Regio-Controlled Nucleophilic Attack of 3-Thiaisatoic Anhydride by α-Amino Acids: One-Pot Synthesis of 3-(2-Thienyl)imidazolidine-2,4-dione and 3,4-Substituted Thieno[2,3-*e*][1,4]diazepine-2,5-dione Analogues

Yann Brouillette, Guillaume Sujol, Jean Martinez, Vincent Lisowski*

Institut des Biomolécules Max-Mousseron (IBMM), UMR 5247, Universités Montpellier I et II, UFR des Sciences Pharmaceutiques et Biologiques, 15 Avenue Charles Flahault, 34093 Montpellier, France
Fax +33(4)67548654; E-mail: vincent.lisowski@univ-montp1.fr

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Abstract: Convenient syntheses of optically pure 3-(2-thienyl)imidazolidine-2,4-dione (35–63% yields) and 3,4-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione (35–81% yields) analogues are described. The regioselective ring opening of 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (3-thiaisatoic anhydride), using inexpensive natural and synthetic α-amino acids under aqueous conditions, has been investigated to afford two libraries in a one-pot process.

Key words: thiaisatoic anhydride, 3-(2-thienyl)imidazolidine-2,4-dione, thieno[2,3-*e*][1,4]diazepine-2,5-dione, diazepine, oxazinedione

The androgen receptor (AR), a member of the steroid and nuclear receptor superfamily, constitutes an important target in medicinal chemistry.[1] Among non-steroidal AR ligands, the hydantoin scaffold[2,3] was found to be useful in the design of various antagonists such as nilutamide,[4] which is currently involved in the management of prostate cancer (Figure 1). More recently, this antiandrogen was chemically modified, leading to the discovery of novel selective androgen receptor modulators (SARMs) such as *N*-arylbicyclohydantoins **1** (Figure 1).[5] These anabolic SARMs are presently under clinical trials for the treatment of muscle wasting, the hypogonadism of aging, osteoporosis and female sexual dysfunction.[6] In conjunction with our ongoing interest in the reactivity of ring-fused oxazinediones and our library screening program, we have recently reported an efficient chemical process for the generation of a series of optically pure hydantoin derivatives from thieno[3,2-*d*][1,3]oxazinedione **2** (Figure 1).[7] In contrast to isatoic anhydride **4** (Figure 1), for which the nucleophilic attack only takes place on the carboxylic carbonyl,[8] its five-membered fused analogues such as pyrazole,[9] furan[10,11] or thiophene[12] display a different reactivity occurring mainly at their carbamic carbonyl. Alternatively, we demonstrated that ring opening of the cyclic anhydride of 3-aminothenoic acid **2** by natural amino acids can be regiocontrolled in protic conditions towards either the diazepine[13] or the hydantoin[7] scaffolds, in neutral or basic medium, respectively. In these biological and chemical contexts, we now report a reactivity study of

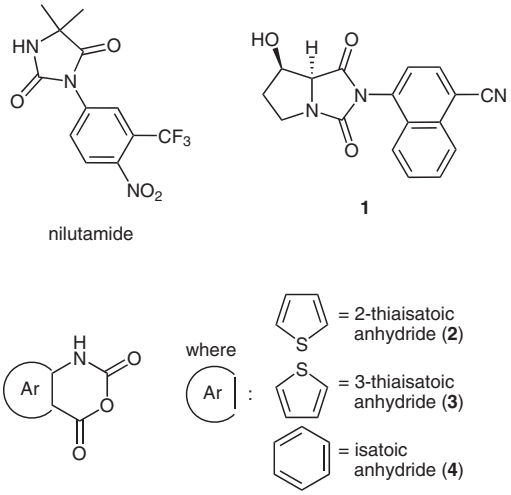

Figure 1 Representative chemical structures

the isomeric thieno[2,3-*d*][1,3]oxazinedione **3** (Figure 1) to generate potential hydantoin-based SARMs.

