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Efficient one-pot microwave-assisted synthesis of 3-(thien-3-yl)imidazolidine-2,4-dione analogs

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Abstract—A series of twenty optically pure 3-(thien-3-yl)imidazolidine-2,4-dione derivatives have been synthesized in 41–89% yield on treatment of 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione with all natural α-amino acids in a quick one-pot microwave-assisted procedure.

1. Introduction

Imidazolidine-2,4-diones (or hydantoins) are well known compounds since their discovery, over a century ago.[1] Hydantoins have found therapeutic applications in drugs such as the well established phenytoin,[2] for the treatment of different types of epileptic seizures, nilutamide,[3] a nonsteroidal orally active antiandrogen in the therapy of metastatic prostate cancer, and azimilide,[4] a class III antiarrhythmic (Fig. 1). Among the wide range of biological activities of substituted hydantoins,[5] we can cite antidiabetic,[6,7] anti-inflammatory,[8] antiviral,[9] GHS[10] and CB_1 receptor antagonists,[11] inhibitors of LFA-1,[12] FAAH,[13] EGFR,[14] Ras farnesyl transferase, and more.[15] This important structural moiety is also commonly found in natural products,[16,17] heat-resistant polymer for electrical conductors,[18] and the agrochemical sector.[19]

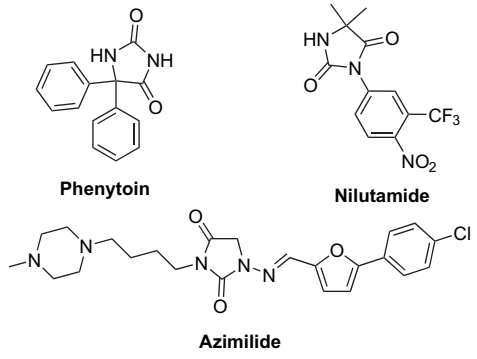

Figure 1. Representative examples of therapeutic imidazolidine-2,4-diones.

In previous studies, reactivity of 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione (also known as thiaisatoic anhydride **1**) was investigated toward various nucleophiles such as amines[20] and alcohols.[21] In contrast to isatoic anhydride,[22] the nucleophilic attack only proceeds on the carbonyl group of the carbamate function and not on the carboxylic carbonyl. However, we recently demonstrated that the nucleophilic attack of amino acids under neutral conditions can favorably be oriented toward the carboxylic carbonyl of the oxazinedione **1**.[23] Nevertheless, in the same reaction conditions, in the presence of a base like Et_3N, the latest reactivity toward the same amino acids can be reversed (Fig. 2).

We took advantage of these results to develop an efficient methodology to obtain 3-(thien-3-yl)imidazolidine-2,4-dione analogs by condensation of thiaisatoic anhydride **1**[21] with all natural α-amino acids. Since the synthetic developments in hydantoin chemistry have been recently reviewed,[5,24] no example of 3-(thien-3-yl)imidazolidine-2,4-dione derivative has been described to our knowledge.

2. Results and discussion

The study of the experimental parameters was initiated using alanine (Ala). The corresponding ureidothenoic acid intermediate **2** was synthesized instantly after addition of Et_3N to a suspension of thiaisatoic anhydride **1** and Ala in H_2O

Keywords: Thiaisatoic anhydride; 3-(Thien-3-yl)imidazolidine-2,4-dione; Hydantoins; Microwave.
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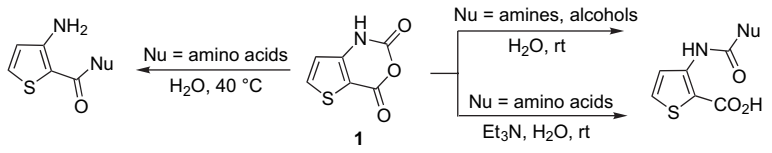
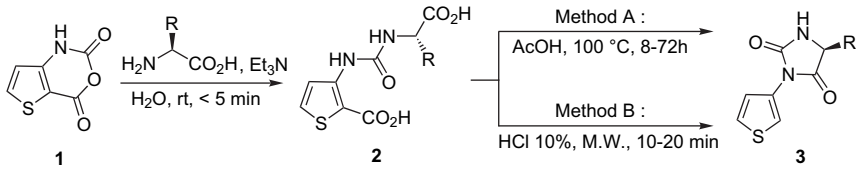


Figure 2. Influence of basic conditions on the nucleophilic attack selectivity.

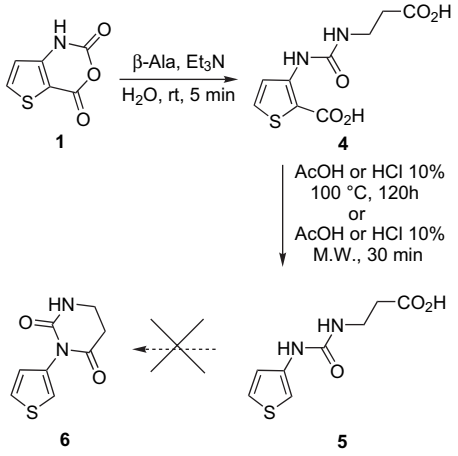


Scheme 1. Synthesis of 3-(thien-3-yl)imidazolidine-2,4-dione analogs.

