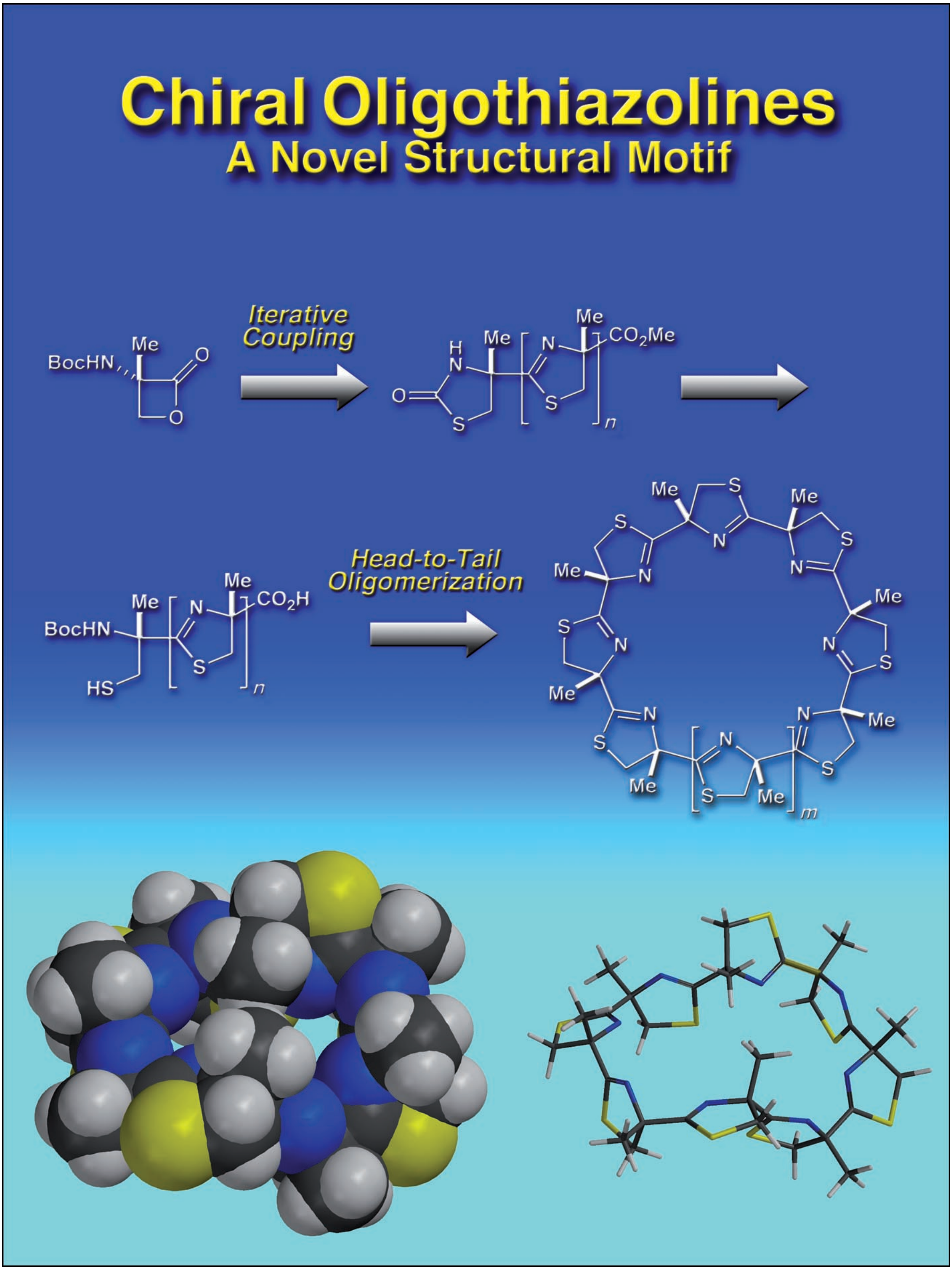
DOI: 10.1002/chem.200601446



Novel Structural Motifs Consisting of Chiral Thiazolines: Synthesis, Molecular Recognition, and Anticancer Activity

Fu She Han,[a] Hiroyuki Osajima,[b] Mui Cheung,[b] Hidetoshi Tokuyama,[c] and Tohru Fukuyama*[b]

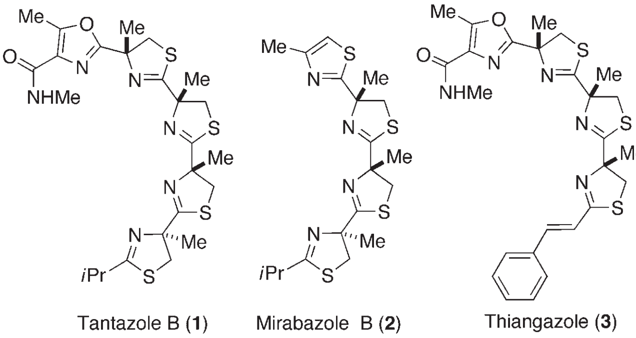
Abstract: The facile synthesis of linear and cyclic chiral oligo(4-α/β-methyl)-thiazolines is described. Linear oligothiazolines have been efficiently synthesized by the iterative formation of thiazoline rings and two-directional block condensation. The construction of 24- to 36-membered cyclic oligothiazolines was achieved through the head-to-tail cyclo-oligomerization of doubly deprotected linear fragments. Studies of the interactions of both the linear and cyclic oligomers with chiral compounds revealed that cyclic oligomers displayed a strong binding affinity towards mandelic acid, whereas linear oligomers showed a poor affinity. Linear oligomers have been proven to inhibit the cell growth of the cancer cell lines HPAC, PC-3, and HCT-116. Studies of the structure–activity relationships showed that the IC_{50} values are clearly dependent on both the length and the terminal functionalities of the linear oligomers. Longer derivatives showed more potent activity (e.g., hexi- and octithiazolines exhibit $IC_{50} < 1\,\mu\text{M}$) against all three cancer cell lines. In sharp contrast, cyclic oligomers were inactive to all three cell lines.

Keywords: anticancer agents · macrocycles · molecular recognition · oligomerization · thiazolines

Introduction

The design and synthesis of macromolecular architectures possessing defined structural motifs is a key issue in the areas of molecular recognition,[1] drug design,[2] and supramolecular chemistry.[3] The most commonly employed strategy for the construction of such macromolecules involves the assembly of heteroaromatic subunits. One of the advantages of incorporating heterocyclic structures into macromolecules is that heterocycles, in general, take part in noncovalent intermolecular interactions such as hydrogen bonding, dipole–dipole, and π–π interactions.[1–3] However, the use of aromatic rings prevents the direct incorporation of chiral centers into the structural framework.[4] In addition, primarily owing to the lack of general synthetic methodologies, only limited types of heteroaromatic rings are amenable to the construction of macromolecules[4] thereby preventing the flexible design of structurally diverse molecules.

In one of our synthetic studies of structurally complex natural products, we focused our attention on oligothiazoline marine natural products such as tantazole B (**1**),[5] mirabazole B (**2**),[6] and thiangazole (**3**)[7] (Scheme 1), and estab-



Scheme 1. Structures of oligothiazoline marine natural products **1**–**3**.

