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NOVEL 1,3-THIAZOLIDINES. SYNTHESIS OF 2-ARYL-4,4-BIS(HYDROXYMETHYL)-1,3-THIAZOLIDINES BY DIRECT THIOAMINALISATION

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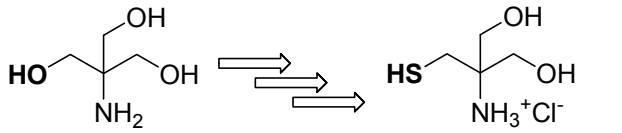
ABSTRACT. The direct cyclocondensation between 2-amino-2-(mercaptomethyl) propane-1,3-diol ("hydroxymethyl-cysteinol") with arylaldehydes was investigated as feasibility and efficiency. A new family of *C*-substituted 1,3-thiazolidines was obtained and fully characterised.

Keywords: *cysteinols, thioaminalisation, serinols, 1,3-thiazolidines*

INTRODUCTION

We have recently reported [1] our improved three steps synthesis of 2-amino-2-(mercaptomethyl)propane-1,3-diol hydrochloride **1**, an S-analogue of TRIS® (*Scheme 1*).



TRIS®
2-(hydroxymethyl)serinol

1
2-(hydroxymethyl)cysteinol hydrochloride

Scheme 1

[a] *Babeş-Bolyai" University, Department of Chemistry, Laboratory of Fine Organic Stereo- and Heterocyclic Chemistry (L.F.O.S.H.C.) 11 Arany János St., 400028 Cluj-Napoca, Romania.*
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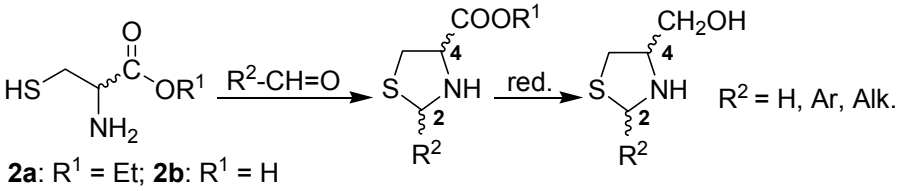
Our incipient result prompted other authors to be also interested in exploiting this protocol by using the free base of **1** as starting material in the preparation of new thiazolidinyloxazolidine fused systems [2].

In fact, the "traditional" way by which elaborated-1,3-thiazolidines can be accessed (*Scheme 2*) starts from (*S*)-or (*R*)-ethylcysteinate **2a** (R^1: Et) (optionally *R* or *S* cysteine **2b**, R^1: H) upon treatment with aldehydes, followed, optionally, by reduction of the carbonyl functionality [2-5].



2a: R^1 = Et; **2b**: R^1 = H

Scheme 2

It appears to us that, in the above context, the 1,3-thiazolidine motif was seen rather as an (non)isolable intermediate in the asymmetric synthesis of C-2 substituted analogous of cysteine [4a, 4b], in total synthesis of *Biotin* (vitamin H, coenzyme R) [6a], of antimicrobial *Micacocidin* [6b], of segments of *Farnesyl Transferase* [6c] and, more recently, in dynamic combinatorial libraries (DCLs) [2].

The same "disfavoured" Baldwin's 5-*endo-trig* cyclisation [7] (*Scheme 2*) was used when the much simpler 2-aminoethanethiol was reacted with various aldehydes [8a, 8b] in order to investigate the behaviour of the resulting 2-substituted-1,3-thiazolidines in ring-chain tautomerism conditions [8c, 8d].

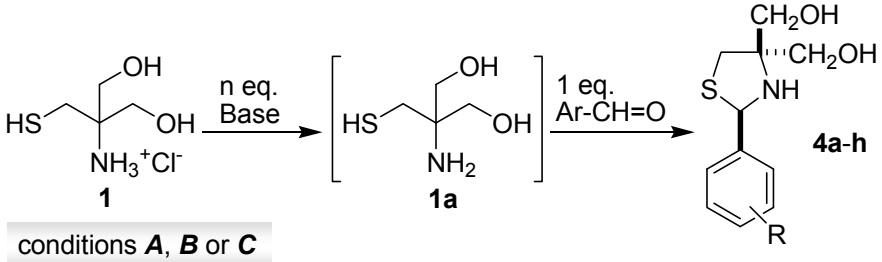
Hence, the aim of the present preliminary report is to account on the synthesis of a new family of condensates of the free base of **1** (*Scheme 1*), the title 2-aryl-4,4-bis(hydroxymethyl)-1,3-thiazolidines, as feasibility and efficiency.

To our knowledge, no similar approach is known up to now.

RESULTS AND DISCUSSION

Scheme 3 depicts our chemistry and the quantitative results. Thus, in the presence of an equimolar amount of an aryl aldehyde, the free base of **1**, the "hydroxymethyl-cysteinol" **1a**, was generated, by acid-base interchange.

