Parallel Solution-phase Synthesis of (2*S*,4*E*)-4-(Arylaminomethylidene)pyroglutamic Acids

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A library of twelve *N*(4′)-substituted di-*tert*-butyl (2*S*,4*E*)-4-arylaminomethylidene-5-oxopyrrolidine-1,2-dicarboxylates **6/6′a** – **l** were prepared in 47 – 90 % yield by parallel acid-catalysed treatment of di-*tert*-butyl (2*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**4**) with anilines **5a** – **j**, ethyl glycinate (**5k**), and ethyl β-alaninate (**3l**). Acidolytic deprotection of compounds **6a** – **c**, **e** – **j** afforded the corresponding (2*S*,4*E*)-4-arylaminomethylidene-5-oxopyrrolidine-2-carboxylic acids **7a** – **c**, **e** – **j** in 39 – 99 % yield. The configuration around the C=C double bond in the enaminones **6** and **7** was determined by NMR spectroscopy.

Key words: Pyroglutamic Acid, Enaminones, Amines, Combinatorial Synthesis, Pyrrolidinone

Introduction

(*S*)-Pyroglutamic acid (**1**) is a naturally occurring heterocyclic α-amino acid which is abundant in peptides and proteins, and its structure can also be found in a variety of other biologically important compounds. On the other hand, **1** is also a useful chiral building block, which is frequently used as a commercially available starting material in chiral-pool syntheses of peptidomimetics, natural products, and their analogues. Therefore it is not surprising, that several reviews on the chemistry of (*S*)-pyroglutamic acid (**1**) have recently been published [1].

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are a group of enamino-masked alkyl α-formylacetates, which are easily available and versatile reagents in heterocyclic synthesis [2]. In addition to their extensive use in the synthesis of various heterocyclic systems, recent applications of enaminones have mostly focused on the synthesis of functionalised heterocyclic compounds including natural product analogues [2 – 4], and on combinatorial syntheses of functionalised heterocycles [5]. Within this context, various functionalised enaminones have been prepared and used as key intermediates in the synthesis of 3-heteroarylalanine derivatives [6], histamine analogues [5b, 7], and heterocyclic analogues of dipeptides containing the (*S*)-pyroglutamic acid structural motif [5c, 8]. Previously, we reported the synthesis of a series of *N*(4′)-substituted methyl (2*S*,4*E*)-1-acyl-4-(aminomethylidene)-5-oxopyrrolidine-2-carboxylates as stable intermediates in the ‘ring switching’ synthesis of 3-heteroarylalanines [9]. Recently, this type of compounds attracted our attention again, since such α-enamino pyroglutamic acids are conformationally constrained heterocyclic dipeptides comprising α,β-dehydro-β-alanine (Δ-β-Ala) and (*S*)-alanine (L-Ala) structural units (Fig. 1).

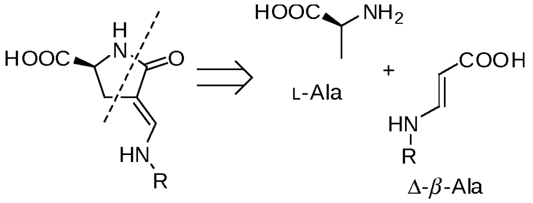

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Fig. 1. α-Enamino (*S*)-pyroglutamic acid **7** as a conformationally constrained heterocyclic analogue of Δ-β-Ala-AlaOH.

Therefore, we were intrigued to study the synthesis of γ-enamino pyroglutamic acids **7**, which might be interesting and useful building blocks for further derivatisation. Herein, we report the result of this study – a simple parallel solution-phase

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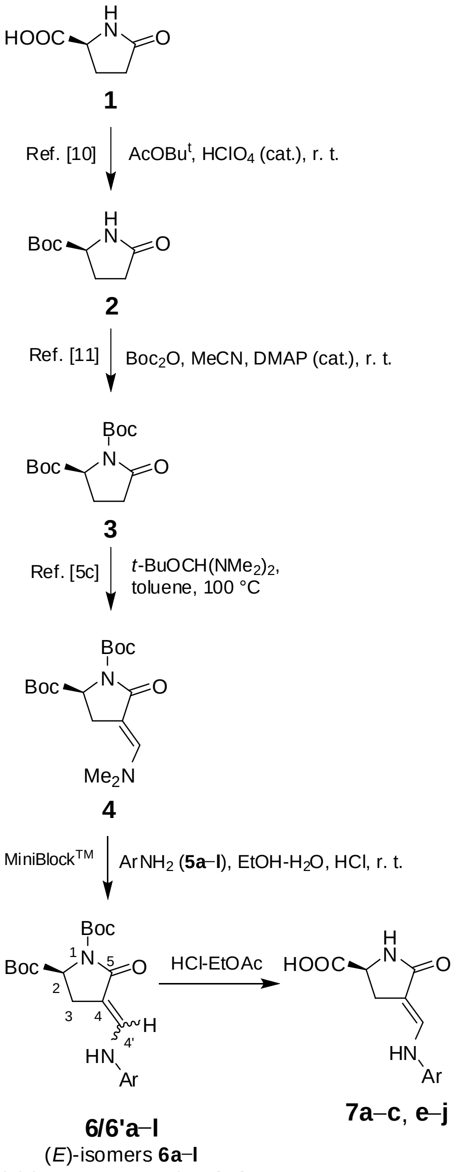
synthesis of di-*tert*-butyl (*S*)-4-arylaminomethylidene-5-oxopyrrolidine-1,2-dicarboxylates **6/6′a – l** and (*S*)-4-arylaminomethylidene-5-oxopyrrolidine-1,2-dicarboxylates **7a – c**, **e – j**.

Results and Discussion

The key intermediate, di-*tert*-butyl (2*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**4**), was prepared in three steps from (*S*)-pyroglutamic acid (**1**) following the literature procedures [5c, 10, 11]. Thus, acid-catalysed esterification of (*S*)-pyroglutamic acid (**1**) with *tert*-butyl acetate gave *tert*-butyl pyroglutamate (**2**) [10], which was *N*-acylated with Boc$_2$O in acetonitrile in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) to afford di-*tert*-butyl (2*S*)-5-oxopyrrolidine-1,2-dicarboxylate (**3**) [11]. Finally, heating of **3** with one equivalent of *tert*-butoxy-bis(dimethylamino)methane (Bredereck′s reagent, TBDMAM) furnished di-*tert*-butyl (2*S*,4*E*)-4-[(dimethylamino)-methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**4**) in 70 % yield over three steps [5c] (Scheme 1).



Scheme 1.

Table 1. Selected experimental data of the di-*tert*-butyl (2*S*,4*E*)-4-arylaminomethylidene-5-oxopyrrolidine-1,2-dicarboxylates **6a – l** and **7a – c**, **e – j**.

