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A stereolibrary of conformationally restricted amino acids based on pyrrolidinyll/piperidinyloxazole motifs

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Abstract: A stereolibrary of conformationally restricted oxazole-containing amino acids, namely all isomers of 5-pyrrolydinyll- and 5-piperidinyloxazole-4-carboxylic acids, were designed and synthesized in three steps by the reaction of the corresponding *N*-Boc-protected amino acids and ethyl isocyanoacetate. These natural products-inspired amino acids are valuable building blocks for the synthesis of peptidomimetics and potential lead compounds for drug discovery.

Keywords: amino acids; conformational restriction; lead-oriented synthesis; oxazoles; peptidomimetics.

Introduction

Providing drug discovery with novel potential biologically active compounds remains one of the most practically important tasks of synthetic organic chemistry. Many therapeutic areas benefit from molecules derived from or inspired by natural products [1–5]. Since many natural compounds violate rules of lead-likeness and have limited metabolic stability, their synthetic counterparts, which are based on similar structural motifs might be advantageous as the starting points for medicinal chemistry. Being guided by these principles, we were intrigued by

the structures of oxazole-containing peptides, which were discovered among marine products in the late 1980s and have attracted much attention since then [6–9]. Design and synthesis of building blocks inspired by oxazole peptidomimetics, which comply with criteria of lead-likeness have been mentioned in the literature (Figure 1) [10–13]. In this work, we aimed at mounting such structural motifs onto conformationally restricted cores, which can provide diverse spatial arrangement of the functional groups. This approach leads to the sets of compounds which are referred to as “stereolibraries” (mini-libraries of isomers and/or homologues which differ only by the relative position of the functional groups in space, while the molecular topology remains the same) [14–19]. Herein we report synthesis of amino acid **1a–e** stereolibrary, where the structural motif is inspired by oxazole peptidomimetics. It should be noted that prior 2014, derivatives of amino acids **1a** and **1e** were mentioned only in patents [20, 21]. Recently, synthesis of *N*-Boc-protected amino acid **1a** was also described [22, 23], and it was shown that its derivatives are promising asymmetric organo- and metallocatalysts. Analysis of the values of predicted physicochemical parameters of the simplest model derivatives of **1a–e** (i.e. *N*-acetyl-*N'*-methanamide) [24] (Table 1) shows that the structures of these building blocks comply with the concept of the lead-oriented synthesis [25] and leave much room for the design of lead-like libraries.

Results and discussion

For the construction of the oxazole ring in the molecules **1a–e**, the reaction of activated carboxylic acid derivatives with ethyl isocyanoacetate was used. Various methods for the co-activation of aliphatic carboxylic acids in this transformation were described in the literature, most of them including formation of chloro anhydrides [26–29], anhydrides [30–36] or azides [22, 37, 38]. We turned our attention to the method mentioned recently by Heiser and coworkers [39], which uses activation of the hydrocinnamic

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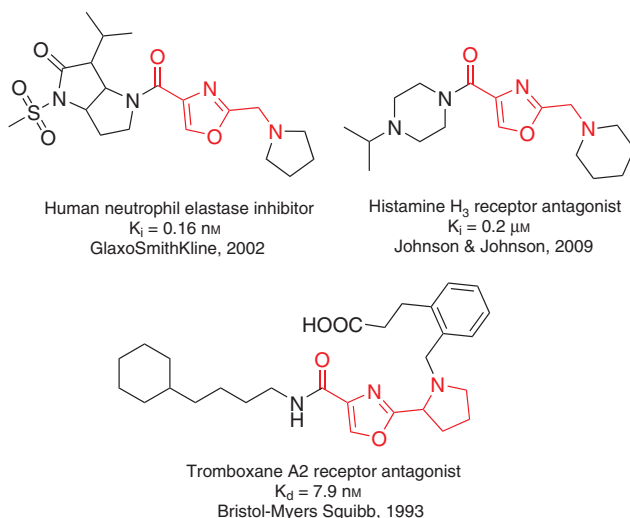
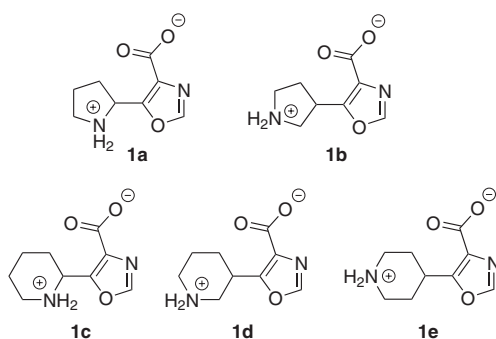