Initially, we thought that, when reacted with **1a**, the electrophilicity of the aryl aldehyde could be modulated by an appropriate selection of its withdrawing *vs.* donating groups *C*-substitution. Accordingly, three types of reaction conditions, ***A***-***C***, were tested. They all were mandatory to manipulations under mild conditions and inert atmosphere. However, it was rapidly clear to us that our direct thioaminalisation protocol was, in fact, a more or less successful "trapping *in situ*" of the free base **1a** by the chosen carbonyl electrophiles.



conditions ***A***, ***B*** or ***C***

A: Benzene / Dean-Stark Trapp / 6-8 h / 0.5 eq. K_2CO_3 aq.
B: EtOH / reflux / 8-10 h / 1.0 eq. Et_3N
C: EtOH / r.t. / 48 h / 1.0 eq. Et_3N

No.	R	Method	Yield (%)	Isolation
4a	*p*-O_2N	**A**	15	c.c.*
4b	*p*-Cl	**C**	36	d.c.**
4c	*p*-Br	**C**	55	d.c.
4d	H	**A**	51	c.c.
		C	52	d.c.
4e	*m*-HO	**B**	40	c.c.
4f	*p*-HO	**B**	40	c.c.
4g	*o*-HO	**B**	50	c.c.
4h	*p*-Me_2N	**B**	44	c.c.

*Column chromatography (see EXPERIMENTAL SECTION for details)
**Direct crystallisations (see EXPERIMENTAL SECTION for details)

Scheme 3

Indeed, **1a** manifested remarkably high redox instability, most likely as 2 R-SH → R-S-S-R + 2H. To this end, we previously reported the isolation of a side dimeric -S-S- cyclisation product resulted upon treatment of the thioaminodiol **1a** (6% conversion) with formaldehyde [1a, 1b]. Soon after, Mahler *et al*. [2] noticed similar intrinsic problems. Actually, we were suspicious ever since that, in the presence of our substrate **1a**, formaldehyde acted not only as an electrophile but, to some extent, *i.e.* 6%, also as an oxidant.

The smallest yield obtained in the case of *p*-nitrobenzaldehyde (compound **4a**, method **A**) confirmed the above hypothesis. If milder conditions we applied, *e.g.* **C** (not depicted in *Scheme 1*), the result was quite the same. We deduced that *p*-nitrobenzaldehyde behaved, by its nitro functionality, rather like an oxidant of **1a** than like an electrophile. Therefore, the complete failure of a similar attempt in the case of *o*-nitrobenzaldehyde was not surprising at all.

All other investigated cases, **b**-**h**, showed our protocol being feasible with satisfactory to medium yields.

It was not possible, however, to infer any influence of the aryl aldehyde *C*-substitution on the reaction conditions ***A***-***C*** and yields.

The TLC monitoring (UV, 254 nm) of our thioaminalisations revealed their evolution being directed, almost exclusively, to the desired products. No nucleophilic competition SH *vs*. OH in the ring closure, previously noticed by Alekseyev and Zelenin [8b] in reaction of sugars with 2-aminoethanethiol was observed.

By contrast, only visualisation in I_2 bath allowed detection of other many side non-aromatic products, issued from the still non-avoidable oxidative degradation of **1a**. That is, in just two cases, compounds **4b** and **4c**, their isolation by direct crystallisation, as pure analytical sample, was fruitful. In all the other manipulations, only column chromatography, with double TLC control (*vide supra*), followed by crystallisation, yielded clean compounds. Once isolated as pure analytical samples, they all were stable indefinitely.

1,3-thiazolidines **4a**-**h** provided convincing analytical data. As a title example, the ^{1}H NMR spectrum of compound **4a** is depicted in **Figure 1**.

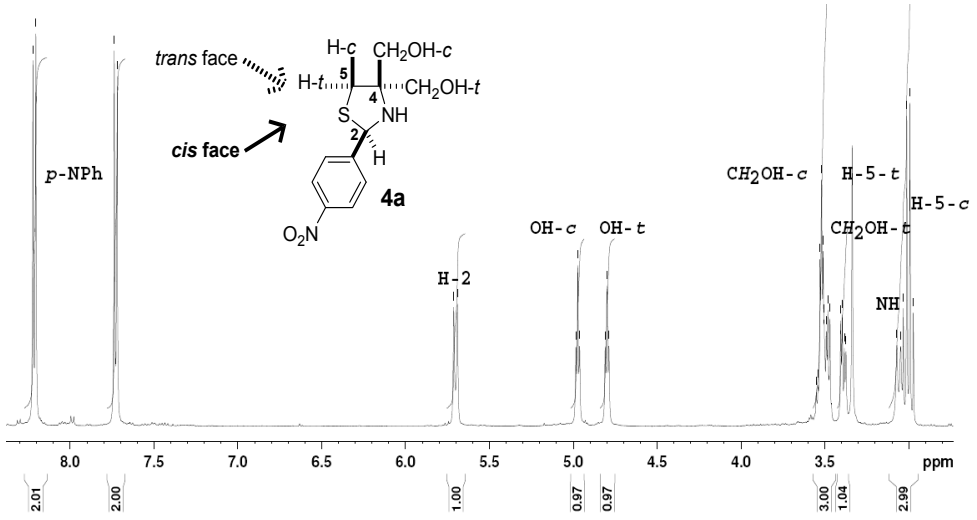


Figure 1. ^{1}H NMR spectrum of compound **4a** (500 MHz, DMSO-d_6, 298 K)

Figure 2 resumes the most relevant dipolar interactions in the 2D-^{1}H, ^{1}H-NOESY Chart of the same compound, illustrating the heterofacial [9] nature of the thiazolidine ring in series **4a**-**h**.

