Synthesis, Dissociation Constants, and Antimicrobial Activity of Novel 2,3-Disubstituted-1,3-thiazolidin-4-one Derivatives

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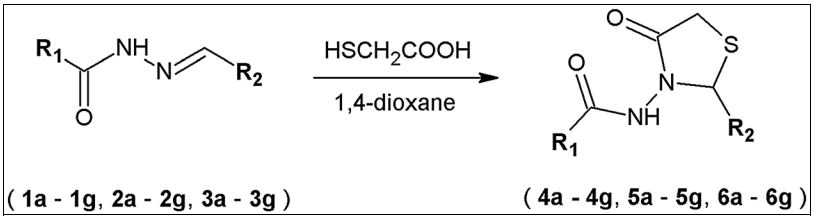

In this article, a new series of 2,3-disubstituted-1,3-thiazolidin-4-one derivatives have been designed, synthesized, and evaluated as antimicrobial agents. New compounds were prepared by the cyclization reaction of *N*-substituted carboxylic acid hydrazide derivatives with mercaptoacetic acid. The structures of the obtained compounds were confirmed by means of IR, ^{1}H NMR, and ^{13}C NMR spectra. The dissociation constants were determined using spectrophotometric method. All synthesized compounds were tested for their *in vitro* antibacterial and antifungal activities using the broth microdilution method.

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INTRODUCTION

In the past few years, the incidence of microbial infections and pathogen resistance to existing drugs grows to an alarming level. These infections are a major cause of increasing mortality, especially in patients with low levels of immunity [1]. Therefore, discovery of a new class of antimicrobial agents is needed to combat multiresistance infections and in the prevention and treatment of certain infection complications [1].

In a wide variety of heterocyclic structures, the 1,3-thiazolidin-4-one nucleus constitutes an important class displaying a broad spectrum of biological activities [2]. It was found that the 1,3-thiazolidin-4-one system, which is a core structure in various synthetic pharmaceuticals, displays antibacterial [3–5], antifungal [6,7], antiviral [8–15], antitumor [16], and anticonvulsant [17] properties.

In view of these facts and in continuation of our work devoted to search new antimicrobial compounds, we design, synthesize, and evaluate for *in vitro* antimicrobial activity a new series of 2,3-disubstituted-1,3-thiazolidin-4-one derivatives.

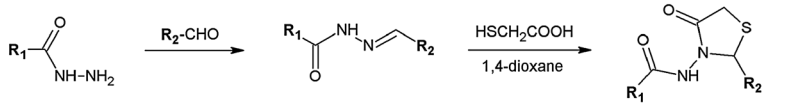
RESULTS AND DISCUSSION

Chemistry. The reaction sequences employed for the synthesis of title compounds (**4a–4g**, **5a–5g**, and **6a–6g**) are shown in Scheme 1. The yields, melting points, and spectral data of compounds **1a–1g, 2a–2g**, **3a–3g**, **4a–4g**, **5a–5g**, and **6a–6g** are given in the Experimental section. The IR, ^{1}H NMR, and ^{13}C NMR spectra, and elemental analyses were in full agreement with the proposed structures of all the compounds (**1a–1g**, **2a–2g**, **3a–3g**, **4a–4g**, **5a–5g**, and **6a–6g**).

The key intermediates *N*-substituted carboxylic acid hydrazide derivatives (**1a–1g**, **2a–2g**, and **3a–3g**) were synthesized by the fusion of three different carboxylic acid hydrazides (**1**, **2**, and **3**) with appropriate aliphatic or aromatic aldehydes in ethanol in the presence of glacial acetic acid for 4 h under reflux (Scheme 1).

The formation of the Schiff base hydrazone derivatives (**1a–1g**, **2a–2g**, and **3a–3g**) was confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra and elemental analyses. The IR spectra of synthesized *N*-substituted carboxylic acid hydrazide derivatives confirmed the presence of C=O and NH groups. The ^{1}H NMR spectra of the compounds (**1a–1g**, **2a–2g**, and **3a–3 g**) showed two singlets at δ 7.82–9.03 ppm and δ 9.50–11.91 ppm corresponding to =CH and NH protons, respectively, whereas in ^{13}C NMR spectra, we observed signals for =CH group at δ 149.0–160.9 ppm and for the C=O group in the range of δ 172.7–177.4 ppm. All other aliphatic and aromatic signals were displayed at expected regions.

Scheme 1. Reactions leading to new 1,3-thiazolidin-4-one derivatives **4a-4g**, **5a-5g**, **6a-6g**.



(1 - 3) (1a - 1g, 2a - 2g, 3a - 3g) (4a - 4g, 5a - 5g, 6a - 6g)

Compound No	R_1	R_2	Compound No	R_1	R_2
1	cyclopropyl	-	**2c, 5c**	cyclopentyl	2-OH-C_6H_4
2	cyclopentyl	-	**2d, 5d**	cyclopentyl	3-NO_2-C_6H_4
3	cyclohexyl	-	**2e, 5e**	cyclopentyl	4-CH_3-C_6H_4
1a, 4a	cyclopropyl	*i*-Pr	**2f, 5f**	cyclopentyl	4-CH_3O-C_6H_4
1b, 4b	cyclopropyl	C_6H_5	**2g, 5g**	cyclopentyl	4-Br-C_6H_4
1c, 4c	cyclopropyl	2-OH-C_6H_4	**3a, 6a**	cyclohexyl	*i*-Pr
1d, 4d	cyclopropyl	3-NO_2-C_6H_4	**3b, 6b**	cyclohexyl	C_6H_5
1e, 4e	cyclopropyl	4-CH_3-C_6H_4	**3c, 6c**	cyclohexyl	2-OH-C_6H_4
1f, 4f	cyclopropyl	4-CH_3O-C_6H_4	**3d, 6d**	cyclohexyl	3-NO_2-C_6H_4
1g, 4g	cyclopropyl	4-Br-C_6H_4	**3e, 6e**	cyclohexyl	4-CH_3-C_6H_4
2a, 5a	cyclopentyl	*i*-Pr	**3f, 6f**	cyclohexyl	4-CH_3O-C_6H_4
2b, 5b	cyclopentyl	C_6H_5	**3g, 6g**	cyclohexyl	4-Br-C_6H_4

The cyclization reaction of *N*-substituted carboxylic acid hydrazide derivatives (**1a–1g**, **2a–2g**, and **3a–3g**) with mercaptoacetic acid in the presence of 1,4-dioxane afforded new 2,3-disubstituted-1,3-thiazolidin-4-one derivatives **4a–4g**, **5a–5g**, and **6a–6g** in good yield (Scheme 1).

All 2,3-disubstituted-1,3-thiazolidin-4-one derivatives displayed (**4a–4g**, **5a–5g**, and **6a–6g**) IR, ^{1}H NMR, and ^{13}C NMR spectra and elemental analyses consistent with the assigned structures. The IR spectra of synthesized 2,3-disubstituted-1,3-thiazolidin-4-one derivatives confirmed the presence of C=O and NH groups. The ^{1}H NMR spectra showed three signals corresponding to the following: CH group in the range of δ 4.41–9.02 ppm, CH_2 group at δ 2.58–3.81 ppm, and NH group at δ 8.59–12.01 ppm. In the ^{13}C NMR spectra, we observed characteristic signals for CH_2 group at about 30 ppm, for CH group at about 70 ppm, and for two C=O groups at δ 168 ppm and δ 174 ppm, respectively. All other aliphatic and aromatic signals were observed at expected regions.

Dissociation constants. The studied acid–base equilibrium is connected with the dissociation of NH group from hydrazide part. As the phenyl group forms the conjugated system with the CH=N bond, the substituents occurring in this ring should exert the influence on p*K* value. The obtained results (Table 1S. in the Supporting Information) confirm this suggestion that electronegative bromine in position 4 causes distinct increase in p*K* value when compared with the respective compound containing methyl. Cycloalkane group does not show so considerable effect although the bromine influence decreases in the following series:

cyclopropane derivatives < cyclopentane derivatives < cyclohexane derivatives.

The spectra of neutral molecules and monoanion forms (Figure 1S. and Figure 2S. in the Supporting Information) of the studied compounds generally were not affected by the structure, which is consistent with the fact that in all compounds, the same conjugated system of double bond occurs.

On the basis of obtained p*K* values, we can also conclude that the increase of antimicrobial activity can be connected with the increase of p*K* value. For example, the tested linear cyclopropane ($\mathbf{R_1}$) carboxylic acid hydrazide derivatives (**1e** and **1g**) had the lowest p*K* values and had no antimicrobial activity compared with the linear cyclohexane ($\mathbf{R_1}$) carboxylic acid hydrazide derivatives that showed some antimicrobial activity (**3e** and **3g**). On the other hand, the activity of *N*-substituted cyclopentane ($\mathbf{R_1}$) carboxylic acid hydrazide derivatives strongly depends on the nature of substituent $\mathbf{R_2}$ in the structure of compound (**2e** and **2g**).