at room temperature (Scheme 1). The ureidothenoic acid **2** was not isolated but its formation was ascertained by RP-LCMS. In the first synthetic pathway (method A, Scheme 1), evaporation of the volatile material, addition of AcOH, and heating under conventional refluxing conditions (over 12 h) delivered 3-(thien-3-yl)imidazolidine-2,4-dione **3b** after cyclocondensation of the ureidoacid moiety and decarboxylation of the 2-thienoic acid motif. However, recovery of some none decarboxylated and degraded crude material gave a product of lower purity. To improve yield and reaction conditions, we developed an one-pot protocol involving microwave irradiation[25–27] and acidic conditions[28] (method B, Scheme 1). The crude mixture of the corresponding intermediate **2** was subjected to microwave irradiation (150 °C, 10 min) in the presence of aqueous 10% HCl to afford pure 3-(thien-3-yl)imidazolidine-2,4-dione **3b** in 78% yield. Even though Et_3N was suspected to induce epimerization,[29] the absence of racemization involved in this one-pot microwave-assisted methodology was ascertained by the comparison of the optical rotation of hydantoin **3b** ($[\alpha]_D^{20}$ −34) and its enantiomer **3c** ($[\alpha]_D^{20}$ +34), and evaluation of the enantiomeric excess (>96%) in each synthesis by chiral HPLC.

To validate this expedient methodology in hand, all natural amino acids were submitted to the reaction conditions. The influence of steric hindrance caused by alkyl branched (Gly, Ala, Leu, Val, and Ile) or bulky aromatic constituent (Phe and Tyr) did not impede with the cyclocondensation. A secondary amine (Pro) proved to be as reactive. Alcohol (Ser, Thr, and Tyr), sulfur (Met), and guanidine (Arg) -containing amino acids reacted accordingly, without any degradation or modification of the side-chain. Aza-heterocyclic side-chains of amino acids (His and Trp) did not interfere with the condensation. Finally, this one-pot synthesis provided a diverse series of 3-(thien-3-yl)imidazolidine-2,4-dione analogs **3a**–**o** in 64–89% yield (Table 1).

Furthermore, the presence of the carboxylic acid functionality on Asp and Glu side-chain suggested a possible competitive cyclocondensation leading to a six(Asp) or seven(Glu) -membered ring in place of the desired five-membered imidazolidine. First, authenticity of the five- versus six-membered ring cyclization of the corresponding Asp ureidothenoic acid intermediate **2p** was assumed by the lack of reactivity of its β-acid moiety. Indeed, only decarboxylation to propanoic acid derivative **5** was observed when diacid **4**, synthesized from thiaisatoic anhydride **1** and β-Ala as described above, was treated with AcOH or HCl 10%, at reflux or under microwave irradiation (Scheme 2). The 5,6-dihydro-3-(thien-3-yl)pyrimidine-2,4-dione **6** was never obtained. Acid containing hydantoin **3p** was synthesized as a pure product as determined by RP-LCMS, ^1H, and ^{13}C NMR analyses.

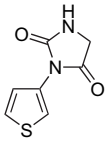
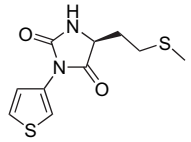
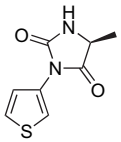
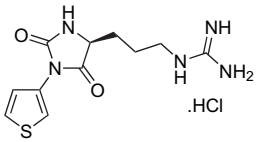
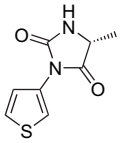
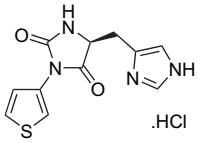
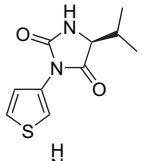
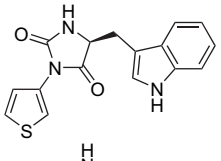
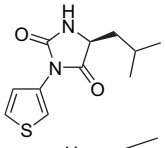
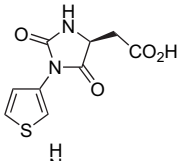
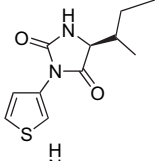
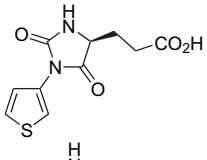
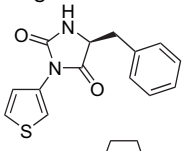
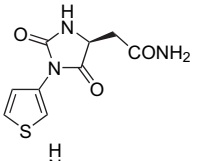
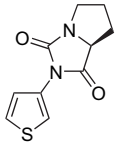
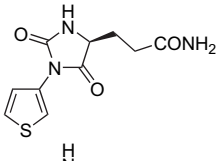
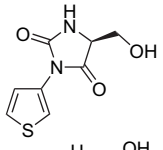
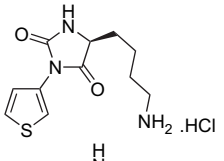
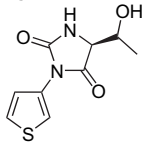
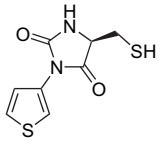
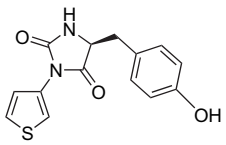


Scheme 2. Absence of six-membered ring cyclization.