Figure 1 Biologically active derivatives of lead-oriented building blocks inspired by oxazole peptidomimetics.

acid with CDI, followed by the reaction of the intermediate *N*-acylimidazolide with ethyl isocyanoacetate in the presence of DBU. The method worked well with all the *N*-Boc-protected amino acids **2a–e**, resulting in the formation of oxazoles **3a–e** in 77–98% yields (Table 2).

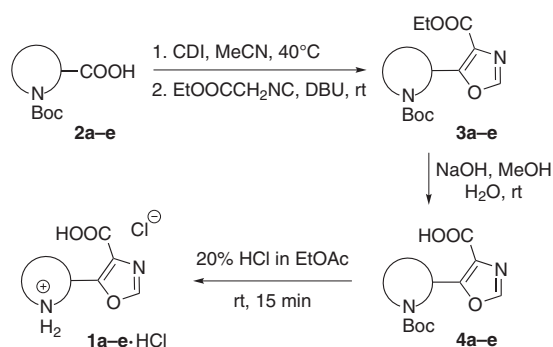
Alkaline hydrolysis of the ester moiety in **3a–e** proceeded without a problem, and the corresponding carboxylic acids **4a–e** were obtained in 81–88% yields. On the contrary, the removal of the Boc protective groups in **4a–e** required some additional efforts. Standard procedures

Table 1 Predicted physico-chemical parameters of *N*-acetyl-*N'*-methylamide derivatives of amino acids **1a–e**.



Parameter	Value range
Molecular weight (MW)	237...251
Hydrophilicity (cLogP)	−1.47...−0.63
H-bond acceptors	3
H-bond donors	1
Total polar surface area (TPSA, Å ²)	75.4
Rotatable bonds number (RotB)	2
Fraction of sp ³ carbons (Fsp ³)	0.54...0.58

Table 2 Synthesis of amino acids **1a–e** (as hydrochlorides).



Starting compound	Yield, %		
	3	4	1·HCl
<i>rac</i> - <i>N</i> -Boc-proline (2a)	86	86	87
<i>rac</i> - <i>N</i> -Boc-β-proline (2b)	77	81	73
<i>rac</i> - <i>N</i> -Boc-pipecolic acid (2c)	83	85	98
<i>rac</i> - <i>N</i> -Boc-nipecotic acid (2d)	98	88	95
<i>N</i> -Boc-isonipecotic acid (2e)	93	86	98

including prolonged reaction with TFA – CH₂Cl₂ or HCl – EtOAc led to partial decomposition of the products, especially with oxazoles **4a** and **4c** derived from α-amino acids. It was found, however, that short-time treatment of neat **4** with concentrated HCl in EtOAc upon vigorous stirring led to the formation of the target amino acids **1a–e** as hydrochlorides in good to excellent yields (73–98%). The pure crystalline compounds **1a–e** are stable and could be stored at least for a month; however, partial decomposition was observed for some samples if the excessive HCl was not removed thoroughly.

Obviously, the method can be applied for the preparation of optically pure compounds **1b** and **1d**, if the corresponding optically pure Boc-amino acids **2b** and **2d** available from commercial sources are used as the starting materials. In the case of amino acids **1a** and **1c**, racemization is possible at the oxazole formation step. Experiments with both (*R*)- and (*S*)-**2a** showed that this is the case for the derivatives of α-amino acids. For this reason, we recommend using DPPA instead of CDI for the activation of the carboxylic acid moiety in the molecules of **2a** and **2c** as described recently by Kamal and co-workers [22].

Conclusions

A stereolibrary of conformationally restricted oxazole-containing amino acids was designed and synthesized in only three steps starting from easily available materials.

These natural product-inspired compounds fit well the restrictions imposed by the lead-oriented synthesis and can be used as starting points in drug discovery programs; they are also of interest in the search of unusual secondary structure elements when incorporated into peptidomimetics.

