1256 (s) (ν C–O), 1173 (vs) (δ NH + ν CN), 1022 (s) (ν C–O), 848 (s), 814 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.80 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 8.98 (1H, br dd, ^3J = 4.9, ^4J = 2.0 Hz, $N_{(4)}H$), 7.35–7.41 (2H, m, ArH), 7.06–7.11 (2H, m, ArH), 6.86–6.88 (1H, m, ArH), 6.80–6.85 (1H, m, ArH), 6.64–6.70 (1H, m, ArH), 4.85 (1H, ddd, ^3J = 6.3, ^3J = 4.9, ^3J = 2.6 Hz, H-5), 3.65 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.58 (1H, dd, ^2J = 14.7, ^3J = 6.3 Hz, H_A-6), 3.15 (1H, dd, ^2J = 14.7, ^3J = 2.6 Hz, H_B-6), 2.25 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 176.9 (C-3), 158.3 (C-7), 148.3 (C), 147.9 (C), 139.1 (C), 134.5 (C), 134.4 (C), 128.8 (2CH), 125.9 (2CH), 118.1 (CH), 111.3 (CH), 110.1 (CH), 58.7 (C-5), 55.43 (OCH_3), 55.41 (OCH_3), 36.4 (C-6), 20.8 (CH_3). Anal. Calcd for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.96; N, 11.82. Found: C, 64.12; H, 6.10; N, 11.89.

*4.4.11. 2-Methyl-5,7-diphenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8j**). Method A*: Compound **8j** (0.690 g, 72%, very light yellow solid) was obtained from hydrazone **7j** (1.07 g, 3.28 mmol) and TsOH·H_2O (0.693 g, 3.65 mmol) in MeCN (33 mL) (reflux, 1.5 h) as described for **7a** in Method A. The crude product was purified using column chromatography on aluminium oxide (44.40 g) eluting with petroleum ether–$CHCl_3$ (from 12:1 to 4:1). The main fraction was concentrated. The residue was dried in vacuum (water pump), and triturated with ether. The obtained suspension was cooled (–15 °C), the precipitate was filtered on cold (–15 °C) filter, washed with cold (–15 °C) ether (3 × 5 mL), and dried to give triazepine **8j**. Analytically pure sample (white crystals) was obtained by crystallization from EtOH. Mp 176.5–177.5 °C (EtOH); IR (Nujol) ν, cm^{-1}: 3216 (br vs) (ν NH), 3083 (w), 3060 (w), 3047 (w) (ν CH_{arom}), 1604 (w) (ν C=N), 1572 (w) (ν CC_{arom}), 1516 (s) (thioamide-II), 1493 (w) (ν CC_{arom}), 1274 (s) (δ NH + ν CN), 760 (s), 698 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz,

DMSO-d_6) δ: 8.18 (1H, br d, ^3J = 2.5 Hz, NH), 7.66–7.72 (2H, m, ArH), 7.28–7.48 (7H, m, ArH), 7.20–7.27 (1H, m, ArH), 4.94 (1H, ddd, ^3J = 9.0, ^3J = 4.4, ^3J = 2.5 Hz, H-5), 3.64 (3H, s, NCH_3), 3.33 (1H, ddd, ^2J = 13.6, ^3J = 4.4, ^4J = 0.9 Hz, H_A-6), 3.25 (1H, dd, ^2J = 13.6, ^3J = 9.0 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 179.9 (C-3), 165.3 (C-7), 143.3 (C), 135.0 (C), 130.6 (CH), 128.5 (2CH), 128.3 (2CH), 127.5 (CH), 126.6 (2CH), 126.1 (2CH), 63.6 (C-5), 45.2 (CH_3), 35.1 (C-6). Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 68.98; H, 5.91; N, 13.93.

Method B: Compound **8j** (0.486 g, 89%, white solid) was obtained from thiosemicarbazide **5c** (0.606 g, 1.93 mmol) and AcOH (1.15 mL, 20.09 mmol) in EtOH (21 mL) (reflux, 8 h) as described for **8a** in Method B. The crude product was purified using column chromatography on silica gel (20.12 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 2:1). The main fraction was concentrated. The residue was dried in vacuum (water pump), and triturated with ether. The obtained suspension was cooled (–15 °C), the precipitate was filtered on cold (–15 °C) filter, washed with cold (–15 °C) ether (3 × 5 mL), and dried to give triazepine **8j**.

*4.4.12. 2-Methyl-5-(4-methylphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8k**).* *Method A*: Compound **8k** (0.342 g, 48%, light yellow solid) was obtained from hydrazone **7k** (0.785 g, 2.30 mmol) and TsOH·H_2O (0.489 g, 2.57 mmol) in MeCN (25 mL) (reflux, 1.5 h) as described for **8a** in Method A. The crude product was purified using column chromatography on silica gel (20.41 g) eluting with petroleum ether–$CHCl_3$ (from 3:2 to 2:1). The main fraction was concentrated. The residue was dried in vacuum (water pump)) until the stable foam formed. The foam was dissolved in EtOAc (3 mL) upon heating, then petroleum ether (9 mL) was added. The solution was cooled (5 °C), crystallization was caused by triturating with spatula, and the obtained suspension was left overnight at 5 °C. The precipitated was filtered, washed with cold petroleum ether–EtOAc (3:1, v/v) (3 × 3 mL), and dried to give triazepine **5b**. The analytically pure sample (very light yellow solid) was obtained by crystallization from EtOH. Mp 115–116 °C (EtOH); IR (Nujol) ν, cm^{-1}: 3368 (s) (ν NH), 3048 (w), 3029 (w) (ν CH_{arom}), 1609 (m) (ν C=N), 1571 (m), 1509 (w) (ν CC_{arom}), 1488 (s) (thioamide-II), 1249 (s) (δ NH + ν CN), 819 (s), 764 (s), 693 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.11 (1H, br d, ^3J = 2.4 Hz, NH), 7.68–7.74 (2H, m, ArH), 7.35–7.49 (3H, m, ArH), 7.24–7.30 (2H, m, ArH), 7.10–7.16 (2H, m, ArH), 4.88 (1H, ddd, ^3J = 9.0, ^3J = 4.6, ^3J = 2.4 Hz, H-5), 3.63 (3H, s, NCH_3), 3.28 (1H, ddd, ^2J = 13.6, ^3J = 4.6, ^4J = 1.0 Hz, H_A-6), 3.23 (1H, dd, ^2J = 13.6, ^3J = 9.0 Hz, H_B-6), 2.25 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 179.9 (C-3), 165.1 (C-7), 140.4 (C), 136.6 (C), 135.0 (C), 130.6 (CH), 128.8 (2CH), 128.5 (2CH), 126.6 (2CH), 126.0 (2CH), 63.4 (C-5), 45.2 (NCH_3), 35.2 (C-6), 20.7 (CH_3). Anal. Calcd for $C_{18}H_{19}N_3S$: C, 69.87; H, 6.19; N, 13.58. Found: C, 69.91; H, 6.23; N, 13.38.

