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Synthesis of new thiazole analogues of pyochelin, a siderophore of *Pseudomonas aeruginosa* and *Burkholderia cepacia*. A new conversion of thiazolines into thiazoles

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Abstract—Three pyochelin analogues and their methyl esters all containing a thiazole ring have been synthesised from the same Weinreb amide key intermediate. One of these analogues called HPTT-COOH, a molecule released in the course of pyochelin and yersiniabactin biosynthesis, was efficiently synthesised using a new base induced conversion of the key compound 2′-(2-hydroxyphenyl)-2′-thiazoline-4′-(*N*-methoxy,*N*-methyl) carboxamide into 2′-(2-hydroxyphenyl)-2′-thiazole-4′-(*N*-methoxy,*N*-methyl) carboxamide.

1. Introduction

Under iron deficient conditions, microorganisms synthesise and excrete small molecules called siderophores which strongly chelate iron (III) and transport it into the cell.[1] In Gram-negative bacteria, the ferrisiderophore is recognised by a specific receptor in the outer membrane and the metal ion is then transported into the cytoplasm by a proton-motive force energised multiproteic system.[2] Our interest is focused on iron uptake systems in *Pseudomonas aeruginosa* and *Burkholderia cepacia*.[3] These bacteria are nosocomial opportunistic pathogens, causing severe and often lethal lung infections especially in cystic fibrosis patients. Both *P. aeruginosa* and *B. cepacia* excrete pyochelin **1**,[4] a hydroxyphenylthiazolinyl-thiazolidine type of siderophore which chelates iron (III) with a 2:1 stoichiometry.[5] We have recently reported the synthesis and biological properties of several synthetic pyochelin analogues and shown that both the 4′*R* and 4′*S* enantiomers of pyochelin chelate and transport iron(III) at very similar rates, suggesting that the configuration at carbon C-4′ has no effect on the biological properties of pyochelin.[6] These results prompted us to synthesise the thiazole pyochelin analogues **2**, **3** and **4** and to explore furthermore the influence of the C-4′, C-2″ and C-4″ assymetric centers on iron chelation and transport.

In compounds **2** and **3**, the thiazoline moiety was replaced by a thiazole ring where C-4′ and C-5′ are both sp^2, in contrast to pyochelin. In analogue **4** by replacement of the thiazolidine moiety with a thiazoline ring, C-4′ and C-2″ become sp^2 and C-4″ remains the only assymetric center (Fig. 1).

In this paper we describe the synthesis of two thiazole analogues of pyochelin **2** and **3** using the route developed in our laboratory for the synthesis of natural pyochelin **1** via

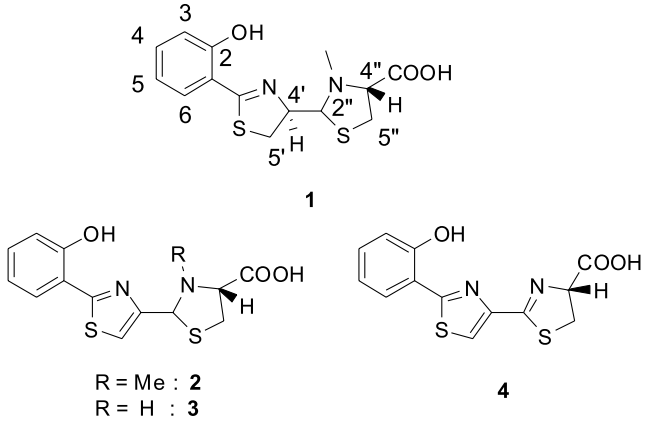

Figure 1.

Keywords: Pseudomonas; Siderophore; Pyochelin; Yersiniabactin; HPTT-COOH; Thiazole; Thiazoline; Weinreb amide.

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the thiazole hydroxamate **5** (Fig. 2).[7] We also report a new conversion procedure of thiazolines into thiazoles which we have applied to the synthesis of **4** a third thiazolic analogue of pyochelin.

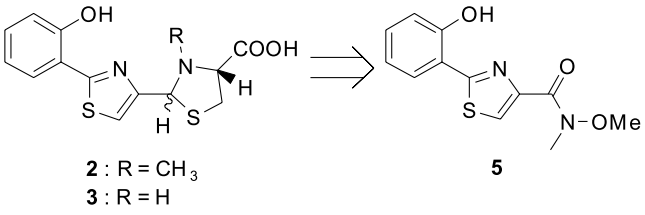
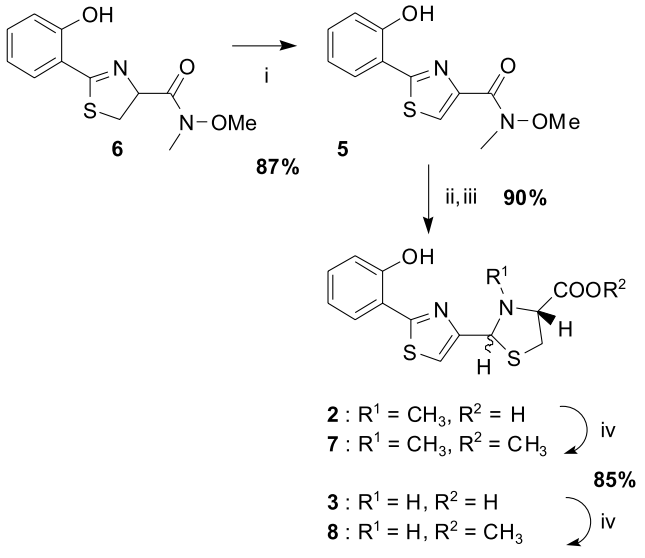


Figure 2.

