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One-Pot Synthesis of 3-Aryltetramic Acids

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Tetramic acids substituted in the 3-position by various aryl groups were prepared in one-pot from amino esters and methyl arylacetates, by treatment with potassium *tert*-butoxide. A tandem process, involving the formation of an amide and a condensation reaction, is likely to occur. *N*-Unsubstituted tetramic acids were obtained from adducts containing a *N*-(2,4-dimethoxybenzyl) group.

Introduction

The tetramic acid unit is a structural feature found in many natural products, which display a wide spectrum of biological activities.[1] Examples include the phytotoxin tenuazonic acid and the antibiotic tirandamycin A (Figure 1). Most of these compounds contain a 3-acyl group. However, non-natural, 3-aryltetramic acid derivatives have been reported as herbicides, acaricides, insecticides, and pesticides.[2] For example, spirotetramat (movento®), which acts as a lipid biosynthesis inhibitor, is currently under development at Bayer CropScience as an insecticide.[3] Several 5-arylidene-3-phenyltetramic acids have been reported as glycine-site *N*-methyl-D-aspartate receptor antagonists.[4]

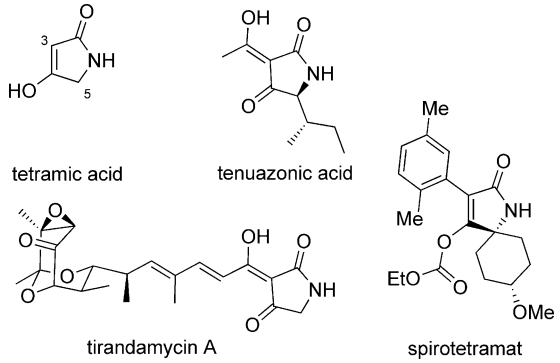
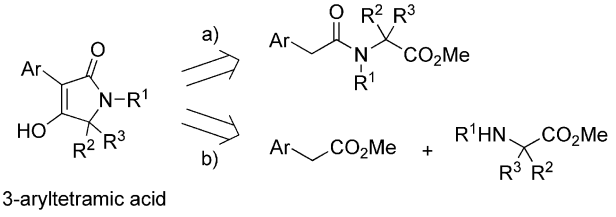


Figure 1. Structural formulas of the parent tetramic acid, natural products tenazuonic acid and tyrandamycin A, and the insecticide spirotetramat.

Since the first report by King and McMillan,[5] the Dieckmann condensation of a previously synthesized amide is usually employed for the preparation of 3-aryltetramic acids (Scheme 1, route a).[6] Interestingly, a synthesis that made use of a palladium-catalyzed arylation was recently reported.[7] In a recent study, we described a one-pot preparation of 3-aryltetronic acids from the corresponding aryl- and hydroxyacetates, by a tandem process involving a transesterification and a subsequent Dieckmann condensation.[8] It was of interest to evaluate the preparation of 3-aryltetramic acids by means of an analogous process (Scheme 1, route b), which would make use of arylacetic acid esters and α-amino esters as reaction partners and proceed by the formation of an amide bond prior to the Dieckmann condensation. The results obtained are reported herein.



Scheme 1.

Results and Discussion

Initially, we tested the feasibility of the reaction starting from methyl (4-methoxyphenyl)acetate (**1a**) and glycine methyl ester hydrochloride (**2a**, Scheme 2). We employed this hydrochloride directly in the reactions; hence we employed an additional base equivalent in order to neutralize the acid.

Several tests, carried out in refluxing THF with variable quantities of potassium *tert*-butoxide, did not lead to tetramic acid **3**. On the other hand, starting from glycine *tert*-butyl ester hydrochloride (**2b**), we isolated tetramic acid **3**, albeit only in 20% yield, using 2.5 base equiv. after 1 night. We observed unreacted ester **1a** in the crude product. However, we could not improve the yield by increasing either the number of base equivalents or the reaction time.

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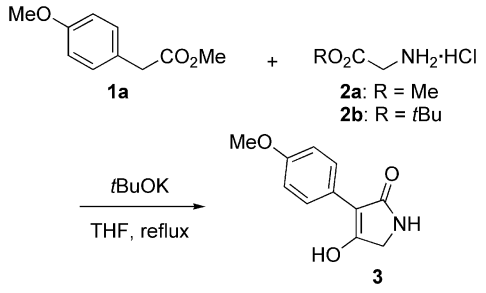
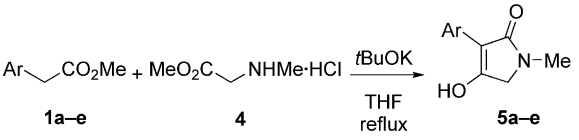


Scheme 2.

We then employed *N*-alkylamino esters as starting materials. We first carried out experiments with sarcosine methyl ester hydrochloride (**4**) and methyl 2-(4-methoxyphenyl)acetate (**1a**). Thus, we treated **4** with **1a** in the presence of 2.5 equiv. of potassium *tert*-butoxide in refluxing THF (Scheme 3). After 4 h, we obtained tetramic acid **5a** in 38% yield (Table 1, Entry 1). The yield improved when we refluxed the reaction mixture overnight (Table 1, Entry 2). Moreover, we obtained a better yield (76%) when was purified **5a** by precipitation instead of silica gel chromatography (Table 1, Entry 3). Indeed, since this *N*-methyltetramic acid was not very soluble in most solvents, we observed significant losses during the chromatographic purification. We note that the use of sarcosine *tert*-butyl ester hydrochloride instead of **4** also led to **5a** in a satisfying 73% yield.



Scheme 3.

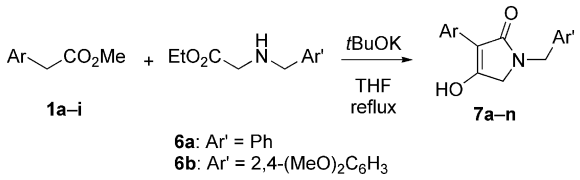
Table 1. One-pot synthesis of *N*-methyltetramic acids **5**.

Entry	Ar	Reaction time	1	5	Yield [%]
1	4-(MeO)C_6H_4	4 h	**1a**	**5a**	38[a]
2	4-(MeO)C_6H_4	overnight	**1a**	**5a**	62[a]
3	4-(MeO)C_6H_4	overnight	**1a**	**5a**	76[b]
4	3-(MeO)C_6H_4	overnight	**1b**	**5b**	50[b]
6	4-BrC_6H_4	overnight	**1c**	**5c**	32[a]
7	4-ClC_6H_4	overnight	**1d**	**5d**	48[a]
9	thien-2-yl	overnight	**1e**	**5e**	28[a]

[a] Purified by silica gel chromatography. [b] Purified by precipitation.