CONCLUSIONS

In summary, we reported the synthesis of a previously unknown series of C-trisubstituted-1,3-thiazolidines by direct thioaminalisation of 2-amino-2-(mercaptomethyl)propane-1,3-diol with various aryl aldehydes. The efficiency of the protocol is satisfactory up to middle, the feasibility being mandatory to manipulation in mild conditions. The dynamic behaviour of our compounds, as pseudorotation *vs*. stereoelectronic effects and the extension of their heterofacial skeleton will be reported in the near future.

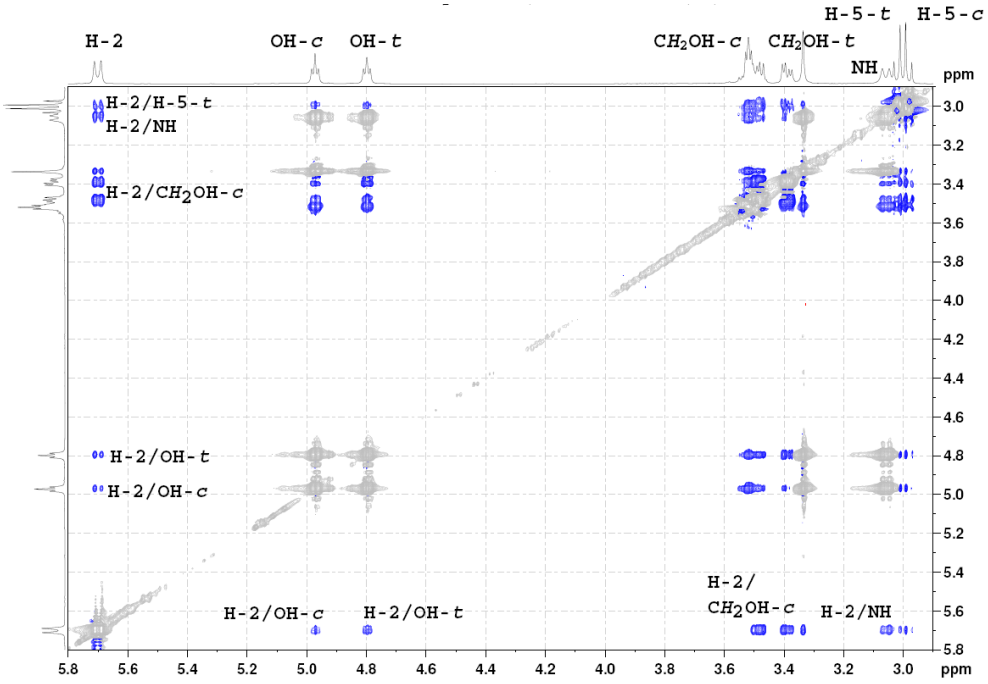


Figure 2. Relevant $^{1}H,^{1}H$ dipolar interactions in the 2D-$^{1}H,^{1}H$-NOESY Experiment of compound **4a** (500 MHz, DMSO-d_6 298 K)

EXPERIMENTAL SECTION

Melting points are uncorrected; they were carried out on ELECTROTHERMAL® instrument. Conventional NMR spectra were recorded on a Bruker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei, respectively. Related 2D-$^{1}H,^{1}H$-NOESY and DEPT Experiments were recorded on a Bruker® AM 500 instrument operating at 500 and 125 MHz for ^{1}H and ^{13}C nuclei or respectively. All chemical shifts (δ values) are given throughout in parts per million (ppm); all homocoupling patterns ($^{n}J_{H,H}$ values)

are given throughout in Hertz. TLC was performed by using aluminium sheets with silica gel 60 F254 (Merck®); column chromatography was conducted on Silica gel Si 60 (40–63 mm, Merck®). IR spectra were performed on a JASCO® FT-IR 6100 Spectrometer. Only relevant absorption maxima are listed, throughout, in cm^{-1}: s (strong), m (medium) and w (weak). Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra (MS) as ESI were recorded on a Bruker® Esquire Instrument with ions trapping in electrospray mode.

The synthesis and data of compound **1** (*Scheme 1*) we reported elsewhere [1].

In the NMR descriptions, some specific abbreviations were used: "bt" (broad triplet), "bd" (broad doublet), "bdd" (broad doublet of doublets). Stereochemical descriptors -*c* (*cis*) and -*t* (*trans*) are, throughout, referred to the fiducial substituent [9], the Ar group at position C-2 (see **Figure 2**).

Typical procedures for the preparation of 1,3-thiazolidines 4a-h

Method A

*Preparation of compound **4d***

Under dry nitrogen atmosphere, to a benzene (40 mL) solution containing benzaldehyde (0.613 g, 0.587 mL, 5.78 mmol), 2-amino-2-(mercaptomethyl) propane-1,3-diol hydrochloride **1** (1.000 g, 5.78 mmol) was added with vigorous stirring. In the resulted suspension, a solution obtained by dissolving anh. K_2CO_3 (0.400 g, 2.89 mmol) in water (1.500 mL) was injected. The reaction mixture was refluxed, under N_2, for about 8 h. (until no more water separated in a Dean-Stark trap). At room temperature, the suspension was filtered off and minerals were well washed with dry THF (50 mL). The organic filtrate was evaporated under reduced pressure to dryness and the solid residue was chromatographed on silica gel (eluent ligroin/acetone 1.5:1) to provide the desired compound **4d** as a single pure analytical sample fraction (0.665 g, 51% yield).