2. Results and discussion

The thiazole intermediate **5**, was prepared from the known Weinreb amide **6**[7] which was used as starting material and reacted under several different conditions. First attempts performed using manganese dioxide under various conditions yielded the expected thiazole intermediate **5** but in poor to average yields. Better results were obtained when a mixture of $CBrCl_3$/DBU was used, giving compound **5** as a single product in 87% yield.[8] The Weinreb amide **5** was then reduced with lithium aluminum hydride,[9] into a very labile aldehyde. This latter was straightforwardly condensed with either (*R*)-cysteine or (*R*)-*N*-methylcysteine hydrochloride[10] in the presence of potassium acetate leading to the pyochelin analogues **3** and **2** respectively, both isolated in 90% yield over two steps. Compounds **2** and **3** were further converted into the corresponding methyl esters **7** and **8**, both isolated in 85% yield, using trimethylsilyldiazomethane (Scheme 1).



Scheme 1. (i) DBU, $CBrCl_3$, CH_2Cl_2, 20 °C. (ii) $LiAlH_4$, THF, −40 to −20 °C. (iii) (*R*)-cysteine or (*R*)-*N*-methylcysteine.HCl, AcOK, EtOH/H_2O, 20 °C. (iv) $TMSCHN_2$, MeOH/CH_2Cl_2, 20 °C.

Pyochelin is usually extracted from culture broth or synthesised as a mixture of diastereoisomers. Actually the very labile C-2″ position is readily epimerised in absence of metal.

Previous reports strongly suggest a template effect of both the metal ion and the configuration of the C-4″ asymmetric center, in the definition of the C-2″ stereocenter.[7c] In our hands, compounds **2**, **3**, **7** and **8** were isolated as mixtures of two diastereoisomers **a** (2″*R*, 4″*R*) and **b** (2″*S*, 4″*R*) in equimolar proportions. The relative configurations of the stereocenters were unambiguously assigned by NOESY experiments.[7,11] When proton H-2″ was saturated a marked Overhauser effect with H-4″ proton was observed for **a** (2″*R*, 4″*R*) isomer (i.e. *cis* isomer) whereas no NOE was observed for **b** (2″*S*, 4″*R*). In addition, using COSY and ^1H–^{13}C correlation it was then possible to assign the chemical shifts of both diastereoisomers for **2**, **3**, **7** and **8** (Fig. 3).

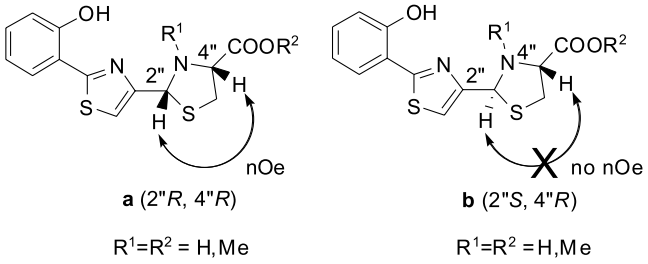
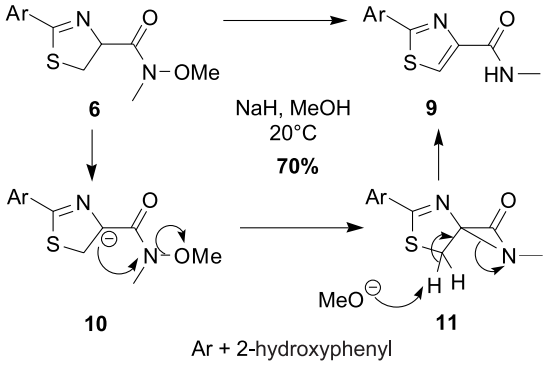


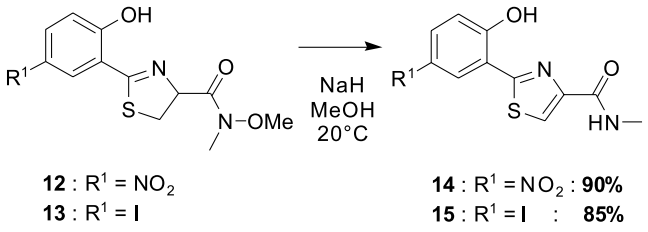
Figure 3.

In the course of the synthesis of hydroxamic ester **5** we have observed that if DBU was added a long time before $CBrCl_3$, the thiazole by-product **9** was isolated in significant amounts along with thiazole **5**. Moreover when $CBrCl_3$ was omitted, conversion of **6** into **9** proceeded sluggishly indicating that the basic nature of DBU promotes the conversion of **6** into **9**. Other base/solvent combinations were tested (TMSOK/THF, *t*BuOK/*t*BuOH, TBAF/THF, NaH/MeOH). The best yields were obtained when an excess of sodium hydride in dry methanol was used, where compound **6** was efficiently converted into compound **9** in 70% isolated yield. A plausible explanation of this result is illustrated in Scheme 2. First the base abstracts the acidic proton of the Schiff base **6** giving the intermediate **10**. Subsequent intramolecular attack of the carbanion on the methoxy amide and release of the methoxide anion affords the second intermediate **11**. Finally aromatisation and strain release favour the proton elimination and the cleavage of the aziridone moiety to yield compound **9** (Scheme 2).



