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Synthesis and Structure of 1-Substituted Semithioglycolurils

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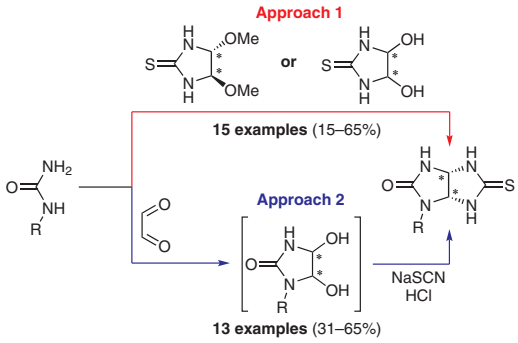

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Abstract Two methods for the synthesis of previously unavailable 1-substituted semithioglycolurils were developed. These methods consist of the cyclocondensation of 1-substituted ureas with 4,5-dihydroxy- or 4,5-dimethoxyimidazolidine-2-thione or glyoxal, followed by the reaction of the resulting 1-substituted 4,5-dihydroxyimidazolidine-2-ones with HSCN in a two-step one-pot procedure. Two of the desired semithioglycolurils were obtained as conglomerates.

Key words semithioglycolurils, cyclocondensation, heterocycles, urea derivatives, thiourea derivatives, glyoxal

Since the first synthesis of a glycoluril, published by Hugo Schiff in 1877,[1] the chemistry of these compounds has been actively developing. Hundreds of glycolurils with different combinations of substituents at nitrogen and carbon atoms have been synthesized.[2–5] Thio-, amino-, and sulfo-based analogues of glycolurils are less available.[2,6] More and more research has focused on semithioglycolurils **I–IX** (Figure 1),[2,6–26] including compounds **I**, **II**, **V**, **VII**, and **VIII** that were synthesized in our laboratory.[6,12–26]

Although a wide range of trisubstituted semithioglycolurils **I** and **II** have been reported, they are still actively investigated, as some of them have antifungal and cytotoxic activities.[12,13] Other compounds **III–IX** are represented by several examples and used as scaffolds in the synthesis of semithiobambusurils (**III** and **VII**),[11,27] in Claisen condensation matrices (**IV**),[10] and in the synthesis of tri-, tetra-, and polycyclic systems (**V**)[28–31] and iminoglycolurils (**V**, **VII**, **VIII**).[6] Methods for the preparation of a small number of compounds **III–IX** reported in the literature are underdeveloped. The focus of this article is on a methodology for the synthesis of 1-substituted semithioglycolurils.

Semithioglycolurils have so far been represented by only three examples (Scheme 1).[6,14,25] Compounds **1a**,**b** were obtained by the reaction of 1-alkylureas **2a**,**b** with 4,5-dimethoxyimidazolidine-2-thione (DMIT; **3**) or 4,5-dihydroxyimidazolidine-2-thione (DHIT; **4**) (approach 1).[6,25] Semithioglycoluril **1c** was prepared by the condensation of 1-cyclohexyl-4,5-dihydroxyimidazolidin-2-one (**5a**) with KSCN and hydrochloric acid (approach 2).[14] Here, these approaches were studied in detail, and two methods for the synthesis of 1-substituted semithioglycolurils were developed.

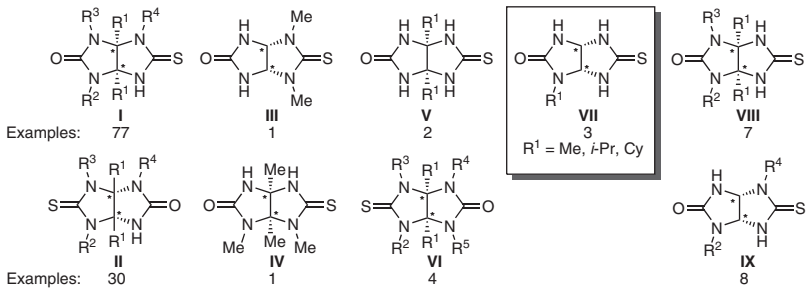

Figure 1 Previously reported semithioglycolurils

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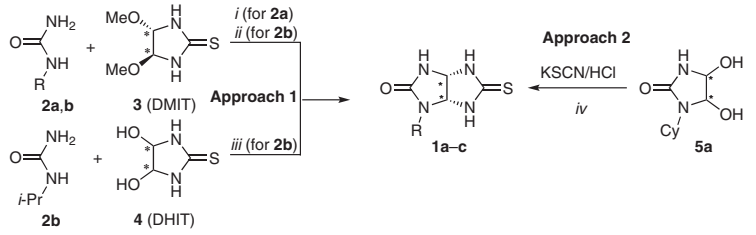


Scheme 1 Two approaches for the synthesis of 1-alkyl-substituted semithioglycolurils **1a–c**

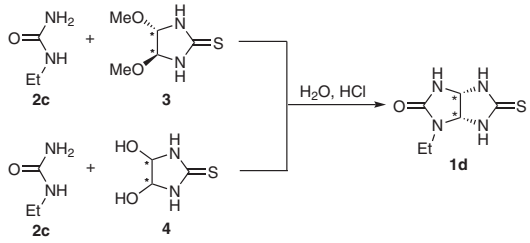
To develop approach 1, we started with the reactions of DMIT (**3**) and DHIT (**4**) with ethylurea (**2c**) in water by varying the amount of hydrochloric acid (pH 1) and time used for heating the reaction mixture (10 min, 30 min, 1 h, and 2 h) at 76–80 °C (Table 1). By ^{1}H NMR monitoring of dried reaction mixture aliquots, the dependence of the conversion of ethylurea (**2c**) into thioglycoluril **1d** on the reaction conditions was analyzed. The conversion rate was estimated by analyzing the proton signals of the Me groups of urea **2c** (t, δ = 0.96) and thioglycoluril **1d** (t, δ = 1.02) and the CH–CH group of thioglycoluril **1d** (d, δ = 5.46). It was established that the conversion of **2c** to **1d** is 33% and 37% when the reaction of urea **2c** with DMIT (**3**) is carried out with hydrochloric acid (0.027 mL) for 30 minutes and 1 hour, respectively (Table 1, entries 1, 2).

