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Different modes of acid-catalyzed cyclization of 4-(γ-oxoalkyl) semicarbazide hydrazones: 7-membered versus 14-membered cyclic semicarbazones formation

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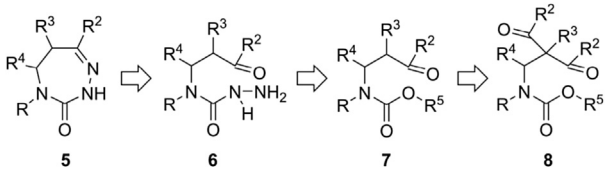
ABSTRACT

Acid-catalyzed cyclization of 4-(γ-oxoalkyl)semicarbazide hydrazones has been studied. 7-Membered cyclic semicarbazones, 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones, were obtained from the γ-phenyl-substituted semicarbazides, while the cyclization of the γ-methyl-substituted semicarbazides involved two molecules of the starting material to result in 14-membered cyclic bis-semicarbazones, 1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-diones. The 4-(γ-oxoalkyl)semicarbazide hydrazones were prepared according to a four-step synthesis based on amidoalkylation of the sodium enolates of 1,3-diketones with ethyl *N*-(1-tosylalk-1-yl)carbamates followed by base-promoted retro-Claisen reaction and treatment of the obtained ethyl *N*-(γ-oxoalkyl)carbamates with hydrazine.

1. Introduction

Five- and six-membered cyclic semicarbazones, 2,4-dihydro-3*H*-1,2,4-triazol-3-ones **1** and 2,3,4,5-tetrahydro-1,2,4-triazin-3-ones **2** are readily available and well-studied heterocycles[1,2] possessing a wide range of biological activities.[3–10] In contrast to **1** and **2**, no general approaches to their seven-membered analogs, 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **3**, or cyclic semicarbazones with larger ring sizes have been described. Several compounds of type **3** have been prepared by the reaction of 4-isocyanato-4-methylpentan-2-one with methylhydrazine,[11] oxidation of 5,5,7-trimethyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione,[12] or cyclizations of two semicarbazones.[13] Thus, the development of a convenient and general synthesis of triazepinones **3** is of significant synthetic and medicinal value.

In continuation of our studies on the application of amidoalkylation in heterocyclic synthesis,[14] we were interested to use this method for the preparation of seven-membered cyclic semicarbazones **3**, particularly their 2-unsubstituted representatives **5**. We hypothesized that the latter could form via cyclization of 4-(γ-oxoalkyl)semicarbazides **6** prepared by reaction of β-carbamato ketones **7** with hydrazine (Scheme 1).



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

Published data show that, compounds **7** can be synthesized by aza-Michael addition of carbamates to α,β-unsaturated ketones,[15] Mannich condensation of aldehydes with methyl ketones and carbamates,[16] reactions of *N*-alkoxycarbonylimines with ketones,[17] etc. Small-scale preparation and use of chromatography for isolation of the target products are the main drawbacks of the reported syntheses.[18] We supposed that compounds **7** could be prepared on a multi-gram scale by retro-Claisen reaction of carbamates **8**, which are readily available using our previously described protocol based on amidoalkylation reactions.[19]

According to the synthetic sequence described above we have prepared two ethyl *N*-(2-acetyl-3-oxobut-1-yl)carbamates **8** (R^2=Me) in two steps.[20] Compounds **8** were converted into the corresponding carbamates **7** under the action of aqueous KOH followed by treatment with hydrazine to give hydrazones of semicarbazides **9**. Surprisingly, acid-catalyzed cyclization of hydrazones

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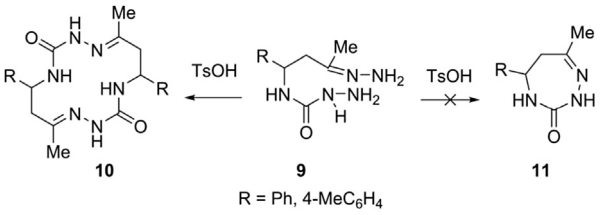
9 involved two molecules of the starting material and stereoselectively afforded previously unknown 14-membered cyclic bis-semicarbazones **10** instead of the expected triazepinones **11** (Scheme 2).[20]



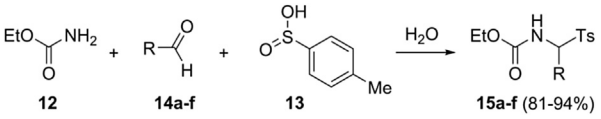
Scheme 2. Acid-catalyzed cyclization of semicarbazides **9** into 14-membered cyclic bis-semicarbazones **10**.

We focused our further attention on the elucidation of the factors that determine the course of the acid-catalyzed cyclization of hydrazones of 4-(γ-oxoalkyl)semicarbazides, particularly on the effect of substituents and the reaction conditions, to develop general approaches to both 7-membered and 14-membered cyclic semicarbazones. Here we report the three-step multi-gram synthesis of ethyl carbamates **7** bearing various R^2, R^3, and R^4 groups involving the preparation of carbamates **8** followed by retro-Claisen reaction, and the transformation of compounds **7** under the action of hydrazine to provide the hydrazones of semicarbazides **6**. The acid-catalyzed cyclization of the obtained hydrazones affording 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones or 1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-diones depending on the structure of the starting material is described.

2. Results and discussion

2.1. Synthesis of ethyl *N*-[(β-acyl-γ-oxo)alkyl]carbamates

For preparation of the starting amidoalkylation reagents, ethyl *N*-(1-tosylalk-1-yl)carbamates **15**, we applied a modified Engberts method based on condensation of carbamates with aldehydes and arylsulfinic acids generated by treatment of their sodium salts with excess formic acid.[21] The modification involved the use of pure sulfinic acids instead of their in situ formation. Our experience has shown that both yield and purity of products formed under these conditions are satisfactory.[19] Thus, carbamates **15a**–**f** were obtained by the three-component condensation of ethyl carbamate (**12**) (1–1.21 equiv) with *p*-toluenesulfinic acid (**13**) (1 equiv) and aldehydes **14a**–**f** (1 equiv) in water (Scheme 3).



Scheme 3. Synthesis of ethyl *N*-(1-tosylalk-1-yl)carbamates **15a**–**f**.

Table 1 shows the optimized reaction conditions for this reaction and yields of sulfones **15a**–**f**. The condensation of ethyl carbamate (**12**) with aldehydes **14a**,**b**,**e**,**f** and sulfinic acid **13** proceeded in water at 70 °C for 1–1.5 h to give the corresponding sulfones **15a**,**b**,**e**,**f** in 86–94% yields. For aldehydes **14c**,**d**, the best result was achieved when the condensation proceeded at room temperature for 24 h to afford sulfones **15c**,**d** in 92 and 81% yields, respectively. Heating of the reaction mixtures in this case (70 °C, 1.5 h) led to a significant decrease in both yield and purity of isolated products **15c**,**d**.

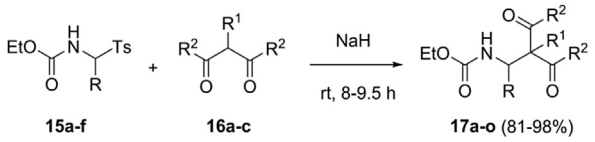
Table 1
Reaction of aldehydes **14a**–**f** with ethyl carbamate (**12**) and *p*-toluenesulfinic acid (**13**) in water

Entry	14	*R*	Reaction conditions[a]	Product	Yield (%)[b]
1	**14a**	Ph	70 °C, 1 h	**15a**	88
2	**14b**	4-MeC_6H_4	70 °C, 1.5 h	**15b**	86
3	**14c**	4-$MeOC_6H_4$	rt, 24 h	**15c**	92
4	**14d**	4-*t*-BuC_6H_4	rt, 24 h	**15d**	81
5	**14e**	4-ClC_6H_4	70 °C, 1.5 h	**15e**	93
6	**14f**	Pr	70 °C, 1.5 h	**15f**	94

[a] Temperature in a water bath (entries 1, 2, 5, and 6).
[b] Isolated yields (>95% purity).

Under optimized conditions sulfones **15a**–**f** precipitated from the reaction mixtures formed after the addition of all reagents. They were isolated as white solids by filtration with >95% purity according to ^{1}H NMR spectroscopic data of the crude products and used in the amidoalkylation step without additional purification.

The nucleophilic substitution of the tosyl group in sulfones **15a**–**f** under the action of sodium enolates of acetylacetone (**16a**), 3-methylpentane-2,4-dione (**16b**), or dibenzoylmethane (**16c**), generated by the treatment of the corresponding CH-acid with NaH in dry MeCN or THF, readily proceeded at room temperature to give carbamates **17a**–**o** in high yields (Scheme 4).



Scheme 4. Synthesis of ethyl *N*-[(β-acyl-γ-oxo)alkyl]carbamates **17a**–**o**.

The reaction conditions and yields of the prepared ethyl *N*-[(β-acyl-γ-oxo)alkyl]carbamates **17a**–**o** are summarized in Table 2.

The Na-enolate of acetylacetone (**16a**) was readily formed in dry MeCN and smoothly reacted with sulfones **15a**–**d**,**f** to afford carbamates **17a**–**e** (entries 1–5). In contrast to **16a**, deprotonation of **16c** with NaH in MeCN proceeded with the formation of a dense suspension which complicated the completion of the reaction. The rate of deprotonation of **16b** under these conditions was very slow. Therefore, dry THF was used as solvent for generation of the Na-enolates of **16b**,**c** followed by their reaction with sulfones **15a**–**f** (entries 6–15).

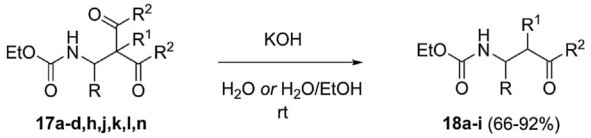
Table 2
Reaction of sulfones **15a**–**f** with 1,3-diketones **16a**–**c** in the presence of NaH at room temperature[a]

Entry	15	16	*R*	R^1	R^2	Solvent	Reaction time (h)	Product	Isolated yield (%)
1	**15a**	**16a**	Ph	H	Me	MeCN	8	**17a**	93
2	**15b**	**16a**	4-MeC_6H_4	H	Me	MeCN	9.5	**17b**	91
3	**15c**	**16a**	4-$MeOC_6H_4$	H	Me	MeCN	8.67	**17c**	90
4	**15d**	**16a**	4-*t*-BuC_6H_4	H	Me	MeCN	8.17	**17d**	93
5	**15f**	**16a**	Pr	H	Me	MeCN	8.17	**17e**	89
6	**15a**	**16b**	Ph	Me	Me	THF	8.08	**17f**	81
7	**15b**	**16b**	4-MeC_6H_4	Me	Me	THF	8.17	**17g**	87
8	**15c**	**16b**	4-$MeOC_6H_4$	Me	Me	THF	8.08	**17h**	83
9	**15d**	**16b**	4-*t*-BuC_6H_4	Me	Me	THF	8.33	**17i**	84
10	**15a**	**16c**	Ph	H	Ph	THF	8	**17j**	95
11	**15b**	**16c**	4-MeC_6H_4	H	Ph	THF	8	**17k**	96
12	**15c**	**16c**	4-$MeOC_6H_4$	H	Ph	THF	8	**17l**	93
13	**15d**	**16c**	4-*t*-BuC_6H_4	H	Ph	THF	8	**17m**	98
14	**15e**	**16c**	4-ClC_6H_4	H	Ph	THF	8	**17n**	98
15	**15f**	**16c**	Pr	H	Ph	THF	8	**17o**	95

[a] **15**/**16**/NaH molar ratios: 1:1.11:1.10 (entry 1), 1:1.02:1.01 (entry 2), 1:(1.02–1.04):1 (entries 3–5), 1:(1.00–1.01):1 (entries 5–9), and 1:(1.03–1.05):1 (entries 10–15).

2.2. Synthesis of ethyl *N*-(γ-oxoalkyl)carbamates

According to the retrosynthetic analysis (Scheme 1), the next step of cyclic semicarbazone synthesis included removal of one of two geminal acyl groups from ethyl *N*-[(β-acyl-γ-oxo)alkyl]carbamates **17** using the retro-Claisen reaction. This transformation proceeded under treatment of **17** with KOH in water or aqueous EtOH at room temperature to give the corresponding *N*-(γ-oxoalkyl)carbamates **18a**–**i** (Scheme 5).



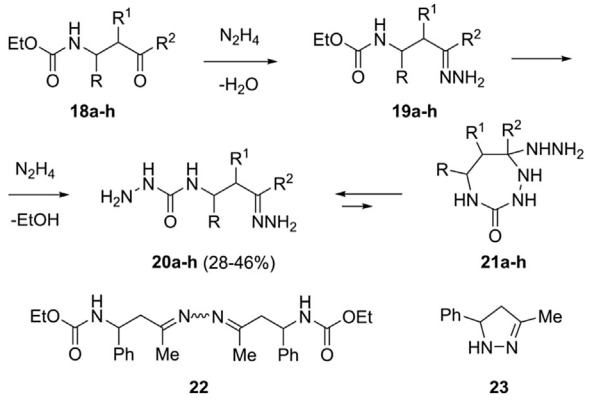
Scheme 5. Synthesis of ethyl *N*-(γ-oxoalkyl)carbamates **18a**–**i**.

Table 3 shows the optimized reaction conditions for the preparation of *N*-(γ-oxoalkyl)carbamates **18a**–**i** from **17a**–**d**,**h**,**j**,**k**,**l**,**n** by the retro-Claisen reaction.

Ethyl *N*-(3-oxobutyl)carbamates **18a**–c were prepared in high isolated yields by treatment of compounds **17a**–c with aqueous solutions of KOH (5.06–5.12 equiv) at room temperature for 3 h (entries 1–3). Ethyl *N*-(2-methyl-3-oxobutyl)carbamate **17h** underwent the retro-Claisen reaction under the described conditions over 1 h 50 min to give compound **18e** in 74% yield as a mixture of two isomers (entry 5). With longer reaction time the yield of compound **17h** significantly decreased. The conditions of retro-Claisen reaction for carbamates prepared from dibenzoylmethane were optimized using compound **17j** as a starting material. With aqueous KOH (5.00 equiv) the reaction did not proceed due to the low solubility of carbamate **17j** in H_2O. Therefore, EtOH was added as a co-solvent and **17j** was reacted with KOH (4.87 equiv) at room temperature for 8 h 45 min. After extractive workup of the resulting reaction mixture the ^{1}H NMR spectrum of the obtained material showed the complete conversion of starting compound but significant amounts of side products (up to 60%) formed along with carbamate **18f**. When the reaction time was reduced to 3 h and the amount of KOH to 2.99 equiv, a 17:83 mixture of starting **17j** and product **18f** was obtained. Under these conditions the formation of side products was not observed. Thus, 3-phenyl substituted carbamate **18f** was isolated in 69% yield by the reaction of **17j** with KOH (3.01 equiv) in aqueous EtOH at room temperature for 8 h (entry 6). Under the described conditions carbamates **18g**–**i** were prepared in 66–83% yields (entries 7–9). Carbamates **18a**–**c**,**e**–**i** were isolated with >95% purity (^{1}H NMR data) by the filtration of the precipitate formed in the reaction mixture. Only compound **18d** (oily substance) was isolated using an extractive workup. Thus, a simple and convenient method for the preparation of ethyl *N*-(γ-oxoalkyl)carbamates in a multi-gram scale was developed.[18]

2.3. Synthesis of hydrazones of 4-(γ-oxoalkyl)semicarbazides

Next, ethyl *N*-(γ-oxoalkyl)carbamates **18** were reacted with hydrazine. Previously, we studied the reaction of carbamate **18a** with hydrazine under various conditions using ^{1}H NMR spectroscopy.[22] We found that this reaction proceeded in two sequential steps involving a relatively fast formation of hydrazone **19a** followed by slow substitution of the ethoxy group resulting in the target hydrazone of semicarbazide **20a** (Scheme 6).



Scheme 6. Synthesis of the hydrazones of 4-(γ-oxoalkyl)semicarbazides **20a**–**h**.

The reaction of **18a** with hydrazine hydrate or anhydrous hydrazine in different solvents (EtOH, *n*-BuOH, Py) at room temperature or at reflux gave mixtures of hydrazone **19a** and azine **22**. The substitution of the ethoxy group by a hydrazino group did not proceed under these conditions. In contrast, in refluxing anhydrous hydrazine or hydrazine hydrate, gradual transformation of the intermediate hydrazone **19a** into semicarbazide **20a** (a mixture of *E*- and *Z*-isomers) was practically complete in 24 h and formation of azine **22** was completely suppressed. Dihydropyrazole **23** resulting from elimination of semicarbazide in **20a** followed by ring closure was the major by-product (up to 61%) formed in the reaction with hydrazine hydrate. According to ^{1}H NMR data, the best results were achieved in refluxing anhydrous hydrazine for 20–24 h[20] In this case, compound **20a** was isolated in a 36% yield after evaporation of the reaction mixture in vacuo to dryness followed by washing of the residue with Et_2O and water (Table 4, entry 1).

Similar trends were observed for the reaction of other *N*-(γ-oxoalkyl)carbamates **18b**–**h** with hydrazine under the above described conditions: the first step involved a fast formation of hydrazones of carbamates **19b**–**h** followed by their slow conversion to hydrazones of semicarbazides **20b**–**h** (Scheme 6). Formation of variable amounts of the corresponding azines and dihydropyrazoles similar to **22** and **23** was also observed. As for **18a**, reaction of **18b**–**h** in refluxing anhydrous hydrazine for 20–24 h

Table 3
Transformation of **17a**–**d**,**h**,**j**,**k**,**l**,**n** into ethyl *N*-(γ-oxoalkyl)carbamates **18a**–**i** in the presence of KOH

Entry	17	*R*	R^1	R^2	KOH (equiv)	Solvent	Reaction time	Product	Isolated yield (%)
1	**17a**	Ph	H	Me	5.06	H_2O	3 h	**18a**	83
2	**17b**	4-MeC_6H_4	H	Me	5.12	H_2O	3 h	**18b**	91
3	**17c**	4-$MeOC_6H_4$	H	Me	5.12	H_2O	3 h	**18c**	92
4	**17d**	4-*t*-BuC_6H_4	H	Me	5.17	H_2O	4 h	**18d**	—[a]
5	**17h**	4-$MeOC_6H_4$	Me	Me	3.00	H_2O	1 h 50 min	**18e**	74[b]
6	**17j**	Ph	H	Ph	3.01	H_2O–EtOH (5:3)	8 h	**18f**	69
7	**17k**	4-MeC_6H_4	H	Ph	3.00	H_2O–EtOH (5:3)	9 h 20 min	**18g**	67
8	**17n**	4-ClC_6H_4	H	Ph	3.31	H_2O–EtOH (5:3)	8 h	**18h**	83
9	**17l**	4-$MeOC_6H_4$	H	Ph	2.98	H_2O–EtOH (17:9)	9 h	**18i**	66

[a] After extractive workup followed by removal of solvent compound **18d** was isolated as an oil (93% purity) and used in the next step.
[b] A mixture of two diastereomers, 51:49.