Method B: Compound **8k** (0.501 g, 82%, very light yellow solid) was obtained from thiosemicarbazide **5d** (0.647 g, 1.98 mmol) and AcOH (1.20 mL, 20.97 mmol) in EtOH (22 mL) (reflux, 8 h) as described for **8a** in Method B. The crude product was purified using column chromatography on silica gel (20.12 g) eluting with petroleum ether–$CHCl_3$ (from 60:25 to 60:30). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The obtained foam was dissolved in EtOH (3 mL) upon heating. The solution was cooled to room temperature, crystallization was caused by triturating with spatula, and the solvent was removed in vacuum. The residual solid was dried in vacuum (water pump), and triturated with petroleum ether. The precipitate was filtered, washed with petroleum ether (4 × 3 mL), and dried to give triazepine **8k**.

*4.4.13. 2-Methyl-5,7-di(4-methylphenyl)-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**8l**).* Compound **8l** (0.679 g, 81%, very light yellow solid) was obtained from semicarbazide **5e** (0.881 g, 2.58 mmol) and AcOH (1.50 mL, 26.21 mmol) in EtOH (25 mL) (reflux, 8 h) as described for **8a** in Method B. The crude product was purified using column chromatography on silica gel (32.41 g) eluting with petroleum ether–$CHCl_3$ (from 60:25 to 60:30). The main fraction was concentrated. The residue was dried in vacuum (water pump) until the stable foam formed. The obtained foam was dissolved in EtOH (3 mL) upon heating. The solution was cooled to room temperature, crystallization was caused by triturating with spatula, and the solvent was removed in vacuum. The residual solid was dried in vacuum (water pump), and triturated with petroleum ether. The precipitate was filtered, washed with petroleum ether (4 × 3 mL), and dried to give triazepine **8l**. The analytically pure sample (white crystals) was obtained by crystallization from EtOH. Mp 140.5–141.5 °C (EtOH); IR (Nujol) ν, cm^{-1}: 3381 (w), 3357 (s) (ν NH), 1611 (sh) (ν C=N), 1601 (m), 1558 (w), 1509 (sh) (ν CC_{arom}), 1492 (s) (thioamide-II), 1256 (s) (δ NH + ν CN), 817 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.01 (1H, br d, ^3J = 2.2 Hz, NH), 7.59–7.64 (2H, m, ArH), 7.25–7.30 (2H, m, ArH), 7.18–7.23 (2H, m, ArH), 7.11–7.17 (2H, m, ArH), 4.84 (1H, ddd, ^3J = 9.3, ^3J = 4.6, ^3J = 2.2 Hz, H-5), 3.62 (3H, s, NCH_3), 3.25 (1H, ddd, ^2J = 13.5, ^3J = 4.6, ^4J = 1.0 Hz, H_A-6), 3.19 (1H, dd, ^2J = 13.5, ^3J = 9.3 Hz, H_B-6), 2.32 (3H, s, CH_3), 2.26 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 179.9 (C-3), 165.1 (C-7), 140.52 (C), 140.50 (C), 136.6 (C), 132.1 (C), 129.1 (2CH), 128.8 (2CH), 126.5 (2CH), 126.0 (2CH), 63.5 (C-5), 45.1 (NCH_3), 35.0 (C-6), 20.9 (CH_3), 20.6 (CH_3). Anal. Calcd for $C_{19}H_{21}N_3S$: C, 70.55; H, 6.54; N, 12.99. Found: C, 70.29; H, 6.83; N, 13.09.

4.5. Synthesis of 5-unsubstituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione 15

*4.5.1. 4-[(3-Oxo-3-phenyl)prop-1-yl]thiosemicarbazide (**12**).* To a cooled in an ice-bath, stirred solution of isothiocyanatoketone **11**[25] (2.22 g, 79 mol% mixture with Ph_3PS, 8.24 mmol) in MeCN (9 mL) was