When the volume of hydrochloric acid (0.08 mL) was increased, the conversion of **2c** into **1d** increased to 41 and 64%, for 10 minutes and 1 hour of reaction time, respectively (Table 1, entries 3 and 5), and remained constant even after 2 hours of reaction (entry 6). Similar results were observed when we used DHIT (**4**); however, the reaction rate of forming semithioglycoluril **1d** increased. After 10 minutes, the conversion of **2c** into **1d** was 52% (entry 7), and increased to 64% after 30 minutes (entry 8). Therefore, it is more efficient to use DHIT (**4**) rather than DMIT (**3**), with a reaction time of 30 minutes. Apart from that, we noticed that DHIT (**4**) is partially consumed in a competing reaction to produce the earlier reported 2-thioxoimidazolidin-4-one (thiohydantoin)[32] (the most characteristic signal of CH_2 protons: s, δ = 4.06); we also detected ethylurea (**2c**) in the reaction mixture.

For a more complete transformation of ethylurea (**2c**) into semithioglycoluril **1d**, we used a larger amount of DHIT (**4**) (1.2 and 1.5 equiv; Table 1, entries 12 and 11, respectively). ^{1}H NMR monitoring of this reaction showed that the conversion of **2c** into **1d** was 65% with DHIT (1.5 equiv) after 30 minutes of heating, but DHIT was still present in the resulting product (entry 11). The use of DHIT (**4**; 1.2 equiv) in this reaction led to an increase of the conversion of ethylurea (**2c**) to thioglycoluril **1d** up to 71% after 30 minutes (entry 12). The yield of thioglycoluril **1d** was 52% after its purification (Table 2, approach 1, entry 3). Thus, the best yield of thioglycoluril **1d** was achieved in the reaction of DHIT (**4**; 2.5 mmol, 1 equiv) with ethylurea (**2c**) in a **4**/**2c** ratio of 1.2:1 in water with 35% hydrochloric acid (0.08 mL) at 76–80 °C for 30 min (Table 1, entry 12).

The target glycolurils **1a–m**,**o**,**p** were synthesized in 15–65% yield by using the optimized conditions of condensation of DHIT (**4**) with 1-substituted ureas **2a–m**,**o**,**p** (Table 2, approach 1, entries 1–13, 15, 16). In total, 15 compounds were synthesized by approach 1.

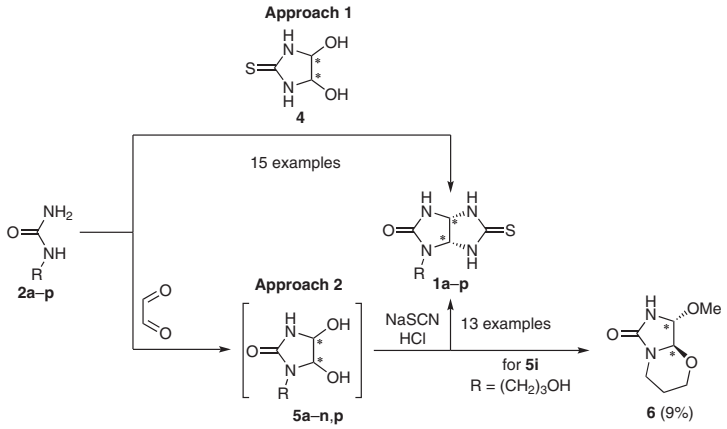
Table 1 Screening of Conditions for the Synthesis of Thioglycoluril **1d** (Approach 1)[a]



Entry	Reagents (ratio)	Aq HCl (35%) (mL)	Time	Conversion (%)[b]
1	**2c**, **3** (1:1)	0.027	30 min	33
2	**2c**, **3** (1:1)	0.027	1 h	37
3	**2c**, **3** (1:1)	0.08	10 min	41
4	**2c**, **3** (1:1)	0.08	30 min	59
5	**2c**, **3** (1:1)	0.08	1 h	64
6	**2c**, **3** (1:1)	0.08	2 h	64
7	**2c**, **4** (1:1)	0.08	10 min	52
8	**2c**, **4** (1:1)	0.08	30 min	64
9	**2c**, **4** (1:1)	0.08	1 h	65
10	**2c**, **4** (1:1)	0.08	2 h	65
11	**2c**, **4** (1:1.5)	0.08	30 min	65
12	**2c**, **4** (1:1.2)	0.08	30 min	71[c]

[a] Reaction conditions: **2c** (2.5 mmol, 1 equiv), **3** or **4**, H_2O (10 mL), aq HCl (35%), 76–80 °C.
[b] Conversion of **2c** into **1d** according to ^{1}H NMR spectroscopy.
[c] Reaction conditions: **2c** (0.22 g, 2.5 mmol), **4** (0.40 g, 3.0 mmol), H_2O (10 mL), aq HCl (35%, 0.08 mL), 76–80 °C, 30 min.