To confirm the structure of the five- vs seven-membered ring cyclization of the Glu intermediate **2q** and the absolute configuration of the synthesized hydantoin **3q**, X-ray structure analysis was performed (Fig. 3). Crystallographic data of compound **3q** unambiguously confirmed the imidazolidine structure in the solid state, as anticipated on the basis of NMR data. Two independent molecules, designated as A and B, were found in the asymmetric crystallographic unit of hydantoin **3q**. Its configuration was determined by observing and calculating the $F(+)/F(-)$ ratios of Bijvoet pairs with the mean F value of each independent reflection. Based on the results, the absolute configuration at C(9) (molecule A) and at C(59) (molecule B) in position 3 of the imidazolidine ring of **3q** was determined to be *S*.[30]

Moreover, our synthetic pathway (method B, Scheme 1) applied on amino acids bearing amide side-chains (Asn and Gln) caused hydrolysis of the amide moiety in the presence of aqueous 10% HCl under microwave irradiation, as

Table 1. Synthesis of 3-(thien-3-yl)imidazolidine-2,4-dione analogs **3a–u** from method B

Entry	a.a.	Structure **3**	Time (min)	Yield (%)	Entry	a.a.	Structure **3**	Time (min)	Yield (%)
a	Gly		10	70	l	L-Met		20	89
b	L-Ala		10	78	m	L-Arg		20	69
c	D-Ala		10	79	n	L-His		10	73
d	L-Val		10	72	o	L-Trp		20	71
e	L-Leu		20	69	p	L-Asp		10	61
f	L-Ile		20	68	q	L-Glu		20	69
g	L-Phe		10	81	r	L-Asn		20[a]	41
h	L-Pro		10	79	s	L-Gln		20[a]	56
i	L-Ser		20	72	t	L-H-Lys(Z)-OH		40	63
j	L-Thr		20	64	u	L-H-Cys(Trt)-OH		20	62
k	L-Tyr		10	86					

[a] HCl 10% was replaced by AcOH in the protocol of method B.

observed by the complete recovery of acids **3p–q** instead of **3r–s**. As an alternative procedure, after evaporation of water from the corresponding ureidothenoic acid intermediate **2**, AcOH in method B replaced HCl to deliver the desired amide **3r–s** (Table 1). Consequently, amides **3r–s** can be converted to the corresponding acids **3p–q** after heating under microwave irradiation in aqueous 10% HCl for 20 min. Comparison of the RP-HPLC retention time, ^{1}H and ^{13}C

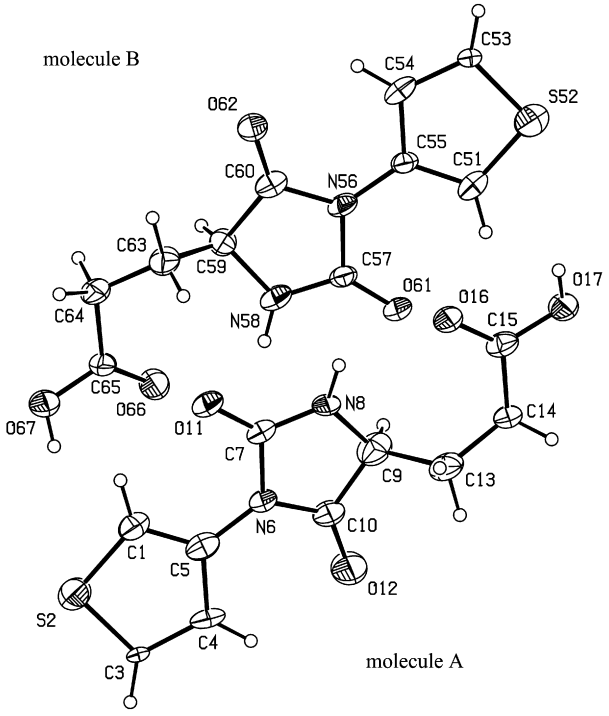


Figure 3. View of the crystal structure of 3-((*S*)-2,5-dioxo-1-(thien-3-yl)-imidazolidin-4-yl)propanoic acid **3q** {molecules A [label C(1)···O(17)], and B [label C(51)···O(67)]}with our numbering scheme, displacement ellipsoids are drawn at the 30% probability level.

NMR spectra with the previously obtained hydantoins **3p–q** also confirmed the five-membered ring structure.

Reaction of thiaisatoic anhydride **1** with Lys and Et_3N in H_2O instantly gave products corresponding to the two different possible nucleophilic attacks of lysine. Competition between the primary α-amine and the ω-primary amine was avoided using an acid labile protecting group on the amine side-chain of Lys. The corresponding ureidoacid intermediate **2** was synthesized using H–Lys(*Z*)–OH, which was then cyclized and deprotected in aqueous 10% HCl under microwave irradiation for 40 min to give hydantoin **3t** in 63% yield.

Similarly, protection of the thiol functionality of Cys was necessary to avoid degradation of the product. The acid labile trityl protecting group was used but was not cleaved in the conditions described for method B. The addition of TFA/TIS (95:5) was used to cleave the trityl group and afford the hydantoin **3u** in 62% yield.