Microbiology. The results of our study indicated that all the newly synthesized compounds had no inhibitory effect on the growth of reference strains of Gram-negative bacteria. According to the data presented in Tables 1 and 2, the compounds **1a–1g**, **2a**, **2b**, **3b**, **3d**, **3g**, **4b**, **5b**, **5c**, **5e,** and **6d** had no influence also on the growth of Gram-positive bacteria. On the basis of minimal inhibitory concentration (MIC) values obtained by the broth microdilution method, it was shown that among the examined compounds, the widest spectrum of antibacterial activity possessed **2c**, **2g**, **3c**, and **6e**. These compounds were found to be active against Gram-positive bacteria, both pathogenic staphylococci, that is, *Staphylococcus aureus* ATCC 25923 with MIC = 64–500 μg/mL and *S. aureus* ATCC 6538 with MIC = 128–500 μg/mL, and opportunistic bacteria, such as *Staphylococcus epidermidis* ATCC 12228, *Micrococcus*

Table 1

The activity data expressed as MIC [μg/mL] for tested *N*-substituted carboxylic acid hydrazide derivatives (**2c**, **2d**, **2e**, **2f**, **2g**, **3c**, **3f**, **3g**) against the reference strains of bacteria and fungi.

Compound number/species	2c	2d	2e	2f	2g	3c	3e	3f	3g	CIP/FLU*
Staphylococcus aureus ATCC 25923	256	1000	1000	1000	500	64	-	1000	-	0.488
S. aureus ATCC 6538	128	1000	-	-	500	64	-	500	-	0.244
S. aureus NCTC 4163	256	nt	nt	nt	nt	64	nt	nt	nt	0.25
S. aureus ATCC 29213	128	nt	nt	nt	nt	64	nt	nt	nt	0.5
Staphylococcus epidermidis ATCC 12228	128	1000	-	-	1000	32	1000	1000	-	0.122
S. epidermidis ATCC 35984	256	nt	nt	nt	nt	64	nt	nt	nt	0.125
Bacillus subtilis ATCC 6633	128	250	1000	250	250	64	-	1000	-	0.031
Bacillus cereus ATCC 10876	nt	-	-	-	1000	1000	-	1000	-	0.061
B. cereus ATCC 11778	128	nt	nt	nt	nt	32	nt	nt	nt	1.000
Micrococcus luteus ATCC 10240	128	1000	1000	-	1000	64	-	1000	-	0.976
M. luteus ATCC 9341	128	nt	nt	nt	nt	32	nt	nt	nt	2.000
Candida albicans ATCC 2091	nt	-	500	-	500	1000	1000	1000	1000	0.244
C. albicans ATCC 10231	-	-	1000	-	500	1000	1000	1000	1000	0.976
Candida parapsilosis ATCC 22019	-	-	1000	-	1000	1000	1000	1000	-	1.953

-, no activity; nt, not tested.

Table 2

The activity data expressed as MIC [μg/mL] for tested 2,3-disubstituted-1,3-thiazolidin-4-one derivatives (**4g**, **5c**, **5d**, **5g**, **6b**, **6c**, **6e**, **6g**) against the reference strains of bacteria and fungi.

Compound number/species	4g	5c	5d	5g	6b	6c	6e	6g	CIP/FLU*
Staphylococcus aureus ATCC 25923	-	-	-	-	1000	1000	64	-	0.488
S. aureus ATCC 6538	-	-	-	-	-	1000	64	-	0.244
S. aureus NCTC 4163	nt	nt	nt	nt	nt	nt	64	nt	0.25
S. aureus ATCC 29213	nt	nt	nt	nt	nt	nt	64	nt	0.5
Staphylococcus epidermidis ATCC 12228	-	-	-	-	1000	1000	32	-	0.122
S. epidermidis ATCC 35984	nt	nt	nt	nt	nt	nt	64	nt	0.125
Bacillus subtilis ATCC 6633	-	-	1000	1000	1000	1000	64	-	0.031
Bacillus cereus ATCC 10876	-	-	-	-	1000	-	nt	-	0.061
B. cereus ATCC 11778	nt	nt	nt	nt	nt	nt	64	nt	1.000
Micrococcus luteus ATCC 10240	1000	-	1000	-	1000	-	64	1000	0.976
M. luteus ATCC 9341	nt	nt	nt	nt	nt	nt	32	nt	2.000
Candida albicans ATCC 2091	-	-	-	1000	-	-	1000	250	0.244
C. albicans ATCC 10231	-	500	-	-	-	-	nt	1000	0.976
Candida parapsilosis ATCC 22019	500	-	-	-	-	-	nt	1000	1.953

The standard antibiotics used as positive controls: ciprofloxacin (CIP) for bacteria and fluconazole (FLU) for fungi. -, no activity; nt, not tested.

luteus ATCC 10240, *M. luteus* ATCC 9341, *Bacillus subtilis* ATCC 6633, and *Bacillus cereus* ATCC 11778 with MIC = 32–1000 μg/mL. Moreover, the highest good bioactivity against *S. epidermidis* ATCC 12228 and *M. luteus* ATCC 9341 with MIC = 32 μg/mL showed **3c** and **6e**. Compounds **3c** and **6e** also showed good activity against *M. luteus* ATCC 10240 and *B. cereus* with MIC = 32–64 μg/mL. The remaining compounds exhibited some bacteriostatic activity or no activity to reference strains of Gram-positive bacteria. The minimal bactericidal concentration (MBC) of these compounds was >1000 μg/mL.

It was showed also that some of the tested compounds, especially **2e**, **2g**, **4g**, **5c**, and **6g**, showed fungistatic activity with MIC = 250–500 μg/mL against all or some of *Candida* spp. ATCC strains. Moreover, the minimum concentration of **3c**, **3e**, **3f**, **3g**, **5g**, and **6e**, which inhibited the growth of some of these yeasts, was 1000 μg/mL. The minimal fungicidal concentration (MFC) for tested compounds was >1000 μg/mL. Most of the examined compounds had no inhibitory effect on the growth of reference yeasts belonging to *Candida* spp.

In general, both linear and cyclic cyclopropane ($\mathbf{R_1}$) carboxylic acid derivatives (**1a–1g** and **4a–4f**) did not show any antimicrobial activity irrespective of the nature of substituent $\mathbf{R_2}$ presented in the structure of tested compounds. Linear cyclopentane ($\mathbf{R_1}$) carboxylic acid hydrazide derivatives had higher activity than their corresponding cyclic 1,3-thiazolidin-4-one derivatives (**5a–5g**). The influence of the substituent $\mathbf{R_2}$ is especially significant in the case of compound **2c**, which had 2–OH–Ph group and showed the best activity among all linear cyclopentane derivatives

(**2a–2g**). In the midst of linear cyclohexane (**R_1**) carboxylic acid derivatives (**3a–3g**), the best activity showed the compound (**3c**) with 2–OH–Ph substituent as **R_2**, whereas among cyclic 1,3-thiazolidin-4-one derivatives (**6a–6g**), the most significant activity was connected with the 4–CH_3–Ph substituent in the compound (**6e**).

In conclusion, our results indicate that some of the obtained compounds showed mild or moderate activity with bacteriostatic or fungistatic effect against Gram-positive bacteria or yeasts belonging to *Candida* spp.

EXPERIMENTAL

Chemistry. ***General.*** All reagents were purchased from Sigma-Aldrich (Munich, Germany) and Merck Co. (Darmstadt, Germany) and used without further purification. Melting points were determined in Fisher-Johns blocks (Fisher Scientific, Schwerte, Germany) and presented without any corrections. The IR spectra (ν, cm^{-1}) were recorded in KBr tablets using a Specord IR-75 spectrophotometer (VEB Carl Zeiss, Jena, Germany). The ^{1}H NMR spectra were recorded on a Bruker Avance 300 apparatus (Bruker BioSpin GmbH, Rheinstetten/Karlsruhe, Germany) in DMSO-d_6 with TMS as internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance 300 apparatus. Chemical shifts are given in ppm (δ-scale). The purity of obtained compounds was checked by TLC on aluminium oxide 60 F254 plates (Merck Co. Whitehouse Station, NJ), in a $CHCl_3/C_2H_5OH$ (10:1, v/v) solvent system. The spots were detected by exposure to a UV lamp at 254 nm. Elemental analyses of the obtained compounds were performed for C, H, and N on AMZ 851 CHX analyser (PG, Gdańsk, Poland). The maximum percentage differences between the calculated and found values for each element were within the error and amounted to ±0.4%.

Synthesis of carboxylic acid hydrazide (1, 2, 3). To the solution of appropriate ethyl ester of carboxylic acid (10 mmol) in ethanol (15 mL), an equimolar of 100% hydrazine hydrate was added. The solution was heated under reflux for 3 h. After that, the solution was cooled to room temperature. The obtained precipitate was filtered and crystallized from ethanol.

Cyclopropane carboxylic acid hydrazide (1). CAS Registry Number: 6952-93-8. Yield: 78.4%, mp. 98–99°C (dec.).

Cyclopentane carboxylic acid hydrazide (2). CAS Registry Number: 3400-07-5. Yield: 94.2%, mp. 108–109°C (dec.).

Cyclohexane carboxylic acid hydrazide (3). CAS Registry Number: 38941-47-8. Yield: 90.1%, mp. 158–159°C (dec.).

Synthesis of N-substituted carboxylic acid hydrazide derivatives (1a–1g, 2a–2g, 3a–3g), ***General method.*** To a suspension of hydrazides (**1–3**) (10 mmol) in ethanol (20 mL), an equimolar amount of various aliphatic or aromatic aldehydes (10 mmol) was added. The suspension was heated until clear solution was obtained. Then few drops of glacial acetic acid were added as a catalyst. The solution was refluxed for 4 h. After the completion of the reaction, the solution was cooled to room temperature. The obtained precipitate was filtered and crystallized from ethanol.