Table 2 Comparison of Two Approaches to the Synthesis of Semithioglycolurils **1a–p**



Entry	R	Urea	DHI	Product	Yield (%) of **1** by approach 1[a]	Yield (%) of **1** by approach 2[b,c]
1	Me	**2a**	**5b**	**1a**	51	31[b]
2	*i*-Pr	**2b**	**5c**	**1b**	50	52[b]
3	Et	**2c**	**5d**	**1d**	52	58[b]
4	Pr	**2d**	**5e**	**1e**	20	55[b]
5	*t*-Bu	**2e**	**5f**	**1f**	61	50[b]
6	Cy	**2f**	**5a**	**1c**	65	9[d]
7	CH_2c-C_3H_5	**2g**	**5g**	**1g**	45	53[b]
8	$(CH_2)_2OH$	**2h**	**5h**	**1h**	26	54[b]
9	$(CH_2)_3OH$	**2i**	**5i**	**1i**	15	0 (**1i**)[b], 9 (**6**)[b]
10	Me_2CCH_2OH	**2j**	**5j**	**1j**	41	45[b]
11	All	**2k**	**5k**	**1k**	40	62[c]
12	Bn	**2l**	**5l**	**1l**	45	63[c]
13	PMB	**2m**	**5m**	**1m**	46	65[c]
14	$(CH_2)_2Ph$	**2n**	**5n**	**1n**	–	61[c]
15	Ph	**2o**	–	**1o**	34	–
16	$(CH_2)_3CO_2H$	**2p**	**5p**	**1p**	36	–

[a] Reaction conditions: **2** (2.5 mmol), **4** (0.40 g, 3.0 mmol), H_2O (10 mL), aq HCl (35%, 0.08 mL), 76–80 °C, 30 min.
[b] Reaction conditions: 1. **2** (20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), H_2O (10 mL), NaOH (to pH 10), 50–55 °C, 3 h. 2. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), aq HCl (35%, 4.4 mL); NaCl precipitate removed by filtration; filtrate refluxed, 30 min.
[c] Reaction conditions: 1. **2** (20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), *i*-PrOH (10 mL), reflux, 5 h. 2. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), aq HCl (35%, 4.4 mL); NaCl precipitate removed by filtration; filtrate refluxed, 30 min.
[d] Total yield of **1c** [**5a**: 12% (stage 1),[33] **1c**: 74% (stage 2)[14]].

As 1-cyclohexyl-DHI **5a** had been prepared before,[32] approach 2 made use of the condensation of DHI **5** with NaSCN and hydrochloric acid, so that 1-substituted DHI **5b–o** had to be prepared (Table 2). To do so, a model reaction of ethylurea (**2c**) and glyoxal was examined under the same conditions that were used for the synthesis of 1,3-dimethyl-DHI, with H_2O as the solvent, at pH 10 and 50–55 °C.[34] The next goal was to determine the reaction time needed for ethylurea **2c** to completely transform into DHI **5d**. We used ^{1}H NMR monitoring of dried reaction mixture aliquots (after 5 min, 1 h, 2 h and 3 h; Figure 2). It was established that the conversion of urea **2c** into DHI **5d** was complete after 3 hours. After this time, the signals of the protons of urea **2c** disappeared, while new signals of the DHI protons appeared in the ^{1}H NMR spectrum (Figure 2d). As no side products were detected (Figure 2d), we used a reaction mixture in the reaction with NaSCN and hydrochloric acid, without isolation of DHI **5d** (as well as of DHI **5b**,**c**,**e–h**,**j**). Target compound **1d** was obtained in 58% yield (Table 2, approach 2, entry 3). Condensation of ureas **2a–e**,**g**,**h**,**j** with glyoxal was carried out in water for 3 hours at 50–55 °C. As a result, we synthesized a series of thioglycolurils **1a**,**b**,**d**,**e**,**f**,**g**,**h**,**j** in 31–58% yield (Table 2, approach 2, entries 1–5, 7, 8, 10). It turned out that DHI **5i**,**p** do not produce

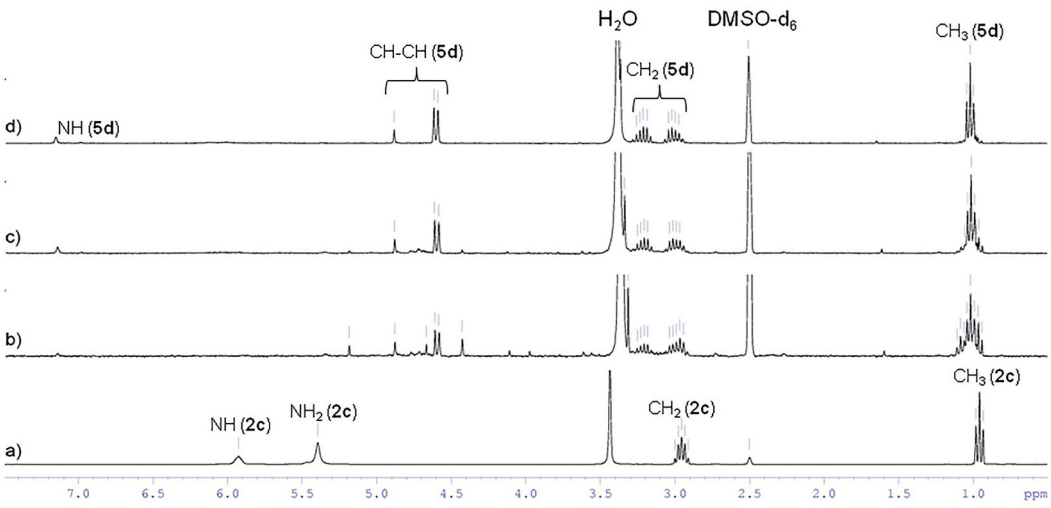


Figure 2 Conversion of ethylurea (**2c**) into DHI **5d**, followed by ^{1}H NMR spectra (DMSO-d_6) of ethylurea (**2c**) (a) and the reaction mixture after 10 min (b), 2 h (c), and 3 h (d).

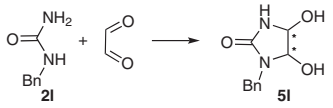
semithioglycolurils **1i**,**p** (entries 9, 16). Imidazooxazine **6** was isolated in 9% yield instead of product **1i** (entry 9), although signals of the protons of compound **1i** were found in a ^{1}H NMR spectrum of the reaction mixture.