Method B

*Preparation of compound **4g***

Under dry nitrogen atmosphere, to an ethanol (25 mL) solution containing 2-hydroxybenzaldehyde (0.247 g, 0.210 mL, 2.022 mmol), 2-amino-2-(mercaptomethyl)propane-1,3-diol hydrochloride **1** (0.350 g, 2.022 mmol) was added with vigorous stirring. To the resulted suspension, triethylamine (0.204 g, 0.280 mL, 2.022 mmol) was injected. The reaction mixture was refluxed for 8 h. At room temperature, the suspension was evaporated under reduced pressure to dryness. The residue was taken with anh. THF on heating (40°C, 3×15 mL) and filtered off. The remaining triethylamine hydrochloride

was well washed with anh. THF, and then the combined THF solution was evaporated under reduced pressure to dryness. The residue was chromatographed on silica gel, the desired compound being isolated as the single fraction. This was additionally triturated with DCM/ligroin at -18°C to yield compound **4g** as pure analytical sample (0.244 g, 50% yield).

Method C

*Preparation of compound **4b***

Under dry nitrogen atmosphere, to an ethanol (15 mL) solution containing 4-chlorobenzaldehyde (0.284 g, 2.022 mmol), 2-amino-2-(mercaptomethyl) propane-1,3-diol hydrochloride **1** (0.350 g, 2.022 mmol) was added with vigorous stirring. To the resulted suspension, triethylamine (0.204 g, 0.280 mL, 2.022 mmol) was injected. The reaction mixture was stirred at room temperature for 24 h. and then evaporated under reduced pressure to dryness. The residue was taken with anh. THF on heating (40°C, 3×15 mL) and filtered off. The remaining triethylamine hydrochloride was well washed with anh. THF, and then the combined THF solution was evaporated under reduced pressure to dryness. The residue was first triturated with THF/Et_2O. The resulted product was supplementary crystallised from EtOH/DCM/Et_2O 0.5:5:3 at -18°C to yield the desire compound **4b** as pure analytical sample (0.188 g, 36% yield).

(rac)-4,4-Bis(hydroxymethyl)-2-(4-nitrophenyl)-1,3-thiazolidine (**4a**); yield 15% (column chromatography, eluent ligroin/acetone 1.5:1), yellow powder, mp 119-121°C; [Found: C, 49.09; H, 5.31; N, 9.98%. $C_{11}H_{14}N_2O_4S$ (270.07) requires: C, 48.88; H, 5.22; N, 10.36%]; R_f (60% ligroin/acetone) 0.48. $\nu_{max.}$ (KBr) 3392 (m), 3281 (m), 3214 (m), 2927 (m), 2861 (m), 1608 (m), 1525 (s), 1458 (m), 1353 (s), 1317 (m), 1108 (m), 1094 (m), 1056 (s), 1034 (s), 942 (m), 914 (m), 863 (s), 833 (s), 751 (m), 709 (m), 593 (m) cm^{-1}. ^1H NMR, 2D-^1H, ^1H-COSY and 2D-^1H,^1H-NOESY (500 MHz, DMSO-d_6, 298 K) δ_H 2.99 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*c*), 3.02 (1 H, d, $^2J_{H,H}$=10.5 Hz, H-5-*t*), 3.06 (1 H, d, $^3J_{H,H}$=11.5 Hz, NH), 3.39 (1 H, dd, $^2J_{H,H}$=11.0 Hz, $^3J_{H,H}$=5.0 Hz, CH_2OH-*t*), 3.48 (1 H, dd, $^2J_{H,H}$=11.0 Hz, $^3J_{H,H}$=6.5 Hz, CH_2OH-*t*), 3.51 (1 H, dd as t, $^2J_{H,H}$=8.0 Hz, $^3J_{H,H}$=5.0 Hz, CH_2OH-*c*), 3.54 (1 H, dd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=5.0 Hz, CH_2OH-*c*), 4.80 (1 H, dd as t, $^3J_{H,H}$=5.8 Hz, OH-*t*), 4.97 (1 H, dd as t, $^3J_{H,H}$=5.5 Hz, OH-*c*), 5.70 (1 H, d, $^3J_{H,H}$=11.0 Hz, H-2), 7.73 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, Ar), 8.21 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, Ar) ppm. ^{13}C NMR, J_{mod}, DEPT, HSQS and HMBC (125 MHz, DMSO-d_6, 298 K) δ_C 37.8 (C-5), 62.5 (CH_2OH-*t*), 63.3 (CH_2OH-*c*), 69.5 (C-2), 74.7 (C-4), 124.0 (C-3, -5, Ar), 128.7 (C-2, -6, Ar), 147.4 (C-1, Ar), 149.6 (C-4, Ar) ppm. MS (ESI^+, ACN) *m*/*z* (rel. int. %) 272 (M+2H) (19), 271 (M+H) (100), 252 (M-18) (41).