Compound	Ar	Yield (%)	*E* : *Z*[a]	Purity (%)[b]
6a/6′a	phenyl	90	56 : 44[c,d]	> 95
6/6′b	3-methylphenyl	65	21 : 79	> 95
6/6′c	4-methylphenyl	83	17 : 83	> 95
6d	3-hydroxyphenyl	62	100 : 0	> 95
6e	4-hydroxyphenyl	69	100 : 0	> 95
6/6′f	3-methoxyphenyl	73	16 : 84	> 95
6/6′g	3-bromophenyl	73	15 : 85	> 95
6/6′h	4-bromophenyl	79	15 : 85	> 95
6′i	3-nitrophenyl	65	100 : 0	> 95
6j	4-nitrophenyl	81	100 : 0	> 95
6/6′k	CH_2COOEt	47	85 : 15	> 95
6/6′l	CH_2CH_2COOEt	68	88 : 12	> 95
7a	phenyl	39	100 : 0	> 95
7b	3-methylphenyl	96	100 : 0	> 95
7c	4-methylphenyl	90	100 : 0	> 95
7e	4-hydroxyphenyl	37	100 : 0	> 95
7f	3-methoxyphenyl	99	100 : 0	> 95
7g	3-bromophenyl	87	100 : 0	> 95
7h	4-bromophenyl	86	100 : 0[d]	> 95
7i	3-nitrophenyl	90	100 : 0[c,d]	> 95
7j	4-nitrophenyl	88	100 : 0[d]	> 95

[a] Determined by ^{1}H-NMR spectroscopy; [b] determined by CHN-analyses and ^{1}H-NMR spectroscopy. The values found for C, H, and N were within ±0.4 % with respect to the calculated values; [c] the configuration around the C=C double bond was determined by HMBC NMR spectroscopy; [d] the configuration around the C=C double bond was determined by NOESY spectroscopy.

Further parallel treatment of the enamino lactam **4** with 1.2 equivalents of amine hydrochlorides **5a – l** in 50 % aqueous ethanol at r. t. resulted in the formation of the dimethylamine substitution products, *N*(4′)-substituted di-*tert*-butyl (2*S*,4*EZ*)-4-aminomethylidene-5-oxopyrrolidine-1,2-dicarboxylates **6/6′ a – l**, which precipitated from the reaction mixtures and were isolated by filtration. Upon washing with water and thorough drying *in vacuo* over P_4O_{10}, a library of twelve analytically pure esters **6/6′a – l** was

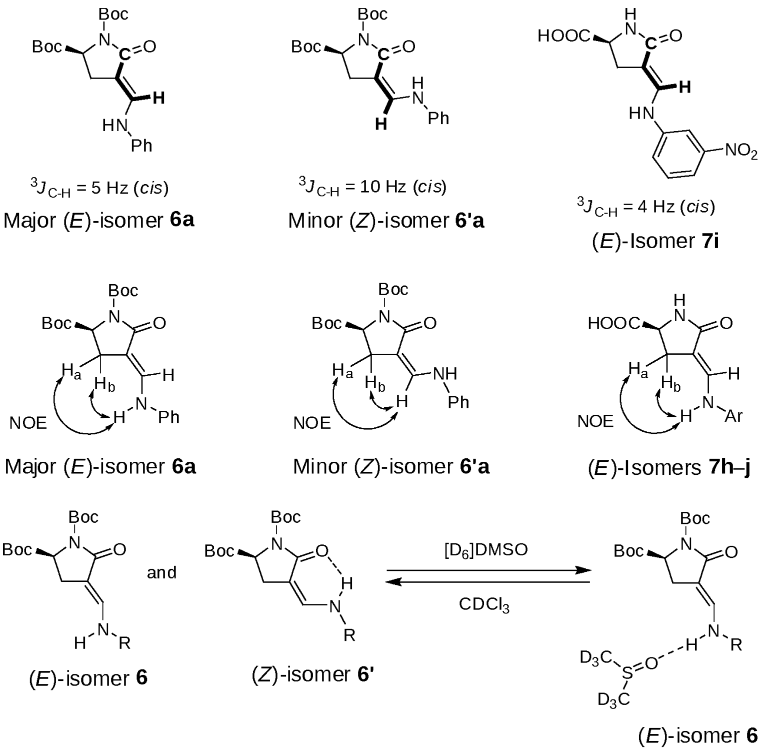


Fig. 2. Structure determination by HMBC and NOESY spectroscopy.

obtained in 47 – 90 % yield. In the final step, parallel acidolytic deprotection of compounds **6**/**6′a – l** was carried out. Stirring of esters **6**/**6′** with 2 M HCl/EtOAc at r. t. for 12 h resulted in the initial formation of clear colourless or yellow solutions followed by formation of precipitates, which were then collected by filtration, washed with EtOAc, and dried *in vacuo* over P_4O_{10}. In this manner, analytically pure carboxylic acids **7a – c**, **e – j** were prepared in 37 – 99 % yield. Acidolysis of compounds **6d**, **k**, **l** did not produce precipitates. Attempts to isolate the final products **7d**, **k**, **l** by evaporation of the reaction mixtures followed by crystallisation and/or chromatographic workup failed. Since we were particularly interested in a simple and practical procedure using just a filtration work-up, no further attempts to isolate compounds **7d**, **k**, **l** were made (Scheme 1, Table 1).

The structures of the novel compounds **6**/**6′a – l** and **7a – c**, **e – j** were determined by spectroscopic (NMR, IR, MS) methods and by elemental analyses. The configuration around the exocyclic C=C bond in compounds **6a**, **6′a**, and **7i** was determined by HMBC NMR spectroscopy on the basis of the long-range coupling constant ($^3J_{C-H}$) between the methylidene proton (*H*–C(4′)) and the carbonyl carbon atom (O=*C*(5)), measured from the antiphase splitting of cross peaks. Generally, the magnitude of this coupling constant, $^3J_{C-H}$, for nuclei with *cis*-configuration around the C=C double bond is smaller (2 – 6 Hz) than that for *trans*-oriented nuclei (8 – 12 Hz) [2, 12]. In compounds **6a** and **7i**, the magnitude of the coupling constants, $^3J_{C(1)-H(4')}$ = 4 Hz (*cis*) and 5 Hz (*cis*), respectively, confirmed the (*E*)-configuration around the exocyclic C=C double bond. In the minor isomer **6′a**, on the other hand, a large coupling constant, $^3J_{C(1)-H(4')}$ = 10 Hz (*trans*), confirmed the (*Z*)-configuration around the C=C double bond (Fig. 2). Additionally, the configuration around the exocyclic C=C double bond in compounds **6a**, **6′a**, and **7h – j** was confirmed by NOESY spectroscopy. A NOE between the NH and the CH_2 group in compounds **6a** and **7h – j** was in agreement with the (*E*)-configuration around the exocyclic C=C double bond, whilst a NOE between the 4′-H and the CH_2 group in the minor isomer **6′a** supported the (*Z*)-configuration (Fig. 2).

Finally, the configurations around the C=C double bond in compounds **6** and **7** were confirmed by correlation of chemical shifts for 4′-H and NH and vicinal coupling constants, $^3J_{H-H}$. The major and most characteristic difference was observed in chemical shifts δ

Table 2. Correlation between the chemical shifts for 4′-H and (4′)N-H and coupling constants, $^3J_{\mathrm{H3-H4}}$ and $^3J_{\mathrm{CH-NH}}$, in compounds **6a – l**, **6′a – c**, **f – h**, **k**, **l**, and **7a – c**, **e – j**.