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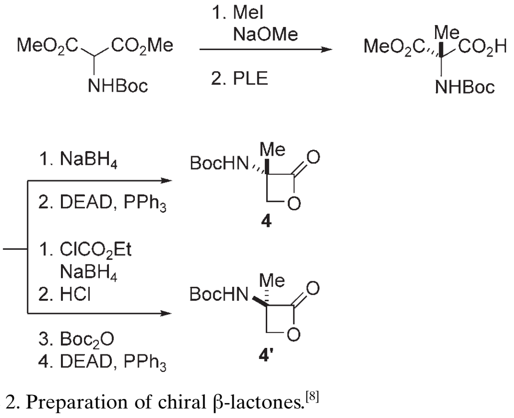
lished a synthetic route leading to tantazole B (**1**).[8] These compounds consist of a combination of thiazoline subunits possessing *R* or *S* stereochemistry, providing a highly diverse set of structures. In addition to their structural characteristics, this class of compound displays significant biological activity, including antitumor, antifungal, and insecticidal activities. In view of these characteristics, we considered that a chiral thiazoline moiety would potentially be a unique subunit with which to construct macromolecules of a defined chiral architecture and we thus initiated a study of the synthesis and properties of polythiazolines. Herein, we describe the development of a facile and iterative protocol for the synthesis of linear and cyclic chiral polythiazolines and an evaluation of the binding affinity of both linear and cyclic thiazolines towards chiral molecules and of their antitumor activity.

Results and Discussion

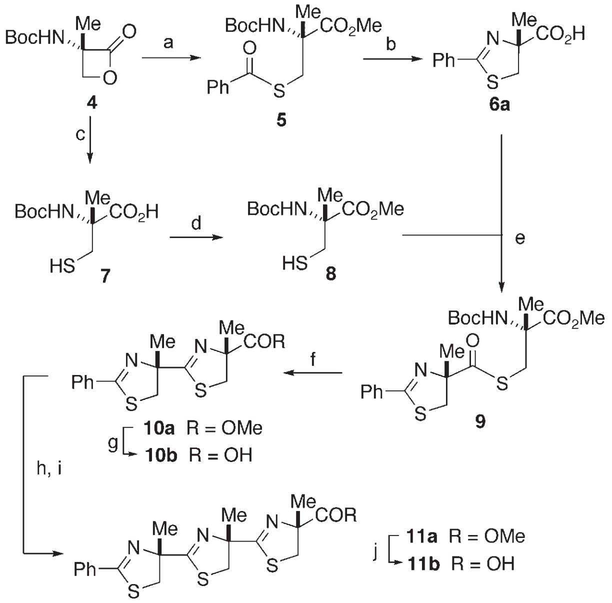
Synthesis of oligothiazolines by the repetitive and block condensation protocol:[9] At the outset of this project, we established a general and efficient protocol for thiazoline chain elongation. Although a number of approaches to the assembly of three to four units into linear arrays of oligothiazolines have been developed during synthetic studies on natural products,[10] these methods are unsatisfactory for the construction of higher homologues owing to their low efficiency. Accordingly, we have developed a repetitive protocol for the synthesis of oligothiazolines based on the strategy that we developed during our synthetic study of tantazole B (**1**).[8]

As the key intermediate, we used chiral β-lactone **4** (Scheme 2), which is readily prepared from dimethyl *N*-Boc-aminomalonate by alkylation, enzymatic desymmetrization, and β-lactone formation.[8] One of the advantages of this method is the accessibility of both enantiomers **4** and **4′**, potentially enabling us to synthesize both enantiomers of the target oligothiazolines or alternatively structurally diverse compounds with various combinations of *R* and *S* subunits.

The construction of a thiazoline chain was started by nucleophilic ring-opening of β-lactone **4** with thiobenzoic acid to provide thioester **5** (Scheme 3). After removal of the Boc group with TFA, the thiazoline ring was formed in refluxing benzene as the monothiazoline unit **6a**. Compound **6a** was then condensed with α-methylcysteine derivative **8**, a key fragment in the repetitive elongation of the thiazoline chain which was prepared by ring-opening of **4** with H_2S, followed by conversion to the methyl ester. The second thiazoline ring was formed by TFA treatment of **9** and subsequent refluxing in benzene. By repetition of a four-step sequence, saponification, condensation with **8**, removal of the Boc group, and cyclization under heating, the chiral thiazoline chain can be elongated in a step-by-step manner to produce **11a**.

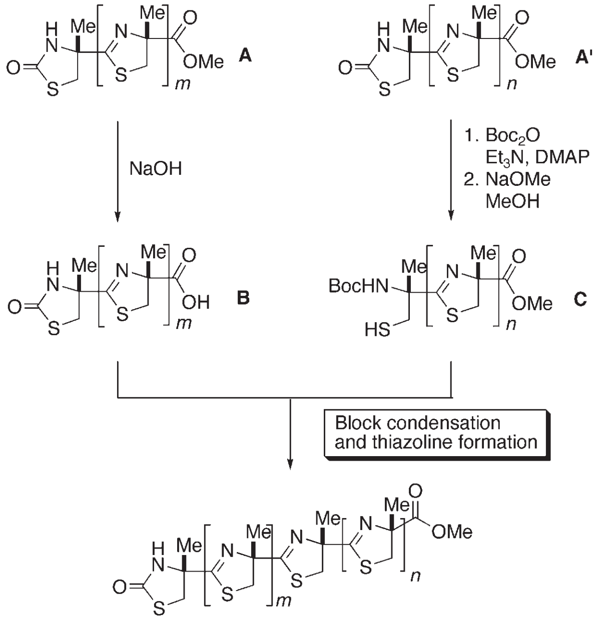


Scheme 2. Preparation of chiral β-lactones.[8]



Scheme 3. Reagents and conditions: a) thiobenzoic acid, K_2CO_3, THF, 0°C to RT, 4 h, 94%; b) TFA, RT, benzene, reflux, 84%; c) H_2S, Et_3N (2.5 equiv), CH_2Cl_2, 0°C, 30 min; d) CH_2N_2 in Et_2O (3.0 equiv), THF, 0°C (88%, 2 steps); e) BOP-Cl, Et_3N, CH_2Cl_2, RT, 92%; f) TFA, RT, benzene, reflux, 96%; g) LiOH, THF–H_2O, RT, 100%; h) BOP-Cl, Et_3N, CH_2Cl_2, RT, 97%; i) TFA, RT, benzene, reflux, 94%; j) LiOH, THF–H_2O, RT, 100%.

Furthermore, we have developed a block condensation protocol for the facile construction of longer thiazoline chains. We designed a thiazoline oligomer possessing a thiazolidinone and an ester function (e.g., segment **A** or **A′** in Scheme 4) at each terminus as a useful segment for a two-directional block condensation. The methyl ester and thiazolidinone moieties are chemically orthogonal to each other. Thus, free carboxylic acid (segment **B**) could be obtained by selective hydrolysis of the ester of **A** under basic conditions. On the other hand, thiazolidinone could be selectively converted to the corresponding *N*-Boc-thiol (segment **C**) by activation of the thiazolidinone with the Boc group, followed by ring-opening by methanolysis. These two segments, **B** and **C**, were then condensed and the resulting product was treated with TFA and heated to form a thiazoline, thereby

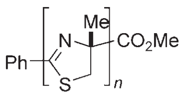


Scheme 4. Strategy for two-directional elongation of the oligomer chain.

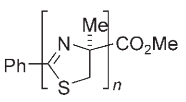
producing longer thiazoline chains bearing thiazolidinone and ester functionalities.

The thiazolidinone terminus was formed by removal of the Boc group in **7**, followed by treatment of the resultant amino-thiol with triphosgene to provide **12** (Scheme 5). Application of the repetitive elongation protocol (see above) to carboxylic acid **12** provided thiazoline **13**, which was converted to either carboxylic acid **14** or *N*-Boc-amino-thiol **15** by chemoselective reactions. These fragments were then condensed and the resulting thioester intermediate **16** was treated with TFA and heated to form a further thiazoline unit, thereby furnishing trimer fragment **17**. Repetition of this sequence provided the thiazoline heptamer **20** efficiently.