Experimental

The solvents were purified according to standard procedures. Racemic compounds **2a–e** were used for the synthesis. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 spectrometer (at 400 MHz for protons and 100 MHz for carbon-13). Elemental analysis was conducted at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Mass spectra were recorded on an Agilent 1200 LCMSD SL instrument [electrospray ionization (ESI)] and Agilent 1100 LCMS instrument [chemical ionization (APCI)].

General procedure for the preparation of **3**

To a solution of *N*-Boc-protected amino acid **2** (0.140 mol) in CH_3CN (250 mL), CDI (27.31 g, 0.168 mol) was added. The mixture was stirred at 40°C for 1 h, then cooled and treated with methyl isocynoacetate (17.5 g, 0.154 mol) and DBU (23.5 g, 0.154 mol) and then stirred at room temperature overnight. The solution was concentrated under reduced pressure to half a volume, and 10% aqueous citric acid (600 mL) was added. The mixture was extracted with EtOAc (4×150 mL). The combined organic phases were washed with water (2×150 mL), 10% aqueous citric acid (150 mL), and brine (150 mL), then dried over Na_2SO_4 and concentrated *in vacuo* to give **3**.

Ethyl 5-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)oxazole-4-carboxylate (3a) This compound was obtained as a 3:1 mixture of rotamers; yield 86%; yellowish solid; mp 54–55°C; ^1H NMR (CDCl_3): δ 7.76 (s, 0.75H), 7.72 (s, 0.25H), 5.61–5.49 (m, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.64–3.53 (m, 1.5H), 3.52–3.43 (m, 0.5H), 2.42–2.29 (m, 1H), 2.12–2.01 (m, 0.75H), 2.01–1.88 (m, 2.25H), 1.38 (t, J = 7.1 Hz, 3H), 1.23 (s, 9H); ^{13}C NMR (CDCl_3): δ 161.2, 159.7, 153.2, 148.3, 126.2, 79.4, 60.8, 52.1, 46.2, 32.3, 27.7, 23.5, 14.0; ESI-MS: m/z 333 (Mn^+). Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.31; H, 6.89; N, 9.25.

Ethyl 5-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)oxazole-4-carboxylate (3b) This compound was obtained as a 1:1 mixture of rotamers; yield 77%; yellowish oil; ^1H NMR (CDCl_3): δ 7.79 (s, 1H), 4.38 (q, J = 7.0 Hz, 2H), 4.29–4.17 (m, 1H), 3.80–3.70 (m, 1H), 3.68–3.61 (m, 0.5H), 3.61–3.53 (m, 0.5H), 3.52–3.36 (m, 2H), 2.30–2.20 (m, 1H), 2.19–2.09 (m, 1H), 1.46 (s, 4.5H), 1.44 (s, 4.5H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl_3): δ 161.3, 158.0 and 157.9, 153.8, 148.8, 127.0, 79.1, 60.7, 49.1 and 48.7, 45.2 and 44.9, 35.2 and 34.4, 30.2 and 29.3, 28.0, 13.8; ESI-MS: m/z 333 (Mn^+), 255 ($\text{MH}^+ - \text{C}_4\text{H}_8$), 211 ($\text{MH}^+ - \text{C}_4\text{H}_8 - \text{CO}_2$), 165. Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 57.73; H, 7.23; N, 8.68.

Ethyl 5-(1-(tert-butoxycarbonyl)piperidin-2-yl)oxazole-4-carboxylate (3c) Yield 83%; yellowish oil; ^1H NMR (CDCl_3): δ 7.79 (s, 1H), 5.97 (dd, J = 5.5, 2.8 Hz, 1H), 4.45–4.31 (m, 2H), 4.09 (d, J = 11.2 Hz, 1H), 3.26 (td, J = 13.0, 3.6 Hz, 1H), 2.05–1.85 (m, 2H), 1.83–1.73 (m, 1H), 1.72–1.64 (m, 1H), 1.60–1.50 (m, 1H), 1.47–1.43 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.36 (s, 9H); ^{13}C NMR (CDCl_3): δ 160.9, 160.2, 154.6, 148.5, 125.9, 79.7, 60.8, 46.9, 41.2, 28.9, 27.8, 24.3, 19.3, 13.9; ESI-MS: m/z 347 (Mn^+), 225 ($\text{MH}^+ - \text{C}_4\text{H}_8 - \text{CO}_2$), 179. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.07; H, 7.80; N, 8.48.