Compound	Solvent	δ (ppm)		$^3J_{\mathrm{H-H}}$ (Hz)		
		4′-H	4′-NH	3 – 4′	3a – 3b	CHNH
		(2*S*,4*E*)-Isomers **6** and **7**				
6a	CDCl$_3$	7.79	6.09	2.2	15.8	13.7
6b	CDCl$_3$	7.79	6.14	[a]	[a]	13.5
6c	CDCl$_3$	7.76	6.09	[a]	[a]	13.6
6d	[D$_6$]DMSO	7.50	8.89	1.9	16.4	13.1
6e	[D$_6$]DMSO	7.47	8.77	1.8	16.1	13.4
6f	CDCl$_3$	7.76	6.09	[a]	[a]	13.5
6g	CDCl$_3$	7.70	6.24	[a]	[a]	13.3
6h	CDCl$_3$	7.68	6.42	2.1	16.1	13.4
6i	CDCl$_3$	7.74	7.39	2.3	16.4	13.0
6j	CDCl$_3$	7.74	7.18	2.2	16.5	13.2
6j	[D$_6$]DMSO	7.79	9.62	2.4	17.0	[b]
6k	CDCl$_3$	7.11	~ 4.5[c]	2.0	15.4	13.2
6l	CDCl$_3$	7.17	4.65	1.9	15.3	13.6
7a	[D$_6$]DMSO	7.37	8.59	2.1	16.7	11.6
7b	[D$_6$]DMSO	7.37	8.53	2.1	16.7	12.0
7c	[D$_6$]DMSO	7.33	8.47	2.1	16.7	10.4
7e	[D$_6$]DMSO	7.29	8.34	2.0	16.7	[b]
7f	[D$_6$]DMSO	7.33	8.53	2.2	16.7	12.3
7g	[D$_6$]DMSO	7.27	8.65	2.1	16.9	12.3
7h	[D$_6$]DMSO	7.28	8.65	2.2	16.7	12.7
7i	[D$_6$]DMSO	7.37	9.04	2.2	17.0	12.3
7j	[D$_6$]DMSO	7.43	9.44	2.4	16.7	12.2
		(2*S*,4*Z*)-Isomers **6′**				
6′a	CDCl$_3$	7.17	9.95	1.3	15.2	12.3
6′b	CDCl$_3$	7.17	9.89	1.2	15.2	12.2
6′c	CDCl$_3$	7.13	9.90	1.2	15.1	12.3
6′f	CDCl$_3$	7.14	9.92	1.3	15.3	12.4
6′g	CDCl$_3$	~ 7.1[a]	9.94	1.4	15.4	12.0
6′h	CDCl$_3$	7.09	9.94	1.4	15.4	12.1
6′k	CDCl$_3$	6.46	7.96	[a]	[a]	12.6
6′l	CDCl$_3$	6.56	~ 7.9[c]	[a]	[a]	12.6

[a] Overlapped by other signals; [b] the signals for the CHNH fragment appeared as two broad singlets; [c] broad signal.

for the aminomethylidene –N*H*–C*H*= protons. In the ^{1}H-NMR spectra of the *E*/*Z*-mixtures **6/6′a – c**, **f – h**, **k**, **l** taken in CDCl$_3$, the NH protons of the (*E*)-isomers **6a – c**, **f – h**, **k**, **l** had lower δ values (~ 6.2 ppm) than the 4′-H protons (~ 7.7 ppm), while in the (*Z*)-isomers **6′a – c**, **f – h**, **k**, **l** the NH protons exhibited higher δ values (~ 9.9 ppm) than the 4′-H protons (~ 7.2 ppm). Such a difference in chemical shifts of the NH protons in CDCl$_3$ solution could be explained by intramolecular N–*H* ··· *O*=C hydrogen bonding, which is possible only in the (*Z*)-isomers **6′a – c**, **f – h**, **k**, **l** and not in the (*E*)-isomers **6a – c**, **f – h**, **k**, **l**. Accordingly, in [D$_6$]DMSO as a hydrogen bond acceptor, the NH protons of the (*E*)-isomers **6d**, **e**, **j** and **7a – c**, **e – j** appear at ~ 8.5 ppm. Similarly, small yet characteristic differences between typical coupling constant values, $^2J_{\mathrm{H3aH3b}}$, $^3J_{\mathrm{NHCH}}$, and $^4J_{\mathrm{H3H4'}}$, were also observed; typical values were larger in case of the (*E*)-isomers: $^2J_{\mathrm{H3aH3b}} \sim 16$ Hz (*E*) $>$ $^2J_{\mathrm{H3aH3b}} \sim 15$ Hz (*Z*), $^3J_{\mathrm{NHCH}} \sim 13.5$ Hz (*E*) $>$ $^3J_{\mathrm{NHCH}} \sim 12.5$ Hz (*Z*), and $^4J_{\mathrm{H3H4'}} \sim 2$ Hz (*E*) $>$ $^4J_{\mathrm{H3H4'}} \sim 1.3$ Hz (*Z*). These characteristic values are also in agreement with the literature data for related aminomethylidene compounds [2 – 4, 13] (Table 2, Fig. 2).

Conclusion

Di-*tert*-butyl(2*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**4**) is an easily available reagent, which is suitable for two-step parallel solution-phase synthesis of 4-arylaminomethylidene-substituted (*S*)-pyroglutamic acids **7** as conformationally constrained analogues of *N*-[*N*-(aryl)-α,β-didehydro-β-alanyl]-(*S*)-alanine (*c.f.* Fig. 1). The synthesis comprises acid-catalysed substitution of the dimethylamino group in the enamino lactam **4** with aromatic and aliphatic primary amines **5** to give the substitution products **6/6′**, followed by acidolytic deprotection to furnish the title compounds **7** in good yields over two steps. Furthermore, all intermediates

6a – l and final products **7a – c**, **e – j** were obtained in analytical purity following a simple parallel filtration work-up protocol in both synthetic steps. In conclusion, this synthetic method offers an easy access to diversity-oriented libraries of (*S*)-4-[(substituted amino)methylidene]pyroglutamic acid derivatives in search for novel bioactive compounds.

Experimental Section

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance DPX 300 spectrometer at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C, using $CDCl_3$ and [D_6]DMSO (with TMS as the internal standard) as solvents. Mass spectra were recorded on a Q-TOF Premier spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN analyser 2400 II.

(*S*)-Pyroglutamic acid (**1**), di-*tert*-butoxy-bis(dimethylamino)methane (Bredereck′s reagent), and amines **5a – l** are commercially available (Sigma Aldrich). Di-*tert*-butyl (2*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**4**) was prepared from **1** following the literature procedures [5c, 10, 11].

Parallel stirring and filtrations were carried out on a Mettler-Toledo Bohdan MiniBlock™ Compact Shaking and Washing Station and Vacuum Collection Base (12 positions, Vortex stirring, 400 r. p. m. in all cases).

*Parallel solution-phase synthesis of N(4′)-substituted di-tert-butyl (2S)-4-aminomethylidene-5-oxopyrrolidine-1,2-dicarboxylates **6/6′a – l***

The MiniBlock™ was assembled with 12 fritted vessels, and the frits were wetted with ethanol (0.5 mL each). A stock solution of enaminone **4** (0.25 M in ethanol, 12 × 4 mL, 12 × 1 mmol) was added followed by addition of aqueous solutions of amines **5a – l** hydrochlorides* (0.25 M in water, 12 × 5 mL, 12 × 1.2 mmol). The MiniBlock™ was closed and the reaction mixtures were stirred at 20 °C for 24 h. The precipitates were collected by filtration, washed with water (12 × 3 mL), and dried *in vacuo* at r. t. over P_4O_{10} for 24 h to give **6/6′a – l**.