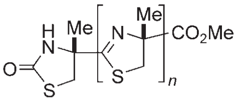
By using a combination of the iterative and block condensation protocols, we could efficiently synthesize linear arrays of oligothiazolines with diverse structures, including mono- to octithiazoline derivatives **6b**, **10a**, **11a**, and **21a–23a** having a phenyl group at the terminus, the corresponding opposite enantiomers of **6b**, **10a**, **11a**, and **22a** (**6′b**, **10′a**, **11′a**, and **22′a**, respectively), and mono- to septithiazolines **13**, **17**, **20**, and **24** having a thiazolidinone terminus.



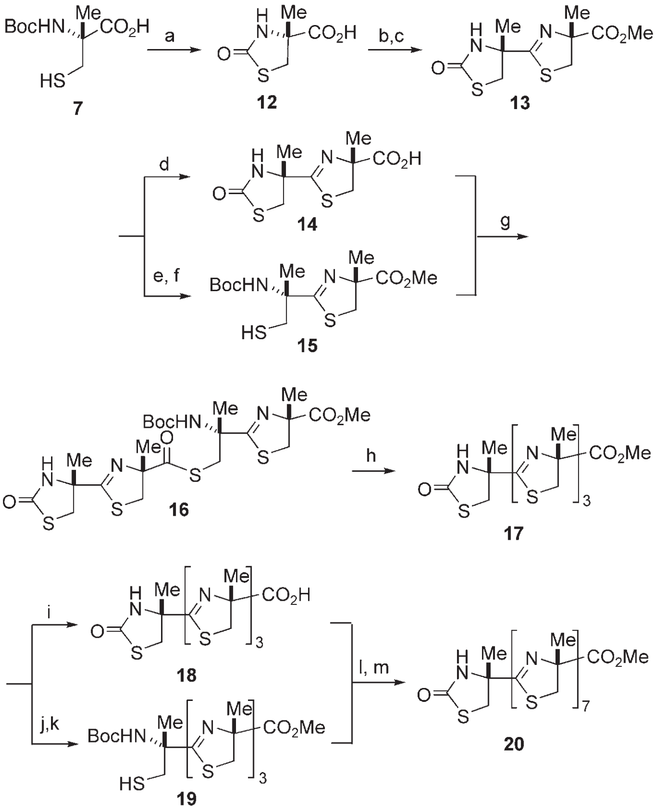
6b $n = 1$
10a $n = 2$
11a $n = 3$
21a $n = 4$
22a $n = 6$
23a $n = 8$



6′b $n = 1$
10′a $n = 2$
11′a $n = 3$
22′a $n = 6$



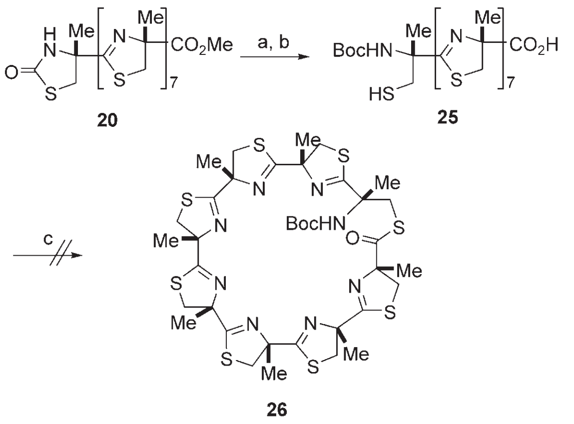
13 $n = 1$
24 $n = 2$
17 $n = 3$
20 $n = 7$



Scheme 5. Reagents and conditions: a) TFA, RT, 15 min; evaporated to dryness; triphosgene, 20% aq. KOH, dioxane, 0 °C to RT, 4 h (71%, 2 steps); b) **8** (1.0 equiv), BOP-Cl (1.5 equiv), Et_3N (2.5 equiv), CH_2Cl_2, RT, 3 h, 79%; c) TFA, RT, 15 min; evaporated to dryness; benzene, reflux, 2 h, 96%; d) 10% aq. NaOH (1.2 equiv), dioxane/MeOH (4:1 v/v), RT, 30 min, 78%; e) Boc_2O (1.2 equiv), Et_3N (2.5 equiv), DMAP (cat.), CH_2Cl_2, RT, 40 min, quant.; f) NaOMe (1.0 M in MeOH) (1.2 equiv), THF, 0 °C, 30 min, 81%; g) BOP-Cl (1.5 equiv), Et_3N (2.5 equiv), CH_2Cl_2, RT, 3 h, 77%; h) TFA, RT, 15 min; evaporated to dryness; benzene, reflux, 4 h, 93%; i) 10% aq. NaOH (1.2 equiv), dioxane/MeOH (4:1 v/v), RT, 30 min, 84%; j) Boc_2O (1.2 equiv), Et_3N (2.5 equiv), DMAP (cat.), CH_2Cl_2, RT, 40 min, 93%; k) NaOMe (1.0 M in MeOH) (1.2 equiv), THF, 0 °C, 30 min, 81%; l) BOP-Cl (1.5 equiv), Et_3N (2.5 equiv), CH_2Cl_2, RT, 4 h; m) TFA, RT, 20 min, evaporated to dryness; benzene, reflux, 4 h (64%, 2 steps).

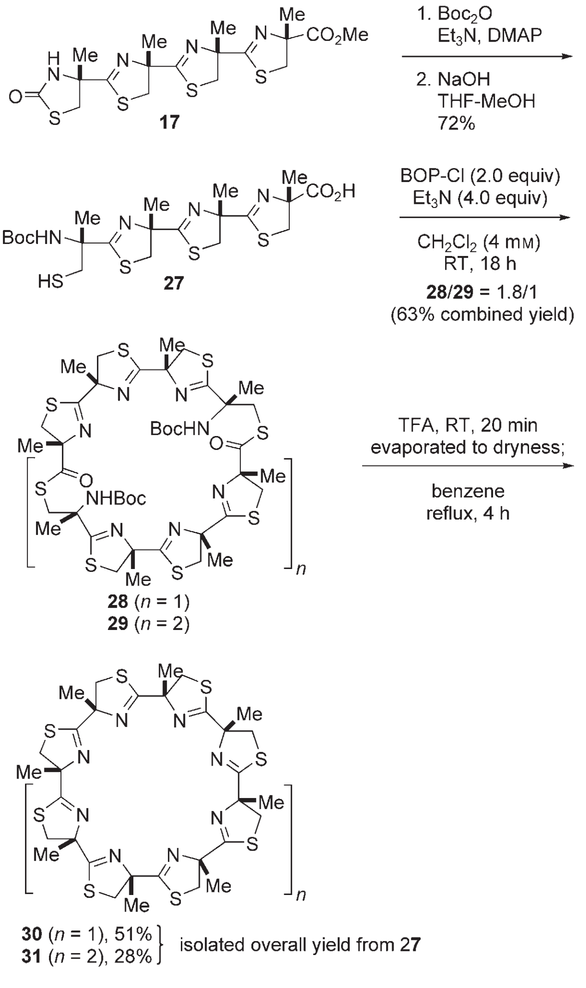
Synthesis of cyclic oligothiazolines: Having established a protocol for the synthesis of linear oligothiazolines, our efforts were then directed towards the construction of cyclic oligothiazolines. We have considered that upon cyclization of the linear oligothiazoline chains, a chiral, wheel-shaped binding cavity would be formed, which would give us an opportunity to study the binding of chiral host molecules. As the most straightforward way to form a cyclic compound should be the cyclization of a linear precursor, we initially converted **20** into thiol–carboxylic acid **25** (Scheme 6) and examined its cyclization. However, extensive efforts to cyclize **25** proved fruitless, probably as a result of the limited conformational flexibility of **25**.

