Thiohydantoins: Selective N- and S-Functionalization for Liebeskind–Srogl Reaction Study

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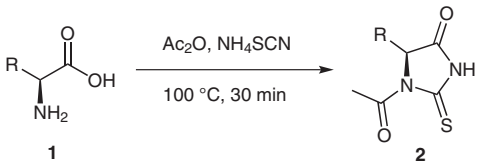
Abstract: Thiohydantoins formed by the Schlack–Kumpf protocol were selectively functionalized at the nitrogen, sulfur, or carbon atom to test the Liebeskind–Srogl reaction possibilities.

Key words: heterocycles, palladium, cross-coupling, amino acids, sulfur

2-Thiohydantoins are simple heterocycles obtained through condensation of an amino acid with a source of thiocyanate.[1] One of the earliest methods of synthesis is the Schlack–Kumpf protocol.[2] Since then numerous methods have been developed to prepare 2-thiohydantoins: reaction of an α-amino acid with ammonium thiocyanate under acetic anhydride activation or coupling of an isothiocyanate with an α-amino acid have been the most popular conditions applied to synthesize 2-thiohydantoins.[3] Some other methods of preparation have been developed, for example, the condensation of thiourea with α-amino acids[4] or with α-halo acids,[5] or the condensation of 1,1′-thiocarbonyldiimidazole with α-amino amides.[6] All of these procedures have been applied in combinatorial chemistry[7] and also explored on carbohydrate templates.[8] Considering the good accessibility to 2-thiohydantoins, it is surprising that the chemistry of this heterocyclic system has been so little explored.[9] In the present paper, we have reconsidered the synthesis of some thiohydantoins using the Burgess-modified protocol of the Schlack–Kumpf reaction and explored the reactivity of the newly formed thiohydantoins.[10]

The conditions developed by Reyes and Burgess – ammonium thiocyanate in acetic anhydride at 100 °C for 30 minutes – were applied to nine α-amino acids (Scheme 1) and the results are reported in Table 1. As expected, the yields range from satisfactory (Table 1, entries 1–4) to mediocre or poor when the side chain bears a protic function, in which case concomitant acetylation takes place. The stability of the amide function formed in situ allowed formation of **2e** in a reasonable yield of 51% (entry 5). In contrast, the acetoxyphenyl side chain in **2f** or the thioacetate in **2g** rendered purification of the thiohydantoins difficult, thus leading to poor yields (entries 6 and 7). From L-serine, only the *exo*-methylene derivative **2h** resulting from elimination could be isolated in low yield (entry 8). L-Aspartic acid was reacted as its γ-methyl ester (entry 9) and gave a reasonable yield of thiohydantoin **2i**.



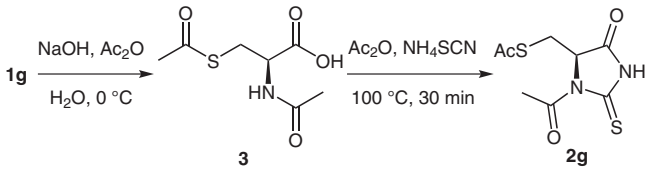
1 2

Scheme 1 Conditions used for the synthesis of thiohydantoins

Table 1 Preparation of Thiohydantoins **2** from α-Amino Acids **1**

Entry	α-Amino acid **1**, R	Thiohydantoin **2**, R	Yield (%)
1	Gly **1a**, H	**2a**, H	68
2	L-Phe **1b**, $PhCH_2$	**2b**, $PhCH_2$	76
3	L-Trp **1c**, 3-indolylCH_2	**2c**, 3-indolylCH_2	72
4	L-Met **1d**, $MeS(CH_2)_2$	**2d**, $MeS(CH_2)_2$	76
5	L-Lys **1e**, $H_2N(CH_2)_4$	**2e**, $AcNH(CH_2)_4$	51
6	L-Tyr **1f**, 4-$HOC_6H_4CH_2$	**2f**, $AcOC_6H_4CH_2$	19
7	L-Cys **1g**, $HSCH_2$	**2g**, $AcSCH_2$	20
8	L-Ser **1h**, $HOCH_2$	**2h**, H_2C=	7
9	L-Asp **1i**, MeO_2CCH_2	**2i**, MeO_2CCH_2	53

Thus the Burgess modified process proved efficient with amino acids devoid of side chain functionality. Better results could be attained with priorly protected side chains. For example, L-cysteine was acetylated on both the amino and the thiol groups[11] to afford the N,S-diacetylated α-amino acid **3**, which could be further converted into thiohydantoin **2g** in 73% yield (Scheme 2).



Scheme 2 Preparation of **2g** from N,S-diacetylated cysteine

Some of the thiohydantoins prepared were submitted to chemical tests with a view to explore the reactivity of the nucleophilic sites. S-Alkylation was first studied on the

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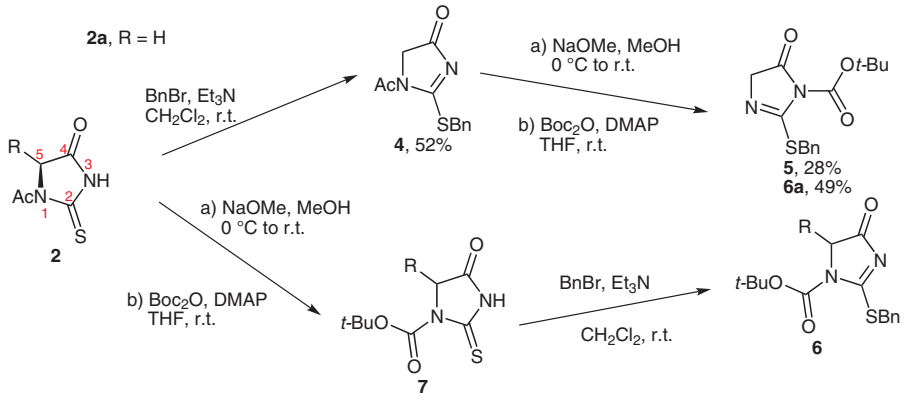


Scheme 3 N-Protection of thiohydantoins; for yields, see Table 2

thiohydantoin **2a**, which was reacted under previously established conditions to afford the selectively S-benzylated derivative **4** in 52% yield (Scheme 3) and was subsequently N-protected with a *tert*-butoxycarbonyl group in 77% yield.[12] All attempts to reach selective Boc introduction either on N-1 or N-3 were not successful, but the mixture of regioisomers could be separated by chromatography to afford **5** and **6a** in 28% and 49% yield, respectively. Modifications of the reaction sequence were devised in order to select more efficiently the N-protection site (Scheme 3).

An exchange of acyl protections of N-1 was performed on **2a** through base-induced deacetylation, then *N*-*tert*-butoxycarbonylation to afford thiohydantoin **7a** in very good yield. The S-benzylated derivative **6a** was also produced more efficiently under the same reaction conditions (Scheme 3). Considering the efficiency of this two-step reaction sequence, it was extended to thiohydantoins **2b**, **2e**, **2g**, and **2i** (Table 2).

The efficiency of the above three-step sequence was attested by the yields obtained and the selectivity observed for the nitrogen protection. The case of the L-Cys-derived thiohydantoin **2g** was particular, because standard methanolysis conditions caused full N- and S-deacetylation of the thiohydantoin. Selective N-deacetylation was experienced with moderate yields using catalytic hydrazine acetate as base. In other respects, S-methylation of the Boc-protected intermediate **7b** using iodomethane under similar conditions was performed to provide an 80% yield of **6j**, the S-methyl analogue of **6b**.

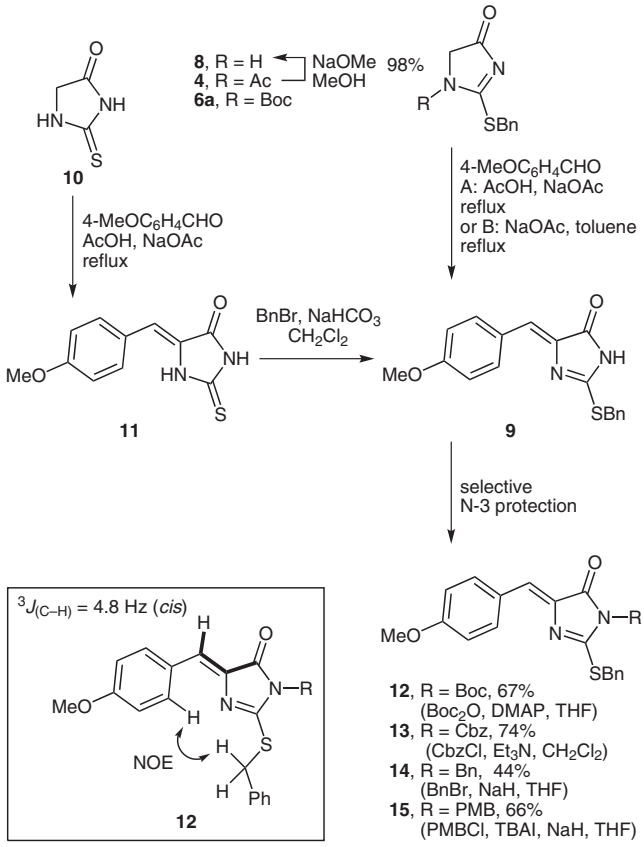
Our interest in this study was centered on the Liebeskind–Srogl coupling reaction using the ability of the benzylsulfanyl moiety.[13] Previous results from our lab have shown on small heterocycles an efficient C–C bond formation using this methodology.[14] We have also experienced the variability of these coupling reactions depending on the starting sulfur precursor – aromatic or nonaromatic, thioether- or thione-type.[14a] It was therefore decided to prepare some *exo*-methylenic substrates **9**, **11**–**15** in which all carbons in the heterocycle are sp^2-hybridized (Scheme 4).

Knoevenagel condensation of aldehydes on thiohydantoins is a well-known process used to generate libraries of pharmaceutical compounds.[15] Direct condensation was explored with N-protected compounds **4** and **6a**, together with unprotected **8** resulting from deacetylation of **4** (Scheme 4). Two protocols have been used: under conditions A, compound **9** was obtained, respectively, in 83% from **4**, 71% from **6a**, and 56% from **8**; under conditions B, the yield of **9** was much lower; 34% from **4**, 42% from **6a**, and 40% from **8**, respectively. From this comparative set of experiments it appeared that whatever the conditions (A or B) used, neither the *N*-acetyl nor the *N*-Boc protecting groups could be stable towards the severe conditions applied for the condensation. Surprisingly, the best yield from the *N*-acetyl derivative **4** was obtained under protic conditions A. Compound **9** could also be prepared following an alternative route. Nearly quantitative deacetylation of **2a** (Table 2) delivered the 2-thiohydantoin **10**, which was converted through Knoevenagel condensation into compound **11**.[16] Final S-benzylation under

Table 2 Selective Functionalization of Thiohydantoins **2**

Entry	Side chain, R	Deacetylation	Boc protection	S-Benzylation	Overall yield (%)
1	Gly **2a**, H	98%	94% (**7a**)	81% (**6a**)	75
2	L-Phe **2b**, $PhCH_2$	87%	96% (**7b**)	86% (**6b**)	72
3	L-Lys **2e**, $H_2N(CH_2)_4$	80%	99% (**7e**)	81% (**6e**)	64
4	L-Cys **2g**, $AcSCH_2$	46%[a]	73% (**7g**)	–	–
5	L-Asp **2i**, MeO_2CCH_2	96%	88% (**7i**)	98% (**6i**)	83

[a] Deacetylation with hydrazine acetate.