added a solution of $N_2H_4 \cdot H_2O$ (0.522 g, 10.42 mmol) in MeCN (3 mL) and the resulting suspension was stirred in ice-bath for 10 min. The reaction mixture was cooled (–15 °C), the precipitate was filtered, washed with cold (–15 °C) MeCN (3 × 5 mL), cold (–15 °C) ether (2 × 5 mL), and dried to give product (1.84 g, 100%) as a 98:2 mixture of thiosemicarbazide **12** and 1-amino-6-hydroxy-6-phenylhexahydropyrimidine-2-thione (**13**). After crystallization from MeCN the isomeric composition of the product did not change. Mp 168–169 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3326 (s), 3279 (s), 3174 (sh), 3155 (br s) (ν NH), 3084 (w), 3065 (w), 3057 (w) (ν CH_{arom}), 1682 (s) (ν C=O), 1640 (s) (δ NH_2), 1594 (m), 1578 (sh) (ν CC_{arom}), 1562 (s) (thioamide-II), 1505 (m) (ν CC_{arom}), 763 (s), 688 (s) (δ CH_{arom}); ^{1}H NMR of thiosemicarbazide **12** (300.13 MHz, DMSO-d_6) δ: 8.71 (1H, br s, N*H*NH_2), 7.96–8.02 (2H, m, ArH), ≈7.96 (1H, br unresolved t, N*H*CH_2), 7.61–7.68 (2H, m, ArH), 7.49–7.57 (2H, m, ArH), 4.46 (2H, br s, NH_2), 3.81 (2H, dt, ^3J = 6.7, ^3J = 6.0 Hz, NCH_2), 3.32 (2H, t, ^3J = 6.7 Hz, CH_2C=O); ^{1}H NMR of pyrimidine **13** (300.13 MHz, DMSO-d_6) δ: 8.44 (1H, br s, $N_{(3)}H$), 7.25–7.39 (5H, m, ArH), 6.70 (1H, s, OH), 4.73 (2H, br s, NH_2), signals of other protons overlap with proton signals of the acyclic isomer; ^{13}C NMR of thiosemicarbazide **12** (75.48 MHz, DMSO-d_6) δ: 199.2 (C=O), 181.0 (C=S), 136.4 (C), 133.4 (CH), 128.8 (2CH), 127.9 (2CH), 38.4, 38.3 (CH_2CH_2). Anal. Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82. Found: C, 53.72; H, 5.91; N, 18.94.

*4.5.2. Hydrazone of 4-[(3-oxo-3-phenyl)prop-1-yl]thiosemicarbazide (**14**).* Compound **14** (0.529 g, 90%) as a 92:8 mixture of geometric isomers was prepared from thiosemicarbazide **12** (0.553 g, 2.48 mmol) and $N_2H_4 \cdot H_2O$ (1.23 g, 24.5 mmol) in EtOH (17 mL) (reflux, 6 h 20 min) as described for **7j**. After crystallization from MeCN the isomeric ratio changed to 97:3, respectively. Mp 131.5–132.5 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3393 (m), 3281 (sh), 3214 (br s), 3195 (br s) (ν NH), 3079 (w), 3060 (w), 3037 (w), 3017 (w) (ν CH_{arom}), 1627 (s) (ν C=N, δ NH_2), 1591 (w) (ν CC_{arom}), 1557 (br s) (thioamide-II), 1500 (s) (ν CC_{arom}), 758 (s), 690 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.77 (1H, br s, N*H*NH_2), 8.21 (1H, br unresolved t, ^3J ≈ 6.2 Hz, N*H*CH), 7.72–7.78 (2H, m, ArH), 7.28–7.35 (2H, m, ArH), 7.19–7.26 (1H, m, ArH), 6.84 (2H, br s, NH_2N=C), 4.51 (2H, br s, N*H*$_2$NH), 3.49–3.59 (2H, m, CH_2N), 2.76–2.85 (2H, m, CH_2C=N); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 8.60 (1H, br s, N*H*NH_2), 7.43–7.50 (2H, m, ArH), 5.74 (2H, br s, NH_2N=C), 4.42 (2H, br s, N*H*$_2$NH), 3.62 (2H, dt, ^3J = 7.0, ^3J = 6.1 Hz, CH_2N), 2.63 (2H, t, ^3J = 7.0 Hz, CH_2C=N), signals of other protons overlap with signals of analogous protons of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.9 (C=S), 141.2 (C=N), 138.9 (C), 128.1 (2CH), 126.9 (CH), 124.5 (2CH), 38.5 (CH_2N), 26.0 (*C*H_2C=N). Anal. Calcd for $C_{10}H_{15}N_5S$: C, 50.61; H, 6.37; N, 29.51. Found: C, 50.61; H, 6.57; N, 29.62.

*4.5.3. 7-Phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-thione (**15**).* Compound **15** (0.616 g, 74%, very light yellow solid) was obtained from semicarbazide **12** (0.906 g, 4.06 mmol) and AcOH (0.95 mL, 16.60 mmol) in EtOH (40 mL) (reflux, 3 h) as described for **8a** in Method B. The crude product was purified using column chromatography on silica gel (31.24 g) eluting with petroleum ether–$CHCl_3$ (from 1:1 to 1:3). The main fraction was concentrated. The residue was dried in vacuum (water pump), the resulting solid was triturated with ether, the obtained suspension was cooled (–15 °C), the precipitate was filtered on cold (–15 °C) filter, washed with cold (–15 °C) ether (3 × 5 mL), and dried to give triazepine **15**. Analytically pure sample (white crystals) was obtained by crystallization from MeCN. Mp 152.5–153.5 °C (MeCN); IR (Nujol) ν, cm^{-1}: 3374 (s), 3168 (br s), 3115 (m), 3081 (m) (ν NH), 3060 (w) (ν CH_{arom}), 1625 (m) (ν C=N), 1577 (s) (thioamide-II), 1504 (m), 1486 (m) (ν CC_{arom}), 1175 (vs) (δ NH + ν CN), 768 (s), 695 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.63 (1H, br d, ^4J = 2.3 Hz, $N_{(2)}H$), 8.95 (1H, br dt, ^3J = 4.3, ^4J = 2.3 Hz, $N_{(4)}H$), 7.64–7.72 (2H, m, ArH), 7.35–7.45 (3H, m, ArH), 3.36–3.42 (2H, m, H-5), 3.04–3.09 (2H, m, H-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 178.3 (C-3), 156.6 (C-7), 137.7 (C), 129.3 (CH), 128.3 (2CH), 126.0 (2CH), 43.1 (C-5), 31.6 (C-6). Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47. Found: C, 58.48; H, 5.52; N, 20.54.