Scheme 2.

In addition, when hydroxamic esters **12** and **13**, were treated in the same conditions, conversion into the corresponding 2-arylthiazole-4-methylcarboxamides **14** and **15** proceeded similarly, in very high yield. It is worthwhile pointing out that the best yield was obtained with the derivatives bearing the strongly electron withdrawing nitro group (Scheme 3).



12 : $R^1 = NO_2$
13 : R^1 = I

14 : $R^1 = NO_2$: **90%**
15 : R^1 = I : **85%**

Scheme 3.

To the best of our knowledge this conversion of the Weinreb amide is unprecedented and we wished to apply it to the synthesis of other pyochelin thiazole analogues. In the literature, such thiazole-4-methylcarboxamide structurally related compounds were described recently as powerful synthons in an approach to natural thiazolylthiazoline compounds.[12] In connection to this observation, thiazole **9** should be a good substrate for a straightforward synthesis of molecules such as analogue **4**. This compound, called HPTT-COOH, was previously isolated and described as an oxidised form of an hydrolytic intermediate in the nonribosomal biosynthesis of pyochelin **1** and yersiniabactin **16** (Fig. 4).[13,14]

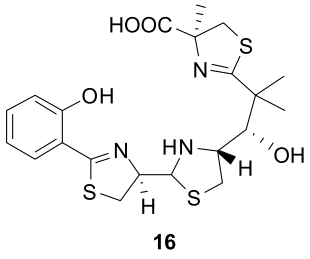


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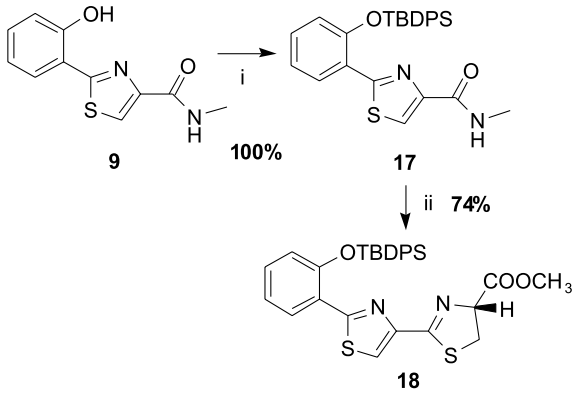
Figure 4.

Initially, the phenol function of compound **9** was protected with a silyl group. Both *t*-butyldimethylsilyl and *t*-butyldiphenylsilyl groups were introduced in parallel studies but the latter proved to be more suitable due to its higher stability during the synthetic sequence.[7] Thus, compound **9** was treated with *t*-butyldiphenylsilyl chloride in presence of triethylamine, leading quantitatively to the corresponding silyl ether **17**. Using the conditions reported by Charette and co-workers,[12] compound **17** was successively treated with triflic anhydride and with *O*-methylcysteine hydrochloride, in the presence of pyridine, leading to the expected tricyclic compound **18**, isolated in 74% yield (Scheme 4).



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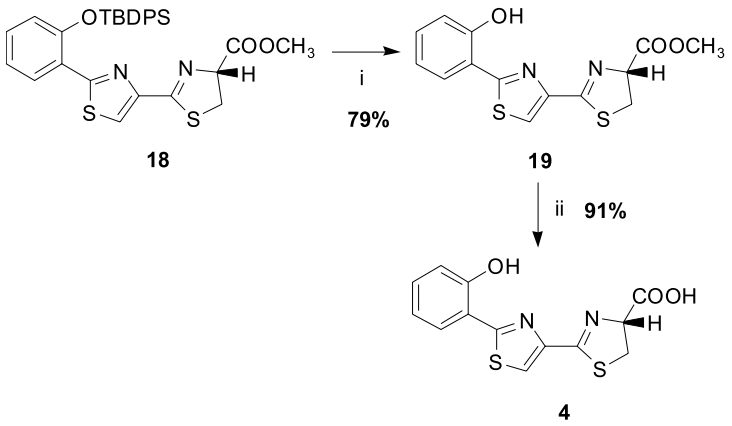
Scheme 4. (i) TBDPSCl, NEt_3, CH_2Cl_2, 20 °C. (ii) (a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −30 to 20 °C. (b) *O*-Methylcysteine.HCl, pyridine, −30 to 20 °C.

The silylated compound **18** appeared to be unstable and was therefore immediately deprotected with TBAF, leading to the methylester **19**, isolated in 79% yield. This ester was converted into the expected HPTT-COOH **4** after saponification with lithium hydroxide in wet tetrahydrofurane. This compound, which has been previously described in the literature,[13d] was actually prepared from a multienzymatic synthetic pathway and to the best of our knowledge the present report is the first which describes a straightforward efficient chemical synthetic access to HPTT-COOH (Scheme 5).