3. Conclusion

In conclusion, we have developed a straightforward cost-effective method for making a library of optically pure 3-(thien-3-yl)imidazolidine-2,4-dione analogs in 41–89% yield by condensation of 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione with all natural amino acids, in a quick two-step one-pot microwave-assisted process. From all the natural amino acids, only Lys and Cys required side-chain protection to directly form the desired hydantoin. The further extension of this methodology to non-natural aminoacids is underway and a solid-phase combinatorial approach is under investigation for the SAR of thienylimidazolidines in a specific medicinal application.

4. Experimental

4.1. General

Starting materials and solvents were obtained commercially and used as received. Melting points were determined in open capillaries and are uncorrected. Optical rotations were measured on a Perkin–Elmer polarimeter 341 using a 100 mm path length cell at λ=589 nm (Sodium D line) in low concentrations due to colored solutions. Mass spectral data, HRMS/LRMS were obtained by (FAB/ESI) analyses. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in DMSO-d_6. Chemical shifts are reported in parts per million (δ units) downfield/upfield from residual DMSO (δ 2.50 and 39.5); coupling constants (*J*) are reported in hertz (Hz). HPLC analyses were performed on Merck Chromolith Flash RP18e (5 μm, 225×4.6 mm) analytical reversed-phase column using a flow rate of 3.0 mL/min, and gradient of 100/0 to 0/100 eluents A/B over 5 min (method A), in which eluents A=H_2O/0.1% TFA and B=CH_3CN/0.1% TFA. Retention times (t_R) are reported as follows: t_R (min) and elution conditions. HPLC preparative purification was performed on Chromolith SemiPrep RP-18 (5 μm, 100×10 mm) semi preparative column, using a flow rate of 15 mL/min and gradient of 100/0 to 0/100 eluents A/B over 40 min (method B). Enantiomeric excess (ee) were measured on a Chiracel OD (5 μm, 250×10 mm) normal phase column, using a flow rate of 1 mL/min and isocratic gradient of 40:60 eluents hexanes/*iso*-propanol over 20 min (method C). Analytical thin layer chromatography (TLC) was performed using aluminum-backed silica gel plates coated with a 0.2 mm thickness of silica gel. Microwave-assisted reactions were carried in a Biotage Initiator 60 EXP® microwave synthesizer, with 300 W heating power and temperature controlled with an IR sensor on the outer surface of the capped reaction vials.

4.2. Typical experimental procedure for 3-(thien-3-yl)-imidazolidine-2,4-diones (3) synthesis

Et_3N was added to a stirring suspension of 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione **1** (0.100 g, 0.60 mmol) and the corresponding α-amino acid (0.66 mmol) in water (4 mL). The suspension was stirred at room temperature until homogeneity (<5 min). A solution of HCl 10% (2 mL) was added until pH=1. The reaction vial was capped and the sealed solution was stirred under microwave irradiation at 150 °C for 10–40 min (see Table 1). The resulting solution was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc (10 mL×3) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, evaporated and triturated with Et_2O to afford the corresponding imidazolidinedione **3**, which was stored in stoppered flasks. The terminal-guanidine, -histidine, -amide, and -amine containing hydantoins **3m**,**n**, and **3r–t** were soluble in water, and therefore needed reverse-phase chromatographic purifications (method C) to remove salts and excess amino acid.

4.2.1. 3-(Thien-3-yl)imidazolidine-2,4-dione (3a). Yield 70%; brown solid; mp 156 °C; ^{1}H NMR (DMSO-d_6): δ 8.32 (s, 1H), 7.67 (dd, 1H, J=3.1, 1.2 Hz), 7.58 (dd, 1H, J=5.2, 3.2 Hz), 7.38 (dd, 1H, J=5.2, 1.2 Hz), 4.04 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 170.4, 155.9, 130.2, 125.0, 123.6, 117.8, 45.7; HRMS: calcd for [M+H$^+$] $C_7H_7N_2O_2S$ 183.0228, found 183.0213; t_R: 1.13 (method A).

4.2.2. (*S*)-5-Methyl-3-(thien-3-yl)imidazolidine-2,4-dione (3b). Yield 78%; brown solid; mp 117 °C (decomp.); $[\alpha]_D^{20}$ −34.2 (c 0.3, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.48 (s, 1H), 7.67 (dd, 1H, J=3.1, 1.0 Hz), 7.57 (dd, 1H, J=5.1, 3.2 Hz), 7.39 (dd, 1H, J=5.2, 1.0 Hz), 4.23 (quad, 1H, J=6.9 Hz), 1.33 (d, 3H, J=6.9 Hz); ^{13}C NMR (DMSO-d_6): δ 173.4, 154.8, 130.2, 125.0, 123.5, 117.8, 51.7, 17.2; HRMS: calcd for [M+H$^+$] $C_8H_9N_2O_2S$ 197.0385, found 197.0384; t_R: 1.40 (method A).

4.2.3. (*R*)-5-Methyl-3-(thien-3-yl)imidazolidine-2,4-dione (3c). Yield 79%; brown solid; mp 117 °C (decomp.); $[\alpha]_D^{20}$ +33.8 (c 0.3, DMSO); ^{1}H NMR, ^{13}C NMR (DMSO-d_6), HRMS and t_R are consistent with compound **3b**.