As ureas **2k–o** do not dissolve in H_2O, it was necessary to develop another synthetic approach to DHI **5k–n**. As a model reaction, we chose the reaction between 1-benzylurea **2l** and glyoxal. The reaction was carried out in MeOH or *i*-PrOH at pH 7 or 10 (Table 3). Reaction progress was again monitored by ^{1}H NMR spectroscopy. The best results were achieved in refluxing *i*-PrOH at pH 7. Under these conditions, a 100% conversion of urea **2l** to DHI **5l** (Table 3, entry 9; see also Supporting Information, SI, Figure S1) was observed, so there was no need to isolate DHI **5l** for the following reaction with NaSCN and hydrochloric acid. Target thioglycoluril **1l** was synthesized in 63% yield (Table 2, approach 2, entry 12). The same methodology was applied for the synthesis of DHI **5k**,**m**,**n** and semithioglycolurils **1k**,**m**,**n** (yields 61–65%) (entries 11, 13, 14). Urea **2o** did not produce DHI **5o**, and it was separated from the reaction mixture without any change.

Semithioglycolurils **1i**,**o**,**p** can be synthesized only by approach 1, while compound **2n** can only be obtained by approach 2 (Table 2). The yields of semithioglycolurils **1e**,**g**,**h**,**k–m** from approach 2 are 8–35% higher. For compounds **1a**,**c**,**f**, the approach 1 resulted in higher yields (by 11–56%). The yields of compounds **1b**,**d**,**j** were almost the same (50–52%, 52–58%, 41–45%, respectively), so that they can be synthesized by either of the proposed two methods.

The formation of the target semithioglycolurils **1** was unambiguously confirmed by X-ray diffraction data collected for **1a**,**b**,**d**,**j** (SI, Figures S2 and S3), which revealed two conglomerates (**1a** and **1j** crystallized in the $P2_12_12_1$ space group) and two racemates (**1b** and **1d** crystallized in the *C*2/*c* space group) among these semithioglycololurils. Of the four, only **1j** has a substituent at one of its nitrogen atoms, the $C(Me)_2CH_2OH$ group, which is able to form a hydrogen bond; however, its resulting crystal structure is isostructural with the one for **1a** with the methyl group in the same position of the urea. In both cases, the formation of a conglomerate can be attributed to homochiral chains of semithioglycoluril molecules (SI, Figure S4), held together

Table 3 Screening of Conditions for the Synthesis of DHI **5l** (Approach 2)[a]



Entry	Solvent	pH	Time (h)	Conv. (%)[b]
1	MeOH	7	1	15
2	MeOH	7	2	20
3	MeOH	7	3	24
4	MeOH	7	4	25
5	*i*-PrOH	7	1	59
6	*i*-PrOH	7	2	71
7	*i*-PrOH	7	3	77
8	*i*-PrOH	7	4	85
9	*i*-PrOH	7	5	100[c]
10	*i*-PrOH	10	3	33

[a] Reaction conditions: **2l** (2 mmol), glyoxal hydrate trimer (0.8 mmol), reflux.
[b] Conversion of **2l** into **5l** according to ^{1}H NMR spectroscopy.
[c] Reaction conditions: **2l** (0.30 g, 2 mmol), glyoxal hydrate trimer (0.16 g, 0.8 mmol), *i*-PrOH (5 mL), reflux, 5 h.

by hydrogen bonds of the NH groups that are on the opposite side of the molecule from the above substituent (N···O 2.820(3) Å, NHO 178(1)° and N···S 3.406(2) Å, NHS 173(1)° in **1a** and N···O 2.765(5) Å, NHO 176(1)° and N···S 3.464(4) Å, NHS 172(1)° in **1j**). The third NH group links these homochiral chains (N···O 2.834(3) Å, NHO 163(1)° in **1a** and N···O 3.018(5) Å, NHO 167(1)° in **1j**), which are rotated to each other by ca. 90° to result in a non-centrosymmetric hydrogen-bonded 3D framework. The OH group in **1j** is involved in an intramolecular hydrogen bond with an adjacent oxygen atom O(1) (O···O 2.614(5) Å, OHO 156(1)°) and in a hydrogen bond with the third NH group from the molecule in a perpendicular chain, as the oxygen atom O(1) in **1a** does (see above). In contrast, the semithioglycolorils **1b** and **1d** (SI, Figure S5) form centrosymmetric dimers through N–H···S hydrogen bonds (N···S 3.358(6) Å, NHS 160(1)° in **1b** and N···S 3.569(3) Å, NHS 149(1)° in **1d**). They assemble chiral chains produced by an N–H···O hydrogen bond (N···O 2.874(8) Å, NHO 177(1)° in **1b** and N···O 2.885(4) Å, NHO 144(1)° in **1d**) of the NH group that is on the same side of the molecule as the above substituents, into centrosymmetric sheets. Additionally stabilized by N–H···S hydrogen bonds formed the third NH group in **1b** (N···S 3.464(6) Å, NHS 156(1)°), those are held together by weak van der Waals interactions. In **1d**, the same NH group is involved in an N–H···S hydrogen bond with the neighboring chiral chain (N···S 3.564(3) Å, NHS 137(1)°), thus completing a centrosymmetric hydrogen-bonded 3D framework. As a result, the semithioglycolorils **1b** and **1d** were crystallized as racemates (SI, Table S1), and **1a** and **1j**, as conglomerates. A possible explanation for this behavior is that the isopropyl and ethyl substituents are diverted towards the NH group in the former two compounds, somehow favoring the centrosymmetric arrangement of their molecules.

In summary, reactions of 1-substituted ureas with 4,5-dihydroxy- or 4,5-dimethoxyimidazolidine-2-thione (approach 1) or with glyoxal, using the resulting 1-substituted 4,5-dihydroxyimidazolidine-2-ones, with NaSCN and hydrochloric acid in a two-step one-pot procedure (approach 2) were studied in detail by ^{1}H NMR spectroscopy. As a result of this comprehensive study, two new methods for the synthesis of 1-substituted semithioglycolorils were developed to provide 16 different products, 13 of which were reported for the first time. Two of these compounds produced the first conglomerates reported for semithioglycolorils, as unambiguously identified by X-ray diffraction. This research has made 1-substituted semithioglycolorils available, so that they can now be used in the synthesis of new heterocyclic compounds.