This previously described[14] 3-thiaisatoic anhydride **3**, has already been used as the key intermediate in the synthesis of thienopyridinones,[15–18] thienopyrimidinediones,[19] thienoimidazolones[20] and tricyclic pyrrolothienodiazepines.[21] In the case of this study, the anhydride **3** was prepared using a three-step process from 2,5-dihydroxy-1,4-dithiane and ethylcyanoacetate.[16,22] The first part of this work was dedicated to demonstrating that regioselective ring opening of this anhydride by α-amino acids could be performed. Relying on our precedent studies of the isomeric anhydride **2**,[13] our primary assays were carried in neutral water with 1000 mol% of alanine (R^1 = H and R^2 = CH_3; Scheme 1) and monitored by LC-MS at 214 nm. From room temperature to 50 °C, no conversion of the starting material was observed after 48 hours of stirring. At higher temperatures (50–100 °C), progressive amounts of hydrolyzed products were observed (5% at 50 °C rising to 35% at 100 °C), with concomitant but less significant formation of the expected amide **5**. This preliminary result seemed to prove that 3-thiaisatoic anhydride **3** was more stable than its isomeric counterpart **2**. This observation prompted us to envisage the use of dioxane, tetrahydrofuran or *N*,*N*-dimethylformamide as organic solvents. Unfortunately, only ureido-diacid **7** (20%) was formed, with residual starting material (80%) and no

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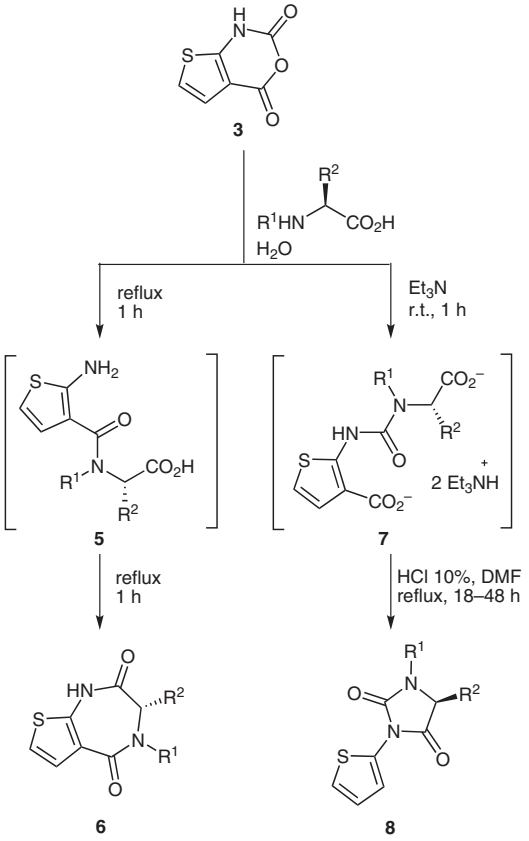
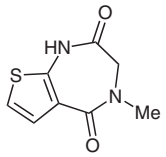
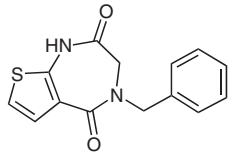
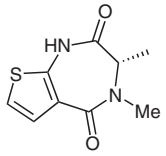
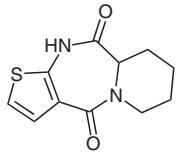
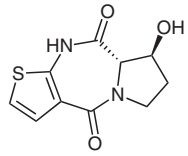
hydrolyzed products after stirring for two hours at reflux. By using a water–dioxane (1:1) mixture, as previously described for access to the pyrrolothienodiazepine scaffold,[21] no selectivity was observed (35% ureido-diacid **7**, 40% amide **5**, 35% hydrolyzed products) and similar results were obtained with other *N*-unsubstituted α-amino acids (R^1 = H). On the other hand, when alanine was replaced by its *N*-alkylated analogue ($R^1 = R^2 = CH_3$), the reaction in water after one hour at reflux, allowed a quantitative and chemo-selective ring opening at the carboxylic carbonyl. Interestingly, it was observed that extended heating allowed direct cyclocondensation in a one-pot process (Scheme 1). Therefore, *N*-benzylglycine, sarcosine, pipecolic acid and 3-hydroxyproline were also submitted to the same protic neutral conditions to form the corresponding optically pure thienodiazepines **6a**–**e** in yields of 35–81% (Table 1). Even though the reaction with acyclic natural α-amino acids was not regioselective for ring opening at the carboxylic carbonyl, it appears that the nucleophilic character of *N*-alkylated α-amino acid plays an essential role in the kinetics of this opening versus hydrolysis under neutral aqueous conditions. Moreover, due to partial *cis*/*trans* geometry induced by *N*-alkylation of the amide bond ($R^1 \neq$ H), the classical intramolecular ring closure to afford diazepines under acidic conditions (AcOH) was overcome by an additional one hour reflux in water.