The following compounds were prepared in this manner:

*Di-tert-butyl (2S,4E)-4-anilinomethylidene-5-oxopyrrolidine-1,2-dicarboxylate (**6a**) and its minor (4Z)-isomer **6′a***

Compound **6a** was prepared from **4** and aniline hydrochloride (**5a**). Yield: 365 mg (90 %) of a pale-beige solid. – M. p. 177 – 180 °C; **6a** : **6′a** = 56 : 44. – $[\alpha]^{20}_{589}$ +19.5 (*c* = 0.33, CH_2Cl_2). – IR (KBr): ν = 3237, 3120, 3040, 2978, 1757, 1710, 1686, 1639, 1594, 1495, 1445, 1369, 1313, 1231, 1151, 1000, 959, 866, 806, 775, 753, 692 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major* (*E*)*-isomer* **6a**: δ = 1.48 and 1.53 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.54 (1H, ddd, *J* = 2.2, 3.6, 15.8 Hz, 3-Ha), 2.98 (1H, ddd, *J* = 2.2, 10.7, 15.8 Hz, 3-Hb), 4.56 (1H, dd, *J* = 3.6, 10.7 Hz, 2-H), 6.09 (1H, d, *J* = 13.7 Hz, NH), 6.90 – 7.05 (3H, m, *o*,*p*-C_6H_5), 7.24 – 7.35 (2H, m, *m*-C_6H_5), 7.79 (1H, dt, *J* = 1.9, 13.7 Hz, 4′-H); *minor* (*Z*)*-isomer* **6′a**: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.61 (1H, ddd, *J* = 1.3, 3.5, 15.2 Hz, 3-Ha), 3.06 (1H, ddd, *J* = 1.3, 10.6, 15.2 Hz, 3-Hb), 4.51 (1H, dd, *J* = 3.7, 10.6 Hz, 2-H), 6.90 – 7.05 (3H, m, *o*,*p*-C_6H_5), 7.17 (1H, br d, *J* = 12.3 Hz, 4′-H), 7.24 – 7.35 (2H, m, *m*-C_6H_5), 9.95 (1H, d, *J* = 12.3 Hz, NH). – $C_{21}H_{28}N_2O_5$ (388.5): calcd. C 64.93, H 7.27, N 7.21; found C 65.11, H 7.48, N 7.44.

*Di-tert-butyl (2S,4Z)-4-[(3-methylanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6′b**) and its minor (4E)-isomer **6b***

Compound **6′b** was prepared from **4** and 3-methylaniline hydrochloride (**5b**). Yield: 260 mg (65 %) of a pale-beige solid. – M. p. 155 – 157 °C; **6b** : **6′b** = 21 : 79. – $[\alpha]^{20}_{589}$ +17.4 (*c* = 0.48, CH_2Cl_2). – IR (KBr): ν = 3464, 3318, 2979, 2933, 1756, 1686, 1632, 1599, 1368, 1321, 1246, 1231, 1155, 1001, 1155, 781 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major* (*Z*)*-isomer* **6′b**: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.31 (3H, s, Me), 2.60 (1H, ddd, *J* = 1.2, 3.6, 15.2 Hz, 3-Ha), 3.06 (1H, ddd, *J* = 1.2, 10.6, 15.2 Hz, 3-Hb), 4.50 (1H, dd, *J* = 3.6, 10.6 Hz, 2-H), 6.69 – 6.85 (3H, m, *o*,*p*-C_6H_4), 7.12 – 7.20 (1H, m, *m*-C_6H_4), 7.17 (1H, br d, *J* = 12.2 Hz, 4′-H), 9.89 (1H, d, *J* = 12.2 Hz, NH); *minor* (*E*)*-isomer* **6b**: δ = 2.32 (3H, s, Me), 4.55 (1H, dd, *J* = 3.4, 10.7 Hz, 2-H), 6.14 (1H, broad signal, NH), 7.79 (1H, br d, *J* = 13.5 Hz, 4′-H). – $C_{22}H_{30}N_2O_5$ (402.5): calcd. C 65.65, H 7.51, N 6.96; found C 65.81, H 7.72, N 7.17.

*Di-tert-butyl (2S,4Z)-4-[(4-methylanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6′c**) and its minor (4E)-isomer **6c***

Compound **6′c** was prepared from **4** and 4-methylaniline hydrochloride (**5c**). Yield: 334 mg (83 %) of a pale-beige solid. – M. p. 163 – 170 °C; **6c** : **6′c** = 17 : 83. – $[\alpha]^{20}_{589}$ +21.5 (*c* = 0.40, CH_2Cl_2). – IR (KBr): ν = 3454, 3285, 2980, 2930, 1761, 1710, 1684, 1641, 1524, 1454, 1366, 1307, 1233, 1153, 999, 962, 870, 810, 774 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major* (*Z*)*-isomer* **6′c**: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.28 (3H, s, Me), 2.60 (1H, ddd, *J* = 1.2, 3.7, 15.1 Hz, 3-Ha), 3.05 (1H, ddd, *J* = 1.2, 10.6, 15.1 Hz, 3-Hb), 4.50 (1H, dd, *J* = 3.7, 10.6 Hz, 2-H), 6.83 (2H, br d, *J* = 8.3 Hz, *m*-C_6H_4), 7.08 (2H, br d, *J* = 8.3 Hz, *o*-C_6H_4), 7.13 (1H, br

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*In the case of anilines **5i**, **j**, the solid-free nitroanilines **5i** and **5j** were added to ethanolic solutions of **4**, followed by addition of 0.25 M aq. HCl.

d, J = 12.3 Hz, 4′-H), 9.90 (1H, d, J = 12.3 Hz, NH); *minor* (*E*)*-isomer* **6c**: δ = 2.29 (3H, s, Me), 4.55 (1H, dd, J = 3.6, 10.6 Hz, 2-H), 6.09 (1H, broad signal, NH), 6.83 (2H, br d, J = 8.3 Hz, *m*-C_6H_4), 7.76 (1H, br d, J = 13.6 Hz, 4′-H). – $C_{22}H_{30}N_2O_5$ (402.5): calcd. C 65.65, H 7.51, N 6.96; found C 65.73, H 7.72, N 7.28.

*Di-tert-butyl (2S,4E)-4-[(3-hydroxyanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6d**)*

Compound **6d** was prepared from **4** and 3-hydroxyaniline hydrochloride (**5d**). Yield: 251 mg (62 %) of a pale-grey solid. – M. p. 180 – 181 °C; **6d** : **6′d** = 100 : 0. – $[\alpha]_{589}^{20}$ +2.0 (c = 0.49, EtOH). – IR (KBr): ν = 3383, 3307, 2978, 1757, 1709, 1688, 1634, 1612, 1500, 1460, 1392, 1369, 1346, 1305, 1240, 1156, 979, 959, 779 cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 1.42 and 1.44 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.53 (1H, ddd, J = 1.9, 3.4, 16.4 Hz, 3-Ha), 2.99 (1H, ddd, J = 1.9, 10.7, 16.4 Hz, 3-Hb), 4.52 (1H, dd, J = 3.4, 10.7 Hz, 2-H), 6.36 (1H, dd, J = 1.6, 7.9 Hz, *o*-C_6H_4), 6.49 – 6.57 (2H, m, *o*,*m*-C_6H_4), 7.06 (1H, t, J = 8.0 Hz, *m*-C_6H_4), 7.50 (1H, br d, J = 13.1 Hz, 4′-H), 8.89 (1H, d, J = 13.1 Hz, NH), OH exchanged. – $C_{21}H_{28}N_2O_6$ (404.5): calcd. C 62.36, H 6.98, N 6.93; found C 62.62, H 7.22, N 6.92.

