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Powerful Approach to Heterocyclic Skeletal Diversity by Sequential Three-Component Reaction of Amines, Isothiocyanates, and 1,2-Diaza-1,3-dienes

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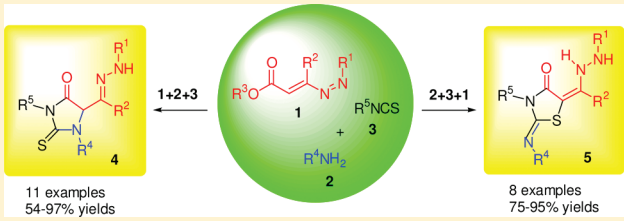
Supporting Information

ABSTRACT: By highly efficient, one-pot, three-component reactions, combining one set of 1,2-diaza-1,3-dienes (DDs), primary amines, and isothiocyanates in a different sequential order of addition, heterocyclic skeletal diversity can be achieved. The key feature discriminating the different heterocyclic core formation is the availability of the *N* or *S* heteronucleophile to give the first Michael addition step affording regioselective substituted 2-thiohydantoins or 2-iminothiazolidinones. The hydrazone or enehydrazino side chain at the 5-position of both heterocycles represents a valuable functionality to reach novel 5-hydroxyethylidene derivatives difficult to obtain by other methods.



Five-membered rings containing two heteroatoms are privileged structures as they belong to a class of compounds with proven utility in medicinal chemistry. As an example, 2-thiohydantoin-[1] and 2-iminothiazolidin-4-one-based[2] scaffolds can play an important role as synthetic intermediates with a wide range of applications as therapeutics[1b−f] and have been found to possess significant pharmacological activities[2c−f] as well as fungicides and herbicides.[3]

Multicomponent reactions (MCRs)[4] are well-appreciated procedures to reach skeletal diversity since they perform molecular construction in a modular manner in such a way that the final product incorporates in its structure one or more units of each module in a precise and determined order.

Within this context, here we report a chemo-/regioselective approach to heterocyclic skeletal diversity that can be achieved by sequential three-component reactions involving acyclic reagents, namely 1,2-diaza-1,3-dienes (DDs),[5] primary amines, and isothiocyanates, as an efficient method for the collection of 2-thiohydantoins and of 2-iminothiazolidin-4-ones simply by varying the order of the addition of the three reagents taking into account the mutual reactivity of the components of the reactions.

In connection with our recent paper describing a synthetic strategy for selectively trisubstituted hydantoin ring,[6] we envisaged the feasibility to apply the same approach to tentatively achieve regioselective substituted 2-thiohydantoin derivatives.

Since the electrophilic nature of the conjugated azo-ene system of DDs **1** makes it subject to nucleophilic attack, initially we explored the reaction of **1a** (1 mmol) with benzylamine (**2a**) (1 mmol) at room temperature in $CHCl_3$ (4 mL) that afforded the expected α-aminohydrazone intermediate.[6] The sequential one-pot addition of 4-methoxyphenylisothiocyanate (**3a**) successfully gave the 2-thiohydantoin derivative **4a** in 86% yield (Table 1, entry 1).

From a mechanistic point of view (Scheme 1), the 2-thiohydantoin **4** core assembly arises from the initial *N*-nucleophilic addition of **2** at the high-electrophilic center (C4) of the conjugated azo-ene system of **1** to produce intermediate **A** that rapidly coupled with isothiocyanate **3** affording the intermediate **B** in which the unsymmetrical thiourea framework is directly bonded to the α-carbon of the hydrazone moiety. Although the contemporary presence in **B** of *S* and *N* nucleophile centers could give rise to different intramolecular ring closure, exclusive and spontaneous regioselective heteroring closure by the thioureic nitrogen at the C4 ester function of the azo-ene system with the loss of an alcohol molecule was observed.

On the basis of this first result, primary alkylamines **2a−d** were reacted with **1a−g** in $CHCl_3$ at room temperature, and subsequently (after the quickly disappearance of the reagents, TLC check), isothiocyanates **3a−f** were added to afford the relevant 2-thiohydantoin derivatives **4a−l** in good to excellent yields (54−97%) (Table 1). The structural characterization of **4a−l** was achieved by spectroscopic data (^1H and ^{13}C NMR, IR, and MS) and unambiguously confirmed by X-ray crystal structure analysis of **4h** (see the Supporting Information).[7]

As expected, although primary aromatic amines worked well in the Michael addition step, the resulting α-aminohydrazone

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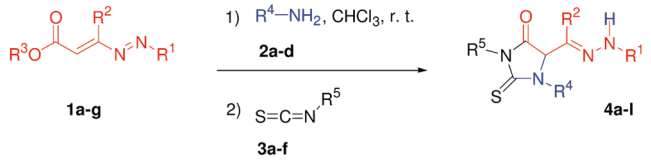
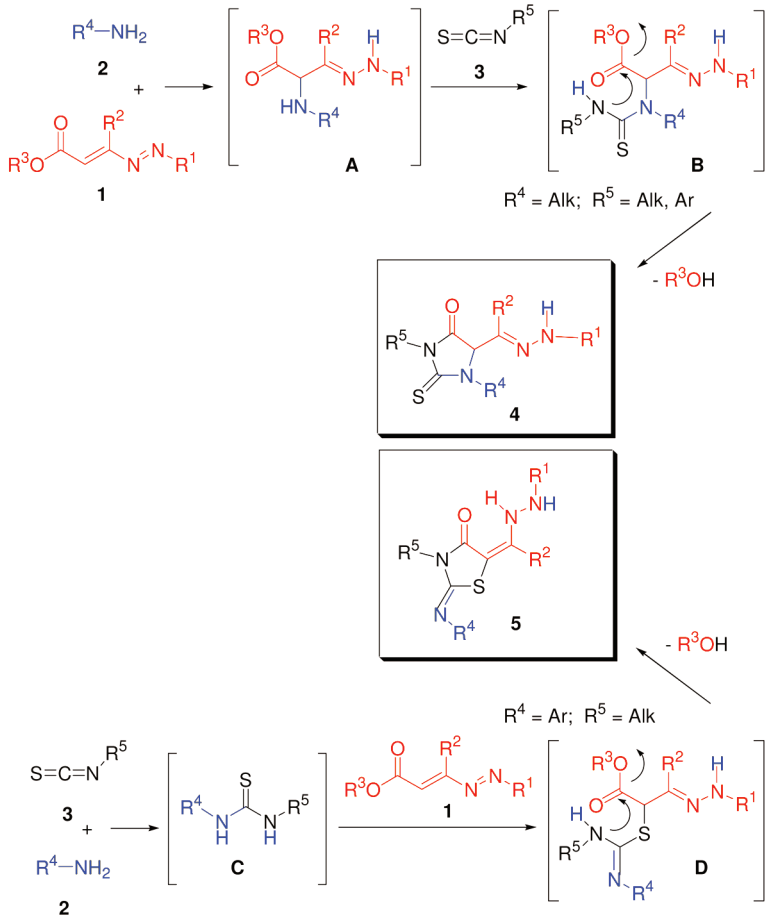
Table 1. One-Pot, Three-Component Synthesis of 2-Thiohydantoins 4a–l