Table 4
Reaction of ethyl *N*-(γ-oxoalkyl)carbamates **18a**–**h** with anhydrous hydrazine at reflux

Entry	18	R	R^1	R^2	Reaction time (h)	Product	*E*/*Z* isomer ratio	Isolated yield (%)
1	**18a**	Ph	H	Me	23	**20a**	84:16	36
2	**18b**	4-MeC_6H_4	H	Me	20	**20b**	90:10	41
3	**18c**	4-$MeOC_6H_4$	H	Me	24	**20c**	92:8	29
4	**18d**	4-*t*-BuC_6H_4	H	Me	22	**20d**	94:6	42[a]
5	**18e**	4-$MeOC_6H_4$	Me	Me	23	**20e**	95:5	40
6	**18f**	Ph	H	Ph	19.66	**20f**	75:25	46
7	**18g**	4-MeC_6H_4	H	Ph	24	**20g**	84:16	28
8	**18h**	4-ClC_6H_4	H	Ph	20	**20h**	75:25	32

[a] Counting on carbamate **17d**.

gave the best results. Though the conversion of **18a**–**h** into **20a**–**h** proceeded under drastic conditions and was accompanied by some side reactions, the impurities were completely removed from the crude products during isolation. After evaporation of all the volatiles and treatment of the residues with diethyl ether, the resulting solids were filtered, washed with ether to remove all side products, and then with ice-cold H_2O to remove the residual hydrazine. All compounds **20a**–**h** are poorly soluble in ether and ice-cold H_2O. Table 5 shows the optimized reaction times, yields and *E*/*Z*-isomer ratios of all prepared hydrazones of semicarbazides **20a**–**h**.

The crude semicarbazides **20a**–**h** were isolated as mixtures of *E*- and *Z*-isomers with significant predominance of one of them (up to 95%) (Table 4). Configurations of the major and minor isomers of compound **20a** were determined unambiguously using a $^1H,^1H$-NOESY experiment in DMSO-d_6. For the major isomer NOE was observed between the CH_3 and C=NNH_2 protons, thus indicating the *E*-configuration of the C=N double bond in this isomer. The stereochemical assignments for **20a** were confirmed by comparison of the experimental carbon chemical shifts for the CH_2 and CH_3 groups of the $CH_2C(=NNH_2)CH_3$ moiety with those calculated by the GIAO method at the RHF/6-311+G(2d,p) level using the DFT-B3LYP/6-31+G(d,p) optimized geometries for both *E*-**20a** and *Z*-**20a**.[23] The DFT calculations at the B3LYP/6-31+G(d,p) level also showed that the *E*-isomer of **20a** was more stable (1.91 kcal/mol in DMSO) than the *Z*-isomer. Since the ^1H and ^{13}C NMR spectra of the major isomers of **20a** and **20b**–**e** were similar, we concluded that the major isomers of **20b**–**e** also had the *E*-configuration.

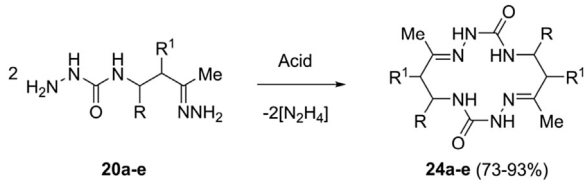
A $^1H,^1H$-NOESY experiment in DMSO-d_6 was used to assign stereochemistry of the isomers of compound **20h**. For the major isomer, NOEs were observed between the C=NNH_2 and CH_2 protons and between the C=NNH_2 and CHN protons, thus giving evidence for the *E*-configuration of the C=N double bond in this isomer. As for the minor isomer of compound **20h**, these correlations were not detected. Comparison of ^1H and ^{13}C NMR spectra of **20h** and **20f**,**g** allowed us to conclude that the major isomers of **20f**,**g** had the same *E*-configuration.

It is important to note that the relative configurations of the major stereoisomers of **20a**–**e** and **20f**–**h** were different, namely, the CH_3 and NH_2 groups of **20a**–**e** had *cis*-orientation with respect to the C=N bond, and the Ph and NH_2 groups of **20f**–**h** were in the *trans*-position.

2.4. Acid-catalyzed cyclizations of 4-(γ-oxoalkyl)semicarbazide hydrazones

Finally, we studied heterocyclization of hydrazones of 3-oxobutyl- **20a**–**e** and (3-oxo-3-phenyl)propyl-substituted semicarbazides **20f**–**h** under acidic conditions.

Previously, we found that reflux of semicarbazides **20a**,**b** in EtOH or MeCN for 4 h in the presence of TsOH (1.2 equiv) gave 14-membered cyclic bis-semicarbazones instead of the expected 1,2,4-triazepin-3-ones (see Scheme 2).[20] In continuation of this research we studied acid-catalyzed cyclization of **20a**,**b** and their close analogues **20c**–**e** into hexaazamacrocycles **24a**–**e** in more details (Scheme 7, Table 5).



Scheme 7. Synthesis of 1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-diones **24a**–**e**.

We found that TsOH was an effective acid promoter for the synthesis of **24a**–**e**. The optimal amount of TsOH was shown to be 1.03–1.07 equiv. With 2.05 equiv of TsOH (entry 5), the yield and purity of isolated macrocycle **24a** significantly decreased, while the *trans*/*cis* diastereoselectivity of the reaction changed only slightly (entry 1 vs entry 5). Relatively weak AcOH also induced the cyclization of semicarbazide **20b** in refluxing EtOH (entry 9). Both in the case of AcOH (entry 9) and with the use of 2.05 equiv of TsOH (entry 5), the ^1H NMR spectra of isolated crude **24a**,**b** showed some unidentified side products. A change of solvent from EtOH to MeCN had no effect on the yield and diastereoselectivity of the formation of macrocycle **24a** (entry 1 vs entry 2).

Table 5
Acid-catalyzed transformation of hydrazones of 4-(3-oxobut-1-yl)semicarbazides **20a**–**e** into 1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-diones **24a**–**e**

Entry	20	*R*	R^1	Conc. of **20** (mol/L)	Acid (equiv)	Solvent	Reaction conditions	Product	Yield (%)[a]	Dr[c]
1	**20a**	Ph	H	0.191	TsOH (1.03)	EtOH	Reflux, 1 h 50 min	**24a**	85	95:5
2	**20a**	Ph	H	0.172	TsOH (1.05)	MeCN	Reflux, 1 h 50 min	**24a**	85	96:4
3	**20a**	Ph	H	0.060	TsOH (1.06)	EtOH	Reflux, 1 h 50 min	**24a**	76	82:18
4	**20a**	Ph	H	0.177	TsOH (1.05)	EtOH	rt, 4 h	**24a**	80	57:43
5	**20a**	Ph	H	0.182	TsOH (2.05)	EtOH	Reflux, 1 h 50 min	**24a**	—[b]	98:2
6	**20b**	4-MeC_6H_4	H	0.203	TsOH (1.05)	EtOH	Reflux, 1 h 50 min	**24b**	92	71:29
7	**20b**	4-MeC_6H_4	H	0.062	TsOH (1.05)	EtOH	Reflux, 1 h 50 min	**24b**	83	26:74
8	**20b**	4-MeC_6H_4	H	0.183	TsOH (1.04)	EtOH	rt, 4 h	**24b**	82	23:77
9	**20b**	4-MeC_6H_4	H	0.156	AcOH (1.27)	EtOH	Reflux, 2 h	**24b**	—[b]	32:68
10	**20c**	4-$MeOC_6H_4$	H	0.200	TsOH (1.06)	EtOH	Reflux, 1 h 50 min	**24c**	86	69:31
11	**20d**	4-*t*-BuC_6H_4	H	0.165	TsOH (1.06)	EtOH	Reflux, 1 h 50 min	**24d**	90	65:35
12	**20d**	4-*t*-BuC_6H_4	H	0.076	TsOH (1.07)	EtOH	Reflux, 1 h 50 min	**24d**	93	55:45
13	**20e**	4-$MeOC_6H_4$	Me	0.270	TsOH (1.04)	EtOH	Reflux, 1 h 50 min	**24e**	73	81:13:6

[a] Isolated yields (>96% purity).
[b] Some unidentified side products were formed.
[c] Diastereomeric ratio (*trans*/*cis* for **20a**–**d**). According to ^1H NMR spectroscopic data for the crude products.

Decrease in concentration led to a slight decrease in the yield of **24a** (entry 1 vs entry 3) and **24b** (entry 6 vs entry 7) and had no effect on the yield of **24d** (entry 11 vs entry 12). In relatively diluted solutions the stereoselectivity of formation of macrocycles **24a** and **24d** decreased (entry 1 vs entry 3; entry 11 vs entry 12), but in the case of **24b**, the reversed selectivity was observed (entry 6 vs entry 7).

Transformation of semicarbazides **20a**,**b** into macrocycles **24a**,**b** smoothly proceeded at room temperature under the action of TsOH (entries 4, 8). For both compounds the yields slightly decreased compared with those achieved in refluxing solvents. The obtained data clearly demonstrated that the reaction temperature had a dramatic effect on the diastereoselectivity of the reaction (entry 1 vs entry 4; entry 6 vs entry 8).

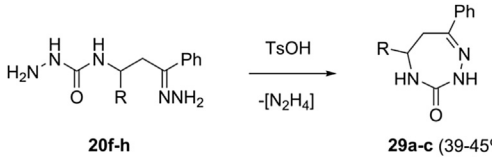
Under similar conditions, the reaction stereoselectivity also decreased with increasing steric bulk of the substituent at the 4-position of the aromatic ring (from H to *t*-Bu; entries 1, 6, 10, and 11). As expected, in the case of **24e** possessing four stereocenters, the number of the formed diastereomers increased, but one of them significantly predominated (entry 13).

Compounds **24a**–**e** were formed as white solids which were extremely poorly soluble (especially **24b**) in common solvents including DMSO, DMF, etc. Their structures were established by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and powder X-ray diffraction[24] (for **24a**,**b**). According to NMR spectral data and X-ray analysis, the major diastereomer of **24a**–**d** had a *trans*-orientation of the aryl groups.

Since macrocycles **24a**–**d** have two distant stereocenters, we expected them to form as mixtures of two diastereomers in approximately equal amounts. However, as mentioned above, the stereoselectivity varied in a wide range and strongly depended on the reaction conditions and the structure of the starting material (Table 5). Thus, the formation of **24a**–**d** via intermediates **25a**–**d** could be excluded (Scheme 8). We suppose that immediate precursors to **24a**–**d** possess only one stereogenic center, and formation of the second stereocenter proceeds during the cyclization. A plausible pathway for the transformation of **20a**–**e** into **24a**–**e** presumably could include acid-catalyzed elimination of semicarbazide resulting in unsaturated hydrazones **26a**–**e** followed by the formation of semicarbazones **27a**–**e**. Dimerization of compounds **27a**–**e** via intermolecular aza-Michael addition affords intermediates **28a**–**e** which cyclize through an intramolecular aza-Michael reaction to give the final products **24a**–**e**. The stereochemical outcome of the synthesis could be explained by a high sensitivity of the cyclization step to multiple factors. The possibility of the formation of intermediates **28a**–**e** from **25a**–**d** in two steps can not also be excluded.

Thus, 4-(3-oxobutyl)semicarbazides **20a**–**e** under acidic conditions afford cyclic bis-semicarbazones **24a**–**e**, but not the corresponding 1,2,4-triazepin-3-ones. We suppose that the formation of the latters is completely suppressed, since the major isomers (84–95%, Table 4) of **20a**–**e** have *E*-configuration, which is unfavorable for cyclization into 7-membered cyclic semicarbazones.

In contrast to **20a**–**e**, TsOH-catalyzed cyclization of hydrazones of γ-phenyl substituted semicarbazides **20f**–**h** resulted in formation of triazepines **29a**–**c** (Scheme 9). No corresponding macrocyclic bis-semicarbazones were detected in the crude isolated materials (^{1}H NMR data).

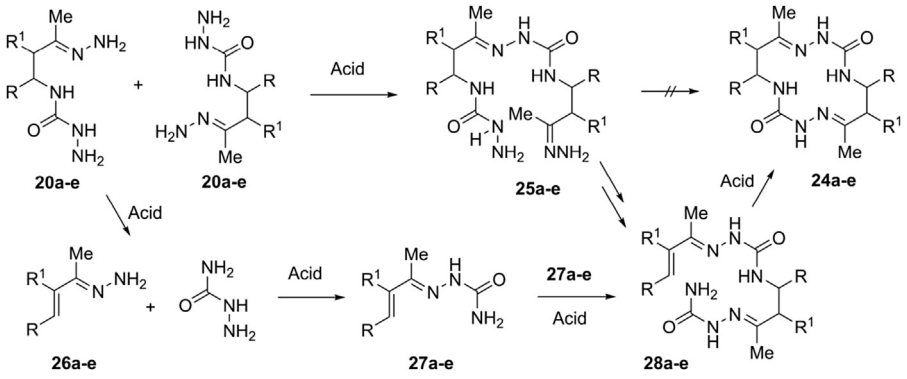


Scheme 9. Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **29a**–**c**.

The reaction conditions for the transformation of **20f**–**h** into **29a**–**c** were optimized using semicarbazide **20f** as a starting material (Table 6).

First of all, we found that more than 1 equiv of TsOH was required for the complete conversion of the starting material, otherwise the reaction did not proceed (entries 1, 2). Under all studied conditions some amount of unidentified side products always formed along with triazepinone **29a** according to ^{1}H NMR spectroscopic data for the isolated crude materials. The characteristic features of these spectra were an increase in the relative integral intensity of the aromatic protons region (6.6–8.2 ppm), the unresolved very broad signals at 2.8–3.6, 4.8–5.3, and 9.7–10.5 ppm. The amount of these side products depended on the starting concentration of **20f**. At higher concentrations, the amount of side products increased (entries 5, 6, and 7). Solvent polarity had little effect on the product formation (entries 3–5). The reaction temperature caused dramatic changes (entries 3–7 vs entry 8). At room temperature triazepinone **29a** was formed in insignificant amounts (^{1}H NMR data). Triazepinones **29a**–**c** were very soluble in common solvents and were isolated using column chromatography on silica gel in moderate yields (entries 7, 9, and 10).

The structures of **29a**–**c** were established by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry. The values of vicinal coupling constants between $N_{(4)}H$, H-5, H_A-6, and H_B-6 have proved that triazepinones **29a**–**c** exist predominantly in a puckered conformation with a pseudo axial orientation of the aryl-group at the C-5 position (in DMSO-d_6).



Scheme 8. A plausible pathway for the transformation of **20a**–**e** into macrocycles **24a**–**e**.

Table 6
TsOH-catalyzed transformation of hydrazones of 4-(3-oxo-3-phenylprop-1-yl)semicarbazides **20f**–**h** into 7-phenyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **29a**–**c**

Entry	**20**	*R*	Conc. of **20** (mol/L)	Equiv of TsOH	Solvent	Reaction conditions	Product	Purity of crude **29** (%)[b]	Yield (%)[c]
1	**20f**	Ph	0.102	0.10	MeOH	Reflux, 2.5 h	NR[a]	—	—
2	**20f**	Ph	0.102	0.51	MeOH	Reflux, 50 min	NR[a]	—	—
3	**20f**	Ph	0.102	1.04	MeOH	Reflux, 1 h	**29a**	19	—
4	**20f**	Ph	0.146	1.21	MeCN	Reflux, 5 h	**29a**	23	—
5	**20f**	Ph	0.112	0.98	EtOH	Reflux, 1 h 50 min	**29a**	28	—
6	**20f**	Ph	0.019	1.01	EtOH	Reflux, 1 h 50 min	**29a**	49	—
7	**20f**	Ph	0.030	1.04	EtOH	Reflux, 1 h 50 min	**29a**	39	39
8	**20f**	Ph	0.093	1.10	EtOH	rt, 2 h	**29a**	3	—
9	**20g**	4-MeC_6H_4	0.030	1.05	EtOH	Reflux, 1 h 50 min	**29b**	—	45
10	**20h**	4-ClC_6H_4	0.023	1.02	EtOH	Reflux, 1 h 50 min	**29c**	—	41

[a] NR=no reaction occurred (TLC analysis).
[b] Purity was estimated as ratio of the expected integral intensity of the aromatic protons region (10H for **29a**) to the observed integral intensity in this region in the ^{1}H NMR spectrum of the crude product multiplied by 100. The starting material was consumed (entries 3–8).
[c] For analytically pure samples after column chromatography.

Thus, in contrast to **20a**–**e**, semicarbazides **20f**–**h** under acidic conditions gave the corresponding 7-membered cyclic semicarbazones. The reason for this difference is apparently due to opposite configurations of the major isomers of compounds **20a**–**e** and **20f**–**h**. The major isomers of **20f**–**h** (75–84%, Table 4) have the *E*-configuration, which is favorable for intramolecular nucleophilic attack of the NH_2 group of hydrazone moiety in **20f**–**h** on the carbonyl carbon to give **29a**–**c**.

3. Conclusion

We have demonstrated that the acid-catalyzed cyclization of the hydrazones of 4-(3-oxobutyl)semicarbazides involves two molecules of the starting material to give a general access to novel 14-membered cyclic bis-semicarbazones. In contrast, the hydrazones of 4-(3-oxo-3-phenylpropyl)semicarbazides under similar conditions transform into 7-membered cyclic semicarbazones. Such a difference was explained by the opposite stereochemistry of the major isomers of the starting semicarbazides. These compounds were prepared by the treatment of *N*-(γ-oxoalkyl)carbamates with refluxing hydrazine. For the preparation of *N*-(γ-oxoalkyl)carbamates[18] a simple multi-gram three-step approach has been developed. The method is based on the amidoalkylation of 1,3-diketone enolates with *N*-(α-tosylbenzyl)carbamates followed by base-promoted retro-Claisen reaction. We believe that the obtained classes of heterocycles, which are representatives of rare heterocyclic scaffolds, may find broad applications in synthetic organic and medicinal chemistry, e.g., as new polyazamacrocyclic ligands for metal complexes, as a basis for the development of new therapeutics, etc.