4.6. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones 16a-e

*4.6.1. 5,7-Diphenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**16a**).* To a stirred solution of KOH (0.195 g, 3.48 mmol) in H_2O (0.7 mL) were added triazepinethione **8a** (0.193 g, 0.69 mmol) and EtOH (3.5 mL). The resulting suspension was cooled (10–15 °C, cold water), H_2O_2 (0.49 mL, 7.11 mmol; d = 1.175 g/mL, 43%) was added over 1 min and cooling was removed. The reaction mixture was stirred at room temperature for 1.5 h, AcOH (0.18 mL, 3.06 mmol) was added, and the solvent was removed under vacuum (temperature of bath below 35 °C). To the residue was added saturated aqueous $NaHCO_3$ (3 mL), and the obtained suspension was cooled. The precipitate was filtered, washed with ice cold H_2O, petroleum ether, and dried to give triazepinone **16a** (0.162 g, 89%). Mp 204–205 °C (EtOH). ^{1}H and ^{13}C NMR spectra of **16a** were identical to those in the literature.[13]

*4.6.2. 5-(4-Methylphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**16b**).* Compound **16b** (0.232 g, 87%) was obtained from triazepinethione **8b** (0.264 g, 0.89 mmol), KOH (0.247 g, 4.40 mmol) and H_2O_2 (0.64 mL, 9.19 mmol; d = 1.175 g/mL, 43%) in EtOH (4.5 mL) and H_2O (1 mL) (rt, 2 h), then AcOH (0.23 mL, 4.02 mmol) as described for **16a**. Mp 189–191 °C (EtOH). ^{1}H and ^{13}C NMR spectra of **16b** were identical to those in the literature.[13]

*4.6.3. 5-(4-Methoxyphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**16c**).* Compound **16c** (0.258 g, 88%) was obtained from triazepinethione **8c** (0.310 g, 0.99 mmol), KOH (0.284 g, 5.05 mmol) and H_2O_2 (0.70 mL, 10.05 mmol; d = 1.175 g/mL, 43%) in EtOH (5 mL) and H_2O (1 mL) (rt, 2 h), then AcOH (0.22 mL, 3.84 mmol) as described for **16a**. Mp 188.5–189.5 °C (dec, MeCN); IR (Nujol) ν, cm^{-1}: 3346 (w), 3240 (br s), 3226 (br s), 3100 (br s) (ν NH), 3054 (w), 3029 (w), 3000 (w) (ν CH_{arom}), 1685 (s) (amide-I), 1642 (m) (ν C=N), 1613 (m), 1585 (m), 1511 (s) (ν CC_{arom}), 1251 (s), 1035 (m) (ν C–O), 823 (s), 766 (s), 707 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.54 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 7.19–7.47 (8H, m, ArH and $N_{(4)}H$), 6.81–6.87 (2H, m, ArH), 4.74 (1H, ddd, ^3J = 7.0, ^3J = 4.0, ^3J = 3.1 Hz, H-5), 3.31 (1H, dd, ^2J = 14.4, ^3J = 7.0 Hz, H_A-6), 3.14 (1H, dd, ^2J = 14.4, ^3J = 3.1 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 158.3 (C), 155.5, 155.1 (C-3, C-7), 137.7 (C), 135.2 (C), 128.7 (CH), 128.1 (2CH), 127.0 (2CH), 125.6 (2CH), 113.6 (2CH), 55.2 (C-5), 55.0 (OCH_3), 36.3 (C-6). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.09; H, 5.76; N, 14.42.

*4.6.4. 5-(4-tert-Butylphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**16d**).* Compound **16d** (0.331 g, 58%) was obtained from triazepinethione **8e** (0.594 g, 1.76 mmol), KOH (0.492 g, 8.77 mmol) and H_2O_2 (1.27 mL, 18.24 mmol; d = 1.175 g/mL, 43%) in EtOH (10 mL) and H_2O (2 mL) (rt, 2.5 h), then AcOH (0.39 mL, 6.81 mmol) as described for **16a**. The crude product was purified using column chromatography on silica gel (10.24 g) eluting with $CHCl_3$. Mp 232–233 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3347 (w), 3229 (br s), 3098 (br s) (ν NH), 3060 (w), 3030 (w) (ν CH_{arom}), 1686 (s) (amide-I), 1637 (m) (ν C=N), 1574 (w), 1511 (m) (ν CC_{arom}), 823 (s), 758 (m), 699 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.56 (1H, br d, ^4J = 2.1 Hz, $N_{(2)}H$), 7.20–7.41 (10H, m, ArH and $N_{(4)}H$), 4.75 (1H, ddd, ^3J = 7.0, ^3J = 3.6, ^3J = 3.4 Hz, H-5), 3.26 (1H, ddd, ^2J = 14.4, ^3J = 7.0, ^4J = 0.7 Hz, H_A-6), 3.17 (1H, dd, ^2J = 14.4, ^3J = 3.4 Hz, H_B-6), 1.22 (9H, s, 3×CH_3 in *t*-Bu); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.8, 155.6 (C-3, C-7), 149.7 (C), 140.3 (C), 137.6 (C), 128.8 (CH), 128.1 (2CH), 125.74 (2CH), 125.7 (2CH), 125.0 (2CH), 55.8 (C-5), 36.4 (C-6), 34.2 (*C*Me_3), 31.1 (3×CH_3 in *t*-Bu). Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.83; H, 7.10; N, 13.10.