		DD **1**			amine **2**		isothiocyanate **3**		2-thiohydantoin **4**	
entry		R^1	R^2	R^3		R^4		R^5		yield[a] (%)
1	**1a**	CO_2t-Bu	Me	Me	**2a**	Bn	**3a**	4-MeO-Ph	**4a**	86
2	**1b**	CO_2Me	Me	Me	**2b**	*n*-Bu	**3b**	Ph	**4b**	81
3	**1c**	$CONH_2$	Me	Et	**2c**	All	**3c**	4-Cl-Ph	**4c**	97
4	**1d**	CONHPh	Me	Et	**2a**	Bn	**3c**	4-Cl-Ph	**4d**	90
5	**1e**	CO_2Me	Me	Et	**2c**	All	**3a**	4-MeO-Ph	**4e**	90
6	**1a**	CO_2t-Bu	Me	Me	**2b**	*n*-Bu	**3c**	4-Cl-Ph	**4f**	87
7	**1f**	CO_2t-Bu	Ph	Me	**2a**	Bn	**3a**	Ph	**4g**	75
8	**1g**	$CONH_2$	Me	Me	**2d**	*n*-Pr	**3b**	Ph	**4h**	81
9	**1c**	$CONH_2$	Me	Et	**2b**	*n*-Bu	**3d**	Bn	**4i**	76
10	**1c**	$CONH_2$	Me	Et	**2a**	Bn	**3e**	*n*-Bu	**4j**	77
11	**1c**	$CONH_2$	Me	Et	**2c**	All	**3d**	Bn	**4k**	79
12	**1c**	$CONH_2$	Me	Et	**2a**	Bn	**3f**	All	**4l**	54

[a]Yield of isolated pure product based on amine **2**.

Scheme 1. Mechanism Pathways for Sequential Three-Component Reaction of DDs, Amines, and Isothiocyanates



derivative proved to be inefficient in the subsequent thioacylation reaction.[6a]

Nevertheless, this three-component sequence allows the total regiocontrol of the aliphatic substitution pattern at N1 and N3 of the 2-thiohydantoin template (Table 1, **4i–l**, entries 9–12) not efficiently achievable through phosphine-catalyzed tandem umpolung addition/intramolecular cyclization of weakly asymmetric thioureas on alkynoates[8] or by coupling of the reductive alkylation of α-imino acid esters with isothiocyanates.[9]

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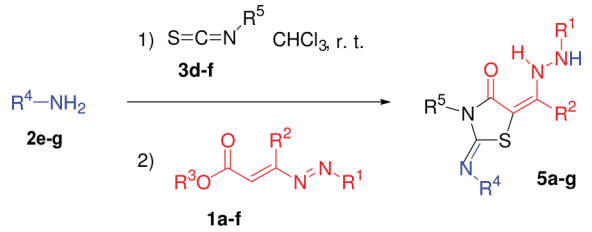
Table 2. One-Pot, Three-Component Synthesis of 5-Hydrazinoethylidene-2-iminothiazolidin-4-ones 5a–g



		DD 1			amine 2		isothiocyanate 3		2-iminothiazolidin-4-one 5	
entry		R^1	R^2	R^3		R^4		R^5		yield[a,b] (%)
1	**1a**	CO_2t-Bu	Me	Me	**2e**	4-MeO-Ph	**3d**	Bn	**5a**	95
2	**1b**	CO_2Me	Me	Me	**2f**	Ph	**3e**	*n*-Bu	**5b**	90
3	**1c**	$CONH_2$	Me	Et	**2g**	4-Cl-Ph	**3f**	All	**5c**	91
4	**1d**	CONHPh	Me	Et	**2g**	4-Cl-Ph	**3d**	Bn	**5d**	84
5	**1e**	CO_2Me	Me	Et	**2e**	4-MeO-Ph	**3f**	All	**5e**	85
6	**1a**	CO_2t-Bu	Me	Me	**2g**	4-Cl-Ph	**3e**	*n*-Bu	**5f**	88
7	**1f**	CO_2t-Bu	Ph	Me	**2f**	Ph	**3d**	Bn	**5g**	75

[a]Yield of isolated pure product based on amine **2**. [b]Yield referred to the mixture of *E* and *Z* isomers (approximately 3:1 ratio).

Next, to verify the possibility to perform a "classic" one-pot three-component reaction, we carried out the reaction by putting all the reagents **1a**, **2a**, and **3a** in one flask under the same reaction conditions. After the disappearance of the starting materials and chromatoraphic purification of the crude, a mixture of 2-thiohydantoin **4a** (30%) and 5-alkylidene-2-iminothiazolidin-4-one **5a** was obtained (23%).

The unexpected formation of the 2-iminothiazolidin-4-one nucleus can be explained by the initial regioselective *S*-Michael addition of the thiourea intermediate **C**, resulted from the coupling of **2** and **3**, at the electrophilic center of **1** followed by intramolecular attack of the NH of the resulted isothiourea derivative **D** at the ester function on C4 of the hydrazone chain with a loss of an alcohol molecule (Scheme 1). Since the formation of two regioisomers was possible, the regiochemistry of **5a** as the unique regioisomer formed was established by $^1H\{^{13}C\}$ HMBC experiment in which the benzylic protons on N3 were found to correlate to both the sp^2-hybridized carbon atoms (C=O and C=N) of the heterocycle. The formation of **5a** was in accordance with the results of Patel and co-workers[10] who reported that regioselective formation of 5-unsubstituted 2-iminothiazolidin-4-ones is observed for unsymmetrical thioureas in which the amine attached to the thiourea having lower pK_a is a part of the imino component and the amine having higher pK_a is the contributor to the other heterocyclic nitrogen.