*Di-tert-butyl (2S,4E)-4-[(4-hydroxyanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6e**)*

Compound **6e** was prepared from **4** and 4-hydroxyaniline hydrochloride (**5e**). Yield: 279 mg (69 %) of a pale-grey solid. – M. p. 167 – 168 °C; **6e** : **6′e** = 100 : 0. – $[\alpha]_{589}^{20}$ −2.1 (c = 0.34, EtOH). – IR (KBr): ν = 3402, 3321, 2978, 2935, 1724, 1695, 1634, 1519, 1433, 1391, 1369, 1321, 1225, 1150, 1005, 962, 822, 791, 745, 673 cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 1.42 and 1.44 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.48 (1H, ddd, J = 1.8, 3.5, 16.1 Hz, 3-Ha), 2.96 (1H, ddd, J = 1.8, 10.7, 16.1 Hz, 3-Hb), 4.51 (1H, dd, J = 3.5, 10.8 Hz, 2-H), 6.70 (2H, d, J = 8.8 Hz, *o*-C_6H_4), 6.95 (2H, d, J = 8.8 Hz, *m*-C_6H_4), 7.47 (1H, br d, J = 13.4 Hz, 4′-H), 8.77 (1H, d, J = 13.4 Hz, NH), OH exchanged. – $C_{21}H_{28}N_2O_6$ (404.5): calcd. C 62.36, H 6.98, N 6.93; found C 62.66, H 7.21, N 7.09.

*Di-tert-butyl (2S,4Z)-4-[(3-methoxyanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6′f**) and its minor (4E)-isomer **6f***

Compound **6′f** was prepared from **4** and 3-methoxyaniline hydrochloride (**5f**). Yield: 304 mg (73 %) of a grey solid. – M. p. 151 – 156 °C; **6f** : **6′f** = 16 : 84. – $[\alpha]_{589}^{20}$ +19.5 (c = 1.00, CH_2Cl_2). – IR (KBr): ν = 3453, 3251, 3127, 2978, 2934, 1761, 1733, 1682, 1637, 1593, 1537, 1497, 1481, 1456, 1391, 1368, 1310, 1286, 1244, 1223, 1196, 1155, 1146, 1047, 997, 964, 929, 842, 768, 688 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major* (*Z*)*-isomer* **6′f**: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 1.58 (0.7 H, s, 1/3H_2O), 2.61 (1H, ddd, J = 1.3, 3.6, 15.3 Hz, 3-Ha), 3.06 (1H, ddd, J = 1.3, 10.6, 15.3 Hz, 3-Hb), 3.79 (3H, s, OMe), 4.51 (1H, dd, J = 3.6, 10.6 Hz, 2-H), 6.46 (1H, br t, J = 2.2 Hz, *o*-C_6H_4), 6.52 (1H, d, J = 8.1 Hz, *p*-C_6H_4), 6.53 (1H, d, J = 8.1 Hz, *o*-C_6H_4), 7.14 (1H, dt, J = 1.3, 12.3 Hz, 4′-H), 7.17 (1H, t, J = 8.1 Hz, *m*-C_6H_4), 9.92 (1H, d, J = 12.3 Hz, NH); *minor* (*E*)*isomer* **6f**: δ = 3.80 (3H, s, OMe), 6.09 (1H, br d, J = 13.5 Hz, NH), 7.76 (1H, br d, J = 13.5 Hz, 4′-H). – $C_{22}H_{30}N_2O_6 \cdot 1/3H_2O$ (424.5): calcd. C 62.25, H 7.28, N 6.60; found C 62.35, H 7.34, N 6.58.

*Di-tert-butyl (2S,4Z)-4-[(3-bromoanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6′g**) and its minor (4E)-isomer **6g***

Compound **6′g** was prepared from **4** and 3-bromoaniline hydrochloride (**5g**). Yield: 341 mg (73 %) of a pale-grey solid. – M. p. 163 – 166 °C; **6g** : **6′g** = 15 : 85. – $[\alpha]_{589}^{20}$ +29.0 (c = 1.00, CH_2Cl_2). – IR (KBr): ν = 3447, 3295, 3260, 2979, 2933, 1763, 1734, 1716, 1686, 1638, 1594, 1475, 1368, 1312, 1236, 1223, 1154, 964, 899, 964, 773, 680 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major* (*Z*)*-isomer* **6′g**: δ = 1.48 and 1.54 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.61 (1H, ddd, J = 1.4, 3.5, 15.4 Hz, 3-Ha), 3.06 (1H, ddd, J = 1.4, 10.5, 15.4 Hz, 3-Hb), 4.51 (1H, dd, J = 3.5, 10.5 Hz, 2-H), 6.82 (1H, br dt, J = 1.8, 7.4 Hz, *o*-C_6H_4), 7.05 – 7.16 (4H, m, 3H of C_6H_4 and 4′-H), 9.94 (1H, d, J = 12.0 Hz, NH); *minor* (*E*)*-isomer* **6g**: δ = 6.24 (1H, br d, J = 13.3 Hz, NH), 7.70 (1H, br d, J = 13.3 Hz, 4′-H). – $C_{21}H_{27}BrN_2O_5$ (467.4): calcd. C 53.97, H 5.82, N 5.99; found C 54.01, H 5.95, N 6.01.

*Di-tert-butyl (2S,4E)-4-[(4-bromoanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6h**) and its minor (4Z)-isomer **6′h***

Compound **6′h** was prepared from **4** and 4-bromoaniline hydrochloride (**5h**). Yield: 369 mg (79 %) of a pale-grey solid. – M. p. 175 – 177 °C; **6h** : **6′h** = 85 : 15. – $[\alpha]_{589}^{20}$ −17.4 (c = 0.35, CH_2Cl_2). – IR (KBr): ν = 3264, 2980, 2934, 1759, 1725, 1687, 1638, 1588, 1485, 1454, 1368, 1312, 1231, 1152, 999, 960, 820, 775 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major*(*E*)*isomer* **6h**: δ = 1.47 and 1.52 (18H, 2s, 1 : 1, 2 × ^{t}-Bu), 2.55 (1H, ddd, J = 2.1, 3.5, 16.1 Hz, 3-Ha), 2.99 (1H, ddd, J = 2.1, 10.6, 16.1 Hz, 3-Hb), 4.53 (1H, dd, J = 3.5, 10.6 Hz, 2-H), 6.42 (1H, d, J = 13.4 Hz, NH), 6.87 (2H, d, J = 8.8 Hz, *o*-C_6H_4), 7.39 (2H, d, J = 8.8 Hz, *m*-C_6H_4), 7.68 (1H, dt, J = 2.1, 13.4 Hz, 4′-H); *minor* (*Z*)*isomer* **6′h**: δ = 1.53 (9H, s, ^{t}-Bu), 2.60 (1H, ddd, J = 1.4, 3.5, 15.4 Hz, 3-Ha), 3.05 (1H, ddd, J = 1.4, 10.5, 15.4 Hz, 3-Hb), 4.51 (1H, dd, J = 3.5, 10.5 Hz, 2-H), 6.80 (2H, br d, J = 8.8 Hz, *o*-C_6H_4), 7.09 (1H, br d, J = 12.2 Hz, 4′-H), 7.37 (2H, br d, J = 8.8 Hz, *m*-C_6H_4; 9.94 (1H, br d, J = 12.2 Hz, NH). – $C_{21}H_{27}BrN_2O_5$ (467.4): calcd. C 53.97, H 5.82, N 5.99; found C 54.18, H 5.96, N 6.00.