4. Experimental section

4.1. General

All solvents were distilled before use. Petroleum ether had a distillation range of 40–60 °C. Dry solvents (MeCN, THF) were obtained according to standard procedures. *p*-Toluenesulfinic acid (**13**) was synthesized by treatment of a saturated aqueous solution of sodium *p*-toluenesulfinate[25] with hydrochloric acid at 0 °C, dried over P_2O_5, and stored at −18 °C. Sodium hydride (60% suspension in mineral oil) was thoroughly washed with dry pentane and dried under vacuum prior to use. Anhydrous hydrazine was obtained by refluxing with an equal weight of KOH pellets for 3 h under argon followed by distillation, and this operation was repeated twice. 3-Methylpentane-2,4-dione (**14b**) was prepared as described in the literature[26] with 86.7 wt % purity (a 3:1 mixture of ketone and enol form in $CDCl_3$) (3,3-dimethylpentane-2,4-dione was the admixture, 12 mol % according to ^{1}H NMR data). All other reagents were purchased from commercial sources and used without additional purification. FTIR spectra were recorded using a Bruker Vector 22 spectrophotometer in Nujol. Band characteristics in the IR spectra are defined as very strong (vs), strong (s), medium (m), weak (w), shoulder (sh), and broad (br). NMR spectra were acquired using a Bruker DPX-300 spectrometer at 300.13 (^{1}H) and 75.48 (^{13}C) MHz and a Bruker Avance 600 spectrometer at 600.13 MHz (^{1}H and ^{1}H,^{1}H-NOESY for **20h**) as solutions in DMSO-d_6. ^{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. Mass spectra were obtained on a Finnigan MAT INCOS 50 instrument (electron impact, 70 eV). Elemental analyses (CHN) were performed using a Thermo Finnigan Flash EA1112 apparatus. Thin-layer chromatography was carried out on Aldrich silica gel 60 F_{254} aluminum backed plates in chloroform/methanol (9:1, v/v) and chloroform/methanol (5:1, v/v) as solvent systems. Spots were visualized with UV light. Column chromatography was performed with Macherey–Nagel silica gel 60 (0.063–0.200 mm). All yields refer to isolated, spectroscopically and TLC pure compounds. The color of substances was white, if not otherwise mentioned. Evaporation of solvent from all the reaction mixtures formed after the preparation of carbamates **17** was carried out, at the beginning, upon cooling (temperature of water bath about 5–10 °C), and low vacuum (about 100 mmHg), otherwise the vigorous foaming complicated evaporation. In some complex cases the reaction mixture was transferred into a larger flask prior the evaporation of solvent.

4.2. Synthesis of ethyl *N*-[(β-acyl-γ-oxo)alkyl]carbamates

*4.2.1. Ethyl N-[(phenyl)(tosyl)methyl]carbamate (**15a**).* To a stirred emulsion of benzaldehyde (5.660 g, 53.34 mmol) in H_2O (25 mL) were added *p*-toluenesulfinic acid (**13**) (8.342 g, 53.40 mmol) and H_2O (25 mL) and the resulting mixture was stirred for 20 min at room temperature. To the formed suspension were added ethyl carbamate (**12**) (4.767 g, 53.51 mmol) and H_2O (16 mL) and the suspension was heated under stirring in a water bath (70 °C). After 5 min, an oily material formed and after 25 min it started to solidify. Heating of the reaction mixture (70 °C, water bath) was continued for 1 h in total. After completion of the reaction, the obtained suspension was cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give carbamate **15a** (15.622 g, 88%) which was used without additional purification. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.93 (1H, d, ^3J=10.8 Hz, NH), 7.56–7.72 (4H, m, ArH), 7.35–7.45 (5H, m, ArH),

5.99 (1H, d, ^3J=10.8 Hz, CHN), 3.76–3.92 (2H, m, OCH_2), 2.40 (3H, s, CH_3 in Ts), 1.01 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.26 (C=O), 144.57 (C), 133.75 (C), 130.39 (C), 129.59 (2CH), 129.46 (2CH), 129.26 (CH), 129.16 (2CH), 128.07 (2CH), 74.88 (CHN), 60.62 (OCH_2), 21.08 (CH_3 in Ts), 14.35 (CH_3 in OEt).

*4.2.2. Ethyl N-[(4-methylphenyl)(tosyl)methyl]carbamate (**15b**).* Compound **15b** (37.72 g, 86%) was prepared from 4-methylbenzaldehyde (15.14 g, 126 mmol), *p*-toluenesulfinic acid (**13**) (19.71 g, 126 mmol) and ethyl carbamate (**12**) (12.97 g, 146 mmol) in H_2O (126 mL) (70 °C, 1 h 30 min) as described for **15a**. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.87 (1H, d, ^3J=10.8 Hz, NH), 7.65–7.72 (2H, m, ArH), 7.38–7.51 (4H, m, ArH), 7.16–7.22 (2H, m, ArH), 5.93 (1H, d, ^3J=10.8 Hz, CHN), 3.75–3.91 (2H, m, OCH_2), 2.40 (3H, s, CH_3 in Ts), 2.32 (3H, s, CH_3 in 4-MeC_6H_4), 1.00 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.22 (C=O), 144.48 (C), 138.79 (C), 133.87 (C), 129.49 (2CH), 129.44 (2CH), 129.14 (2CH), 128.63 (2CH), 127.33 (C), 74.72 (CHN), 60.58 (OCH_2), 21.07 (CH_3 in Ts), 20.78 (CH_3 in 4-MeC_6H_4), 14.35 (CH_3 in OEt).

*4.2.3. Ethyl N-[(4-methoxylphenyl)(tosyl)methyl]carbamate (**15c**).* To 4-methoxylbenzaldehyde (0.451 g, 3.31 mmol) were added *p*-toluenesulfinic acid (**13**) (0.519 g, 3.33 mmol), ethyl carbamate (**12**) (0.351 g, 3.94 mmol) and H_2O (3 mL) and the resulting mixture was stirred at room temperature. At the beginning of the reaction the oily material formed and after 1 h it completely solidified. The obtained solid was triturated and the resulting suspension was stirred at room temperature for 24 h in total. After completion of the reaction, the suspension was cooled to 0 °C, the precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give carbamate **15c** (1.112 g, 92%) which was used without additional purification. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.86 (1H, d, ^3J=10.8 Hz, NH), 7.64–7.71 (2H, m, ArH), 7.49–7.56 (2H, m, ArH), 7.38–7.45 (2H, m, ArH), 7.91–7.97 (2H, m, ArH), 5.92 (1H, d, ^3J=10.8 Hz, CHN), 3.75–3.91 (2H, m, OCH_2), 3.77 (3H, s, OCH_3), 2.40 (3H, s, CH_3 in Ts), 1.00 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 160.02 (C), 155.23 (C=O), 144.46 (C), 133.91 (C), 131.01 (2CH), 129.46 (2CH), 129.16 (2CH), 122.14 (C), 113.53 (2CH), 74.45 (CHN), 60.59 (OCH_2), 55.20 (OCH_3), 21.12 (CH_3 in Ts), 14.40 (CH_3 in OEt).

*4.2.4. Ethyl N-[(4-tert-butylphenyl)(tosyl)methyl]carbamate (**15d**).* Compound **15d** (11.833 g, 81%) was prepared from 4-*tert*-butylbenzaldehyde (6.090 g, 37.54 mmol), *p*-toluenesulfinic acid (**13**) (5.879 g, 37.63 mmol) and ethyl carbamate (**12**) (4.040 g, 45.34 mmol) in H_2O (74 mL) (rt, 24 h) as described for **15c**. Solidification of initially formed oily material completed in 4 h. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.91 (1H, d, ^3J=10.7 Hz, NH), 7.68–7.75 (2H, m, ArH), 7.51–7.58 (2H, m, ArH), 7.37–7.45 (4H, m, ArH), 5.94 (1H, d, ^3J=10.7 Hz, CHN), 3.73–3.88 (2H, m, OCH_2), 2.40 (3H, s, CH_3 in Ts), 1.29 (9H, s, CH_3 in *t*-Bu), 0.98 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.19 (C=O), 151.84 (C), 144.52 (C), 133.93 (C), 129.45 (2CH), 129.39 (2CH), 129.17 (2CH), 127.28 (C), 124.94 (2CH), 74.56 (CHN), 60.57 (OCH_2), 34.42 (CMe_3), 31.02 (3×CH_3 in *t*-Bu), 21.11 (CH_3 in Ts), 14.39 (CH_3 in OEt).

*4.2.5. Ethyl N-[(4-chlorophenyl)(tosyl)methyl]carbamate (**15e**).* To a finely powdered 4-chlorobenzaldehyde (5.251 g, 37.36 mmol) were added *p*-toluenesulfinic acid (**13**) (5.856 g, 37.49 mmol), ethyl carbamate (**12**) (3.969 g, 37.49 mmol) and H_2O (42 mL) and the reaction mixture was heated under stirring in a water bath (70 °C). After 15 min, an oily material formed and after 30 min it completely solidified. The obtained solid was triturated and the resulting suspension was heated (70 °C, water bath) under stirring for 1 h 30 min in total. The obtained suspension was cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give carbamate **15e** (12.726 g, 93%) which was used without additional purification. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.96 (1H, d, ^3J=10.8 Hz, NH), 7.62–7.73 (4H, m, ArH), 7.40–7.51 (4H, m, ArH), 6.07 (1H, d, ^3J=10.8 Hz, CHN), 3.75–3.91 (2H, m, OCH_2), 2.40 (3H, s, CH_3 in Ts), 1.00 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.20 (C=O), 144.78 (C), 134.29 (C), 133.52 (C), 131.48 (2CH), 129.56 (2CH), 129.45 (C), 129.25 (2CH), 128.19 (2CH), 74.05 (CHN), 60.72 (OCH_2), 21.14 (CH_3 in Ts), 14.38 (CH_3 in OEt).

*4.2.6. Ethyl N-(1-tosylbut-1-yl)carbamate (**15f**).* Compound **15f** (33.76 g, 94%) was prepared from butanal (8.65 g, 120 mmol), *p*-toluenesulfinic acid (**13**) (18.75 g, 120 mmol) and ethyl carbamate (**12**) (12.83 g, 144 mmol) in H_2O (120 mL) (70 °C, 1 h 30 min) as described for **15a**. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.12 (1H, d, ^3J=9.8 Hz, NH), 7.64–7.70 (2H, m, ArH), 7.39–7.45 (2H, m, ArH), 4.70 (1H, ddd, ^3J=11.4, ^3J=9.8, ^3J=3.3 Hz, CHN), 3.72–3.88 (2H, m, OCH_2), 2.39 (3H, s, CH_3 in Ts), 1.82–1.93 (1H, m, CH_A in $CH_2CH_2CH_3$), 1.57–1.70 (1H, m, CH_B in $CH_2CH_2CH_3$), 1.17–1.48 (2H, m, $CH_2CH_2CH_3$), 0.99 (3H, t, ^3J=7.1 Hz, CH_3 in OEt), 0.84 (3H, t, ^3J=7.4 Hz, CH_3 in Pr).

4.3. Synthesis of ethyl *N*-[(β-acyl-γ-oxo)alkyl]carbamates

*4.3.1. Ethyl N-[(2-acetyl-3-oxo-1-phenyl)but-1-yl]carbamate (**17a**).* To an ice-cooled stirred suspension of NaH (0.316 g, 13.18 mmol) in dry MeCN (10 mL) was added a solution of acetylacetone (**16a**) (1.341 g, 13.39 mmol) in MeCN (12 mL), and the resulting mixture was stirred for 30 min. The ice-bath was removed, and to the obtained suspension were added sulfone **15a** (4.007 g, 12.02 mmol) and MeCN (4 mL). The mixture was stirred at room temperature for 8 h, and the solvent was removed in vacuo. The oily residue was triturated with saturated aqueous $NaHCO_3$ (10 mL) and petroleum ether (10 mL), the obtained suspension was left overnight at room temperature and cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give compound **17a** (3.099 g, 93%). Mp 100.5–101.5 °C (EtOH–H_2O, 1:1) (lit.[17a] mp 87–88 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.78 (1H, d, ^3J=9.2 Hz, NH), 7.19–7.35 (5H, m, ArH), 5.15 (1H, dd, ^3J=11.3, ^3J=9.2 Hz, CHN), 4.48 (1H, d, ^3J=11.3 Hz, $CHAc_2$), 3.83–3.98 (2H, m, OCH_2), 2.23 (3H, s, CH_3 in Ac), 1.88 (3H, s, CH_3 in Ac), 1.09 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 201.48 (C=O in Ac), 201.32 (C=O in Ac), 155.32 (C=O in COOEt), 140.64 (C), 128.38 (2CH), 127.51 (CH), 127.28 (2CH), 71.73 ($CHAc_2$), 59.95 (OCH_2), 54.13 (CHN), 30.78 (CH_3 in Ac), 30.14 (CH_3 in Ac), 14.45 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3372 (s) (ν NH), 3086 (w), 3064 (w), 3035 (w) (ν CH_{arom}), 1735 (s) (ν C=O in Ac), 1693 (vs) (amide-I), 1603 (w), 1584 (w) (ν CC_{arom}), 1529 (s) (amide-II), 1255 (s), 1146 (s) (ν C–O), 758 (m), 704 (s) (δ CH_{arom}). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.98; H, 6.97; N, 5.26.

*4.3.2. Ethyl N-{[2-acetyl-1-(4-methylphenyl)-3-oxo]but-1-yl}carbamate (**17b**).* Compound **17b** (3.270 g, 91%) was prepared from acetylacetone (**16a**) (1.270 g, 12.67 mmol), NaH (0.299 g, 12.46 mmol) and sulfone **15b** (4.230 g, 12.38 mmol) in dry MeCN (26 mL) (rt, 9 h 30 min) as described for **17a**. (*Note*: the reaction was carried out in a 50 mL round-bottomed flask, the reaction mixture was transferred into a 250 mL round-bottomed flask prior to evaporation since the vigorous foam formation during the evaporation complicated removal of the solvent when the flask of lower volume was used). Mp 94–95 °C (EtOH–H_2O, 1:1). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.70 (1H, d, ^3J=9.3 Hz, NH), 7.16–7.21 (2H, m, ArH), 7.08–7.13 (2H, m, ArH), 5.12 (1H, dd, ^3J=11.2, ^3J=9.3 Hz, CHN), 4.45 (1H, d, ^3J=11.2 Hz, $CHAc_2$), 3.82–3.98 (2H, m,

OCH_2), 2.25 (3H, s, CH_3 in 4-MeC_6H_4), 2.22 (3H, s, CH_3 in Ac), 1.88 (3H, s, CH_3 in Ac), 1.09 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 201.53 (C=O in Ac), 201.28 (C=O in Ac), 155.25 (C=O in COOEt), 137.64 (C), 136.61 (C), 128.87 (2CH), 127.14 (2CH), 71.79 (*C*HAc_2), 59.85 (OCH_2), 53.84 (CHN), 30.67 (CH_3 in Ac), 30.04 (CH_3 in Ac), 20.60 (CH_3 in 4-MeC_6H_4), 14.42 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3327 (s) (ν NH), 3037 (m) (ν CH_{arom}), 1701 (s) (ν C=O in Ac), 1683 (s) (amide-I), 1618 (w) (ν CC_{arom}), 1532 (s) (amide-II), 1256 (s), 1157 (s) (ν C–O), 823 (m) (δ CH_{arom}). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.69; H, 7.15; N, 4.82.

*4.3.3. Ethyl N-{[2-acetyl-1-(4-methoxyphenyl)-3-oxo]but-1-yl}carbamate (**17c**).* Compound **17c** (2.344 g, 90%) was prepared from acetylacetone (**16a**) (0.885 g, 8.84 mmol), NaH (0.204 g, 8.51 mmol) and sulfone **15c** (3.089 g, 8.50 mmol) in dry MeCN (26 mL) (rt, 8 h 40 min) as described for **17a**. Mp 99–101 °C (EtOH–H_2O, 1:2). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.71 (1H, d, ^3J=9.3 Hz, NH), 7.19–7.25 (2H, m, ArH), 6.83–6.89 (2H, m, ArH), 5.10 (1H, dd, ^3J=11.4, ^3J=9.3 Hz, CHN), 4.43 (1H, d, ^3J=11.4 Hz, C*H*Ac_2), 3.83–3.98 (2H, m, OCH_2), 3.71 (3H, s, OCH_3), 2.22 (3H, s, CH_3 in Ac), 1.88 (3H, s, CH_3 in Ac), 1.09 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 201.58 (C=O in Ac), 201.36 (C=O in Ac), 158.47 (C), 155.26 (C=O in COOEt), 132.63 (C), 128.45 (2CH), 113.68 (2CH), 72.01 (*C*HAc_2), 59.88 (OCH_2), 55.00 (OCH_3), 53.60 (CHN), 30.74 (CH_3 in Ac), 30.04 (CH_3 in Ac), 14.46 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3362 (s) (ν NH), 3061 (w), 3039 (w) (ν CH_{arom}), 1727 (s) (ν C=O in Ac), 1690 (s) (amide-I), 1612 (m), 1586 (w) (ν CC_{arom}), 1531 (s), 1520 (s) (amide-II), 1257 (s), 1029 (s) (ν C–O), 827 (m) (δ CH_{arom}). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.66; H, 6.90; N, 4.70.

*4.3.4. Ethyl N-{[2-acetyl-1-(4-tert-butylphenyl)-3-oxo]but-1-yl}carbamate (**17d**).* Compound **17d** (2.519 g, 93%) was prepared from acetylacetone (**16a**) (0.848 g, 8.47 mmol), NaH (0.195 g, 8.14 mmol) and sulfone **15d** (3.170 g, 8.14 mmol) in dry MeCN (22 mL) (rt, 8 h 10 min) as described for **17a**. Mp 100.5–101.5 °C (EtOH–H_2O, 1:1). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.72 (1H, d, ^3J=9.3 Hz, NH), 7.30–7.35 (2H, m, ArH), 7.20–7.25 (2H, m, ArH), 5.14 (1H, dd, ^3J=11.3, ^3J=9.3 Hz, CHN), 4.47 (1H, d, ^3J=11.3 Hz, CHC=O), 3.82–3.98 (2H, m, OCH_2), 2.22 (3H, s, CH_3 in Ac), 1.89 (3H, s, CH_3 in Ac), 1.24 (9H, s, CH_3 in *t*-Bu), 1.10 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 201.63 (C=O in Ac), 201.34 (C=O in Ac), 155.29 (C=O in COOEt), 149.76 (C), 137.66 (C), 126.92 (2CH), 125.12 (2CH), 71.70 (*C*HAc_2), 59.91 (OCH_2), 53.66 (CHN), 34.20 (*C*Me_3), 31.09 (3×CH_3 in *t*-Bu), 30.64 (CH_3 in Ac), 30.07 (CH_3 in Ac), 14.45 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3530 (br w), 3396 (br m), 3348 (br m) (ν NH), 3060 (w) (ν CH_{arom}), 1734 (s) (ν C=O in Ac), 1701 (s) (amide-I), 1520 (s) (amide-II), 1270 (s), 1051 (m) (ν C–O), 832 (w) (δ CH_{arom}). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.10; H, 8.36; N, 4.19.