N-(2-Methylpropylidene)cyclopropanecarbohydrazide (1a). CAS Registry Number: 545346-60-9. Yield: 1.38 g (98.9%), mp. 90–92°C (dec.). IR (KBr), ν (cm^{-1}): 3020, 1448 (CH aliphatic), 1710 (C=O), 1580 (C=N), 1590 (N–H), 1442 (CH_2-cyclopropyl), 1410 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.77–0.84 (m, 2H, CH_2-cyclopropyl), 1.09–1.14 (m, 2H, CH_2-cyclopropyl), 1.39 (d, 6H, 2xCH_2), 1.89–1.94 (m, 1H, CH-cyclopropyl), 2.26–2.29 (m, 1H, CH), 7.88 (s, 1H,=CH), 10.04 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.7 (2xCH_2-cyclopropyl), 15.9 (CH-cyclopropyl), 18.2 (2xCH_3), 29.7 (CH), 150.9 (=CH), 173.8 (C=O). *Anal*. Calcd for $C_8H_{14}N_2O$ (154.21): C, 62.31; H, 9.15; N, 18.17; Found: C, 62.51; H, 9.11; N, 18.09%.

N-(Phenylmethylidene)cyclopropanecarbohydrazide (1b). CAS Registry Number: 91350-09-3. Yield: 1.65 g (87.5%), mp. 140–142°C (dec.). IR (KBr), ν (cm^{-1}): 3055 (CH aromatic), 3030, 1460 (CH aliphatic), 1715 (C=O), 1590 (C=N), 1596 (N–H), 1442 (CH_2–cyclopropyl), 1396 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.24–1.47 (m, 2H, CH_2-cyclopropyl), 1.67–1.77 (m, 2H, CH_2-cyclopropyl), 2.17–2.25 (m, 1H, CH-cyclopropyl), 7.41–7.69 (m, 4H, Ar–H), 8.18 (s, 1H,=CH), 11.32 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.7 (2xCH_2-cyclopropyl), 15.9 (CH-cyclopropyl), 127.0, 128.7, 129.1, 134.7 (6C_{ar}), 149.4 (=CH), 172.7 (C=O). *Anal*. Calcd for $C_{11}H_{12}N_2O$ (188.22): C, 70.19; H, 6.43; N, 14.88; Found: C, 70.23; H, 6.45; N, 14.93%.

N-[(2-Hydroxyphenyl)methylidene]cyclopropanecarbohydrazide (1c). CAS Registry Number: 444049-35-8. Yield: 1.39 g (68.1%), mp. 176–178°C (dec.). IR (KBr), ν (cm^{-1}): 3055 (CH aromatic), 3030, 1460 (CH aliphatic), 1715 (C=O), 1590 (C=N), 1596 (N–H), 1442 (CH_2–cyclopropyl), 1396 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.79–0.89 (m, 2H, CH_2–cyclopropyl), 1.62–1.70 (m, 2H, CH_2–cyclopropyl), 2.54–2.63 (m,1H, CH–cyclopropyl), 6.84–773 (m, 4H, Ar–H), 8.37 (s, 1H,=CH), 9.03 (s, 1H, OH), 11.90 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2–cyclopropyl), 15.9 (CH–cyclopropyl), 117.4, 120.4, 121.2, 128.5, 129.7 (5C_{ar}), 152.1 (=CH), 158.3 (C_{ar}), 173.7 (C=O). *Anal*. Calcd for $C_{11}H_{12}N_2O_2$ (204.22): C, 64.69; H, 5.92; N, 13.72; Found: C, 64.68; H, 5.95; N, 13.70%.

N-[(3-Nitrophenyl)methylidene]cyclopropanecarbohydrazide (1d). CAS Registry Number: 35559-15-0. Yield: 2.26 g (97.1%), mp. 196–198°C (dec.). IR (KBr), ν (cm^{-1}): 3032 (CH aromatic), 3011, 1448 (CH aliphatic), 1702 (C=O), 1611 (C=N), 1600 (N–H), 1442 (CH_2–cyclopropyl), 1410 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.82–0.96 (m, 2H, CH_2–cyclopropyl), 1.65–1.72 (m, 2H, CH_2–cyclopropyl), 2.65–2.73 (m, 1H, CH–cyclopropyl), 7.72–8.52 (m, 4H, Ar–H), 8.93 (s, 1H,=CH), 11.91 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 7.7, 8.6 (2xCH_2–cyclopropyl), 10.2 (CH–cyclopropyl), 121.4, 124.3, 130.9, 133.3, 134.9, 141.1 (6C_{ar}), 143.4 (=CH), 175.3 (C=O). *Anal*. Calcd for $C_{11}H_{11}N_3O_3$ (233.22): C, 56.65; H, 4.75; N, 18.02; Found: C, 56.68; H, 4.78; N, 18.06%.

N-[(4-Methylphenyl)methylidene]cyclopropanecarbohydrazide (1e). CAS Registry Number: 443975-38-0. Yield: 1.42 g (70.2%), mp. 146–148°C (dec.). IR (KBr), ν (cm^{-1}): 3011 (CH aromatic), 2990, 1450 (CH aliphatic), 1710 (C=O), 1615 (C=N), 1605 (N–H), 1442 (CH_2–cyclopropyl), 1396 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.78–0.88 (m, 2H, CH_2–cyclopropyl), 1.60–1.68 (m, 2H, CH_2–cyclopropyl), 2.34 (s, 3H, CH_3), 2.63–2.71 (m, 1H, CH–cyclopropyl), 7.24–7.26 (dd, 2H, J = 6Hz, Ar–H), 7.57–7.59 (dd, 2H, J = 6Hz, Ar–H), 8.14 (s, 1H,=CH), 11.58 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2–cyclopropyl); 15.9 (CH–cyclopropyl), 21.1 (CH_3), 127.3, 129.1, 131.9, 138.5 (6C_{ar}), 149.0 (=CH), 173.8 (C=O). *Anal*. Calcd for $C_{12}H_{14}N_2O$ (202.25): C, 71.26; H, 6.98; N, 13.85; Found: C, 72.33; H, 6.97; N, 13.81%.

N-[(4-Methoxyphenyl)methylidene]cyclopropanecarbohydrazide (1f). CAS Registry Number: 468102-53-6. Yield: 1.91 g (87.7%), mp. 176–178°C (dec.). IR (KBr), ν (cm^{-1}): 3089 (CH aromatic), 3050, 1442 (CH aliphatic), 1714 (C=O), 1622 (C=N), 1590 (N–H), 1442 (CH_2–cyclopropyl), 1402 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 0.77–0.87 (m, 2H, CH_2–cyclopropyl), 1.59–1.67 (m, 2H, CH_2–cyclopropyl), 2.62–2.70 (m, 1H, CH–cyclopropyl), 3.80 (s, 3H, CH_3), 6.98–7.02 (m, 4H, Ar–H), 8.13 (s, 1H,=CH), 11.51 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 7.9, 8.2 (2xCH_2–cyclopropyl), 10.2 (CH–cyclopropyl), 55.8 (–CH_3), 114.8, 127.4, 128.7, 128.9, 143.2, 145.7 (6C_{ar}), 160.9 (=CH), 174.8 (C=O). *Anal*. Calcd for $C_{12}H_{14}N_2O_2$ (218.25): C, 66.04; H, 6.47; N, 12.84; Found: C, 66.10; H, 6.44; N, 12.79%.

N-[(4-Bromophenyl)methylidene]cyclopropanecarbohydrazide (1g). CAS Registry Number: 468102-56-9. Yield: 2.14 g (80.2%), mp. 166–168°C (dec.). IR (KBr), ν (cm^{-1}): 3070 (CH aromatic), 3025, 1458 (CH aliphatic), 1718 (C=O), 1611 (C=N), 1605 (N–H), 1442 (CH_2–cyclopropyl), 1408 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 0.80–0.89 (m, 2H, CH_2–cyclopropyl), 1.61–1.70 (m, 2H, CH_2–cyclopropyl), 2.63–2.71 (m, 1H, CH–cyclopropyl), 7.61–8.16 (m, 4H, Ar–H), 8.72 (s, 1H,=CH), 11.72 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2–cyclopropyl), 15.9 (CH–cyclopropyl), 123.9, 129.3, 132.3, 132.5 (6C_{ar}), 149.0 (=CH), 173.8 (C=O). *Anal*. Calcd for $C_{11}H_{11}BrN_2O$ (267.12): C, 49.46; H, 4.15; N, 10.49; Found: C, 49.49; H, 4.17; N, 10.51%.

N-(2-Methylpropylidene)cyclopentanecarbohydrazide (2a). Yield: 1.54 g (84.5%), mp. 102–104°C (dec.).IR (KBr), ν (cm^{-1}): 2990, 1451 (CH aliphatic), 1703 (C=O), 1618 (C=N), 1598 (N–H), 1455 (CH_2–cyclopentyl), 1396 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.32 (s, 6H, 2xCH_3), 1.57–1.59 (m, 4H, 2xCH_2–cyclopentyl), 1.64–1.66 (m, 4H, 2xCH_2–cyclopentyl), 2.22–2.25 (m, 1H, CH), 2.55–2.59 (m, 1H, CH–cyclopentyl), 7.86 (s, 1H,=CH), 10.07 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 18.2 (2xCH_3), 26.1 (2xCH_2–cyclopentyl), 29.7 (CH), 32.9 (2xCH_2–cyclopentyl), 32.9 (2xCH_2–cyclopentyl), 46.7 (CH–cyclopentyl), 150.9 (=CH), 176.2 (C=O). *Anal*. Calcd for $C_{10}H_{18}N_2O$ (182.26): C, 65.90; H, 9.95; N, 15.37; Found: C, 65.92; H, 9.91; N, 15.39%.