(rac)-2-(4-Chlorophenyl)-4,4-bis(hydroxymethyl)-1,3-thiazolidine (**4b**); yield 36% (triturating with THF/Et_2O then crystallisation from EtOH/DCM/Et_2O 0.5:5:3), white powder, mp 100-102°C; [Found: C, 51.11; H, 5.35; N, 5.61%. $C_{11}H_{14}ClNO_2S$ (259.04) requires: C, 50.86; H, 5.43; N, 5.39%]; R_f (CH_2Cl_2/Et_2O/EtOH 0.5:5:3) 0.53. $\nu_{max.}$ (KBr) 3354 (s), 3267 (s), 2927 (m), 2874 (m), 1592 (m), 1490 (m), 1412 (m), 1093 (m), 1027 (s), 1015 (m), 803 (m), 777 (m), 723 (w), 581 (w), 524 (w) cm^{-1}. ^1H NMR and 2D-^1H,^1H-COSY (300 MHz, DMSO-d_6, 298 K) δ_H 2.97 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*c*), 3.01 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*t*), 3.33 (1 H, d, $^2J_{H,H}$=10.8 Hz, CH_2OH-*t*), 3.45 (1 H, d, $^2J_{H,H}$=11.1 Hz, CH_2OH-*t*), 3.53 (1 H, d, $^2J_{H,H}$=12.6 Hz, CH_2OH-*c*), 3.57 (1 H, d, $^2J_{H,H}$=12.6 Hz, CH_2OH-*c*), 4.90 (2 H, bs, OH-*c, -t*), 5.54 (1 H, s, H-2), 7.42 (2 H, d, $^3J_{H,H}$=8.7 Hz, H-2, -6, Ar), 7.49 (2 H, d, $^3J_{H,H}$=8.4 Hz, H-3, -5, Ar) ppm. ^{13}C NMR and J_{mod} (75 MHz, DMSO-d_6, 298 K) δ_C 37.6 (C-5), 62.6 (CH_2OH-*t*), 63.1 (CH_2OH-*c*), 70.0 (C-2), 74.5 (C-4), 128.8 (C-3, -5, Ar), 129.5 (C-2, -6, Ar), 132.8 (C-4, Ar), 140.3 (C-1, Ar) ppm. MS (ESI^+, ACN) *m*/*z* (rel. int. %) 260 (M+H).

(rac)-2-(4-Bromophenyl)-4,4-bis(hydroxymethyl)-1,3-thiazolidine (**4c**); yield 55% (triturating with THF/Et_2O then crystallisation from EtOH/DCM/Et_2O 0.5:5:3), white powder, mp 102-104°C; [Found: C, 43.34; H, 4.46; N, 5.61%. $C_{11}H_{14}BrNO_2S$ (302.99) requires: C, 43.43; H, 4.64; N, 5.60%]; R_f (CH_2Cl_2/Et_2O/EtOH 0.5:5:3) 0.53. $\nu_{max.}$ (KBr) 3356 (s), 3321 (s), 3261 (s), 2929 (m), 2869 (m), 1587 (w), 1486 (s), 1458 (s), 1192 (m), 1055 (s), 1044 (s), 1028 (s), 1010 (s), 777 (s), 719 (w), 525 (w) cm^{-1}. ^1H NMR and 2D-^1H,^1H-COSY (300 MHz, DMSO-d_6, 298 K) δ_H 2.87 (1 H, d, $^3J_{H,H}$=11.4 Hz, NH), 2.96 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*c*), 3.01 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*t*), 3.33 (1 H, d, $^2J_{H,H}$=10.8 Hz, CH_2OH-*t*), 3.45 (1 H, d, $^2J_{H,H}$=11.1 Hz, CH_2OH-*t*), 3.53 (1 H, d, $^2J_{H,H}$=12.3 Hz, CH_2OH-*c*), 3.57 (1 H, d, $^2J_{H,H}$=11.7 Hz, CH_2OH-*c*), 4.99 (2 H, bs, OH-*c, -t*), 5.52 (1 H, d, $^3J_{H,H}$=10.5 Hz, H-2), 7.42 (2 H, d, $^3J_{H,H}$=8.4 Hz, H-2, -6, Ar), 7.55 (2 H, d, $^3J_{H,H}$=8.4 Hz, H-3, -5, Ar) ppm. ^{13}C NMR and J_{mod} (75 MHz, DMSO-d_6, 298 K) δ_C 37.6 (C-5), 62.6 (CH_2OH-*t*), 63.1 (CH_2OH-*c*), 70.1 (C-2), 74.5 (C-4), 121.3 (C-4, Ar), 129.8 (C-2, -6, Ar), 131.7 (C-3, -5, Ar), 140.7 (C-1, Ar) ppm. MS (ESI^+, ACN) *m*/*z* (rel. int. %) 306 [M+2] (86), 304 [M+1] (100), 302.13 (15), 273.2 (22), 226.13 (15), 184.13 (16).