The recognition of the predominant isomer with *E*-geometry of the exocyclic C=C bond of **5a** was based on our previous results.[11]

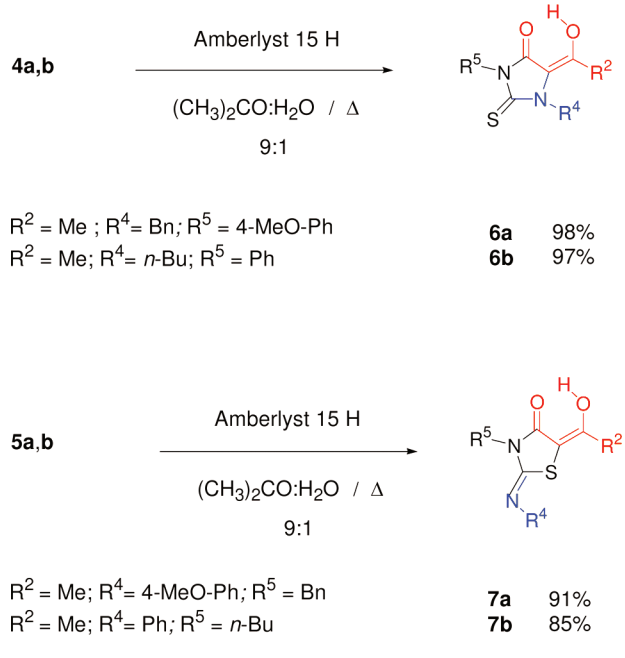
Based on these findings and taking into account that 5-alkylidene-2-iminothiazolidin-4-ones with distinct substitution patterns on each of the nitrogen atoms are scarcely represented,[2d,e] we planned to achieve an array of regioselectively substituted 5-hydrazinoethylidene-2-iminothiazolidin-4-one derivatives **5** by a sequential one-pot three-component reaction.

Thus, by addition of alkylisothiocyanates **3d–f** (1 mmol) to a solution of primary aromatic amines **2e–g** (1 mmol) in $CHCl_3$ (4 mL) at room temperature, the corresponding unsymmetrical thiourea derivative **C** (Scheme 1, Table 2) was formed quickly (0.2–0.5 h by TLC, checked with authentic sample prepared according to Ottanà et al.[2d]) and ready available for the coupling with DDs **1a–f** (0.5–5 h) yielding 5-hydrazinoethylidene-2-iminothiazolidin-4-ones **5a–g** (75–95%) (Table 2).

It is noteworthy that the present method is able to install directly the hydrazinoalkylidene functionality at 5-position that, at best of our knowledges, is difficult to obtain from the Knoevenagel condensation of 5-unsubstituted 2-iminothiazolidin-4-one derivatives.

Both protocols, moreover, offer a valuable point of diversity at C5 of the two different heterocycles providing directly hydrazono or enehydrazino functionalities as masked carbonyl function derived from the conjugated azo-ene system of DDs. In general, as exemplified in Scheme 2, the simple hydrolytic cleavage of the hydrazide moiety of **4a,b** and **5a,b**, under heterogeneus acid conditions (Amberlyst 15 H), afforded

Scheme 2. Synthesis of 5-Hydroxyethylidene-thiohydantoins 6a,b and -thiazolidinones 7a,b by Hydrolytic Cleavage of 4a,b and 5a,b



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unknown 5-hydroxyethylidenethiohydantoins **6a,b** and 5-hydroxyethylidenethiazolidinones **7a,b** in excellent yields (85−98%) both being difficult to access by reacting imidazoledithioate[12] and amino acid esters building blocks,[9,13,14] or by a compatible subsequent condensation process of 5-unsubstituted thiazolidinone derivative, respectively.[15]

In summary, by combining a set of acyclic substrates/reagents, namely 1,2-diaza-1,3-dienes, primary amines, and isothiocyanates in a different order of addition under the same reaction conditions, a robust chemo-/regioselective approach to heterocyclic skeletal diversity can be achieved by means of high-yielding, one-pot, three-component reactions. The protocols here described afforded selectively substituted 1,3,5-trisubstituted 2-thiohydantoins or 2-iminothiazolidin-4-ones bearing a valuable point of diversity at the 5-position of the heterorings. Both of the different heterocyclic scaffolds can be easily transformed into their corresponding 5-acetyl enol form derivatives. These latter ones, obtained in near-quantitative yields, are not easy accessible by other methods and could be useful for further chemical transformations. Moreover, despite the presence in the literature of many examples of 5-arylidene-2-iminothiazolidin-4-one of therapeutic interest,[2d,e] there are no reports concerning the formation of 5-alkylidene-functionalized 2-iminothiazolidin-4-one. In addition, the mild and simple reaction conditions of these procedures (no catalyst, no dry solvents, or inert atmosphere) make them suitable for the generation of library of functionalized 2-iminothiazolidinone and 1,3,5-thiohydantoin derivatives.

EXPERIMENTAL SECTION

General Methods. All chemicals and solvents were purchased from commercial suppliers and used as received. 1,2-Diaza-1,3-dienes (DDs) were prepared as reported[5,16] and used as *EE/EZ* isomer mixtures. Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectra were obtained as Nujol mulls or neat. Mass spectra (MS) were carried out by electron impact (EI) at an ionizing voltage of 70 eV. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 or in $CDCl_3$ as specified below. Chemical shifts (δ_H) and (δ_C) are reported in parts per million (ppm) and were referred to solvent signals as follows: δ = 2.50 ppm for proton (middle peak) and δ = 39.50 ppm for carbon in DMSO; δ = 7.26 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in $CDCl_3$. All coupling constants (J values) are given in hertz (Hz). The following abbreviations are used to describe peak patterns where appropriate: s, singlet; d, doublet; dd, double−doublet; t, triplet; q, quartet; m, multiplet; br, broad. All the NH exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35−70 μm for column chromatography. All new compounds showed satisfactory elemental analysis. The nomenclature was generated using ACD/IUPACName (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON, Canada.

General One-Pot, Three-Component Procedure for the Synthesis of 2-Thiohydantoin Derivatives 4a−l. To a stirred solution of DD **1a−g** (1 mmol) in $CHCl_3$ (4 mL) was added primary alkyl amine derivative **2a−d** (1 mmol) at room temperature. After the disappearance of the reagents (0.1−0.5 h) (TLC check), isothiocyanate derivative **3a−f** was added, and the reaction mixture was allowed to stand at room temperature until completion of the reaction (0.5−18 h). After removal of the reaction solvent, thiohydantoins **4a−f** and **4h,i,l** were obtained by crystallization from appropriate solvents, whereas **4g,j,k** were achieved after chromatographic purification (cyclohexane/ethyl acetate mixtures) and subsequent crystallization.