Scheme 4 Knoevenagel condensation

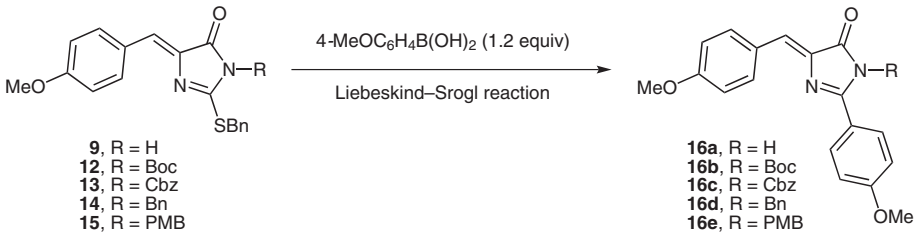
standard conditions afforded **9** in an excellent 91% yield over three steps. Protection at N-3 was performed with four different groups: carbamates **12** and **13** were obtained in 67% and 74% yield, respectively. *N*-Arylalkyl derivatives **14** and **15** were produced in somewhat lower yield, 44% and 66%, respectively. Nitrogen substitution as well as configuration of the alkenyl moiety in **12** was ascertained by using HMBC NMR experiments, which show the alkenyl proton H-6 to be coupled with the carbonyl C-4 with a *J* value of 4.8 Hz indicating a *cis* relationship.[17] Further NOESY experiments clearly indicated the proximity of the benzylic protons to the 4-methoxyphenyl moiety. These combined data indicate both the location of the N-protecting group and the configuration of the double bond, thus adding more understanding of the observed instability of protecting groups under Knoevenagel conditions and of the N-3 selectivity in protection processes.

The Liebeskind–Srogl reaction was explored on the modified thiohydantoins **2b**, **6b**, **6i**, **7b**, and **10**–**15**. Whatever the conditions used for the chiral substrates **2b**, **6b**, **6i**, and **7b**, no Suzuki coupling was observed with 4-methoxyphenylboronic acid: changing the solvent (THF, DMF) or the reaction conditions (thermal or microwave activation) brought no improvement. On the contrary, the *exo*-methylenic derivatives followed a coupling behavior comparable to previous results obtained with an analogous molecule.[18]

On our model structure, the benzylsulfanyl thiohydantoin **12**, the first conditions proved disappointing (Scheme 5, Table 3). The deprotected compound **16a** was isolated in very low yields (Table 3, entries 1–4), instead of the expected coupled product **16b**. Changing the solvent (THF or DMF) or the activation process (microwave or heating), did not change much the yields (5 to 9%) of the deprotected compound. Focusing on the nonprotected molecule **10** and applying the same conditions (entries 5, 7, 8) gave some improvement. The microwave conditions in DMF gave an encouraging 35% yield.

Taking into account the possibility of some negative effect resulting from the unprotected N-3 position, the N-benzylated thiohydantoin **14** was tested under similar conditions (entries 9–12). In this four set of reactions, THF proved more efficient than DMF, while microwave or thermal activation gave similar results. At this stage, entry 11 would represent the set of standard conditions. We have further tested some other palladium catalysts (entries 13–17) without significant changes in the efficiency of the reaction and yields ranging from 63% with Pd_2dba_3 (entry 13) to 14% with $PdCl_2/Ph_3P$ (entry 16). Further exploration of the coupling reaction called for changing the source of copper (entry 18), increasing the amount of boronic acid to 2.2 equivalent (entry 19) or adding an inorganic base (entry 20). However, none of these modifications resulted in significant yield improvement. As the moderate yields observed throughout could stand as a consequence of some inactivation of the catalytic cycle, the amount of palladium catalyst was increased (entries 21, 22) albeit without significant change.

Applying the latter conditions of higher palladium ratio on the 4-methoxybenzyl derivative **15** (entries 23–25) did seem to improve the yield as compared with the benzyl derivative **14**. A final assay (entry 26) was performed with the *N*-benzyloxycarbonyl-protected substrate **13**, which was converted in 50% yield into **16c**, thus showing the carbamate protection to be able to stand the reaction conditions.



Scheme 5 Liebeskind–Srogl reaction

From the above results, the Liebeskind–Srogl reaction proved to be moderately efficient on 2-alkylsulfanylimidazolones bearing an sp^2 C-5 atom while under the same conditions, analogue substrates with an sp^3-hybridized C-5 proved surprisingly unreactive.

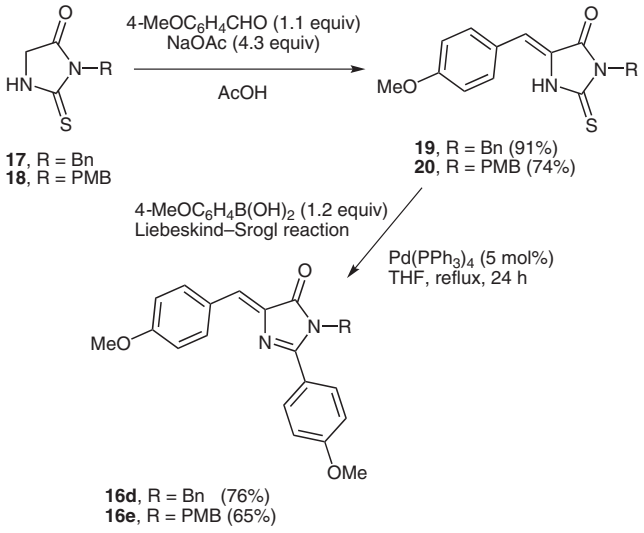
Recent approaches of the Liebeskind–Srogl reaction emphasized the direct reactivity of thionocarboxamido derivatives.[14a,19] Previous studies have shown that direct coupling could be effected on both heterocyclic types, aromatic and nonaromatic, albeit slightly less efficiently in the latter case. We were therefore interested in testing the direct coupling process on a thiohydantoin. To perform such a test, a free N-1/protected N-3 thiohydantoin was needed. The protocol described in Scheme 4 being inappropriate to achieve selective N-3-alkylation, we used the Edman condensation of benzyl isothiocyanate or 4-methoxybenzyl isothiocyanate with glycine methyl ester to prepare thiohydantoins **17** and **18**. Through Knoevenagel condensation, the model substrates **19** and **20** were obtained in good yield and further reacted with 4-methoxyphenylboronic acid under Liebeskind–Srogl conditions (Scheme 6). We were pleased to observe that these

Table 3 Optimization of Cross-Coupling Reactions[a]

Entry	Alkyl sulfanyl	Solvent (conditions)	Pd source	Cu source (equiv)	Time	Product (yield)
1	**12**	THF (60 °C, MW)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	1 h	**16a** (5%)
2	**12**	DMF (130 °C, MW)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	1 h	**16a** (7%)
3	**12**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16a** (6%)
4	**12**	DMF (130 °C)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16a** (9%)
5	**9**	THF (60 °C, MW)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	1 h	**16a** (9%)
6	**9**	DMF (130 °C, MW)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	1 h	**16a** (36%)
7	**9**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16a** (10%)
8	**9**	DMF (130 °C)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16a** (11%)
9	**14**	THF (60 °C, MW)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	1 h	**16d** (45%)
10	**14**	DMF (130 °C, MW)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	1 h	**16d** (31%)
11	**14**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16d** (51%)
12	**14**	DMF (130 °C)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16d** (12%)
13	**14**	THF (reflux)	Pd_2dba_3 (5%)	CuTC (3 equiv)	24 h	**16d** (63%)
14	**14**	THF (reflux)	Pd_2dba_3 (5%)/Ph_3P (10%)	CuTC (3 equiv)	24 h	**16d** (53%)
15	**14**	THF (reflux)	Pd_2dba_3 (5%)/TFP (10%)[b]	CuTC (3 equiv)	24 h	**16d** (61%)
16	**14**	THF (reflux)	Pd_2Cl_2 (5%)/ Ph_3P (10%)	CuTC (3 equiv)	24 h	**16d** (14%)
17	**14**	THF (reflux)	$Pd_2(OAc)_2$ (5%)/Ph_3P (10%)	CuTC (3 equiv)	24 h	**16d** (52%)
18	**14**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuMeSal (2.2 equiv)	24 h	**16d** (47%)
19	**14**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16d** (55%)[b]
20	**14**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16d** (40%)[c]
21	**14**	THF (reflux)	$Pd(PPh_3)_4$ (10%)	CuTC (3 equiv)	24 h	**16d** (51%)
22	**14**	THF (reflux)	$Pd(PPh_3)_4$ (2 × 5%)	CuTC (3 equiv)	24 h	**16d** (52%)
23	**15**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16e** (47%)
24	**15**	THF (reflux)	$Pd(PPh_3)_4$ (2 × 5%)	CuTC (3 equiv)	24h	**16e** (52%)
25	**15**	THF (reflux)	$Pd(PPh_3)_4$ (10%)	CuTC (3 equiv)	24 h	**16e** (61%)
26	**13**	THF (reflux)	$Pd(PPh_3)_4$ (5%)	CuTC (3 equiv)	24 h	**16c** (50%)

[a] Pd_2dba_3: tris(dibenzylideneacetone)dipalladium(0); CuTC: copper(I) thiophene-2-carboxylate; CuMeSal: copper(I) 3-methylsalicylate; TFP: tris 2-furylphosphine.
[b] Methoxyphenylboronic acid used: 2.2 equiv.
[c] Na_2CO_3 (1.2 equiv) was added.

thionocarboxamido derivatives proved more efficient than their benzylsulfanyl counterparts, with 76% coupling yield for the benzyl derivative **16d** and 65% yield for the 4-methoxybenzyl derivative **16e** .



Scheme 6 Direct coupling on thiohydantoins

In conclusion, the Schlack–Kumpf condensation gave access to selectively functionalized thiohydantoins derived from various amino acids. The Liebeskind–Srogl reaction needs a sp^2 hybridation at the C-5 atom. Indeed, after a Knoevenagel condensation on C-5, the cross coupling reaction on the 2-alkylsulfanyl gave reasonable yields of the C–C bond formation (up to 62%). A direct cross-coupling on the 2-thione derivatives (obtained from the Edman degradation method) gave a more efficient palladium cross-coupling (76%). Further explorations on this latter approach and its potential will be published in due course.

The reactions requiring anhydrous conditions were performed in oven-dried glassware with anhydrous solvents under argon atmosphere. CH_2Cl_2 was distilled over P_2O_5, THF was distilled in the presence of Na/benzophenone. Toluene was distilled over CaH_2. DMF (HPLC) was dried over MS 4 Å and MeOH (HPLC) over MS 3 Å. Most reagents were used as obtained from commercial suppliers (Acros, Aldrich, Lancaster, or Apollo). Copper(I) 3-methylsalicylate (CuMeSal) and copper(I) thiophene-2-carboxylate (CuTC) were prepared as described by Liebeskind.[20] Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. Analytical TLC was performed on Merck Silica gel 60 F254 precoated plates. Visualization of the compounds was made by UV light (254 nm) and by staining either with a 1% aq $KMnO_4$ or with 5% phosphomolybdic acid followed by heating. Flash column chromatography was carried out using Merck Silica gel 60N (spherical, neutral, 40–63 μm) under N_2 pressure. NMR spectra were recorded on 400 MHz Bruker Avance 2 or 250 MHz Bruker Avance DPX250 spectrometers using TMS as the internal standard. Chemical shifts are reported in parts per million (ppm, δ units). Coupling constants (*J*) are expressed in hertz (Hz); standard abbreviations are used for denoting signal multiplicity. Mass spectra were recorded with a Perkin-Elmer Sciex API 300 spectrometer for negative (ISN) and positive (ISP) electrospray ionization. High-resolution mass spectra (HRMS) were recorded with a TOF spectrometer in electrospray ionization (ESI) mode or in chemical ionization (CI) mode. IR spectra were recorded on Thermo-Nicolet AVATAR 320 AEK0200713. Melting points were measured using a Thermo Scientific 9200 capillary apparatus and are uncorrected. Optical rotations were recorded at 20 °C using a Perkin-Elmer 341 polarimeter (path length 1 dm).