We then prepared several other *N*-methyltetramic acids from **4** and various methyl arylacetates **1b**–**e** (Scheme 3, Table 1). We characterized the products particularly by ^{1}H NMR (400 MHz, [D$_6$]DMSO) chemical shifts of the methylene protons (δ = 3.88–3.92 ppm) and the methyl group (δ = 2.85–2.87 ppm). In most cases, the precipitation of the crude product was not efficient, and purification by chromatography was needed. We note, however, that whatever the starting ester, the yields obtained were not satisfactory. This could be due to the use of an amino ester hydrochloride, for which a delicate drying operation was needed prior to the reaction. It thus seemed more judicious to use an amino ester in the free amine form as the starting material.

We selected two amino esters, the commercially available ethyl benzylaminoacetate (**6a**) and ethyl 2-[(2,4-dimethoxybenzyl)amino]acetate (**6b**,[9] Scheme 4). We initially carried out reactions with **6a** and **1a**, using various numbers (from 1.0 to 2.2) of base equivalents. A comparison of the ^{1}H NMR spectra of the crude products indicated that 1.2 equiv. of potassium *tert*-butoxide was sufficient to obtain a good conversion to the expected *N*-benzyltetramic acid **7a**. In this case, we obtained **7a** in 67% yield after purification (Table 2, Entry 1). An excess of base led to the formation of secondary products.



Scheme 4.

We then prepared tetramic acids **7** substituted in position 3 by various aryl groups in a similar way (Scheme 4, Table 2). We synthesized *N*-benzyltetramic acids **7b**–**g** first. As we observed in the tetronic acids synthesis,[8] the position of the methoxy substituent on the aromatic nucleus of the starting ester had little influence on the yield (Table 2, Entries 3 and 4). We also isolated tetramic acids substituted by 4-halophenyl groups in good yields, varying between 54 and 64% (Table 2, Entries 5 to 7). On the other hand, when the phenyl group was *para*-substituted by a nitro group, we did not obtain the expected tetramic acid **7h** (Table 2, Entry 8). This result was similar to that observed during an attempt to prepare the corresponding tetronic acid.[8] We assumed that under the reaction conditions, ester **1i** was readily converted into the corresponding stable potassium enolate. We prepared tetramic acids **7j**–**n**, *N*-substituted by a 2,4-dimethoxybenzyl group, by the same process in 54–71% yield.

Direct access to *N*-unsubstituted tetramic acids was not readily feasible from glycine esters **2a** and **2b**. On the other hand, we quantitatively converted **7i**–**m**, in which the amide function was protected by a 2,4-dimethoxybenzyl group, into the corresponding *N*-unsubstituted tetramic acids by treatment with trifluoroacetic acid (Scheme 5).[10] However, we observed that **7n**, substituted by a 2-thienyl group, decomposed under these conditions.

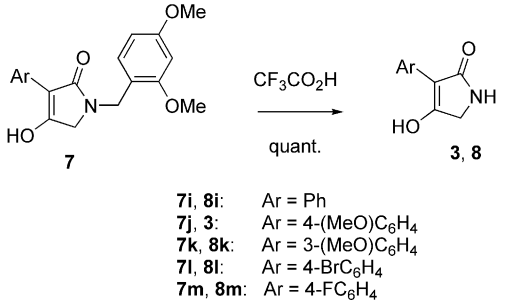
Several bicyclic tetramic acids have been shown to display biological activities.[6c,11] It was thus of interest to evaluate the preparation of such a compound using this one-pot method. As an example, we obtained indolizinone **9** in 37% yield from methyl pipecolinate and ester **1a** under the usual conditions.

A suggested pathway for the formation of *N*-methyl-3-aryltetramic acids under these conditions is outlined in Scheme 6. The reaction of the anion generated from the

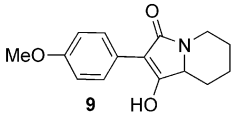
Table 2. One-pot synthesis of *N*-benzyl- and *N*-(2,4-dimethoxybenzyl)tetramic acids **7**.

Entry	6	Ar′	1	Ar	7	Yield [%]
1	**6a**	C_6H_5	**1a**	4-(MeO)C_6H_4	**7a**	67
2	**6a**	C_6H_5	**1f**[a]	C_6H_5	**7b**	54
3	**6a**	C_6H_5	**1b**	3-(MeO)C_6H_4	**7c**	62
4	**6a**	C_6H_5	**1g**	3,4-$(MeO)_2C_6H_3$	**7d**	52
5	**6a**	C_6H_5	**1c**	4-BrC_6H_4	**7e**	64
6	**6a**	C_6H_5	**1d**	4-ClC_6H_4	**7f**	62
7	**6a**	C_6H_5	**1h**	4-FC_6H_4	**7g**	54
8	**6a**	C_6H_5	**1i**	4-$(NO_2)C_6H_4$	**7h**	0
9	**6b**	2,4-$(MeO)_2C_6H_3$	**1f**[a]	C_6H_5	**7i**	63
10	**6b**	2,4-$(MeO)_2C_6H_3$	**1a**	4-(MeO)C_6H_4	**7j**	59
11	**6b**	2,4-$(MeO)_2C_6H_3$	**1b**	3-(MeO)C_6H_4	**7k**	53
12	**6b**	2,4-$(MeO)_2C_6H_3$	**1c**	4-BrC_6H_4	**7l**	55
13	**6b**	2,4-$(MeO)_2C_6H_3$	**1h**	4-FC_6H_4	**7m**	71
14	**6b**	2,4-$(MeO)_2C_6H_3$	**1e**	thien-2-yl	**7n**	54

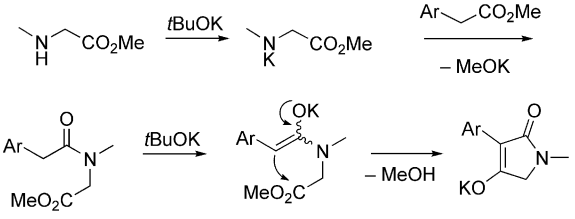
[a] Ethyl phenylacetate was used in this reaction.



Scheme 5.