*4.3.5. Ethyl N-[(3-acetyl-2-oxo)hept-4-yl]carbamate (**17e**).* Compound **17e** (2.401 g, 89%) was prepared from acetylacetone (**16a**) (1.128 g, 11.26 mmol), NaH (0.265 g, 11.04 mmol) and sulfone **15f** (3.305 g, 11.04 mmol) in dry MeCN (25 mL) (rt, 8 h 10 min) as described for **17a**. Mp 89.5–90.5 °C (EtOH–H_2O, 1:2). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.02 (1H, d, ^3J=9.4 Hz, NH), 4.07–4.17 (1H, m, CHN), 3.87–4.02 (3H, m, OCH_2 and CHC=O), 2.17 (3H, s, CH_3 in Ac), 2.10 (3H, s, CH_3 in Ac), 1.15–1.34 (4H, m, $CH_2CH_2CH_3$), 1.12 (3H, t, ^3J=7.1 Hz, CH_3 in OEt), 0.82 (3H, t, ^3J=7.0 Hz, CH_3 in Pr); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 203.05 (C=O in Ac), 202.98 (C=O in Ac), 155.93 (C=O in COOEt), 71.74 (*C*HAc_2), 59.72 (OCH_2), 49.83 (CHN), 35.06 ($CH_2CH_2CH_3$), 30.80 (CH_3 in Ac), 29.53 (CH_3 in Ac), 18.57 ($CH_2CH_2CH_3$), 14.55 (CH_3 in OEt), 13.57 (CH_3 in Pr); IR (Nujol) ν, cm^{-1}: 3322 (s) (ν NH), 1723 (s) (ν C=O in Ac), 1691 (s) (amide-I), 1544 (s) (amide-II), 1300 (s) (ν C–O). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.18; H, 8.80; N, 5.90.

*4.3.6. Ethyl N-[(2-acetyl-2-methyl-3-oxo-1-phenyl)but-1-yl]carbamate (**17f**).* Compound **17f** (3.053 g, 81%) was prepared from 3-methylpentane-2,4-dione (**16b**) (86.7% wt, 1.716 g, 13.04 mmol), NaH (0.312 g, 13.00 mmol) and sulfone **15a** (4.333 g, 12.99 mmol) in dry THF (26 mL) (rt, 8 h 5 min) as described for **17a**. Mp 84–85 °C (EtOH–H_2O, 1:1). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.80 (1H, d, ^3J=10.6 Hz, NH), 7.19–7.33 (5H, m, ArH), 5.77 (1H, d, ^3J=10.6 Hz, CHN), 3.86–4.03 (2H, m, OCH_2), 2.11 (3H, s, CH_3 in Ac), 1.92 (3H, s, CH_3 in Ac), 1.29 (3H, s, C*H*$_3$CAc_2), 1.12 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 206.18 (C=O in Ac), 204.19 (C=O in Ac), 155.82 (C=O in COOEt), 139.31 (C), 128.31 (2CH), 127.85 (2CH), 127.27 (CH), 70.65 (*C*Ac_2), 60.17 (OCH_2), 56.40 (CHN), 27.39 (CH_3 in Ac), 26.46 (CH_3 in Ac), 14.50 (CH_3 in OEt), 14.19 (*C*H_3CAc_2); IR (Nujol) ν, cm^{-1}: 3352 (s) (ν NH), 3057 (w), 3029 (w) (ν CH_{arom}), 1722 (s) (ν C=O in Ac), 1699 (vs) (amide-I), 1600 (w), 1580 (w) (ν CC_{arom}), 1525 (s) (amide-II), 1499 (w) (ν CC_{arom}), 1239 (s), 1043 (s) (ν C–O), 768 (m), 713 (s) (δ CH_{arom}). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.01; H, 7.27; N, 4.81.

*4.3.7. Ethyl N-{[2-acetyl-1-(4-methylphenyl)-2-methyl-3-oxo]but-1-yl}carbamate (**17g**).* Compound **17g** (2.508 g, 87%) was prepared from 3-methylpentane-2,4-dione (**16b**) (86.7% wt, 1.246 g, 9.47 mmol), NaH (0.227 g, 9.44 mmol) and sulfone **15b** (3.275 g, 9.42 mmol) in dry THF (24 mL) (rt, 8 h 10 min) as described for **17a**. Mp 93–94 °C (EtOH–H_2O, 1:1). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.73 (1H, d, ^3J=10.6 Hz, NH), 7.15–7.21 (2H, m, ArH), 7.05–7.11 (2H, m, ArH), 5.72 (1H, d, ^3J=10.6 Hz, CHN), 3.85–4.02 (2H, m, OCH_2), 2.24 (3H, s, CH_3 in 4-MeC_6H_4), 2.10 (3H, s, CH_3 in Ac), 1.92 (3H, s, CH_3 in Ac), 1.28 (3H, s, C*H*$_3$CAc_2), 1.12 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 206.20 (C=O in Ac), 204.31 (C=O in Ac), 155.79 (C=O in COOEt), 136.38 (C), 136.32 (C), 128.41 (2CH), 128.23 (2CH), 70.68 (*C*Ac_2), 60.12 (OCH_2), 56.25 (CHN), 27.39 (CH_3 in Ac), 26.46 (CH_3 in Ac), 20.58 (CH_3 in 4-MeC_6H_4), 14.51 (CH_3 in OEt), 14.20 (*C*H_3CAc_2); IR (Nujol) ν, cm^{-1}: 3387 (s) (ν NH), 3091 (w) (ν CH_{arom}), 1720 (s) (ν C=O in Ac), 1693 (s) (amide-I), 1615 (w) (ν CC_{arom}), 1525 (s) (amide-II), 1233 (s), 1039 (s) (ν C–O), 820 (m) (δ CH_{arom}). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.87; H, 7.59; N, 4.59. Found: C, 66.99; H, 7.67; N, 4.77.

*4.3.8. Ethyl N-{[2-acetyl-1-(4-methoxylphenyl)-2-methyl-3-oxo]but-1-yl}carbamate (**17h**).* Compound **17h** (2.731 g, 83%) was prepared from 3-methylpentane-2,4-dione (**16b**) (86.7% wt, 1.354 g, 10.29 mmol), NaH (0.246 g, 10.26 mmol) and sulfone **15c** (3.726 g, 10.25 mmol) in dry THF (25 mL) (rt, 8 h 5 min) as described for **17a**. Mp 91–92 °C (EtOH–H_2O, 1:1). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.72 (1H, d, ^3J=10.6 Hz, NH), 7.19–7.25 (2H, m, ArH), 6.81–6.87 (2H, m, ArH), 5.71 (1H, d, ^3J=10.6 Hz, CHN), 3.85–4.02 (2H, m, OCH_2), 3.71 (3H, s, OCH_3), 2.10 (3H, s, CH_3 in Ac), 1.91 (3H, s, CH_3 in Ac), 1.28 (3H, s, C*H*$_3$CAc_2), 1.12 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 206.27 (C=O in Ac), 204.37 (C=O in Ac), 158.30 (C), 155.78 (C=O in COOEt), 131.23 (C), 129.49 (2CH), 113.17 (2CH), 70.78 (*C*Ac_2), 60.12 (OCH_2), 55.93 (CHN), 54.97 (OCH_3), 27.38 (CH_3 in Ac), 26.46 (CH_3 in Ac), 14.51 (CH_3 in OEt), 14.19 (*C*H_3CAc_2); IR (Nujol) ν, cm^{-1}: 3385 (s) (ν NH), 3071 (w), 3037 (w) (ν CH_{arom}), 1714 (vs), 1706 (sh) (ν C=O in Ac and amide-I), 1608 (m), 1581 (w) (ν CC_{arom}), 1528 (vs) (amide-II), 1234 (s), 1032 (s) (ν C–O), 841 (m) (δ CH_{arom}). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.58; H, 7.18; N, 4.39.

*4.3.9. Ethyl N-{[2-acetyl-1-(4-tert-butylphenyl)-2-methyl-3-oxo]but-1-yl}carbamate (**17i**).* Compound **17i** (2.002 g, 84%) was prepared from 3-methylpentane-2,4-dione (**16b**) (86.7% wt, 0.902 g,

6.85 mmol), NaH (0.164 g, 6.84 mmol) and sulfone **15d** (2.664 g, 6.84 mmol) in dry THF (22 mL) (rt, 8 h 20 min) as described for **17a**. Mp 100.5–101.5 °C (EtOH–H_2O, 1:1). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.75 (1H, d, ^3J=10.6 Hz, NH), 7.27–7.32 (2H, m, ArH), 7.20–7.25 (2H, m, ArH), 5.74 (1H, d, ^3J=10.6 Hz, CHN), 3.85–4.02 (2H, m, OCH_2), 2.10 (3H, s, CH_3 in Ac), 1.93 (3H, s, CH_3 in Ac), 1.29 (3H, s, CH_3CAc_2), 1.24 (9H, s, CH_3 in *t*-Bu), 1.12 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 206.14 (C=O in Ac), 204.29 (C=O in Ac), 155.81 (C=O in COOEt), 149.44 (C), 136.36 (C), 128.05 (2CH), 124.58 (2CH), 70.71 (CAc_2), 60.13 (OCH_2), 56.02 (CHN), 34.14 (CMe_3), 31.08 (3×CH_3 in *t*-Bu), 27.33 (CH_3 in Ac), 26.45 (CH_3 in Ac), 14.51 (CH_3 in OEt), 14.24 (CH_3CAc_2); IR (Nujol) ν, cm^{-1}: 3356 (s) (ν NH), 1721 (s) (ν C=O in Ac), 1700 (s) (amide-I), 1533 (s) (amide-II), 1236 (s), 1041 (s) (ν C–O), 846 (m) (δ CH_{arom}). Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.09; H, 8.58; N, 4.03.

*4.3.10. Ethyl N-[(2-benzoyl-3-oxo-1,3-diphenyl)prop-1-yl]carbamate (**17j**).* To a mixture of dibenzoylmethane (**16c**) (2.138 g, 9.53 mmol) and NaH (0.218 g, 9.07 mmol) was added dry THF (17 mL), the mixture was stirred in an ice-cold bath for 15 min, and to the resulting solution were added sulfone **15a** (3.024 g, 9.07 mmol) and THF (7 mL). The suspension was stirred at room temperature for 8 h, and solvent was removed in a vacuum. To a solid residue was added saturated aqueous $NaHCO_3$ (10 mL), the obtained mixture was triturated until complete crystallization, the resulting suspension was left overnight at room temperature, and cooled to 0 °C. The precipitate was filtered, washed with ice-cold water and petroleum ether, and dried to give **17j** (3.465 g, 95%). Mp 140–143 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.99–8.04 (2H, m, ArH), 7.74–7.79 (2H, m, ArH), 7.74 (1H, d, ^3J=9.1 Hz, NH, signals partly overlap with signals of aromatic protons), 7.60–7.66 (1H, m, ArH), 7.47–7.57 (3H, m, ArH), 7.36–7.43 (4H, m, ArH), 7.15–7.22 (2H, m, ArH), 7.05–7.12 (1H, m, ArH), 6.38 (1H, d, ^3J=10.1 Hz, CHC=O), 5.53 (1H, dd, ^3J=10.1, ^3J=9.1 Hz, CHN), 3.78–3.93 (2H, m, OCH_2), 1.03 (3H, t, ^3J=7.1 Hz, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 193.32 (C=O in Bz), 193.09 (C=O in Bz), 155.18 (C=O in COOEt), 140.56 (C), 136.30 (C), 135.59 (C), 133.85 (CH), 133.81 (CH), 128.95 (2CH), 128.85 (2CH), 128.61 (2CH), 128.34 (2CH), 128.10 (2CH), 127.54 (2CH), 127.25 (CH), 59.85 (OCH_2), 59.75 ($CHBz_2$), 55.22 (CHN), 14.39 (CH_3); IR (Nujol) ν, cm^{-1}: 3354 (br s), 3317 (sh) (ν NH), 3062 (w), 3031 (w) (ν CH_{arom}), 1724 (s), 1693 (s), 1661 (m) (amide-I and ν C=O in Bz), 1595 (m) (ν CC_{arom}), 1527 (s) (amide-II), 1499 (w) (ν CC_{arom}), 1284 (s), 1041 (s) (ν C–O), 762 (s), 699 (s) (δ CH_{arom}). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49. Found: C, 74.73; H, 5.67; N, 3.64.

*4.3.11. Ethyl N-{[2-benzoyl-1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}carbamate (**17k**).* Compound **17k** (3.916 g, 96%) was prepared from dibenzoylmethane (**16c**) (2.326 g, 10.17 mmol), NaH (0.237 g, 9.88 mmol) and sulfone **15b** (3.428 g, 9.87 mmol) in dry THF (25 mL) (rt, 8 h) as described for **17j**. Mp 162–163.5 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.00–8.05 (2H, m, ArH), 7.75–7.81 (2H, m, ArH), 7.67 (1H, d, ^3J=9.2 Hz, NH), 7.47–7.66 (4H, m, ArH), 7.37–7.44 (2H, m, ArH), 7.25–7.31 (2H, m, ArH), 6.96–7.02 (2H, m, ArH), 6.37 (1H, d, ^3J=10.1 Hz, CHC=O), 5.51 (1H, dd, ^3J=10.1, ^3J=9.2 Hz, CHN), 3.77–3.91 (2H, m, OCH_2), 2.14 (3H, s, CH_3 in 4-MeC_6H_4), 1.02 (3H, t, ^3J=7.1 Hz, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 193.23 (C=O in Bz), 193.21 (C=O in Bz), 155.14 (C=O in COOEt), 137.67 (C), 136.33 (C), 136.31 (C), 135.67 (C), 133.83 (CH), 133.77 (CH), 128.92 (2CH), 128.87 (2CH), 128.65 (2CH), 128.63 (2CH), 128.34 (2CH), 127.46 (2CH), 59.87 ($CHBz_2$), 59.80 (OCH_2), 54.99 (CHN), 20.55 (CH_3 in 4-MeC_6H_4), 14.38 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3288 (br s) (ν NH), 3061 (w) (ν CH_{arom}), 1694 (s), 1682 (s) (amide-I and ν C=O in Bz), 1596 (m), 1579 (w) (ν CC_{arom}), 1551 (s) (amide-II), 1516 (w) (ν CC_{arom}), 1289 (s), 1045 (s) (ν C–O), 808 (m), 764 (m), 690 (m) (δ CH_{arom}). Anal. Calcd for $C_{26}H_{25}NO_4 \cdot 0.05H_2O$: C, 75.00; H, 6.08; N, 3.36. Found: C, 74.61; H, 6.03; N, 3.47.

*4.3.12. Ethyl N-{[2-benzoyl-1-(4-methoxyphenyl)-3-oxo-3-phenyl]prop-1-yl}carbamate (**17l**).* Compound **17l** (3.598 g, 93%) was prepared from dibenzoylmethane (**16c**) (2.112 g, 9.42 mmol), NaH (0.215 g, 8.98 mmol) and sulfone **15c** (3.263 g, 8.98 mmol) in dry THF (24 mL) (rt, 8 h) as described for **17j**. Mp 156–157.5 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.00–8.05 (2H, m, ArH), 7.75–7.80 (2H, m, ArH), 7.67 (1H, d, ^3J=9.2 Hz, NH), 7.47–7.66 (4H, m, ArH), 7.37–7.45 (2H, m, ArH), 7.28–7.34 (2H, m, ArH), 6.71–6.77 (2H, m, ArH), 6.35 (1H, d, ^3J=10.2 Hz, CHC=O), 5.49 (1H, dd, ^3J=10.2, ^3J=9.2 Hz, CHN), 3.77–3.91 (2H, m, OCH_2), 3.62 (3H, s, OCH_3), 1.03 (3H, t, ^3J=7.1 Hz, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 193.25 (C=O in Bz), 193.17 (C=O in Bz), 158.26 (C), 155.11 (C=O in COOEt), 136.35 (C), 135.70 (C), 133.82 (CH), 133.77 (CH), 132.64 (C), 128.93 (2CH), 128.86 (2CH), 128.72 (2CH), 128.62 (2CH), 128.35 (2CH), 113.43 (2CH), 60.01 ($CHBz_2$), 59.78 (OCH_2), 54.94 (OCH_3), 54.72 (CHN), 14.39 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3365 (m) (ν NH), 3063 (w) (ν CH_{arom}), 1693 (s), 1662 (m) (amide-I and ν C=O in Bz), 1612 (w), 1594 (m) (ν CC_{arom}), 1509 (s) (amide-II), 1278 (s), 1035 (s) (ν C–O), 835 (m), 690 (m) (δ CH_{arom}). Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.46; H, 5.72; N, 3.22.

*4.3.13. Ethyl N-{[2-benzoyl-1-(4-tert-butylphenyl)-3-oxo-3-phenyl]prop-1-yl}carbamate (**17m**).* Compound **17m** (2.044 g, 98%) was prepared from dibenzoylmethane (**16c**) (1.072 g, 4.78 mmol), NaH (0.109 g, 4.56 mmol) and sulfone **15d** (1.774 g, 4.55 mmol) in dry THF (21 mL) (rt, 8 h) as described for **17j**. Mp 170–172 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.98–8.04 (2H, m, ArH), 7.71–7.76 (2H, m, ArH), 7.69 (1H, d, ^3J=9.1 Hz, NH), 7.59–7.66 (1H, m, ArH), 7.47–7.55 (3H, m, ArH), 7.34–7.41 (2H, m, ArH), 7.25–7.30 (2H, m, ArH), 7.15–7.20 (2H, m, ArH), 6.33 (1H, d, ^3J=10.0 Hz, CHC=O), 5.49 (1H, dd, ^3J=10.0, ^3J=9.1 Hz, CHN), 3.78–3.92 (2H, m, OCH_2), 1.13 (9H, s, CH_3 in *t*-Bu), 1.03 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 193.60 (C=O in Bz), 193.31 (C=O in Bz), 155.16 (C=O in COOEt), 149.50 (C), 137.55 (C), 136.31 (C), 135.63 (C), 133.78 (CH), 133.61 (CH), 128.94 (2CH), 128.71 (2CH), 128.55 (2CH), 128.34 (2CH), 127.12 (2CH), 124.79 (2CH), 59.80 (OCH_2), 59.67 ($CHBz_2$), 54.76 (CHN), 34.04 (CMe_3), 30.98 (3×CH_3 in *t*-Bu), 14.40 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3367 (br m) (ν NH), 3061 (w) (ν CH_{arom}), 1722 (s), 1696 (s), 1654 (m) (amide-I and ν C=O in Bz), 1595 (m), 1578 (w) (ν CC_{arom}), 1518 (s) (amide-II), 1283 (s), 1042 (m) (ν C–O), 809 (m), 768 (m), 690 (m) (δ CH_{arom}). Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.07; H, 6.81; N, 2.94.