*4.6.5. 7-(4-Methylphenyl)-5-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**16e**).* Compound **16e** (0.289 g, 93%) was obtained from triazepinethione **8f** (0.331 g, 1.12 mmol), KOH (0.315 g, 5.61 mmol) and H_2O_2 (0.78 mL, 11.20 mmol; d = 1.175 g/mL, 43%) in EtOH (5 mL) and H_2O (1 mL) (rt, 2 h), then AcOH (0.25 mL, 4.37 mmol) as described for **16a**. Mp 208–209 °C (dec, EtOH); IR (Nujol) ν, cm^{-1}: 3369 (s), 3325 (m), 3223 (br s), 3109 (br s) (ν NH), 3069 (w), 3032 (w) (ν CH_{arom}), 1674 (vs) (amide-I), 1615 (m) (ν C=N), 1509 (w) (ν CC_{arom}), 814 (s), 752 (m), 706 (m) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.49 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}H$), 7.15–7.33 (8H, m, ArH and $N_{(4)}H$),

7.02–7.08 (2H, m, ArH), 4.79 (1H, ddd, ^{3}J = 6.9, ^{3}J = 3.2, ^{3}J = 3.0 Hz, H-5), 3.31 (1H, ddd, ^{2}J = 14.3, ^{3}J = 6.9, ^{4}J = 1.0 Hz, H_A-6), 3.16 (1H, dd, ^{2}J = 14.3, ^{3}J = 3.2 Hz, H_B-6), 2.24 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.6, 155.5 (C-3, C-7), 143.2 (C), 138.3 (C), 134.8 (C), 128.6 (2CH), 128.1 (2CH), 127.1 (CH), 125.9 (2CH), 125.5 (2CH), 56.0 (C-5), 35.9 (C-6), 20.6 (CH_3). Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.04; H, 6.07; N, 15.09.

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Supplementary data

Supplementary data (copies of IR, ^{1}H and ^{13}C NMR spectra of synthesized compounds, results of X-ray analysis, computational details) associated with this article can be found, in the online version, at http://dx.doi.org/

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17. Previously[39] we proposed a convenient criterion for the determination of the substituent orientation at C-4 and C-6 in hexahydropyrimidine-2-thiones(ones), which was based on the values of vicinal coupling constants $J_{N(1)H,H-6}$ and $J_{N(3)H,H-4}$.
18. The observation of long-range coupling constant $^{4}J_{OH,5-H}$ in ^{1}H NMR spectra of 4-hydroxyhexahydropyrimidine-2-thiones(ones,imines) indicates *trans*-diaxial orientation of the hydroxyl group and H-5 proton (a W-shaped arrangement of the protons).[25,27b,c,e-g,40]
19. The DFT B3LYP/6-311++G(d,p) optimized geometries of *E*-**7a** and *Z*-**7a** for the gas phase and DMSO solution using the PCM solvation model were considered in this analysis.
20. For example, the pKa values for the conjugated acids of semicarbazide and acetophenone hydrazone in water are 3.53[41] (at 30 °C) and 4.70[42] (at 22 °C), respectively.
21. The pKa value for $PhSO_2OH$ in water is -2.8 (at 25 °C).[43]
22. For example, the pKa values for the conjugated acids of thiosemicarbazide and acetophenone hydrazone in water are 1.50[41] (at 30 °C) and 4.70[42] (at 22 °C), respectively.
23. The most stable conformers of these anions around the amide bonds were taken into consideration (see Scheme 4; s-*trans*,s-*cis*-conformer for anion **A**, s-*cis*,s-*cis*-conformer for anion **B**).
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30. To the best of our knowledge, to date there is only one report on the crystal structure of monocyclic 1,2,4-triazepine-2-thiones/ones, namely 2-methyl-7-phenyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3,5-dithione.[44]
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35. After two crystallization from EtOH followed by prolonged drying under vacuum at 56 °C over P_2O_5. Compound **7h** formed a strong solvate with EtOH (^{1}H NMR and elemental analysis data).
36. The presence of C_6H_6 in the analytical pure sample ($C_{18}H_{19}N_3O_2S\cdot 0.5C_6H_6$) was also confirmed by its ^{1}H NMR spectrum.
37. After prolonged drying under vacuum (0.1 mmHg) at 56 °C over P_2O_5. Compound **8d** formed a strong solvate with $CHCl_3$ (^{1}H NMR and elemental analysis data).
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Table 1. Reaction of isothiocyanato ketones **4a,b,g** with hydrazine hydrate or methyl hydrazine.[a]

Entry	**4**	R	R^1	R^3	Product(s)	**5**/**6** ratio[b]	Yield (%)[c]
1	**4a**	H	H	H	**5a**+**6a**	89:11[d]	99
2	**4g**	Me	Me	H	**5b**+**6b**	95:5[e]	98
3	**4a**	H	H	Me	**5c**	-	99
4	**4b**	H	Me	Me	**5d**	-	98
5	**4g**	Me	Me	Me	**5e**	-	98

[a] 1:1 molar ratio of reagents, EtOH, rt, 1 h.
[b] According to ^{1}H NMR spectroscopic data for the crude products.
[c] Isolated yields.
[d] Diastereomeric ratio for **6a** was 69:31.
[e] Diastereomeric ratio for **6b** was 67:33.