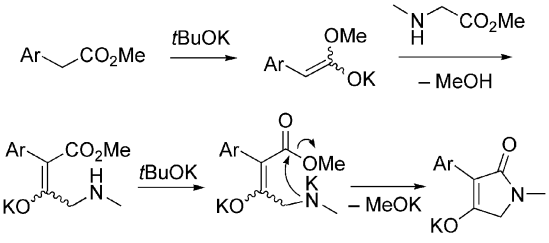


amino ester with the methyl arylacetate would give the corresponding amide. This precursor can then undergo a Dieckmann condensation, yielding the tetramic acid salt.



Scheme 6.

However, we could not produce evidence that the formation of the tetramic acids actually follows this route. Hence, an alternative pathway, depicted in Scheme 7, cannot be ruled out. A Claisen condensation between the methyl arylacetate-derived enolate and the amino ester would lead to a β-keto ester. Under the reaction conditions, this compound would easily cyclize, affording the tetramic acid salt. This pathway might actually be more favorable, since the methylene protons of the arylacetate are more acidic than the secondary amine proton.



Scheme 7.

Conclusions

In summary, a convenient, one-pot synthesis of 3-aryltetramic acids from amino esters and methyl arylacetates is described. It consists of a tandem process involving the formation of an amide and a condensation reaction. Good yields were obtained in particular from ethyl benzylaminoacetate (**6a**) and ethyl (2,4-dimethoxybenzyl)aminoacetate (**6b**). The facile cleavage of the 2,4-dimethoxybenzyl group of adducts **7i**–**m** allows for an efficient preparation of *N*-unsubstituted tetramic acids.

Experimental Section

General Methods: THF was freshly distilled from sodium benzophenone ketyl. Reactions were performed under an argon atmosphere. TLC: Silica Gel $60F_{254}$ plates with detection by UV light and by an ethanol solution of phosphomolybdic acid. Column chromatography: 40–63 μm silica gel. Melting points were not corrected. NMR: 400.133 and 100.624 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are given in ppm (s singlet, d doublet, t triplet, m multiplet, and br. broad), coupling constants (J) are given in Hz.

General Procedure for the Synthesis of a Tetramic Acid from an Amino Ester Hydrochloride: To a solution of alkyl arylacetate (1 equiv.) and amino ester hydrochloride (1.5 equiv.) in anhydrous THF was added potassium *tert*-butoxide (1 M in THF, 2.5 equiv.). The suspension obtained was then refluxed under argon overnight. After the mixture was cooled to room temperature, it was poured into cooled aqueous HCl (1 M). The aq phase was extracted with AcOEt, and the combined organic layers were then washed with water and dried with Na_2SO_4. After the mixture was filtered and

concentrated under vacuum, the residue was precipitated in diethyl ether, or chromatographed on silica gel, to give the corresponding tetramic acid.

General Procedure for the Synthesis of a Tetramic Acid from an *N*-Alkylamino Ester: To a solution of alkyl arylacetate (1 equiv.) and *N*-alkylamino ester (1.2 equiv.) in anhydrous THF was added potassium *tert*-butoxide (1 M in THF, 1.2 equiv.). The suspension obtained was then refluxed under argon overnight, and the reaction was then processed as described above.

4-Hydroxy-3-(4-methoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (3): Following the general procedure, from methyl (4-methoxyphenyl)acetate (**1a**, 0.18 g, 1.0 mmol), glycine *tert*-butyl ester hydrochloride (**2b**, 0.25 g, 1.5 mmol), and potassium *tert*-butoxide (2.5 mL, 2.5 mmol, 1 M in THF) in THF (5 mL), tetramic acid **3** (40 mg, 20%) was obtained as a yellow solid; m.p. 226–227 °C; TLC: R_f = 0.30 (9:1 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3349, 2918, 2597, 1624, 1605, 1514, 1440, 1383, 834, 750 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.33 (br. s, 1 H, OH), 7.91 (d, J = 9.1 Hz, 2 H, Ar-H), 7.38 (br. s, 1 H, NH), 6.88 (d, J = 9.1 Hz, 2 H, Ar-H), 3.82 (s, 2 H, CH_2), 3.74 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.3, 167.2, 157.0, 127.9, 125.0, 113.1, 102.9, 54.9, 44.7 ppm. HRMS (ESI-TOF): calcd. for $C_{11}H_{11}NNaO_3$ [M + Na]$^+$ 228.0637; found 228.0642.

4-Hydroxy-3-(4-methoxyphenyl)-1-methyl-1*H*-pyrrol-2(5*H*)-one (5a): Following the general procedure, from methyl (4-methoxyphenyl)-acetate (**1a**, 0.23 g, 1.3 mmol), methyl sarcosinate hydrochloride (**4**, 0.26 g, 1.9 mmol), and potassium *tert*-butoxide (3.2 mL, 3.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **5a** (0.21 g, 76%) was obtained as a white solid; m.p. 232–233 °C (dec.); TLC: R_f = 0.30 (9:1 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2935, 2569, 1598, 1515, 1450, 1384, 1288, 1252, 1214, 1177, 1028, 836, 727 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.35 (br. s, 1 H, OH), 7.90 (d, J = 9.1 Hz, 2 H, Ar-H), 6.89 (d, J = 9.1 Hz, 2 H, Ar-H), 3.91 (s, 2 H, CH_2), 3.74 (s, 3 H, CH_3O), 2.86 (s, 3 H, CH_3N) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.3, 164.8, 157.0, 127.8, 125.0, 113.2, 100.8, 54.9, 50.7, 28.2 ppm. HRMS (ESI-TOF): calcd. for $C_{12}H_{12}NNaO_3$ [M – H]$^-$ 218.0817; found 218.0813.

4-Hydroxy-3-(3-methoxyphenyl)-1-methyl-1*H*-pyrrol-2(5*H*)-one (5b): Following the general procedure, from methyl (3-methoxyphenyl)-acetate (**1b**, 0.25 g, 1.4 mmol), methyl sarcosinate hydrochloride (**4**, 0.29 g, 2.1 mmol), and potassium *tert*-butoxide (3.5 mL, 3.5 mmol, 1 M in THF) in THF (8 mL), tetramic acid **5b** (0.15 g, 50%) was obtained as a beige solid; m.p. 195–196 °C (dec.); TLC: R_f = 0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2937, 2562, 1743, 1600, 1380, 1287, 1239, 1215, 1053, 914, 785, 731, 693 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.64 (br. s, 1 H, OH), 7.58 (d, J = 8.0 Hz, 1 H, Ar-H), 7.22 (t, J = 8.0 Hz, 1 H, Ar-H), 6.74 (d, J = 8.0 Hz, 1 H, Ar-H), 3.92 (s, 2 H, CH_2), 3.72 (s, 3 H, CH_3O), 2.87 (s, 3 H, CH_3N) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.4, 167.2, 159.1, 134.1, 128.9, 119.6, 112.6, 111.3, 103.2, 55.2, 51.2, 28.6 ppm. MS (ESI-TOF): m/z = 220 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{12}H_{13}NO_3Na$ [M + Na]$^+$ 242.0793; found 242.0794.