We eventually found that short fragments of thiol–carboxylic acid underwent smooth cyclodimerization or -trimerization in a head-to-tail fashion, affording macrocyclic thioest-

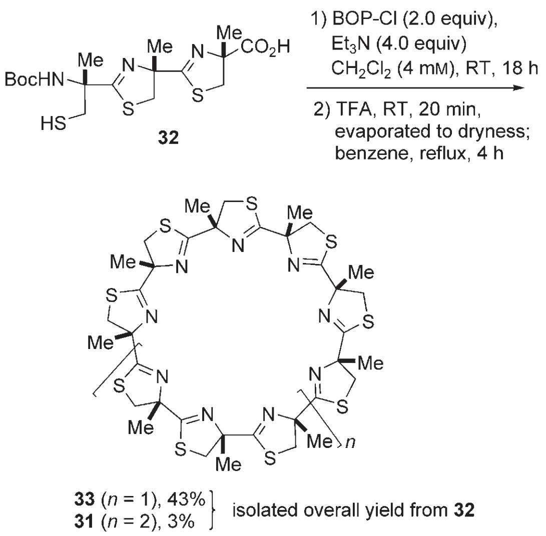


Scheme 6. Reagents and conditions: a) Boc_2O (1.2 equiv), Et_3N (2.5 equiv), DMAP (cat.), CH_2Cl_2, RT, 1 h; b) 10 % aq. NaOH (2.2 equiv), THF/MeOH (4/1 v/v), 0 °C to RT, 30 min (81 %, 2 steps); c) BOP-Cl (2.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2 (2 or 4 mM), RT, 36 h.

ers. Thus, compound **17** was converted to thiol–carboxylic acid **27** (Scheme 7) and its condensation reaction was examined by using several dehydrating agents, including BOP-Cl/Et_3N, DCC/HOBt, and FDPP, and by changing the concentration of the substrate. To this end, the use of BOP-Cl led to the clean formation of a mixture of cyclic dimer **28** and trimer **29**. Other coupling reagents, DCC/HOBt and FDPP, might also produce the desired cyclic compounds (as detected by TLC), however, their use resulted in complex mixtures. The effect of concentration on the cyclization reaction was then examined by using BOP-Cl as the coupling reagent. At low (2 mM) and high (20 mM) substrate concentrations, cyclization gave a mixture of **28** and **29** in 20 and 36 % total yields, respectively. Surprisingly, the yield was dramatically improved to over 60 % when the reaction was carried out with substrate concentrations of 4 and 8 mM (ratio of **28**/**29** ≈ 1.8:1 with 4 mM and 1:1 with 8 mM). Thus, the optimal cyclo-oligomerization conditions are BOP-Cl (2.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2 (4 mM) at room temperature for 18 h. Under these conditions, the desired cyclic dimer **28** and trimer **29** could be obtained in 63 % combined yield. Finally, treatment of the mixture of cyclic thioesters **28** and **29** with TFA at room temperature, followed by refluxing in benzene after removal of TFA furnished cyclic octithiazoline **30** and dodecithiazoline **31** in high yields. The two macrocyclic compounds could be isolated easily by preparative thin-layer chromatography (PTLC). Cyclic novithiazoline **33** and dodecithiazoline **31** were synthesized in a similar manner in 43 and 3 % yields over two steps from **32** derived from **24** (Scheme 8).



Scheme 7. Synthesis of macrocycles **30** and **31**.



Scheme 8. Synthesis of macrocycles **33** and **31**.

The structures of all the linear and cyclic oligothiazolines were determined by standard spectroscopic techniques, including ^1H and ^{13}C NMR, high-resolution mass spectrometry, and elemental analyses. The structure of cyclic octamer **30** was also confirmed by X-ray crystallographic analysis (Figure 1).[11] Note that in contrast to the complex NMR spectra of the linear oligomers, the cyclic oligomers exhibited a simple, single set of signals in their ^1H (Figure 2) and ^{13}C NMR spectra.[12] Furthermore, a variable-temperature

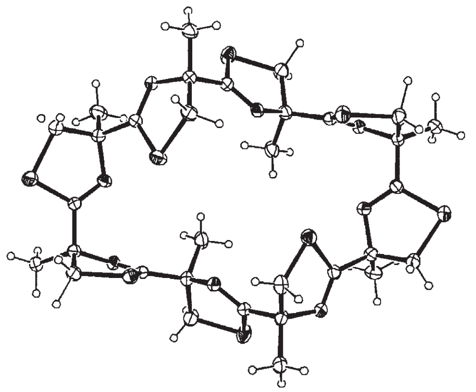


Figure 1. X-ray crystal structure of macrocycle **30**. Displacement ellipsoids represent 30 % probability.

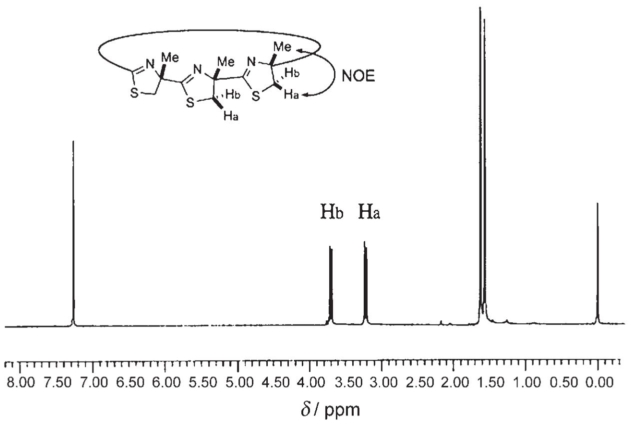
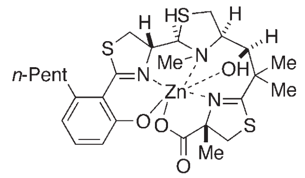


Figure 2. ^1H NMR spectrum of cyclic octithiazoline **30** (the peak at 1.56 ppm corresponds to H_2O in the sample.

^1H NMR study showed that the spectroscopic properties of the cyclic oligomers do not change even at −60 °C. These observations suggest that the macrocyclic structures are highly flexible and adopt C_n symmetric conformations in the solution state (*n* corresponds to the number of thiazoline units). A 1D-NOESY study of **30** revealed a strong nuclear Overhauser effect between the methyl and methylene signals at $\delta = 3.19$ ppm (H_a), but no effect was observed between the methyl and methylene signals at $\delta = 3.70$ ppm (H_b), indicating that H_a points outwards from the cyclic cavity and H_b points inwards.

Binding studies: Having synthesized a unique structural array of chiral oligothiazolines, both in linear and cyclic forms, we then carried out an investigation into the interactions of these chiral macromolecules with small chiral compounds. As is shown in the metal-chelating structure of micacocidin A (Scheme 9),[13] the sp^2 nitrogen atoms of the thiazolines act as Lewis bases to bind a metal cation or to accept hydrogen bonds. In addition, C=N double bonds can interact with aromatic rings through π–π stacking. Thus, we believed that the chiral environment of oligothiazolines, consisting of Lewis basic nitrogen sites and C=N double bonds, could differentiate chiral molecules by forming selective interactions. As a guest molecule we selected mandelic acid (MA), a representative chiral α-hydroxy carboxylic acid,[14] which could form hydrogen bonds at two sites, through the hydroxy and the carboxy groups.[15]



Micacocidin A

Scheme 9. Structure of micacocidin A.