Scheme 5. (i) TBAF, THF, 20 °C. (ii) $LiOH \cdot H_2O$, THF/H_2O, 25 °C.

3. Conclusion

In conclusion we have synthesised in good overall yields, three pyochelin analogues **2**, **3** and **4** and their methyl esters **7**, **8** and **19**, bearing all a thiazole moiety. During the synthetic exploration, we have discovered a new base induced conversion of 2-aryl-4,5-dihydrothiazole-4-methoxymethylcarboxamide into the corresponding 2-arylthiazole-4-methylcarboxamide. This reaction was applied to the synthesis of HPTT-COOH **4**. The different pyochelin analogues described herein might be useful tools in order to investigate the pyochelin dependent iron uptake systems from siderophore biosynthesis to the ferripyochelin internalisation processes. Detailed analysis of pyochelin-dependent iron transport should help us to develop a new generation of antibiotics focused against emerging multi-resistant strains of *P. aeruginosa* and *B. cepacia*.

4. Experimental

4.1. General procedures

All reactions were carried out under argon. Solvents used were of analytical grade purity. Amines were distilled and stored on KOH before use. All reactions were monitored by thin-layer chromatography (TLC) using Merck precoated silica gel $60F^{254}$ (0.25 mm). Column chromatography purifications were performed using Merck kieselgel 60 (63–200 μm). Melting points were determined with a Stuart Scientific Bibby SMP3 apparatus. IR spectra were scanned neat using a Perkin–Elmer Spectrum one spectrophotometer. UV–visible spectra were measured on a Kontron Uvikon 930 spectrophotometer. NMR spectra were recorded either on a Bruker Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) or a Bruker Avance 400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C). Elemental analysis were performed at the Service d'Analyses de l'Institut de Chimie at Université Louis Pasteur of Strasbourg. Mass were performed on a Bruker Daltonic MicroTOF mass spectrometer.

4.1.1. 2′-(2-Hydroxyphenyl)-2′-thiazole-4′-(*N*-methoxy-*N*-methyl) carboxamide (5). To a solution of **6**[7] (521 mg, 1.96 mmol) and DBU (589 μL, 599 mg, 3.93 mmol, 2.00 equiv) in CH_2Cl_2 (20 mL), cooled to 0 °C was added dropwise $CBrCl_3$ (338 μL, 680 mg, 3.43 mmol, 1.75 equiv). After 20 h of gentle stirring at 20 °C, the mixture was adsorbed onto silica gel and filtered through a silica gel column (30 g SiO_2, hexane/acetone: 85/15). The expected thiazole **5** (452 mg, yield: 87%) was isolated as a white powder. Mp 111–114 °C, R_f 0.43 (hexane/acetone: 2/1), IR (neat) 3167, 2925, 2160, 1634, 1583, 1478, 1399, 1378, 1275, 1219, 1183, 1153, 1132, 1070, 1037, 1006, 976, 934, 889, 837, 818, 798, 751, 743, 706, 663 cm^{-1}. UV (MeOH) 214 (25240), 277 (10070), 323 (8320), ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3H), 3.82 (s, 3H), 6.92–6.97 (m,1H), 7.08 (dd, J=8.2, 0.9 Hz, 1H), 7.36 (ddd, J=8.8, 7.3, 1.6 Hz, 1H), 7.65 (dd, J=7.9, 1.6 Hz, 1H), 8.03 (s, 1H), 11.96 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.89, 61.86, 116.50, 117.89, 119.58, 123.78, 127.34, 132.34, 147.44, 161.56, 163.75, 168.57. MS (ES+) *m/z* 265 ($M+H^+$, 100), 287 ($M+Na^+$, 49), 551 ($2M+Na^+$, 12), 582 (20). Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60. Found: C, 54.73; H, 4.64; N, 10.53.

4.1.2. ′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″,4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid (2) and 2′-(2-hydroxyphenyl)-4′-(2″,3″,4″,5″-tetrahydro)-[2″,4′]-bisthiazolyl-4″-carboxylic acid (3). To a solution of Weinreb amide **5** (150 mg, 0.57 mmol) in dry THF (8 mL), cooled down −60 °C, $LiAlH_4$ (0.74 mL of a 1 M solution in THF, 0.73 mmol, 1.30 equiv) was added dropwise by syringe. The reaction temperature was allowed to raise to −20 °C over 30 mn and then hydrolysed by successive additions of saturated aqueous solution of NH_4Cl (12 mL) and 1 M aqueous solution of $KHSO_4$ (5 mL). The mixture was allowed to warm to room temperature and vigorous stirring was applied until two phases were formed. After extraction with Et_2O (2×30 mL), the organic layers were combined, dried over Na_2SO_4 and filtered before being evaporated. The crude aldehyde, isolated as a yellow powder, was very sensitive to oxidation and was used directly for subsequent reactions. It was dissolved into a mixture of ethanol (20 mL) and water (6 mL) and to this solution were successively added, potassium acetate (650 mg, 3.79 mmol, 6.65 equiv) and either (*R*)-*N*-methyl-cysteine hydrochloride (207 mg, 1.21 mmol, 2.12 equiv) for the synthesis of **2** or (*R*)-cysteine (255 mg, 2.11 mmol, 3.70 equiv) for **3**. The mixture was then gently stirred in the dark during one hour before being successively washed with hexane (30 mL) and diluted with water (30 mL). This aqueous layer was then acidified to pH 2.0 by addition of solid citric acid before being extracted with CH_2Cl_2 (2× 35 mL). The organic layers were collected, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The expected pyochelin analogues **2** (165 mg, yield: 90%) and **3** (160 mg, yield: 90%) were respectively isolated as yellow powders.