Table 2. Synthesis of 4-(3-aryl-3-oxopropyl)thiosemicarbazide hydrazones **7a-k** by reaction of isothiocyanates **4a-i** or thiosemicarbazides **5c,d** with excess hydrazine.[a]

Entry	Starting compd	R	R^1	R^2	R^3	Product	Isomer ratio[b]	Yield (%)[c]
1	**4a**	H	H	H	H	**7a**	87:13	92
2[d]	**4a**	H	H	H	H	**7a**	100:0	84
3	**4b**	H	Me	H	H	**7b**	83:17	91
4	**4c**	H	OMe	H	H	**7c**	84:16	94
5	**4d**	H	OMe	OMe	H	**7d**	84:16	89
6	**4e**	H	*t*-Bu	H	H	**7e**	90:10	89
7	**4f**	Me	H	H	H	**7f**	97:3	93
8	**4g**	Me	Me	H	H	**7g**	83:17	89
9	**4h**	Me	OMe	H	H	**7h**	88:12	89
10	**4i**	Me	OMe	OMe	H	**7i**	83:17	92
11	**5c**	H	H	H	Me	**7j**[e]	78:22	94
12	**5d**	H	Me	H	Me	**7k**[f]	78:22	97

[a] 20 equiv. of $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 h.
[b] According to ^{1}H NMR spectra of the crude products.
[c] Isolated yields.
[d] 20 equiv. of $N_2H_4 \cdot H_2O$, EtOH, rt, 24 h.
[e] Along with 5 mol% of **7a**.
[f] Along with 5 mol% of **7b**.

Table 3. Acid-catalyzed cyclization of hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **7a-k** into 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a-k**.

Entry	**7**[a]	R	R^1	R^2	R^3	Solvent	Acid (equiv.)	Conc. of **7** (mol/L)	Reaction conditions	**8**	Purity of **8**[b] (%)	Yield[c] (%)
1	**7a**	H	H	H	H	EtOH	TsOH (1.05)	0.300	rt, 2 h	**8a**	37	–
2	**7a**	H	H	H	H	MeCN	TsOH (1.03)	0.300	rt, 2 h	**8a**	35	–
3	**7a**	H	H	H	H	EtOH	TsOH (1.05)	0.300	reflux, 1.5 h	**8a**	61	–
4	**7a**	H	H	H	H	EtOH	TsOH (1.10)	0.097	reflux, 1.5 h	**8a**	79	–
5	**7a**[d]	H	H	H	H	EtOH	TsOH (1.11)	0.097	reflux, 1.5 h	**8a**	78	76
6	**7a**	H	H	H	H	EtOH	TsOH (1.52)	0.098	reflux, 1.5 h	**8a**	77	–
7	**7a**	H	H	H	H	EtOH	TsOH (1.07)	0.054	reflux, 1.5 h	**8a**	80	–
8	**7a**	H	H	H	H	EtOH	HCl (1.05)	0.107	reflux, 1.5 h	**8a**	72	–
9	**7a**	H	H	H	H	AcOH	AcOH	0.100	reflux, 1.67 h	**8a**	68	–
10	**7b**	H	Me	H	H	EtOH	TsOH (1.10)	0.095	reflux, 1.5 h	**8b**	80	76
11	**7c**	H	OMe	H	H	EtOH	TsOH (1.10)	0.098	reflux, 1.5 h	**8c**	75	75
12	**7d**	H	OMe	OMe	H	EtOH	TsOH (1.15)	0.091	reflux, 1.5 h	**8d**	74	73
13	**7e**	H	*t*-Bu	H	H	EtOH	TsOH (1.12)	0.096	reflux, 1.5 h	**8e**	80	78
14	**7f**	Me	H	H	H	EtOH	TsOH (1.12)	0.098	reflux, 1.5 h	**8f**	84	81
15	**7g**	Me	Me	H	H	EtOH	TsOH (1.11)	0.097	reflux, 1.5 h	**8g**	81	76
16	**7h**	Me	OMe	H	H	EtOH	TsOH (1.12)	0.095	reflux, 1.5 h	**8h**	81	81
17	**7i**	Me	OMe	OMe	H	EtOH	TsOH (1.11)	0.098	reflux, 1.5 h	**8i**	83	82
18	**7j**	H	H	H	Me	MeCN	TsOH (1.12)	0.092	reflux, 1.5 h	**8j**	78	72
19	**7j**	H	H	H	Me	MeOH	TsOH (1.11)	0.095	reflux, 1.5 h	**8j**	75	–
20	**7j**	H	H	H	Me	EtOH	TsOH (1.11)	0.102	reflux, 1.5 h	**8j**	72	–
21	**7k**	H	Me	H	Me	MeCN	TsOH (1.12)	0.092	reflux, 1.5 h	**8k**	71	48

[a] The crude products obtained by the reaction of **4a-i** or **6c,d** with excess N_2H_4 in refluxing EtOH were used. Their *E*/*Z* ratios are presented in Table 2 (enties 2, 3–12).
[b] Purity of the isolated crude product was estimated as ratio of the expected integral intensity of the aromatic protons region (10 H for **8a,j**, 9 H for **8b,c,e,f,k**, 8 H for **8d,g,h**, and 7 H for **8i**) to the observed integral intensity in this region in the ^{1}H NMR spectrum of the crude product multiplied by 100. In all cases complete conversion of the starting material was observed.
[c] Isolated yield (after column chromatography).
[d] The crude product obtained by the reaction of **4a** with excess N_2H_4 in EtOH at rt was used (Table 2, entry 2).