4.2.4. (*S*)-5-Isopropyl-3-(thien-3-yl)imidazolidine-2,4-dione (3d). Yield 72%; brown solid; mp 115 °C; $[\alpha]_D^{20}$ −92.8 (c 0.3, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.55 (s, 1H), 7.67 (d, 1H, J=3.1 Hz), 7.58 (dd, 1H, J=5.0, 3.3 Hz), 7.37 (d, 1H, J=5.2 Hz), 4.11 (d, 1H, J=3.1 Hz), 2.12 (m, 1H), 1.00 (d, 3H, J=6.8 Hz), 0.85 (d, 3H, J=6.8 Hz); ^{13}C NMR (DMSO-d_6): δ 172.1, 155.5, 130.0, 125.1, 123.5, 117.8, 61.1, 29.9, 18.4, 15.9; HRMS: calcd for [M+H$^+$] $C_{10}H_{13}N_2O_2S$ 225.0698, found 225.0680; t_R: 1.94 (method A).

4.2.5. (*S*)-5-Isobutyl-3-(thien-3-yl)imidazolidine-2,4-dione (3e). Yield 67%; brown solid; mp 151 °C; $[\alpha]_D^{20}$ −4.6 (c 0.2, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.61 (s, 1H), 7.67 (s, 1H), 7.58 (s, 1H), 7.40 (s, 1H), 4.22 (s, 1H), 1.83 (m, 1H), 1.57 (m, 2H), 0.93 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 173.1, 155.1, 130.2, 125.0, 123.5, 117.7, 54.5, 40.7, 24.0, 23.0, 21.5; HRMS: calcd for [M+H$^+$] $C_{11}H_{15}N_2O_2S$ 239.0854, found 239.0846; t_R: 2.25 (method A).

4.2.6. (*S*)-5-*sec*-Butyl-3-(thien-3-yl)imidazolidine-2,4-dione (3f). Yield 68%; black solid; mp 100 °C; $[\alpha]_D^{20}$ −71.6 (c 0.1, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.54 (s, 1H), 7.66 (dd, 1H, J=3.2, 0.8 Hz), 7.58 (dd, 1H, J=5.1, 3.2 Hz), 7.37 (dd, 1H, J=5.1, 0.8 Hz), 4.16 (d, 1H, J= 3.0 Hz), 1.88 (m, 1H), 1.36 (m, 1H), 1.23 (m, 1H), 0.96 (d, 3H, J=6.9 Hz), 0.87 (t, 3H, J=7.4 Hz); ^{13}C NMR (DMSO-d_6): δ 172.1, 155.4, 130.0, 125.1, 123.5, 117.8, 60.6, 36.6, 23.4, 15.1, 11.5; HRMS: calcd for [M+H$^+$] $C_{11}H_{15}N_2O_2S$ 239.0854, found 239.0852; t_R: 2.15 (method A).

4.2.7. (*S*)-5-Benzyl-3-(thien-3-yl)imidazolidine-2,4-dione (3g). Yield 81%; grey solid; mp 161 °C (decomp.); $[\alpha]_D^{20}$ −22.2 (c 0.2, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.54 (s, 1H), 7.52 (dd, 1H, J=5.2, 3.2 Hz), 7.46 (dd, 1H, J=3.2, 1.3 Hz), 7.26 (m, 5H), 7.11 (dd, 1H, J=5.2, 1.3 Hz), 4.53 (t, 1H, J=5.0 Hz), 3.06 (d, 2H, J=4.9 Hz); ^{13}C NMR (DMSO-d_6): δ 172.0, 154.8, 135.1, 129.8, 129.7, 128.1, 126.8, 125.1, 123.4, 118.0, 56.8, 36.7; HRMS: calcd for [M+H$^+$] $C_{14}H_{13}N_2O_2S$ 273.0698, found 273.0667; t_R: 2.26 (method A).

4.2.8. (*S*)-Tetrahydro-2-(thien-3-yl)-2*H*-pyrrolo[1,2-*e*]-imidazole-1,3-dione (3h). Yield 79%; isolated as brown oil; $[\alpha]_D^{20}$ −34.9 (c 0.2, DMSO); ^{1}H NMR (DMSO-d_6): δ 7.69 (dd, 1H, J=3.1, 1.0 Hz), 7.59 (dd, 1H, J=5.2, 3.2 Hz), 7.37 (dd, 1H, J=5.2, 1.0 Hz), 4.33 (dd, 1H, J=8.9, 7.6 Hz), 3.56 (m, 1H), 3.25 (m, 1H), 2.08 (m, 3H), 1.83 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 172.1, 158.3, 130.2, 125.2, 123.5, 118.2, 62.5, 45.4, 26.7, 26.5; HRMS: calcd for [M+H$^+$] $C_{10}H_{11}N_2O_2S$ 223.0541, found 223.0545; t_R: 1.73 (method A).