*tert-Butyl 2-[1-[3-Benzyl-1-(4-methoxyphenyl)-5-oxo-2-thioxoimidazolidin-4-yl]ethylidene]hydrazinecarboxylate (**4a**).* Yield: 402.9 mg (86%). White powder. Mp: 193−195 °C (from $CHCl_3$−light petroleum ether). IR (Nujol, ν, cm^{-1}): 3230, 1755, 1715, 1638, 1620, 1592. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.48 (s, 9H), 1.55 (s, 3H), 3.80 (s, 3H), 4.84 (d, J = 15.2 Hz, 1H), 5.01 (s, 1H), 5.11 (d, J = 15.2 Hz, 1H), 7.04 (d, J = 6.8 Hz, 2H), 7.29−7.39 (m, 7H), 9.98 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.5 (q), 28.0 (q), 48.8 (t), 55.4 (q), 69.1 (d), 79.8 (s), 114.1 (d), 126.3 (s), 127.7 (d), 128.4 (d), 128.5 (d), 129.9 (d), 135.3 (s), 142.9 (s), 152.7 (s), 159.4 (s), 170.1 (s), 183.1 (s). MS (EI): m/z = 468 (M$^+$, 5), 412 (15), 368 (17), 352 (25), 311 (9), 277 (12), 165 (100), 106 (40). Anal. Calcd for $C_{24}H_{28}N_4O_4S$ (468.56): C, 61.52; H, 6.02; N, 11.96. Found: C, 61.38; H, 6.14; N, 11.89.

*Methyl 2-[1-(3-Butyl-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)-ethylidene]hydrazinecarboxylate (**4b**).* Yield: 293.5 mg (81%). White powder. Mp: 180−183 °C (from EtOAc−Et_2O). IR (Nujol, ν, cm^{-1}): 3329, 1749, 1734, 1644, 1507. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, J = 7.2 Hz, 3H), 1.27−1.36 (m, 2H), 1.53−1.61 (m, 2H) 1.81 (s, 3H), 3.35−3.43 (m, 1H), 3.70 (s, 3H), 3.93−4.01 (m, 1H), 5.15 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.43−7.50 (m, 3H), 10.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.5 (q), 13.5 (q), 19.3 (t), 28.4 (t), 45.2 (t), 52.1 (q), 68.9 (d), 128.7 (d), 128.8 (d), 133.6 (s), 144.0 (s), 154.4 (s), 169.9 (s), 181.9 (s). MS (EI): m/z = 362 (M$^+$, 38), 288 (100), 247 (20), 171 (61), 135 (42), 115 (46). Anal. Calcd for $C_{17}H_{22}N_4O_3S$ (362.44): C, 56.33; H, 6.12; N, 15.46. Found: C, 56.49; H, 5.99; N, 15.37.

*1-[3-Allyl-1-(4-chlorophenyl)-5-oxo-2-thioxoimidazolidin-4-yl)]-ethan-1-one Semicarbazone (**4c**).* Yield: 354.8 mg (97%). White powder. Mp: 182−184 °C (from $CHCl_3$−Et_2O). IR (Nujol, ν, cm^{-1}): 3444, 3216, 3159, 1751, 1713, 1688, 1653, 1582. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.75 (s, 3H), 4.15 (dd, J = 6.0 Hz, J = 15.6 Hz, 1H), 4.52 (dd, J = 6.0 Hz, J = 15.6 Hz, 1H), 5.02 (s, 1H), 5.23−5.27 (m, 2H), 5.79−5.86 (m, 1H), 6.49 (br s, 2H), 7.40−7.42 (m, 2H), 7.56−7.59 (m, 2H), 9.65 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.4 (q), 47.9 (t), 69.2 (d), 119.2 (t), 129.0 (d), 130.7 (d), 130.8 (d), 132.5 (s), 133.6 (s), 138.3 (s), 156.7 (s), 169.9 (s), 181.6 (s). MS (EI): m/z = 367 [M$^+$ + 2 (1)], 365 (M$^+$, 2), 306 (100), 265 (11), 225 (46), 169 (33), 111 (22), 100 (35). Anal. Calcd for $C_{15}H_{16}ClN_5O_2S$ (365.83): C, 49.25; H, 4.41; N, 19.14. Found: C, 49.18; H, 4.28; N, 19.04.

*1-[3-Benzyl-1-(4-chlorophenyl)-5-oxo-2-thioxoimidazolidin-4-yl]-ethan-1-one N-Phenylsemicarbazone (**4d**).* Yield: 442.8 mg (90%). White powder. Mp: 207−209 °C (from $CHCl_3$−Et_2O). IR (Nujol, ν, cm^{-1}): 3392, 3209, 1754, 1713, 1635, 1598, 1544, 1501. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.51 (s, 3H), 5.00 (d, J = 15.6 Hz, 1H), 5.05 (d, J = 15.6 Hz, 1H), 5.19 (s, 1H), 7.03 (t, J = 7.2 Hz, 1H), 7.29−7.61 (m, 13H), 8.87 (s, 1H), 9.90 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.1 (q), 49.1 (t), 69.4 (d), 119.4 (d), 122.5 (d), 127.7 (d), 128.3 (d), 128.6 (d), 128.9 (d), 130.7 (d), 132.5 (s), 133.6 (s), 135.3 (s), 138.8 (s), 139.8 (s), 152.7 (s), 169.7 (s), 182.3 (s). MS (EI): m/z = 491 (M$^+$, 3), 398 (10), 315 (8), 241 (31), 176 (87), 169 (80), 119 (100). Anal. Calcd for $C_{25}H_{22}ClN_5O_2S$ (491.99): C, 61.03; H, 4.51; N, 14.23. Found: C, 60.91; H, 4.59; N, 14.14.

*Methyl 2-[1-[3-Allyl-1-(4-methoxyphenyl)-5-oxo-2-thioxoimidazolidin-4-yl]ethylidene]hydrazinecarboxylate (**4e**).* Yield: 338.8 mg (90%). White powder. Mp: 177−180 °C (from EtOAc−Et_2O). IR (Nujol, ν, cm^{-1}): 3205, 1751, 1712, 1649, 1614, 1545, 1524. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.79 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 4.15 (dd, J = 6.4 Hz, J = 15.6 Hz, 1H), 4.53 (dd, J = 6.4 Hz, J = 15.6 Hz, 1H), 5.07 (s, 1H), 5.21−5.27 (m, 2H), 5.78−5.87 (m, 1H), 7.01−7.04 (m, 2H), 7.22−7.25 (m, 2H), 10.39 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.8 (q), 48.0 (t), 52.1 (q), 55.3 (q), 68.8 (d), 114.1 (d), 119.2 (t), 126.1 (s), 129.9 (d), 130.9 (d), 143.9 (s), 154.4 (s), 159.3 (s), 170.1 (s), 182.5 (s). MS (EI): m/z = 376 (M$^+$, 10), 302 (100), 261 (11), 247 (13), 220 (49), 165 (67). Anal. Calcd for $C_{17}H_{20}N_4O_4S$ (376.43): C, 54.24; H, 5.36; N, 14.88. Found: C, 54.11; H, 5.44; N, 14.75.