3-(4-Bromophenyl)-4-hydroxy-1-methyl-1*H*-pyrrol-2(5*H*)-one (5c): Following the general procedure, from methyl (4-bromophenyl)-acetate (**1c**, 0.38 g, 1.7 mmol), methyl sarcosinate hydrochloride (**4**, 0.35 g, 2.5 mmol), and potassium *tert*-butoxide (4.2 mL, 4.2 mmol, 1 M in THF) in THF (9 mL), tetramic acid **5c** (0.14 g, 32%) was obtained as an orange solid; m.p. 212–214 °C (dec.); TLC: R_f = 0.20 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2931, 2719, 1605, 1490, 1444, 1379, 1216, 827 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]-DMSO): δ = 7.98 (d, J = 8.2 Hz, 2 H, Ar-H), 7.48 (d, J = 8.2 Hz, 2 H, Ar-H), 3.92 (s, 2 H, CH_2), 2.85 (s, 3 H, CH_3N) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.1, 167.8, 132.2, 131.0, 128.7, 118.6, 102.1, 51.2, 28.6 ppm. MS (ESI-TOF): m/z = 268, 270 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{11}H_{10}{}^{79}BrNNaO_2$ [M + Na]$^+$ 289.9793; found 289.9780; calcd. for $C_{11}H_{10}{}^{81}BrNNaO_2$ [M + Na]$^+$ 291.9772; found 291.9765.

3-(4-Chlorophenyl)-4-hydroxy-1-methyl-1*H*-pyrrol-2(5*H*)-one (5d): Following the general procedure, from methyl (4-chlorophenyl)acetate (**1d**, 0.28 g, 1.5 mmol), methyl sarcosinate hydrochloride (**4**, 0.32 g, 2.3 mmol), and potassium *tert*-butoxide (3.8 mL, 3.8 mmol, 1 M in THF) in THF (7 mL), tetramic acid **5d** (0.16 g, 48%) was obtained as a white solid; m.p. 236–238 °C; TLC: R_f = 0.20 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3096, 2907, 2616, 2522, 1666, 1604, 1589, 1439, 1414, 1385, 1223, 1084, 1012, 973, 905, 826, 757, 704 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.04 (d, J = 9.6 Hz, 2 H, Ar-H), 7.34 (d, J = 9.6 Hz, 2 H, Ar-H), 3.92 (s, 2 H, CH_2), 2.85 (s, 3 H, CH_3N) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 171.2, 167.7, 131.9, 130.0, 128.4, 128.1, 102.1, 51.2, 28.6 ppm. MS (ESI-TOF): m/z = 224, 226 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{11}H_{10}{}^{35}ClNNaO_2$ [M + Na]$^+$ 246.0298; found 246.0289.

4-Hydroxy-1-methyl-3-(thien-2-yl)-1*H*-pyrrol-2(5*H*)-one (5e): Following the general procedure, from methyl 2-thienylacetate (**1e**, 0.19 g, 1.2 mmol), methyl sarcosinate hydrochloride (**4**, 0.25 g, 1.8 mmol), and potassium *tert*-butoxide (3.0 mL, 3.0 mmol, 1 M in THF) in THF (9 mL), tetramic acid **5e** (65 mg, 28%) was obtained as a white solid; m.p. 202–203 °C (dec.); TLC: R_f = 0.20 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2930, 2566, 1665, 1604, 1435, 1397, 1337, 1226, 933, 842, 725, 677 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.52 (d, J = 3.6 Hz, 1 H, SCH=CH-C*H*), 7.23 (d, J = 4.8 Hz, 1 H, SCH), 6.98 (dd, J = 4.8, 3.6 Hz, 1 H, SCH=C*H*), 3.88 (s, 2 H, CH_2), 2.85 (s, 3 H, CH_3N) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 170.3, 165.0, 133.6, 126.6, 123.4, 123.0, 100.8, 51.4, 28.7 ppm. MS (ESI-TOF): m/z = 196 [M + H]$^+$.

Ethyl (2,4-Dimethoxybenzyl)aminoacetate (6b): Ethyl bromoacetate (6.63 mL, 59.8 mmol, 1 equiv.) was added dropwise to a solution of (2,4-dimethoxybenzyl)amine (10 g, 59.8 mmol, 1 equiv.) and triethylamine (20.8 mL, 149.5 mmol, 2.5 equiv.) in anhydrous THF (75 mL) cooled to 0 °C under argon. The reaction mixture was warmed to room temperature and then stirred overnight. Brine (250 mL) was added, and the aq phase was extracted with AcOEt (2 × 200 mL). The combined organic layers were dried with $MgSO_4$. After filtration and concentration under vacuum, the residue was purified by column chromatography (silica gel, 4:1 → 1:1 cyclohexane/AcOEt), to give amino ester **6b** as a colorless oil (11.5 g, 76%). TLC: R_f = 0.30 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3342, 2938, 2836, 1737, 1613, 1588, 1507, 1464, 1290, 1261, 1208, 1187, 1156, 1134, 1035, 933, 832, 789 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.1 Hz, 1 H, Ar-H), 6.41–6.37 (m, 2 H, Ar-H), 4.11 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 3.76 (s, 3 H, CH_3O), 3.74 (s, 3 H, CH_3O), 3.70 (s, 2 H, NCH_2Ar), 3.33 (s, 2 H, CH_2CO$_2$Et), 2.03 (br. s, 1 H, NH), 1.21 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 172.4, 160.2, 158.7, 130.5, 120.1, 103.7, 98.5, 60.5, 55.3, 55.2, 50.1, 48.1, 14.2 ppm. HRMS (ESI-TOF): calcd. for $C_{13}H_{19}NNaO_4$ [M + Na]$^+$ 276.1212; found 276.1215.