Table 4. Acid-catalyzed cyclization of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **5a-e** into 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a,g,j-l**.[a]

Entry	**5**	R	R^1	R^3	Solvent	Acid (equiv.)	Additive (equiv.)	Reaction time (h)	Conv.[b] (%)	**8**	Purity of **8**[c] (%)	Yield[d] (%)
1	**5a**	H	H	H	EtOH	TsOH (0.11)	–	1	100	**8a**	17	–
2	**5a**	H	H	H	MeCN	TsOH (0.10)	–	1	100	**8a**	23	–
3	**5a**	H	H	H	EtOH	TsOH (1.12)	$N_2H_4\cdot H_2O$ (1.01)	1	100	**8a**	32	–
4	**5a**	H	H	H	EtOH	TsOH (1.00)	$N_2H_4\cdot H_2O$ (1.01)	1	100	**8a**	33	–
5	**5a**	H	H	H	MeCN	TsOH (1.04)	$N_2H_4\cdot H_2O$ (1.04)	1	100	**8a**	26	–
6	**5a**	H	H	H	EtOH	AcOH (4.05)	–	1	87	**8a**	68	–
7	**5a**	H	H	H	EtOH	AcOH (4.10)	–	3	100	**8a**	85	83
8	**5a**	H	H	H	MeCN	AcOH (4.14)	–	3	55	**8a**	22	–
9	**5b**	Me	Me	H	EtOH	AcOH (4.13)	–	3	100	**8g**	83	79
10	**5c**	H	H	Me	EtOH	TsOH (0.10)	–	1	85	**8j**	31	–
11	**5c**	H	H	Me	MeCN	TsOH (0.10)	–	1	100	**8j**	58	–
12	**5c**	H	H	Me	EtOH	AcOH (4.01)	–	1	39	**8j**	26	–
13	**5c**	H	H	Me	MeCN	AcOH (4.13)	–	5	21	**8j**	10	–
14	**5c**	H	H	Me	EtOH	AcOH (10.40)	–	8	100	**8j**	89	89
15	**5d**	H	Me	Me	EtOH	AcOH (10.62)	–	8	100	**8k**	89	82
16	**5e**	Me	Me	Me	EtOH	AcOH (10.16)	–	8	100	**8l**	88	81

[a] The reactions were performed at reflux with concentrations of the starting material ranging from 0.091 to 0.136 mol/L.
[b] Level of conversion of the starting material according to ^{1}H NMR of the crude product.
[c] Purity of the isolated crude product was estimated as ratio of the expected integral intensity of the aromatic protons region (10 H for **8a,j**, 9 H for **8k**, 8 H for **8g,l**) to the observed integral intensity in this region in the ^{1}H NMR spectrum of the crude product multiplied by 100.
[d] Isolated yield (after column chromatography).

Table 5. Oxidative transformation of triazepine-3-thiones **8a-c,e,f** into their 3-oxo-analogs **16a-e**.[a]

Entry	**8**	R	R^1	Product	Yield[b] (%)
1	**8a**	H	H	**16a**	89
2	**8b**	H	Me	**16b**	87
3	**8c**	H	OMe	**16c**	88
4	**8e**	H	*t*-Bu	**16d**	58
5	**8f**	Me	H	**16e**	93

[a] Reaction conditions: H_2O_2 (10 equiv.), KOH (5 equiv.), EtOH/H_2O, rt, 1.5–2.5 h.
[b] Isolated yield (for **16d** after column chromatography).

Legends for Schemes and Figures

Scheme 1. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **2**.

Scheme 2. Synthesis of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **5a-e** and their hydrazones **7a-k**.

Scheme 3. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a-k** from hydrazones of 4-(3-aryl-3-oxopropyl)thiosemicarbazides **7a-k**.

Scheme 4. A plausible pathway for the acid-catalyzed (HA) cyclization of *E*-**7a** into **8a**.

Scheme 5. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a,g,j-l** from 4-(3-aryl-3-oxopropyl)thiosemicarbazides **5a-e**.

Scheme 6. Synthesis of 5-unsubstituted triazepine **15** from isothiocyanate **11**.

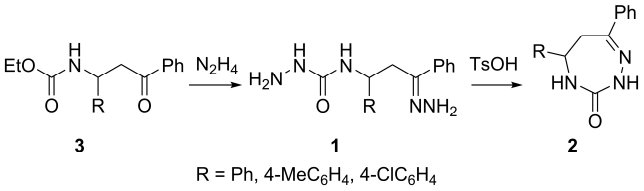
Scheme 7. Transformation of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **8a-c,e,f** into their 3-oxo-analogs **16a-e**.

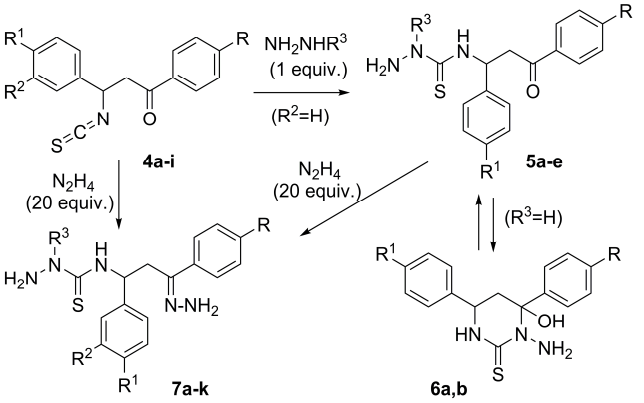
Figure 1. Views of molecular X-ray structures of *R*-**8b** (a) and *S*-**8b** (b) with ellipsoids drawn at the 50% probability level.

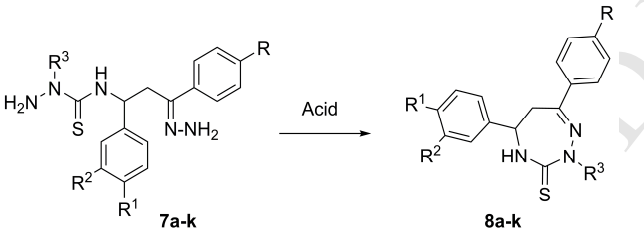
Figure 2. A view of molecular X-ray structure of **8i** with ellipsoids drawn at the 50% probability level.