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at 25–29 °C with a Bruker AM300 and Bruker DRX500 spectrometer and TMS as internal standard. HRMS (ESI) data were collected using a Bruker micrOTOF II mass spectrometer. 1-Methyl- and 1-isopropyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (**1a**,**b**) were synthesized earlier from 1-methyl- and 1-isopropylurea and **3** (DMIT).[6,25] 1-Cyclohexyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (**1c**) was prepared earlier from 1-cyclohexyl-4,5-dihydroxyimidazolidine-2-one, KSCN, and HCl.[14] 1-Alkylureas **2b**,[35] **2c**,[36] **2e**,[37] **2f**,[35] **2h**,[38] **2i**,[39] **2j**,[38] and **2p**[38] were synthesized by previously reported procedures from the corresponding amines, hydrochloric acid, and KOCN. 1-Phenethylurea (**2n**)[40] was synthesized from 2-phenylethanamine, hydrochloric acid, and urea. 4,5-Dimethoxyimidazolidine-2-thione (**3**) was prepared from 4,5-dihydroxyimidazolidine-2-thione (**4**), MeOH, and hydrochloric acid.[32] 4,5-Dihydroxyimidazolidine-2-thione was synthesized by the condensation of thiourea with 40% aq glyoxal.[41]

Thioglycolurils 1a–m,o,p; Approach 1

4,5-Dihydroxyimidazolidine-2-thione (**4**; 0.40 g, 3.0 mmol) and the appropriate urea **2a–m**,**o**,**p** (2.5 mmol) were suspended in H_2O (10 mL). Aq HCl (35%, 0.08 mL) was added, and the solution was heated to 76–80 °C and stirred for 30 min. The next day, the resulting precipitate was collected by filtration and air-dried (for **1a–k**,**p**). The resulting precipitates of **1l**,**m**,**o** were purified by recrystallization (EtOH).

Thioglycolurils 1a,b,d–h,j ; Approach 2

A mixture of the appropriate 1-alkylurea **2a–e**,**g–j** (20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), and H_2O (10 mL) was heated to 50–55 °C. Aq NaOH was added dropwise until pH 10 was reached by the reaction mixture, which was then stirred for 3 h. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), and 35% aq HCl (4.4 mL) were added to the reaction mixture. The precipitate was removed by filtration and washed with MeOH (5 mL). The filtrate was refluxed for 30 min. Then the reaction mixture was cooled to r.t.

*For **1h**:* The next day, the resulting precipitate of thioglycoluril **1h** was collected by filtration, washed with MeOH, and dried in air.

*For **1a**,**b**,**d–g**:* The reaction mixture was evaporated to dryness, after which $CHCl_3$ (10 mL) was added under stirring. The precipitate was collected by filtration and washed with H_2O (5 mL).

*For **1j**:* The reaction mixture of **1j** was evaporated to dryness, and then the resulting mixture was dissolved in H_2O (10 mL) and $CHCl_3$ (15 mL). The organic layer was collected and then evaporated to dryness. After the addition of MeOH (5 mL), the precipitate was collected by filtration and air-dried.

Thioglycolurils 1k–n; Approach 2

A mixture of the appropriate 1-alkylurea **2k–n** (20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), and *i*-PrOH (10 mL) was heated to reflux and stirred for 5 h. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), and 35% aq HCl (4.4 mL) were added to the reaction mixture. The precipitate was removed by filtration and washed with MeOH (5 mL). The filtrate was refluxed for 30 min. Then the reaction mixture was cooled to r.t. The resulting precipitate was collected by filtration and air-dried.

1-Methyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1a)[6]

Beige powder; yield: 0.22 g (51%) (approach 1); brown crystals; yield: 1.07 g (31%) (approach 2); mp 283–285 °C (MeOH) (283–285 °C (H_2O)[6]).

1-Isopropyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1b)[25]

Beige powder; yield: 0.25 g (50%) (approach 1); brown crystals; yield: 2.08 g (52%) (approach 2); mp 260–261 °C (MeOH) (260–261 °C (H_2O)[25]).

IR (KBr): 2975, 2894, 1677, 1533, 1492, 1337, 1225, 1210, 1105, 880, 755, 634, 586 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.61 (d, ^3J = 6.6 Hz, 6 H, Me), 3.78–3.92 (m, 1 H, CH), 5.37 (d, ^3J = 8.4 Hz, 1 H, CH), 5.52 (d, ^3J = 8.5 Hz, 1 H, CH), 7.42 (s, 1 H, NH), 8.99 (s, 1 H, NH), 9.04 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.98, 21.42 (Me), 43.20 (CH), 66.61, 69.87 (CH–CH), 158.34 (C=O), 182.80 (C=S).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{12}N_4OS$ + H: 201.0805; found: 201.0805.

1-Cyclohexyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1c)[14]

Beige powder; yield: 0.39 g (65%) (approach 1); mp 294–296 °C (H_2O) (294–296 °C (H_2O)[14]).

1-Ethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1d)

Beige powder; yield: 0.24 g (52%) (approach 1); brown crystals; yield: 2.15 g (58%) (approach 2); mp 256–258 °C (MeOH).