As the simplest case, the interaction between bithiazoline **10a** and MA was investigated. Bithiazoline **10a** and (*R*)-MA were mixed in $CDCl_3$, changing the molar ratio of (*R*)-MA/**10a** from 1:1 to 15:1, and their ^1H NMR spectra were determined. Despite careful inspection of the ^1H NMR spectra, we observed only a slight change in the chemical shifts ($\Delta\delta < 0.010$ ppm), even in the presence of a large excess of (*R*)-MA. In the same experiments with (*S*)-mandelic acid, no significant change in the chemical shifts was observed. A longer, linear thiazoline, **22a**, consisting of six thiazoline units, again produced no significant change in the chemical shifts.

In contrast to the behavior of these linear oligothiazolines, significant changes in the chemical shifts were observed when cyclic oligothiazolines were mixed with MA. When (*S*)-MA was added to a $CDCl_3$ solution of cyclic octithiazoline **30** (1.5×10^{-3} M), the doublet signals corresponding to the inward methylene proton H_b at 3.70 ppm (see above) were shifted upfield (line 2# in Figure 3). The magnitude of the upfield shift was dependent on the molar ratio of (*S*)-MA and reached a plateau with more than 8 equivalents of (*S*)-MA. This observation clearly indicates that mandelic acid has specific interactions with cyclic octithiazoline **30**. The stoichiometry of the interaction was further studied

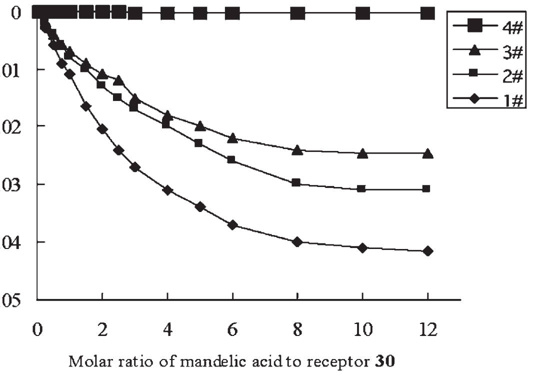


Figure 3. ^1H NMR titration curves for receptor **30** with mandelic acid (MA): Line 1# ($\Delta\delta H_b$ of **30**·(*R*)-MA); line 2# ($\Delta\delta H_b$ of **30**·(*S*)-MA); line 3# ($\Delta\delta H_a$ of **30**·(*R*)-MA); line 4# ($\Delta\delta H_a$ of **30**·(*S*)-MA). All of the titrations were duplicated.

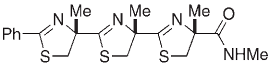
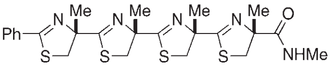
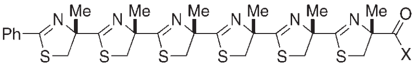
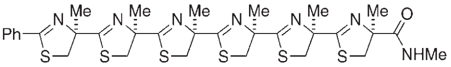
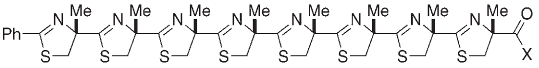
using the continuous variation method.[16] ^{1}H NMR titration at a constant total concentration of 5.0×10^{-3} M indicated that several possible complexes, such as 1:1, 1:2, 1:4, and 1:8, were formed between octithiazoline **30** and mandelic acid, although the 1:4 complex should be the major one, as judged from the continuous variation titration combined with Job plots. As a result of the complex interactions, calculation of the association constants was difficult. Interestingly, when (*R*)-MA was used instead of (*S*)-MA, much larger upfield shifts in both the H$_a$ (line 3#) and the H$_b$ signals (line 1#) were observed (e.g., 1# versus 2#, 3# versus 4#). In addition, in the experiments using either (*R*)- or (*S*)-MA, the upfield shift of the inward proton H$_b$ is always larger than that of the outward proton H$_a$ (1# versus 3#, 2# versus 4#). A large upfield shift of the inward proton can be attributed to the higher shielding effect due to the phenyl ring of MA on the inner H$_b$ than on the outer H$_a$, suggesting that MA is buried inside the wheel-shaped cavity of the macrocycle. This is possibly the reason why significant changes in the chemical shifts were observed in the NMR spectra of the cyclic oligothiazolines, but not in the NMR experiments using linear compounds.

Similar titration studies of the other chiral cyclic oligomers, dodecamer **31** and nonamer **33**, were carried out to show that these compounds exhibited similar behavior. Accordingly, NMR titration studies of oligothiazolines clearly indicate that macrocyclic thiazolines recognize (*R*)- and (*S*)-MA by forming specific interactions. Thus, this class of macrocycle could potentially serve as receptors for small chiral molecules. Further binding studies with other types of molecules, such as amino acids, peptides, oligonucleotides, and sugars, as well as detailed extensive binding studies to determine binding affinity are currently under investigation.

Biological activity: A number of natural products[5–7] consisting of three to four contiguous thiazolines have demonstrated significant biological activity, including antitumor, antifungal, and insecticidal properties (Scheme 1). However, systematic structure–activity relationships (SARs) of this class of compound and its higher homologues have not yet been widely studied owing to the lack of an efficient synthetic methodology. As we have developed an efficient protocol that enables us to access diverse structural analogues of oligothiazolines, including cyclic and linear forms, preliminary SAR studies on the anticancer activity of various oligothiazolines were carried out.

The inhibitory activities of the linear and cyclic oligothiazolines towards cell growth in three cancer cell lines, PC-3, HCT-116, and HPAC, were evaluated in vitro by using the WST-1 assay protocol. Although none of the cyclic oligomers (**30**, **31**, and **33**), mono-, or bithiazolinecarboxamides possessed appreciable inhibitory activity, even at high concentrations (100 μM), relatively long linear compounds displayed distinct activity. In addition, a clear structure–activity profile was revealed by evaluation of a series of linear oligothiazolines.

Table 1. Inhibitory activity against cell growth of tumor cell lines PC-3, HTC-116, and HPAC as a measure of IC$_{50}$.[a]

Thiazoline oligomer		IC$_{50}$ [μM] PC-3	HTC-116	HPAC
	**10c**	8.4	17.8	7.9
	**21c**	7.2	5.2[b]	5.7
	**22a**: X = OMe	37.0	–[c]	>50
	22b: X = OH	8.6	7.4	7.3
	22c: X = NHMe	0.7	0.7	0.6
	**22c′**	n.d.[d]	n.d.[d]	0.4
	**23a**: X = OMe	1.2	0.9	1.7
	23b: X = OH	24.0	19.4	31.0
	23c: X = NHMe	0.3	0.5	0.6

[a] Unless otherwise noted, IC$_{50}$ is the concentration required to inhibit cancer-cell proliferation by 50% after exposure of the cells to a tested compound for 72 h. [b] Concentration required to inhibit cancer cell proliferation by 60%. [c] Not available. [d] Not determined.