Thiohydantoin Formation;[21] General Procedure A

In a round-bottom flask, the amino acid **1** (1 equiv) and NH_4SCN (1 equiv) were mixed in Ac_2O (6 equiv). The resulting mixture was heated at 100 °C for 30 min in an oil bath, by which time all solids dissolved. The reaction was then quenched with ice and H_2O (30 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the crude product purified by column chromatography on silica gel (Table 1).

1-Acetyl-2-thioxoimidazolidin-4-one (2a)[10]

[584-26-9]

Glycine (5.0 g, 66.6 mmol) was used to prepare **2a**. The reaction mixture was poured into an ice/H_2O mixture (60 mL) and stored in a freezer overnight. The resulting orange solid was filtered, washed with cold H_2O (15 mL), and dried under vacuum to afford **2a** as an orange solid; yield: 7.18 g (68%); mp 167–169 °C (Lit.[10] mp 173–174 °C); R_f = 0.31 (PE–EtOAc, 7:3).

MS (IS): *m*/*z* = 181.0 $[M + Na]^+$.

Physical and spectral data matched those previously reported.[10]

(5*S*)-1-Acetyl-5-benzyl-2-thioxoimidazolidin-4-one (2b)[2a,10]

[182002-59-1]

L-Phenylalanine (2.0 g, 12.1 mmol) was used to prepare **2b**. Flash chromatographic purification (PE–EtOAc, 7:3) afforded the thiohydantoin **2b** as a yellow solid; yield: 2.28 g (76%); mp 166–168 °C (Lit.[10] mp 168–169 °C); $[\alpha]_D$ +23 (*c* 1.10, $CHCl_3$); R_f = 0.38 (PE–EtOAc, 7:3).

MS (IS): *m*/*z* = 245.0 $[M - C_2H_2O + K]^+$.

Physical and spectral data matched those previously reported.[10]

(5*S*)-1-Acetyl-5-(1*H*-indol-3-ylmethyl)-2-thioxoimidazolidin-4-one (2c)

[182002-62-6]

L-Tryptophan (500 mg, 2.45 mmol) was used to prepare **2c**. Flash chromatographic purification (PE–EtOAc, 7:3) afforded the thiohydantoin **2c** as a yellow solid; yield: 505 mg (75%); mp 177–179 °C (Lit.[2] mp 183–185 °C); $[\alpha]_D$ +69 (*c* 1.07, MeOH); R_f = 0.26 (PE–EtOAc, 7:3).

MS (IS): *m*/*z* = 246.0 $[M - C_2H_2O + H]^+$, 310.0 $[M + Na]^+$.

Physical and spectral data matched those previously reported.[2]

(5*S*)-1-Acetyl-5-[2-(methylsulfanyl)ethyl]-2-thioxoimidazolidin-4-one (2d)

[875782-19-9]

L-Methionine (500 mg, 3.35 mmol) was used to prepare **2d**. Flash chromatographic purification (PE–EtOAc, 7:3) afforded the thiohydantoin **2d** as a yellow solid; yield: 589 mg (76%); mp 99–101 °C (Lit.[20] mp 102–103 °C); $[\alpha]_D$ +43 (*c* 1.13, MeOH); R_f = 0.53 (PE–EtOAc, 7:3).

IR (neat): 3114.2 (NH), 1747.8 (C=O ring), 1678.0 (C=O Ac), 1454.2 (NC=S), 1213.5–1184.0 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 2.08 (s, 3 H, $NCOCH_3$), 2.49 (m, 2 × 2 H, H-6 and H-7), 2.83 (s, 3 H, SCH_3), 4.88 (dd, $J_{5,6a}$ = 3.4 Hz, $J_{5,6b}$ = 6.5 Hz, 1 H, H-5), 9.32 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 15.2 (SCH_3), 27.5 (CH_3, NAc), 28.4 (2 × CH_2, C-6 and C-7), 62.1 (C-5), 170,4 (C=O, NAc), 171.8 (C-4), 180.1 (C-2).

MS (IS): *m*/*z* = 213.0 [M – C_2H_2O + Na]$^+$.

HRMS-ES: *m*/*z* [M – C_2H_2O + H]$^+$ calcd for $C_6H_{11}N_2OS_2$: 191.03073; found: 191.03080; [M + H]$^+$ calcd for $C_8H_{13}N_2O_2S_2$: 233.04130; found: 233.04120; [M + Na]$^+$ calcd for $C_8H_{12}N_2O_2S_2$ + Na: 255.02324; found: 255.02328.

(5*S*)-5-(4-Acetamidobutyl)-1-acetyl-2-thioxoimidazolidin-4-one (2e)
[182153-42-0]

L-Lysine (500 mg, 3.40 mmol) was used to prepare **2e**. Flash chromatographic purification (CH_2Cl_2–MeOH, 95:5) afforded the thiohydantoin **2e** as a yellow solid; yield: 470 mg (51%); mp 132–134 °C (Lit.[2] mp 131–133 °C); $[\alpha]_D$ +42 (*c* 1.14, $CHCl_3$); R_f = 0.45 (CH_2Cl_2–MeOH, 95:5).

MS (IS): *m*/*z* = 272.0 [M + H]$^+$, 294.0 [M + Na].

Physical and spectral data matched those previously reported.[2]

(5*S*)-5-(4-Acetoxybenzyl)-1-acetyl-2-thioxoimidazolidin-4-one (2f)
[182002-68-2]

L-Tyrosine (500 mg, 2.76 mmol) was used to prepare **2f**. Flash chromatographic purification (PE–EtOAc, 6:4) afforded the thiohydantoin **2f** as a yellow solid; yield: 161 mg (22%); mp 134–136 °C (Lit.[2] mp 137–139 °C); $[\alpha]_D$ +34 (*c* 0.96, MeOH); R_f = 0.76 (PE–EtOAc, 1:1).

MS (IS): *m*/*z* = 307.0 [M + H]$^+$, 329.0 [M + Na].

Physical and spectral data matched those previously reported.[2]

(5*S*)-1-Acetyl-5-[(acetylsulfanyl)methyl]-2-thioxoimidazolidin-4-one (2g)
[182002-87-5]

L-Cysteine (1.00 g, 8.25 mmol) was used to prepare **2g**. Flash chromatographic purification (PE–EtOAc, 6:4) afforded the thiohydantoin **2g** as a yellow solid; yield: 0.42 g (20%); mp 137–139 °C (Lit.[2] mp 138–143 °C); $[\alpha]_D$ –1 (*c* 1.07, MeOH); R_f = 0.62 (PE–EtOAc, 1:1).

MS (IS): *m*/*z* = 227.0 [M – C_2H_2O + Na]$^+$, 269.0 [M + Na]$^+$.

Physical and spectral data matched those previously reported.[2]

1-Acetyl-5-methylidene-2-thioxoimidazolidin-4-one (2h)
L-Serine (1.0 g, 9.52 mmol) was used to prepare **2h**. Flash chromatographic purification (PE–EtOAc, 8:2) afforded the thiohydantoin **2h** as a white solid; yield: 109 mg (7%); mp 223–225 °C (dec.); R_f = 0.27 (PE–EtOAc, 8:2).

IR (neat): 3119.5 (NH), 1745.9 (C=O ring), 1679.1 (C=O Ac), 1458.2 (NC=S), 1199.6–1134.5 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 2.91 (s, 3 H, $NCOCH_3$), 5.95 (s, 1 H, H-6a), 6.49 (s, 1 H, H-6b), 9.02 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.0 (CH_3, NAc), 109.7 (C-6), 134.1 (C-5), 161.1 (C-4), 170.7 (C=O, NAc), 210.5 (C-2).

HRMS-ES: *m*/*z* [2 M + Na]$^+$ calcd for $C_{12}H_{12}N_4O_4S_2$ + Na: 363.01922; found: 363.01914; [3 M + H]$^+$ calcd for $C_{18}H_{19}N_6O_6S_3$: 511.05227; found: 511.05193; [3 M + NH_4]$^+$ calcd for $C_{18}H_{22}N_7O_6S_3$: 528.07882; found: 528.07878; [3 M + Na]$^+$ calcd for $C_{18}H_{18}N_6O_6S_3$ + Na: 533.03422; found: 533.03424.

(5*S*)-1-Acetyl-5-methoxycarbonylmethyl-2-thioxoimidazolidin-4-one (2i)
The γ-methyl ester of L-aspartic acid (500 mg, 3.40 mmol) was used to prepare **2i**. Flash chromatographic purification (PE–EtOAc, 7:3) afforded the thiohydantoin **2i** as a white solid; yield: 416 mg (53%); mp 119–122 °C; $[\alpha]_D$ +1 (*c* 1.02, MeOH); R_f = 0.68 (PE–EtOAc, 1:1).

IR (neat): 3124.8 (NH), 1765.8 (C=O ring), 1736.9 (C=O ester), 1675.6 (C=O Ac), 1461.1 (NC=S), 1209.4–1177.6 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 2.81 (s, 3 H, $NCOCH_3$), 3.11 (dd, $J_{6a,5}$ = 3.4 Hz, $J_{6a,6b}$ = 17.8 Hz, 1 H, H-6a), 3.43 (dd, $J_{6b,5}$ = 4.7 Hz, $J_{6a,6b}$ = 17.8 Hz, 1 H, H-6b), 3.69 (s, 3 H, CO_2CH_3), 4.84 (dd, $J_{5,6a}$ = 3.4 Hz, $J_{5,6b}$ = 4.7 Hz, 1 H, H-5), 9.51 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 27.5 (CH_3, NAc), 33.6 (C-6), 52.4 (CH_3 ester), 59.5 (C-5), 169.7 (C=O, NAc), 170.8 (C-4), 171.1 (C=O ester), 180.7 (C-2).

MS (IS): *m*/*z* = 253.0 [M + Na]$^+$.

HRMS-ES: *m*/*z* [M – C_2H_2O + H]$^+$ calcd for $C_6H_9N_2O_3S$: 189.03284; found: 189.03282; [M + Na]$^+$ calcd for $C_8H_{10}N_2O_4S$ + Na: 253.02535; found: 253.02556.