*Di-tert-butyl (2S,4E)-4-[(3-nitroanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6i**)*

Compound **6i** was prepared from **4** and 3-nitrolaniline (**5i**) in the presence of one equivalent of hydrochloric acid. Yield: 282 mg (65 %) of a yellow solid. – M. p. 149 – 152 °C; **6i** : **6i** = 100 : 0. – $[\alpha]_{589}^{20}$ −16.0 (*c* = 0.50, CH_2Cl_2). – IR (KBr): ν = 3458, 3285, 3090, 2981, 2935, 1761, 1719, 1688, 1648, 1616, 1588, 1535, 1749, 1369, 1352, 1317, 1238, 1224, 1155, 999, 966, 845, 814, 777, 737, 674 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.48 and 1.51 (18H, 2s, 1 : 1, $2 \times {}^t$-Bu), 2.67 (1H, ddd, *J* = 2.3, 2.9, 16.4 Hz, 3-Ha), 3.09 (1H, ddd, *J* = 2.3, 10.5, 16.4 Hz, 3-Hb), 4.56 (1H, dd, *J* = 3.3, 10.5 Hz, 2-H), 7.07 (2H, d, *J* = 9.2 Hz, *o*-C_6H_4), 7.39 (1H, br d, *J* = 13.0 Hz, NH), 7.71 (1H, br dt, *J* = 2.3, 13.0 Hz, 4′-H), 8.17 (2H, d, *J* = 9.2 Hz, *m*-C_6H_4). – $C_{21}H_{27}N_3O_7$ (433.5): calcd. C 58.19, H 6.28, N 9.69; found C 58.34, H 6.44, N 9.73.

*Di-tert-butyl (2S,4E)-4-[(4-nitroanilino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6j**)*

Compound **6j** was prepared from **4** and 4-nitrolaniline (**5j**) in the presence of one equivalent of hydrochloric acid. Yield: 351 mg (81 %) of a pale-grey solid. – M. p. 169 – 170 °C; **6j** : **6′j** = 100 : 0. – $[\alpha]_{589}^{20}$ −2.1 (*c* = 0.34, EtOH). – IR (KBr): ν = 3480, 3379, 3260, 3224, 3188, 2977, 1760, 1726, 1686, 1648, 1589, 1506, 1492, 1371, 1315, 1285, 1236, 1224, 1153, 1109, 999, 965, 876, 844, 775, 753, 693 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.48 and 1.52 (18H, 2s, 1 : 1, $2 \times {}^t$-Bu), 2.65 (1H, ddd, *J* = 2.2, 3.4, 16.5 Hz, 3-Ha), 3.08 (1H, ddd, *J* = 2.2, 10.5, 16.5 Hz, 3-Hb), 4.56 (1H, dd, *J* = 3.4, 10.5 Hz, 2-H), 7.08 (2H, dt, *J* = 2.6, 9.1 Hz, *o*-C_6H_4), 7.18 (1H, br d, *J* = 13.2 Hz, NH), 7.74 (1H, br dt, *J* = 2.2, 13.2 Hz, 4′-H), 8.18 (2H, dt, *J* = 2.6, 9.1 Hz, *m*-C_6H_4). – ^{1}H-NMR ([D_6]DMSO): δ = 1.54 and 1.55 (18H, 2s, 1 : 1, $2 \times {}^t$-Bu), 2.72 (1H, br dt, *J* = 2.4, 17.0 Hz, 3-Ha), 3.18 (1H, ddd, *J* = 2.4, 10.6, 17.0 Hz, 3-Hb), 4.68 (1H, dd, *J* = 3.3, 10.6 Hz, 2-H), 7.44 (2H, br d, *J* = 9.2 Hz, *o*-C_6H_4), 7.79 (1H, br s, 4′-H), 8.26 (2H, br d, *J* = 9.2 Hz, *m*-C_6H_4), 9.62 (1H, br s, NH). – $C_{21}H_{27}N_3O_7$ (433.5): calcd. C 58.19, H 6.28, N 9.69; found C 58.12, H 6.45, N 9.62.

*Di-tert-butyl (2S,4E)-4-[(2-ethoxy-2-oxoethylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6k**) and its minor (4Z)-isomer **6′k***

Compound **6′k** was prepared from **4** and ethyl glycinate hydrochloride (**5k**). Yield: 188 mg (47 %) of a colourless solid. – M. p. 128 – 132 °C; **6k** : **6′k** = 85 : 15. – $[\alpha]_{589}^{20}$ −20.2 (*c* = 1.00, CH_2Cl_2). – IR (KBr): ν = 3286, 2979, 2936, 1755, 1728, 1686, 1622, 1458, 1370, 1314, 1257, 1194, 1152, 1094, 1025, 989, 945, 861, 846, 778, 764, 739, 716 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major* (*E*)*isomer* **6k**: δ = 1.29 (3H, t, *J* = 7.1 Hz, CH_3CH$_2$), 1.47 and 1.51 (18H, 2s, 1 : 1, $2 \times {}^t$-Bu), 2.42 (1H, ddd, *J* = 2.0, 3.6, 15.4 Hz, 3-Ha), 2.87 (1H, ddd, *J* = 2.0, 10.6, 15.4 Hz, 3-Hb), 3.96 (2H, d, *J* = 5.5 Hz, NHCH_2), 4.23 (2H, q, *J* = 7.1 Hz, CH_2CH$_3$), 4.40 – 4.52 (1H, broad signal, NH), 4.49 (1H, dd, *J* = 3.6, 10.6 Hz, 2-H), 7.11 (1H, dt, *J* = 2.0, 13.2 Hz, 4′-H); *minor* (*Z*)*isomer* **6′k**: δ = 3.85 (1H, dd, *J* = 1.1, 6.3 Hz, NHCH_2), 4.20 (2H, q, *J* = 7.2 Hz, CH_2CH$_3$), 4.44 (1H, dd, *J* = 4.0, 10.7 Hz, 2-H), 6.46 (1H, br d, *J* = 12.6 Hz, 4′-H), 7.96 (1H, br dt, *J* = 6.3, 12.6 Hz, NH). – $C_{19}H_{30}N_2O_7$ (398.5): calcd. C 57.27, H 7.59, N 7.03; found C 57.54, H 7.78, N 7.33.

*Di-tert-butyl (2S,4E)-4-[(3-ethoxy-3-oxopropylamino)methylidene]-5-oxopyrrolidine-1,2-dicarboxylate (**6l**) and its minor (4Z)-isomer **6′l***

Compound **6l** was prepared from **4** and ethyl β-alaninate hydrochloride (**5l**). Yield: 279 mg (68 %) of a pale-yellow solid. – M. p. 85 – 87 °C; **6l** : **6′l** = 88 : 12. – $[\alpha]_{589}^{20}$ −20.2 (*c* = 0.50, CH_2Cl_2). – IR (KBr): ν = 3447, 3291, 3259, 2981, 2935, 1750, 1678, 1626, 1458, 1369, 1317, 1253, 1155, 1081, 1024, 1001, 952, 848, 773 cm^{-1}. – ^{1}H-NMR ($CDCl_3$), *major* (*E*)*isomer* **6l**: δ = 1.27 (3H, t, *J* = 7.1 Hz, CH_3CH$_2$), 1.47 and 1.51 (18H, 2s, 1 : 1, $2 \times {}^t$-Bu), 2.33 (1H, ddd, *J* = 1.9, 3.7, 15.3 Hz, 3-Ha), 2.56 (2H, t, *J* = 5.9 Hz, CH_2COOEt), 2.79 (1H, ddd, *J* = 1.9, 10.7, 15.3 Hz, 3-Hb), 3.46 (2H, deg q, *J* = 6.0 Hz, NHCH_2), 4.17 (2H, q, *J* = 7.1 Hz, CH_2CH$_3$), 4.46 (1H, dd, *J* = 3.8, 10.7 Hz, 2-H), 4.65 (1H, deg. quintet, *J* = 6.4 Hz, NH), 7.17 (1H, dt, *J* = 1.7, 13.6 Hz, 4′-H); *minor* (*Z*)*isomer* **6′l**: δ = 2.51 (2H, t, *J* = 6.4 Hz, CH_2COOEt), 4.15 (2H, q, *J* = 7.1 Hz, CH_2CH$_3$), 4.41 (1H, dd, *J* = 4.3, 10.9 Hz, 2-H), 6.56 (1H, br d, *J* = 12.6 Hz, 4′-H), 7.84 – 7.96 (1H, broad signal, NH). – $C_{20}H_{32}N_2O_7$ (412.5): calcd. C 58.24, H 7.82, N 6.79; found C 58.35, H 8.13, N 6.71.