4.2.9. (*S*)-5-(Hydroxymethyl)-3-(thien-3-yl)imidazolidine-2,4-dione (3i). Yield 72%; brown solid; mp 111 °C; $[\alpha]_D^{20}$ −86.4 (c 0.3, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.41 (s, 1H), 7.66 (d, 1H, J=3.2 Hz), 7.57 (dd, 1H, J=5.0, 3.3 Hz), 7.40 (d, 1H, J=5.2 Hz), 5.16 (t, 1H, J=5.1 Hz), 4.21 (s, 1H), 3.76 (m, 1H), 3.66 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 171.4, 155.6, 130.3, 125.0, 123.3, 117.3, 60.0, 58.8; HRMS: calcd for [M+H$^+$] $C_8H_9N_2O_3S$ 213.0334, found 213.0334; t_R: 0.92 (method A).

4.2.10. (*S*)-5-((*R*)-1-Hydroxyethyl)-3-(thien-3-yl)imidazolidine-2,4-dione (3j). Yield 64%; isolated as brown gum; ^{1}H NMR (DMSO-d_6): δ 8.52 (s, 1H), 7.66 (dd, 1H, J=3.2, 1.3 Hz), 7.57 (dd, 1H, J=5.2, 3.2 Hz), 7.40 (dd, 1H, J=5.2, 1.3 Hz), 5.04 (d, 1H, J=4.8 Hz), 4.06 (d, 1H, J=0.8 Hz), 4.05 (br s, 1H), 1.20 (d, 1H, J=6.4 Hz); ^{13}C NMR (DMSO-d_6): δ 171.5, 155.9, 130.4, 124.9, 123.3, 117.1, 65.4, 62.2, 20.2; HRMS: calcd for [M+H$^+$] $C_9H_{11}N_2O_3S$ 227.0490, found 227.0506; t_R: 1.07 (method A).

4.2.11. (*S*)-5-(4-Hydroxybenzyl)-3-(thien-3-yl)imidazolidine-2,4-dione (3k). Yield 86%; beige solid; mp 165 °C; $[\alpha]_D^{20}$ −11.0 (c 0.2, DMSO); ^{1}H NMR (DMSO-d_6): δ 9.22 (s, 1H), 8.47 (s, 1H), 7.52 (dd, 1H, J=3.2, 1.0 Hz), 7.46 (dd, 1H, J=5.1, 3.2 Hz), 7.12 (dd, 1H, J=5.1, 1.0 Hz), 7.00 (d, 2H, J=8.2 Hz), 6.67 (d, 2H, J=8.2 Hz), 4.43 (t, 1H, J=4.4), 2.94 (d, 2H, J=2.5 Hz); ^{13}C NMR (DMSO-d_6): δ 172.1, 156.2, 154.9, 130.7, 129.9, 125.1, 125.0, 123.5, 118.0, 114.9, 57.1, 35.9; HRMS: calcd for [M+H$^+$] $C_{14}H_{13}N_2O_3S$ 289.0647, found 289.0665; t_R: 1.77 (method A).

4.2.12. (*S*)-5-(2-(Methylthio)ethyl)-3-(thien-3-yl)imidazolidine-2,4-dione (3l). Yield 89%; beige solid; mp 94 °C; $[\alpha]_D^{20}$ −4.8 (c 0.3, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.58 (s, 1H), 7.66 (s, 1H), 7.58 (d, 1H, J=4.6 Hz), 7.38 (d, 1H, J=4.6 Hz), 4.30 (t, 1H, J=5.4 Hz), 2.60 (t, 2H, J=7.2 Hz), 2.06 (s, 3H), 1.93 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 172.5, 155.1, 130.2, 125.0, 123.6, 117.9, 54.9, 30.7, 28.7, 14.4; HRMS: calcd for [M+H$^+$] $C_{10}H_{13}N_2O_2S_2$ 257.0418, found 257.0422; t_R: 1.95 (method A).

4.2.13. (3-((*S*)-2,5-Dioxo-1-(thien-3-yl)imidazolidin-4-yl)propyl)guanidine hydrochloride salt (3m). Soluble in water, yield 69%; beige oil; $[\alpha]_D^{20}$ −26.5 (c 0.4, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.64 (s, 1H), 7.89 (br s, 1H), 7.66 (dd, 1H, J=3.0, 1.0 Hz), 7.58 (dd, 1H, J=5.0, 3.2 Hz), 7.37 (dd, 1H, J=5.1, 0.9 Hz), 7.32 (br s, 3H), 4.22 (t, 1H, J=5.6 Hz), 3.15 (d, 2H, J=5.7 Hz), 1.82 (m, 1H), 1.60 (m,

3H); ^{13}C NMR (DMSO-d_6): δ 172.7, 157.0, 155.2, 130.1, 125.1, 123.6, 118.0, 55.7, 40.3, 28.7, 24.3; HRMS: calcd for [M+H$^+$] $C_{11}H_{16}N_5O_2S$ 282.1025, found 282.1022; t_R: 1.26 (method A).