4.1.3. 2′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″,4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid (2). Mp 100–103 °C. IR (neat) 3432, 2956, 2526, 1977, 1716, 1619, 1579, 1456, 1380, 1307, 1248, 1207, 1156, 1017, 948, 856, 821, 751. SM (ES−) *m/z* 321 ($M-H^+$, 100), 643 ($2M-H^+$, 8).

4.1.4. (2″*R*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″, 4″, 5″-tetrahydro)-[2″,4′]bisthiazolyl-4″carboxylic carboxylic acid (2a). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 2.63 (s, 3H), 3.34 (ABX, J_{AX}=6.6 Hz, J_{BX}=7.7 Hz, J_{AB}= 11.0 Hz, 2H), 3.80 (dd, J=7.7, 6.6 Hz, 1H), 5.35 (s, 1H), 6.94 (t, J=7.6 Hz, 1H), 6.99 (d, J=8.8 Hz, 1H), 7.33–7.39 (m, 1H), 7.69 (s, 1H), 7.72–7.77 (m, 1H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 34.33, 41.50, 72.07, 73.00, 115.92, 117.72, 118.19, 120.45, 128.09, 132.74, 156.51, 157.28, 169.69, 172.00.

4.1.5. (2″*S*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″, 4″,5″-tetrahydro-[2″,4′]bisthiazolyl-4″-carboxylic acid (2b). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 2.52 (s, 3H), 3.24 (dd, J=10.4, 4.0 Hz, 1H), 3.46 (dd, J=10.4, 6.8 Hz, 1H), 4.30 (dd, J=6.8, 4.2 Hz, 1H), 5.62 (s, 1H), 6.94 (t, J= 7.6 Hz, 1H), 6.99 (d, J=8.8 Hz, 1H), 7.33–7.39 (m, 1H), 7.60 (s, 1H), 7.72–7.77 (m, 1H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 33.13, 36.71, 69.38, 69.96, 116.08, 117.83,

118.24, 120.42, 128.04, 132.74, 156.31, 157.41, 169.74, 171.52.

4.1.6. 2′-(2-Hydroxyphenyl)-4′-(2″,3″,4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid (3). Mp 165–168 °C. IR (neat) 3119, 3062, 3021, 2161, 1641, 1615, 1573, 1479, 1429, 1361, 1336, 1311, 1292, 1270, 1248, 1200, 1167, 1145, 1127, 1068, 1036, 1023, 1010, 950, 933, 906, 866, 843, 831, 819, 772, 729, 682. SM (ES−) *m/z* 307 ($M-H^+$, 100), 615 ($2M-H^+$, 51).

4.1.7. (2″*R*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(2″,3″,4″,5″-tetra hydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid (3a). ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 3.01 (dd, $J=10.0$, 9.0 Hz, 1H), 3.39 (dd, $J=10.0$, 7.0 Hz, 1H), 3.93 (dd, $J=9.0$, 7.0 Hz, 1H), 5.73 (s, 1H), 6.92–7.02 (m, 2H), 7.28–7.33 (m, 1H), 7.72 (s, 1H), 8.06 (dd, $J=7.9$, 1.6 Hz, 1H), 11.14 (bs, 1H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 38.33, 65.33, 66.99, 116.45, 116.56, 118.82, 119.45, 127.34, 131.08, 155.42, 163.66, 172.64, 174.52.

4.1.8. (2″*S*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(2″,3″,4″,5″-tetra hydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid (3b). ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 3.06 (dd, $J=10.2$, 5.8 Hz, 1H), 3.31 (dd, $J=10.1$, 6.8 Hz, 1H), 4.31 (dd, $J=6.4$, 5.9 Hz, 1H), 5.89 (s, 1H), 6.92–7.02 (m, 2H), 7.28–7.33 (m, 1H), 7.56 (s, 1H), 8.01 (dd, $J=7.9$, 1.2 Hz, 1H), 11.22 (bs, 1H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 38.00, 64.94, 66.90, 114.75, 116.56, 118.60, 119.43, 127.39, 131.08, 154.92, 164.13, 171.19, 172.21.

4.1.9. 2′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″,4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid methyl ester (7) and 2′-(2-hydroxyphenyl)-4′-(2″,3″,4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid methylester (8). To a solution of **2** (77 mg, 0.24 mmol) or **3** (70 mg, 0.23 mmol) in a mixture of CH_2Cl_2 (8 mL) and MeOH (3 mL), trimethylsilyldiazomethane (480 μL of an approx. 2 M solution in hexane, 0.91 mmol, 4.00 equiv) was added dropwise in four successive injections (every 20 mn). After 16 h stirring at 20 °C, the mixture was evaporated and chromatographed on a silica gel column (5 g SiO_2, hexane/Et_2O: 1/1) leading respectively to methyl esters **7** (71 mg, yield: 85%) or **8** (63 mg, yield: 84%) isolated respectively as an orange oil and an yellow solid. Before NMR measurements, these compounds were purified again on preparative thin layer chromatography (eluent: Et_2O).