Ethyl 5-(1-(tert-butoxycarbonyl)piperidin-3-yl)oxazole-4-carboxylate (3d) Yield 98%; white solid; mp 70–71°C; ^1H NMR (CDCl_3): δ 7.77 (s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.02 (br s, 1H), 4.02 (d, J = 12.7 Hz, 1H), 3.62 (td, J = 10.5, 5.3 Hz, 1H), 3.08 (br s, 1H), 2.93–2.85 (m, 1H), 2.08–1.98 (m, 1H), 1.85–1.68 (s, 2H), 1.66–1.52 (m, 1H), 1.45 (s, 9H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl_3): δ 161.3, 159.7, 154.0, 148.6, 126.5, 79.4, 60.8, 46.9 and 45.8, 44.1 and 43.1, 33.7, 28.4, 28.0, 24.0, 13.9; ESI-MS: m/z 347 (Mn^+), 225 ($\text{MH}^+ - \text{C}_4\text{H}_8 - \text{CO}_2$), 179. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.57; H, 7.18; N, 8.55.

Ethyl 5-(1-(tert-butoxycarbonyl)piperidin-4-yl)oxazole-4-carboxylate (3e) Yield 93%; light yellowish solid; mp 72–73°C; ^1H NMR (CDCl_3): δ 7.77 (s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.22 (d, J = 12.1 Hz, 2H), 3.65 (tt, J = 11.7, 3.9 Hz, 1H), 2.84 (t, J = 12.0 Hz, 2H), 1.84 (dd, J = 13.1, 3.0 Hz, 2H), 1.81–1.69 (m, 2H), 1.48 (s, 9H), 1.44–1.38 (m, 3H); ^{13}C NMR (CDCl_3): δ 161.6, 161.3, 154.2, 148.5, 125.7, 79.3, 60.8, 43.5, 43.1, 33.5, 29.2, 28.1, 14.0; ESI-MS: m/z 347 (Mn^+), 225 ($\text{MH}^+ - \text{C}_4\text{H}_8 - \text{CO}_2$), 179. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.28; H, 7.07; N, 8.94.

General procedure for the preparation of **4**

To a solution of **3** (0.05 mol) in MeOH (300 mL), a pre-cooled solution of NaOH (0.15 mol) in water (12 mL) was added in one portion. The mixture was stirred at room temperature overnight (monitored by TLC), then concentrated *in vacuo* to 70–80 mL (below 35°C), diluted with water (100 mL) and washed with CH_2Cl_2 (2×50 mL). The aqueous phase was acidified with 15% citric acid (200–220 mL) and extracted with EtOAc (3×150 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give **5**.

5-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)oxazole-4-carboxylic acid (4a) This compound was obtained as a 3: 2 mixture of rotamers; yield 86%; white solid; mp 158–160°C; ^1H NMR (CDCl_3): δ 7.84 (s, 1H), 5.55 (br s, 0.6H), 5.48 (br s, 0.4H), 3.70–3.47 (br m, 2H), 2.49–2.28 (br m, 1H), 2.21–1.91 (br m, 3H), 1.44 (s, 3.6H), 1.27 (s, 5.4H). COOH is exchanged with D_2O ; ^{13}C NMR (CDCl_3): δ 164.7 and 163.6, 160.7 and 158.4, 154.4 and 153.5, 149.0 and 148.7, 126.9 and 125.8, 80.5 and 79.8, 52.1, 46.6 and 46.3, 32.3 and 31.4, 28.0 and 27.7, 24.1 and 23.5; ESI-MS: m/z 305 (Mn^+). Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.05; H, 6.52; N, 10.10.

5-(1-(tert-Butoxycarbonyl)pyrrolidin-3-yl)oxazole-4-carboxylic acid (4b) Yield 81%; yellowish oil; ^1H NMR (CDCl_3): δ 7.88 (s, 1H), 4.17–4.34 (m, 1H), 3.71–3.89 (m, 1H), 3.54–3.68 (m, 1H), 3.37–3.51 (m, 2H), 2.24–2.32 (m, 2H), 1.46 (s, 9H). COOH is exchanged with H $_2\text{O}$; ^{13}C NMR (CDCl_3): δ 163.6, 158.4 and 158.3, 154.3, 149.4, 126.9, 79.7, 49.2 and 48.7, 45.3 and 45.0, 35.1 and 34.4, 30.0 and 29.3, 28.0; ESI-MS: m/z 305

(MNa⁺). Anal. Calcd for C₁₃H₁₈N₂O₅: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.47; H, 6.81; N, 9.67.