1-Benzyl-4-hydroxy-3-(4-methoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (7a): Following the general procedure, from methyl (4-methoxyphenyl)-acetate (**1a**, 0.18 g, 1.0 mmol), *N*-benzylglycine ethyl ester (**6a**, 0.22 mL, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7a** (0.19 g, 67%) was obtained as a yellow solid; m.p. 196–197 °C; TLC: R_f =

0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3349, 2918, 2597, 1624, 1605, 1514, 1440, 1383, 834, 750 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 8.07 (d, J = 9.1 Hz, 2 H, Ar-H), 7.26–7.36 (m, 5 H, Ph-H), 6.90 (d, J = 9.1 Hz, 2 H, Ar-H), 4.62 (s, 2 H, CH_2Ph), 3.80 (s, 3 H, CH_3O), 3.90 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 45.7, 49.4, 55.4, 105.1, 113.9, 125.9, 128.0, 128.6, 129.4, 139.5, 158.8, 165.0, 172.2 ppm. MS (ESI-TOF): m/z = 296 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{18}H_{17}NNaO_3$ $[M + Na]^+$ 318.1106; found 318.1109.

1-Benzyl-4-hydroxy-3-phenyl-1*H*-pyrrol-2(5*H*)-one (7b): Following the general procedure, from ethyl phenylacetate (**1f**, 0.16 g, 1.0 mmol), *N*-benzylglycine ethyl ester (**6a**, 0.22 mL, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7b** (0.14 g, 54%) was obtained as a yellow solid; m.p. 197–198 °C; TLC: R_f = 0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2923, 2610, 1656, 1595, 1497, 1453, 1391, 1312, 1217, 780, 696 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 8.12 (d, J = 6.9 Hz, 2 H, Ar-H), 7.25–7.37 (m, 7 H, Ar-H), 7.16–7.21 (m, 1 H, Ar-H), 4.63 (s, 2 H, CH_2Ph), 3.93 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 171.9, 166.4, 139.4, 133.4, 129.5, 128.6, 128.5, 128.3, 128.0, 126.8, 105.4, 49.5, 45.7 ppm. MS (ESI-TOF): m/z = 266 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{17}H_{15}NNaO_3$ $[M + Na]^+$ 288.1000; found 288.1011.

1-Benzyl-4-hydroxy-3-(3-methoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (7c): Following the general procedure, from methyl (3-methoxyphenyl)-acetate (**1b**, 0.22 mL, 1.0 mmol), *N*-benzylglycine ethyl ester (**6a**, 0.22 mL, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7c** (0.18 g, 62%) was obtained as a white solid; m.p. 191–192 °C (dec.); TLC: R_f = 0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2934, 2617, 1666, 1596, 1491, 1461, 1398, 1287, 1261, 1215, 1052, 883, 781, 730, 692 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 7.82 (dd, J = 2.7, 1.4 Hz, 1 H, Ar-H), 7.71–7.73 (m, 1 H, Ar-H), 7.22–7.37 (m, 6 H, Ar-H), 6.77 (ddd, J = 8.2, 2.7, 0.9 Hz, 1 H, Ar-H), 4.62 (s, 2 H, CH_2Ph), 3.93 [s, 2 H, NCH_2C(OH)=], 3.78 (s, 3 H, CH_3O) ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 171.9, 166.8, 160.3, 139.3, 134.6, 129.5, 129.4, 128.6, 128.0, 120.7, 113.7, 112.4, 105.2, 55.3, 49.4, 45.7 ppm. MS (ESI-TOF): m/z = 296 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{18}H_{17}NNaO_3$ $[M + Na]^+$ 318.1106; found 318.1101.

1-Benzyl-3-(3,4-dimethoxyphenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (7d): Following the general procedure, from methyl (3,4-dimethoxyphenyl)acetate (**1g**, 0.22 mL, 1.0 mmol), *N*-benzylglycine ethyl ester (**6a**, 0.22 mL, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7d** (0.17 g, 52%) was obtained as a white solid; m.p. 171 °C (dec.); TLC: R_f = 0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2936, 2838, 2626, 1665, 1596, 1521, 1448, 1370, 1262, 1221, 1146, 1025, 817, 764, 714, 697 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 7.88 (d, J = 2.5 Hz, 1 H, Ar-H), 7.70 (dd, J = 8.5, 2.5 Hz, 1 H, Ar-H), 7.27–7.37 (m, 5 H, Ph-H), 6.92 (d, J = 8.5 Hz, 1 H, Ar-H), 4.62 (s, 2 H, CH_2Ph), 3.91 [s, 2 H, NCH_2C(OH)=], 3.80 (s, 6 H, 2 CH_3O) ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 172.2, 165.1, 149.7, 148.8, 139.4, 129.5, 128.6, 128.0, 126.4, 121.1, 112.5, 112.4, 105.2, 56.1, 56.0, 49.4, 45.7 ppm. MS (ESI-TOF): m/z = 326 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{19}H_{19}NNaO_4$ $[M + Na]^+$ 348.1212; found 348.1210.

1-Benzyl-3-(4-bromophenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (7e): Following the general procedure, from methyl (4-bromophenyl)acetate (**1c**, 0.22 mL, 1.0 mmol), *N*-benzylglycine ethyl ester (**6a**, 0.22 mL, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7e** (0.22 g, 64%) was obtained as a yellow solid; m.p. 216–217 °C (dec.); TLC: R_f = 0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3026, 2920, 2701, 1665, 1622, 1492, 1459, 1448, 1436, 1413, 1379, 1214, 829, 737, 697 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 8.14 (d, J = 8.3 Hz, 2 H, Ar-H), 7.51 (d, J = 8.3 Hz, 2 H, Ar-H), 7.27–7.37 (m, 5 H, Ph-H), 4.63 (s, 2 H, CH_2Ph), 3.94 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 171.6, 167.1, 139.2, 132.7, 131.6, 129.9, 129.5, 128.6, 128.1, 119.9, 104.2, 49.5, 45.7 ppm. MS (ESI-TOF): m/z = 344, 346 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{17}H_{14}{}^{79}BrNNaO_2$ $[M + Na]^+$ 366.0106; found 366.0112; calcd. for $C_{17}H_{14}{}^{81}BrNNaO_2$ $[M + Na]^+$ 368.0085; found 368.0099.