IR (KBr): 3348, 3185, 2980, 2877, 1680, 1527, 1489, 1341, 1309, 1251, 1099, 887, 585 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.02 (t, ^3J = 7.1 Hz, 3 H, Me), 3.01 (dq, ^2J = 14.2 Hz, ^3J = 7.1 Hz, 1 H, CH_2), 3.26 (dq, ^2J = 14.4 Hz, ^3J = 7.2 Hz, 1 H, CH_2), 5.37 (d, ^3J = 8.4 Hz, 1 H, CH), 5.46 (d, ^3J = 8.4 Hz, 1 H, CH), 7.49 (s, 1 H, NH), 9.02 (s, 1 H, NH), 9.15 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.83 (Me), 35.09 (CH_2), 66.31, 71.1 (CH–CH), 158.46 (C=O), 182.74 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_6H_{10}N_4OS$ + Na: 209.0468; found: 209.0464.

1-Propyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1e)

Beige powder; yield: 0.10 g (20%) (approach 1), 2.20 g (55%) (approach 2); mp 243–245 °C (MeOH).

IR (KBr): 2967, 2932, 2879, 1682, 1531, 1492, 1250, 1206, 1100, 886 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.61 (t, ^3J = 7.3 Hz, 3 H, Me), 1.37–1.57 (m, 2 H, CH_2), 2.91–3.00 (m, 1 H, CH_2), 3.08–3.33 (m, 1 H, CH_2), 5.38 (d, ^3J = 8.5 Hz, 1 H, CH), 5.44 (d, ^3J = 8.5 Hz, 1 H, CH), 7.45 (s, 1 H, NH), 8.98 (s, 1 H, NH), 9.11 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.07 (Me), 20.31, 41.91 (CH_2), 66.27, 71.45 (CH–CH), 158.66 (C=O), 182.71 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_{12}N_4OS$ + Na: 223.0624; found: 223.0627.

1-*tert*-Butyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1f)

Violet powder; yield: 0.33 g (61%) (approach 1); beige powder; yield: 2.61 g (50%) (approach 2); mp 278–280 °C (H_2O).

IR (KBr): 3182, 2974, 2900, 1687, 1535, 1487, 1254, 1214, 1158, 775, 744 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.32 (s, 9 H, Me), 5.25 (d, ^3J = 8.3 Hz, 1 H, CH), 5.65 (d, ^3J = 8.3 Hz, 1 H, CH), 7.33 (s, 1 H, NH), 8.99 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.10 (Me), 53.52 (C), 66.63, 72.75 (CH–CH), 159.83 (C=O), 184.09 (C=S).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{14}N_4OS$ + H: 215.0961; found: 215.0962.

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1g)

Beige powder; yield: 0.24 g (45%) (approach 1), 2.25 g (53%) (approach 2); mp 249–250 °C (MeOH).

IR (KBr): 3346, 3171, 3007, 2872, 1680, 1524, 1486, 1334, 1520, 1199, 1097, 1060, 1020, 886,724 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.08–0.14 (m, 1 H, CH_2), 0.28–0.50 (m, 3 H, CH_2), 0.83–0.96 (m, 1 H, CH), 2.68 (dd, ^2J = 14.3 Hz, ^3J = 7.7 Hz, 1 H, CH_2), 3.22 (dd, ^2J = 13.6 Hz, ^3J = 7.2 Hz, 1 H, CH_2), 5.41 (d, ^3J = 8.4, Hz, 1 H, CH), 5.58 (d, ^3J = 8.3, Hz, 1 H, CH), 7.51 (s, 1 H, NH), 9.01 (s, 1 H, NH), 9.15 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 3.29, 3.96 (CH_2), 9.31 (CH), 44.62 (CH_2), 66.37, 71.39 (CH–CH), 158.57 (C=O), 182.79 (C=S).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}N_4OS$ + H: 213.0810; found: 213.0807.

1-(2-Hydroxyethyl)-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1h)

Beige thin needles; yield: 0.13 g (26%) (approach 1), 2.18 g (54%) (approach 2); mp 250–252 °C (MeOH).

IR (KBr): 3409, 3247, 2886, 2055, 1730, 1501, 1322, 1243, 1196, 1047, 876, 757 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.08 (dt, ^2J = 14.2 Hz, ^3J = 5.7 Hz, 1 H, CH_2), 3.24 (dt, ^2J = 14.1 Hz, ^3J = 6.1 Hz, 1 H, CH_2), 3.47 (t, ^3J = 5.9 Hz, 2 H, CH_2), 4.45–5.11 (br. s, 1 H, OH), 5.38 (d, ^3J = 8.4 Hz, 1 H, CH), 5.49 (d, ^3J = 8.3 Hz, 1 H, CH), 7.53 (s, 1 H, NH), 8.99 (s, 1 H, NH), 9.04 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.94, 58.68 (CH_2), 66.31, 72.17 (CH–CH), 158.75 (C=O), 182.63 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_6H_{10}N_4O_2S$ + Na: 225.0417; found: 225.0417.

1-(3-Hydroxypropyl)-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1i)

Beige powder; yield: 0.08 g (15%) (approach 1); mp 222–225 °C (H_2O).

IR (KBr): 3421, 3317, 1680, 1528, 1494, 1249, 1203, 1094, 1058, 884 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.55–1.68 (m, 2 H, CH_2), 3.03 (dt, ^2J = 14.0 Hz, ^3J = 6.8 Hz, 1 H, CH_2), 3.26 (dt, ^2J = 14.0 Hz, ^3J = 7.0 Hz, 1 H, CH_2), 3.39 (t, ^3J = 6.2 Hz, 2 H, CH_2), 5.38 (d, ^3J = 8.3 Hz, 1 H, CH), 5.44 (d, ^3J = 8.4 Hz, 1 H, CH), 7.49 (s, 1 H, NH), 9.01 (s, 1 H, NH), 9.12 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.45, 37.71, 58.39 (CH_2), 66.29, 71.62 (CH–CH), 159.72 (C=O), 182.72 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{12}N_4O_2S$ + Na: 238.0573; found: 238.0567.

1-(1-Hydroxy-2-methylpropan-2-yl)-5-thioxohexahydroimidazo-[4,5-*d*]imidazol-2(1*H*)-one (1j)

Beige powder; yield: 0.24 g (41%) (approach 1), 2.07 g (45%) (approach 2); mp 264–266 °C (MeOH).