(rac)-4,4-Bis(hydroxymethyl)-2-phenyl-1,3-thiazolidine (**4d**); yield 51%, (column chromatography, eluent ligroin/acetone 1.5:1), white powder, mp 119-121°C; [Found: C, 58.46; H, 7.05; N, 5.91%. $C_{11}H_{15}NO_2S$ (225.08) requires: C, 58.64; H, 6.71; N, 6.22%]; R_f (60% ligroin/acetone) 0.55. $\nu_{max.}$ (KBr) 3368 (s), 3325 (s), 3259 (s), 2959 (m), 2921 (s), 2872 (m), 2361 (m), 1602 (w), 1586 (w), 1492 (s), 1454 (s), 1437 (m), 1231 (m), 1192 (m), 1073 (s), 1044 (s), 1028 (s), 962 (w), 883 (m), 867 (s), 799 (s), 753 (s), 698 (s), 614 (m), 579 (w), 565 (w), 524 (w) cm^{-1}.

^{1}H NMR and 2D-^{1}H,^{1}H-COSY (300 MHz, DMSO-d_6, 298 K) δ_H 2.86 (1 H, d, $^3J_{H,H}$=12.0 Hz, NH), 2.99 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*c*), 3.04 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*t*), 3.34 (1 H, dd, $^2J_{H,H}$=11.0, $^3J_{H,H}$=5.0 Hz, CH_2OH-*t*), 3.47 (1 H, dd, $^2J_{H,H}$=11.1 Hz, $^3J_{H,H}$=6.6 Hz, CH_2OH-*t*), 3.57 (1 H, d, $^2J_{H,H}$=12.3 Hz, CH_2OH-*c*), 3.63 (1 H, d, $^2J_{H,H}$ 12.0 Hz, CH_2OH-*c*), 4.77 (1 H, dd as t, $^3J_{H,H}$=5.7 Hz, OH-*t*), 5.07 (1 H, dd as t, $^3J_{H,H}$=5.7 Hz, OH-*c*), 5.54 (1 H, d, $^3J_{H,H}$=12.0 Hz, H-2), 7.29 (1 H, m, H-4, Ph), 7.36 (2 H, dd as t, $^3J_{H,H}$=7.2 Hz, H-3, -5, Ph), 7.47 (2 H, d, $^3J_{H,H}$=6.9 Hz, H-2, -6, Ph) ppm. ^{1}H NMR, 2D-^{1}H,^{1}H-COSY and 2D-^{1}H,^{1}H-NOESY (500 MHz, DMSO-d_6, 298 K) δ_H 2.85 (1 H, bs, NH), 2.98 (1 H, d, $^2J_{H,H}$=10.0 Hz, H-5-*c*), 3.02 (1 H, d, $^2J_{H,H}$=10.0 Hz, H-5-*t*), 3.34 (1 H, d, $^2J_{H,H}$=11.0, CH_2OH-*t*), 3.45 (1 H, dd, $^2J_{H,H}$=11.0 Hz, $^3J_{H,H}$=4.0 Hz, CH_2OH-*t*), 3.57 (1 H, dd, $^2J_{H,H}$=13.0 Hz, $^3J_{H,H}$=4.0 Hz, CH_2OH-*c*), 3.58 (1 H, dd, $^2J_{H,H}$=13.2 Hz, $^3J_{H,H}$=3.5 Hz, CH_2OH-*c*), 4.72 (1 H, bs, OH-*t*), 5.02 (1 H, bs, OH-*c*), 5.53 (1 H, bs, H-2), 7.30 (1 H, dd as t, $^3J_{H,H}$=7.3 Hz, H-4, Ph), 7.36 (2 H, dd as t, $^3J_{H,H}$=7.3 Hz, H-3, -5, Ph), 7.47 (2 H, d, $^3J_{H,H}$=7.0 Hz, H-2, -6, Ph) ppm. ^{13}C NMR, J_{mod}, DEPT, HSQC and HMBC (125 MHz, DMSO-d_6, 298 K) δ_C 37.6 (C-5), 62.8 (CH_2OH-*t*), 63.2 (CH_2OH-*c*), 71.0 (C-2), 74.5 (C-4), 127.6 (C-2, -6, Ph), 128.4 (C-4, Ph), 128.8 (C-3, -5, Ph), 141.1 (C-1, Ph) ppm. MS (ESI$^+$, ACN) *m*/*z* (rel. int. %) 226 (M+H) (100), 227 (M+2) (14).