*tert-Butyl 2-[1-[3-Butyl-1-(4-chlorophenyl)-5-oxo-2-thioxoimidazolidin-4-yl]ethylilene]hydrazinecarboxylate (**4f**).* Yield: 351.2 mg (87%). White powder. Mp: 181−183 °C (from $CHCl_3$−light petroleum ether). IR (Nujol, ν, cm^{-1}): 3204, 1758, 1752, 1707, 1639, 1536. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, J = 7.2 Hz,

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3H), 1.27−1.36 (m, 2H), 1.46 (s, 9H), 1.51−1.63 (m, 2H), 1.80 (s, 3H), 3.35−3.39 (m, 1H), 3.95−4.01 (m, 1H), 5.13 (s, 1H), 7.36−7.39 (m, 2H), 7.54−7.58 (m, 2H), 10.12 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.6 (q), 13.5 (q), 19.3 (t), 28.0 (q), 28.4 (t), 45.1 (t), 69.0 (d), 79.8 (s), 128.9 (d), 130.6 (d), 132.4 (s), 133.5 (s), 143.2 (s), 152.7 (s), 169.8 (s), 181.4 (s). MS (EI): m/z (%) = 438 (M^+, 5), 382 (41), 338 (56), 322 (100), 308 (57), 282 (79), 169 (70), 113 (97). Anal. Calcd for $C_{20}H_{27}ClN_4O_3S$ (438.97): C, 54.72; H, 6.20; N, 12.76. Found: C, 54.61; H, 6.29; N, 12.69.

*tert-Butyl 2-[(3-Benzyl-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)(phenyl)methylene]hydrazinecarboxylate (**4g**).* Yield: 375.4 mg (75%). White powder. Mp: 176−179 °C (from Et_2O). IR (Nujol, ν, cm^{-1}): 3357, 1752, 1739, 1710, 1596. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.43 (s, 9H), 4.68 (d, J = 15.6 Hz, 1H), 5.24 (s, 1H), 5.41 (d, J = 15.6 Hz, 1H), 6.99 (d, J = 6.0 Hz, 2H), 7.07−7.10 (m, 2H), 7.34−7.50 (m, 11H), 9.60 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.9 (q), 48.4 (t), 68.8 (d), 80.2 (s), 127.5 (d), 127.8 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.9 (d), 129.2 (d), 130.0 (s), 133.5 (s), 134.9 (s), 142.8 (s), 152.2 (s), 169.7 (s), 182.3 (s). MS (EI): m/z = 500 (M^+, 6), 444 (34), 400 (46), 384 (100), 309 (35), 281 (43), 241 (14), 160 (40). Anal. Calcd for $C_{28}H_{28}N_4O_3S$ (500.61): C, 67.18; H, 5.64; N, 11.19. Found: C, 67.05; H, 5.81; N, 11.23.

*1-(5-Oxo-1-pheny1-3-propyl-2-thioxoimidazolidin-4-yl)ethan-1-one Semicarbazone (**4h**).* Yield: 270.0 mg (81%). Colorless crystals. Mp: 169−171 °C (from EtOH). IR (Nujol, ν, cm^{-1}): 3429, 3285, 3202 1742, 1710, 1693, 1678, 1590. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, J = 7.2 Hz, 2H), 1.57−1.69 (m, 2H), 1.77 (s, 3H), 3.31−3.38 (m, 1H), 3.90−3.96 (m, 1H), 5.07 (s, 1H), 6.51 (br s, 2H), 7.33 (d, J = 7.2 Hz, 2H), 7.45−7.52 (m, 3H), 9.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.1 (q), 12.0 (q), 19.9 (t), 47.0 (t), 69.0 (d), 128.8 (d), 128.9 (d), 133.7 (s), 138.5 (s), 156.7 (s), 170.2 (s), 181.9 (s). MS (EI): m/z = 333 (M^+, 19), 316 (25), 290 (12), 274 (88), 233 (38), 135 (91), 100 (100). Anal. Calcd for $C_{15}H_{19}N_5O_2S$ (333.40): C, 54.04; H, 5.74; N, 21.01. Found: C, 54.20; H, 5.87; N, 20.09.

*1-(1-Benzyl-3-butyl-5-oxo-2-thioxoimidazolidin-4-yl)ethan-1-one Semicarbazone (**4i**).* Yield: 274.7 mg (76%). White powder. Mp: 173−176 °C (from EtOAc). IR (Nujol, ν, cm^{-1}): 3396, 3283, 3184, 1748, 1697, 1685, 1671, 1638, 1585. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85−0.90 (m, 3H), 1.24−1.28 (m, 2H), 1.50−1.59 (m, 5H), 3.24−3.30 (m, 1H), 3.92−3.99 (m, 1H), 4.90 (d, J = 15.2 Hz, 1H), 4.96−5.01 (m, 2H), 6.44 (br s, 2H), 7.26−7.34 (m, 5H), 9.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.1 (q), 13.5 (q), 19.3 (t), 28.4 (t), 44.6 (t), 44.9 (t), 68.2 (d), 127.3 (d), 127.4 (d), 128.4 (d), 136.1 (s), 138.3 (s), 156.6 (s), 170.6 (s), 181.8 (s). MS (EI): m/z = 361 (M^+, 17), 344 (22), 302 (51), 261 (26), 111 (62), 100 (100). Anal. Calcd for $C_{17}H_{23}N_5O_2S$ (361.46): C, 56.49; H, 6.41; N, 19.38. Found: C, 56.57; H, 6.57; N, 19.30.

*1-(3-Benzyl-1-butyl-5-oxo-2-thioxoimidazolidin-4-yl)ethan-1-one Semicarbazone (**4j**).* Yield: 278.3 mg (77%). White powder. Mp: 138−140 °C (from MeOH). IR (Nujol, ν, cm^{-1}): 3395, 3352, 3201, 1743, 1723, 1648, 1577. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, J = 7.2 Hz, 3H), 1.25−1.30 (m, 5H), 1.55−1.61 (m, 2H), 3.73−3.78 (m, 2H), 4.83−4.87 (m, 2H), 4.93 (d, J = 15.2 Hz, 1H), 6.41 (br s, 2H), 7.29−7.31 (m, 5H), 9.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.7 (q), 13.5 (q), 19.4 (t), 29.2 (t), 41.4 (t), 48.7 (t), 68.8 (d), 127.6 (d), 128.3 (d), 128.4 (d), 135.5 (s), 138.2 (s), 156.5 (s), 170.5 (s), 182.7 (s). MS (EI): m/z = 361 (M^+, 12), 344 (14), 302 (22), 286 (46), 261 (61), 106 (100), 100 (50). Anal. Calcd for $C_{17}H_{23}N_5O_2S$ (361.46): C, 56.49; H, 6.41; N, 19.38. Found: C, 56.42; H, 6.52; N, 19.34.