*Parallel solution-phase synthesis of (2S,4E)-4-(anilinomethylidene)pyroglutamic acids **7a – c, e – j***

The MiniBlock™ was assembled with 12 fritted vessels and charged with compounds **6/6′a – l** (12 × 0.5 mmol) and 2M HCl-EtOAc (12 × 5 mL). The MiniBlock™ was closed and the reaction mixtures were stirred at 20 °C for 12 h. The precipitates were collected by filtration, washed with EtOAc (4 × 3 mL), and dried *in vacuo* at r. t. with P_4O_{10} for 24 h to give **7a – c**, **e – j**. Compounds **7d**, **k**, **l**, which did not precipitate from the reaction mixtures, were not isolated.

The following compounds were prepared in this manner:

*(2S,4E)-4-(Anilinomethylidene)pyroglutamic acid hydrochloride (**7a**)*

Compound **7a** was prepared from **6/6′a**. Yield: 49 mg (39 %) of a light-yellow solid. – M. p. 159 – 163 °C (partial decomposition above 125 °C). – $[\alpha]_{589}^{20}$ +116.3 (*c* = 0.52, MeOH). – IR (KBr): ν = 3269, 3236, 3086, 2543,2473, 1732, 1666, 1595, 1575, 1500, 1323, 1247, 1203, 1086, 924, 804, 754, 719, 687 cm^{-1}. – ^1H-NMR ($[D_6]$DMSO): δ = 2.77 (1H, ddd, J = 2.1, 3.7, 16.8 Hz, 3-Ha), 3.06 (1H, ddd, J = 2.1, 9.9, 16.7 Hz, 3-Hb), 4.19 (1H, dd, J = 3.8, 9.9 Hz, 2-H), 6.85 (1H, br t, J = 7.3 Hz, p-C_6H_5), 7.05 (2H, br d, J = 7.8 Hz, o-C_6H_5), 7.05 (2H, br dd, J = 7.3, 7.8 Hz, m-C_6H_5), 7.37 (1H, br d, J = 11.5 Hz, 4′-H), 8.59 (1H, d, J = 11.7 Hz, NH), 1-NH_2^+ and COOH exchanged. – $C_{12}H_{12}N_2O_3 \cdot HCl$ (268.7): calcd. C 53.64, H 4.88, N 10.43; found C 53.52, H 4.83, N 10.15.

*(2S,4E)-4-(3-Methylanilinomethylidene)pyroglutamic acid hydrochloride (**7b**)*

Compound **7b** was prepared from **6/6′b**. Yield: 136 mg (96 %) of a colourless solid. – M. p. 169 – 173 °C (partial decomposition above 140 °C). – $[\alpha]^{20}_{589}$ +104.8 (c = 0.65, MeOH). – IR (KBr): ν = 3269, 2920, 1738, 1665, 1616, 1508, 1309, 1264, 1219, 1171, 1108, 1091, 827, 785, 706 cm^{-1}. – ^1H-NMR ($[D_6]$DMSO): δ = 2.26 (3H, s, Me), 2.76 (1H, ddd, J = 2.1, 3.7, 16.7 Hz, 3-Ha), 3.05 (1H, ddd, J = 2.1, 9.9, 16.7 Hz, 3-Hb), 4.19 (1H, dd, J = 3.7, 9.9 Hz, 2-H), 6.68 (1H, br d, J = 7.4 Hz, o-C_6H_4), 6.84 (1H, br t, J = 8.1 Hz, p-C_6H_4), 6.88 (1H, br s, o-C_6H_4), 7.12 (1H, t, J = 7.7 Hz, m-C_6H_4), 7.37 (1H, br d, J = 8.2 Hz, 4′-H), 7.66 (2H, broad signal, 1-NH_2^+), 8.53 (1H, d, J = 12.0 Hz, NH), COOH exchanged. – $C_{13}H_{14}N_2O_3 \cdot 1^1/_8HCl$ (287.3): calcd. C 54.35, H 5.31, N 9.75; found C 54.15, H 5.39, N 9.51.

*(2S,4E)-4-(4-Methylanilinomethylidene)pyroglutamic acid hydrochloride (**7c**)*

Compound **7c** was prepared from **6/6′c**. Yield: 127 mg (90 %) of a light-yellow solid. – M. p. 162 – 167 °C (partial decomposition above 130 °C). – $[\alpha]^{20}_{589}$ +81.6 (c = 0.91, MeOH). – IR (KBr): ν = 3268, 3233, 3084, 3037, 2546, 1732, 1665, 1597, 1514, 1326, 1246, 1204, 1087, 984, 812, 718, 661 cm^{-1}. – ^1H-NMR ($[D_6]$DMSO): δ = 2.21 (3H, s, Me), 2.74 (1H, ddd, J = 2.1, 3.8, 16.7 Hz, 3-Ha), 3.04 (1H, ddd, J = 2.1, 9.9, 16.7 Hz, 3-Hb), 4.17 (1H, dd, J = 3.8, 9.9 Hz, 2-H), 6.94 (2H, d, J = 8.4 Hz, o-C_6H_4), 7.05 (2H, br d, J = 8.4 Hz, m-C_6H_4), 7.33 (1H, br d, J = 10.4 Hz, 4′-H), 8.47 (1H, d, J = 10.4 Hz, NH), 10.32 (1H, br s, COOH), 1-NH_2^+ exchanged. – $C_{13}H_{14}N_2O_3 \cdot 11/6HCl$ (288.8): calcd. C 54.06, H 5.29, N 9.70; found C 54.15, H 5.39, N 9.51.

*(2S,4E)-4-(4-Hydroxyanilinomethylidene)pyroglutamic acid hydrochloride (**7e**)*

Compound **7e** was prepared from **6e**. Yield: 53 mg (37 %) of a colourless solid. – M. p. 153 – 156 °C (partial decomposition above 130 °C). – $[\alpha]^{20}_{589}$ +93.0 (c = 0.54, MeOH). – IR (KBr): ν = 3263, 2926, 2566, 1740, 1665, 1616, 1605, 1508, 1321, 1310, 1265, 1234, 1209, 1171, 1091, 827, 785, 691 cm^{-1}. – ^1H-NMR ($[D_6]$DMSO): δ = 2.70 (1H, ddd, J = 2.0, 3.9, 16.5 Hz, 3-Ha), 3.05 (1H, ddd, J = 2.0, 10.0, 16.5 Hz, 3-Hb), 4.16 (1H, dd, J = 3.9, 10.0 Hz, 2-H), 6.66 (2H, br d, J = 8.8 Hz, o-C_6H_4), 6.86 (2H, br d, J = 8.8 Hz, m-C_6H_4), 7.29 (1H, br s, 4′-H), 8.34 (1H, br s, NH), 1-NH_2^+, OH, and COOH exchanged. – $C_{12}H_{12}N_2O_4 \cdot HCl$ (284.7): calcd. C 50.63, H 4.60, N 9.84; found C 50.24, H 4.67, N 9.54.