Scheme 1 Synthesis of 3,4-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione (**6**) and 3-(2-thienyl)imidazolidine-2,4-dione (**8**) analogues

Table 1 Synthesis of 3,4-Dihydro-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione Analogues **6a**–**e**

Product	Structure	Yield (%)
6a		81
6b		75
6c		80
6d		63
6e		35

Therefore, in order to develop access to the hydantoin scaffold, 3-thiaisatoic anhydride **3** was submitted to nucleophilic attack of natural and synthetic α-amino acids under basic conditions. It was found that addition of triethylamine in water was required to allow ring opening by α-amino acids at room temperature. Under these conditions, totally opposite reactivity was observed, which led to ureido-diacids **7** (Scheme 1), as previously reported with isomer **2**.[7] This result is in accordance with the existence of a putative highly reactive isocyanate intermediate, for which the formation could be subordinated to ionization of oxazine **3** under basic conditions, directing the nucleophilic attack towards the carbamic carbonyl.[23] Moreover, under such conditions, quantitative transformation was observed in one hour at room temperature versus five minutes for the anhydride **2**, confirming the higher stability of this isomer, as also observed in the diazepine pathway. To validate the method, acyclic, cyclic, α-disubstituted and *N*-alkylated α-amino acids were examined in order to provide only the corresponding ureido-diacids **7**. Ascertained by LC-MS, once all the starting material was consumed, the subsequent cyclocondensation was performed by addition of 10% aqueous hydrochloric acid, DMF and conventional heating at reflux for 18 to 48 hours. In this reaction, the hydantoins **8** were predominantly formed with residual persistence (~10%) of their non-decarboxylated analogues (such as **9c**,

Table 2 Synthesis of 3-(2-Thienyl)imidazolidine-2,4-dione Analogues **8** and **9**

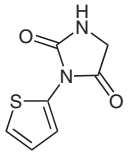
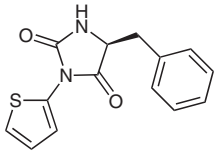
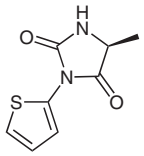
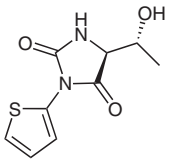
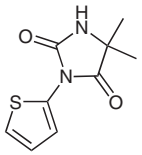
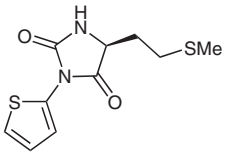
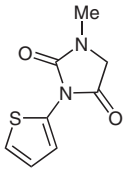
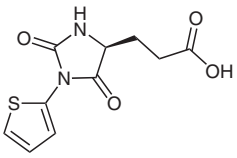
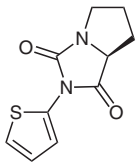
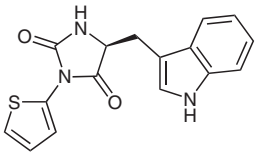
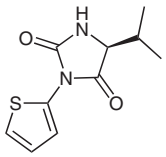
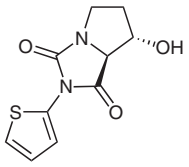
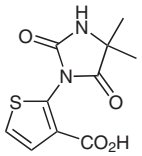
Product	Structure	Yield (%)	Product	Structure	Yield (%)
8a		55	**8g**		54
8b		36	**8h**		56
8c		51	**8i**		37
8d		37	**8j**		55
8e		45	**8k**		63
8f		53	**8l**		35
9c		10			