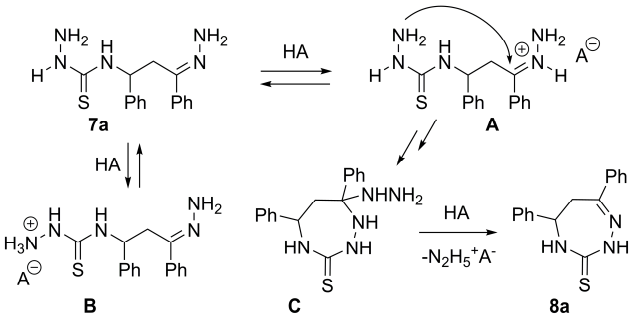
Figure 3. A view of molecular X-ray structure of **8j** with ellipsoids drawn at the 50% probability level. Only *R*-isomer is represented.

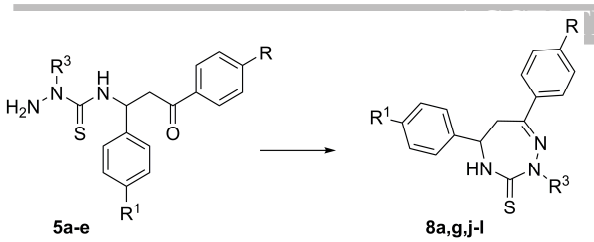
Schemes

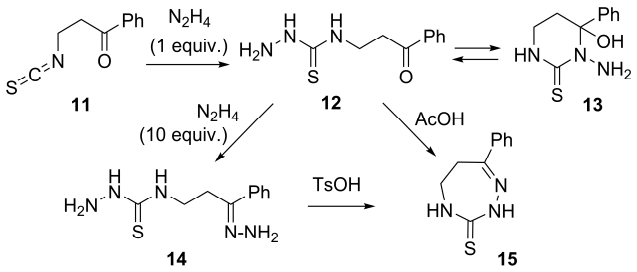


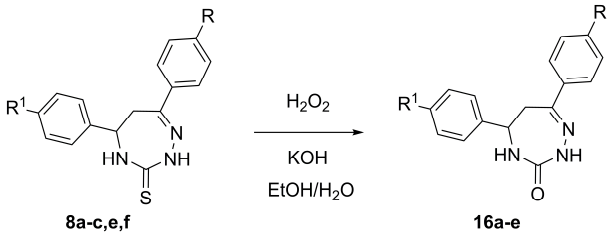




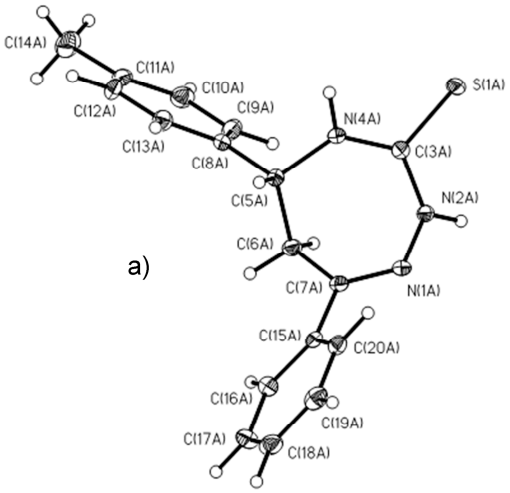








Figures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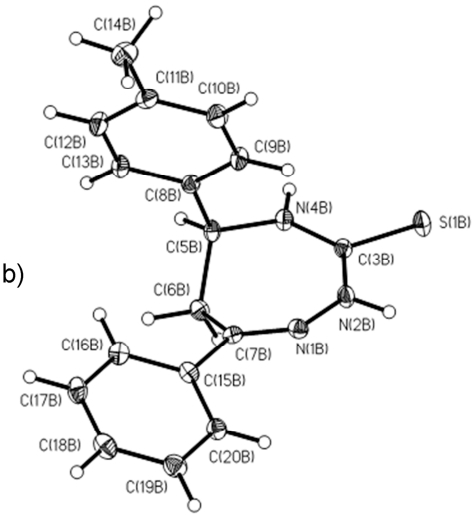
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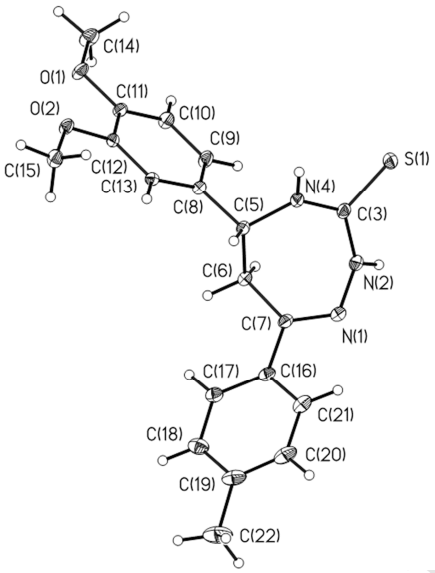
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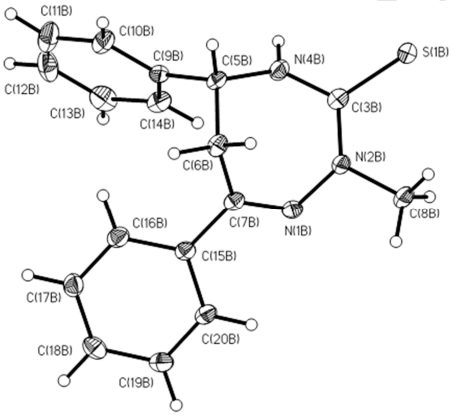
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