S-Benzylation; General Procedure B
The 2-thioxoimidazolidin-4-one derivative **2** (1 mmol, 1 equiv) was dissolved in CH_2Cl_2 (15 mL) under argon. Et_3N (4 equiv) and benzyl bromide (1.5 equiv) were added and the mixture was stirred for 2 h at r.t., after which the solution was concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

1-Acetyl-2-(benzylsulfanyl)-4,5-dihydro-1*H*-imidazol-4-one (4)
Following general procedure B, **2a** (4.00 g, 25.2 mmol, 1 equiv) was converted into the S-benzylated derivative. Flash chromatographic purification (PE–EtOAc, 7:3) afforded **4** as a yellow solid; yield: 3.19 g (51%); mp 149–151 °C; R_f = 0.26 (PE–EtOAc, 7:3).

IR (neat): 1730.7 (C=O ring), 1698.1 (C=O Ac), 1449.3 (NC=S), 1376.6 (C–S), 1226.3–1171.3 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 4.32 (s, 2 H, H-5), 4.41 (s, 2 H, CH_2Ph), 7.35 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 23.8 (CH_3, Ac), 37.9 (CH_2Ph,), 52.7 (C-5), 127.8, 128.7, 129.3 (CH_{arom}), 134.9 (C_{arom}), 166.9 (C=O, NAc), 182.0 (C-4), 184.9 (C-2).

MS (IS): *m*/*z* = 249.0 [M + H]$^+$, 271.0 [M + Na]$^+$.

HRMS-ES: *m*/*z* [M – C_2H_2O + H]$^+$ calcd for $C_{10}H_{11}N_2OS$: 207.05866; found: 207.05871; [M – C_2H_2O + Na]$^+$ calcd for $C_{10}H_{10}N_2OS$ + Na: 229.04060; found: 229.04048; [M + H]$^+$ calcd for $C_{12}H_{13}N_2O_2S$: 249.06922; found: 249.06933; [M + Na]$^+$ calcd for $C_{12}H_{12}N_2O_2S$ + Na: 271.05117; found: 271.05120.

N-Deacetylation; General Procedure C
The 1-acetyl-2-thiohydantoin (1 mmol, 1 equiv) was dissolved in anhyd MeOH (MS 3 Å, 10 mL) under argon. The solution was cooled in an ice-salt bath, then Na metal was added at 0 °C until the pH value reached 9–10. The resulting solution was stirred for 2 h at r.t., then quenched with Amberlite IR120 H$^+$ until neutral pH, after which the solution was concentrated in vacuo. The crude product was purified on silica gel column chromatography.

***tert*-Butoxycarbonyl Protection; General Procedure D**
The 2-thiohydantoin (1 mmol, 1 equiv) was dissolved in THF (20 mL) under argon atmosphere. $(Boc)_2O$ (1 equiv) and DMAP (0.1 equiv) were added and the mixture was stirred for 2 h at r.t. after which the solution was concentrated in vacuo. The crude product was purified on silica gel column chromatography.

Regioselective *N*-*tert*-Butoxycarbonylation of 2-(Benzylsulfanyl)-4,5-dihydro-1*H*-imidazol-4-one (8)

Compound **8** (100 mg, 0.48 mmol, 1 equiv) resulting from the deacetylation of **4** (general procedure C) was submitted to *tert*-butoxycarbonylation according to general procedure D. Flash chromatographic purification (PE–EtOAc, 7:3) allowed the separation of 2 regioisomers **5** and **6a**.

2-(Benzylsulfanyl)-1-*tert*-butoxycarbonyl-4,5-dihydro-1*H*-imidazol-5-one (5)

Yield: 42 mg (28%); yellow solid; mp 133–135 °C; R_f = 0.77 (PE–EtOAc, 1:1).

IR (neat): 1789.6 (C=O ring), 1730.5 (C=O Boc), 1574.5 (NC–S), 1308.4–1151.0 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 1.47 (s, 9 H, *t*-C_4H_9), 4.12 (s, 2 H, H-4), 4.17 (s, 2 H, CH_2Ph), 7.21 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 27.7 (CH_3, *t*-C_4H_9), 35.2 (CH_2Ph), 59.0 (C-4), 85.9 (C_{IV} *t*-C_4H_9), 127.3, 128.4, 129.1 (CH_{arom}), 135.8 (C_{arom}), 147.2 (C=O, Boc), 160.1 (C-5), 174.9 (C-2).

MS (IS): *m*/*z* = 307.0 $[M + H]^+$, 329.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M - C_5H_8O_2 + H]^+$ calcd for $C_{10}H_{11}N_2OS$: 207.05866; found: 207.05877; $[M - C_5H_8O_2 + Na]^+$ calcd for $C_{10}H_{10}N_2OS$ + Na: 229.04060; found: 229.04066; $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3S$: 307.11109; found: 307.11098; $[M + Na]^+$ calcd for $C_{15}H_{18}N_2O_3S$ + Na: 329.09303; found: 329.09312; $[2 M + Na]^+$ calcd for $C_{30}H_{36}N_4O_6S_2$ + Na: 635.19685; found: 635.19681.

2-(Benzylsulfanyl)-1-*tert*-butoxycarbonyl-4,5-dihydro-1*H*-imidazol-4-one (6a)

Yield: 72 mg (49%); brown solid; mp 124–126 °C; R_f = 0.55 (PE–EtOAc, 1:1).

IR (neat): 1716.2 (C=O ring), 1716.2 (C=O Boc), 1455.5 (NC–S), 1145.6–1255.4 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 1.53 (s, 9 H, *t*-C_4H_9), 4.23 (s, 2 H, H-5), 4.45 (s, 2 H, CH_2Ph), 7.33 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 28.0 (CH_3, *t*-C_4H_9), 37.3 (SCH_2), 52.6 (C-5), 85.6 (C_{IV} *t*-C_4H_9), 127.9, 128.7, 129.4 (CH_{arom}), 135.2 (C_{arom}), 148.2 (C=O, Boc), 182.0 (C-4), 184.9 (C-2).

MS (IS): *m*/*z* = 307.0 $[M + H]^+$, 329.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M - C_4H_8 + H]^+$ calcd for $C_{11}H_{11}N_2O_3S$: 251.04849; found: 251.04860; $[M - C_4H_8 + Na]^+$ calcd for $C_{11}H_{10}N_2O_3S$ + Na: 273.03043; found: 273.03045; $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3S$: 307.11109; found: 307.11123; $[M + Na]^+$ calcd for $C_{15}H_{18}N_2O_3S$ + Na: 329.09303; found: 329.09302.

Alternative Preparation of 2-(Benzylsulfanyl)-1-*tert*-butoxycarbonyl-4,5-dihydro-1*H*-imidazol-4-one (6a)

1-*tert*-Butoxycarbonyl-2-thioxoimidazolidin-4-one (**7a**; 3.00 g, 13.87 mmol, 1 equiv) was S-alkylated according to general procedure B. Flash chromatographic purification (PE–EtOAc, 7:3) afforded **6a** in 95% yield.

(5*S*)-5-Benzyl-2-(benzylsulfanyl)-1-*tert*-butoxycarbonyl-4,5-dihydro-1H-imidazol-4-one (6b)

5-Benzyl-1-*tert*-butoxycarbonyl-2-thioxoimidazolidin-4-one (**7b**; 240 mg, 0.78 mmol, 1 equiv) was S-alkylated according to general procedure B. Flash chromatographic purification (PE–EtOAc, 7:3) afforded compound **6b** as a yellow solid; yield: 283 mg (91%); mp 132–135 °C; $[\alpha]_D$ +2 (*c* 1.02, MeOH); R_f = 0.26 (PE–EtOAc, 7:3).

IR (neat): 1719.2 (C=O ring), 1719.2 (C=O Boc), 1436.9 (NC–S), 1265.5–1146.5 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 1.60 (s, 9 H, *t*-C_4H_9), 3.34 (dd, $J_{6a,5}$ = 2.7 Hz, $J_{6a,6b}$ = 13.8 Hz, 1 H, H-6a), 3.43(dd, $J_{6b,5}$ = 5.8 Hz, $J_{6a,6b}$ = 13.8 Hz, 1 H, H-6b), 4.21 (dd, $J_{7a,7b}$ = 13.4 Hz, 1 H, SCH_a), 4.27 (dd, $J_{7b,7a}$ = 13.4 Hz, 1 H, SCH_b), 4.53 (dd, $J_{5,6a}$ = 2.7 Hz, $J_{5,6b}$ = 5.8 Hz, 1 H, H-5), 7.18 (m, 10 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 28.1 (CH_3, *t*-C_4H_9), 36.1 (C-6), 37.5 (SCH_2), 64.3 (C-5), 85.7 (C_{IV} *t*-C_4H_9), 127.4, 127.7, 128.5, 128.6, 129.2, 129.4 (CH_{arom}), 133.6, 135.3 (C_{arom}), 148.3 (C=O, Boc), 184.7 (C-4), 184.9 (C-2).

MS (IS): *m*/*z* = 397.0 $[M + H]^+$, 419.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M - C_4H_8 + H]^+$ calcd for $C_{18}H_{17}N_2O_3S$: 341.09544; found: 341.09560; $[M - C_4H_8 + Na]^+$ calcd for $C_{18}H_{16}N_2O_3S$ + Na: 363.07738; found: 363.07738; $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_3S$: 397.15804; found: 397.15813; $[M + Na]^+$ calcd for $C_{22}H_{24}N_2O_3S$ + Na: 419.13998; found: 419.14014.

(5*S*)-5-(4-Acetamidobutyl)-2-(benzylsulfanyl)-1-*tert*-butoxycarbonyl-4,5-dihydro-1*H*-imidazol-4-one (6e)

5-(4-Acetamidobutyl)-1-*tert*-butoxycarbonyl-2-thioxoimidazolidin-4-one (**7e**; 150 mg, 0.46 mmol, 1 equiv) was S-alkylated following general procedure B. Flash chromatographic purification (EtOAc) afforded compound **6e** as a colorless syrup; yield: 150 mg (78%); $[\alpha]_D$ –1 (*c* 0.5, $CHCl_3$); R_f = 0.40 (CH_2Cl_2–MeOH, 9:1).

IR (neat): 3304.6 (NH lysine), 1720.2 (C=O ring), 1652.3 (C=O Ac), 1652.3 (C=O Boc), 1438.8 (NC–S), 1241.6–1145.0 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 1.29 (m, 2 H, H-7), 1.49 (m, 2 H, H-8), 1.54 (s, 9 H, *t*-C_4H_9), 1.96 (s, 3 H, $NCOCH_3$ Lys), 2.06 (m, 2 H, H-6), 3.22 (qd, $J_{9-8/9-NH}$ = 6.9 Hz, $J_{9a,9b}$ = 2.9 Hz, 2 H, H-9), 4.31 (t, $J_{5,6}$ = 4.9 Hz, 1 H, H-5), 4.43 (dd, $J_{10a,10b}$ = 13.2 Hz, 1 H, CH_aPh), 4,47 (dd, $J_{10b,10a}$ = 13.2 Hz, 1 H, CH_bPh), 5.63 (br, 1 H, NH Lys), 7.33 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 20.3 (C-7), 23.3 (CH_3, NAc Lys), 28.0 (CH_3, *t*-C_4H_9), 28.9 (C-8), 29.7 (C-6), 37.9 (SCH_2), 39.1 (C-9), 63.2 (C-5), 85.7 (C_{IV} *t*-C_4H_9), 127.9, 128.7, 129.4 (CH_{arom}), 135.0 (C_{arom}), 148.3 (C=O, Boc), 170.1 (C=O, NAc Lys), 184.9 (C-4), 185.4 (C-2).