Table 2).[24] In comparison with 2-thiaisatoic anhydride **2**, decarboxylation at the β-position of the thiophene ring was slower. When cyclization occurs faster than the decarboxylation, it is no longer possible to decarboxylate the hydantoin formed. Prolonged heating, microwave irradiation and classical decarboxylative conditions, such as copper catalysis in quinoline,[25,26] were all ineffective. Nevertheless, this by-product could be easily removed by alkaline aqueous washing (when R^2 is not an acid-containing side chain) to provide the expected optically pure hydantoins **8** in 35–63% yields (Table 2).

Even though 3-thiaisatoic anhydride **3** is more stable than its 2-thiaisatoic anhydride isomer **2**, in the presence of α-amino acids it still proved to be a flexible intermediate in the synthesis of valuable heterocycles. To this end, a series of five 3,4-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione analogues **6** was synthesized in 35–81% yields through treatment of 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (**3**) with *N*-substituted α-amino acids under neutral conditions. Hence, a library of twelve optically pure 3-(2-thienyl)imidazolidine-2,4-dione derivatives **8** was also synthesized in 35–63% yields from the same precursor with natural and synthetic α-amino acids in a one-pot procedure. This versatile reactivity of thiaisatoic anhydride prompts us to apply this convenient methodology to the design of potential SARMS, comparable to compound **8l**.

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 ESI-Q or Q-TOF analyses. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at r.t. in DMSO-d_6. Chemical shifts (δ) are reported in parts per million (ppm) downfield/upfield from residual DMSO (δ = 2.50 and 39.5 ppm) or residual $CHCl_3$ (δ = 7.26 and 77.2 ppm); coupling constants (*J*) are reported in hertz (Hz). The quaternary carbon of the thiophene ring emits a very weak signal on the ^{13}C NMR spectrum in comparison to all other signals of the molecule. 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 gradients of eluents A:B, 100:0→0:100 [eluents: A (H_2O + 0.1% TFA) and B (MeCN + 0.1% TFA)] over 5 min (method A). Retention times (t_R) are reported as: 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→0:100, A:B over 40 min (method B). Analytical thin-layer chromatography (TLC) was performed using aluminum-backed silica gel plates coated with a 0.2 mm thickness of silica gel.

3,4-Dihydro-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione Analogues (6); General Procedure

A suspension of 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (**3**; 0.300 g, 1.80 mmol) and the corresponding α-amino acid (4.50 mmol) in H_2O (15 mL) was stirred under reflux for 1–2 h. The resulting suspension was filtered over a frit and partitioned between H_2O (15 mL) and EtOAc (15 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried over Na_2SO_4, filtered, evaporated and purified by flash chromatography[27] to afford the corresponding diazepinedione **6**, which was stored in a stoppered flask.

3,4-Dihydro-4-methyl-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione (6a)

Yield: 81%; brown solid; mp 170 °C (dec); t_R = 1.08 min (method A).

^{1}H NMR (DMSO-d_6): δ = 11.19 (s, 1 H), 7.09 (s, 2 H), 3.93 (s, 2 H), 3.04 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 168.3, 163.3, 144.0, 127.2, 123.2, 117.6, 53.0, 35.6.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_8H_9N_2O_2S$: 197.0385; found: 197.0381.

4-Benzyl-3,4-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione (6b)

Yield: 75%; black solid; mp 145–148 °C; t_R = 1.78 min (method A).