5-(1-(tert-Butoxycarbonyl)piperidin-2-yl)oxazole-4-carboxylic acid (4c) Yield 85%; white powder; mp 164–166°C; ¹H NMR (CDCl₃): δ 9.13 (br s, 1H), 7.87 (s, 1H), 5.98 (dd, *J* = 5.6, 2.9 Hz, 1H), 4.10 (d, *J* = 11.6 Hz, 1H), 3.26 (td, *J* = 13.0, 3.4 Hz, 1H), 2.06–1.89 (m, 2H), 1.80 (d, *J* = 12.4 Hz, 1H), 1.75–1.64 (m, 1H), 1.64–1.43 (m, 2H), 1.38 (s, 9H); ¹³C NMR (CDCl₃): δ 164.0, 160.6, 154.9, 149.0, 125.7, 80.2, 46.9, 41.2, 28.9, 27.9, 24.3, 19.3; ESI-MS: *m/z* 319 (MNa⁺), 263 (MNa⁺–C₄H₈). Anal. Calcd for C₁₄H₂₀N₂O₅: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.36; H, 7.13; N, 9.27.

5-(1-(tert-Butoxycarbonyl)piperidin-3-yl)oxazole-4-carboxylic acid (4d) Yield 88%; white amorphous solid; ¹H NMR (CDCl₃): δ 10.66 (br s, 1H), 7.87 (s, 1H), 4.08 (br s, 1H), 4.01 (d, *J* = 12.7 Hz, 1H), 3.66 (ddd, *J* = 13.8, 10.4, 3.6 Hz, 1H), 3.09 (br s, 1H), 2.90 (td, *J* = 11.1, 2.5 Hz, 1H), 2.09–1.99 (m, 1H), 1.84–1.69 (m, 2H), 1.65–1.52 (m, 1H), 1.44 (s, 9H); ¹³C NMR (CDCl₃): δ 164.2, 160.5, 154.3, 149.0, 126.2, 79.8, 47.0 and 45.7, 44.0 and 43.2, 33.6, 28.4, 28.1, 24.0; ESI-MS: *m/z* 319 (MNa⁺). Anal. Calcd for C₁₄H₂₀N₂O₅: C, 56.75; H, 6.80; N, 9.45. Found: C, 57.03; H, 6.53; N, 9.39.

5-(1-(tert-Butoxycarbonyl)piperidin-4-yl)oxazole-4-carboxylic acid (4e) Yield 86%; white solid; mp 180–182°C; ¹H NMR (CDCl₃): δ 7.84 (s, 1H), 4.23 (d, *J* = 12.0 Hz, 2H), 3.68 (ddd, *J* = 11.8, 7.9, 3.8 Hz, 1H), 2.87 (t, *J* = 11.9 Hz, 2H), 1.87 (dd, *J* = 13.3, 2.8 Hz, 2H), 1.83–1.70 (m, 2H), 1.49 (s, 9H), COOH is exchanged with D₂O; ¹³C NMR (CDCl₃): δ 164.3, 162.0, 154.4, 149.0, 125.4, 79.7, 43.2, 33.4, 29.2, 28.1; ESI-MS: *m/z* 319 (MNa⁺). Anal. Calcd for C₁₄H₂₀N₂O₅: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.47; H, 7.00; N, 9.48.

General procedure for the preparation of 1·HCl

To the finely powdered compound **4** (3.37 mmol), a pre-cooled saturated solution of HCl in EtOAc (~20%) was added. The resultant slurry was vigorously stirred at room temperature for 15 min (if the clots are formed at this stage, it is recommended to split them with a spatula). CAUTION! Violent gas emission! The mixture was filtered, and the precipitate was washed thoroughly with EtOAc (15 mL) and acetone (15 mL). The product was dried in vacuo thoroughly to give 1·HCl. The complete structures of these products are given in Table 1.