*4.3.14. Ethyl N-{[2-benzoyl-1-(4-chlorophenyl)-3-oxo-3-phenyl]prop-1-yl}carbamate (**17n**).* Compound **17n** (3.656 g, 98%) was prepared from dibenzoylmethane (**16c**) (2.015 g, 8.98 mmol), NaH (0.206 g, 8.58 mmol) and sulfone **15e** (3.148 g, 8.56 mmol) in dry THF (24 mL) (rt, 8 h) as described for **17j**. Mp 160–161 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.00–8.05 (2H, m, ArH), 7.76–7.81 (2H, m, ArH), 7.76 (1H, d, ^3J=9.1 Hz, NH, signals partly overlap with signals of aromatic protons), 7.48–7.67 (4H, m, ArH), 7.38–7.45 (4H, m, ArH), 7.23–7.29 (2H, m, ArH), 6.38 (1H, d, ^3J=10.1 Hz, CHC=O), 5.51 (1H, dd, ^3J=10.1, ^3J=9.1 Hz, CHN), 3.78–3.92 (2H, m, OCH_2), 1.03 (3H, t, ^3J=7.1 Hz, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 193.28 (C=O in Bz), 193.00 (C=O in Bz), 155.18 (C=O in COOEt), 139.58 (C), 136.19 (C), 135.49 (C), 133.93 (CH), 133.92 (CH), 131.84 (C), 129.47 (2CH), 128.96 (2CH), 128.91 (2CH), 128.64 (2CH), 128.36 (2CH), 128.08 (2CH), 59.94 (OCH_2), 59.55 ($CHBz_2$), 54.63 (CHN), 14.35 (CH_3); IR (Nujol) ν, cm^{-1}: 3379 (br m), 3366 (sh) (ν NH), 3062 (w) (ν CH_{arom}), 1694 (vs), 1660 (m) (amide-I and ν C=O in Bz), 1595 (m), 1578 (w) (ν CC_{arom}), 1515 (s) (amide-II), 1490 (w) (ν CC_{arom}), 1294

(s), 1039 (m) (ν C–O), 829 (m), 759 (w), 690 (m) (δ CH_{arom}). Anal. Calcd for $C_{25}H_{22}ClNO_4$: C, 68.89; H, 5.09; N, 3.21. Found: C, 68.84; H, 5.05; N, 3.28.

*4.3.15. Ethyl N-[(2-benzoyl-1-oxo-1-phenyl)hex-3-yl]carbamate (**17o**).* Compound **17o** (3.381 g, 95%) was prepared from dibenzoylmethane (**16c**) (2.282 g, 10.17 mmol), NaH (0.233 g, 9.70 mmol) and sulfone **15f** (2.903 g, 9.70 mmol) in dry THF (25 mL) (rt, 8 h) as described for **17j**. Mp 131–132 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.94–8.01 (4H, m, ArH), 7.60–7.68 (2H, m, ArH), 7.48–7.57 (4H, m, ArH), 6.92 (1H, d, ^3J=9.1 Hz, NH), 5.96 (1H, d, ^3J=7.6 Hz, CHC=O), 4.34 (1H, dddd, ^3J=10.6, ^3J=9.1, ^3J=7.6, ^3J=3.0 Hz, CHN), 3.75–3.90 (2H, m, OCH_2), 1.13–1.66 (4H, m, $CH_2CH_2CH_3$), 0.99 (3H, t, ^3J=7.1 Hz, CH_3 in OEt), 0.81 (3H, t, ^3J=7.1 Hz, CH_3 in Pr); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 195.08 (C=O in Bz), 194.72 (C=O in Bz), 155.68 (C=O in COOEt), 136.33 (C), 136.12 (C), 133.85 (CH), 133.65 (CH), 128.09 (2CH), 128.89 (2CH), 128.49 (2CH), 128.37 (2CH), 59.53 (OCH_2), 58.96 ($CHBz_2$), 51.27 (CHN), 34.65 ($CH_2CH_2CH_3$), 18.99 ($CH_2CH_2CH_3$), 14.44 (CH_3 in OEt), 13.53 (CH_3 in Pr); IR (Nujol) ν, cm^{-1}: 3350 (s) (ν NH), 3108 (w), 3064 (w) (ν CH_{arom}), 1699 (br s) (amide-I and ν C=O in Bz), 1597 (w), 1579 (w) (ν CC_{arom}), 1545 (s) (amide-II), 1270 (s) (ν C–O), 766 (m), 691 (m) (δ CH_{arom}). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.96; H, 6.84; N, 3.91.

4.4. Synthesis of ethyl *N*-(γ-oxoalkyl)carbamates

*4.4.1. Ethyl N-[(3-oxo-1-phenyl)but-1-yl]carbamate (**18a**).* To a solution of KOH (5.269 g, 93.91 mmol) in H_2O (90 mL) was added carbamate **17a** (5.150 g, 18.57 mmol) and the obtained mixture was stirred at room temperature. An emulsion formed at the beginning of stirring, and after about 50 min, the oily substance started to solidify and was triturated immediately [since at the beginning of the solidification this was easy to do (soft material), otherwise, the material becomes too hard to be easily triturated]. The obtained suspension was stirred for an additional 2 h 10 min (the overall reaction time was 3 h). After completion of the reaction the suspension was cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give compound **18a** (3.644 g, 83%). Mp 52.5–56.5 °C (EtOH–H_2O, 1:3).[27] ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.64 (1H, d, ^3J=8.2 Hz, NH), 7.18–7.35 (5H, m, ArH), 4.95 (1H, ddd, ^3J=9.2, ^3J=8.2, ^3J=5.5 Hz, CHN), 3.85–4.01 (2H, m, OCH_2), 2.88 (1H, dd, ^2J=16.6, ^3J=9.2 Hz, H_A in CH_2C=O), 2.76 (1H, dd, ^2J=16.6, ^3J=5.5 Hz, H_B in CH_2C=O), 2.07 (3H, s, CH_3 in Ac), 1.13 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 205.68 (C=O in Ac), 155.45 (C=O in COOEt), 143.34 (C), 128.22(2CH), 126.79 (CH), 126.22 (2CH), 59.62 (OCH_2), 50.47 (CHN), 49.47 (CH_2C=O), 30.01 (CH_3 in Ac), 14.53 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3329 (vs) (ν NH), 3064 (w), 3029 (w) (ν CH_{arom}), 1713 (s) (ν C=O in Ac), 1688 (vs) (amide-I), 1603 (w), 1582 (w) (ν CC_{arom}), 1545 (vs) (amide-II), 1496 (w) (ν CC_{arom}), 1265 (vs), 1158 (s) (ν C–O), 758 (s), 705 (s) (δ CH_{arom}). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.38; H, 7.29; N, 6.02.

*4.4.2. Ethyl N-{[1-(4-methylphenyl)-3-oxo]but-1-yl}carbamate (**18b**).* Compound **18b** (2.972 g, 91%) was prepared from carbamate **17b** (3.597 g, 12.35 mmol) and KOH (3.550 g, 63.24 mmol) in H_2O (60 mL) (rt, 3 h) as described for **18a**. An analytically pure sample (0.285 g) was obtained from crude **18b** (0.362 g) using column chromatography on silica gel 60 (6 g) eluting with petroleum ether–$CHCl_3$ (from 3:1 to 1:2). After the removal of solvent the residue was triturated with hexane until complete crystallization, obtained solid was filtered, washed with hexane, and dried under high vacuum (0.1 mmHg). Mp 57–58 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.61 (1H, d, ^3J=8.4 Hz, NH), 7.14–7.19 (2H, m, ArH), 7.07–7.12 (2H, m, ArH), 4.91 (1H, ddd, ^3J=9.1, ^3J=8.4, ^3J=5.6 Hz, CHN), 3.84–4.00 (2H, m, OCH_2), 2.86 (1H, dd, ^2J=16.5, ^3J=9.1 Hz, H_A in CH_2C=O), 2.73 (1H, dd, ^2J=16.5, ^3J=5.6 Hz, H_B in CH_2C=O), 2.25 (3H, s, CH_3 in 4-MeC_6H_4), 2.06 (3H, s, CH_3 in Ac), 1.12 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 205.83 (C=O in Ac), 155.46 (C=O in COOEt), 140.37 (C), 135.89 (C), 127.80 (2CH), 126.21 (2CH), 59.63 (OCH_2), 50.25 (CHN), 49.54 (CH_2C=O), 30.08 (CH_3 in Ac), 20.63 (CH_3 in 4-MeC_6H_4), 14.59 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3318 (vs) (ν NH), 3051 (w) (ν CH_{arom}), 1714 (s) (ν C=O in Ac), 1690 (vs) (amide-I), 1546 (s) (amide-II), 1268 (s), 1160 (m) (ν C–O), 804 (m) (δ CH_{arom}). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.44; H, 7.70; N, 5.69.

*4.4.3. Ethyl N-{[1-(4-methoxylphenyl)-3-oxo]but-1-yl}carbamate (**18c**).* Compound **18c** (2.007 g, 92%, pale yellow solid) was prepared from carbamate **17c** (2.521 g, 8.20 mmol) and KOH (2.355 g, 41.96 mmol) in H_2O (41 mL) (rt, 3 h) as described for **18a**. An analytically pure sample (0.246 g, white solid) was obtained from crude **18c** (0.353 g) using column chromatography on silica gel 60 (10 g) eluting with petroleum ether–$CHCl_3$ (from 4:1 to 1.5:1). After the removal of solvent the residue was dissolved in $CHCl_3$ (about 1 mL), hexane (about 2 mL) was added until crystallization began. Obtained solid was filtered, washed with hexane and dried under high vacuum (0.1 mmHg). Mp 101.5–102.5 °C ($CHCl_3$–hexane, 1:2). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.59 (1H, d, ^3J=8.4 Hz, NH), 7.18–7.24 (2H, m, ArH), 6.83–6.89 (2H, m, ArH), 4.90 (1H, ddd, ^3J=9.0, ^3J=8.4, ^3J=5.8 Hz, CHN), 3.85–4.00 (2H, m, OCH_2), 3.71 (3H, s, OCH_3), 2.86 (1H, dd, ^2J=16.5, ^3J=9.0 Hz, H_A in CH_2C=O), 2.74 (1H, dd, ^2J=16.5, ^3J=5.8 Hz, H_B in CH_2C=O), 2.06 (3H, s, CH_3 in Ac), 1.12 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 205.87 (C=O in Ac), 158.12 (C), 155.41 (C=O in COOEt), 135.30 (C), 127.43 (2CH), 113.59 (2CH), 59.60 (OCH_2), 55.02 (OCH_3), 49.95 (CHN), 49.60 (CH_2C=O), 30.07 (CH_3 in Ac), 14.57 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3349 (s) (ν NH), 1715 (s) (ν C=O in Ac), 1684 (s) (amide-I), 1612 (w), 1584 (w) (ν CC_{arom}), 1536 (s) (amide-II), 1518 (m) (ν CC_{arom}), 1268 (s), 1061 (s) (ν C–O), 812 (m) (δ CH_{arom}). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.48; H, 7.13; N, 5.44.

*4.4.4. Ethyl N-{[1-(4-methoxyphenyl)-2-methyl-3-oxo]but-1-yl}carbamate (**18e**).* To a solution of KOH (1.533 g, 27.31 mmol) in H_2O (27 mL) was added carbamate **17h** (2.925 g, 9.10 mmol), the obtained suspension was stirred at room temperature for 1 h 50 min and cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give compound **18e** (1.886 g, 74%) as a mixture of two diastereomers (51:49). An analytically pure sample (0.295 g; a 54:46 diastereomeric mixture) was obtained from crude **18e** (0.357 g) using column chromatography on silica gel 60 (9 g) eluting with petroleum ether–$CHCl_3$ (from 5:1 to 2:1). After the removal of solvent the residue was triturated with hexane until complete crystallization, obtained solid was filtered, washed with hexane and dried under high vacuum (0.1 mmHg). Mp 77.5–79.5 °C. ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.65 (1H, d, ^3J=9.8 Hz, NH), 7.17–7.23 (2H, m, ArH, signals partly overlap with signals of analogous protons of the minor isomer), 6.82–6.88 (2H, m, ArH, signals partly overlap with signals of analogous protons of the minor isomer), 4.76 (1H, dd, ^3J=9.8, ^3J=8.8 Hz, CHN), 3.87–4.02 (2H, m, OCH_2, signals partly overlap with signals of analogous protons of the minor isomer), 3.71 (3H, s, OCH_3), 2.98 (1H, dq, ^3J=8.8, ^3J=6.9 Hz, C*H*Ac), 1.91 (3H, s, CH_3 in Ac), 1.13 (3H, t, ^3J=7.1 Hz, CH_3 in OEt), 0.98 (3H, d, ^3J=6.9 Hz, C*H*$_3$CH); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.69 (1H, d, ^3J=9.2 Hz, NH), 7.20–7.26 (2H, m, ArH, signals partly overlap with signals of analogous protons of the major isomer), 6.85–6.91 (2H, m, ArH, signals partly overlap with signals of analogous protons of the major isomer), 4.55 (1H, dd, ^3J=10.6, ^3J=9.2 Hz, CHN), 3.81–3.96 (2H, m, OCH_2, signals partly overlap with signals of analogous protons of the

major isomer), 3.73 (3H, s, OCH_3), 2.86 (1H, dq, ^3J=10.6, ^3J=7.1 Hz, C*H*Ac), 2.17 (3H, s, CH_3 in Ac), 1.09 (3H, t, ^3J=7.1 Hz, CH_3 in OEt), 0.69 (3H, d, ^3J=7.1 Hz, C*H*$_3$CH); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 209.87 (C=O in Ac), 158.13 (C), 155.87 (C=O in COOEt), 133.98 (C), 128.04 (2CH), 113.52 (2CH), 59.75 (OCH_2), 55.59 (CHN), 54.98 (OCH_3), 51.71 (*C*HAc), 29.25 (CH_3 in Ac), 14.49 (CH_3 in OEt), 12.88 (*C*H$_3$CHAc); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 210.74 (C=O in Ac), 158.28 (C), 155.26 (C=O in COOEt), 133.55 (C), 128.36 (2CH), 113.58 (2CH), 59.63 (OCH_2), 54.44 (CHN), 54.98 (OCH_3), 51.13 (*C*HAc), 28.78 (CH_3 in Ac), 14.56 (CH_3 in OEt), 12.88 (*C*H$_3$CHAc); IR (Nujol) ν, cm^{-1}: 3353 (s) (ν NH), 1712 (s), 1702 (m) (ν C=O in Ac), 1685 (s) (amide-I), 1615 (w), 1584 (w) (ν CC$_{arom}$), 1535 (s) (amide-II), 1517 (m) (ν CC$_{arom}$), 1264 (s), 1031 (s) (ν C–O), 832 (m) (δ CH$_{arom}$). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.69; H, 7.57; N, 5.26.

*4.4.5. Ethyl N-[(3-oxo-1,3-diphenyl)prop-1-yl]carbamate (**18f**).* To a cooled (10 °C) solution of KOH (1.765 g, 31.45 mmol) in H_2O (26 mL) were added carbamate **17j** (4.200 g, 10.46 mmol) and EtOH (15.5 mL), the obtained suspension was stirred at room temperature for 8 h. Then H_2O (26 mL) was added, the resulting suspension was cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give compound **18f** (2.158 g, 69%, pale yellow solid). Mp 96.5–97.5 °C (EtOH–H_2O, 2:1) (lit.[28] mp 98–99 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.91–7.97 (2H, m, ArH), 7.70 (1H, d, ^3J=8.2 Hz, NH), 7.60–7.67 (1H, m, ArH), 7.48–7.56 (2H, m, ArH), 7.28–7.39 (4H, m, ArH), 7.19–7.26 (1H, m, ArH), 5.15 (1H, ddd, ^3J=9.2, ^3J=8.2, ^3J=4.9 Hz, CHN), 3.85–4.00 (2H, m, OCH_2), 3.58 (1H, dd, ^2J=17.1, ^3J=9.2 Hz, H_A in CH_2C=O), 3.29 (1H, dd, ^2J=17.1, ^3J=4.9 Hz, H_B in CH_2C=O), 1.11 (3H, t, ^3J=7.1 Hz, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 197.09 (C=O in Bz), 155.49 (C=O in COOEt), 143.52 (C), 136.63 (C), 133.26 (CH), 128.73 (2CH), 128.29 (2CH), 128.02 (2CH), 126.87 (CH), 126.44 (2CH), 59.64 (OCH_2), 50.75 (CHN), 44.73 (*C*H$_2$C=O), 14.57 (CH_3); IR (Nujol) ν, cm^{-1}: 3377 (s) (ν NH), 3085 (w), 3066 (w), 3056 (w), 3028 (w), 3004 (w) (ν CH$_{arom}$), 1717 (s) (amide-I), 1679 (s) (C=O in Bz), 1596 (w), 1579 (w) (ν CC$_{arom}$), 1525 (s) (amide-II), 1494 (w) (ν CC$_{arom}$), 1294 (s), 1038 (s) (ν C–O), 769 (m), 705 (s) (δ CH$_{arom}$). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.80; H, 6.45; N, 4.72.

*4.4.6. Ethyl N-{[1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}carbamate (**18g**).* Compound **18g** (1.707 g, 67%, pale yellow solid) was prepared from carbamate **17k** (3.415 g, 8.22 mmol) and KOH (1.383 g, 24.64 mmol) in EtOH (15 mL) and H_2O (25 mL for reaction, 25 mL for dilution after completion of the reaction) (rt, 9 h 20 min) as described for **18f**. Mp 105–108 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.90–7.96 (2H, m, ArH), 7.65 (1H, d, ^3J=8.2 Hz, NH, signals overlap with signals of aromatic proton), 7.60–7.67 (1H, m, ArH), 7.48–7.55 (2H, m, ArH), 7.21–7.26 (2H, m, ArH), 7.08–7.14 (2H, m, ArH), 5.10 (1H, ddd, ^3J=9.1, ^3J=8.2, ^3J=5.2 Hz, CHN), 3.84–3.99 (2H, m, OCH_2), 3.56 (1H, dd, ^2J=17.0, ^3J=9.1 Hz, H_A in CH_2C=O), 3.27 (1H, dd, ^2J=17.0, ^3J=5.2 Hz, H_B in CH_2C=O), 2.26 (3H, s, CH_3 in 4-MeC_6H_4), 1.11 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 197.15 (C=O in Bz), 155.42 (C=O in COOEt), 140.47 (C), 136.65 (C), 135.90 (C), 133.22 (CH), 128.79 (2CH), 128.72 (2CH), 127.99 (2CH), 126.36 (2CH), 59.58 (OCH_2), 50.50 (CHN), 44.72 (*C*H$_2$C=O), 20.63 (CH_3 in 4-MeC_6H_4), 14.56 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3319 (s) (ν NH), 3062 (w), 3052 (w), 3038 (w), 3022 (w) (ν CH$_{arom}$), 1706 (s), 1694 (s), 1685 (s) (amide-I and C=O in Bz), 1595 (w), 1578 (w) (ν CC$_{arom}$), 1546 (s) (amide-II), 1512 (w) (ν CC$_{arom}$), 1273 (s), 1051 (s) (ν C–O), 814 (w), 761 (m), 691 (m) (δ CH$_{arom}$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.29; H, 7.03; N, 4.32.