MS (IS): *m*/*z* = 420.0 $[M + H]^+$, 442.5 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M - C_5H_8O_2 + H]^+$ calcd for $C_{16}H_{22}N_3O_2S$: 320.14272; found: 320.14279; $[M + H]^+$ calcd for $C_{21}H_{30}N_3O_4S$: 420.19515; found: 420.19502; $[M + Na]^+$ calcd for $C_{21}H_{29}N_3O_4S$ + Na: 442.17710; found: 442.17606.

(5*S*)-2-(Benzylsulfanyl)-1-*tert*-butoxycarbonyl-5-(methoxycarbonylmethyl)-4,5-dihydro-1*H*-imidazol-4-one (6i)

5-(Methoxycarbonylmethyl)-1-*tert*-butoxycarbonyl-2-thioxoimidazolidin-4-one (**7i**; 50.0 mg, 0.17 mmol, 1 equiv) was S-alkylated following general procedure B. Flash chromatographic purification (CH_2Cl_2–MeOH, 95:5) afforded compound **6i** as a yellow solid; yield: 63 mg (98%); mp 142–144 °C; $[\alpha]_D$ +1 (*c* 1.10 MeOH); R_f = 0.54 (CH_2Cl_2–MeOH, 95:5).

IR (neat): 1723.0 (C=O ring), 1723.0 (C=O ester), 1723.0 (C=O Boc), 1450.2 (NC–S), 1256.2–1141.7 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 1.53 (s, 9 H, *t*-C_4H_9), 3.08 (dd, $J_{6a,5}$ = 3.7 Hz, $J_{6a,6b}$ = 16.8 Hz, 1 H, H-6a), 3.18 (dd, $J_{6b,5}$ = 5.3 Hz, $J_{6a,6b}$ = 16.8 Hz, 1 H, H-6b), 3.65 (s, 3 H, CO_2CH_3), 4.45 (dd, $J_{5,6a}$ = 3.7 Hz, $J_{5,6b}$ = 5.3 Hz, 1 H, H-5), 4.48 (s, 2 H, CH_2Ph), 7.36 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 27.9 (CH_3, *t*-C_4H_9), 34.8 (C-6), 37,9 (SCH_2), 52.1 (CH_3 ester), 59.4 (C-5), 85,1 (C_{IV} *t*-C_4H_9), 127.8, 128.7, 129.4 (CH_{arom}), 135.2 (C_{arom}), 148.2 (C=O, Boc), 169.1 (C=O ester), 184.0 (C-4), 185.1 (C-2).

MS (IS): *m*/*z* = 379.0 $[M + H]^+$, 401.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* calcd for $[M - C_5H_8O_2 + H]^+$ calcd for $C_{13}H_{15}N_2O_3S$: 279.07979; found: 279.08004; $[M - C_4H_8 + H]^+$ cal-

cd for $C_{14}H_{15}N_2O_5S$: 323.06962; found: 323.06963; [M – C_4H_8 + Na]$^+$ calcd for $C_{14}H_{14}N_2O_5S$ + Na: 345.05156; found: 345.05157; [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_5S$: 379.13222; found: 379.13223; [M + Na]$^+$ calcd for $C_{18}H_{22}N_2O_5S$ + Na: 401.11416; found: 401.11410.

(5*S*)-5-Benzyl-1-*tert*-butoxycarbonyl-2-(methylsulfanyl)-4,5-dihydro-1*H*-imidazol-4-one (6j)

To a solution of **7b** (50 mg, 0.16 mmol, 1 equiv) in CH_2Cl_2 (5 mL) placed under argon were added Et_3N (0.65 mmol, 4 equiv) and MeI (0.56 mmol, 3.5 equiv). The mixture was stirred for 30 min at r.t., after which the solution was concentrated in vacuo. Flash chromatographic purification (PE–EtOAc, 7:3) afforded compound **6j** as a white solid; yield: 42 mg (82%); mp 108–111 °C; $[\alpha]_D$ –1 (*c* 0.95, $CHCl_3$); R_f = 0.50 (PE–EtOAc, 1:1).

IR (neat): 1718.5 (C=O ring), 1718.5 (C=O Boc), 1455.2 (NC=S), 1258.3–1141.4 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 9 H, *t*-C_4H_9), 2.38 (s, 3 H, SCH_3), 3.33 (dd, $J_{6a,5}$ = 2.7 Hz, $J_{6a,6b}$ = 13.8 Hz, 1 H, H-6a), 3.43 (dd, $J_{6b,5}$ = 5.9 Hz, $J_{6a,6b}$ = 13.8 Hz, 1 H, H-6b), 4.53 (dd, $J_{5,6a}$ = 2.7 Hz, $J_{5,6b}$ = 5.9 Hz, 1 H, H-5), 7.16 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 28.1 (CH_3, *t*-C_4H_9), 36.0 (C-6), 64.4 (C-5), 85.6 (C_{IV} *t*-C_4H_9), 127.3, 128.5, 129.3 (CH_{arom}), 133.7 (C_{arom}), 148.3 (C=O, Boc), 184.6 (C-4), 185.9 (C-2).

MS (IS): *m*/*z* = 321.5 [M + H]$^+$, 345.0 [M + Na]$^+$.

HRMS-ES: *m*/*z* [M – C_4H_8 + H]$^+$ calcd for $C_{12}H_{13}N_2O_3S$: 265.06414; found: 265.06428; [M – C_4H_8 + Na]$^+$ calcd for $C_{12}H_{12}N_2O_3S$ + Na: 287.04608; found: 287.04619; [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_3S$: 321.12674; found: 321.12656; [M + Na]$^+$ calcd for $C_{16}H_{20}N_2O_3S$ + Na: 343.10868; found: 343.10858.

1-*tert*-Butoxycarbonyl-2-thioxoimidazolidin-4-one (7a)

[1253964-00-9]

Compound **8** (2.00 g, 17.2 mmol) was *N*-*tert*-butoxycarbonylated according to general procedure D. Flash chromatographic purification (PE–EtOAc, 7:3) afforded **7a** as a yellow solid; yield: 3.53 g (95%); mp 145–146 °C; R_f = 0.68 (PE–EtOAc, 1:1).

IR (neat): 3227.4 (NH), 1750.3 (C=O ring), 1718.9 (C=O Boc), 1459.5 (NC=S), 1217.2–1144.0 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 1.56 (s, 9 H, *t*-C_4H_9), 4.41 (s, 2 H, H-5), 9.01 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 27.9 (CH_3, *t*-C_4H_9), 52.7 (C-5), 85.6 (C_{IV} *t*-C_4H_9), 148.3 (C=O, Boc), 168.2 (C-4), 178.5 (C-2).

MS (IS): *m*/*z* = 217.0 [M + H]$^+$, 239.0 [M + Na]$^+$.

HRMS-ES: *m*/*z* [M – $C_5H_8O_2$ + Na]$^+$ calcd for $C_3H_4N_2OS$ + Na: 138.99365; found: 138.99362; [M – C_4H_8 + H]$^+$ calcd for $C_4H_5N_2O_3S$: 161.00154; found: 161.00149, [M + Na]$^+$ calcd for $C_8H_{12}N_2O_3S$ + Na: 239.04608; found: 239.04617.

(5*S*)-5-Benzyl-1-*tert*-butoxycarbonyl-2-thioxoimidazolidin-4-one (7b)

5-Benzyl-2-thioxoimidazolidin-4-one (0.3 g, 1.45 mmol, 1 equiv) prepared (general procedure C) from **2b** was *N*-*tert*-butoxycarbonylated according to general procedure D. Flash chromatographic purification (PE–EtOAc, 7:3) afforded **7b** as a yellow solid; yield: 426 mg (96%); mp 98–100 °C; $[\alpha]_D$ +1 (*c* 1.00 MeOH); R_f = 0.30 (PE–EtOAc, 1:1).

IR (neat): 3245.2 (NH), 1739.3 (C=O ring), 1739.3 (C=O Boc), 1438.5 (NC=S), 1223.6–1138.7 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 1.64 (s, 9 H, *t*-C_4H_9), 3.29 (dd, $J_{6a,5}$ = 2.8 Hz, $J_{6a,6b}$ = 14.1 Hz, 1 H, H-6a), 3.49 (dd, $J_{6b,5}$ = 5.7 Hz, $J_{6a,6b}$ = 14.1 Hz, 1 H, H-6b), 4.81 (dd, $J_{5,6a}$ = 2.8 Hz, $J_{5,6b}$ = 5.7 Hz, 1 H, H-5), 7.08 (m, 2 H, C_6H_5), 7.26 (m, 3 H, C_6H_5), 8.64 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 28.1 (CH_3, *t*-C_4H_9), 35.9 (C-6), 64.4 (C-5), 85.5 (C_{IV} *t*-C_4H_9), 127.8, 128.8, 129.5 (CH_{arom}), 132.9 (C_{arom}), 148.5 (C=O, Boc), 170.9 (C-4), 178.1 (C-2).

MS (IS): *m*/*z* = 307.0 [M + H]$^+$, 329.0 [M + Na]$^+$.

HRMS-ES: *m*/*z* [M – $C_5H_8O_2$ + H]$^+$ calcd for $C_{10}H_{11}N_2OS$: 207.05866; found: 207.05888; [M – $C_5H_8O_2$ + Na]$^+$ calcd for $C_{10}H_{10}N_2OS$ + Na: 229.04060; found: 229.04078; [M – C_4H_8 + H]$^+$ calcd for $C_{11}H_{11}N_2O_3S$: 251.04849; found: 251.04863; [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_3S$ + Na: 329.09303; found: 329.09333.

(5*S*)-5-(4-Acetamidobutyl)-1-*tert*-butoxycarbonyl-2-thioxoimidazolidin-4-one (7e)

5-(4-Acetamidobutyl)-2-thioxoimidazolidin-4-one (100 mg, 0.44 mmol, 1 equiv) prepared (general procedure C) from **2e** was *N*-*tert*-butoxycarbonylated according to general procedure D. Flash chromatographic purification (EtOAc) afforded **7e** as a colorless syrup; yield: 140 mg (97%); $[\alpha]_D$ –2 (*c* 0.8 $CHCl_3$); R_f = 0.20 (PE–EtOAc, 1:1).

IR (neat): 2931.0 (NH), 1744.8 (C=O ring), 1628.9 (C=O Boc), 1442.0 (NC=S), 1237.8–1144.9 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 1.36 (m, 4 H, H-7 and H-8), 1.56 (s, 9 H, *t*-C_4H_9), 1.98 (s, 3 H, $NCOCH_3$ Lys), 2.08 (m, 2 H, H-6), 3.23 (q, $J_{9\text{-NH}/9\text{-}8}$ = 6.5 Hz, 2 H, H-9), 4.56 (t, $J_{5,6}$ = 4.8 Hz, 1 H, H-5), 5,76 (t, $J_{NH,9}$ = 5,1 Hz, 1 H, NH Lys), 9.92 (br, 1 H, NH hydantoin).

^{13}C NMR ($CDCl_3$): δ = 20.5 (C-7), 23.3 (CH_3, NAc Lys), 28.0 (CH_3, *t*-C_4H_9), 29.0 (C-8), 30.1 (C-6), 39.2 (C-9), 63.2 (C-5), 85.4 (C_{IV} *t*-C_4H_9), 148.5 (C=O, Boc), 170.6 (C=O, NAc Lys), 172.0 (C-4), 179.2 (C-2).