*1-(3-Allyl-1-benzyl-5-oxo-2-thioxoimidazolidin-4-yl)ethan-1-one Semicarbazone (**4k**).* Yield: 272.9 mg (79%). White powder. Mp: 145−147 °C (from EtOAc−cyclohexane). IR (Nujol, ν, cm^{-1}): 3486, 3210, 3157, 1750, 1714, 1638, 1588. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.33 (s, 3H), 4.38 (br s, 2H), 4.83−4.96 (m, 3H), 5.10−5.17 (m, 2H), 5.78−5.90 (m, 1H), 6.39 (br s, 2H), 7.23−7.35 (m, 5H), 9.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.9 (q), 43.7 (t), 48.8 (t), 68.8 (d), 117.1 (t), 127.7 (d), 128.4 (d), 131.4 (d), 135.5 (s), 138.2 (s), 156.5 (s), 170.1 (s), 182.4 (s). MS (EI): m/z = 345 (M^+, 14), 328 (11), 286 (18), 270 (22), 245 (17), 204 (48), 111 (42), 106 (100), 100 (53). Anal. Calcd for $C_{16}H_{19}N_5O_2S$ (345.42): C, 55.63; H, 5.54; N, 20.27. Found: C, 55.78; H, 5.47; N, 20.38.

*1-(1-Allyl-3-benzyl-5-oxo-2-thioxoimidazolidin-4-yl)ethan-1-one Semicarbazone (**4l**).* Yield: 186.5 mg (54%). White powder. Mp: 163−166 °C (from EtOAc−cyclohexane). IR (Nujol, ν, cm^{-1}): 3414, 3287, 3285, 3157, 1750, 1702, 1671, 1628, 1584. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.58 (s, 3H), 4.09 (dd, J = 6.0 Hz, J = 15.4 Hz, 1H), 4.49 (dd, J = 6.0 Hz, J = 15.4 Hz, 1H), 4.89−5.01 (m, 3H), 5.16−5.20 (m, 2H), 5.75−5.82 (m, 1H), 6.39 (br s, 2H), 7.26−7.35 (m, 5H), 9.59 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.5 (q), 44.7 (t), 47.8 (t), 68.3 (d), 119.0 (t), 127.4 (d), 128.4 (d), 130.9 (d), 136.0 (s), 138.3 (s), 156.5 (s), 170.6 (s), 182.0 (s). MS (EI): m/z = 345 (M^+, 2), 328 (7), 286 (100), 270 (43), 245 (17), 205 (52), 106 (27), 100 (58). Anal. Calcd for $C_{16}H_{19}N_5O_2S$ (345.42): C, 55.63; H, 5.54; N, 20.27. Found: C, 55.50; H, 5.66; N, 20.34.

General One-Pot, Three-Component Procedure for the Synthesis of 2-Iminothiazolidin-4-one Derivatives 5a−g. To a stirred solution of primary aromatic amine derivative **2e−g** (1 mmol) in $CHCl_3$ (4 mL) was added alkylisothiocyanate **3d−f** at room temperature. After the formation of the corresponding thiourea derivative (0.2−0.5 h, TLC check with an authentic sample), DD **1a−f** (1 mmol) was added as solid or dissolved in $CHCl_3$ (1 mL), and the reaction mixture was left at room temperature until the reaction was complete (0.5−6 h, TLC check). In general, the solvent was removed under reduced pressure and the crude reaction mixture was purified by column chromatography (cyclohexane/ethyl acetate mixtures) to afford **5** as mixture of C5 E/Z isomers (approximately ratio 3:1). In the case of **5b−e** solid compound was obtained by precipitation from the reaction medium and subsequent recrystallization from the appropriate solvents.

*tert-Butyl 2-[1-[3-Benzyl-2-[(4-methoxyphenyl)imino]-4-oxo-1,3-thiazolidin-5-ylidene]ethyl]hydrazinecarboxylate (**5a**).* Yield: 445.1 mg (95%). Light yellow foam. IR (Nujol, ν, cm^{-1}): 3301, 3278, 1736, 1718, 1670, 1618, 1507. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.31 and 1.40 (2s, 9H), 1.85 and 2.31 (2s, 3H), 3.71 and 3.72 (2s, 3H), 4.92 and 4.96 (2s, 2H), 6.79 and 6.90 (m, 4H), 7.25−7.36 (m, 5H), 8.80 and 9.77 (br s and s, 1H), 9.28 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.6 (q), 26.3 (q), 27.9 (q), 44.3 (t), 44.6 (t), 55.2 (q), 80.0 (s), 80.1 (s), 84.1 (s), 114.3 (d), 114.6 (d), 122.1 (d), 122.3 (d), 127.1 (d), 127.6 (d), 128.3 (d), 128.4 (d), 136.8 (s), 137.3 (s), 141.7 (s), 142.5 (s), 151.1 (s), 154.9 (s), 155.7 (s), 155.9 (s), 166.3 (s). MS (EI): m/z = 468 (M^+, 3), 368 (3), 275 (50), 197 (100), 122 (51). Anal. Calcd for $C_{24}H_{28}N_4O_4S$ (468.56): C, 61.52; H, 6.02; N, 11.96. Found: C, 61.67; H, 5.91; N, 11.87.

*Methyl 2-[1-[3-Butyl-4-oxo-2-(phenylimino)-1,3-thiazolidin-5-ylidene]ethyl]hydrazinecarboxylate (**5b**).* Yield: 326.2 mg (90%). White powder (from Et_2O−light petroleum ether). IR (Nujol, ν, cm^{-1}): 3337, 3295, 1742, 1729, 1664, 1616, 1587, 1497. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89−0.94 (m, 3H), 1.26−1.36 (m, 2H), 1.56−1.65 (m, 2H), 1.85 and 2.34 (2s, 3H), 3.56 and 3.63 (2s, 3H), 3.72−3.78 (m, 2H), 6.90−6.95 (m, 2H), 7.04−7.11 (m, 1H), 7.30−7.36 (m, 2H), 8.74 and 9.85 (br s and s, 1H), 9.51 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.6 (q), 16.7 (q), 19.5 (t), 19.6 (t), 29.0 (t), 41.0 (t), 41.2 (t), 52.3 (q), 84.3 (s), 87.5 (s), 121.1 (d), 121.3 (d), 123.5 (d), 123.9 (d), 129.1 (d), 129.3 (d), 149.0 (s), 149.3 (s), 151.5 (s), 152.1 (s), 154.6 (s), 156.6 (s), 165.7 (s), 166.1 (s). MS (EI): m/z = 362 (M^+, 67), 330 (9), 288 (12), 274 (33), 175 (54), 119 (78), 101 (100). Anal. Calcd for $C_{17}H_{22}N_4O_3S$ (362.44): C, 56.33; H, 6.12; N, 15.46. Found: C, 56.21; H, 6.22; N, 15.39.