4.1.10. 2′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″, 4″,5″-tetra hydro)-[2″,4′]bisthiazolyl-4″carboxylic acid methyl ester (7). IR (neat) 3108, 3043, 2992, 2950, 2850, 2790, 1737, 1619, 1580, 1475, 1456, 1436, 1400, 1346, 1269, 1250, 1216, 1201, 1155, 1057, 1018, 947, 909, 857, 821, 739. (ES+) *m/z* 337 ($M+H^+$, 100).

4.1.11. (2″*R*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″, 4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″carboxylic acid methyl ester (7a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 3.20 (dd, $J=11.0$, 6.2 Hz, 1H), 3.33 (dd, $J=10.8$, 9.2 Hz, 1H), 3.69 (dd, $J=9.2$, 6.1 Hz, 1H), 3.76 (s, 3H), 5.20 (s, 1H), 6.90 (m, 1H), 7.05 (m, 1H), 7.32 (m, 1H), 7.48 (s, 1H), 7.60 (d, $J=10.5$ Hz, 1H), 12.00 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.76, 41.49, 52.46, 71.11, 72.43, 114.26, 116.90, 117.77, 119.36, 127.01, 131.80, 155.27, 156.78, 169.46, 171.16.

4.1.12. (2″*S*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(3″-methyl-2″,3″, 4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid methyl ester (7b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.20 (dd, $J=10.8$, 4.6 Hz, 1H), 3.46 (dd, $J=10.5$, 6.7 Hz, 1H), 3.80 (s, 3H), 4.20 (dd, $J=6.6$, 4.1 Hz, 1H), 5.54 (s, 1H), 6.90 (m, 1H), 7.05 (m, 1H), 7.27 (s, 1H), 7.32 (m, 1H), 7.61 (d, $J=10.5$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.71, 36.61, 52.13, 68.36, 69.26, 113.95, 117.74, 119.37, 127.01, 131.80, 156.13, 156.70, 169.57, 171.69.

4.1.13. 2′-(2-Hydroxyphenyl)-4′-(2″,3″,4″,5″-tetrahydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid methylester (8). Mp 80–83 °C. IR (neat) 3482, 3272, 3101, 3000, 2949, 1732, 1619, 1582, 1475, 1431, 1402, 1377, 1332, 1304, 1265, 1203, 1175, 1157, 1137, 1037, 1005, 974, 948, 925, 880, 845, 821, 790, 743, 721, 700. (ES+) *m/z* 323 ($M+H^+$, 100).

4.1.14. (2″*R*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(2″,3″,4″,5″-tetra hydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid methyl ester (8a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11–3.19 (m, 1H), 3.40–3.52 (m, 1H), 3.84 (s, 3H), 4.04 (m, 1H), 5.71 (s, 1H), 6.88–6.95 (m, 1H), 7.04–7.08 (m, 1H), 7.29–7.37 (m, 1H), 7.31 (d, $J=0.5$ Hz, 1H), 7.59–7.64 (m, 1H), 11.76 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.83, 52.73, 65.80, 66.94, 114.11, 116.72, 117.91, 119.54, 127.24, 132.19, 152.67, 155.90, 170.10, 171.23.

4.1.15. (2″*S*,4″*R*)-2′-(2-Hydroxyphenyl)-4′-(2″,3″,4″,5″-tetra hydro)-[2″,4′]bisthiazolyl-4″-carboxylic acid methyl ester (8b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11–3.19 (m, 1H), 3.40–3.52 (m, 1H), 3.83 (s, 3H), 4.27 (t, $J=6.6$ Hz, 1H), 5.94 (s, 1H), 6.88–6.95 (m, 1H), 7.04–7.08 (m, 1H), 7.22 (d, $J=0.9$ Hz, 1H), 7.29–7.37 (m, 1H), 7.59–7.64 (m, 1H), 11.95 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.42, 52.73, 64.64, 66.30, 112.62, 116.86, 117.80, 119.45, 127.13, 132.02, 152.67, 156. 75, 170.10, 171.83.

4.1.16. 2′-(2-Hydroxyphenyl)-thiazole-4′-*N*-methyl carboxamide (9). To a solution of **6** (469 mg, 1.76 mmol) in MeOH (50 mL) stirred at 23 °C was added portionwise NaH (220 mg of a 60% w/w dispersion in mineral oil, 132 mg, 5.52 mmol, 3.13 equiv). After 20 mn of gentle stirring, the mixture was carefully hydrolysed with saturated aqueous NH_4Cl (5 mL), diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was dried over Na_2SO_4, filtered and adsorbed onto silica gel before being filtered through a silica gel column (30 g SiO_2, cyclohexane/Et_2O: 1/1). The resulting pale yellow solid was then crystallised from hot cyclohexane/ethanol leading to the expected methylamide **9** (286 mg, yield: 70%) isolated as a white solid. Mp 172–174 °C, R_f 0.51 (CH_2Cl_2/MeOH: 95/5), IR (neat) 3397, 3113, 3050, 2949, 2735, 2577, 1650, 1602, 1486, 1457, 1412, 1378, 1322, 1306, 1278, 1261, 1247, 1209, 1157, 1107, 1036, 984, 948, 921, 847, 834, 802, 777, 749, 720, 693 cm^{-1}. UV (MeOH) 214 (28455), 223 (20855), 277 (10870), 323 (10678), ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (d, $J=5.0$ Hz, 3H), 6.86 (bs, 1H), 6.96 (ddd, $J=7.9$, 7.1, 1.1 Hz, 1H), 7.08 (dd, $J=8.3$, 0.8 Hz, 1H), 7.38 (ddd, $J=8.6$, 7.36, 1.5 Hz, 1H), 7.65 (dd, $J=7.9$, 1.7 Hz,