IR (KBr): 3200, 2065, 1693, 1533, 1489, 1339, 1249, 1203, 1061, 888 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.26 (s, 6 H, Me), 3.37 (d, ^2J = 10.9 Hz, 1 H, CH_2), 3.64 (d, ^2J = 10.7 Hz, 1 H, CH_2), 4.77–5.14 (br. s, 1 H, OH), 5.28 (d, ^3J = 8.4 Hz, 1 H, CH), 5.67 (d, ^3J = 8.4 Hz, 1 H, CH), 7.38 (s, 1 H, NH), 8.83 (s, 1 H, NH), 9.00 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.21, 24.29 (Me), 57.55 (CH_2), 66.92, 73.16 (CH–CH), 67.82 (CMe_2), 160.16 (C=O), 183.93 (C=S).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{14}N_4O_2S$ + H: 231.0910; found : 231.0905.

1-Allyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1k)

Beige powder; yield: 0.20 g (40%) (approach 1); white powder; yield: 2.45 g (62%) (approach 2); mp 245–247 °C (MeOH).

IR (KBr): 3200, 2879, 1719, 1529, 1490, 1340, 1294, 1245, 1201, 1115, 1049, 885, 678 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.49 (dd, ^2J = 15.9 Hz, ^3J = 6.8 Hz, 1 H, CH_2), 3.92 (dd, ^2J = 15.5 Hz, ^3J = 3.7 Hz, 1 H, CH_2), 5.08–5.25 (m, 2 H, CH_2), 5.37 (q, ^3J = 8.3 Hz, 2 H, CH–CH), 5.63–5.78 (m, 1 H, CH), 7.6 (s, 1 H, NH), 9.05 (s, 1 H, NH), 9.17 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.46 (CH_2), 66.32, 71.02 (CH–CH), 117.49 (CH_2), 133.06 (CH), 158.31 (C=O), 182.78 (C=S).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{10}N_4OS$ + H: 199.0654; found: 199.0646

1-Benzyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1l)

Beige powder; yield: 0.27 g (45%) (approach 1), 3.00 g (63%) (approach 2); mp 259–261 °C (MeOH).

IR (KBr): 3350, 3143, 3006, 2871, 1675, 1528, 1484, 1334, 1250, 1122, 1081 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 4.01 (d, ^2J = 15.5 Hz, 1 H, CH_2), 4.61 (d, ^2J = 15.4 Hz, 1 H, CH_2), 5.22 (d, ^3J = 8.3 Hz, 1 H, CH), 5.42 (d, ^3J = 8.3 Hz, 1 H, CH), 7.27–7.39 (m, 5 H, Ph), 7.72 (s, 1 H, NH), 9.12 (s, 1 H, NH), 9.31 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 43.31 (CH_2), 66.33, 70.77 (CH–CH), 127.25, 127.82, 128.49 (CH(Ph)), 137.25 (C(Ph)), 158.48 (C=O), 182.83 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}N_4OS$ + Na: 271.0624; found: 271.0625.

1-(4-Methoxybenzyl)-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1m)

Beige powder; yield: 0.32 g (46%) (approach 1), 3.61 g (65%) (approach 2); mp 264–265 °C (MeOH).

IR (KBr): 3348, 3133, 3003, 2871, 1673, 1518, 1483, 1334, 1246, 1178, 1101, 1023 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3 H, Me), 3.91 (d, ^2J = 15.1 Hz, 1 H, CH_2), 4.56 (d, ^2J = 15.1 Hz, 1 H, CH_2), 5.17 (d, ^3J = 8.4 Hz, 1 H, CH), 5.39 (d, ^3J = 8.4 Hz, 1 H, CH), 6.91 (d, ^3J = 8.5 Hz, 2 H, CH(PMB)), 7.23 (d, ^3J = 8.5 Hz, 2 H, CH(PMB)), 7.07 (s, 1 H, NH), 9.10 (s, 1 H, NH), 9.31 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 42.70 (CH_2), 55.11 (OMe), 66.30, 70.55 (CH–CH), 113.95, 129.40, 128.49 (CH(PMB)), 119.04 (C(PMB)), 158.44, 158.62 (C=O+C-OMe), 182.83 (C=S).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_4O_2S$ + H: 279.0910; found: 279.0912.

1-Phenethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1n)

Beige powder; yield: 3.20 g (61%) (approach 2); mp 259–260 °C (MeOH).

IR (KBr): 3331, 3164, 1677, 1527, 1487, 1340, 1252, 1024, 1123, 1096, 885, 751, 702, 580 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.69–2.90 (m, 2 H, CH_2), 3.19–3.48 (m, 2 H, CH_2), 5.38 (d, ^3J = 8.4 Hz, 1 H, CH), 5.47 (d, ^3J = 8.3 Hz, 1 H, CH), 7.18–7.33 (m, 5 H, Ph), 7.44 (s, 1 H, NH), 8.92 (s, 1 H, NH), 9.20 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.38, 41.96 (CH_2), 66.36, 71.55 (CH–CH), 126.19, 128.36, 128.71 (CH(Ph)), 139.03 (C(Ph)), 158.52 (C=O), 182.70 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}N_4OS$ + Na: 285.0781; found: 285.0777.

1-Phenyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (1o)

Violet powder; yield: 0.20 g (34%) (approach 1); mp >300 °C (MeOH).