5-(Pyrrolidin-2-yl)oxazole-4-carboxylic acid, hydrochloride (1a·HCl) Yield 87%; white crystals; mp 163–165°C; ¹H NMR (D₂O) δ 8.28 (s, 1H), 5.41 (t, *J* = 8.2 Hz, 1H), 5.41 (t, *J* = 7.2 Hz, 2H), 2.56–2.13 (m, 4H); ¹³C NMR (D₂O) δ 165.7, 154.4, 153.1, 132.1, 55.6, 48.2, 30.6, 26.0; ESI-MS: *m/z* 183 (MH⁺). Anal. Calcd for C₈H₁₁ClN₂O₃: C, 43.95; H, 5.07; Cl, 16.22; N, 12.81. Found: C, 44.15; H, 5.44; Cl, 16.36; N, 12.72.

5-(Pyrrolidin-3-yl)oxazole-4-carboxylic acid, hydrochloride (1b·HCl) Yield 73%; white solid; mp 168–170°C; ¹H NMR (DMSO-*d*₆): δ 9.71 (s, 2H), 8.42 (s, 1H), 4.29–4.12 (m, 1H), 3.62–3.50 (m, 1H), 3.41–3.32 (m, 1H), 3.29 (m, 1H), 3.23–3.17 (m, 1H), 2.39–2.27 (m, 1H), 2.13–2.01 (m, 1H), 1H is exchanged with D₂O; ¹³C NMR (DMSO-*d*₆): δ 162.5, 155.6, 150.6, 127.7, 47.2, 44.5, 34.3, 29.1; ESI-MS: *m/z* 183 (MH⁺), 139 (MH⁺–CO₂). Anal. Calcd for C₈H₁₁ClN₂O₃: C, 43.95; H, 5.07; Cl, 16.22; N, 12.81. Found: C, 43.68; H, 5.1; Cl, 16.46; N, 12.50.

5-(Piperidin-2-yl)oxazole-4-carboxylic acid, hydrochloride (1c·HCl) Yield 98%; white crystals; mp 144–146°C; ¹H NMR (D₂O) δ 8.30 (s, 1H), 5.04 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.60 (d, *J* = 12.6 Hz, 1H), 3.24 (td, *J* = 12.5, 2.8 Hz, 1H), 2.24–1.98 (m, 4H), 1.89–1.67 (m, 2H); ¹³C NMR (DMSO-*d*₆): δ 162.0, 152.1, 151.6, 129.0, 50.3, 44.3, 27.0, 21.5, 21.2; ESI-MS: *m/z* 197 (MH⁺). Anal. Calcd for C₉H₁₃ClN₂O₃: C, 46.46; H, 5.63; Cl, 15.24; N, 12.04. Found: C, 46.27; H, 6.01; Cl, 15.54; N 11.73.

5-(Piperidin-3-yl)oxazole-4-carboxylic acid, hydrochloride (1d·HCl) Yield 95%; white crystals; mp 131–133°C; ¹H NMR (D₂O): δ 8.16 (s, 1H), 4.01–3.90 (m, 1H), 3.57 (dd, *J* = 12.7, 3.0 Hz, 1H), 3.46 (d, *J* = 12.7 Hz, 1H), 3.28 (t, *J* = 12.1 Hz, 1H), 3.09 (t, *J* = 11.9 Hz, 1H), 2.16–1.79 (m, 4H); ¹³C NMR (D₂O): δ 166.1, 159.7, 153.4, 128.7, 47.4, 45.9, 33.5, 27.9, 23.6; ESI-MS: *m/z* 197 (MH⁺). Anal. Calcd for C₉H₁₃ClN₂O₃: C, 46.46; H, 5.63; Cl, 15.24; N, 12.04. Found: C, 46.38; H, 5.95; Cl, 15.36; N, 11.71.

5-(Piperidin-4-yl)oxazole-4-carboxylic acid, hydrochloride (1e·HCl) Yield 98%; white crystals; mp 245–247°C; ¹H NMR (D₂O) δ 8.15 (s, 1H), 3.92–3.80 (m, 1H), 3.56 (d, *J* = 13.2 Hz, 2H), 3.20 (td, *J* = 12.2, 2.3 Hz, 2H), 2.24–2.02 (m, 4H); ¹³C NMR (D₂O): δ 166.4, 162.3, 153.0, 127.7, 45.5, 33.0, 28.0; ESI-MS: *m/z* 197 (MH⁺), 153 (MH⁺–CO₂). Anal. Calcd for C₉H₁₃ClN₂O₃: C, 46.46; H, 5.63; Cl, 15.24; N, 12.04. Found: C, 46.40; H, 5.49; Cl, 14.91; N, 12.16.

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