1-Benzyl-3-(4-chlorophenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (7f): Following the general procedure, from methyl (4-chlorophenyl)acetate (**1d**, 0.23 g, 1.0 mmol), *N*-benzylglycine ethyl ester (**6a**, 0.22 mL, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7f** (0.18 g, 62%) was obtained as a yellow solid; m.p. 207–208 °C (dec.); TLC: R_f = 0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2920, 2700, 1666, 1620, 1494, 1460, 1449, 1437, 1414, 1381, 1215, 831, 816, 740, 699 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 8.20 (d, J = 9.0 Hz, 2 H, Ar-H), 7.36 (d, J = 9.0 Hz, 2 H, Ar-H), 7.24–7.38 (m, 5 H, Ph-H), 4.63 (s, 2 H, CH_2Ph), 3.95 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 171.7, 167.2, 139.2, 132.3, 131.7, 129.6, 129.5, 128.6, 128.6, 128.1, 104.0, 49.5, 45.7 ppm. MS (ESI-TOF): m/z = 300, 302 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{17}H_{14}{}^{35}ClNNaO_2$ $[M + Na]^+$ 322.0611; found 322.0604.

1-Benzyl-3-(4-fluorophenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (7g): Following the general procedure, from methyl (4-fluorophenyl)-acetate (**1h**, 0.22 mL, 1.0 mmol), *N*-benzylglycine ethyl ester (**6a**, 0.22 mL, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7g** (0.15 g, 54%) was obtained as a white solid; m.p. 180–181 °C (dec.); TLC: R_f = 0.25 (95:5 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 2927, 2614, 1659, 1588, 1511, 1452, 1420, 1383, 1301, 1277, 1239, 1216, 1161, 972, 844, 815, 698 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 8.19 (dd, J = 9.1, 5.7 Hz, 2 H, Ar-H), 7.25–7.36 (m, 5 H, Ph-H), 7.10 (t, J = 9.1 Hz, 2 H, Ar-H), 4.63 (s, 2 H, CH_2Ph), 3.94 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 171.8, 166.3, 160.8 (d, J = 243 Hz), 139.3, 129.9 (d, J = 7 Hz), 129.7 (d, J = 3 Hz), 129.5, 128.6, 128.0, 115.2 (d, J = 21 Hz), 104.4, 49.4, 45.7 ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{14}FNNaO_2$ $[M + Na]^+$ 306.0906; found 306.0895.

1-(2,4-Dimethoxybenzyl)-4-hydroxy-3-phenyl-1*H*-pyrrol-2(5*H*)-one (7i): Following the general procedure, from methyl phenylacetate (**1f**, 150 mg, 1.0 mmol), ethyl 2-[(2,4-dimethoxybenzyl)amino]-acetate (**6b**, 304 mg, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7i** (205 mg, 63%) was obtained as a white solid; m.p. 169–170 °C; TLC: R_f = 0.20 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3002, 2971, 2913, 2839, 2618, 1652, 1614, 1504, 1456, 1397, 1358, 1315, 1210, 1181, 1134, 1038, 907, 822, 779, 739, 698 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone): δ = 10.20 (br. s, 1 H, OH), 8.10 (d, J = 7.4 Hz, 2 H, Ar-H), 7.32 (t, J = 7.4 Hz, 2 H, Ar-H), 7.17 (t, J = 7.4 Hz, 1 H, Ar-H), 7.10 (d, J = 8.3 Hz, 1 H, Ar-H), 6.56 (d, J = 2.2 Hz, 1 H, Ar-H), 6.48 (dd, J = 8.3, 2.2 Hz, 1 H, Ar-H), 4.53 (s, 2 H, CH_2Ar), 3.93 [s, 2 H, NCH_2C(OH)=], 3.85 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O) ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 171.8, 166.4, 161.4, 159.3, 133.4, 130.9, 128.5, 128.2, 126.7, 119.2, 105.6, 105.4, 99.1, 55.8, 55.6, 50.0, 40.0 ppm. MS (ESI-TOF): m/z

= 326 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{19}H_{19}NNaO_4$ [M + Na]$^+$ 348.1212; found 348.1204.

1-(2,4-Dimethoxybenzyl)-4-hydroxy-3-(4-methoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (7j): Following the general procedure, from methyl (4-methoxyphenyl)acetate (**1a**, 180 mg, 1.0 mmol), ethyl 2-[(2,4-dimethoxybenzyl)amino]acetate (**6b**, 304 mg, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7j** (153 mg, 43%) was obtained as a white solid; m.p. 170–171 °C; TLC: R_f = 0.15 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3002, 2958, 2921, 2839, 2536, 1674, 1591, 1514, 1455, 1442, 1392, 1358, 1290, 1246, 1210, 1178, 1117, 1032, 974, 948, 939, 902, 836, 819, 726, 661, 564 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 11.37 (br. s, 1 H, OH), 7.94 (d, J = 9.0 Hz, 2 H, Ar-H), 7.00 (d, J = 8.3 Hz, 1 H, Ar-H), 6.90 (d, J = 9.0 Hz, 2 H, Ar-H), 6.58 (d, J = 2.3 Hz, 1 H, Ar-H), 6.49 (dd, J = 8.3, 2.3 Hz, 1 H, Ar-H), 4.43 (s, 2 H, CH_2Ar), 3.81 [s, 2 H, NCH_2C(OH)=], 3.80 (s, 3 H, CH_3O), 3.74 (s, 6 H, 2 CH_3O) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.1, 165.2, 159.9, 157.9, 157.1, 129.6, 127.9, 125.0, 117.9, 113.19, 104.7, 102.7, 98.4, 55.5, 55.2, 54.9, 49.1, 39.2 ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{21}NNaO_5$ [M + Na]$^+$ 378.1317; found 378.1320.

1-(2,4-Dimethoxybenzyl)-4-hydroxy-3-(3-methoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (7k): Following the general procedure, from methyl (3-methoxyphenyl)acetate (**1b**, 156 mg, 1.0 mmol), ethyl 2-[(2,4-dimethoxybenzyl)amino]acetate (**6b**, 304 mg, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7k** (190 mg, 53%) was obtained as a brown solid; m.p. 150–151 °C; TLC: R_f = 0.15 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3433, 3005, 2956, 2836, 2624, 1609, 1510, 1455, 1382, 1290, 1211, 1160, 1035, 987, 936, 878, 828, 815, 778, 691, 647 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.81 (dd, J = 2.6, 1.4 Hz, 1 H, Ar-H), 7.70 (ddd, J = 7.8, 1.4, 1.0 Hz, 1 H, Ar-H), 7.22 (t, J = 8.0 Hz, 1 H, Ar-H), 7.10 (d, J = 8.3 Hz, 1 H, Ar-H), 6.75 (ddd, J = 8.2, 2.6, 1.0 Hz, 1 H, Ar-H), 6.56 (d, J = 2.4 Hz, 1 H, Ar-H), 6.48 (dd, J = 8.3, 2.4 Hz, 1 H, Ar-H), 4.52 (s, 2 H, CH_2Ar), 3.93 [s, 2 H, NCH_2C(OH)=], 3.85 (s, 3 H, CH_3O), 3.78 (s, 6 H, 2 CH_3O) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 171.7, 166.6, 161.4, 160.2, 159.3, 134.7, 130.9, 129.3, 120.7, 119.2, 113.6, 112.3, 105.4, 105.3, 99.1, 55.8, 55.6, 55.3, 49.9, 40.1 ppm. MS (ESI-TOF): m/z = 356 [M + H]$^+$.