*(2S,4E)-4-(3-Methoxyanilinomethylidene)pyroglutamic acid hydrochloride (**7f**)*

Compound **7f** was prepared from **6/6′f**. Yield: 153 mg (99 %) of a yellowish solid. – M. p. 153 – 155 °C (partial decomposition above 130 °C). – $[\alpha]^{20}_{589}$ +106.6 (c = 0.65, MeOH). – IR (KBr): ν = 3225, 3068, 2619, 2471, 1731, 1669, 1603, 1513, 1495, 1485, 1322, 1244, 1208, 1197, 1159, 1088, 1050, 985, 804, 766, 720, 681 cm^{-1}. – ^1H-NMR ($[D_6]$DMSO): δ = 2.75 (1H, ddd, J = 2.2, 3.8, 16.7 Hz, 3-Ha), 3.05 (1H, ddd, J = 2.2, 9.9, 16.7 Hz, 3-Hb), 3.73 (3H, s, OMe), 4.18 (1H, dd, J = 3.8, 9.9 Hz, 2-H), 6.44 (1H, dd, J = 2.1, 8.1 Hz, o-C_6H_4), 6.59 (1H, t, J = 2.1 Hz, o-C_6H_4), 6.63 (1H, dd, J = 2.1, 8.1 Hz, p-C_6H_4), 7.14 (1H, t, J = 8.1 Hz, m-C_6H_4), 7.33 (1H, br d, J = 12.3 Hz, 4′-H), 7.72 (2H, br s, 1-NH_2^+), 8.53 (1H, d, J = 12.3 Hz, NH), COOH exchanged. – $C_{13}H_{14}N_2O_4 \cdot 1^1/_4HCl$ (307.8): calcd. C 50.72, H 4.99, N 9.10; found C 50.77, H 5.04, N 8.81.

*(2S,4E)-4-(3-Bromoanilinomethylidene)pyroglutamic acid (**7g**)*

Compound **7g** was prepared from **6g**. Yield: 152 mg (87 %) of a colourless solid. – M. p. 188 – 190 °C (partial decomposition above 140 °C). – $[\alpha]^{20}_{589}$ +85.6 (c = 1.03, MeOH). – IR (KBr): ν = 3267, 3233, 2707, 2635, 2471, 1731, 1666, 1592, 1479, 1326, 1246, 1206, 1088, 985, 923, 888, 766, 717, 674 cm^{-1}. – ^1H-NMR ($[D_6]$DMSO): δ = 2.73 (1H, ddd, J = 2.2, 3.7, 16.9 Hz, 3-Ha), 3.03 (1H, ddd, J = 2.2, 9.8, 16.9 Hz, 3-Hb), 4.15 (1H, dd, J = 3.7, 9.8 Hz, 2-H), 6.98 (1H, br d, J = 7.8 Hz, o-C_6H_4), 7.04 (1H, br d, J = 8.0 Hz, p-C_6H_4), 7.16 (1H, t, J = 8.0 Hz, m-C_6H_4), 7.22 (1H, br s, o-C_6H_4), 7.27 (1H, br d, J = 12.3 Hz, 4′-H), 7.75 (2H, br s, 1-NH_2^+), 8.65 (1H, d, J = 12.3 Hz, NH), COOH exchanged. – $C_{12}H_{11}BrN_2O_3 \cdot {}^9/_{10}HCl$ (343.9): calcd. C 41.90, H 3.49, N 8.14; found C 41.94, H 3.27, N 8.11.

*(2S,4E)-4-(4-Bromoanilinomethylidene)pyroglutamic acid (**7h**)*

Compound **7h** was prepared from **6h**. Yield: 149 mg (86 %) of a light-yellow solid. – M. p. 170 – 174 °C (partial decomposition above 114 °C). – $[\alpha]^{20}_{589}$ −23.6 (c = 0.45, MeOH). – IR (KBr): ν = 3269, 3231, 3073, 2538, 1730, 1665, 1587, 1489, 1325, 1244, 1204, 1086, 1075, 984, 819, 718, 652 cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.75 (1H, ddd, J = 2.2, 3.8, 16.9 Hz, 3-Ha), 3.04 (1H, ddd, J = 2.2, 9.9, 16.9 Hz, 3-Hb), 4.17 (1H, dd, J = 3.8, 9.9 Hz, 2-H), 7.02 (2H, d, J = 8.9 Hz, o-C_6H_4), 7.28 (1H, br d, J = 12.7 Hz, 4′-H), 7.38 (2H, br d, J = 8.9 Hz, m-C_6H_4), 8.65 (1H, d, J = 12.7 Hz, NH), 1-NH_2^+ and COOH exchanged. – $C_{12}H_{11}BrN_2O_3 \cdot HCl$ (347.6): calcd. C 41.46, H 3.48, N 8.06; found C 41.50, H 3.32, N 7.95.

(2S,4E)-4-(3-Nitroanilinomethylidene)pyroglutamic acid (7i)

Compound **7i** was prepared from **6i**. Yield: 141 mg (90 %) of a yellow solid. – M. p. 190 – 194 °C (partial decomposition above 150 °C). – $[\alpha]_{589}^{20}$ +52.3 (c = 0.78, MeOH). – IR (KBr): ν = 3233, 3072, 2615, 2524, 2445, 1728, 1669, 1621, 1602, 1532, 1483, 1447, 1347, 1328, 1244, 1206, 1087, 986, 930, 814, 796, 739, 720, 663 cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.79 (1H, ddd, J = 2.2, 3.7, 17.0 Hz, 3-Ha), 3.09 (1H, ddd, J = 2.2, 9.8, 17.0 Hz, 3-Hb), 4.20 (1H, dd, J = 3.7, 9.8 Hz, 2-H), 7.37 (1H, br d, J = 12.3 Hz, 4′-H), 7.44 – 7.55 (2H, m, 2H of C_6H_4), 7.62 – 7.69 (1H, m, 1H of C_6H_4), 7.84 – 7.87 (1H, m, 1H of C_6H_4), 9.04 (1H, d, J = 12.3 Hz, NH), 1-NH_2^+ and COOH exchanged. – $C_{12}H_{11}N_3O_5 \cdot HCl$ (313.7): calcd. C 45.95, H 3.86, N 13.40; found C 45.95, H 3.66, N 13.32.

(2S,4E)-4-(4-Nitroanilinomethylidene)pyroglutamic acid (7j)

Compound **7j** was prepared from **6j**. Yield: 137 mg (88 %) of a yellow solid. – M. p. 177 – 180 °C (partial decomposition above 140 °C). – $[\alpha]_{589}^{20}$ +90.6 (c = 0.63, MeOH). – IR (KBr): ν = 3296, 2920, 2533, 2440, 1725, 1669, 1593, 1556, 1500, 1317, 1242, 1218, 1111, 840, 750, 686 cm^{-1}. – ^{1}H-NMR ([D$_6$]DMSO): δ = 2.89 (1H, ddd, J = 2.4, 3.5, 17.3 Hz, 3-Ha), 3.17 (1H, ddd, J = 2.4, 9.7, 17.3 Hz, 3-Hb), 4.26 (1H, dd, J = 3.5, 9.7 Hz, 2-H), 7.29 (2H, br d, J = 9.2 Hz, o-C_6H_4), 7.43 (1H, br d, J = 12.2 Hz, 4′-H), 8.01 (2H, br s, 1-NH_2^+), 8.17 (2H, br d, J = 9.2 Hz, m-C_6H_4), 9.44 (1H, d, J = 12.2 Hz, NH), COOH exchanged. – $C_{12}H_{11}N_3O_5 \cdot HCl$ (313.7): calcd. C 45.95, H 3.86, N 13.40; found C 46.26, H 4.12, N 13.31.

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