*2-[1-[3-Allyl-2-[(4-chlorophenyl)imino]-4-oxo-1,3-thiazolidin-5-ylidene]ethyl]hydrazinecarboxamide (**5c**).* Yield: 332.9 mg (91%). White powder (from EtOAc−Et_2O). IR (Nujol, ν, cm^{-1}): 3426, 3311, 3252, 3200, 1711, 1677, 1633, 1617, 1588, 1536, 1496. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.88 and 2.33 (2s, 3H), 4.33−4.38 (m, 2H), 5.07−5.21 (m, 2H), 5.83−5.91 (m, 1H), 6.18 and 6.20 (2s, 2H), 6.91−7.00 (m, 2H), 7.33−7.43 (m, 2H), 8.15 (s, 1H), 8.80 and 9.78 (br s and s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.6 (q), 16.8 (q), 43.1 (t), 43.4 (t), 83.5 (s), 85.6 (s), 116.4 (t), 116.7 (t), 123.0 (d), 123.2 (d), 127.3 (s), 129.1 (d), 129.3 (d), 132.3 (d), 147.8 (s), 148.1 (s), 152.1 (s), 153.3 (s), 156.5 (s), 156.7 (s), 158.5 (s), 158.6 (s),

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165.1 (s), 165.8 (s). MS (EI): m/z = 367 [M^+ + 2 (15)], 365 (M^+, 43), 348 (100), 307 (8), 292 (13), 225 (35), 193 (45), 130 (79), 101 (97). Anal. Calcd for $C_{15}H_{16}ClN_5O_2S$ (365.83): C, 49.25; H, 4.41; N, 19.14. Found: C, 49.32; H, 4.29; N, 19.23.

*2-[1-[3-Benzyl-2-[(1-(4-chlorophenyl)imino]-4-oxo-1,3-thiazolidin-5-ylidene]ethyl]-N-phenylhydrazinecarboxamide (**5d**).* Yield: 413.3 mg (84%). White crystals (from EtOAc–Et_2O–light petroleum ether). IR (Nujol, ν, cm^{-1}): 3276, 3201, 3099, 1711, 1698, 1652, 1629, 1603, 1573, 1547. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.82 and 2.41 (2s, 3H), 4.94 and 4.99 (2s, 2H), 6.96–7.01 (m, 2H), 7.25–7.55 (m, 12H), 8.48 (br s, 1H), 8.85 (s, 1H), 8.94 and 9.99 (br s and s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.5 (q), 16.9 (q), 44.3 (t), 44.6 (t), 84.0 (s), 85.9 (s), 118.7 (d), 119.2 (d), 122.3 (d), 122.7 (d), 123.0 (d), 123.1 (d), 127.3 (d), 127.4 (d), 127.5 (s), 127.6 (d), 127.9 (s), 128.3 (d), 128.4 (d), 128.5 (d), 128.7 (d), 129.0 (d), 129.3 (d), 136.6 (s), 137.1 (s), 139.1 (s), 139.3 (s), 147.6 (s), 147.9 (s), 152.9 (s), 153.4 (s), 155.1 (s), 155.4 (s), 165.3 (s), 166.0 (s). MS (EI): m/z = 493 [M^+ + 2 (5)], 491 (M^+, 13), 398 (52), 274 (100), 241 (57), 179 (79), 119 (83). Anal. Calcd for $C_{25}H_{22}ClN_5O_2S$ (491.99): C, 61.03; H, 4.51; N, 14.23. Found: C, 61.12; H, 4.39; N, 14.32.

*Methyl 2-[1-[3-allyl-2-[(4-methoxyphenyl)imino]-4-oxo-1,3-thiazolidin-5-ylidene]ethyl]hydrazinecarboxylate (**5e**).* Yield: 319.9 mg (85%). Light gray powder (from EtOAc–Et_2O). IR (Nujol, ν, cm^{-1}): 3317, 3290, 1742, 1653, 1616, 1585. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.86 and 2.34 (2s, 3H), 3.58 and 3.62 (2s, 3H), 3.73 (s, 3H), 4.33–4.38 (m, 2H), 5.09–5.17 (m, 2H), 5.84–5.94 (m, 1H), 6.83–6.92 (m, 4H), 8.75 and 9.82 (br and s, 1H), 9.52 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.2 (q), 16.7 (q), 43.4 (t), 43.5 (t), 52.4 (q), 55.2 (q), 84.7 (s), 86.7 (s), 114.4 (d), 114.6 (d), 116.5 (t), 116.7 (t), 122.1 (d), 122.3 (d), 132.0 (d), 132.4 (d), 141.9 (s), 142.1 (s), 150.8 (s), 155.7 (s), 155.9 (s), 156.7 (s), 156.8 (s), 165.4 (s), 165.8 (s). MS (EI): m/z = 376 (M^+, 46), 344 (8), 287 (2), 189 (36), 147 (100), 101 (53). Anal. Calcd for $C_{17}H_{20}N_4O_4S$ (376.43): C, 54.24; H, 5.36; N, 14.88. Found: C, 54.16; H, 5.49; N, 14.79.

*tert-Butyl 2-[1-[3-Butyl-2-[(4-chlorophenyl)imino]-4-oxo-1,3-thiazolidin-5-ylidene]ethyl]hydrazinecarboxylate (**5f**).* Yield: 386.3 mg (88%). Pale yellow foam. IR (Nujol, ν, cm^{-1}): 3298, 3280, 1739, 1734, 1718, 1671, 1623, 1617, 1587. ^1H NMR (400 MHz, DMSO-d_6) δ: 0.88–0.93 (m, 3H), 1.23–1.63 (m, 13H), 1.85 and 2.31 (2s, 3H), 3.70–3.77 (m, 2H), 6.88–6.97 (m, 2H), 7.32–7.39 (m, 2H), 8.81 and 9.81 (br s and s, 1H), 9.28 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.6 (q), 16.7 (q), 19.5 (t), 19.6 (t), 27.9 (q), 28.9 (t), 29.0 (t), 40.8 (t), 79.9 (s), 84.1 (s), 123.0 (d), 123.3 (d), 127.5 (s), 129.0 (d), 129.3 (d), 147.9 (s), 148.8 (s), 152.0 (s), 154.8 (s), 155.3 (s), 165.6 (s), 166.2 (s). MS (EI): m/z = 440 [M^++2 (7)], 438 (M^+, 17), 382 (91), 338 (52), 282 (55), 209 (63), 130 (100), 101 (89). Anal. Calcd for $C_{20}H_{27}ClN_4O_3S$ (438.97): C, 54.72; H, 6.20; N, 12.76. Found: C, 54.59; H, 6.29; N, 12.83.