3-(4-Bromophenyl)-1-(2,4-dimethoxybenzyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (7l): Following the general procedure, from methyl (4-bromophenyl)acetate (**1c**, 229 mg, 1.0 mmol), ethyl 2-[(2,4-dimethoxybenzyl)amino]acetate (**6b**, 304 mg, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7l** (226 mg, 55%) was obtained as a white solid; m.p. 196–198 °C; TLC: R_f = 0.20 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3009, 2924, 2834, 2587, 1665, 1608, 1509, 1454, 1409, 1379, 1297, 1209, 1157, 1116, 1030, 826, 746 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.94 (br. s, 1 H, OH), 8.02 (d, J = 8.7 Hz, 2 H, Ar-H), 7.50 (d, J = 8.7 Hz, 2 H, Ar-H), 7.01 (d, J = 8.3 Hz, 1 H, Ar-H), 6.57 (d, J = 2.3 Hz, 1 H, Ar-H), 6.48 (dd, J = 8.3, 2.3 Hz, 1 H, Ar-H), 4.43 (s, 2 H, CH_2Ar), 3.84 [s, 2 H, NCH_2C(OH)=], 3.80 (s, 3 H, CH_3O), 3.74 (s, 3 H, CH_3O) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 170.6, 168.0, 159.9, 157.9, 131.9, 130.7, 129.6, 128.3, 118.2, 117.7, 104.7, 101.5, 98.4, 55.5, 55.2, 49.2, 39.2 ppm. MS (ESI-TOF): m/z = 404, 406 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{19}H_{18}{}^{79}BrO_4NNa$ [M + Na]$^+$ 426.0317; found 426.0301; calcd. for $C_{19}H_{18}{}^{81}BrO_4NNa$ [M + Na]$^+$ 428.0296; found 428.0285.

1-(2,4-Dimethoxybenzyl)-3-(4-fluorophenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (7m): Following the general procedure, from methyl (4-fluorophenyl)acetate (**1h**, 168 mg, 1.0 mmol), ethyl 2-[(2,4-dimethoxybenzyl)amino]acetate (**6b**, 304 mg, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7m** (245 mg, 71%) was obtained as a yellow solid; m.p. 144–145 °C; TLC: R_f = 0.20 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3415, 3008, 2942, 2838, 2620, 1664, 1613, 1510, 1455, 1419, 1385, 1301, 1209, 1158, 1034, 832, 815, 732, 570 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.17 (dd, J = 9.1, 5.7 Hz, 2 H, Ar-H), 7.11–7.06 (m, 3 H, Ar-H), 6.56 (d, J = 2.4 Hz, 1 H, Ar-H), 6.48 (dd, J = 8.3, 2.4 Hz, 1 H, Ar-H), 4.52 (s, 2 H, CH_2Ar), 3.94 [s, 2 H, NCH_2C(OH)=], 3.85 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 171.8, 166.2, 161.7 (d, J = 243.3 Hz), 161.5, 159.4, 130.9, 129.9 (d, J = 7.7 Hz), 119.1, 115.1 (d, J = 20.7 Hz), 105.4, 104.4, 99.1, 55.8, 55.6, 49.9, 40.1 ppm. MS (ESI-TOF): m/z = 344 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{19}H_{18}FNNaO_4$ [M + Na]$^+$ 366.1118; found 366.1123.

1-(2,4-Dimethoxybenzyl)-4-hydroxy-3-(2-thienyl)-1*H*-pyrrol-2(5*H*)-one (7n): Following the general procedure, from methyl 4-thienylacetate (**1e**, 156 mg, 1.0 mmol), ethyl 2-[(2,4-dimethoxybenzyl)amino]acetate (**6b**, 304 mg, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (7 mL), tetramic acid **7n** (205 mg, 61%) was obtained as a brown solid; m.p. 135–136 °C; TLC: R_f = 0.15 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3399, 3002, 2939, 2836, 2686, 1667, 1613, 1591, 1509, 1456, 1438, 1401, 1337, 1294, 1266, 1209, 1157, 1131, 1035, 835, 694 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.71 (d, J = 3.6 Hz, 1 H, SCH=CH-C*H*), 7.28 (d, J = 5.2 Hz, 1 H, SCH), 7.10 (d, J = 8.5 Hz, 1 H, Ar-H), 7.03 (dd, J = 5.2, 3.6 Hz, 1 H, SCH=C*H*), 6.55 (d, J = 2.3 Hz, 1 H, Ar-H), 6.47 (dd, J = 8.5, 2.3 Hz, 1 H, Ar-H), 4.52 (s, 2 H, CH_2Ar), 3.88 [s, 2 H, NCH_2C(OH)=], 3.84 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 170.9, 163.8, 161.5, 159.4, 134.3, 130.9, 126.9, 124.4, 124.0, 119.1, 105.4, 102.3, 99.1, 55.8, 55.6, 50.1, 40.3 ppm. MS (ESI-TOF): m/z = 332 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{17}H_{17}NNaO_4S$ [M + Na]$^+$ 354.0776; found 354.0765.

4-Hydroxy-3-phenyl-1*H*-pyrrol-2(5*H*)-one (8i): A solution of tetramic acid **7i** (100 mg, 0.31 mmol) in trifluoroacetic acid (3 mL) was stirred at room temperature for 1 h. After the mixture was concentrated under vacuum, toluene was added to the residue. Concentration of the mixture under vacuum afforded tetramic acid **8i** as a white solid (quantitative yield); m.p. 187–188 °C; TLC: R_f = 0.55 (8:2 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3355, 3277, 3000, 2939, 2834, 2709, 1642, 1615, 1508, 1453, 1391, 1315, 1299, 1223, 1202, 1184, 1116, 1094, 1037, 814, 784, 751, 697, 627 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.55 (br. s, 1 H, OH), 7.96 (d, J = 7.3 Hz, 2 H, Ar-H), 7.42 (br. s, 1 H, NH), 7.30 (t, J = 7.3 Hz, 2 H, Ar-H), 7.14 (t, J = 7.3 Hz, 1 H, Ar-H), 3.86 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 173.8, 168.8, 132.5, 127.6, 126.7, 125.4, 103.1, 44.8 ppm. MS (ESI-TOF): m/z = 176 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{10}H_9NNaO_2$ [M + Na]$^+$ 198.0531; found 198.0522.