^{1}H NMR (DMSO-d_6): δ = 11.19 (s, 1 H), 7.30 (m, 5 H), 7.14 (m, 2 H), 4.70 (s, 2 H), 3.94 (s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 168.3, 163.3, 144.4, 137.2, 128.5, 127.6, 127.4, 127.3, 122.7, 117.6, 51.7, 51.0.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{14}H_{13}N_2O_2S$: 273.0698; found: 273.0674.

(*S*)-3,4-Dihydro-3,4-dimethyl-1*H*-thieno[2,3-*e*][1,4]diazepine-2,5-dione (6c)

Yield: 80%; light-beige solid; mp 180 °C (dec); $[\alpha]_D^{20}$ +314.2 (*c* 0.1, DMSO); t_R = 1.18 min (method A).

^{1}H NMR (DMSO-d_6): δ = 11.15 (s, 1 H), 7.09 (d, *J* = 0.6 Hz, 2 H), 4.24 (q, *J* = 7.0 Hz, 1 H), 2.89 (s, 3 H), 1.33 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 169.4, 163.6, 143.4, 127.0, 124.3, 117.7, 52.4 (br s), 28.7 (br s), 12.4.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_9H_{11}N_2O_2S$: 211.0541; found: 211.0527.

7,8,9,9*a*-Tetrahydropyrido[1,2-*a*]thieno[2,3-*e*][1,4]diazepine-4,10(6*H*, 11*H*)dione (6d)

Yield: 63% (from a racemic mixture of piperidine-2-carboxylic acid); white solid; mp 170–172 °C; t_R = 1.49 min (method A).

^{1}H NMR (DMSO-d_6): δ (mixture of two conformers) = 11.13 (s, 1 H), 7.12 (d, *J* = 5.7 Hz, 1 H), 7.09 (d, *J* = 5.7 Hz, 1 H), 4.23 (m, 2 H), 2.82 (m, 1 H), 2.07 (m, 1 H), 1.62 (m, 5 H).

^{13}C NMR (DMSO-d_6): δ (conformer A) = 169.6, 163.8, 143.8, 126.8, 123.9, 117.8, 51.8, 39.1, 22.5, 22.1, 18.3; δ (conformer B) = 171.6, 162.4, 152.0, 137.0, 127.5, 125.7, 56.8, 39.1, 26.6, 24.6, 22.0.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{11}H_{13}N_2O_2S$: 237.069; found: 237.0668.

(8*S*,8*aS*)-8-Hydroxy-6,7,8,8*a*-tetrahydro-4*H*-pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine-4,9(10*H*)-dione (6e)

Yield: 35%; white solid; mp >200 °C; $[\alpha]_D^{20}$ +200.8 (*c* 0.2, DMSO); t_R = 0.82 min (method A).

^{1}H NMR (DMSO-d_6): δ = 11.27 (br s, 1 H), 7.12 (m, 2 H), 5.23 (s, 1 H), 4.75 (s, 1 H), 3.94 (s, 1 H), 3.56 (m, 2 H), 1.91 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 168.5, 161.6, 143.5, 126.4, 124.1, 117.9, 70.4, 65.4, 44.6, 31.7.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{11}N_2O_3S$: 239.0490; found: 239.0477.

3-(Thien-3-yl)imidazolidine-2,4-diones (8); General Procedure

Et_3N (0.72 mmol) was added to a stirring suspension of 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (**3**; 0.100 g, 0.60 mmol) and the corresponding α-amino acid (0.66 mmol) in H_2O (4 mL). The suspension was stirred at r.t. for 1 h until homogeneity. HCl (10%, 2 mL) was added until pH 1. Drops of DMF were added until the solution became homogenous. The reaction was stirred under reflux for 18–48 h, then the resulting solution was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ (10%, 3 × 10 mL; except for **8j**) and brine (2 × 10 mL), dried over Na_2SO_4, filtered, evaporated and purified by reverse-phase preparative HPLC to afford the corresponding imidazolidinedione **8**, which were stored in stoppered flasks.