1H), 8.10 (s, 1H), 11.16 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.32, 116.39, 117.79, 120.05, 121.79, 127.60, 132.57, 148.00, 156.17, 162.00, 169.52. SM (ES+) *m/z* 235 ($M+H^+$, 26), 257 ($M+Na^+$, 100), 491 ($2M+Na^+$, 20), 522 (29). Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.51; H, 4.63; N, 11.73.

4.1.17. 2′-[2-(*t*-Butyldiphenylsilyloxy)-phenyl]-thiazole-4′-*N*-methylcarboxamide (17). To a solution of methylamide **9** (161 mg, 0.69 mmol) dissolved in a 3:1 mixture of CH_2Cl_2 and NEt_3 (4 mL) at 20 °C was added TBDPSCl (500 μL, 537 mg, 1.95 mmol, 2.84 equiv). After 16 h of gentle stirring, the mixture was evaporated under reduced pressure. The crude product was filtered through a silica gel column (20 g SiO_2, cyclohexane/EtOAc: 90/10 then cyclohexane/EtOAc: 80/20) leading to the expected protected phenol **17** (330 mg, yield: 100%) isolated as a white foam. Mp 130–133 °C, R_f 0.70 (Et_2O), IR (neat) 3643, 3340, 3076, 2950, 2932, 2856, 2161, 1978, 1655, 1636, 1579, 1539, 1496, 1449, 1427, 1404, 1392, 1361, 1290, 1239, 1222, 1189, 1163, 1112, 1052, 1031, 1017, 988, 944, 923, 890, 859, 826, 807, 775, 758, 746, 736, 706, 693, 681 cm^{-1}. UV (MeOH) 213 (50223), 289 (13000), 308 (12130), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 3.06 (d, J=5.1 Hz, 3H), 6.55 (dd, J=7.9, 1.6 Hz, 1H), 6.89–6.99 (m, 2H), 7.36–7.46 (m, 6H), 7.53 (bs, 1H), 7.74–7.77 (m, 4H), 8.19–8.22 (m, 1H), 8.21 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.38, 26.03, 26.48, 120.52, 121.28, 123.15, 123.38, 128.01, 129.25, 130.16, 130.48, 131.87, 135.30, 149.22, 153.08, 162.15, 162.95. SM (ES+) *m/z* 473 ($M+H^+$, 50), 495 ($M+Na^+$, 91), 967 ($2M+Na^+$, 100). Anal. Calcd for $C_{27}H_{28}N_2O_2SSi$: C, 68.61; H, 5.97; N, 5.93. Found: C, 68.28; H, 6.22; N, 5.42.

4.1.18. 2′-[2-(*t*-Butyldiphenylsilyloxy)-phenyl]-4″,5″-dihydro-[2″,4′]bisthiazolyl-4″-carboxylic acid methyl ester (18). To a solution of **17** (330 mg, 0.71 mmol) in CH_2Cl_2 (5 mL) cooled to −30 °C, was added pyridine (218 μL, 215 mg, 2.71 mmol, 3.87 equiv). After 5 mn, Tf_2O (183 μL, 305 mg, 1.08 mmol, 1.55 equiv) was added dropwise by syringe. The mixture was allowed to warm to 21 °C and stirred gently for 2 h. The resulting orange solution was cooled down again to −30 °C before pyridine (218 μL, 215 mg, 2.71 mmol, 3.87 equiv) and *O*-methylcysteine hydrochloride (186 mg, 1.08 mmol, 1.55 equiv) were successively introduced. After 15 mn stirring at −30 °C, the mixture was warmed up to room temperature and stirred overnight. The mixture was then adsorbed onto silica gel before being purified by chromatography on a silica gel column (20 g SiO_2, cyclohexane/EtOAc: 8/2) leading to compound **18** (289 mg, yield: 74%) isolated as an unstable deliquescent colorless solid. R_f 0.86 (Et_2O), IR (neat) 3073, 2930, 2858, 1742, 1674, 1598, 1577, 1535, 1493, 1472, 1449, 1429, 1391, 1362, 1326, 1289, 1240, 1219, 1197, 1173, 1111, 1049, 1009, 973, 901, 882, 821, 804, 758, 735, 699, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 3.70 (ABX, J_{AX}=9.0 Hz, J_{BX}=9.7 Hz, J_{AB}=11.3 Hz, 2H), 3.86 (s, 3H), 5.36 (t, J=9.3 Hz, 1H), 6.52 (dd, J=8.2, 1.1 Hz, 1H), 6.86–6.99 (m, 2H), 7.36–7.48 (m, 4H), 7.75–7.78 (m, 6H), 8.18 (s, 1H), 8.32 (dd, J=7.9, 2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.14, 26.51, 34.95, 52.80, 78.51, 120.27, 121.37, 121.49, 123.12, 128.01, 129.71, 130.13, 130.40, 131.87, 135.32, 147.82, 152.97, 162.94, 166.50, 171.41. SM (ES+) *m/z* 559 ($M+H^+$, 100), 581 ($M+Na^+$, 20), 1117 ($2M+H^+$, 23), 1139 ($2M+Na^+$, 50).