N-(Phenylmethylidene)cyclopentanecarbohydrazide (2b). CAS Registry Number: 5547-59-1. Yield: 2.12 g (98.1%), mp. 158–160°C (dec.). IR (KBr), ν (cm^{-1}): 2990, 1451 (CH aliphatic), 1703 (C=O), 1618 (C=N), 1598 (N–H), 1455 (CH_2–cyclopentyl), 1396 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.55–1.88 (m, 8H, CH_2–cyclopentyl), 2.60–2.70 (m, 1H, CH–cyclopentyl), 7.42–7.70 (m, 5H, Ar–H), 8.19 (s, 1H,=CH), 11.35 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2–cyclopentyl), 46.3 (CH–cyclopentyl), 127.0, 128.7, 129.1, 134.7 (6C_{ar}), 149.0 (=CH), 176.2 (C=O). *Anal*. Calcd for $C_{13}H_{16}N_2O$ (216.28): C, 72.19; H, 7.46; N, 12.95; Found: C, 72.23; H, 7.48; N, 12.98%.

N-[(2-Hydroxyphenyl)methylidene]cyclopentanecarbohydrazide (2c). CAS Registry Number: 1030556-24-1. Yield: 0.79 g (34.1%), mp. 204–206°C (dec.). IR (KBr), ν (cm^{-1}): 3055 (CH aromatic), 3011, 1459 (CH aliphatic), 1701 (C=O), 1614 (C=N), 1595 (N–H), 1455 (CH_2–cyclopentyl), 1410 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.05–1.23 (m, 6H, CH_2–cyclopentyl), 1.67–1.71 (m, 2H, CH_2–cyclopentyl), 2.09–2.11(m 1H, CH–cyclopentyl), 6.91–7.72 (m, 4H, Ar–H), 8.37 (s, 1H,=CH), 9.02 (s,1H, OH), 11. 16 (s, 1H, OH). ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2–cyclopentyl), 46.3 (CH–cyclopentyl), 117.4, 120.4, 121.2, 128.5, 129.7 (5C_{ar}), 152.1 (=CH), 158.3 (C_{ar}), 176.2 (C=O). *Anal*. Calcd for $C_{13}H_{16}N_2O_2$ (232.28): C, 67.22; H, 6.94; N, 12.06; Found: C, 67.25; H, 6.96; N, 12.10%.

N-[(3-Nitrophenyl)methylidene]cyclopentanecarbohydrazide (2d). Yield: 2.57 g (98.4%), mp. 171–173°C (dec.). IR (KBr), ν (cm^{-1}): 3040 (CH aromatic), 3035, 1441 (CH aliphatic), 1710 (C=O), 1633 (C=N), 1615 (N–H), 1455 (CH_2–cyclopentyl), 1404 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.54–1.90 (m, 8H, CH_2–cyclopentyl), 2.64–2.74 (m, 1H, CH–cyclopentyl), 7.70–8.52 (m, 4H, Ar–H), 8.31 (s, 1H,=CH), 11.63 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 26.2, 26.3, 29.8, 30.4 (4xCH_2–cyclopentyl), 43.6 (CH–cyclopentyl), 121.3, 124.3, 130.9, 133.1, 140.5, 143.8 (6C_{ar}), 148.7 (=CH), 172.3 (C=O). *Anal*. Calcd for $C_{13}H_{15}N_3O_3$ (261.28): C, 59.76; H, 5.79; N, 16.08; Found: C, 59.77; H, 5.80; N, 16.12%.

N-[(4-Methylphenyl)methylidene]cyclopentanecarbohydrazide (2e). Yield: 1.09 g (47.2%), mp. 152–154°C (dec.). IR (KBr), ν (cm^{-1}): 3035 (CH aromatic), 2996, 1459 (CH aliphatic), 1715 (C=O), 1612 (C=N), 1604 (N–H), 1455 (CH_2–cyclopentyl), 1395 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.55–1.88 (m, 8H, CH_2cyclopentyl), 2.34 (s, 3H, CH_3), 2.61–2.66 (m, 1H, CH–cyclopentyl), 7.23–7.58 (m, 4H, Ar–H), 8.15 (s, 1H,=CH), 11.29 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 21.1 (CH_3), 26.1, 32.9 (4xCH_2–cyclopentyl), 46.3 (CH–cyclopentyl), 127.3, 129.1, 131.9, 138.5 (6C_{ar}), 149.5 (=CH), 176.2 (C=O). *Anal*. Calcd for $C_{14}H_{18}N_2O$ (230.30): C, 73.01; H, 7.88; N, 12.16; Found: C, 73.06; H, 7.82; N, 12.14%.

N-[(4-Methoxyphenyl)methylidene]cyclopentanecarbohydrazide (2f). CAS Registry Number: 1030511-26-2. Yield: 0.83 g (33.9%), mp. 134–136°C (dec.). IR (KBr), ν (cm^{-1}): 3046 (CH aromatic), 3025, 1442 (CH aliphatic), 1708 (C = O), 1610 (C = N), 1600 (N–H), 1455 (CH_2-cyclopentyl), 1412 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.56–1.83 (m, 8H, CH_2-cyclopentyl), 2.58–2.68 (m, 1H, CH-cyclopentyl), 6.97–7.63 (m, 4H, Ar–H), 8.13 (s, 1H, =CH), 11.22 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 26.2, 26.3, 29.8, 30.5 (4xCH_2-cyclopentyl), 43.6 (CH-cyclopentyl), 55.7 (CH_3), 114.7, 127.5, 127.5, 128.6, 128.9, 160.9 (6C_{ar}), 146.9 (=CH), 177.4 (C=O). *Anal*. Calcd for $C_{14}H_{18}N_2O_2$ (246.30): C, 68.27; H, 7.37; N, 11.37; Found: C, 68.33; H, 7.36; N, 11.41%.

N-[(4-Bromophenyl)methylidene]cyclopentanecarbohydrazide (2g). Yield: 2.92 g (98.9%), mp. 180–182°C (dec.). IR (KBr), ν (cm^{-1}): 3050 (CH aromatic), 3015, 1454 (CH aliphatic), 1710 (C=O), 1622 (C=N), 1590 (N–H), 1455 (CH_2-cyclopentyl), 1415 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.55–1.88 (m, 8H, CH_2-cyclopentyl), 2.60–2.74 (m, 1H, CH-cyclopentyl), 7.59–7.86 (m, 4H, Ar–H), 8.16 (s, 1H, =CH), 11.43 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2-cyclopentyl), 46.32 (CH-cyclopentyl), 123.9, 129.3, 132.4, 132.5 (6C_{ar}), 149.0 (=CH), 176.2 (C=O). *Anal*. Calcd for $C_{13}H_{15}BrN_2O$ (295.17): C, 52.90; H, 5.12; N, 9.49; S, Found: C, 52.93; H, 5.15; N, 9.47%.

N-(2-Methylpropylidene)cyclohexanecarbohydrazide (3a). CAS Registry Number: 541518-82-5. Yield: 0.63 g (32.2%), mp. 116–118°C (dec.). IR (KBr), ν (cm^{-1}): 3010, 1460 (CH aliphatic), 1698 (C=O), 1624 (C=N), 1595 (N–H), 1452 (CH_2-cyclohexyl), 1410 (C–N). ^1H NMR (DMSO-d_6): δ (ppm) = 1.33 (s, 6H, 2xCH_3), 1.58–1.60 (m, 8H, CH_2-cyclohexyl), 2.05–2.07 (m, 2H, CH_2-cyclohexyl), 2.23–2.26 (m, 1H, CH), 2.44–2.47 (m, 1H, CH-cyclohexyl), 7.82 (s, 1H, =CH), 10.08 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 18.2 (2xCH_3), 25.1, 27.9 (5xCH_2-cyclohexyl), 29.7 (CH), 41.8 (CH-cyclohexyl), 150.9 (=CH),

174.7 (C=O). *Anal*. Calcd for $C_{11}H_{20}N_2O$ (196.29): C, 67.31; H, 10.27; N, 14.27; Found: C, 67.35; H, 10.22; N, 14.30%.

N-(Phenylmethylidene)cyclohexanecarbohydrazide (3b). CAS Registry Number: 340295-32-1. Yield: 1.54 g (67.1%), mp. 152–153°C (dec.). IR (KBr), ν (cm^{-1}): 3070 (CH aromatic), 3024, 1451 (CH aliphatic), 1701 (C=O), 1612 (C=N), 1602 (N–H), 1452(CH_2-cyclohexyl), 1390 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.53–1.56 (m, 6H, 3xCH_2-cyclohexyl), 1.66–1.68 (m, 2H, CH_2-cyclohexyl), 1.83–1.85 (m, 2H, CH_2-cyclohexyl), 2.61–2.65 (m, 1H, CH-cyclohexyl), 7.33–7.36 (m, 3H, ArH), 7.55–7.58 (m, 2H, ArH) 8.40 (s, 1H, =CH), 9.50 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 41.8 (CH-cyclohexyl), 127.0, 128.7, 129.1, 134.7 (6C_{ar}), 149.0 (=CH), 176.7 (C=O). *Anal*. Calcd for $C_{14}H_{18}N_2O$ (230.30): C, 73.01; H, 7.88; N, 12.16; Found: C, 73.08; H, 7.81; N, 12.18%.