MS (IS): *m*/*z* = 330.0 [M + H]$^+$, 352.0 [M + Na].

HRMS-ES: *m*/*z* [M – $C_5H_8O_2$ + H]$^+$ calcd for $C_9H_{16}N_3O_2S$: 230.09577; found: 230.09590; [M – $C_5H_8O_2$ + Na]$^+$ calcd for $C_9H_{15}N_3O_2S$ + Na: 252.07772; found: 252.07775; [M + Na]$^+$ calcd for $C_{14}H_{23}N_3O_4S$ + Na: 352.13080; found: 352.13035.

(5*S*)-5-[(Acetylsulfanyl)methyl]-1-*tert*-butoxycarbonyl-2-thioxoimidazolidin-4-one (7g)

5-[(Acetylsulfanyl)methyl]-2-thioxo-imidazolidin-4-one (50 mg, 0.24 mmol, 1 equiv) prepared (procedure C) from **2g** was *N*-*tert*-butoxycarbonylated according to general procedure D. Flash chromatographic purification (PE–EtOAc, 7:3) afforded **7g** as a yellow syrup; yield: 56 mg (76%); $[\alpha]_D$ +2 (*c* 0.66, $CHCl_3$); R_f = 0.62 (PE–EtOAc, 1:1).

IR (neat): 3262.1 (NH), 1752.9 (C=O ring), 1701.9 (C=O Boc), 1443.9 (NC=S), 1225.8–1139.9 cm^{-1} (C–N).

^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 9 H, *t*-C_4H_9), 2.35 (s, 3 H, $SCOCH_3$), 3.42 (d, $J_{6a,6b}$ = 12.6 Hz, 1 H, H-6a), 3.90 (d, $J_{6a,6b}$ = 12.6 Hz, 1 H, H-6b), 4.84 (s, 1 H, H-5), 8.92 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 27.9 (CH_3, *t*-C_4H_9), 28.9 (C-6), 30.5 (CH_3, SAc), 62.6 (C-5), 85.9 (C_{IV} *t*-C_4H_9), 169.8 (C=O, Boc), 178.3 (C-4), 193.2 (C=O, SAc), 201.3 (C-2).

MS (IS): *m*/*z* = 305.5 [M + H]$^+$, 327.0 [M + Na].

HRMS-ES: *m*/*z* [M – $C_5H_8O_2$ – C_2H_2O + H]$^+$ calcd for $C_4H_7N_2OS_2$: 162.99943; found: 169.99966; [M – $C_5H_8O_2$ + H]$^+$ calcd for $C_6H_9N_2O_2S_2$: 205.01000; found: 205.01027; [M – $C_5H_8O_2$ + Na]$^+$ calcd for $C_6H_8N_2O_2S_2$ + Na: 226.99194; found: 226.99212; [M + Na]$^+$ calcd for $C_{11}H_{16}N_2O_4S_2$ + Na: 327.04437; found: 327.04458.

(5*S*)-1-*tert*-Butoxycarbonyl-5-(methoxycarbonylmethyl)-2-thioxoimidazolidin-4-one (7i)

5-(Methoxycarbonylmethyl)-2-thioxoimidazolidin-4-one (60.0 mg, 0.32 mmol, 1 equiv) prepared (procedure C) from **2i** was *N*-*tert*-butoxycarbonylated according to general procedure D. Flash chromatographic purification (PE–EtOAc, 7:3) afforded **7i** as a yellow

solid; yield: 80.5 mg (87%); mp 127–128 °C; $[\alpha]_D$ +2 (*c* 1.06, $CHCl_3$); R_f = 0.57 (PE–EtOAc, 1:1).

IR (neat): 3256.4 (NH), 1768.4 (C=O ring), 1733.5 (C=O ester), 1694.2 (C=O Boc), 1454.9 (NC=S), 1214.2–1144.2 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 1.57 (s, 9 H, *t*-C_4H_9), 3.12 (dd, $J_{6a,5}$ = 3.2 Hz, $J_{6a,6b}$ = 17.2 Hz, 1 H, H-6a), 3.26 (dd, $J_{6b,5}$ = 5.2 Hz, $J_{6a,6b}$ = 17.2 Hz, 1 H, H-6b), 3.71 (s, 3 H, CO_2CH_3), 4.70 (dd, $J_{5,6a}$ = 3.2 Hz, $J_{5,6b}$ = 5.2 Hz, 1 H, H-5), 8.95 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 28.0 (CH_3, *t*-C_4H_9), 34.5 (C-6), 52.5 (CH_3 ester), 59.8 (C-5), 85.8 (C_{IV} *t*-C_4H_9), 148.5 (C=O, Boc), 169.0 (C-4), 170.6 (C=O ester), 178.8 (C-2).

MS (IS): *m*/*z* = 289.0 $[M + H]^+$, 311.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{16}N_2O_5S$ + Na: 311.06721; found: 311.06732.

2-Benzylsulfanylimidazolidin-4-one (8)

N-Deacetylation of compound **4** (1.00 g, 4.0 mmol, 1 equiv) was performed following general procedure C. Flash chromatographic purification (CH_2Cl_2–MeOH, 9:1) afforded **8** as a yellow solid; yield: 0.81 g (98%); mp 113–115 °C; R_f = 0.38 (CH_2Cl_2–MeOH, 9:1).

IR (neat): 1667.0 (C=O ring), 1429.5 (NC–S), 1224.9–1157.4 cm^{-1} (C–N).

^1H NMR (DMSO-d_6): δ = 4.03 (s, 2 H, H-5), 4.40 (s, 2 H, CH_2Ph), 7.32 (m, 5 H, C_6H_5), 9.7–11.3 (br, 1 H, NH-1/NH-3).

^{13}C NMR (DMSO-d_6): δ = 32.4 (CH_2Ph), 59.0 (C-5), 127.2, 128.4, 128.9 (CH_{arom}), 137.2 (C_{arom}), 160.0 (C-4), 181.7 (C-2).

MS (IS): *m*/*z* = 207.0 $[M + H]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{11}N_2OS$: 207.05866; found: 207.05868; $[M + Na]^+$ calcd for $C_{10}H_{10}N_2OS$ + Na: 229.04060; found: 229.04053.

(5*Z*)-2-(Benzylsulfanyl)-5-(4-methoxybenzylidene)-4,5-dihydro-1*H*-imidazol-4-one (9)

[385797-51-3]

Compound **11** (3.00 g, 12.8 mmol, 1 equiv) was S-alkylated following general procedure B. Flash chromatographic purification (PE–EtOAc, 7:3) afforded compound **9** as a yellow solid; yield: 4.08 g (98%); mp 199–201 °C; R_f = 0.24 (PE–EtOAc, 7:3).

IR (neat): 2980.4 (NH), 1734.2 (C=O ring), 1511.3–1558.2 (N=CS), 1297.9–1249.7 cm^{-1} (C–N).

^1H NMR (DMSO-d_6): δ = 3.81 (s, 3 H, OCH_3), 4.56 (s, 2 H, CH_2Ph), 6.74 (s, 1 H, H-6), 7.03 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.41 (m, 5 H, C_6H_5), 8.19 (d, *J* = 8.8 Hz, 2 H_{arom}), 11.72 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 33.3 (SCH_2), 55.2 (OCH_3), 114.2 (CH_{aryl}), 121.4 (C-6), 126.9 (C_{aryl}), 127.5, 128.5, 128.9 (CH_{phenyl}), 133.3 (CH_{aryl}), 137.1 (C-4), 137.3 (C_{phenyl}), 160.4 (4-MeOC_{aryl}), 162.1 (C-5), 170.4 (C-2).

MS (IS): *m*/*z* = 325.0 $[M + H]^+$, 347.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.10052; found: 325.10073; $[M + Na]^+$ calcd for $C_{18}H_{16}N_2O_2S$ + Na: 347.08247; found: 347.08253.

2-Thiohydantoin (10)

[503-87-7]

Prepared from 1-acetyl-2-thiohydantoin (**2a**; 1.00 g, 6.32 mmol, 1 equiv) according to general procedure C. Flash chromatographic purification (PE–EtOAc, 7:3) afforded 2-thiohydantoin (**10**) as a brown solid; yield: 0.72 g (98%); mp 228–230 °C; R_f = 0.13 (PE–EtOAc, 1:1).

Physical and spectral data matched those previously reported.[10]

(5*Z*)-5-(4-Methoxybenzylidene)-4,5-dihydro-2-thioxo-1*H*-imidazol-4-one (11)

[95474-45-6]

2-Thiohydantoin (**10**; 2.00 g, 17.22 mmol, 1 equiv) and 4-methoxybenzaldehyde (2.32 mL, 18.94 mmol, 1.1 equiv) were introduced in a round-bottom flask under argon. NaOAc (6.07 g, 74.05 mmol, 4.3 equiv) and AcOH (20 mL) were added and the mixture was stirred under reflux for 2 h, after which the solution was diluted with EtOAc (30 mL). The combined organic layers were washed with H_2O (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatographic purification (PE–EtOAc, 7:3) of the crude product afforded **11** as a yellow solid; yield: 3.17 g (79%); mp 267–268 °C; R_f = 0.36 (PE–EtOAc, 7:3).

IR (neat): 3139.3 (NH), 1720.4 (C=O ring), 1595.5 (NC=S), 1481.5 (C=S), 1258.0 cm^{-1} (C–N).

^1H NMR (DMSO-d_6): δ = 3.81 (s, 3 H, OCH_3), 6.46 (s, 1 H, H-6), 6.98 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.33 (d, *J* = 8.8 Hz, 2 H_{arom}), 12.07 (br, 1 H, NH), 12.26 (br, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 55.3 (OCH_3), 112.1 (C-6), 114.3 (CH_{arom}), 124.8 (C_{arom}), 125.8 (C-5), 132.1 (CH_{arom}), 160.2 (4-MeO-C_{arom}), 165.7 (C-4), 178.5 (C-2).

MS (IS): *m*/*z* = 235.0 $[M + H]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}N_2O_2S$: 235.05357; found: 235.05371; $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_2S$ + Na: 257.03552; found: 257.03548.

(5*Z*)-2-(Benzylsulfanyl)-3-*tert*-butoxycarbonyl-5-(4-methoxybenzylidene)-4,5-dihydro-1*H*-imidazol-4-one (12)

Compound **9** (72.5 mg, 0.22 mmol, 1 equiv) resulting from S-benzylation of **11** (general procedure B) was submitted to *tert*-butoxycarbonylation according to general procedure D. Flash chromatographic purification (PE–EtOAc, 8:2) afforded **12** as a yellow solid; yield: 64 mg (68%); mp 149–151 °C; R_f = 0.58 (PE–EtOAc, 7:3).

IR (neat): 1734.2 (C=O ring), 1511.6–1557.8 (N=CS), 1297.3–1249.1 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 1.53 (s, 9 H, *t*-C_4H_9), 3.78 (s, 3 H, OCH_3), 4.41 (s, 2 H, CH_2Ph), 6.86 (d, *J* = 8.8 Hz, 2 H_{arom}), 6.87 (s, 1 H, H-6), 7.27 (m, 5 H, C_6H_5), 8.04 (d, *J* = 8.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 27.9 (CH_3, *t*-C_4H_9), 36.0 (SCH_2), 55.4 (OCH_3), 114.3 (CH_{aryl}), 125.5 (C-6), 127.0 (C_{aryl}), 127.6, 128.6, 129.2 (CH_{phenyl}), 133.9 (CH_{aryl}), 135.0 (C-4), 135.9 (C_{phenyl}), 159.8 (4-MeOC_{aryl}), 161.4 (C-5), 165.6 (C-2).