4.1.19. 2′-(2-Hydroxyphenyl)-4″,5″-dihydro-[2″,4′]bis thiazolyl-4″-carboxylic acid methyl ester (19). To a stirred solution of **18** (840 mg, 1.50 mmol) in CH_2Cl_2 (40 mL), TBAF (1.70 mL, 1 M solution in THF, 1.70 mmol, 1.20 equiv) was added dropwise at 20 °C. After 20 mn, the mixture was adsorbed onto silica gel then filtered through a silica gel column (20 g SiO_2, pentane/Et_2O: 7/3 then pentane/Et_2O: 3/7). The phenolic compound **19** (376 mg, yield: 79%) was isolated as a white solid. Mp 100–102 °C, R_f 0.61 (Et_2O), IR (neat) 3296, 3123, 3067, 3009, 2954, 2160, 1978, 1719, 1622, 1600, 1584, 1506, 1478, 1443, 1427, 1330, 1304, 1258, 1211, 1172, 1158, 1110, 1030, 997, 971, 931, 896, 840, 827, 788, 743, 699, 684 cm^{-1}. UV (MeOH) 218 (41800), 281 (24600), 325 (16800), ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (ABX, J_{AX}=9.1 Hz, J_{BX}=9.7 Hz, J_{AB}=11.2 Hz, 2H), 3.86 (s, 3H), 5.32 (t, J=9.5 Hz, 1H), 6.93–6.96 (m, 1H), 7.08 (dd, J=8.2, 0.93 Hz, 1H), 7.36 (ddd, J=8.6, 7.3, 1.6 Hz 1H), 7.61 (dd, J=7.9, 1.5 Hz, 1H), 8.02 (s, 1H), 11.53 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.17, 52.88, 78.47, 116.23, 118.02, 118.68, 119.65, 127.32, 132.47, 147.36, 156.73, 164.82, 169.06, 171.02. SM (ES+) *m/z* 321 ($M+H^+$, 60), 343 ($M+Na^+$, 100), 641 ($2M+H^+$, 19), 663 ($2M+Na^+$, 83), 694 (9). Exact mass calcd for $C_{30}H_{31}N_2O_3S_2Si$ ($M+H^+$): 321.0368, found: 321.0406.

4.1.20. 2′-(2-Hydroxyphenyl)-4″,5″-dihydro-[2″,4′]bis thiazolyl-4″-carboxylic acid (*HPTT-COOH*) (4). To a solution of ester **19** (80 mg, 0.25 mmol) in THF (5 mL) and water (2 mL) was added powdered $LiOH\cdot H_2O$ (24 mg, 0.58 mmol, 2.30 equiv). After two hours of gentle stirring at room temperature (25 °C) the mixture was diluted with water (20 mL) and washed with Et_2O (20 mL) before being acidified to pH 2.0 with 0.5 N HCl solution. After evaporation under reduced pressure, the resulting pale yellow solid was extracted twice with hot ethanol. The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting pale yellow powder was then recrystallised from MeOH yielding HPTT-COOH **4** (70 mg, yield: 91%) isolated as a light beige powder. Mp 220 °C (dec), R_f 0.69 (CH_2Cl_2/*i*PrOH/HCOOH: 66/33/1). IR (neat) 3514, 3379, 3094, 3028, 1713, 1672, 1616, 1502, 1475, 1394, 1361, 1314, 1292, 1271, 1251, 1224, 1194, 1180, 1165, 1141, 1053, 1036, 1019, 957, 941, 920, 900, 846, 826, 816, 783, 765, 757, 740, 703, 681, 661 cm^{-1}, ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 3.61 (ABX, J_{AX}=8.2 Hz, J_{BX}=9.7 Hz, J_{AB}=11.3 Hz, 2H), 5.29 (dd, J=8.2, 9.6 Hz, 1H), 6.95–7.01 (m, 1H), 7.08 (d, J=8.2 Hz, 1H), 7.34 (ddd, J=8.4, 7.1, 1.6 Hz 1H), 8.13 (dd, J=7.9, 1.6 Hz, 1H), 8.31 (s, 1H), 11.20 (bs, 1H), 12.99 (sl, 1H). ^{13}C NMR (75 MHz, CD_3SOCD_3) δ 34.32, 78.39, 116.46, 118.78, 119.62, 122.04, 127.37, 131.47, 146.78, 155.04, 162.93, 163.76, 171.86. SM (ES−): 305 ($M-H^+$, 100), 611 ($2M-2H^+$, 95).

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