N-[(2-Hydroxyphenyl)methylidene]cyclohexanecarbohydrazide (3c). CAS Registry Number: 468102-83-2. Yield: 0.85 g (34.5%), mp. 148–150°C (dec.). IR (KBr), ν (cm^{-1}): 3061 (CH aromatic), 3045, 1440 (CH aliphatic), 1710 (C=O), 1618 (C=N), 1605 (N–H), 1452 (CH_2-cyclohexyl), 1400 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.04–1.78 (m, 10H, CH_2-cyclohexyl), 2.19–2.26 (m, 1H, CH-cyclohexyl), 6.88–7.73 (m,4H, Ar–H), 8.26 (s, 1H, =CH), 9.03 (s, 1H, OH), 11.58 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 41.8 (CH-cyclohexyl), 117.4, 120.4, 121.2, 128.5, 129.7 (5C_{ar}), 152.1 (=CH), 158.3 (C_{ar}), 174.7 (C=O). *Anal*. Calcd for $C_{14}H_{18}N_2O_2$ (246.30): C, 68.27; H, 7.37; N, 11.37; Found: C, 68.32; H, 7.41; N, 11.39%.

N-[(3-Nitrophenyl)methylidene]cyclohexanecarbohydrazide (3d). CAS Registry Number: 468102-66-1. Yield: 2.71 g (98.6%), mp. 164–166°C (dec.). IR (KBr), ν (cm^{-1}): 3043 (CH aromatic), 3022, 1456 (CH aliphatic), 1716 (C=O), 1635 (C=N), 1610 (N–H), 1452 (CH_2-cyclohexyl), 1391 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.17–1.78 (m, 10H, CH_2-cyclohexyl), 2.21–2.29 (m, 1H, CH-cyclohexyl), 7.71–8.50 (m, 4H, Ar–H), 8.94 (s, 1H, =CH), 11.59 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.1, 25.9, 17.9 (5xCH_2-cyclohexyl), 41.8 (CH-cyclohexyl), 122.3, 124.1, 129.9, 132.6, 137.8, 147.4 (6C_{ar}), 148.2 (=CH); 174.7 (C=O). *Anal*. Calcd for $C_{14}H_{17}N_3O_3$ (275.30): C, 61.08; H, 6.22; N, 15.26; Found: C, 61.11; H, 6.25; N, 15.22%.

N-[(4-Methylphenyl)methylidene]cyclohexanecarbohydrazide (3e). CAS Registry Number: 468102-75-2. Yield: 1.52 g (62.2%), mp. 130–132°C (dec.). IR (KBr), ν (cm^{-1}): 3090 (CH aromatic), 3047, 1451 (CH aliphatic), 1711 (C=O), 1641 (C=N), 1611 (N–H), 1452 (CH_2-cyclohexyl), 1405 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.24–1.76 (m, 10H, CH_2-cyclohexyl), 2.13–2.24 (m, 1H, CH-cyclohexyl), 2.34 (s, 3H, CH_3), 7.24–7.80 (m, 4H, Ar–H), 8.68 (s, 1H, =CH), 11.25 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 21.5, 25.7, 25.9, 26.1, 28.7 (5xCH_2-cyclohexyl), 39.9 (CH-cyclohexyl), 43.3 (CH_3), 127.4, 129.9, 130.0, 132.2, 140.0, 141.8 (6C_{ar}), 146.3 (=CH); 177.3 (C=O). *Anal.* Calcd for $C_{15}H_{20}N_2O$ (244.33): C, 73.74; H, 8.25; N, 11.47; Found: C, 73.76; H, 8.22; N, 11.51%.

N-[(4-Methoxyphenyl)methylidene]cyclohexanecarbohydrazide (3f). CAS Registry Number: 444767-02-6. Yield: 1.05 g (40.5%), mp. 137–139°C (dec.). IR (KBr), ν (cm^{-1}): 3085 (CH aromatic), 3067, 1452 (CH aliphatic), 1709 (C=O), 1644 (C=N), 1618 (N–H), 1452 (CH_2-cyclohexyl), 1410 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.23–1.26 (m, 10H, CH_2-cyclohexyl), 2.15–2.23 (m, 1H, CH-cyclohexyl), 3.80 (s, 3H, CH_3), 6.99–7.93 (m, 4H, Ar–H), 8.65 (s, 1H, =CH), 11.18 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 41.8 (CH-cyclohexyl), 56.0 (CH_3), 114.3, 127.0, 129.1 (5C_{ar}), 149.0 (=CH), 160.1 (C_{ar}), 174.7 (C=O). *Anal*. Calcd for $C_{15}H_{20}N_2O_2$ (260.33): C, 69.20; H, 7.74; N, 10.76; Found: C, 69.23; H, 7.78; N, 10.80%.

N-[(4-Bromophenyl)methylidene]cyclohexanecarbohydrazide (3g). CAS Registry Number: 468102-70-7. Yield: 2.36 g (76.3%), mp. 181–183°C (dec.). IR (KBr), ν (cm^{-1}): 3032 (CH aromatic), 3008, 1454 (CH aliphatic), 1690 (C=O), 1632 C=N), 1598 (N–H), 1452 (CH_2-cyclohexyl), 1398 (C–N). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.24–1.77 (m, 10H, CH_2-cyclohexyl), 2.17–2.25 (m, 1H, CH-cyclohexyl), 7.58–7.86 (m, 4H, Ar–H), 8.73 (s, 1H, CH), 11.40 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.8, 25.8, 26.1, 28.9, 29.5 (5xCH_2-cyclohexyl), 43.4 (CH-cyclohexyl), 128.9, 129.2, 132.3, 134.2 (6C_{ar}), 149.1 (=CH), 174.7 (C=O). *Anal*. Calcd for $C_{14}H_{17}BrN_2O$ (309.20): C, 54.38; H, 5.54; N, 9.06; Found: C, 54.34; H, 5.58; N, 9.10%.

Preparation of 2,3-disubstituted-1,3-thiazolidin-4-one derivatives (4a–4g, 5a–5g, and 6a–6g). ***General method.*** To a solution of corresponding *N*-substituted carboxylic acid hydrazide derivatives **1a–1g**, **2a–2g**, and **3a–3g** (10 mmol) in 15 mL of 1,4-dioxane, mercaptoacetic acid (0.92 g, 10 mmol) was added dropwise. The mixture was stirred under reflux for 6 h at room temperature. Then the solvent was removed under reduced pressure; after that, 15 mL of 10% water solution of sodium bicarbonate was added. The precipitate was filtered and purified by recrystallization from ethanol.

N-[4-Oxo-2-(propan-2-yl)-1,3-thiazolidin-3-yl]cyclopropanecarboxamide (4a). Yield: 0.99 g (43.2%), mp. 103–104°C (dec.). IR (KBr), ν (cm^{-1}): 3070, 1452 (CH aliphatic), 1710 (C=O), 1600 (N–H), 1442 (CH_2-cyclopropyl), 1411 (C–N), 648 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.77–0.79 (m, 2H, CH_2-cyclopropyl), 1.08 (s, 6H, 2xCH_3), 1.09–1.11 (m, 2H, CH_2-cyclopropyl), 1.83–1.86 (m, 1H, CH-cyclopropyl), 2.48–2.53 (m, 1H, CH), 3.28 (s, 2H, CH_2), 4.42 (d, 1H, CH), 8.87 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.7 (2xCH_2-cyclopropyl), 17.7 (CH-cyclopropyl), 20.4 (2xCH_3), 30.8 (CH_2), 32.3 (CH), 78.2 (CH), 168.8 (C=O), 176.4 (C=O). *Anal*. Calcd for $C_{10}H_{16}N_2O_2S$ (228.31): C, 52.61; H, 7.06; N, 12.27; Found: C, 52,65; H, 7.04; N, 12.29%.

N-(4-Oxo-2-phenyl-1,3-thiazolidin-3-yl)cyclopropanecarboxamide (4b). Yield: 1.41 g (53.6%), mp. 128–130°C (dec.). IR (KBr), ν (cm^{-1}): 3080 (CH aromatic), 3055, 1452 (CH aliphatic), 1715 (C=O), 1595 (N–H), 1442 (CH_2-cyclopropyl), 1390 (C–N), 654 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.76–0.78 (m, 2H, CH_2-cyclopropyl), 1.10–1.12 (m, 2H, CH_2-cyclopropyl), 1.41 (m, 1H, CH-cyclopropyl), 3.40 (s, 2H, CH_2), 6.16 (s, 1H, CH), 7.26–7.32 (m, 5H, ArH), 9.04 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 10.7 (2xCH_2-cyclopropyl), 18.3 (CH-cyclopropyl), 33.2 (CH_2), 67.6 (CH), 126.7, 127.7, 128.9, 140.4 (6C_{ar}), 168.8 (C=O), 172.1 (C=O). *Anal*. Calcd for $C_{13}H_{14}N_2O_2S$ (262.33): C, 59.52; H, 5.38; N, 10.68; Found: C, 59.56; H, 5.34; N, 10.72%.