3-(2-Thienyl)imidazolidine-2,4-dione (8a)

Yield: 55%; brown solid; mp 130–134 °C; t_R = 1.03 min (method A).

^{1}H NMR (DMSO-d_6): δ = 8.49 (s, 1 H), 7.40 (dd, *J* = 3.8, 1.4 Hz, 1 H), 7.36 (dd, *J* = 5.5, 1.4 Hz, 1 H), 7.02 (dd, *J* = 5.5, 3.8 Hz, 1 H), 4.08 (d, *J* = 0.9 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 169.8, 155.3, 132.8, 124.8, 121.7, 119.3, 45.6.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_7H_7N_2O_2S$: 183.0150; found: 183.0147.

(*S*)-5-Methyl-3-(2-thienyl)imidazolidine-2,4-dione (8b)

Yield: 36%; brown solid; mp 99–102 °C; $[\alpha]_D^{20}$ –4.2 (*c* 0.1, DMSO); t_R = 1.31 min (method A).

^{1}H NMR (DMSO-d_6): δ = 8.66 (s, 1 H), 7.40 (d, *J* = 3.4 Hz, 1 H), 7.36 (d, *J* = 5.4 Hz, 1 H), 7.02 (dd, *J* = 5.1, 4.0 Hz, 1 H), 4.28 (q, *J* = 6.9 Hz, 1 H), 1.34 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 173.1, 154.6, 133.2, 125.2, 122.1, 119.6, 52.2, 17.4.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_8H_9N_2O_2S$: 197.0306; found: 197.0316.

5,5-Dimethyl-3-(2-thienyl)imidazolidine-2,4-dione (8c)
Yield: 51%; beige solid (soluble in Et_2O); mp 100–102 °C; t_R = 1.53 min (method A).

^{1}H NMR ($CDCl_3$): δ = 7.51 (dd, *J* = 3.8, 1.3 Hz, 1 H), 7.16 (dd, *J* = 5.5, 1.3 Hz, 1 H), 7.00 (dd, *J* = 5.5, 3.9 Hz, 1 H), 6.36 (br s, 1 H), 1.54 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 174.7, 154.3, 131.1, 125.2, 121.8, 120.1, 58.6, 25.4.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_9H_{11}N_2O_2S$: 211.0541; found: 211.0521.

1-Methyl-3-(2-thienyl)imidazolidine-2,4-dione (8d)
Yield: 37%; brown solid; mp 109 °C; t_R = 1.22 min (method A).

^{1}H NMR (DMSO-d_6): δ = 7.38 (s, 2 H), 7.02 (s, 1 H), 4.12 (s, 2 H), 2.93 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 168.1, 154.4, 132.8, 124.9, 121.8, 119.4, 51.0, 29.5.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_8H_9N_2O_2S$: 197.0385; found: 197.0386.

(*S*)-Tetrahydro-2-(2-thienyl)-2*H*-pyrrolo[1,2-*e*]imidazole-1,3-dione (8e)
Yield: 45%; grey solid; mp 81–84 °C; $[\alpha]_D^{20}$ –8.1 (*c* 0.1, DMSO); t_R = 1.64 min (method A).

^{1}H NMR (DMSO-d_6–D_2O, 9:1): δ = 7.34 (dd, *J* = 5.5, 1.3 Hz, 1 H), 7.25 (dd, *J* = 3.8, 1.3 Hz, 1 H), 7.01 (dd, *J* = 5.5, 3.8 Hz, 1 H), 4.32 (dd, *J* = 9.4, 7.4 Hz, 1 H), 3.50 (m, 1 H), 3.24 (m, 1 H), 2.06 (m, 3 H), 1.85 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 171.8, 157.9, 133.0, 125.3, 122.5, 120.2, 62.9, 45.8, 26.9, 26.9.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{11}N_2O_2S$: 223.0541; found: 223.0548.