As shown in Table 1, the IC$_{50}$ values of the linear oligomers are affected significantly by the length of the oligomer chain. Longer chains are generally much more cytotoxic than shorter chains. The cytotoxicity of the carboxamide series of oligomers increases in the order trimer (**10c**) tetramer (**21c**), hexamer (**22c**), and octamer (**23c**) as shown in Table 1, and oligomers with carboxamide functionalities are generally much more cytotoxic than those with ester and carboxylic acid functionalities (**22c** > **22b** > **22a**, **23c** > **23a** > **23b**, and the ester and carboxylic acid congeners of trimer **10c** and tetramer **21c** were inactive). This observation is in agreement with a previous SAR study in which replacement of the carboxamide moiety in naturally occurring thiangazole by other functions, such as thioamide, ester, carboxylic acid, and aldehyde, generally led to a decrease in biological activity.[17] The effect of *R* versus *S* stereochemistry on biological activity was also investigated. A comparison of the cytotoxicity of **22c** (0.6 μM) and its enantiomer **22′c** (0.4 μM) against the HPAC cell line revealed that stereochemistry has little effect on activity.

Conclusion

We have developed an efficient protocol for the synthesis of both linear and cyclic arrays of chiral oligothiazolines. The linear oligomers were synthesized by a two-directional block condensation protocol, followed by acid-mediated thiazoline ring formation.[8] Construction of 24- to 36-membered cyclic oligothiazolines was achieved by the head-to-tail cyclo-oligomerization of doubly deprotected linear fragments. These synthetic methods are very quick, versatile, result in high yields, and have been successfully applied to the synthesis of new classes of thiazoline/thiazole-based linear and cyclic oligomers. In addition, both the linear and cyclic oligothiazolines are novel structural motifs that exhibit interesting properties. The linear oligomers display interesting cytotoxicity against three cancer cell lines, HPAC, PC-3, and HCT-116. A thorough study of the structure—activity relationships indicated that the IC_{50} values clearly depend on both the length and the terminal functionalities of the linear oligomers. Thus, hexithiazolinecaboxamide **22c** and **22′c**, and octithiazoline methyl ester **23a** and carboxamide **23c** exhibit strong cytotoxicity with $IC_{50} < 1$ μM, indicating that this class of compound could serve as leads in anticancer research. Preliminary studies on chiral recognition revealed that the cyclic macromolecules possess binding affinity for mandelic acids, indicating that cyclic oligomers could potentially serve as chiral receptors through hydrogen bonding. Consequently, the results described in this paper lay the groundwork for further development of new chiral receptors and drugs. Extensive studies on the synthesis of new chiral oligothiazolines employing our methodologies, as well as their application to the development of artificial receptors and biologically active compounds such as enzyme inhibitors and anticancer agents, are currently under investigation.

Experimental Section

General methods: Unless otherwise noted, all reagents were reagent grade and were used without purification. All solvents were purified according to standard procedures. IR spectra were recorded with a JASCO FT/IR-410 spectrometer and only selected absorbencies are reported. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with a JEOL JNM-LA400 instrument. Chemical shifts are given relative to TMS or the appropriate solvent peak. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured using a JEOL JMS-700 or a JEOL JMS-GCmate instrument. Elemental analyses were carried out on a Yanagimoto MT-6 CHN CORDER instrument. Optical rotations were measured using a JASCO DIP-100 Digital Polarimeter. Analytical thin-layer chromatography (TLC) separations were performed on Merck analytical plates precoated with silica gel 60 F254 (0.25 mm thick). Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F254. Flash chromatography separations were performed on Kanto Chemical Silica Gel 60 (normal or neutral, 40–100 mesh).

Monothiazolinecarboxylic acid 6a: Thiobenzoic acid (1.30 mL, 11.0 mmol) and K_2CO_3 (3.71 g, 26.8 mmol) were added to a solution of **4** (1.80 g, 8.96 mmol) in THF (40 mL) at 0 °C. The resulting solution was stirred at room temperature for 4 h. The reaction mixture was acidified with 10 % aq. $KHSO_4$ to pH 4 after being diluted with EtOAc. Separated aqueous layer was extracted with EtOAc (30 mL) three times. The combined organic extracts were dried with $MgSO_4$, filtered, concentrated, and purified by flash column chromatography on acidic silica gel (hexane/EtOAc, 6:1) to give thioester **5** (2.86 g, 94 %). Thioester **5** was then treated with TFA at room temperature for 20 min and evaporated to dryness. The residue was refluxed in benzene (20 mL) for 4 h and then the solvent was removed to give the crude product. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1) to give **6a** (1.64 g, 84 %). $[\alpha]_{\mathrm{D}}^{25}=-6.5$ ($c=0.5$ in acetone). IR (neat): $\tilde{\nu}=3173$, 2984, 2931, 1732, 1596, 1570, 1456, 1195, 1134, 960 cm^{-1}. ^{1}H NMR ([D$_6$]acetone): $\delta=7.87$ (d, $J=8.0$ Hz, 2H; phenyl), 7.56–7.46 (m, 3H; phenyl), 3.95 (d, $J=10.8$ Hz, 1H; CH_2), 3.44 (d, $J=10.8$ Hz, 1H; CH_2), 1.61 ppm (s, 3H; CH_3); ^{13}C NMR ([D$_6$]acetone): $\delta=174.0$, 169.4, 133.1, 133.0, 129.6, 129.3, 84.5, 41.8, 23.8 ppm; MS: $[M^+ + H]$: 222; HRMS: $[M^+ + H]$ calcd for $C_{11}H_{12}NO_2S$: 222.0589; found: 222.0579.

***N*-Boc-methylcysteine (7)**: H_2S was bubbled through a CH_2Cl_2 solution (40 mL) of **4** (4.20 g, 20.9 mmol) and Et_3N (7.30 mL, 52.2 mmol) at 0 °C for 40 min. The solution was then purged with argon for 10 min and acidified with 1 N HCl to pH 3. The biphasic solution was separated and the aqueous layer extracted with CH_2Cl_2 (30 mL) three times. The combined organic extracts were dried with $MgSO_4$, filtered, concentrated, and purified by flash column chromatography on acidic silica gel (hexane/EtOAc, 6:1) to give **7** (4.59 g, 94 %). $[\alpha]_{\mathrm{D}}^{25}=28.0$ ($c=3.70$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3400$, 2990, 2940, 1700, 1600, 1500, 1450, 1400, 1370, 1300, 1260, 1170, 1060, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=8.57$ (br, 1H), 5.67 (br, 1H), 3.10 (m, 2H; CH_2), 1.51 (s, 3H; CH_3), 1.43 ppm (s, 9H; *tert*-butyl); ^{13}C NMR ($CDCl_3$): $\delta=178.5$, 154.9, 80.0, 60.8, 31.1, 28.4, 23.0; HRMS: $[M^+ - C_4H_8]$: calcd for $C_5H_9NO_4S$: 179.0252; found: 179.0251.

***N*-Boc-methylcysteine methyl ester (8)**: A diethyl ether solution of CH_2N_2 (10.4 mmol) was added dropwise to a solution of **7** (810 mg, 3.46 mmol) in THF (15 mL) at 0 °C. The resulting solution was stirred for an additional 30 min. The reaction was terminated by the addition of acetic acid dropwise until the solution became colorless. The solvent was evaporated and the residue purified by flash column chromatography on silica gel (hexane/EtOAc 20:1) to give **8** (815 mg, 94 %). $[\alpha]_{\mathrm{D}}^{25}=8.1$ ($c=0.50$ in $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta=5.48$ (br, 1H), 3.78 (s, 3H; OCH_3), 3.05 (d, $J=9.2$ Hz, 1H; CH_2), 3.01 (d, $J=9.2$ Hz, 1H; CH_2), 1.56 (s, 3H; CH_3), 1.45 ppm (s, 9H; *tert*-butyl); ^{13}C NMR ($CDCl_3$): $\delta=173.5$, 154.0, 79.8, 60.8, 52.8, 30.7, 28.2, 22.9 ppm; MS: $[M^+ + H]$: 250; HRMS: $[M^+ + H]$: calcd for $C_{10}H_{20}NO_4S$: 250.1113; found: 250.1119.