N-[2-(2-Hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopropanecarboxamide (4c). Yield: 0.63 g (22.5%), mp. 186–188°C (dec.). IR (KBr), ν (cm^{-1}): 3065 (CH aromatic), 3059, 1452 (CH aliphatic), 1720 (C=O), 1611 (N–H), 1442 (CH_2-cyclopropyl), 1410 (C–N), 648 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.79–0.89 (m, 4H, 2xCH_2-cyclopropyl), 1.62–1.70 (CH-cyclopropyl), 2.58 (s, 2H, CH_2), 6.83–6.92 (m, 2H, Ar–H), 7.25–7.31 (m, 1H, Ar–H), 7.50–7.71 (m, 1H, Ar–H),

8.36 (s, 1H, CH), 9.02 (s, 1H, OH), 11.46 (s, 1H, NH), ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2-cyclopropyl), 18.3 (CH-cyclopropyl), 33.3 (CH_2), 61.3 (CH), 117.7, 120.4, 122.4, 128.4, 128.9, 149.7 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{13}H_{14}N_2O_3S$ (278.33): C, 56.10; H, 5.07; N, 10.0; Found: C, 56.12; H, 5.06; N, 9.97%.

N-[2-(3-Nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopropanecarboxamide (4d). Yield: 2.03 g (66.1%), mp. 194–196°C (dec.). IR (KBr), ν (cm^{-1}): 3065 (CH aromatic), 3059, 1452 (CH aliphatic), 1720 (C=O), 1611 (N–H), 1442 (CH_2-cyclopropyl), 1410 (C–N), 648 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.67–0.95 (m, 4H, 2xCH_2-cyclopropyl), 1.68–1.76 (CH-cyclopropyl), 3.45 (s, 2H, CH_2), 5.99 (s, 1H, CH), 7.65–8.52 (m, 4H, Ar–H), 12.01 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2-cyclopropyl), 18.3 (CH-cyclopropyl), 33.3 (CH_2), 67.9 (CH), 119.4, 128.4, 130.8, 143.0, 148.3 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{13}H_{13}N_3O_4S$ (307.32): C, 50.81; H, 4.26; N, 13.67; Found: C, 50.85; H, 4.25; N, 13.65%.

N-[2-(4-Methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopropanecarboxamide (4e). Yield: 2.02 g (73.2%), mp. 130–132°C (dec.). IR (KBr), ν (cm^{-1}): 3076 (CH aromatic), 3046, 1448 (CH aliphatic), 1745 (C=O), 1620 (N–H), 1442 (CH_2-cyclopropyl), 1401 (C–N), 656 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.70–0.88 (m, 4H, 2xCH_2-cyclopropyl), 1.48–1.70 (m, 1H, CH-cyclopropyl), 3.41 (s, 2H, CH_2), 5.68 (s, 1H, CH), 7.21–7.60 (m, 4H, ArH), 11.33 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2-cyclopropyl), 18.3 (CH-cyclopropyl), 21.1 (CH_3), 33.3 (CH_2), 67.6 (CH), 125.7, 129.6, 137.5, 138.5 (6C_{ar}), 168.3 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{14}H_{16}N_2O_2S$ (276.35): C, 60.85; H, 5.84; N, 10.14; Found: C, 60.82; H, 5.81; N, 10.10%.

N-[(4-Methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopropanecarboxamide (4f). Yield: 0.52 g (17.9%), mp. 82–84°C (dec.). IR (KBr), ν (cm^{-1}): 3046 (CH aromatic), 3038, 1455 (CH aliphatic), 1710 (C=O), 1615 (N–H), 1442 (CH_2-cyclopropyl), 1406 (C–N), 638 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.68–0.92 (m, 4H, 2xCH_2-cyclopentyl), 1.48–1.57 (CH-cyclopentyl), 3.78 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 6.84–6.98 (m, 2H, Ar–H), 7.33–7.37 (m, 2H, Ar–H), 8.14 (s, 1H, CH), 11.56 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2-cyclopropyl), 18.3 (CH-cyclopropyl), 33.3 (CH_2), 56.0 (CH_3), 67.6 (CH), 114.0, 126.7, 135.5 (5C_{ar}), 161.8 (C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{14}H_{16}N_2O_3S$ (292.35): C, 57.52; H, 5.52; N, 9.58; Found: C, 57.55; H, 5.45; N, 9.56%.

N-[2-(4-Bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopropanecarboxamide (4g). Yield: 3.32 g (97.2%), mp. 232–234°C (dec.). IR (KBr), ν (cm^{-1}): 3078 (CH aromatic), 3047, 1457 (CH aliphatic), 1722 (C=O), 1608 (N–H), 1442 (CH_2-cyclopropyl), 1412 (C–N), 656 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.70–0.89 (m, 4H, 2xCH_2-cyclopropyl), 1.62–1.71 (CH-cyclopropyl), 3.58 (s, 2H, CH_2), 7.38–7.61 (m, 4H, Ar–H), 5.78 (s, 1H, CH), 11.57 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 10.8 (2xCH_2-cyclopropyl), 18.3 (CH-cyclopropyl), 33.3 (CH_2), 67.6 (CH), 121.3, 128.9, 132.7, 140.2 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{13}H_{13}BrN_2O_2S$ (341.22): C, 45.76; H, 3.84; N, 8.21; Found: C, 45.79; H, 3.81; N, 8.23%.

N-[4-Oxo-2-(propan-2-yl)-1,3-thiazolidin-3-yl]cyclopentanecarboxamide (5a). Yield: 1.43 g (55.8%), mp. 111–113°C (dec.). IR (KBr), ν (cm^{-1}): 3078 (CH aromatic), 3047, 1457 (CH aliphatic), 1722 (C=O), 1608 (N–H), 1442 (CH_2-cyclopentyl), 1412 (C–N), 656 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.06 (s, 6H, 2xCH_3), 1.63–1.67 (m, 6H, 2xCH_2-cyclopentyl), 1.90–1.92 (m, 2H, CH_2-cyclopentyl), 2.48–2.52 (m, 1H, CH), 2.66–2.69 (m, 1H, CH-cyclopentyl), 3.29 (s, 2H, CH_2), 4.42 (s, 1H, CH), 8.54 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 20.4 (2xCH_3), 26.1, 26.2 (2xCH_2-cyclopenty), 30.8 (CH_2), 32.3 (CH), 33.3 (2xCH_2-cyclopentyl), 45.8 (CH-cyclopentyl), 78.2 (CH) 168.9 (C=O), 176.4 (C=O). *Anal*. Calcd for $C_{12}H_{20}N_2O_2S$ (256.36): C, 56.22; H, 7.86; N, 10.93; Found: C, 56.26; H, 7.88; N, 10.93%.

N-(4-Oxo-2-phenyl-1,3-thiazolidin-3-yl)cyclopentanecarboxamide (5b). Yield: 2.69 g (92.5%), mp. 124–126°C (dec.). IR (KBr), ν (cm^{-1}): 3091(CH aromatic), 3076, 1460 (CH aliphatic), 1710 (C=O), 1602 (N–H), 1455 (CH_2-cyclopentyl), 1402 (C–N), 620 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.57–1.66 (m, 6H, 3xCH_2-cyclopentyl), 1.90–1.92 (m, 2H, CH_2-cyclopentyl), 2.64–2.68 (m,1H, CH-cyclopentyl), 3.40 (s, 2H, CH_2), 6.11 (s, 1H, CH), 7.25–7.32 (m, 5H, Ar–H), 8.71 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2-cyclopentyl), 33.3 (CH_2), 46.2 (CH-cyclopentyl), 67.6 (CH), 126.6, 127.7, 128.9, 140.4 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{15}H_{18}N_2O_2S$ (290.38): C, 62.04; H, 6.25; N, 9.65; Found: C, 62.07; H, 6.22; N, 9.62%.

N-[2-(2-Hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopentanecarboxamide (5c). Yield: 3.01 g (98.2%), mp. 203–205°C (dec.). IR (KBr), ν (cm^{-1}): 3084 (CH aromatic), 3068, 1459 (CH aliphatic), 1732 (C=O), 1610 (N–H), 1455 (CH_2-cyclopentyl), 1400 (C–N), 645 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.57–1.89 (m, 8H, 4xCH_2-cyclopentyl), 2.62–2.68 (m, 1H, CH-cyclopentyl), 3.39 (s, 2H, CH_2), 6.51 (s, 1H, OH), 6.91–7.06 (m, 2H, Ar–H), 7.36–7.39 (m, 1H, Ar–H), 7.69–7.73 (m, 1H, Ar–H), 9.02 (s, 1H, CH), 11.27 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2-cyclopentyl), 33.3 (CH_2), 46.2 (CH-cyclopentyl), 61.3 (CH), 117.7, 120.4, 122.4, 128.4, 128.9, 149.7 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{15}H_{18}N_2O_3S$ (306.38): C, 58.80; H, 5.92; N, 9.14; Found: C, 58.82; H, 5.94; N, 9.16%.