(*S*)-5-Isopropyl-3-(2-thienyl)imidazolidine-2,4-dione (8f)
Yield: 53%; brown solid; mp 93–95 °C; $[\alpha]_D^{20}$ –62.1 (*c* 0.1, DMSO); t_R = 1.88 min (method A).

^{1}H NMR (DMSO-d_6): δ = 8.74 (s, 1 H), 7.40 (d, *J* = 3.3 Hz, 1 H), 7.37 (d, *J* = 5.5 Hz, 1 H), 7.02 (dd, *J* = 5.4, 3.5 Hz, 1 H), 4.17 (d, *J* = 2.9 Hz, 1 H), 2.13 (m, 1 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 171.4, 154.8, 132.5, 124.9, 121.8, 119.3, 61.1, 29.9, 18.4, 15.9.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{13}N_2O_2S$: 225.0698; found: 225.0698.

(*S*)-5-Benzyl-3-(2-thienyl)imidazolidine-2,4-dione (8g)
Yield: 54%; brown solid; mp 114–115 °C; $[\alpha]_D^{20}$ –69.1 (*c* 0.1, DMSO); t_R = 2.17 min (method A).

^{1}H NMR (DMSO-d_6): δ = 8.71 (s, 1 H), 7.33–7.16 (m, 7 H), 6.96 (dd, *J* = 5.5, 3.8 Hz, 1 H), 4.58 (t, *J* = 4.9 Hz, 1 H), 3.06 (d, *J* = 4.9 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 171.3, 154.2, 135.0, 129.6, 128.1, 128.0, 126.8, 124.8, 122.1, 119.8, 56.9, 36.6.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{14}H_{13}N_2O_2S$: 273.0698; found: 273.0700.

(*S*)-5-[(*R*)-1-Hydroxyethyl]-3-(2-thienyl)imidazolidine-2,4-dione (8h)
Yield: 56%; yellow solid; mp 122 °C; $[\alpha]_D^{20}$ –93.3 (*c* 0.2, DMSO); t_R = 1.05 min (method A).

^{1}H NMR (DMSO-d_6): δ = 8.71 (s, 1 H), 7.41 (dd, *J* = 3.8, 1.2 Hz, 1 H), 7.34 (dd, *J* = 5.4, 1.2 Hz, 1 H), 7.01 (dd, *J* = 5.4, 3.9 Hz, 1 H), 5.07 (d, *J* = 5.8 Hz, 1 H), 4.11 (s, 1 H), 4.05 (m, 1 H), 1.20 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 170.8, 155.2, 132.8, 124.8, 121.3, 118.6, 65.4, 62.2, 20.2.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_9H_{11}N_2O_3S$: 227.0490; found: 227.0487.

(*S*)-5-[2-(Methylthio)ethyl]-3-(2-thienyl)imidazolidine-2,4-dione (8i)
Yield: 37%; beige solid; mp 90–94 °C; t_R = 1.86 min (method A).

^{1}H NMR (DMSO-d_6): δ = 8.75 (s, 1 H), 7.40 (dd, *J* = 3.7, 1.0 Hz, 1 H), 7.36 (dd, *J* = 5.5, 1.0 Hz, 1 H), 7.01 (dd, *J* = 5.4, 3.9 Hz, 1 H), 4.35 (t, *J* = 6.1 Hz, 1 H), 2.60 (t, *J* = 7.3 Hz, 2 H), 2.05 (s, 5 H).

^{13}C NMR (DMSO-d_6): δ = 171.9, 154.5, 132.7, 124.8, 121.8, 119.3, 54.8, 30.4, 28.7, 14.4.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{13}N_2O_2S_2$: 257.0418; found: 257.0421.

3-[(*S*)-2,5-Dioxo-1-(2-thienyl)imidazolidin-4-yl]propanoic Acid (8j)
Yield: 55%; brown solid; mp 124 °C; $[\alpha]_D^{20}$ –5.1 (*c* 0.1, DMSO); t_R = 1.34 min (method A).