General procedure for the synthesis of linear oligothiazoline methyl esters: procedure A: BOP-Cl (1.5 equiv) and Et_3N (2.0 equiv) were added to a CH_2Cl_2 solution of thiol (1.0 equiv) and carboxylic acid (1.0 equiv) and the resulting mixture was stirred at room temperature for 2–4 h. The solution was then washed with 5 % aq. $NaHCO_3$ and brine after being diluted with EtOAc. The organic layer was dried with $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel (hexane/EtOAc 4:1) to give the thioester. The pure thioester intermediate was then treated with neat TFA at room temperature for 20 min and evaporated to dryness. The residue was dissolved in benzene and refluxed for 4 h and then evaporated to leave crude products. The crude products were purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1) to give the corresponding linear oligothiazoline.

Thiazoline thioester 9: Thioester **9** was obtained in 92 % yield from **6a** and **8** according to the general procedure A. $[\alpha]_{\mathrm{D}}^{25}=-102.0$ ($c=0.70$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3385$, 2977, 2934, 2870, 1744, 1714, 1685, 1492, 1449, 1366, 1258, 1167, 1057, 957, 767 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=7.91$ (d, $J=9.2$ Hz, 2H; phenyl), 7.52–7.43 (m, 3H; phenyl), 3.79–3.75 (m, 4H; OCH_3 and CH_2), 3.65 (d, $J=11.2$ Hz, 1H; CH_2), 3.56 (d, $J=12.0$ Hz, 1H; CH_2), 3.33 (d, $J=11.2$ Hz, 1H; CH_2), 1.67 (s, 3H; CH_3), 1.42 (s, 9H; *tert*-butyl), 1.41 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=203.6$, 173.3, 170.3, 154.1, 132.7, 131.8, 128.5 (2C), 90.3, 79.9, 59.1, 52.8, 42.0, 34.6, 28.2, 25.1, 25.0 ppm; MS $[M^+ + H]$: 453; HRMS $[M^+ + H]$: calcd for $C_{21}H_{29}N_2O_5S_2$: 453.1518; found: 453.1529.

Bithiazoline methyl ester 10a: Methyl ester **10a** was obtained in 96 % yield from **9** according to the general procedure A. $[\alpha]_{\mathrm{D}}^{25}=-156.4$ ($c=0.51$ in $CHCl_3$). IR (neat): $\tilde{\nu}=2979$, 2930, 2853, 1738, 1615, 1447, 1291, 1230, 1122, 1016, 958 cm^{-1}. ^{1}H NMR (CDCl$_3$): $\delta = 7.88$ (d, $J = 7.6$ Hz, 2H; phenyl), 7.49–7.42 (m, 3H; phenyl), 3.93 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.81 (s, 3H; OCH$_3$), 3.72 (d, $J = 10.8$ Hz, 1H; CH$_2$), 3.48 (d, $J = 10.8$ Hz, 1H; CH$_2$), 3.12 (d, $J = 12.0$ Hz, 1H; CH$_2$), 1.72 (s, 3H; CH$_3$), 1.54 ppm (s, 3H; CH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 178.4$, 173.8, 168.5, 132.8, 131.6, 128.5 (2C), 83.9 (2C), 52.8, 43.2, 41.1, 26.0, 23.9 ppm; MS: [M^++H]: 335; HRMS: [M^++H]: calcd for $C_{16}H_{19}N_2O_2S_2$: 335.0888; found: 335.0892.

General procedure for the preparation of oligothiazoline carboxylic acids: procedure B: A 10% aq. LiOH solution (3.0 equiv) was added to a THF solution of oligothiazoline methyl ester (1.0 equiv) at 0°C. The resulting solution was then stirred at room temperature for 30 min. The reaction mixture was acidified with 10% KHSO$_4$ to pH 5–6 after being diluted with EtOAc. After extracting the aqueous layer with EtOAc three times, the combined organic layers were dried with MgSO$_4$, filtered, concentrated, and purified by flash column chromatography on acidic silica gel (hexane/EtOAc, 1:1) to give the corresponding oligothiazoline carboxylic acid.

Bithiazolinecarboxylic acid 10b: Carboxylic acid **10b** was obtained in quantitative yield from **10a** according to the general procedure B. $[\alpha]_D^{25} = -201.6$ ($c = 0.68$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 3340$, 2982, 2929, 2865, 1731, 1608, 1577, 1447, 1250, 1176, 1017, 958 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 7.87$ (d, $J = 7.2$ Hz, 2H; phenyl), 7.51–7.43 (m, 3H; phenyl), 3.88 (d, $J = 12.0$ Hz, 1H; CH$_2$), 3.70 (d, $J = 12.0$ Hz, 1H; CH$_2$), 3.45 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.23 (d, $J = 11.2$ Hz, 1H; CH$_2$), 1.73 (s, 3H; CH$_3$), 1.56 ppm (s, 3H; CH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 181.1$, 176.1, 169.2, 132.6, 131.8, 128.6, 83.7, 83.6, 43.1, 40.8, 25.9, 24.0 ppm; MS: [M^++H]: 321; HRMS: [M^++H]: calcd for $C_{15}H_{17}N_2O_2S_2$: 321.0731; found: 321.0730.

Terthiazoline methyl ester 11a: Methyl ester **11a** was obtained in 91% yield from **10b** according to the general procedure A. $[\alpha]_D^{25} = -339.0$ ($c = 0.22$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 2976$, 2945, 2861, 1737, 1618, 1576, 1447, 1367, 1284, 1233, 1122, 1013, 958, 767 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 7.87$ (d, $J = 7.2$ Hz, 2H; phenyl), 7.49–7.40 (m, 3H; phenyl), 3.92 (d, $J = 10.8$ Hz, 1H; CH$_2$), 3.80 (s, 3H; OCH$_3$), 3.72 (d, $J = 12.0$ Hz, 1H; CH$_2$), 3.71 (d, $J = 11.6$ Hz, 1H; CH$_2$), 3.46 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.28 (d, $J = 12.0$ Hz, 1H; CH$_2$), 3.11 (d, $J = 11.2$ Hz, 1H; CH$_2$), 1.74 (s, 3H; CH$_3$), 1.61 (s, 3H; CH$_3$), 1.55 ppm (s, 3H; CH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 178.4$, 178.3, 173.7, 168.6, 132.8, 131.6, 128.6, 128.5, 84.0, 83.9, 83.5, 52.8, 43.3, 43.0, 41.1, 26.1, 25.8, 23.9 ppm; MS: [M^+]: 433; HRMS: [M^++H]: calcd for $C_{20}H_{24}N_3O_2S_3$: 434.1031; found: 434.1058; elemental analysis calcd (%) for $C_{20}H_{23}N_3O_2S_3 \cdot 0.5H_2O$: C 54.27, H 5.46, N 9.49; found: C 54.59, H 5.31, N 9.23.