4.2.14. (*S*)-5-((1*H*-Imidazol-4-yl)methyl)-3-(thien-3-yl)-imidazolidine-2,4-dione hydrochloride salt (3n). Soluble in water, yield 73%; white solid; mp 170 °C; $[\alpha]_D^{20}$ −40.1 (*c* 1.0, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.98 (s, 1H), 8.64 (s, 1H), 7.64 (d, 1H, *J*=3.1 Hz), 7.58 (dd, 1H, *J*=4.9, 3.3 Hz), 7.46 (s, 1H), 7.33 (d, 1H, *J*=5.1 Hz), 4.55 (t, 1H, *J*=6.2 Hz), 3.24 (dd, 1H, *J*=15.2, 4.8 Hz), 3.10 (dd, 1H, *J*=15.2, 7.7 Hz); ^{13}C NMR (DMSO-d_6): δ 171.4, 155.0, 134.2, 129.9, 128.2, 125.2, 123.5, 118.1, 117.4, 55.3, 26.9; HRMS: calcd for [M+H$^+$] $C_{11}H_{11}N_4O_2S$ 263.0603, found 263.0589; t_R: 1.07 (method A).

4.2.15. (*S*)-5-((1*H*-Indol-3-yl)methyl)-3-(thien-3-yl)-imidazolidine-2,4-dione (3o). Yield 71%; beige solid; mp 92 °C; $[\alpha]_D^{20}$ −105.6 (*c* 0.2, DMSO); ^{1}H NMR (DMSO-d_6): δ 10.89 (s, 1H), 8.49 (s, 1H), 7.58 (d, 1H, *J*=7.8 Hz), 7.47 (dd, 1H, *J*=5.2, 3.2 Hz), 7.35 (dd, 1H, *J*=3.2, 1.2 Hz), 7.31 (d, 1H, *J*=8.1 Hz), 7.16 (d, 1H, *J*=2.2 Hz), 7.03 (m, 3H), 4.51 (t, 1H, *J*=4.7 Hz), 3.20 (t, 2H, *J*=4.4 Hz); ^{13}C NMR (DMSO-d_6): δ 173.0, 155.5, 136.3, 130.4, 127.8, 125.4, 124.7, 123.8, 121.3, 119.0, 118.8, 118.1, 111.7, 107.9, 57.2, 27.3; HRMS: calcd for [M+H$^+$] $C_{16}H_{14}N_3O_2S$ 312.0807, found 312.0825; t_R: 2.25 (method A).

4.2.16. 2-((*S*)-2,5-Dioxo-1-(thien-3-yl)imidazolidin-4-yl)-acetic acid (3p). Yield 61%; brown solid; mp >190 °C; $[\alpha]_D^{20}$ −61.7 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6): δ 12.56 (s, 1H), 8.45 (s, 1H), 7.63 (dd, 1H, *J*=3.2, 1.3 Hz), 7.58 (dd, 1H, *J*=5.2, 3.2 Hz), 7.37 (dd, 1H, *J*=5.2, 1.3 Hz), 4.40 (t, 1H, *J*=4.8 Hz), 2.78 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 172.7, 171.3, 155.9, 130.9, 125.4, 123.9, 118.0, 53.1, 35.8; HRMS: calcd for [M+H$^+$] $C_9H_9N_2O_4S$ 241.0283, found 241.0291; t_R: 1.18 (method A).

4.2.17. 3-((*S*)-2,5-Dioxo-1-(thien-3-yl)imidazolidin-4-yl)-propanoic acid (3q). Yield 69%; beige solid, orange crystals; mp 125 °C; $[\alpha]_D^{20}$ −40.2 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6): δ 12.00 (br s, 1H), 8.57 (s, 1H), 7.66 (dd, 1H, *J*=3.2, 1.2 Hz), 7.58 (dd, 1H, *J*=5.2, 3.2 Hz), 7.38 (dd, 1H, *J*=5.2, 1.2 Hz), 4.23 (dd, 1H, *J*=7.3, 5.3 Hz), 2.39 (t, 2H, *J*=7.7 Hz), 2.03 (m, 1H), 1.84 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 173.6, 172.5, 155.1, 130.1, 125.0, 123.6, 118.0, 55.2, 29.1, 26.9; HRMS: calcd for [M+H$^+$] $C_{10}H_{11}N_2O_4S$ 255.0440, found 255.0443; t_R: 1.33 (method A).

4.2.18. 2-((*S*)-2,5-Dioxo-1-(thien-3-yl)imidazolidin-4-yl)acetamide (3r). Et_3N was added to a stirring suspension of 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione **1** (0.100 g, 0.60 mmol) and the L-Asn (0.078 g, 0.60 mmol) in water (4 mL). The suspension was stirred at room temperature for 5 min. Volatile material is evaporated as best as possible. The residue is dissolved in AcOH (5 mL), transferred in a microwave reaction vial, capped, and stirred under microwave irradiation at 150 °C for 20 min. Volatile material is evaporated under reduced pressure and the residue is purified by reverse phase HPLC (method B). Soluble in water; yield 41%; yellow oil; $[\alpha]_D^{20}$ −67.2 (*c* 0.4, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.39 (s, 1H), 7.63 (dd, 1H, *J*=3.0, 1.0 Hz), 7.56 (dd, 1H, *J*=4.8, 3.0 Hz), 7.45 (s, 1H), 7.38 (dd, 1H, *J*=4.7, 1.0 Hz), 6.94 (s, 1H), 4.36 (t, 1H, *J*=4.5 Hz), 2.62 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 172.8, 170.2, 155.5, 130.6, 125.0, 123.6, 117.7, 53.0, 36.1; HRMS: calcd for [M+H$^+$] $C_9H_{10}N_3O_3S$ 240.0443, found 240.0431; t_R: 0.93 (method A).