N-[2-(3-Nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopentanecarboxamide (5d). Yield: 3.28 g (97.9%), mp. 158–160°C (dec.). IR (KBr), ν (cm^{-1}): 3048 (CH aromatic), 3032, 1451 (CH aliphatic), 1734 (C=O), 1620 (N–H), 1455 (CH_2-cyclopentyl), 1390 (C–N), 664 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.57–1.66 (m, 6H, 3xCH_2-cyclopentyl), 1.89–1.91 (m, 2H, CH_2-cyclopentyl), 2.64–2.68 (m, 1H, CH-cyclopentyl), 3.41 (s, 2H, CH_2), 6.19 (s, 1H, CH), 7.56–7.60 (m, 2H, Ar–H), 8.15–8.17 (m, 1H, Ar–H), 8.31–8.33 (m, 1H, Ar–H), 8.69 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2-cyclopentyl), 33.3 (CH_2), 46.2 (CH-cyclopentyl), 67.9 (CH), 119.4, 128.4, 130.8, 143.1, 148.4 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{15}H_{17}N_3O_4S$ (335.40): C, 53.72; H, 5.11; N, 12.53; Found: C, 53.74; H, 5.08; N, 12.55%.

N-[2-(4-Methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopentanecarboxamide (5e). Yield: 2.58 g (84.8%), mp. 130–132°C (dec.). IR (KBr), ν (cm^{-1}): 3089 (CH aromatic), 3060, 1450 (CH aliphatic), 1713 (C=O), 1605 (N–H), 1455 (CH_2-cyclopentyl), 1422 (C–N), 653 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.57–1.66 (m, 6H, 3xCH_2-cyclopentyl), 1.87–1.90 (m, 2H, CH_2-cyclopentyl), 2.32 (s, 3H, CH_3), 2.64–2.67 (m, 1H, CH-cyclopentyl), 3.40 (s, 2H, CH_2), 6.08 (s, 1H, CH), 7.19–7.22 (dd, 2H, Ar–H, J = 7.5Hz), 7.25–7.28 (dd, 2H, Ar–H, J = 7.5Hz), 8.70 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 21.1 (CH_3), 26.1, 32.9 (4xCH_2-cyclopentyl), 33.3 (CH_2), 46.2 (CH-cyclopentyl), 67.6 (CH), 125.7, 129.6, 137.6, 138.5 (6C_{ar}),

168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{16}H_{20}N_2O_2S$ (304.41): C, 63.13; H, 6.62; N, 9.20; Found: C, 63.15; H, 6.68; N, 9.17%.

N-[2-(4-Methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopentanecarboxamide (5f). Yield: 1.48 g (46.1%), mp. 118–120°C (dec.). IR (KBr), ν (cm^{-1}): 3032 (CH aromatic), 3010, 1462 (CH aliphatic), 1722 (C=O), 1613 (N–H), 1455 (CH_2-cyclopentyl), 1411 (C–N), 648 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.55–1.66 (m, 6H, 3xCH_2-cyclopentyl), 1.89–1.92 (m, 2H, CH_2-cyclopentyl), 2.64–2.68 (m, 1H, CH-cyclopentyl), 3.39 (s, 2H, CH_2), 3.79 (s, 3H, CH_3), 6.10 (s, 1H, CH), 6.94–6.97 (dd, 2H, Ar–H, *J* = 7.5 Hz), 7.27–7.30 (dd, 2H, Ar–H, *J* = 7.5 Hz), 8.65 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2-cyclopentyl), 32.3 (CH_2), 46.2 (CH-cyclohexyl), 56.0 (CH_3), 67.6 (CH), 114.0, 126.7, 135.5, 161.8 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{16}H_{20}N_2O_3S$ (320.41): C, 59.98; H, 6.29; N, 8.74; Found: C, 59.96; H, 6.27; N, 8.76%.

N-[2-(4-Bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclopentanecarboxamide (5g). Yield: 3.63 g (98.2%), mp. 152–154°C (dec.). IR (KBr), ν (cm^{-1}): 3056 (CH aromatic), 3035, 1453 (CH aliphatic), 1710 (C=O), 1603 (N–H), 1455 (CH_2-cyclopentyl), 1415 (C–N), 635 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.57–1.66 (m, 6H, 3xCH_2-cyclopentyl), 1.88–1.90 (m, 2H, CH_2-cyclopentyl), 2.64–2.69 (m, 1H, CH-cyclopentyl), 3.39 (s, 2H, CH_2), 6.09 (s, 1H, CH), 7.18–7.22 (dd, 2H, Ar–H, *J* = 7.5 Hz), 7.47–7.50 (dd, 2H, Ar-H, *J* = 7.5 Hz), 8.68 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 26.1, 32.9 (4xCH_2-cyclopentyl), 46.2 (CH-cyclopentyl), 67.9 (CH), 121.3, 128.9, 132.7, 140.2 (6C_{ar}), 168.8 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{15}H_{17}BrN_2O_2S$ (369.28): C, 48.79; H, 4.64; N, 7.59; Found: C, 48.82; H, 4.65; N, 7.62%.

N-[4-Oxo-2-(propan-2-yl)-1,3-thiazolidin-3-yl]cyclohexanecarboxamide (6a). Yield: 1.64 g (60.7%), mp. 124–126°C (dec.). IR (KBr), ν (cm^{-1}): 3004, 1456 (CH aliphatic), 1715 (C=O), 1595 (N–H), 1452 (CH_2-cyclohexyl), 1405 (C–N), 657 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.06 (s, 6H, 2xCH_3), 1.47–1.53 (m, 2H, CH_2-cyclohexyl), 1.61–1.63 (m, 8H, 4xCH_2-cyclohexyl), 2.02–2.05 (m, 2H, CH_2-cyclohexyl), 2.47–2.49 (m, 1H, CH), 2.53–2.55 (m, CH-cyclohexyl), 3.29 (s, 2H, CH_2), 4.41 (d, 1H, CH), 8.52 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 20.4 (2xCH_3), 25.1, 25.9, 28.1 (5xCH_2-cyclohexyl), 30.8 (CH_2), 32.3 (CH), 42.6 (CH-cyclohexyl), 48.2 (CH), 170.5 (C=O), 176.5 (C=O). *Anal*. Calcd for $C_{13}H_{22}N_2O_2S$ (270.39): C, 57.75; H, 8.20; N, 10.36; Found: C, 57.72; H, 8.18; N, 10.38%.

N-(4-Oxo-2-phenyl-1,3-thiazolidin-3-yl)cyclohexanecarboxamide (6b). Yield: 2.99 g (98.1%), mp. 130–132°C (dec.). IR (KBr), ν (cm^{-1}): 3096 (CH aromatic), 3060, 1453 (CH aliphatic), 1735 (C=O), 1619 (N–H), 1452 (CH_2-cyclohexyl), 1403 (C–N), 648 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.31–1.33 (m, 2H, CH_2-cyclohexyl), 1.57–1.59 (m, 8H, 4xCH_2-cyclohexyl), 1.80–1.82 (m, 2H, CH_2-cyclohexyl), 2.42–2.46 (m, 1H, CH-cyclohexyl), 3.39 (s, 2H, CH_2), 6.20 (s, 1H, CH), 7.27–7.33 (m, 5H, Ar–H), 8.76 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 33.3 (CH_2), 42.7 (CH-cyclohexyl), 67.6 (CH), 126.6, 127.7, 128.9, 140.4 (6C_{ar}), 170.5 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{16}H_{20}N_2O_2S$ (304.41): C, 63.13; H, 6.62; N, 9.20; Found: C, 63.15; H, 6.61; N, 9.22%.

N-[2-(2-Hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclohexanecarboxamide (6c). Yield: 3.14 g (97.9%), mp. 150–152°C (dec.). IR (KBr), ν (cm^{-1}): 3085 (CH aromatic), 3055, 1458 (CH aliphatic), 1714 (C=O), 1602 (N–H), 1452 (CH_2-cyclohexyl), 1413 (C–N), 645 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.36–1.38 (m, 2H, CH_2-cyclohexyl), 1.60–1.66 (m, 6H, 3xCH_2-cyclohexyl), 2.18–2.24 (m, 1H, CH-cyclohexyl), 2.52–2.54 (m, 2H, CH_2-cyclohexyl), 3.40 (s, 2H, CH_2), 6.45 (s, 1H, CH), 6.82–6.86 (m, 2H, Ar–H), 7.09–7.20 (m, 2H, Ar–H), 8.62 (s, 1H, OH), 8.95 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 33.3 (CH_2), 42.7 (CH-cyclohexyl), 61.3 (CH), 117.7, 120.4, 122.4, 128.4, 128.9, 149.7 (6C_{ar}), 170.5 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{16}H_{20}N_2O_3S$ (320.41): C, 59.98; H, 6.29; N, 8.74; Found: C, 59.97; H, 6.27; N, 8.75%.

N-[2-(3-Nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclohexanecarboxamide (6d). Yield: 3.39 g (97.1%), mp. 116–118°C (dec.). IR (KBr), ν (cm^{-1}): 3076 (CH aromatic), 3035, 1448 (CH aliphatic), 1722 (C=O), 1610 (N–H), 1452 (CH_2-cyclohexyl), 1415 (C–N), 649 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.01–1.03 (m, 2H, CH_2-cyclohexyl), 1.49–.1.54 (m, 6H, 3xCH_2-cyclohexyl), 2.07–2.09 (m, 2H, CH_2-cyclohexyl), 2.11–2.14 (m, 1H, CH-cyclohexyl), 3.40 (s, 2H, CH_2), 6.27 (s, 1H, CH), 7.58–7.62 (m, 2H, Ar–H), 8.19–8.21 (m, 1H, Ar–H), 8.28–8.33 (m, 1H, Ar–H), 8.59 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 33.3 (CH_2), 42.7 (CH-cyclohexyl), 67.8 (CH), 119.4, 118.4, 130.8, 143.0, 148.4 (6C_{ar}), 170.6 (C=O), 173.3 (C=O). *Anal*. Calcd for $C_{16}H_{19}N_3O_4S$ (349.40): C, 55.00; H, 5.48; N, 12.03; Found: C, 55.04; H, 5.45; N, 12.06%.