^{1}H NMR (DMSO-d_6): δ = 12.28 (br s, 1 H), 8.75 (s, 1 H), 7.40 (dd, *J* = 3.8, 1.4 Hz, 1 H), 7.36 (dd, *J* = 5.5, 1.4 Hz, 1 H), 7.01 (dd, *J* = 5.5, 3.8 Hz, 1 H), 4.27 (t, *J* = 6.0 Hz, 1 H), 2.40 (t, *J* = 7.6 Hz, 2 H), 2.05 (m, 1 H), 1.85 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 173.5, 171.8, 154.4, 132.6, 124.9, 121.8, 119.4, 55.2, 29.1, 26.8.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{11}N_2O_4S$: 255.0361; found: 255.0372.

(*S*)-5-[(1*H*-indol-3-yl)methyl]-3-(2-thienyl)imidazolidine-2,4-dione (8k)
Yield: 63%; yellow solid; mp 66–69 °C; $[\alpha]_D^{20}$ –66.2 (*c* 0.2, DMSO); t_R = 2.16 min (method A).

^{1}H NMR (DMSO-d_6): δ = 10.89 (s, 1 H), 8.67 (s, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.30 (dd, *J* = 5.5, 1.3 Hz, 1 H), 7.12 (d, *J* = 2.3 Hz, 1 H), 7.11 (dd, *J* = 3.8, 1.4 Hz, 1 H), 7.06 (t, *J* = 7.0 Hz, 1 H), 6.96 (t, *J* = 7.4 Hz, 1 H), 6.93 (dd, *J* = 5.5, 3.8 Hz, 1 H), 4.57 (t, *J* = 4.5 Hz, 1 H), 3.21 (dd, *J* = 4.6, 2.0 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 171.9, 154.4, 135.9, 132.5, 127.4, 124.8, 124.2, 121.9, 120.9, 119.4, 118.5, 118.4, 111.3, 107.5, 56.8, 26.8.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{16}H_{14}N_3O_2S$: 312.0807; found: 312.0804.

(7*S*,7a*S*)-Tetrahydro-7-hydroxy-2-(2-thienyl)-2*H*-pyrrolo[1,2-*e*]imidazole-1,3-dione (8l)
Yield: 35%; white solid; mp 142–144 °C; $[\alpha]_D^{20}$ +29.9 (*c* 0.1, DMSO); t_R = 1.24 min (method A).

^{1}H NMR (DMSO-d_6): δ = 7.39 (dd, *J* = 5.5, 1.3 Hz, 1 H), 7.37 (dd, *J* = 3.9, 1.3 Hz, 1 H), 7.03 (dd, *J* = 5.4, 3.9 Hz, 1 H), 5.57 (br s, 1 H), 4.43 (s, 2 H), 3.65 (q, *J* = 10.1 Hz, 1 H), 3.36 (t, *J* = 9.8 Hz, 1 H), 2.12 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 168.6, 158.4, 132.5, 124.9, 121.9, 119.4, 69.0, 68.8, 43.4, 35.5.

HRMS: *m*/*z* [M + H$^+$] calcd for $C_{10}H_{11}N_2O_3S$: 239.0490; found: 239.0477.

2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)thiophene-3-carboxylic Acid (9)

Yield: 10%; beige solid; mp 115–118 °C; t_R = 1.27 min (method A).

^{1}H NMR (DMSO-d_6): δ = 8.61 (s, 1 H), 7.61 (d, J = 5.7 Hz, 1 H), 7.38 (d, J = 5.6 Hz, 1 H), 1.91 (s, 1 H), 1.39 (s, 6 H).

^{13}C NMR (DMSO-d_6): δ = 176.1, 162.6, 153.4, 130.5, 127.7, 125.4, 125.4, 58.3, 24.4.

HRMS: m/z [M + H$^+$] calcd for $C_{10}H_{11}N_2O_4S$: 255.0440; found: 255.0438.

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