4.2.19. 3-((*S*)-2,5-Dioxo-1-(thien-3-yl)imidazolidin-4-yl)-propanamide (3s). Synthetic procedure same as **3r**. Soluble in water; yield 56%; white solid; mp 149 °C; $[\alpha]_D^{20}$ −42.6 (*c* 0.5, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.55 (s, 1H), 7.66 (dd, 1H, *J*=3.0, 1.0 Hz), 7.58 (dd, 1H, *J*=5.1, 3.2 Hz), 7.38 (dd, 1H, *J*=5.2, 1.0 Hz), 7.33 (s, 1H), 6.79 (s, 1H), 4.23 (t, 1H, *J*=5.8 Hz), 2.20 (m, 2H), 1.99 (m, 1H), 1.86 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 173.2, 172.6, 155.1, 130.1, 125.0, 123.6, 117.9, 55.4, 29.8, 27.3; HRMS: calcd for [M+H$^+$] $C_{10}H_{12}N_3O_3S$ 254.0599, found 254.0602; t_R: 1.13 (method A).

4.2.20. (*S*)-5-(4-Aminobutyl)-3-(thien-3-yl)imidazolidine-2,4-dione hydrochloride salt (3t). Soluble in water; yield 63%; white solid; mp 91 °C; $[\alpha]_D^{20}$ −40.2 (*c* 0.1, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.58 (d, 1H, *J*=2.7 Hz), 7.87 (br s, 3H), 7.67 (dd, 1H, *J*=3.1, 1.1 Hz), 7.58 (dd, 1H, *J*=5.1, 3.2 Hz), 7.39 (dd, 1H, *J*=5.2, 1.1 Hz), 4.21 (t, 1H, *J*=5.4 Hz), 2.77 (t, 2H, *J*=6.5 Hz), 1.77–1.40 (m, 6H); ^{13}C NMR (DMSO-d_6): δ 173.1, 155.5, 130.5, 125.5, 124.0, 118.3, 56.1, 39.0, 31.0, 27.0, 21.4; MS (ESI, *m*/*z*) 254.2 [M+H]$^+$; t_R: 1.22 (method A).

4.2.21. (*R*)-5-(Mercaptomethyl)-3-(thien-3-yl)imidazolidine-2,4-dione (3u). From H–Cys(Trt)–OH and deprotection of Trt using TFA/TIS (95:5) and extraction from Et_2O; yield 62%; white solid; mp 115 °C; $[\alpha]_D^{20}$ −75.7 (*c* 0.2, DMSO); ^{1}H NMR (DMSO-d_6): δ 8.50 (s, 1H), 7.67 (d, 1H, *J*=3.2 Hz), 7.59 (dd, 1H, *J*=5.1, 3.4 Hz), 7.37 (d, 1H, *J*=5.2 Hz), 4.50 (t, 1H, *J*=3.9 Hz), 2.90 (dd, 2H, *J*=9.0, 4.0 Hz), 2.38 (t, 1H, *J*=8.4 Hz); ^{13}C NMR (DMSO-d_6): δ 171.7, 155.8, 130.4, 125.6, 123.8, 118.3, 57.7, 25.7; HRMS: calcd for [M+H$^+$] $C_8H_9N_2O_2S_2$ 229.0105, found 229.0115; t_R: 1.49 (method A).

4.2.22. *N*-[(3-Thienylamino)carbonyl]-β-alanine (5). Compound **5** was obtained by the same experimental procedure described for imidazolidine-2,4-dione **3** synthesis. Yield 88%; beige solid; mp 150 °C; ^{1}H NMR (DMSO-d_6): δ 12.21 (s, 1H), 8.79 (s, 1H), 7.36 (t, 1H, *J*=4.0 Hz), 7.13 (d, 1H, *J*=2.3 Hz), 6.93 (d, 1H, *J*=5.0 Hz), 6.13 (t, 1H, *J*=5.5 Hz), 3.28 (q, 2H, *J*=6.2 Hz), 2.40 (t, 2H, *J*=6.4 Hz); ^{13}C NMR (DMSO-d_6): δ 173.3, 154.9, 138.1, 124.3, 121.1, 104.4, 35.3, 34.7; MS (ESI, *m*/*z*) 215.1 [M+H]$^+$; t_R: 1.21 (method A).

4.3. X-ray crystallographic data

The structure of compound **3q** has been established by X-ray crystallography (Fig. 1).[30] Orange single crystal ($0.15\times0.15\times0.20$ mm^3) of **3q** was obtained by slow evaporation from methanol/hexanes (30:70) solution: monoclinic, space group *P*21, *a*=10.3637(11) Å, *b*=5.8786(8) Å, *c*=17.951(2) Å, α=90.0°, β=100.403(8)°, γ=90.0°, *V*=1075.7(2) Å^3, *Z*=4, δ (calcd)=1.570 Mg m^{-3}, FW=254.26 for $C_{10}H_{10}N_2O_2S$, *F*(000)=528. Intensities were collected with a Rigaku R-Axis diffractometer using the CuKα

radiation. The data were corrected for Lorentz and polarization effects and for empirical absorption correction.[31] The structure was solved by direct methods SHELX 86[32] and refined using SHELX 93[33] suite of programs.

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