*4.4.7. Ethyl N-{[1-(4-chlorophenyl)-2-methyl-3-oxo]but-1-yl}carbamate (**18h**).* Compound **18h** (1.808 g, 83%, pale yellow solid) was prepared from carbamate **17n** (2.849 g, 6.54 mmol) and KOH (1.214 g, 21.64 mmol) in EtOH (9 mL) and H_2O (17 mL for reaction, 17 mL for dilution after completion of the reaction) (rt, 8 h) as described for **18f**. Mp 159–161 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.91–7.96 (2H, m, ArH), 7.63 (1H, d, ^3J=8.3 Hz, NH, signals overlap with signals of aromatic proton), 7.60–7.66 (1H, m, ArH), 7.48–7.55 (2H, m, ArH), 7.24–7.30 (2H, m, ArH), 6.84–6.90 (2H, m, ArH), 5.09 (1H, ddd, ^3J=8.9, ^3J=8.3, ^3J=5.3 Hz, CHN), 3.84–3.99 (2H, m, OCH_2), 3.72 (3H, s, OCH_3), 3.55 (1H, dd, ^2J=16.9, ^3J=8.9 Hz, H_A in CH_2C=O), 3.27 (1H, dd, ^2J=16.9, ^3J=5.3 Hz, H_B in CH_2C=O), 1.11 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 197.22 (C=O in Bz), 158.15 (C), 155.41 (C=O in COOEt), 136.67 (C), 135.42 (C), 133.22 (CH), 128.72 (2CH), 127.99 (2CH), 127.59 (2CH), 113.60 (2CH), 59.57 (OCH_2), 55.03 (OCH_3), 50.23 (CHN), 44.79 (*C*H$_2$C=O), 14.57 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3316 (s) (ν NH), 3061 (w) (ν CH$_{arom}$), 1691 (s) (amide-I and C=O in Bz), 1597 (w), 1578 (w) (ν CC$_{arom}$), 1547 (s) (amide-II), 1491 (w) (ν CC$_{arom}$), 1264 (s), 1048 (s) (ν C–O), 824 (m), 759 (m), 691 (m) (δ CH$_{arom}$). Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.21; H, 5.40; N, 4.20.

*4.4.8. Ethyl N-{[1-(4-methoxyphenyl)-3-oxo-3-phenyl]prop-1-yl}carbamate (**18i**).* Compound **18i** (1.725 g, 66%, pale yellow solid) was prepared from carbamate **17l** (3.457 g, 8.01 mmol) and KOH (1.337 g, 23.89 mmol) in EtOH (12.2 mL) and H_2O (20 mL for reaction, 20 mL for dilution after completion of the reaction) (rt, 9 h) as described for **18f**. Mp 159–161 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.91–7.96 (2H, m, ArH), 7.63 (1H, d, ^3J=8.3 Hz, NH, signals overlap with signals of aromatic proton), 7.60–7.66 (1H, m, ArH), 7.48–7.55 (2H, m, ArH), 7.24–7.30 (2H, m, ArH), 6.84–6.90 (2H, m, ArH), 5.09 (1H, ddd, ^3J=8.9, ^3J=8.3, ^3J=5.3 Hz, CHN), 3.84–3.99 (2H, m, OCH_2), 3.72 (3H, s, OCH_3), 3.55 (1H, dd, ^2J=16.9, ^3J=8.9 Hz, H_A in CH_2C=O), 3.27 (1H, dd, ^2J=16.9, ^3J=5.3 Hz, H_B in CH_2C=O), 1.11 (3H, t, ^3J=7.1 Hz, CH_3 in OEt); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 197.22 (C=O in Bz), 158.15 (C), 155.41 (C=O in COOEt), 136.67 (C), 135.42 (C), 133.22 (CH), 128.72 (2CH), 127.99 (2CH), 127.59 (2CH), 113.60 (2CH), 59.57 (OCH_2), 55.03 (OCH_3), 50.23 (CHN), 44.79 (*C*H$_2$C=O), 14.57 (CH_3 in OEt); IR (Nujol) ν, cm^{-1}: 3304 (s) (ν NH), 3069 (w), 3023 (w) (ν CH$_{arom}$), 1703 (s), 1691 (s), 1681 (s) (amide-I and C=O in Bz), 1610 (w), 1595 (w), 1578 (w) (ν CC$_{arom}$), 1551 (s) (amide-II), 1513 (s) (ν CC$_{arom}$), 1276 (s), 1049 (s) (ν C–O), 830 (m), 765 (m), 691 (m) (δ CH$_{arom}$). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.76; H, 6.48; N, 4.31.

4.5. Synthesis of 4-(γ-oxoalkyl)semicarbazide hydrazones

*4.5.1. Hydrazone of 4-[(3-oxo-1-phenyl)but-1-yl]semicarbazide (**20a**).* To carbamate **18a** (2.691 g, 11.44 mmol) was added anhydrous N_2H_4 (25 mL), the flask was flushed with argon, and the resulting solution was refluxed under stirring for 23 h with protection from air moisture and CO_2 using a KOH pellets filled tube. After completion of the reaction, N_2H_4 was removed in vacuo at about 60 °C (bath temperature), the oily residue was co-evaporated 4–6 times with toluene until white solid was formed. The obtained solid was triturated with Et_2O (15 mL) and the resulting suspension was cooled (−18 °C). The precipitate was filtered, washed with cold (−18 °C) diethyl ether, dried on the filter by sucking air through the filter. The powder product was washed on the filter with ice-cold water (4×5 mL), petroleum ether, and dried to give **20a** (0.957 g, 36%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 84:16. An analytically pure sample (a 85:15 isomeric ratio) was obtained after two crystallizations from MeCN. Mp 130–134 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.15–7.40 (5H, m, ArH, signals overlap with signals of aromatic protons of the minor isomer), 6.98 (1H, br s, N*H*NH$_2$), 6.68 (1H, br d, ^3J=8.4 Hz,

N*H*CH), 5.59 (2H, br s, NH_2N=C), 4.89 (1H, ddd, ^3J=8.5, ^3J=8.4, ^3J=6.2 Hz, CHN), 4.11 (2H, br s, NH_2NH), 2.50 (1H, dd, ^2J=14.0, ^3J=6.2 Hz, H_A in CH_2C=N), 2.46 (1H, dd, ^2J=14.0, ^3J=8.5 Hz, H_B in CH_2C=N), 1.59 (3H, s, CH_3C=N); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.15–7.40 (5H, m, ArH, signals overlap with signals of aromatic protons of the major isomer), 7.04 (1H, br s, N*H*NH_2), 6.81 (1H, br d, ^3J=8.5 Hz, N*H*CH), 5.71 (2H, br s, NH_2N=C), 4.98 (1H, ddd, ^3J=9.3, ^3J=8.5, ^3J=6.3 Hz, CHN), 4.11 (2H, br s, NH_2NH, signal fully overlap with signal of analogous protons of the major isomer), 2.80 (1H, dd, ^2J=14.4, ^3J=9.3 Hz, H_A in CH_2C=N), 2.32 (1H, dd, ^2J=14.4, ^3J=6.3 Hz, H_B in CH_2C=N), 1.66 (3H, s, CH_3C=N); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 159.40 (C=O), 144.66, 144.56 (C=N, C-1 in Ph), 128.08 (2CH), 126.41 (CH), 126.24 (2CH), 51.16 (CHN), 45.86 (CH_2), 13.92 (CH_3); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 159.54 (C=O), 144.89, 144.20 (C=N, C-1 in Ph), 128.21 (2CH), 126.78 (CH), 126.41 (2CH), 49.92 (CHN), 35.92 (CH_2), 22.90 (CH_3); IR (Nujol) ν, cm^{-1}: 3395 (s), 3346 (s), 3224 (br s), 3061 (m) (ν NH), 3028 (w) (ν CH_{arom}), 1656 (br vs) (amide-I, ν C=N, δ NH_2), 1579 (w) (ν CC_{arom}), 1528 (vs) (amide-II), 1495 (w) (ν CC_{arom}), 757 (m), 700 (s) (δ CH_{arom}). Anal. Calcd for $C_{11}H_{17}N_5O$: C, 56.15; H, 7.28; N, 29.77. Found: C, 56.31; H, 7.32; N, 29.64.

*4.5.2. Hydrazone of 4-{[1-(4-methylphenyl)-3-oxo]but-1-yl}semicarbazide (**20b**).* Hydrazone **20b** (0.645 g, 41%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 90:10 was prepared from carbamate **18b** (1.585 g, 6.36 mmol) in dry N_2H_4 (11 mL) (reflux, 20 h) as described for **20a**. An analytically pure sample (a 96:4 mixture of isomers) was obtained after two crystallizations from MeCN. Mp 145–146.5 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.14–7.19 (2H, m, ArH), 7.06–7.11 (2H, m, ArH), 6.93 (1H, br s, N*H*NH_2), 6.60 (1H, br d, ^3J=8.4 Hz, N*H*CH), 5.55 (2H, br s, NH_2N=C), 4.86 (1H, ddd, ^3J=8.4, ^3J=8.2, ^3J=6.5 Hz, CHN), 4.07 (2H, br s, NH_2NH), 2.48 (1H, dd, ^2J=13.9, ^3J=6.5 Hz, H_A in CH_2C=N), 2.44 (1H, dd, ^2J=13.9, ^3J=8.2 Hz, H_B in CH_2C=N), 2.26 (3H, s, CH_3 in 4-MeC_6H_4), 1.59 (3H, s, CH_3C=N); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.22–7.27 (2H, m, ArH), 7.06–7.19 (2H, m, ArH, signals fully overlap with signals of aromatic protons of the major isomer), 6.99 (1H, br s, N*H*NH_2), 6.71 (1H, br d, ^3J=8.7 Hz, N*H*CH), 5.69 (2H, br s, NH_2N=C), 4.93 (1H, ddd, ^3J=8.8, ^3J=8.7, ^3J=6.6 Hz, CHN), ≈4.07 (2H, br s, NH_2NH, signal fully overlaps with signal of analogous protons of the major isomer), 2.77 (1H, dd, ^2J=14.2, ^3J=8.8 Hz, H_A in CH_2C=N), 2.32 (1H, dd, ^2J=14.2, ^3J=6.6 Hz, H_B in CH_2C=N), 2.27 (3H, s, CH_3 in 4-MeC_6H_4), 1.64 (3H, s, CH_3C=N); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 159.34 (C=O), 144.61 (C=N), 141.51 (C), 135.31 (C), 128.58 (2CH), 126.12 (2CH), 50.85 (CHN), 45.84 (CH_2), 20.60 (CH_3 in 4-MeC_6H_4), 13.85 (CH_3C=N); IR (Nujol) ν, cm^{-1}: 3392 (s), 3348 (s), 3227 (br s), 3064 (m) (ν NH), 3017 (w) (ν CH_{arom}), 1655 (br vs) (amide-I, ν C=N, δ NH_2), 1527 (vs) (amide-II), 812 (s) (δ CH_{arom}). Anal. Calcd for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09. Found: C, 57.81; H, 7.69; N, 27.81.

*4.5.3. Hydrazone of 4-{[1-(4-methoxyphenyl)-3-oxo]but-1-yl}semicarbazide (**20c**).* Hydrazone **20c** (0.586 g, 29%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 92:8 was prepared from carbamate **18c** (1.988 g, 7.55 mmol) in N_2H_4 (16 mL) (reflux, 24 h) as described for **20a**. An analytically pure sample (a 96:4 mixture of isomers) was obtained after crystallization from MeCN. Mp 132.5–136.5 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.17–7.23 (2H, m, ArH), 6.94 (1H, br s, N*H*NH_2), 6.81–6.87 (2H, m, ArH), 6.59 (1H, br d, ^3J=8.5 Hz, N*H*CH), 5.56 (2H, br s, NH_2N=C), 4.84 (1H, ddd, ^3J=8.5, ^3J=8.0, ^3J=6.8 Hz, CHN), 4.07 (2H, br s, NH_2NH), 3.71 (3H, s, OCH_3), 2.47 (1H, dd, ^2J=13.9, ^3J=6.8 Hz, H_A in CH_2C=N), 2.45 (1H, dd, ^2J=13.9, ^3J=8.0 Hz, H_B in CH_2C=N), 1.58 (3H, s, CH_3C=N); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.26–7.31 (2H, m, ArH), 7.00 (1H, br s, N*H*NH_2), 6.85–6.90 (2H, m, ArH, signals partly overlap with signals of analogous protons of the major isomer), 6.70 (1H, br d, ^3J=8.8 Hz, N*H*CH), 5.70 (2H, br s, NH_2N=C), 4.91 (1H, ddd, ^3J=8.8, ^3J=8.7, ^3J=6.9 Hz, CHN), ≈4.07 (2H, br s, NH_2NH, signal fully overlap with signal of analogous protons of the major isomer), 3.73 (3H, s, OCH_3), 2.77 (1H, dd, ^2J=14.2, ^3J=8.7 Hz, H_A in CH_2C=N), 2.32 (1H, dd, ^2J=14.2, ^3J=6.9 Hz, H_B in CH_2C=N), 1.63 (3H, s, CH_3C=N); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 159.36 (C=O), 157.84 (C), 144.68 (C=N), 136.53 (C), 127.36 (2CH), 113.43 (2CH), 55.00 (OCH_3), 50.55 (CHN), 45.87 (CH_2), 13.89 (CH_3C=N); IR (Nujol) ν, cm^{-1}: 3392 (s), 3341 (s), 3325 (m), 3222 (br s) (ν NH), 3100 (w), 3061 (br m), 3034 (w) (ν CH_{arom}), 1656 (s), 1639 (s) (amide-I, ν C=N, δ NH_2), 1615 (m), 1584 (w) (ν CC_{arom}), 1528 (s) (amide-II), 1513 (s) (ν CC_{arom}), 1252 (s), 1034 (m) (ν C–O), 824 (m) (δ CH_{arom}). Anal. Calcd for $C_{12}H_{19}N_5O_2$: C, 54.33; H, 7.22; N, 26.40. Found: C, 54.51; H, 7.21; N, 26.41.

*4.5.4. Hydrazone of 4-{[1-(4-tert-butylphenyl)-3-oxo]but-1-yl}semicarbazide (**20d**).* To a solution of KOH (1.476 g, 26.30 mmol) in H_2O (25 mL) was added carbamate **17d** (1.698 g, 5.09 mmol), the obtained emulsion was stirred at room temperature for 4 h and extracted with diethyl ether (20 mL, 3×10 mL). The combined extracts were washed with H_2O (3×15 mL), brine (2×15 mL), and dried over Na_2SO_4. Ether was removed in vacuo to give crude oily **18d**.[29] To the obtained residue was added anhydrous N_2H_4 (24 mL), the flask was flushed with argon, the resulting solution was refluxed under stirring for 22 h with the protection from air moisture and CO_2 using a KOH pellets filled tube. Then N_2H_4 was removed in vacuo at about 60 °C (bath temperature), the oily residue was co-evaporated with toluene (4×15 mL). The obtained semisolid was triturated with Et_2O (15 mL) and the resulting suspension was cooled (−18 °C). The precipitate was filtered, washed with cold (−18 °C) diethyl ether, dried on the filter by sucking air through the filter. The powder product was washed on the filter with ice-cold water (4×5 mL), petroleum ether, and dried to give **20d** (0.619 g, 42%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 94:6. An analytically pure sample (a 94:6 isomeric ratio) was obtained after crystallization from MeCN. Mp 151.5–152.5 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.27–7.33 (2H, m, ArH), 7.17–7.23 (2H, m, ArH), 6.94 (1H, br s, N*H*NH_2), 6.60 (1H, br d, ^3J=8.4 Hz, N*H*CH), 5.58 (2H, br s, NH_2N=C), 4.86 (1H, ddd, ^3J=8.7, ^3J=8.4, ^3J=6.1 Hz, CHN), 4.08 (2H, br s, NH_2NH), 2.49 (1H, dd, ^2J=14.0, ^3J=6.1 Hz, H_A in CH_2C=N), 2.44 (1H, dd, ^2J=14.0, ^3J=8.7 Hz, H_B in CH_2C=N), 1.61 (3H, s, CH_3C=N), 1.26 (9H, s, CH_3 in *t*-Bu). ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.00 (1H, br s, N*H*NH_2), 6.74 (1H, br d, ^3J=8.8 Hz, N*H*CH), 5.70 (2H, br s, NH_2N=C), 4.94 (1H, ddd, ^3J=9.4, ^3J=8.8, ^3J=6.2 Hz, CHN), ≈4.08 (2H, br s, NH_2NH, signal fully overlap with signal of analogous protons of the major isomer), 2.78 (1H, dd, ^2J=14.4, ^3J=9.4 Hz, H_A in CH_2C=N), 2.31 (1H, dd, ^2J=14.4, ^3J=6.2 Hz, H_B in CH_2C=N), 1.67 (3H, s, CH_3C=N), 1.27 (9H, s, CH_3 in *t*-Bu). Signals of aromatic protons fully overlap with signals of aromatic protons of the major isomer; ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 159.38 (C=O), 148.60 (C), 144.67 (C=N), 141.64 (C), 125.91 (2CH), 124.80 (2CH), 50.73 (CHN), 45.79 (CH_2), 34.11 (CMe_3), 31.21 (3×CH_3 in *t*-Bu), 13.83 (CH_3C=N); IR (Nujol) ν, cm^{-1}: 3389 (m), 3349 (s), 3225 (br s) (ν NH), 3058 (br m) (ν CH_{arom}), 1655 (vs) (amide-I, ν C=N, δ NH_2), 1528 (vs) (amide-II), 823 (m) (δ CH_{arom}). Anal. Calcd for $C_{15}H_{25}N_5O$: C, 61.83; H, 8.65; N, 24.03. Found: C, 62.12; H, 8.69; N, 23.96.

*4.5.5. Hydrazone of 4-{[1-(4-methoxyphenyl)-2-methyl-3-oxo]but-1-yl}semicarbazide (**20e**).* Hydrazone **20e** (0.746 g, 40%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 95:5 was prepared from carbamate **18e** (1.882 g, 6.74 mmol) in N_2H_4 (16 mL) (reflux, 23 h) as described for **20a**. An analytically pure sample (only *E*-isomer) was

obtained after crystallization from MeCN. Mp 179.5–180.5 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.13–7.19 (2H, m, ArH), 6.89 (1H, br s, N*H*NH$_2$), 6.81–6.87 (2H, m, ArH), 6.74 (1H, br d, ^3J=8.8 Hz, N*H*CH), 5.57 (2H, br s, NH$_2$N=C), 4.57 (1H, dd, ^3J=8.8, ^3J=8.7 Hz, CHN), 4.04 (2H, br s, N*H*$_2$NH), 3.72 (3H, s, OCH$_3$), 2.57 (1H, dq, ^3J=8.7, ^3J=7.0 Hz, CHC=N), 1.52 (3H, s, CH$_3$C=N), 0.82 (3H, d, ^3J=7.0 Hz, C*H*$_3$CH); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 6.58 (1H, br d, ^3J=9.4 Hz, N*H*CH), 5.46 (2H, br s, NH$_2$N=C), 4.75 (1H, dd, ^3J=9.4, ^3J=7.8 Hz, CHN), 2.67 (1H, dq, ^3J=7.8, ^3J=7.0 Hz, CHC=N), 1.48 (3H, s, CH$_3$C=N), 0.94 (3H, d, ^3J=7.0 Hz, C*H*$_3$CH). 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: 159.41 (C=O), 157.79 (C), 149.16 (C=N), 135.72 (C), 127.94 (2CH), 113.28 (2CH), 55.51 (CHN), 54.97 (OCH$_3$), 47.27 (*C*HC=N), 16.25 (*C*H$_3$C=N), 11.96 (*C*H$_3$CH); IR (Nujol) ν, cm^{-1}: 3376 (s), 3306 (s), 3219 (br s) (ν NH), 3107 (w), 3066 (br m), 3031 (w), 3012 (w) (ν CH$_{arom}$), 1664 (s), 1641 (s) (amide-I, ν C=N, δ NH$_2$), 1615 (m), 1588 (w) (ν CC$_{arom}$), 1532 (s) (amide-II), 1515 (s) (ν CC$_{arom}$), 1249 (s), 1037 (m) (ν C–O), 814 (s) (δ CH$_{arom}$). Anal. Calcd for C$_{13}$H$_{21}$N$_5$O$_2$: C, 55.90; H, 7.58; N, 25.07. Found: C, 55.99; H, 7.62; N, 25.35.