(rac)-4,4-Bis(hydroxymethyl)-2-(3-hydroxyphenyl)-1,3-thiazolidine (**4e**); yield 40% (column chromatography, eluent EtOH/CH_2Cl_2/Et_2O 1:5:3, then triturating from THF/ligroine), white powder, mp 133-135°C; [Found: C, 55.05; H, 5.98; N, 5.91%. $C_{11}H_{15}NO_3S$ (241.08) requires: C, 54.75; H, 6.27; N, 5.80%]; R_f (EtOH/CH_2Cl_2/Et_2O 1:5:3) 0.64. $\nu_{max.}$ (KBr) 3403 (s), 3276 (s), 2928 (m), 2734 (m), 2606 (m), 1599 (s), 1458 (s), 1083 (m), 1040 (s), 867 (m), 795 (w), 772 (w), 694 (w), 583 (w) cm^{-1}. ^{1}H NMR and 2D-^{1}H,^{1}H-COSY (300 MHz, DMSO-d_6, 298 K) δ_H 2.79 (1 H, d, $^3J_{H,H}$=12.0 Hz, NH), 2.98 (2 H, s, H-5), 3.33 (1 H, s, CH_2OH-t), 3.42 (1 H, s, CH_2OH-*t*), 3.59 (2 H, s, CH_2OH-*c*), 4.75 (1 H, bs, OH-*t*), 5.07 (1 H, bs, OH-*c*), 5.44 (1 H, d, $^3J_{H,H}$=12.0 Hz, H-2), 6.70 (1 H, d, $^3J_{H,H}$=7.2 Hz, H-4, Ar), 6.86 (1 H, s, H-2, Ar), 6.87 (1 H, d, $^3J_{H,H}$=11.4 Hz, H-6, Ar), 7.14 (1 H, dd as a t, $^3J_{H,H}$=7.1 Hz, H-5, Ar), 9.48 (1 H, s, Ar-O*H*) ppm. ^{13}C NMR and J_{mod} (75 MHz, DMSO-d_6, 298 K) δ_C 37.4 (C-5), 62.8 (CH_2OH-*t*), 63.1 (CH_2OH-*c*), 71.0 (C-2), 74.4 (C-4), 114.2 (C-2, Ar), 115.4 (C-4, Ar), 118.2 (C-6, Ar), 129.8 (C-5, Ar), 142.5 (C-1, Ar), 157.8 (C-2, Ar) ppm; MS (ESI$^+$, MeOH) *m*/*z* (rel. int. %) 242 (M+H) (100).

(rac)-4,4-Bis(hydroxymethyl)-2-(4-hydroxyphenyl)-1,3-thiazolidine (**4f**); yield 40% (column chromatography, eluent EtOH/CH_2Cl_2/Et_2O 1:5:3), beige powder, mp 142-144°C; [Found: C, 54.93; H, 6.16; N, 6.11%. $C_{11}H_{15}NO_3S$ (241.08) requires: C, 54.75; H, 6.27; N, 5.80%]; R_f (EtOH/CH_2Cl_2/Et_2O 1:5:3) 0.63. $\nu_{max.}$ (KBr) 3250 (s), 3033 (m), 2961 (m), 2929 (m), 2807 (m), 2703 (w), 1614 (m),

1594 (m), 1519 (s), 1454 (m), 1378 (w), 1277 (s), 1229 (s), 1171 (m), 1040 (s), 876 (m), 829 (m), 812 (m), 708 (w), 538 (w) cm^{-1}. ^1H NMR and 2D-^1H,^1H-COSY (300 MHz, DMSO-d_6, 298 K) δ_H 2.70 (1 H, d, $^3J_{H,H}$=12.3 Hz, NH), 2.94 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*c*), 2.99 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*t*), 3.29 (1 H, dd, $^2J_{H,H}$=10.8, $^3J_{H,H}$=4.8 Hz, CH_2OH-*t*), 3.42 (1 H, dd, $^2J_{H,H}$=10.5, $^3J_{H,H}$ = 6.6 Hz, CH_2OH-*t*), 3.55 (1 H, dd, $^2J_{H,H}$=12.3, $^3J_{H,H}$=5.1 Hz, CH_2OH-*c*), 3.59 (1H, dd, $^2J_{H,H}$=11.4 $^3J_{H,H}$=5.6 Hz, CH_2OH-*c*), 4.71 (1 H, dd as t, $^3J_{H,H}$=5.6 Hz, OH-*t*), 5.04 (1 H, dd as t, $^3J_{H,H}$=5.7 Hz, OH-*c*), 5.42 (1 H, d, $^3J_{H,H}$=12.0 Hz, H-2), 6.73 (2 H, d, $^3J_{H,H}$=8.4 Hz, H-3, -5, Ar), 7.26 (2H, d, $^3J_{H,H}$=8.4 Hz, H-2, -6, Ar), 9.48 (1 H, s, Ar-O*H*) ppm. ^{13}C NMR and J_{mod} (75 MHz, DMSO-d_6, 298 K) δ_C 37.5 (C-5), 62.8 (CH_2OH-*t*), 63.1 (CH_2OH-*c*), 71.0 (C-2), 74.3 (C-4), 115.5 (C-3, -5, Ar), 128.9 (C-2, -6, Ar), 131.0 (C-1, Ar), 157.6 (C-4, Ar) ppm. MS (ESI^+, MeOH) *m*/*z* (rel. int. %) 242.02 (M+H) (100).