IR (KBr): 3345, 3177, 1689, 1529, 1503, 1422, 1328, 1266, 1142, 1102, 887, 748, 691 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 5.54 (d, ^3J = 8.4 Hz, 1 H, CH), 6.09 (d, ^3J = 8.5 Hz, 1 H, CH), 7.08 (t, ^3J = 7.3 Hz, 1 H, Ph), 7.33 (t, ^3J = 7.8 Hz, 2 H, Ph), 7.56 (d, ^3J = 8.1 Hz, 2 H, Ph), 8.18 (s, 1 H, NH), 9.29 (d, 1 H, NH), 9.42 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 65.77, 71.79 (CH–CH), 119.10, 123.06, 128.63 (CH(Ph)), 138.01 (C(Ph)), 156.35 (C=O), 183.47 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}N_4OS$ + Na: 257.0468; found: 257.0465.

4-[2-Oxo-5-thioxohexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl]-butanoic Acid (1p)

Beige powder; yield: 0.22 g (36%) (approach 1); mp 215–216 °C (H_2O).

IR (KBr): 3405, 3331, 3181, 1715, 1651, 1500, 1337, 1243, 1205, 1129, 1083, 933, 887, 812 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.60–1.80 (m, 2 H, CH_2), 2.16 (t, ^3J = 7.5 Hz, 2 H, CH_2), 3.00 (dt, ^2J = 13.9 Hz, ^3J = 6.8 Hz, 1 H, CH_2), 3.19 (dt, ^2J = 14.0 Hz, ^3J = 7.6 Hz, 1 H, CH_2), 5.37 (d, ^3J = 8.4 Hz, 1 H, CH), 5.44 (d, ^3J = 8.4 Hz, 1 H, CH), 7.53 (s, 1 H, NH), 9.04 (s, 1 H, NH), 9.14 (s, 1 H, NH), 11.81–12.32 (br s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.64, 31.01, 39.78 (CH_2), 66.34, 71.44 (CH–CH), 158.72 (C=O), 174.05 (COOH), 182.74 (C=S).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{12}N_4O_2S$ + Na: 267.0522; found: 267.0524.

1-(4-Methoxybenzyl)urea (2m)

Urea (200 mmol, 12.00 g) was dissolved in H_2O (50 mL); then, (4-methoxyphenyl)methanamine (5.2 mL, 40 mmol) and 35% aq HCl (2.5 mL) were added. The reaction mixture was refluxed for 4 h and then cooled to r.t. The resulting precipitate was collected by filtration, washed with H_2O (50 mL), and dried in air.

White crystalline plates; yield: 3.82 g (53%); mp 159–160 °C (H_2O) (158–159 °C[42]).

Ureas 2d,g

The corresponding amine (38 mmol) was dissolved in H_2O (40 mL), and then 35% aq HCl (2.1 mL) was added dropwise. The reaction mixture was heated to reflux, and then KOCN (40 mmol, 3.24 g) was added portionwise. The reaction mixture was refluxed for 30 min and then cooled to r.t. The resulting precipitate was collected by filtration and recrystallized from EtOH.

1-Propylurea (2d)

White powder; yield: 3.45 g (89%); mp 109–110 °C (173–174 °C[43]).

1-(Cyclopropylmethyl)urea (2g)

Beige powder; yield: 3.81 g (88%); mp 122–124 °C (MeOH).

IR (KBr): 3416, 3217, 1657, 1605, 1547, 1359, 1310, 1145, 559 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.03–0.15 (m, 2 H, CH_2), 0.29–0.42 (m, 2 H, CH_2), 0,76–0.92 (m, 1 H, CH), 2.83 (t, ^3J = 6.1 Hz, 2 H, CH_2), 5.39 (s, 2 H, NH_2), 5.97 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 2.97 (CH_2), 11.47 (CH), 43.50 (CH_2), 158.71 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{10}N_2O$ + H: 115.0871; found: 115.0863

(8*S**,8a*S**)-8-Methoxytetrahydro-2*H*-imidazo[5,1-*b*][1,3]oxazine-6(7*H*)-one (6)

A mixture of **2i** (0.24 g, 20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), and H_2O (10 mL) was heated to 50–55 °C. Then NaOH (H_2O) was added dropwise until pH 10 was achieved by the reaction mixture, which was then stirred for 3 h. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), and 35% aq HCl (4.4 mL) were added to the reaction mixture. The precipitate was removed by filtration and washed with MeOH (5 mL). The filtrate was refluxed for 30 min. Then the reaction mixture was cooled to r.t. The reaction mixture was evaporated to dryness, then acetone (5 mL) was added, and the resulting precipitate of compound **6** was collected by filtration and air-dried.

White powder; yield: 0.31 g (9%); mp 164–166 °C (acetone).

IR (KBr): 3207, 3114, 2920, 1707, 1478, 1434, 1353, 1253, 1080, 953, 780, 679 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.31–1.41 (m, 1 H, CH_2), 1.44–1.62 (m, 1 H, CH_2), 2.96–3.10 (m, 1 H, CH_2), 3.20 (s, 3 H, Me), 3.64–3.77 (m, 2 H, CH_2), 3.89–3.98 (m, 1 H, CH_2), 4.44 (s, 1 H, CH), 4.79 (s, 1 H, CH), 8.02 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.62, 37.48, 65.26 (CH_2), 53.38 (Me), 85.67, 87.58 (CH–CH), 159.03 (C=O).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_{12}N_2O_3$ + Na: 195.0740; found: 195.0737.

X-ray Diffraction

X-ray diffraction data for **1a**,**b**,**d**,**j** were collected at 120 K on a Bruker APEX2 DUO CCD diffractometer, using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Using Olex2,[44] the structures were solved with the ShelXT[45] structure solution program using intrinsic phasing and refined against F^2 in the anisotropic-isotropic approximation with the olex2.refine[46] refinement package using least-squares minimization. The hydrogen atoms of NH and OH groups were found in the difference Fourier synthesis, the positions of other hydrogen atoms were calculated, and they all were refined in the isotropic approximation within the riding model. Crystal data and structure refinement parameters are given in Table S1 (SI). CCDC 1992118, 1992119, 1992120, and 1992121 (**1a**, **1b**, **1d**, and **1j**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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Supporting Information

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