4-Hydroxy-3-(3-methoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (8k): Following the procedure described for **8i**, starting from tetramic acid **7k** (100 mg, 0.28 mmol), tetramic acid **8k** was obtained as a brown solid (quantitative yield); m.p. 180–181 °C; TLC: R_f = 0.55 (8:2 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3305, 2944, 2836, 2627, 1663, 1614, 1508, 1463, 1440, 1371, 1296, 1256, 1204, 1178, 1114, 1095, 1035, 860, 839, 814, 784, 746, 693, 677, 640, 581 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.57 (br. s, 1 H, OH), 7.58 (s, 1 H, Ar-H), 7.53 (d, J = 7.9 Hz, 1 H, Ar-H), 7.38, (br. s, 1 H, NH), 7.16 (t, J = 7.9 Hz, 1 H, Ar-H), 6.68 (d, J = 7.9 Hz, 1 H, Ar-H), 3.80

[s, 2 H, NCH_2C(OH)=], 3.68 (s, 3 H, CH_3O) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 173.7, 169.1, 158.7, 133.8, 128.6, 119.3, 112.4, 110.9, 102.8, 54.8, 4.8 ppm. MS (ESI-TOF): *m*/*z* = 206 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{11}H_{11}NNaO_3$ $[M + Na]^+$ 228.0637; found 228.0633.

3-(4-Bromophenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (8l): Following the procedure described for **8i**, starting from tetramic acid **7l** (100 mg, 0.25 mmol), tetramic acid **8l** was obtained as a brown solid (quantitative yield); m.p. 210 °C (dec.); TLC: R_f = 0.55 (8:2 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3424, 3001, 2920, 2834, 2673, 1633, 1589, 1509, 1491, 1441, 1425, 1378, 1300, 1224, 1202, 1038, 828, 756, 711 cm^{-1}. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 11.86 (br. s, 1 H, OH), 7.99 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.50 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.49 (br. s, 1 H, NH), 3.86 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 173.4, 169.7, 131.9, 130.6, 128.4, 118.2, 101.8, 44.8 ppm. MS (ESI-TOF): *m*/*z* = 254, 256 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{10}H_8{}^{79}BrNNaO_2$ $[M + Na]^+$ 275.9636; found 275.9626; calcd. for $C_{10}H_8{}^{81}BrNNaO_2$ $[M + Na]^+$ 277.9616; found 277.9603.

3-(4-Fluorophenyl)-4-hydroxy-1*H*-pyrrol-2(5*H*)-one (8m): Following the procedure described for **8i**, starting from tetramic acid **7m** (100 mg, 0.29 mmol), tetramic acid **8m** was obtained as a yellow solid (quantitative yield); m.p. 200 °C (dec.); TLC: R_f = 0.55 (8:2 CH_2Cl_2/MeOH). IR (KBr pellet): $\tilde{\nu}$ = 3398, 3002, 2931, 2834, 2355, 1825, 1612, 1591, 1509, 1466, 1442, 1372, 1300, 1203, 1159, 1037, 836, 814, 749, 606, 593, 575 cm^{-1}. ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 11.66 (br. s, 1 H, OH), 8.03 (dd, *J* = 9.0, 5.9 Hz, 2 H, Ar-H), 7.44 (br. s, 1 H, NH), 7.13 (t, *J* = 9.0 Hz, 2 H, Ar-H), 3.86 [s, 2 H, NCH_2C(OH)=] ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 173.7, 168.7, 160.0 (d, *J* = 243.6 Hz), 129.0 (d, *J* = 3.1 Hz), 128.4 (d, *J* = 7.8 Hz), 114.5, 102.1, 44.8 ppm. MS (ESI-TOF): *m*/*z* = 194 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{10}H_8FNNaO_2$ $[M + Na]^+$ 216.0437; found 216.0426.

1-Hydroxy-2-(4-methoxyphenyl)-6,7,8,8a-tetrahydroindolizin-3(5*H*)-one (9): Following the general procedure, from methyl (4-methoxyphenyl)acetate (**1a**, 180 mg, 1.0 mmol), methyl pipecolinate (172 mg, 1.2 mmol), and potassium *tert*-butoxide (1.2 mL, 1.2 mmol, 1 M in THF) in THF (5 mL), tetramic acid **9** (100 mg, 37%) was obtained as a gray solid; m.p. 212–213 °C; TLC: R_f = 0.15 (1:1 cyclohexane/AcOEt). IR (KBr pellet): $\tilde{\nu}$ = 3007, 2934, 2862, 2836, 2678, 1663, 1610, 1514, 1461, 1427, 1378, 1308, 1290, 1248, 1206, 1184, 1165, 1034, 1016, 1000, 880, 834, 792, 718, 586, 532 cm^{-1}. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 11.16 (br. s, 1 H, OH), 7.92 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.89 (d, *J* = 8.8 Hz, 2 H, Ar-H), 4.12 (dd, *J* = 12.8, 4.0 Hz, 1 H, C*H*H′N), 3.81 [dd, *J* = 11.4, 3.5 Hz, 1 H, NC*H*C(OH)=], 3.74 (s, 3 H, CH_3O), 2.72 (dt, *J* = 12.8, 2.8 Hz, 1 H, CH*H*′N), 2.34 [m, 1 H, C*H*H′$(CH_2)_3$NC(O)-], 1.83 [m, 1 H, C*H*H′$(CH_2)_2$NC(O)-], 1.64 [m, 1 H, C*H*H′CH_2NC(O)-], 1.47 [m, 1 H, CH*H*′$(CH_2)_2$NC(O)-], 1.15 [m, 1 H, CH*H*′CH_2NC(O)-], 0.97 [m, 1 H, CH*H*′$(CH_2)_3$NC(O)-] ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 168.6, 168.2, 157.0, 128.0, 125.0, 113.1, 102.0, 56.3, 54.9, 37.6, 30.0, 25.6, 22.4 ppm. MS (ESI-TOF): *m*/*z* = 260 $[M + H]^+$. HRMS (ESI-TOF): calcd. for $C_{15}H_{17}NNaO_3$ $[M + Na]^+$ 282.1106; found 282.1098.

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