(rac)-4,4-Bis(hydroxymethyl)-2-(2-hydroxyphenyl)-1,3-thiazolidine (**4g**); yield 50% (column chromatography, eluent EtOH/CH_2Cl_2/Et_2O 1:5:3, then triturating from DCM/ligroin), yellow powder, mp 86-88°C; [Found: C, 54.61; H, 6.56; N, 5.98%. $C_{11}H_{15}NO_3S$ (241.08) requires: C, 54.75; H, 6.27; N, 5.80%]; R_f (EtOH/CH_2Cl_2/Et_2O 1:5:3) 0.65. $\nu_{max.}$ (KBr) 3374 (s), 3330 (s), 3275 (s), 3220 (s), 2917 (s), 2851 (s), 1604 (m), 1457 (s), 1263 (s), 1229 (m), 1054 (s), 889 (m), 759 (s), 686 (w), 549 (w) cm^{-1}. ^1H NMR and 2D-^1H,^1H-COSY (300 MHz, DMSO-d_6, 298 K); δ_H 2.90 (1 H, d, $^2J_{H,H}$=9.9 Hz, H-5-*c*), 2.96 (1 H, d, $^2J_{H,H}$=10.2 Hz, H-5-*t*), 3.30 (1 H, d, $^3J_{H,H}$=12.3 Hz, NH), 3.34 (1 H, bd, $^2J_{H,H}$=10.2 Hz, CH_2OH-*t*), 3.45 (1 H, bd, $^2J_{H,H}$=10.5 Hz, CH_2OH-*t*), 3.59 (2 H, bs, CH_2OH-*c*), 4.75 (1 H, bs, OH-*t*), 5.04 (1 H, bs, OH-*c*), 5.70 (1 H, d, $^3J_{H,H}$=9.9 Hz, H-2), 6.78 (1 H, d, $^3J_{H,H}$=5.7 Hz, H-3, Ar), 6.79 (1 H, dd as t, $^3J_{H,H}$=3.5 Hz, H-5, Ar), 7.10 (1 H, ddd $^3J_{H,H}$=7.6, 7.6, 1.1 Hz, H-4, Ar), 7.30 (1 H, d, $^3J_{H,H}$=6.6 Hz, H-6, Ar), 9.98 (1 H, bs, Ar-O*H*) ppm. ^{13}C NMR, J_{mod} (75 MHz, DMSO-d_6, 298 K) δ_C 36.7 (C-5), 62.4 (CH_2OH-*t*), 63.2 (CH_2OH-*c*), 65.8 (C-2), 73.6 (C-4), 116.0 (C-3, Ar) 119.3 (C-1, Ar), 126.3 (C-1, Ar), 127.7 (C-4, Ar), 155.6 (C-2, Ar) ppm. MS (ESI^+, MeOH) *m*/*z* (rel. int. %) 242.13 (M+H) (100).

(rac)-4,4-Bis(hydroxymethyl)-2-(4-dimethylaminophenyl)-1,3-thiazolidine (**4h**); yield 44% (column chromatography, eluent EtOH/CH_2Cl_2/Et_2O 1:5:3, then triturating with THF/ligroin), orange powder, mp 145-147°C; [Found: C, 57.88; H, 7.77; N, 10.10%. $C_{13}H_{20}N_2O_2S$ (268.12) requires: C, 58.18; H, 7.51; N, 10.44%]; R_f (EtOH/CH_2Cl_2/Et_2O 1:5:3) 0.85. $\nu_{max.}$ (KBr) 3346 (s), 3261 (s), 3122 (m), 2933 (m), 2873 (m), 2817 (m), 1616 (s), 1530 (s), 1441 (s), 1362 (m), 1222 (s), 1195 (s), 1068 (s), 1032 (s), 892 (m), 818 (s), 539(w) cm^{-1}. ^1H NMR and 2D-^1H,^1H-COSY (300 MHz, DMSO-d_6, 298 K) δ_H 2.70 (1 H, bd, $^3J_{H,H}$=11.7 Hz, NH), 2.88 (6 H, s, NMe_2), 2.95 (1 H, bd, $^2J_{H,H}$=10.2 Hz, H-5-*c*), 3.00 (1 H, bd, $^2J_{H,H}$=9.9 Hz, H-5-*t*), 3.26 (1 H, bdd, $^2J_{H,H}$=10.2 Hz, $^3J_{H,H}$=2.1 Hz, CH_2OH-*t*),

3.43 (1 H, bdd, $^{2}J_{H,H}$=11.6, $^{3}J_{H,H}$= 5.6 Hz, CH_2OH-*t*), 3.56 (1 H, bd, $^{2}J_{H,H}$=13.2 Hz, CH_2OH-*c*), 3.61 (1 H, bd, $^{2}J_{H,H}$=13.2 Hz, CH_2OH-*c*), 4.71 (1 H, bt, OH-*t*), 5.05 (1 H, bt, $^{3}J_{H,H}$=4.7 Hz, OH-*c*), 5.42 (1 H, bd, $^{3}J_{H,H}$=10.5 Hz, H-2), 6.69 (2 H, d, $^{3}J_{H,H}$=8.7 Hz, H-3, -5, Ar), 7.27 (2 H, d, $^{3}J_{H,H}$=8.4 Hz, H-2, -6, Ar) ppm. ^{13}C NMR and J_{mod} (75 MHz, DMSO-d_6, 298 K) δ_C 37.4 (C-5), 40.6 (NMe_2), 62.9 (CH_2OH-*t*), 63.2 (CH_2OH-*c*), 71.2 (C-2), 74.4 (C-4), 112.5 (C-3, -5, Ar), 127.8 (C-1, Ar), 128.3 (C-2, -6, Ar), 150.7 (C-4, Ar) ppm. MS (ESI^+, MeOH) *m*/*z* (rel. int. %) 291.07 [M+Na] (7), 269.20 (M+H) (100).

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