*4.5.6. Hydrazone of 4-{[(3-oxo-1,3-diphenyl)prop-1-yl]}semicarbazide (**20f**).* Hydrazone **20f** (1.346 g, 46%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 75:25 was prepared from carbamate **18f** (2.896 g, 9.74 mmol) in N$_2$H$_4$ (25 mL) (reflux, 19 h 40 min) as described for **20a**. An analytically pure sample (a 97:3 isomeric ratio) was obtained after two crystallizations from MeCN. Mp 167–168.5 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.46–7.52 (2H, m, ArH), 7.13–7.37 (8H, m, ArH), 7.02 (1H, br s, N*H*NH$_2$), 6.88 (1H, br d, ^3J=8.2 Hz, N*H*CH), 6.67 (2H, br s, NH$_2$N=C), 4.93 (1H, ddd, ^3J=8.2, ^3J=7.8, ^3J=7.2 Hz, CHN), 4.08 (2H, br s, N*H*$_2$NH), 3.20 (1H, dd, ^2J=14.3, ^3J=7.8 Hz, H$_A$ in CH$_2$C=N), 2.95 (1H, dd, ^2J=14.3, ^3J=7.2 Hz, H$_B$ in CH$_2$C=N); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.42–7.47 (2H, m, ArH), 7.13–7.40 (8H, m, ArH, signals overlap with signals of analogous protons of the major isomer), 6.96 (1H, br s, N*H*NH$_2$), 6.73 (1H, br d, ^3J=8.4 Hz, N*H*CH), 5.67 (2H, br s, NH$_2$N=C), 4.66 (1H, ddd, ^3J=8.7, ^3J=8.4, ^3J=6.2 Hz, CHN), 4.09 (2H, br s, N*H*$_2$NH, signal overlap with signal of analogous protons of the major isomer), 2.88 (1H, dd, ^2J=14.4, ^3J=6.2 Hz, H$_A$ in CH$_2$C=N), 2.78 (1H, dd, ^2J=14.4, ^3J=8.7 Hz, H$_B$ in CH$_2$C=N); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 159.67 (C=O), 143.54 (C), 142.07 (C=N), 138.96 (C), 128.16 (2CH), 127.85 (2CH), 126.85 (CH), 126.65 (CH), 126.42 (2CH), 124.91 (2CH), 50.75 (CHN), 32.30 (CH$_2$); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 159.33 (C=O), 144.81 (C=N), 144.43 (C), 134.23 (C), 128.94 (2CH), 128.32 (CH), 128.27 (CH), 128.07 (2CH), 127.47 (2CH), 126.33 (2CH), 51.02 (CHN), 44.99 (CH$_2$); IR (Nujol) ν, cm^{-1}: 3393 (s), 3347 (s), 3319 (s), 3224 (br s) (ν NH), 3105 (w), 3062 (w), 3026 (w) (ν CH$_{arom}$), 1658 (br vs) (amide-I, ν C=N, δ NH$_2$), 1604 (w), 1586 (w) (ν CC$_{arom}$), 1539 (s) (amide-II), 1496 (w) (ν CC$_{arom}$), 757 (s), 693 (s) (δ CH$_{arom}$). Anal. Calcd for C$_{16}$H$_{19}$N$_5$O: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.59; H, 6.48; N, 23.76.

*4.5.7. Hydrazone of 4-{[1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}semicarbazide (**20g**).* Hydrazone **20g** (0.474 g, 28%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 84:16 was prepared from carbamate **18g** (1.702 g, 5.46 mmol) in N$_2$H$_4$ (14 mL) (reflux, 24 h) as described for **20a**. An analytically pure sample (a 86:14 isomeric ratio) was obtained after crystallization from MeCN. Mp 141–143.5 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.47–7.53 (2H, m, ArH), 7.13–7.27 (5H, m, ArH), 7.05–7.11 (2H, m, ArH), 7.02 (1H, br s, N*H*NH$_2$), 6.83 (1H, br d, ^3J=8.1 Hz, N*H*CH), 6.66 (2H, br s, NH$_2$N=C), 4.88 (1H, ddd, ^3J=8.1, ^3J=7.7, ^3J=7.4 Hz, CHN), 4.08 (2H, br s, N*H*$_2$NH), 3.16 (1H, dd, ^2J=14.3, ^3J=7.7 Hz, H$_A$ in CH$_2$C=N), 2.93 (1H, dd, ^2J=14.3, ^3J=7.4 Hz, H$_B$ in CH$_2$C=N), 2.25 (3H, s, CH$_3$); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.42–7.47 (2H, m, ArH), 7.34–7.41 (1H, m, ArH), 7.05–7.27 (6H, m, ArH, signals overlap with signals of aromatic protons of the major isomer), 6.93 (1H, br s, N*H*NH$_2$), 6.66 (1H, br d, ^3J=8.2 Hz, N*H*CH, signals partly overlap with the NH$_2$N=C proton signal of the major isomer), 6.62 (2H, br s, NH$_2$N=C), 4.62 (1H, ddd, ^3J=8.7, ^3J=8.2, ^3J=6.5 Hz, CHN), ≈4.08 (2H, br s, N*H*$_2$NH, signal fully overlaps with signal of analogous protons of the major isomer), 2.85 (1H, dd, ^2J=14.3, ^3J=6.5 Hz, H$_A$ in CH$_2$C=N), 2.77 (1H, dd, ^2J=14.3, ^3J=8.7 Hz, H$_B$ in CH$_2$C=N), 2.25 (3H, s, CH$_3$); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 159.68 (C=O), 142.08 (C=N), 140.53 (C), 138.98 (C), 135.90 (C), 128.73 (2CH), 127.90 (2CH), 126.68 (CH), 126.37 (2CH), 124.93 (2CH), 50.55 (CHN), 32.32 (CH$_2$), 20.66 (CH$_3$); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 159.29 (C=O), 144.91 (C=N), 141.32 (C), 135.38 (C), 134.24 (C), 128.91 (2CH), 128.59 (2CH), 128.22 (CH), 127.45 (2CH), 126.24 (2CH), 50.67 (CHN), 45.00 (CH$_2$), 20.64 (CH$_3$); IR (Nujol) ν, cm^{-1}: 3394 (m), 3346 (s), 3225 (br s) (ν NH), 3056 (br m), 3018 (w) (ν CH$_{arom}$), 1658 (br s) (amide-I, ν C=N, δ NH$_2$), 1578 (w), 1494 (w) (ν CC$_{arom}$), 1534 (br s) (amide-II), 815 (m), 760 (m), 692 (m) (δ CH$_{arom}$). Anal. Calcd for C$_{17}$H$_{21}$N$_5$O: C, 65.57; H, 6.80; N, 22.49. Found: C, 65.44; H, 7.07; N, 22.58.

*4.5.8. Hydrazone of 4-{[1-(4-chlorophenyl)-3-oxo-3-phenyl]prop-1-yl}semicarbazide (**20h**).* Hydrazone **20h** (0.870 g, 32%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 75:25 was prepared from carbamate **18h** (2.722 g, 8.20 mmol) in N$_2$H$_4$ (20 mL) (reflux, 20 h) as described for **20a**. An analytically pure sample (a 77:23 isomeric ratio) was obtained after crystallization from MeCN. Mp 157.5–160 °C (dec, MeCN). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.15–7.55 (9H, m, ArH, signals overlap with signals of aromatic protons of the minor isomer), 7.05 (1H, br s, N*H*NH$_2$), 6.95 (1H, br d, ^3J=8.2 Hz, N*H*CH), 6.67 (2H, br s, NH$_2$N=C), 4.94 (1H, ddd, ^3J=8.4, ^3J=8.2, ^3J=7.1 Hz, CHN), 4.09 (2H, br s, N*H*$_2$NH), 3.18 (1H, dd, ^2J=14.3, ^3J=8.4 Hz, H$_A$ in CH$_2$C=N), 2.96 (1H, dd, ^2J=14.3, ^3J=7.1 Hz, H$_B$ in CH$_2$C=N); ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.15–7.55 (9H, m, ArH, signals overlap with signals of aromatic protons of the major isomer), 7.00 (1H, br s, N*H*NH$_2$), 6.79 (1H, br d, ^3J=8.2 Hz, N*H*CH), 5.69 (2H, br s, NH$_2$N=C), 4.65 (1H, ddd, ^3J=8.4, ^3J=8.2, ^3J=6.5 Hz, CHN), 4.09 (2H, br s, N*H*$_2$NH, overlap with signal of analogous protons of the major isomer), 2.88 (1H, dd, ^2J=14.4, ^3J=6.5 Hz, H$_A$ in CH$_2$C=N), 2.80 (1H, dd, ^2J=14.4, ^3J=8.4 Hz, H$_B$ in CH$_2$C=N); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 159.56 (C=O), 142.80 (C), 141.92 (C=N), 138.87 (C), 131.23 (C), 128.38 (2CH), 127.97 (2CH), 127.96 (2CH), 126.77 (CH), 124.94 (2CH), 50.10 (CHN), 31.60 (CH$_2$); ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 159.27 (C=O), 144.38 (C=N), 143.41 (C), 134.11 (C), 130.87 (C), 128.93 (2CH), 128.32 (2CH), 128.27 (CH), 127.92 (2CH), 127.43 (2CH), 50.51 (CHN), 44.47 (CH$_2$); IR (Nujol) ν, cm^{-1}: 3387 (m), 3351 (s), 3320 (m), 3222 (br s) (ν NH), 3060 (br m), 3021 (w) (ν CH$_{arom}$), 1658 (br vs) (amide-I, ν C=N, δ NH$_2$), 1600 (w), 1580 (w) (ν CC$_{arom}$), 1542 (br vs) (amide-II), 1494 (m) (ν CC$_{arom}$), 823 (m), 694 (m) (δ CH$_{arom}$). Anal. Calcd for C$_{16}$H$_{18}$ClN$_5$O: C, 57.92; H, 5.47; N, 21.11. Found: C, 57.89; H, 5.34; N, 21.15.

4.6. Acid-catalyzed cyclizations of 4-(γ-oxoalkyl)semicarbazide hydrazones

*4.6.1. 7,14-Dimethyl-5,12-diphenyl-1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-dione (**24a**).* To semicarbazide **20a** (0.171 g, 0.73 mmol) were added TsOH·H$_2$O (0.143 g, 0.75 mmol) and EtOH (3.8 mL) and the obtained mixture was refluxed for 1 h 50 min under stirring. The solvent was removed in vacuo and the solid residue was triturated with saturated aqueous

$NaHCO_3$ (1 mL). The obtained suspension was cooled (0 °C) and the precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give **24a** (0.126 g, 85%) as a mixture of *trans*- and *cis*-diastereomers in a ratio of 96:4. An analytically pure sample (only *trans*-isomer) was obtained after crystallization from DMF. Mp 273 °C (dec, DMF). ^{1}H NMR of the *trans*-isomer (300.13 MHz, DMSO-d_6) δ: 9.42 (2H, s, two NHN), 7.91 (2H, d, ^3J=7.6 Hz, two NHC), 7.20–7.37 (10H, m, ArH), 5.02 (2H, ddd, ^3J=7.6, ^3J=5.1, ^3J=4.2 Hz, two CHN), 2.69 (2H, dd, ^2J=14.0, ^3J=4.2 Hz, H_A in two CH_2), 2.66 (2H, dd, ^2J=14.0, ^3J=5.1 Hz, H_B in two CH_2), 1.49 (6H, s, two CH_3); ^{1}H NMR of the *cis*-isomer (300.13 MHz, DMSO-d_6) δ: 9.33 (2H, s, two NHN), 7.55 (2H, d, ^3J=7.3 Hz, two NHC), 7.20–7.44 (10H, m, ArH, signals overlap with signals of analogous protons of the major isomer), 4.90 (2H, ddd, ^3J=8.6, ^3J=7.3, ^3J=4.9 Hz, two CHN), 2.56–2.68 (4H, m, two CH_2, signals partly overlap with signals of analogous protons of the major isomer), 1.82 (6H, s, two CH_3); ^{13}C NMR of the *trans*-isomer (75.48 MHz, DMSO-d_6) δ: 155.33 (2C=O), 148.78 (2C=N), 142.74 (2C), 128.22 (4CH), 126.65 (2CH), 125.71 (4CH), 51.12 (2CHN), 43.33 ($2CH_2$), 19.11 ($2CH_3$); IR of the *trans*-isomer (Nujol) ν, cm^{-1}: 3371 (s), 3197 (s), 3087 (s), 3032 (m) (ν NH), 1674 (vs), 1638 (w) (amide-I), 1584 (w) (ν CC_{arom}), 1550 (vs) (ν C=N, amide-II), 1495 (m) (ν CC_{arom}), 756 (s), 696 (s) (δ CH_{arom}); MS (EI) *m*/*z* 407 [5, $(M+1)^+$], 406 (21, M^+), 335 (1), 301 (1), 292 (7), 244 (8), 204 (13), 203 (29), 187 (10), 159 (6), 144 (3), 132 (24), 106 (100), 104 (17), 91 (8), 77 (16), 44 (12). Anal. Calcd for $C_{22}H_{26}N_6O_2$: C, 65.01; H, 6.45; N, 20.68. Found: C, 64.99; H, 6.53; N, 20.77.

*4.6.2. 7,14-Dimethyl-5,12-di(4-methylphenyl)-1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-dione (**24b**).* Compound **24b** (0.252 g, 92%) as a mixture of *trans*- and *cis*-diastereomers in a ratio of 71:29 was prepared from semicarbazide **20b** (0.314 g, 1.26 mmol) and TsOH·H_2O (0.254 g, 1.33 mmol) in EtOH (6.2 mL) (reflux, 1 h 50 min) as described for **24a**. An analytically pure sample was obtained after crystallization from AcOH.[30] Mp 315 °C (dec, AcOH). ^{1}H NMR of the *trans*-isomer (300.13 MHz, DMSO-d_6) δ: 9.36 (2H, s, two NHN), 7.87 (2H, d, ^3J=7.8 Hz, two NHC), 7.11–7.17 (8H, m, two ArH), 4.99 (2H, ddd, ^3J=7.8, ^3J=4.9, ^3J=4.2 Hz, two CHN), 2.66 (2H, dd, ^2J=14.1, ^3J=4.9 Hz, H_A in two CH_2), 2.64 (2H, dd, ^2J=14.1, ^3J=4.9 Hz, H_B in two CH_2), 2.28 (6H, s, CH_3 in two $CH_3C_6H_4$), 1.49 (6H, s, two CH_3C=N); ^{1}H NMR of the *cis*-isomer (300.13 MHz, DMSO-d_6) δ: 9.29 (2H, s, two NHN), 7.53 (2H, d, ^3J=7.5 Hz, two NHC), 7.26–7.32 (4H, m, ArH), 7.13–7.19 (4H, m, ArH), 4.85 (2H, ddd, ^3J=8.3, ^3J=7.5, ^3J=4.7 Hz, two CHN), 2.53–2.70 (4H, m, two CH_2, signals partly overlap with signals of analogous protons of the major isomer), 2.29 (6H, s, CH_3 in two $CH_3C_6H_4$), 1.80 (6H, s, two CH_3C=N); IR (Nujol) ν, cm^{-1}: 3366 (s), 3190 (s), 3084 (s), 3027 (w) (ν NH), 1674 (vs), 1636 (m) (amide-I), 1544 (vs) (ν C=N, amide-II), 1518 (sh) (ν CC_{arom}), 808 (s) (δ CH_{arom}); MS (EI) *m*/*z* 435 [4, $(M+1)^+$], 434 (15, M^+), 320 (3), 277 (1), 258 (3), 218 (9), 217 (26), 201 (9), 173 (7), 158 (5), 146 (44), 120 (100), 118 (20), 91 (24), 44 (7), 42 (9), 41 (10). Anal. Calcd for $C_{24}H_{30}N_6O_2$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.10; H, 6.88; N, 19.46.

*4.6.3. 7,14-Dimethyl-5,12-di(4-methoxyphenyl)-1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-dione (**20c**).* Compound **24c** (0.282 g, 86%) as a mixture of *trans*- and *cis*-diastereomers in a ratio of 69:31 was prepared from semicarbazide **20c** (0.373 g, 1.40 mmol) and TsOH·H_2O (0.284 g, 1.49 mmol) in EtOH (7 mL) (reflux, 1 h 50 min) as described for **24a**. An analytically pure sample (*trans*/*cis*=97:3) was obtained after crystallization from DMF. Mp 289 °C (dec, DMF). ^{1}H NMR of the *trans*-isomer (300.13 MHz, DMSO-d_6) δ: 9.33 (2H, s, two NHN), 7.88 (2H, d, ^3J=7.9 Hz, two NHC), 7.15–7.21 (4H, m, ArH), 6.86–6.93 (4H, m, ArH), 4.99 (2H, ddd, ^3J=7.9, ^3J=4.8, ^3J=4.3 Hz, two CHN), 3.73 (6H, s, two OCH_3), 2.66 (2H, dd, ^2J=14.1, ^3J=4.3 Hz, H_A in two CH_2), 2.64 (2H, dd, ^2J=14.1, ^3J=4.8 Hz, H_B in two CH_2), 1.51 (6H, s, two CH_3); ^{1}H NMR of the *cis*-isomer (300.13 MHz, DMSO-d_6) δ: 9.28 (2H, s, two NHN), 7.48 (2H, d, ^3J=7.4 Hz, two NHC), 7.29–7.35 (4H, m, ArH), 6.88–6.94 (4H, m, ArH), 4.80–4.88 (2H, m, two CHN), 3.74 (6H, s, two OCH_3), 2.52–2.64 (4H, m, two CH_2, signals partly overlap with signals of analogous protons of the major isomer), 1.81 (6H, s, two CH_3); ^{13}C NMR of the *trans*-isomer (75.48 MHz, DMSO-d_6) δ: 157.94 (2C), 155.27 (2C=O), 148.80 (2C=N), 134.59 (2C), 126.76 (4CH), 113.57 (4CH), 55.02 (2 OCH_3), 50.43 (2CHN), 43.35 ($2CH_2$), 19.18 ($2CH_3$); ^{13}C NMR of the *cis*-isomer (75.48 MHz, DMSO-d_6) δ: 157.99 (2C), 155.89 (2C=O), 147.41 (2C=N), 136.00 (2C), 127.12 (4CH), 113.51 (4CH), 55.06 (2 OCH_3), 50.75 (2CHN), 44.68 ($2CH_2$), 16.83 ($2CH_3$); IR (Nujol) ν, cm^{-1}: 3371 (s), 3188 (br s), 3075 (br s) (ν NH), 1666 (vs) (amide-I), 1612 (w), 1583 (w) (ν CC_{arom}), 1541 (s) (ν C=N, amide-II), 1512 (s) (ν CC_{arom}), 1252 (s), 1036 (m) (ν C–O), 828 (m) (δ CH_{arom}); MS (EI) *m*/*z* 468 [1, $(M+2)^+$], 467 [6, $(M+1)^+$], 466 (22, M^+), 352 (14), 309 (9), 267 (8), 234 (23), 233 (97), 218 (8), 217 (39), 190 (7), 189 (20), 174 (10), 163 (16), 162 (96), 137 (10), 136 (98), 135 (17), 134 (46), 121 (11), 109 (9), 91 (13), 77 (9), 18 (100). Anal. Calcd for $C_{24}H_{30}N_6O_4$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.57; H, 6.48; N, 18.19.