*tert-Butyl 2-[[3-Benzyl-4-oxo-2-(phenylimino)-1,3-thiazolidin-5-ylidene](phenyl)methyl]hydrazinecarboxylate (**5g**).* Yield: 375.4 mg (75%). Yellow foam. IR (neat, ν, cm^{-1}): 3348, 3292, 1731, 1671, 1623, 1591. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.29 (s, 9H), 5.10 (s, 2H), 6.18 (br s, 1H), 6.90 (d, J = 7.6 Hz, 2H), 7.27–7.37 (m, 11H), 7.56 (d, J = 6.8 Hz, 2H), 9.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0 (q), 45.4 (t), 81.8 (s), 94.8 (s), 121.2 (d), 124.1 (d), 127.6 (d), 127.9 (d), 128.2 (d), 128.4 (d), 128.7 (d), 128.9 (d), 129.2 (d), 132.7 (s), 136.5 (s), 148.6 (s), 152.0 (s), 155.1 (s), 155.8 (s), 167.3 (s). MS (EI): m/z = 500 (M^+, 12), 444 (84), 400 (56), 385 (21), 370 (17), 282 (13), 167 (100). Anal. Calcd for $C_{28}H_{28}N_4O_3S$ (500.61): C, 67.18; H, 5.64; N, 11.19. Found: C, 67.29; H, 5.77; N, 11.26.

General Procedure for the Synthesis of 5-Hydroxyethylidene 1,3-Disubstituted Thiohydantoins 6a,b and of 5-Hydroxyethylidene-2-iminothiazolidin-4-ones 7a,b. A 1 mmol portion of **4a,b** or **5a,b** was refluxed in 10 mL of acetone/water (9:1 mixture) in the presence of Amberlyst 15 H (250 mg) for the appropriate reaction time (2–8 h, checked by TLC). After the filtration of the resin, washed twice with acetone, the crude reaction mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried on anhydrous sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography eluting with cyclohexane/ethyl acetate mixtures to obtain pure derivatives **6a,b** or **7a,b**.

*1-Benzyl-5-(1-hydroxyethylidene)-3-(4-methoxyphenyl)-2-thioxoimidazolidin-4-one (**6a**).* Compound **6a** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 98% yield (347.3 mg) as a yellow oil. IR (neat, ν, cm^{-1}): 3392, 1766, 1728, 1611, 1590. ^1H NMR (400 MHz DMSO-d_6) δ: 2.38 (s, 3H), 3.80 (s, 3H), 5.64 (s, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.23–7.33 (m, 7H), 12.12 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.0 (q), 49.2 (t), 55.3 (q), 108.6 (s), 113.9 (d), 114.2 (d), 126.4 (d), 126.7 (d), 127.1 (s), 128.1 (d), 128.2 (d), 129.6 (d), 130.0 (d), 137.7 (s), 155.0 (s), 159.0 (s), 163.1 (s), 173.2 (s). MS m/z: 354 (M^+, 44), 327 (69), 312 (100), 166 (19), 149 (49), 108 (14). Anal. Calcd for $C_{19}H_{18}N_2O_3S$ (354.42): C 64.39, H 5.12, N 7.90; Found: C 64.51, H 5.03, N 8.01.

*1-Butyl-5-(1-hydroxyethylidene)-3-phenyl-2-thioxoimidazolidin-4-one (**6b**).* Compound **6b** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 97% yield (281.6 mg) as orange oil. IR (neat, ν, cm^{-1}): 3308, 1759, 1739, 1655, 1599. ^1H NMR (400 MHz DMSO-d_6) δ: 0.92 (t, J = 7.2 Hz, 3H), 1.30–1.36 (m, 2H), 1.64–1.68 (m, 2H), 2.45 (s, 3H), 4.33–4.37 (m, 2H), 7.25–7.48 (m, 5H), 11.15 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.7 (q), 17.7 (q), 19.4 (t), 30.3 (t), 46.0 (t), 108.5 (s), 128.6 (d), 128.7 (d), 128.9 (d), 134.4 (s), 154.7 (s), 163.1 (s), 171.6 (s). MS m/z: 290 (M^+, 66), 263 (88), 248 (100), 234 (11), 215 (75), 136 (57), 119 (33). Anal. Calcd. for $C_{15}H_{18}N_2O_2S$ (290.38): C 62.04, H 6.25, N 9.65; Found: C 62.17, H 6.36, N 9.53.

*3-Benzyl-5-(1-hydroxyethylidene)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (**7a**).* Compound **7a** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 91% yield (322.5 mg) as a yellow oil. IR (neat): 3284, 1750, 1728, 1635, 1614, 1505. ^1H NMR (400 MHz, DMSO-d_6) δ: 2.45 (s, 3H), 3.73 (s, 3H), 4.96 and 4.99 (2s, 2H), 6.85–6.92 (m, 4H), 7.26–7.35 (m, 5H), 11.67 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.2 (q), 44.7 (t), 55.2 (q), 94.6 (s), 114.6 (d), 122.2 (d), 122.4 (d), 127.2 (d), 127.4 (d), 127.5 (d), 128.3 (d), 136.9 (s), 141.5 (s), 141.7 (s), 151.0 (s), 151.1 (s), 156.0 (s), 162.4 (s), 165.5 (s). MS (EI): m/z = 354 (M^+, 38), 310 (5), 263 (3), 238 (10), 197 (100), 165 (10). Anal. Calcd for $C_{19}H_{18}N_2O_3S$ (354.42): C, 64.39; H, 5.12; N, 7.90. Found: C, 64.51; H, 5.20; N, 7.79.

*3-Butyl-5-(1-hydroxyethylidene)-2-(phenylimino)-1,3-thiazolidin-4-one (**7b**).* Compound **7b** was isolated by column chromatography (ethyl acetate/cyclohexane 60:40) in 85% yield (246.8 mg) as yellow-green oil. IR (neat, ν, cm^{-1}): 3280, 1748, 1641, 1625, 1590. ^1H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, J = 7.6 Hz, 3H), 1.28–1.33 (m, 2H), 1.59–1.63 (m, 2H), 2.44 (s, 3H), 3.74–3.77 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 2H), 11.55 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.6 (q), 18.1 (q), 19.5 (t), 29.0 (t), 41.3 (t), 94.8 (s), 121.2 (d), 123.9 (d), 129.2 (d), 148.8 (s), 151.3 (s), 161.9 (s), 165.5 (s). MS m/z: 290 (M^+, 93), 273 (5), 257 (6), 247 (24), 234 (100), 198 (66), 173 (12). Anal. Calcd for $C_{15}H_{18}N_2O_2S$(290.38): C 62.04, H 6.25, N 9.65; Found: C 62.19, H 6.17, N 9.56.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of products and X-ray data for compound **4h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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