N-[2-(4-Methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclohexanecarboxamide (6e). Yield: 3.08 g (96.9%), mp. 134–136°C (dec.). IR (KBr), ν (cm^{-1}): 3068 (CH aromatic), 3034, 1456 (CH aliphatic), 1738 (C=O), 1608 (N–H), 1452 (CH_2-cyclohexyl), 1408 (C–N), 653 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.94–0.96 (m, 2H, CH_2-cyclohexyl), 1.47–1.53 (m, 6H, 3xCH_2-cyclohexyl), 2.08–2.11 (m, 1H, CH-cyclohexyl), 2.12–2.16 (m, 2H, CH_2-cyclohexyl), 2.34 (s, 3H, CH_3), 3.39 (s, 2H, CH_2), 6.17 (s, 1H, CH), 7.21–7.25 (m, 4H, Ar–H), 8.58 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 21.1 (CH_3), 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 33.3 (CH_2), 67.6 (CH), 125.7, 129.6, 137.5, 138.5 (6C_{ar}), 170.5 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{17}H_{22}N_2O_2S$ (318.43): C, 64.12; H, 6.96; N, 8.80; Found: C, 64.14; H, 6.98; N, 8.82%.

N-[2-(4-Methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclohexanecarboxamide (6f). Yield: 2.61 g (78.2%), mp. 156–158°C (dec.). IR (KBr), ν (cm^{-1}): 3068 (CH aromatic), 3022, 1455 (CH aliphatic), 1740 (C=O), 1615 (N–H), 1452 (CH_2-cyclohexyl), 1410 (C–N), 655 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.28–1.31 (m, 2H, CH_2-cyclohexyl), 1.57–1.59 (m, 6H, 3xCH_2-cyclohexyl), 1.79–1.81 (m, 2H, CH_2-cyclohexyl), 2.41–2.44 (m, 1H, CH-cyclohexyl), 3.39 (s, 2H, CH_2), 3.80 (s, 3H, CH_3), 6.12 (s, 1H, CH), 6.94–6.97 (dd, 2H, Ar–H, *J* = 7.5 Hz), 7.27–7.30 (dd, 2H, Ar–H, *J* = 7.5 Hz), 8.56 (s, 1H, NH); ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 33.3 (CH_2), 56.0 (CH_3), 67.6 (CH-cyclohexyl), 114.0, 126.7, 135.5, 161.8 (6C_{ar}), 170.5 (C=O), 172.3 (C=O). *Anal*. Calcd for $C_{17}H_{22}N_2O_3S$ (334.43): C, 61.05; H, 6.63; N, 8.38; Found: C, 61.08; H, 6.61; N, 8.37%.

N-[2-(4-Bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]cyclohexanecarboxamide (6g). Yield: 2.81 g (73.4%), mp. 171–173°C (dec.). IR (KBr), ν (cm^{-1}): 3068 (CH aromatic), 3022, 1455 (CH aliphatic), 1740 (C=O), 1615 (N–H), 1452 (CH_2-cyclohexyl), 1410 (C–N), 655 (C–S). ^{1}H NMR (DMSO-d_6): δ (ppm) = 0.95–0.97 (m, 2H, CH_2-cyclohexyl), 1.48–1.54 (m, 6H, 3xCH_2-cyclohexyl), 2.07–2.09 (m, 2H, CH_2-

cyclohexyl), 2.11–2.13 (m, 1H, CH-cyclohexyl), 3.38 (s, 2H, CH_2), 6.18 (s, 1H, CH), 7.19–7.22 (dd, 2H, Ar–H, $J = 7.5$ Hz), 7.51–7.53 (dd, 2H, Ar–H, $J = 7.5$ Hz), 8.57 (s, 1H, NH). ^{13}C NMR: δ (ppm) = 25.1, 25.9, 27.9 (5xCH_2-cyclohexyl), 33.3 (CH_2), 42.7 (CH-cyclohexyl), 67.6 (CH), 121.3, 128.9, 132.7, 140.2 ($6C_{ar}$), 170.5 (C=O), 172.4 (C=O). *Anal*. Calcd for $C_{16}H_{19}BrN_2O_2S$ (383.30): C, 50.14; H, 5.00; N, 7.31; Found: C, 50.12; H, 5.02; N, 7.28%.

Dissociation constants. Methodology for determining the dissociation constants is presented in the Supporting Information.

Microbiology. The examined compounds were screened *in vitro* for antibacterial and antifungal activities by using the broth microdilution method according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) [18] and Clinical and Laboratory Standards Institute (CLSI) guidelines [19]. The reference strains of microorganisms came from American Type Culture Collection (ATCC) and National Collection of Type Cultures (NCTC) and included Gram-positive bacteria (*S. aureus* ATCC 25923, *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *Streptococcus pyogenes* ATCC 19615, *Streptococcus pneumoniae* ATCC 49619, *Streptococcus mutans* ATCC 25175, *B. subtilis* ATCC 6633, *B. cereus* ATCC 10876, *M. luteus* ATCC 10240, *S. aureus* NCTC 4163, *S. aureus* ATCC 29213, *S. epidermidis* ATCC 35984, *Enterococcus hirae* ATCC 10541, *Enterococcus faecalis* ATCC 29212, *B. cereus* ATCC 11778, *M. luteus* ATCC 9341, *M. luteus* ATCC 10541), Gram-negative bacteria (*Escherichia coli* ATCC 3521, *E. coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 12453, *Bordetella bronchiseptica* ATCC 4617, *Salmonella typhimurium* ATCC 14028, *Pseudomonas aeruginosa* ATCC 9027, *E. coli* ATCC 10538, *E. coli* NCTC 8196, *Proteus vulgaris* NCTC 4635, *P. aeruginosa* ATCC 15442, *P. aeruginosa* NCTC 6749, *P. aeruginosa* ATCC 27863), fungi belonging to yeasts (*Candida albicans* ATCC 2091, *C. albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019, *C. albicans* ATCC 90028). The microbial cultures were first subcultured on nutrient agar or Sabouraud agar at 35°C for 18–24 h or 30°C for 24–48 h for bacteria and fungi, respectively.

The surface of Mueller-Hinton agar or Mueller-Hinton agar with 5% sheep blood (for bacteria) and RPMI 1640 with MOPS (for fungi) were inoculated with the suspensions of bacterial or fungal species. Microbial suspensions were prepared in sterile saline (0.85% NaCl) with an optical density of McFarland standard scale 0.5 approximately 1.5×10^8 colony forming units (CFU)/mL for bacteria and 0.5 McFarland standard scale approximately 5×10^5 CFU/mL for fungi.

Samples containing the examined compounds were dissolved in dimethyl sulfoxide (DMSO) and then diluted appropriately in liquid media. Microbial suspensions were prepared in sterile saline (0.85% NaCl) with an optical density of 0.5 McFarland standard scale approximately 1.5×10^8 CFU/mL for bacteria and 5×10^5 CFU/mL for fungi. Furthermore, solid media Mueller-Hinton or Mueller-Hinton with 5% sheep blood (for bacteria) and RPMI 1640 with MOPS (for fungi) containing 2 mg/mL of the tested compounds were inoculated with 10 μL bacterial or fungal suspensions and followed incubation under the appropriate conditions. The inhibition of microbial growth was judged by comparison with a control culture prepared without any sample tested.

Subsequently MIC of the compounds was examined by the microdilution broth method, using their twofold dilutions in Mueller-Hinton broth or Mueller-Hinton broth with 5% sheep blood (for bacteria) and RPMI 1640 broth with MOPS (for fungi) prepared in 96-well polystyrene plates. Final concentrations of the compounds ranged from 1000 to 0.488 μg/mL. Each well containing 198 μL broth and various concentrations of the examined compounds was added 2 μL of bacterial or fungal suspension. After incubation (35 or 30°C for 24 h for bacteria and fungi, respectively), the MIC was assessed spectrophotometrically as the lowest concentration of the samples showing complete bacterial or fungal growth inhibition. The media with or without tested substances and with or without microbial suspensions incubated under the similar conditions were used as controls. Moreover, ciprofloxacin, vancomycin, or fluconazole (Sigma) was used as reference antimicrobial agents.

The MBC or MFC are defined as the lowest concentration of the compounds that is required to kill a particular bacterial or fungal species. It was determined by removing 20 μL of the culture using for MIC determinations from each well and spotting onto appropriate agar medium which does not contain the tested compounds. After incubation, the lowest compound concentration with no visible growth observed was assessed as a bactericidal/fungicidal concentration [20].

In this study, no bioactivity was defined as a MIC > 1000 μg/mL, mild bioactivity as a MIC in the range 501–1000 μg/mL, moderate bioactivity with MIC from 126 to 500 μg/mL, good bioactivity as a MIC in the range 26–125 μg/mL, strong bioactivity with MIC between 10 and 25 μg/mL and very strong bioactivity as a MIC < 10 μg/mL [21]. The MBC/MIC or MFC/MIC ratios were calculated in order to determine bactericidal/fungicidal or bacteriostatic/fungistatic effect of the tested compounds.

DECLARATION OF INTEREST

The authors declare no conflict of interest.

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