MS (IS): *m*/*z* = 425.5 $[M + H]^+$, 447.5 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M - C_5H_8O_2 + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.10052; found: 325.10058; $[M - C_5H_8O_2 + Na]^+$ calcd for $C_{18}H_{16}N_2O_2S$ + Na: 347.08247; found: 347.08247; $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_4S$: 425.15295; found: 425.15299; $[M + Na]^+$ calcd for $C_{23}H_{24}N_2O_4S$ + Na: 447.13490; found: 447.13487

(5*Z*)-3-Benzyloxycarbonyl-2-(benzylsulfanyl)-5-(4-methoxybenzylidene]-4,5-dihydro-1*H*-imidazol-4-one (13)

Compound **9** (100 mg, 0.31 mmol, 1 equiv) dissolved in anhyd CH_2Cl_2 (4 mL) under argon was cooled to 0 °C (ice-salt bath), then benzyl chloroformate (0.06 mL, 0.37 mmol, 1.2 equiv) and Et_3N (0.18 mL, 1.23 mmol, 4 equiv) were added. The mixture was stirred for 6 h at r.t., after which the mixture was concentrated in vacuo. Flash chromatographic purification (PE–EtOAc, 8:2) of the crude product afforded compound **13** as a yellow solid; yield: 105 mg (74%); mp 160–162 °C; R_f = 0.41 (PE–EtOAc, 7:3).

IR (neat): 1737.9 (C=O ring), 1507.5–1595.0 (N=CS), 1304.3–1260.8 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 4.48 (s, 2 H, CH_2Ph), 5.40 (s, 2 H, CH_2OCO), 6.94 (d, *J* = 8.8 Hz, 2 H_{arom}), 6.98 (s, 1 H, H-6), 7.36 (m, 10 H, 2 × C_6H_5), 8.11 (d, *J* = 8.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 36.0 (SCH_2), 55.4 (CH_3, OCH_3), 69.2 (CH_2OCO), 114.3 (CH_{aryl}), 126.2 (C-6), 126.9 (C_{aryl}), 127.7, 128.2, 128.6, 128.6, 128.7, 129.2 (CH_{phenyl}), 134.0 (CH_{aryl}), 134.3 (C-4), 134.6, 135.8 (C_{phenyl}), 149.5 (OCO), 159.4 (4-MeOC_{aryl}), 161.5 (C-5), 165.2 (C-2).

MS (IS): *m*/*z* = 459.5 $[M + H]^+$.

HRMS-ES: *m*/*z* $[M - CO_2 + H]^+$ calcd for $C_{25}H_{23}N_2O_2S$: 415.14748; found: 415.14734; $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_4S$: 459.13730; found: 459.13724; $[M + Na]^+$ calcd for $C_{26}H_{22}N_2O_4S$ + Na: 481.11925; found: 481.11927.

(4*Z*)-1-Benzyl-2-(benzylsulfanyl)-4-(4-methoxybenzylidene)-4,5-dihydro-1*H*-imidazol-5-one (14)

The thiohydantoin **19** (2.00 g, 6.17 mmol, 1 equiv) was S-alkylated according to general procedure B. Flash chromatographic purification (PE–EtOAc, 7:3) afforded compound **14** as a yellow solid; yield: 2.23 g (87%); mp 146–149 °C; R_f = 0.55 (PE–EtOAc, 7:3).

IR (neat): 1699.6 (C=O ring), 1496.3–1597.6 (N=CS), 1252.2–1172.6 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 4.55 (s, 2 H, SCH_2), 4.76 (s, 2 H, NCH_2), 6.94 (d, $J_{9,10}$ = 8.8 Hz, 2 H_{arom}), 7.00 (s, 1 H, H-6), 7.32 (m, 10 H, 2 × C_6H_5), 8.15 (d, $J_{10,9}$ = 8.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 35.1 (SCH_2), 44.2 (NCH_2), 55.3 (OCH_3), 114.2 (CH_{aryl}), 124.6 (C-6), 127.4 (C_{aryl}), 127.7, 127.8, 128.6, 128.7, 129.2 (CH_{phenyl}), 133.8 (CH_{aryl}), 135.7 (C-4), 136.0, 136.5 (C_{phenyl}), 161.1 (4-MeOC_{aryl}), 162.6 (C-5), 169.8 (C-2).

MS (IS): *m*/*z* = 415.0 $[M + H]^+$, 437.5 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_2S$: 415.14748; found: 415.14765; $[M + Na]^+$ calcd for $C_{25}H_{22}N_2O_2S$ + Na: 437.12942; found: 437.12932.

(4*Z*)-2-(Benzylsulfanyl)-1-(4-methoxybenzyl)-4-(4-methoxybenzylidene)-4,5-dihydro-1*H*-imidazol-5-one (15)

Compound **9** (500 mg, 1.54 mmol, 1 equiv) dissolved in THF (7.5 mL) under argon in a 50 mL round-bottom flask was cooled to 0 °C. Bu_4NI (57.0 mg, 0.154 mmol, 0.1 equiv), NaH (60% in oil; 203 mg, 8.47 mmol, 5.5 equiv), and 4-methoxybenzyl chloride (0.65 mL, 4.93 mmol, 3.2 equiv) were added and the mixture was stirred 4 h at r.t. After quenching with ice and extraction with EtOAc (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. Flash chromatographic purification (PE–EtOAc, 9:1) of the crude product afforded compound **15** as a yellow solid; yield: 301 mg (44%); mp 86–88 °C; R_f = 0.47 (PE–EtOAc, 7:3).

IR (neat): 1700.0 (C=O ring), 1510.0–1594.1 (N=CS), 1260.8–1171.1 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 3.76, 3.84 (2 s, 6 H, OCH_3), 4.55 (s, 2 H, SCH_2), 4,69 (s, 2 H, NCH_2), 6.82 (d, *J* = 8.5 Hz, 2 H_{arom}), 6.94 (d, J_0 = 8.8 Hz, 2 H_{arom}), 6.98 (s, 1 H, H-6), 7.24 (d, *J* = 8.5 Hz, 2 H_{arom}), 7.37 (m, 5 H, C_6H_5), 8.14 (d, *J* = 8.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 35.1 (SCH_2), 43.7 (NCH_2), 55.2, 55.3 (OCH_3), 114.0 (CH_{aryl}), 114.2 (CH_{aryl}), 124.4 (C-6), 127.4 (C_{aryl}), 127.9 (C_{aryl}), 127.8, 128.7, 129.2 (CH_{phenyl}), 129.3 (CH_{aryl}), 133.7 (CH_{aryl}), 136.0 (C-4, C_{phenyl}), 136.6 (C_{phenyl}), 159.2 (4-MeOC_{aryl}), 161.0 (4-MeOC_{aryl}), 162.6 (C-5), 169.8 (C-2).

MS (IS): *m*/*z* = 445.5 $[M + H]^+$, 467.5 [M + Na].

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_3S$: 445.15804; found: 445.15819.

Liebeskind–Srogl Coupling Reaction; General Procedure E

To the N-3 protected imidazolinone (1 mmol, 1 equiv), dissolved in anhyd THF (10 mL) under argon were added $Pd(PPh_3)_4$ (0.1 mmol, 0.1 equiv), copper(I) thiophene-2-carboxylate (CuTC) (3 mmol, 3 equiv), and 4-methoxyphenylboronic acid (1.2 mmol, 1.2 equiv) at r.t. The mixture was stirred for 24 h at 70 °C, after which the solution was diluted with EtOAc (20 mL), and washed with sat. aq $NaHCO_3$ (3 × 50 mL). The combined organic layers were filtered over Celite and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (Table 3).

(4*Z*)-4-(4-Methoxybenzylidene)-2-(4-methoxyphenyl)-4,5-dihydro-1*H*-imidazol-5-one (16a)

The hydantoin **9** (21 mg, 0.18 mmol, 1 equiv), $Pd(PPh_3)_4$ (9.24 μmol, 0.05 equiv), CuTC (0.56 mmol, 3 equiv), and 4-methoxyphenylboronic acid (0.22 mmol, 1.2 equiv) were introduced in DMF (3 mL) in a vial under argon at r.t. The vial was sealed and the mixture was stirred and irradiated (300 W) at 130 °C, for 1 h, after which the solution was diluted with EtOAc (10 mL) and washed with sat. aq of $NaHCO_3$ (3 × 100mL). The combined organic layers were filtered over Celite and concentrated in vacuo. Flash chromatographic purification (PE–EtOAc, 1:1) of the crude product afforded compound **16a** as a yellow solid; yield: 20 mg (36%); mp 264–266 °C; R_f = 0.25 (CH_2Cl_2–MeOH, 19:1).

IR (neat): 2955.8 (NH), 1698.9 (C=O ring), 1595.7–1503.7 (N=CS), 1251.5–1170.6 cm^{-1} (C–N).

^1H NMR (DMSO-d_6): δ = 3.83, 3.86 (2 s, 6 H, OCH_3), 6.92 (s, 1 H, H-6), 7.05 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.14 (d, *J* = 8.8 Hz, 2 H_{arom}), 8.11 (d, *J* = 8.8 Hz, 2 H_{arom}), 8.28 (d, *J* = 8.8 Hz, 2 H_{arom}), 11.91 (br, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 55.3, 55.6 (OCH_3), 114.4 (CH_{arom}), 114.5 (CH_{arom}), 120.4 (C_{arom}), 123.9 (C-6), 127.3 (C_{arom}), 129.1 (CH_{arom}), 133.8 (C-4), 159.9 (C-2), 160.6 (4-MeOC_{arom}), 162.5 (4-MeOC_{arom}), 172.1 (C-5).

MS (IS): *m*/*z* = 309.5 $[M + H]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.12337; found: 309.12349.

(4*Z*)-1-Benzyloxycarbonyl-4-(4-methoxybenzylidene)-2-(4-methoxyphenyl)-4,5-dihydro-1*H*-imidazol-5-one (16c)

Compound **13** (100 mg, 0.22 mmol, 1 equiv) was submitted to the coupling reaction according to general procedure E. Flash chromatographic purification (PE–EtOAc, 8:2) afforded the imidazolone **16c** as a yellow solid; yield: 67 mg (69%); mp 126–128 °C; R_f = 0.34 (PE–EtOAc, 7:3).

IR (neat): 1735.9 (C=O), 1597.0–1502.9 (C=C), 1250.8–1170.3 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 3.85, 3.86 (2 s, 6 H, OCH_3), 5.33 (s, 2 H, CH_2OCO), 6.89 (d, *J* = 8.8 Hz, 2 H_{arom}), 6.96 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.23 (s, 1 H, H-6), 7.59 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.34 (s, 5 H, C_6H_5), 8.19 (d, *J* = 8.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 55.4 (2 × OCH_3), 69.6 (CH_2OCO), 113.6 (CH_{aryl}), 114.4 (CH_{aryl}), 122.1 (C_{aryl}), 126.8 (C_{aryl}), 128.5, 128.6 (CH_{phenyl}), 130.0 (C-6), 130.0 (CH_{aryl}), 134.1 (C_{phenyl}), 134.7 (CH_{aryl}), 135.0 (C-4), 149.5 (OC=O), 156.8 (C-2), 162.0 (4-MeO-C_{arom}), 161.8 (4-MeOC_{arom}), 167.07 (C-5).