*4.6.4. 7,14-Dimethyl-5,12-di(4-tert-butylphenyl)-1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-dione (**24d**).* Compound **24d** (0.331 g, 93%) as a mixture of *trans*- and *cis*-diastereomers in a ratio of 55:45 was prepared from semicarbazide **20d** (0.401 g, 1.37 mmol) and TsOH·H_2O (0.279 g, 1.47 mmol) in EtOH (18 mL) (reflux, 1 h 50 min) as described for **24a**. An analytically pure sample (only *trans*-isomer) was obtained after crystallization from DMF. Mp 308.5 °C (dec, DMF). ^{1}H NMR of the *trans*-isomer (300.13 MHz, DMSO-d_6) δ: 9.36 (2H, s, two NHN), 7.91 (2H, d, ^3J=7.5 Hz, two NHC), 7.32–7.38 (4H, m, ArH), 7.15–7.21 (4H, m, ArH), 4.96 (2H, ddd, ^3J=7.5, ^3J=5.2, ^3J=4.1 Hz, two CHN), 2.68 (2H, dd, ^2J=14.2, ^3J=4.1 Hz, H_A in two CH_2), 2.64 (2H, dd, ^2J=14.2, ^3J=5.2 Hz, H_B in two CH_2), 1.52 (6H, s, two *C*H_3C=N), 1.27 (18H, s, CH_3 in two *t*-Bu); ^{1}H NMR of the *cis*-isomer (300.13 MHz, DMSO-d_6) δ: 9.30 (2H, s, two NHN), 7.54 (2H, d, ^3J=7.3 Hz, two NHC), 7.30–7.39 (8H, m, ArH, signals partly overlap with signals of aromatic protons of the major isomer), 4.84 (2H, ddd, ^3J=9.0, ^3J=7.3, ^3J=5.2 Hz, two CHN), 1.82 (6H, s, two *C*H_3C=N), 1.28 (18H, s, CH_3 in two *t*-Bu). Proton signals of two CH_2 group overlap with signals of analogous protons of the major isomer; ^{13}C NMR of the *trans*-isomer (75.48 MHz, DMSO-d_6) δ: 155.31 (2C=O), 148.98 (2C=N), 148.88 (2C), 139.82 (2C), 125.40 (4CH), 124.90 (4CH), 50.88 (2CHN), 43.02 ($2CH_2$), 34.13 (2*C*Me_3), 31.18 (6×CH_3 in 2 *t*-Bu), 19.11 (2*C*H_3C=N); ^{13}C NMR of the *cis*-isomer (75.48 MHz, DMSO-d_6) δ: 155.85 (2C=O), 148.88 (2C=N), 147.63 (2C), 140.98 (2C), 125.76 (4CH), 124.82 (4CH), 51.08 (2CHN), 44.34 ($2CH_2$), 34.13 (2*C*Me_3), 31.18 (6×CH_3 in 2 *t*-Bu), 16.97 (2*C*H_3C=N); IR of the *trans*-isomer (Nujol) ν, cm^{-1}: 3371 (s), 3197 (br s), 3090 (br s) (ν NH), 3022 (w) (ν CH_{arom}), 1672 (vs) (amide-I), 1638 (w), 1613 (w) (ν CC_{arom}), 1554 (s), 1543 (s) (ν C=N, amide-II), 1517 (w) (ν CC_{arom}), 827 (m) (δ CH_{arom}); MS (EI) *m*/*z* 520 [3, $(M+2)^+$], 519 [16, $(M+1)^+$], 518 (47, M^+), 447 (7), 404 (30), 361 (13), 300 (41), 260 (98), 259 (97), 244 (28), 243 (87), 217 (23), 216 (22), 215 (48), 200 (21), 199 (23), 189 (40), 188 (99), 186 (26), 173 (86), 163 (96), 162 (99), 160 (32), 159 (27), 158 (33), 147 (68), 146 (82), 145 (56), 144 (42), 132 (45), 118 (29), 117 (34), 115 (21), 91 (36), 18 (100). Anal. Calcd for $C_{30}H_{42}N_6O_2$: C, 69.47; H, 8.16; N, 16.20. Found: C, 69.32; H, 8.17; N, 16.22.

*4.6.5. 6,7,13,14-Tetramethyl-5,12-di(4-methoxyphenyl)-1,2,4,8,9,11-hexaazacyclotetradeca-7,14-diene-3,10-dione (**24e**).* To semicarbazide **20e** (0.528 g, 1.89 mmol) were added TsOH·H_2O (0.372 g, 1.96 mmol) and EtOH (7 mL) and the obtained mixture was refluxed for 1 h 50 min under stirring. The obtained suspension was cooled (0 °C). The precipitate was filtered, washed with cold (−18 °C) EtOH (2×3 mL), ice-cold H_2O (4×3 mL) and petroleum ether, and dried to give **24e** (0.340 g, 73%) as a mixture of seven diastereomers, three of

which (a 81:13:6 isomeric ratio) give 97 mol % in total. An analytically pure sample (a 87:12:1 isomeric ratio, respectively) was obtained after crystallization from *n*-BuOH. Mp 256.5 °C (dec, *n*-BuOH). ^{1}H NMR of the major isomer (81%) (300.13 MHz, DMSO-d_6) δ: 8.93 (2H, s, two NHN), 7.30–7.37 (4H, m, ArH), 6.91–6.96 (4H, m, ArH), 6.56 (2H, d, ^3J=10.6 Hz, two NHC), 4.93 (2H, dd, ^3J=11.5, ^3J=10.6 Hz, two CHN), 3.74 (6H, s, two OCH_3), 2.82 (2H, dq, ^3J=11.5, ^3J=7.0 Hz, two *CH*CH_3), 1.79 (6H, s, two CH_3C=N), 0.66 (6H, d, ^3J=7.0 Hz, two C*H*$_3$CH); ^{1}H NMR of the first minor isomer (13%) (300.13 MHz, DMSO-d_6) δ: 9.30 (2H, s, two NHN), 8.27 (2H, br d, ^3J=8.6 Hz, two NHC), 7.20–7.26 (4H, m, ArH), 6.89–6.95 (4H, m, ArH), 4.76 (2H, dd, ^3J=8.6, ^3J=4.0 Hz, two CHN), 3.75 (6H, s, two OCH_3), 2.86 (2H, dq, ^3J=7.0, ^3J=4.0 Hz, two *CH*CH_3, signals partly overlap with signals of analogous protons of the major isomer), 1.57 (6H, s, two CH_3C=N), 1.24 (6H, d, ^3J=7.0 Hz, two C*H*$_3$CH); ^{1}H NMR of the second minor isomer (6%) (300.13 MHz, DMSO-d_6) δ: 9.43 (2H, s, two NHN), 7.94 (2H, br d, ^3J=10.3 Hz, two NHC), 1.41 (6H, s, two CH_3C=N). Signals of other protons overlap with proton signals of other isomers; ^{13}C NMR of the major isomer (81%) (75.48 MHz, DMSO-d_6) δ: 158.33 (2C), 155.02 (2C=O), 152.39 (2C=N), 134.02 (2C), 128.51 (4CH), 113.95 (4CH), 55.04 (2 OCH_3), 54.20 (2CHN), 47.46 (2*C*HCH$_3$), 16.36 (2*C*H$_3$C=N), 11.47 (2*C*H$_3$CH); ^{13}C NMR of the first minor isomer (13%) (75.48 MHz, DMSO-d_6) δ: 157.88 (2C), 155.83 (2C=O), 152.89 (2C=N), 135.24 (2C), 127.02 (4CH), 113.46 (4CH), 56.10 (2CHN), 55.00 (2 OCH_3), 46.15 (2*C*HCH$_3$). Signals of the other methyl groups are not detectable; IR (Nujol) ν, cm^{-1}: 3401 (br m), 3371 (m), 3213 (br s), 3087 (br m) (ν NH), 1675 (vs) (amide-I), 1612 (w), 1584 (w) (ν CC_{arom}), 1529 (s), 1512 (s) (ν C=N, amide-II), 1253 (s), 1034 (m) (ν C–O), 835 (m) (δ CH_{arom}); MS (EI) *m*/*z* 496 [2, $(M+2)^+$], 495 [9, $(M+1)^+$], 494 (20, M^+), 254 (17), 248 (59), 247 (96), 232 (11), 231 (27), 204 (19), 203 (25), 189 (12), 188 (12), 163 (19), 162 (96), 148 (19), 147 (11), 137 (11), 136 (98), 135 (83), 134 (97), 121 (11), 119 (13), 91 (15), 77 (14), 18 (100). Anal. Calcd for $C_{26}H_{34}N_6O_4\cdot 0.25H_2O$: C, 62.57; H, 6.97; N, 16.84. Found: C, 62.32; H, 7.01; N, 16.56.

*4.6.6. 5,7-Diphenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**29a**).* Triazepine **29a** was prepared from semicarbazide **20f** (1.344 g, 4.52 mmol) and TsOH·H_2O (0.893 g, 4.70 mmol) in EtOH (150 mL) (1 h 50 min, reflux) as described for **24a**. The crude product was purified by column chromatography on silica gel 60 (31 g) eluting with $CHCl_3$–MeOH (from 100:0 to 200:1), the main fraction was concentrated and crystallized from EtOH (15 mL) to give **29a** (0.472 g, 39%). Mp 204–205 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.62 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 7.36–7.43 (2H, m, ArH), 7.35 (1H, br dd of unresolved d, ^3J=4.2, ^4J=2.1, $^4J\approx$0.7 Hz, $N_{(4)}H$), 7.14–7.33 (8H, m, ArH), 4.81 (1H, ddd, ^3J=6.7, ^3J=4.2, ^3J=3.2 Hz, H-5), 3.34 (1H, ddd, ^2J=14.4, ^3J=6.7, ^4J=0.7 Hz, H_A-6), 3.18 (1H, dd, ^2J=14.4, ^3J=3.2 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.58 (C-3), 155.37 (C-7), 143.19 (C), 137.63 (C), 128.80 (CH), 128.25 (2CH), 128.12 (2CH), 127.20 (CH), 125.97 (2CH), 125.64 (2CH), 55.90 (C-5), 36.10 (C-6); IR (Nujol) ν, cm^{-1}: 3347 (w), 3243 (br s), 3226 (br s), 3098 (br s), 3060 (m), 3032 (m) (ν NH), 1685 (s) (amide-I), 1639 (br m) (ν C=N), 1588 (w), 1511 (w) (ν CC_{arom}), 767 (m), 698 (s) (δ CH_{arom}); MS (EI) *m*/*z* 266 [2, $(M+1)^+$], 265 (14, M^+), 221 (13), 162 (11), 161 (100), 145 (14), 133 (17), 132 (16), 119 (7), 118 (15), 115 (8), 104 (31), 103 (31), 102 (5), 92 (5), 91 (23), 89 (6), 78 (11), 77 (46). Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.39; H, 5.65; N, 15.67.

*4.6.7. 5-(4-Methylphenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepine-3-one (**29b**).* Triazepine **29b** was prepared from semicarbazide **20g** (0.471 g, 1.51 mmol) and TsOH·H_2O (0.280 g, 1.58 mmol) in EtOH (50 mL) (reflux, 1 h 50 min) as described for **24a**. The crude product was purified by column chromatography on silica gel 60 (11 g) eluting with $CHCl_3$–petroleum ether (from 5:1 to 1:0) to afford pure **29b** (0.201 g, 45%). Mp 189–191 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.59 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 7.39–7.46 (2H, m, ArH), 7.31 (1H, br dd of unresolved d, ^3J=4.0, ^4J=2.1, $^4J\approx$0.8 Hz, $N_{(4)}H$, signals partly overlap with signals of aromatic protons), 7.22–7.31 (3H, m, ArH), 7.16–7.21 (2H, m, ArH), 7.06–7.11 (2H, m, ArH), 4.74 (1H, ddd, ^3J=7.0, ^3J=4.0, ^3J=3.1 Hz, H-5), 3.33 (1H, ddd, ^2J=14.5, ^3J=7.0, ^4J=0.8 Hz, H_A-6), 3.13 (1H, dd, ^2J=14.5, ^3J=3.1 Hz, H_B-6), 2.22 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.60 (C-3), 154.99 (C-7), 140.25 (C), 137.73 (C), 136.22 (C), 128.77 (3CH), 128.15 (2CH), 125.87 (2CH), 125.65 (2CH), 55.46 (C-5), 36.24 (C-6), 20.61 (CH_3); IR (Nujol) ν, cm^{-1}: 3330 (w), 3249 (br s), 3191 (br m), 3092 (br s) (ν NH), 3016 (w) (ν CH_{arom}), 1683 (s) (amide-I and ν C=N), 1616 (w), 1595 (w), 1575 (w), 1497 (w) (ν CC_{arom}), 803 (s), 760 (m), 697 (m) (δ CH_{arom}); MS (EI) *m*/*z* 281 [1, $(M+2)^+$], 280 [8, $(M+1)^+$], 279 (42, M^+), 235 (34), 221 (5), 191 (6), 189 (4), 178 (3), 174 (3), 165 (4), 162 (8), 161 (59), 147 (5), 146 (51), 145 (13), 133 (12), 132 (3), 128 (4), 127 (3), 120 (5), 119 (19), 118 (99), 117 (22), 116 (5), 115 (10), 105 (4), 104 (8), 103 (20), 102 (4), 92 (5), 91 (29), 90 (3), 89 (5), 78 (3), 77 (14), 18 (100). Anal. Calcd for $C_{17}H_{17}N_3O\cdot 0.11$EtOH: C, 72.72; H, 6.26; N, 14.78. Found: C, 72.46; H, 6.22; N, 14.81.

*4.6.8. 5-(4-Chlorophenyl)-7-phenyl-2,4,5,6-tetrahydro-3H-1,2,4-triazepin-3-one (**29c**).* Triazepine **29c** was prepared from semicarbazide **20h** (0.346 g, 1.04 mmol) and TsOH·H_2O (0.203 g, 1.06 mmol) in EtOH (45 mL) (reflux, 1 h 50 min) as described for **24a**. The crude product was purified by column chromatography on silica gel 60 (10 g) eluting with $CHCl_3$ to afford pure **29c** (0.129 g, 41%). Mp 200.5–201.5 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.65 (1H, br d, ^4J=2.1 Hz, $N_{(2)}H$), 7.39–7.45 (2H, m, ArH), 7.38 (1H, br dd of unresolved d, ^3J=4.2, ^4J=2.1, $^4J\approx$0.9 Hz, $N_{(4)}H$), 7.22–7.36 (7H, m, ArH), 4.82 (1H, ddd, ^3J=6.7, ^3J=4.2, ^3J=3.2 Hz, H-5), 3.36 (1H, ddd, ^2J=14.4, ^3J=6.7, ^4J=0.9 Hz, H_A-6), 3.18 (1H, dd, ^2J=14.4, ^3J=3.2 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 155.43 (C-3), 155.17 (C-7), 142.13 (C), 137.51 (C), 131.63 (C), 128.88 (CH), 128.15 (4CH), 127.92 (2CH), 125.60 (2CH), 55.22 (C-5), 35.74 (C-6); IR (Nujol) ν, cm^{-1}: 3239 (br s), 3095 (br s) (ν NH), 3023 (w) (ν CH_{arom}), 1683 (s) (amide-I), 1632 (m) (ν C=N), 1600 (w), 1577 (w), 1510 (w), 1488 (w) (ν CC_{arom}), 819 (s), 762 (m), 701 (m) (δ CH_{arom}); MS (EI) *m*/*z* 302 [3, $(M+3)^+$], 301 [16, $(M+2)^+$], 300 [9, $(M+1)^+$], 299 (46, M^+), 257 (9), 256 (6), 255 (27), 214 (4), 199 (4), 192 (4), 191 (7), 189 (8), 188 (5), 168 (5), 166 (15), 165 (5), 162 (20), 161 (98), 146 (6), 145 (14), 140 (10), 139 (5), 138 (23), 133 (22), 127 (6), 125 (4), 119 (6), 118 (18), 117 (5), 115 (7), 111 (7), 110 (4), 104 (9), 103 (30), 102 (7), 92 (4), 91 (17), 89 (6), 77 (23), 76 (4), 75 (5), 18 (100). Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.04; H, 4.69; N, 13.92.

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Supplementary data

Supplementary data (copies of IR spectra of all the synthesized compounds, copies of ^{1}H and ^{13}C NMR spectra of compounds **24a**–**e**, **29a**–**c**, copies of ^{1}H,^{1}H-NOESY spectra of compounds **20a,h**) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.10.079. These data include MOL files and InChiKeys of the most important compounds described in this article.

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18. At the beginning of the current study, we attempted to prepare compounds **7** using the literature procedures involving addition of carbamates to α,β-unsaturated ketones in the presence of various catalysts. We repeated the reaction of 1,3-diphenylprop-2-en-1-one (chalcone) (1 equiv) with ethyl carbamate (1.2 equiv) promoted by $FeCl_3$ (0.1 equiv)/Me_3SiCl (1.1 equiv) (CH_2Cl_2, rt, 12 and 24 h)[31] or $BF_3{\cdot}Et_2O$ (0.2 equiv)/Bu_4NBr (0.1 equiv) (CH_2Cl_2, rt, 24 h).[32] ^1H NMR spectra of the obtained crude material showed low levels of conversion (chalcone/product ratios were 65:35, 73:27, and 89:11, respectively) and formation of some byproducts. In the first case ($FeCl_3$/Me_3SiCl, 12 h), the calculated yield of the addition product determined by ^1H NMR spectroscopy with 1,4-dioxane as an internal standard was only 22%. We also repeated the reaction of 4-phenylbut-3-en-2-one (1 equiv) with ethyl carbamate (1.2 equiv) in the presence of $FeCl_3$ (0.1 equiv)/Me_3SiCl (1.1 equiv) (CH_2Cl_2, rt, 24 h).[31] However, the addition did not proceed at all. Therefore, the reported isolated yields (40–48% after purification using column chromatography)[31,32] in the above reactions appear to be significantly overestimated.
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22. The detailed results of this investigation were described in our preliminary communication.[20]
23. The results of the DFT calculations were presented in the Supplementary data to our preliminary communication.[20]
24. Crystallographic data for the structural analyses of macrocycles **24a** and **24b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 928685 and 1003952, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. See also the Supplementary data to Ref. 20.
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