MS (IS): *m*/*z* = 399.0 $[M - CO_2 + H]^+$, 443.5 $[M + H]^+$, 465.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M - CO_2 + H]^+$ calcd for $C_{25}H_{23}N_2O_3$: 399.17032; found: 399.17032; $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_5$: 443.16015; found: 443.16031; $[M + Na]^+$ calcd for $C_{26}H_{22}N_2O_5$ + Na: 465.14209; found: 465.14207.

(4*Z*)-1-Benzyl-4-(4-methoxybenzylidene-2-(4-methoxyphenyl)-4,5-dihydro-1*H*-imidazol-5-one (16d)

Compound **14** (150 mg, 0.36 mmol, 1 equiv) was submitted to the coupling reaction according to general procedure E. Flash chromatographic purification (PE–EtOAc, 8:2) afforded the imidazolone **16d** as a yellow solid; yield: 90 mg (62%); mp 90–92 °C; R_f = 0.24 (PE–EtOAc, 7:3).

IR (neat): 1704.1 (C=O ring), 1502.2–1596.8 (N=CS), 1250.0–1176.2 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 3.83, 3.85 (2 s, 6 H, OCH_3), 4.97 (s, 2 H, NCH_2), 6.91 (d, *J* = 8.8 Hz, 2 H_{arom}), 6.95 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.17 (m, 2 H, C_6H_5), 7.29 (s, 1 H, H-6), 7.54 (m, 3 H, C_6H_5), 7.65 (d, *J* = 8.8 Hz, 2 H_{arom}), 8.23 (d, *J* = 8.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 45.3 (NCH_2), 55.3, 55.4 (OCH_3), 114.1 (CH_{aryl}), 114.3 (CH_{aryl}), 121.7 (C_{aryl}), 127.4 (C-4), 126.5, 127.5, 128.8 (CH_{phenyl}), 128.3 (C-6), 130.3 (CH_{aryl}), 134.4 (CH_{aryl}), 136.8 (C_{phenyl}), 136.9 (CH_{aryl}), 161.1 (C-2), 161.4 (4-MeOC_{aryl}), 162.0 (4-MeOC_{aryl}), 171.9 (C-5).

MS (IS): *m*/*z* = 399.0 $[M + H]^+$, 421.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_3$: 399.17032; found: 399.17054.

(4*Z*)-1-(4-Methoxybenzyl-4-(4-methoxybenzylidene)-2-(4-methoxyphenyl)-4,5-dihydro-1*H*-imidazol-5-one (16e)

Compound **15** (160 mg, 0.36 mmol, 1 equiv) was submitted to the coupling reaction according to general procedure E. Flash chromatographic purification (PE–EtOAc, 8:2) afforded the imidazolone **16e** as a yellow solid; yield: 94 mg (61%); mp 74–76 °C; R_f = 0.21 (PE–EtOAc, 7:3).

IR (neat): 1703.0 (C=O ring), 1599.9–1507.3 (N=CS), 1248.7–1174.0 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 3.77, 3.85 (2 s, 9 H, OCH_3), 4.91 (s, 2 H, CH_2Ar), 6.83 (d, *J* = 8.7 Hz, 2 H_{arom}), 6.93 (d, *J* = 8.8 Hz, 2 H_{arom}), 6.96 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.09 (d, *J* = 8.7 Hz, 2 H_{arom}), 7.24 (s, 1 H, H-6), 7.67 (d, *J* = 8.8 Hz, 2 H_{arom}), 8.23 (d, *J* = 8.8 Hz, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 44.8 (NCH_2), 55.2, 55.3, 55.4 (OCH_3), 114.1, 114.2, 114.3 (CH_{arom}), 121.8 (C_{arom}), 127.4 (C_{arom}), 128.0 (CH_{arom}), 128.2 (C-6), 128.9 (C_{arom}), 130.4 (CH_{arom}), 134.4 (CH_{arom}), 137.0 (C-4), 158.9 (C-2), 161.2, 161.4, 162.0 (4-MeOC_{arom}), 171.9 (C-5).

MS (IS): *m*/*z* = 429.0 $[M + H]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_4$: 429.18088; found: 429.18105.

3-Benzyl-2-thiohydantoin (17)[22]

[39123-65-4]

To a solution of glycine methyl ester hydrochloride (2.00 g, 15.9 mmol, 1 equiv) and Et_3N (2.25 mL, 15.9 mmol, 1 equiv) in CH_2Cl_2 (150 mL) was added benzyl isothiocyanate (2.12 mL, 15.9 mmol, 1 equiv) and the solution was stirred for 6 h at r.t. The reaction mixture was washed with H_2O (3 × 50 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were dried ($MgSO_4$), and evaporated in vacuo. Flash chromatographic purification (PE–EtOAc, 7:3) of the crude residue afforded compound **17** as a yellow solid; yield: 3.00 g (91%); mp 143–144 °C; R_f = 0.15 (PE–EtOAc, 7:3).

MS (IS): *m*/*z* = 207.5 $[M + H]^+$, 229.5 [M + Na].

Physical and spectral data matched those previously reported.[22]

3-(4-Methoxybenzyl)-2-thiohydantoin (18)

[287918-21-2]

Similarly, 4-methoxybenzyl isothiocyanate (214 mg, 1.19 mmol, 1 equiv) was added to a solution of glycine methyl ester hydrochloride (150 mg, 1.19 mmol, 1 equiv), and Et_3N (0.17 mL, 1.19 mmol, 1 equiv) in CH_2Cl_2 (10 mL) and the solution was stirred for 1 h at r.t., then 4 h at 40 °C. The reaction mixture was washed with H_2O (3 × 10 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$), and evaporated in vacuo. Flash chromatographic purification (PE–EtOAc, 1:1) of the crude residue afforded compound **18** as a yellow solid; yield: 246 mg (87%); mp 177–179 °C; R_f = 0.44 (PE–EtOAc, 4:6).

IR (neat): 3200.0 (NH), 1733.5 (C=O ring), 1509.8 (NC=S), 1241.8–1169.1 cm^{-1} (C–N).

^1H NMR (DMSO-d_6): δ = 3.72 (s, 3 H, OCH_3), 4.18 (s, 2 H, H-5), 4.79 (s, 2 H, CH_2Ar), 6.87 (d, *J* = 8.7 Hz, 2 H_{arom}), 7.28 (d, *J* = 8.7 Hz, 2 H_{arom}), 10.24 (br, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 43.7 (NCH_2Ar), 48.4 (C-5), 55.0 (OCH_3), 113.6 (CH_{arom}), 128.4 (CH_{arom}), 129.2 (C_{arom}), 158.5 (4-MeOC_{arom}), 172.5 (C-4), 183.2 (C-2).

MS (IS): *m*/*z* = 237.5 $[M + H]^+$.

HRMS-ES: *m*/*z* $[M - C_3H_4N_2OS + H]^+$ calcd for C_8H_9O: 121.06479; found: 121.06483; $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2S$: 237.06922; found: 237.06919; $[M + Na]^+$ calcd for $C_{11}H_{12}N_2O_2S$ + Na: 259.05117; found: 259.05131.

(5*Z*)-3-Benzyl-5-(4-methoxybenzylidene)-2-thiohydantoin (19)

[875424-21-8]

3-Benzyl-2-thiohydantoin (**17**; 2.00 g, 9.7 mmol, 1 equiv) and 4-methoxybenzaldehyde (1.31 mL, 10.67 mmol, 1.1 equiv) were introduced in a round-bottom flask under argon. NaOAc (3.55 g, 41.7 mmol, 4.3 equiv) and AcOH (10 mL) were added and the mixture was stirred under reflux for 2 h, after which the solution was diluted with EtOAc (30 mL). The combined organic layers were washed with H_2O (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatographic purification (PE–EtOAc, 7:3) of the crude product afforded thiohydantoin **19** as a yellow solid; yield: 2.86 g (91%); mp 209–211 °C; R_f = 0.31 (PE–EtOAc, 7:3).

IR (neat): 3239.9 (NH), 1724.7 (C=O ring), 1593.7 (NC=S), 1254.4–1232.5 cm^{-1} (C–N).

^1H NMR (DMSO-d_6): δ = 3.82 (s, 3 H, OCH_3), 5.01 (s, 2 H, NCH_2), 6.65 (s, 1 H, H-6), 7.00 (d, *J* = 8.7 Hz, 2 H_{arom}), 7.30 (m, 5 H, C_6H_5), 7.78 (d, *J* = 8.7 Hz, 2 H_{arom}), 12.42 (br, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 55.3 (OCH_3), 113.9 (C-6), 114.3 (CH_{aryl}), 124.0 (CH_{aryl}), 124.7 (C-5), 127.3, 127.4, 128.3 (CH_{phenyl}), 132.3 (C_{aryl}), 160.4 (4-MeOC_{aryl}), 163.9 (C-4), 177.9 (C-2).

MS (IS): *m*/*z* = 347.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.10052; found: 325.10066; $[M + Na]^+$ calcd for $C_{18}H_{16}N_2O_2S$ + Na: 347.08247; found: 347.08230.

(5*Z*)-3-(4-Methoxybenzyl)-5-(4-methoxybenzylidene)-2-thiohydantoin (20)

3-(4-Methoxybenzyl)-2-thiohydantoin (**18**; 240 mg, 1.02 mmol, 1 equiv) and 4-methoxybenzaldehyde (0.14 mL, 1.12 mmol, 1.1 equiv) were mixed in a round-bottom flask under argon. NaOAc (359 mg, 4.37 mmol, 4.3 equiv) and AcOH (2 mL) were added and the mixture was stirred under reflux for 2 h. The solution was then diluted with EtOAc (10 mL) and washed with H_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatographic purification (PE–EtOAc, 7:3) of the crude product afforded thiohydantoin **20** as a yellow solid; yield: 266 mg (74%); mp 237–239 °C; R_f = 0.67 (PE–EtOAc, 1:1).

IR (neat): 3218.7 (NH), 1730.1 (C=O ring), 1512.0 (NC=S), 1271.7–1175.1 cm^{-1} (C–N).

^1H NMR ($CDCl_3$): δ = 3.77, 3.84 (2 s, 6 H, OCH_3), 5.03 (s, 2 H, NCH_2Ar), 6.69 (s, 1 H, H-6), 6.83 (d, *J* = 8.6 Hz, 2 H_{arom}), 6.94 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.38 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.46 (d, *J* = 8.6 Hz, 2 H_{arom}), 8.98 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 44.2 (NCH_2), 55.2, 55.4 (OCH_3), 113.8 (CH_{arom}), 114.1 (C-6), 115.0 (CH_{arom}), 124.7 (C-5), 125.2 (C_{arom}), 127.8 (CH_{arom}), 130.4 (CH_{arom}), 131.0 (4-MeOC_{arom}), 159.3 (4-MeOC_{arom}), 160.9 (4-MeOC_{arom}), 163.7 (C-4), 177.5 (C-2).

MS (IS): *m*/*z* = 355.0 $[M + H]^+$, 377.0 $[M + Na]^+$.

HRMS-ES: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_3S$: 355.11109; found: 355.11118; $[M + Na]^+$ calcd for $C_{19}H_{18}N_2O_3S$ + Na: 377.09303; found: 377.09292.

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