Terthiazolinecarboxylic acid 11b: Carboxylic acid **11b** was obtained in 97% yield from **11a** according to the general procedure B. $[\alpha]_D^{25} = -342$ ($c = 0.42$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 3358$, 2977, 2929, 2860, 1731, 1717, 1616, 1575, 1447, 1371, 1254, 1176, 1015, 958, 767 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 7.87$ (d, $J = 7.2$ Hz, 2H; phenyl), 7.50–7.43 (m, 3H; phenyl), 3.90 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.69 (d, $J = 12.0$ Hz, 1H; CH$_2$), 3.68 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.46 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.25 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.24 (d, $J = 12.0$ Hz, 1H; CH$_2$), 1.73 (s, 3H; CH$_3$), 1.62 (s, 3H; CH$_3$), 1.57 ppm (s, 3H; CH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 180.4$, 179.3, 175.7, 168.9, 132.8, 131.7, 128.5 (2C), 83.9, 83.8, 83.4, 43.2, 42.9, 40.7, 25.9, 25.8, 24.0 ppm; MS: [M^++H]: 420; HRMS: [M^++2H]: calcd for $C_{19}H_{23}N_3O_2S_3$: 421.0952; found: 421.0970; elemental analysis calcd (%) for $C_{19}H_{21}N_3O_2S_3 \cdot 0.5H_2O$: C 53.24, H 5.17, N 9.80; found: C 53.48, H 5.35, N 9.34.

2-Oxothiazolidinecarboxylic acid 12: *N*-Boc-methylcysteine **7** (3.30 g, 14.1 mmol) was treated with neat TFA (10 mL) at room temperature for 20 min and evaporated to dryness. The residue was dissolved in 20% aq. KOH (40 mL) and cooled to 0°C. A dioxane solution (40 mL) of triphosgene (1.40 g, 19.7 mmol) was added slowly over 20 min. After stirring for an additional 1 h, the ice-bath was removed and the solution was stirred at room temperature for 3 h. The solution was acidified with 1 N HCl to pH 3 and extracted thoroughly with EtOAc (50 mL) five times. The combined organic extracts were dried with MgSO$_4$, filtered, and concentrated to give a crude product, which was then crystallized from acetone/ether to give pure **12** (1.59 g, 71% yield). $[\alpha]_D^{25} = -92.4$ ($c = 0.5$ in MeOH). IR (neat): $\tilde{\nu} = 3417$, 3225, 2982, 2940, 2870, 1680, 1618 cm^{-1}; ^{1}H NMR (CD$_3$OD): $\delta = 3.72$ (d, $J = 10.8$ Hz, 1H; CH$_2$), 3.36 (d, $J = 10.8$ Hz, 1H; CH$_2$), 1.55 ppm (s, 3H; CH$_3$); ^{13}C NMR (CD$_3$OD): $\delta = 178.1$, 176.3, 65.3, 40.2, 24.5 ppm; MS: [M^++H]: 162; HRMS: [M^++H]: calcd for $C_5H_8NO_3S$: 162.0225; found: 162.0227.

2-Oxothiazolidinylthiazoline 13: Compound **13** was obtained in 75% yield from **12** according to the general procedure A. $[\alpha]_D^{25} = -108.8$ ($c = 0.65$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 3287$, 2984, 2936, 1735, 1698, 1684, 1457, 1437, 1294, 1238, 1203, 1128, 1020 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 6.15$ (s, 1H; *NH*), 3.78–3.83 (m, 5H; OCH$_3$ and CH$_2$), 3.38 (d, $J = 10.8$ Hz, 1H; CH$_2$), 3.24 (d, $J = 10.8$ Hz, 1H; CH$_2$), 1.68 (s, 3H; CH$_3$), 1.55 ppm (s, 3H; CH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 176.3$, 173.8, 173.1, 84.7, 62.9, 53.0, 42.3, 40.5, 25.8, 23.6 ppm; MS: [M^++H]: 275; HRMS: [M^++H]: calcd for $C_{10}H_{15}N_2O_3S_2$: 275.0524; found: 275.0516.

2-Oxothiazolidinylthiazolinecarboxylic acid 14: Compound **14** was obtained in 78% yield from **13** according to the general procedure B. $[\alpha]_D^{25} = -38.6$ ($c = 0.50$ in acetone). IR (neat): $\tilde{\nu} = 3345$, 2990, 2936, 2860, 1732, 1710, 1684, 1457, 1437, 1296, 1238, 1203, 1128, 1021 cm^{-1}; ^{1}H NMR ([D$_6$]acetone): $\delta = 7.73$ (br, 1H), 3.80 (t, $J = 12.0$ Hz, 2H; CH$_2$), 3.49 (d, $J = 10.8$ Hz, 1H; CH$_2$), 3.32 (d, $J = 10.8$ Hz, 1H; CH$_2$), 1.66 (s, 3H; CH$_3$), 1.53 ppm (s, 3H; CH$_3$); ^{13}C NMR ([D$_6$]acetone): $\delta = 177.2$, 173.7, 172.6, 85.2, 63.3, 42.2, 40.8, 25.5, 23.4 ppm; MS: [M^++H]: 261; HRMS: [M^++H]: calcd for $C_9H_{13}N_2O_3S_2$: 261.0368; found: 261.0369.

***N*-Boc-amino-thiol–monothiazoline 15**: Boc$_2$O (713 mg, 3.27 mmol), Et$_3$N (759 μL, 5.45 mmol), and DMAP (30 mg, 5% w/w) were added to a CH$_2$Cl$_2$ (10 mL) solution of **13** (600 mg, 2.18 mmol) at 0°C. The resulting solution was stirred at room temperature for 1 h and washed with 5% aq. KHSO$_4$, saturated NaHCO$_3$, and brine after being diluted with EtOAc. The organic layer was then dried with MgSO$_4$, filtered, concentrated, and purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to give the desired *N*-Boc thiazolidinone (814 mg, quantitative yield). $[\alpha]_D^{25} = -77.0$ ($c = 1.00$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 2982$, 2934, 1774, 1734, 1372, 1284, 1257, 1155, 1125, 941 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 3.81$ (d, $J = 11.6$ Hz, 1H; CH$_2$), 3.80 (s, 3H; OCH$_3$), 3.53 (d, $J = 11.6$ Hz, 1H; CH$_2$), 3.26 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.07 (d, $J = 10.8$, CH$_2$), 1.94 (s, 3H; CH$_3$), 1.51 (s, 3H; CH$_3$), 1.50 ppm (s, 9H; *tert*-butyl); ^{13}C NMR (CDCl$_3$): $\delta = 173.9$, 172.7, 169.2, 148.2, 84.2, 84.1, 67.2, 52.6, 41.9, 37.0, 27.6, 23.0, 22.8 ppm; MS: [M^++H]: 375; HRMS: [M^++H]: calcd for $C_{15}H_{23}N_2O_5S_2$: 375.1048; found: 375.1032.

NaOMe (0.54 mmol, 1.0 M in MeOH) was added to a THF (3 mL) solution of *N*-Boc-thiazolidinone (168 mg, 0.45 mmol) at 0°C and the resulting mixture was stirred for an additional 30 min. The solution was acidified with 10% KHSO$_4$ to pH 5–6 after being diluted with EtOAc at 0°C. The aqueous layer was extracted with EtOAc (15 mL) three times. The combined organic extracts were dried with MgSO$_4$, filtered, concentrated, and purified by flash column chromatography on silica gel (hexane/EtOAc, 6:1) to give **15** (126 mg, 81%). $[\alpha]_D^{25} = -15.4$ ($c = 0.50$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 3392$, 2979, 2932, 1739, 1718, 1616, 1490, 1456, 1368, 1282, 1245, 1166, 1123, 1063, 1011 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 5.67$ (br, 1H; *NH*), 3.77 (m, 5H; OCH$_3$ and CH$_2$), 3.18 (m, 2H; CH$_2$), 1.61 (s, 3H; CH$_3$), 1.51 (s, 3H; CH$_3$), 1.44 ppm (s, 9H; *tert*-butyl); ^{13}C NMR (CDCl$_3$): $\delta = 173.0$, 153.8, 83.7, 59.0, 52.6, 41.7, 32.4, 24.7, 28.1, 23.3 ppm; MS: [M^++H]: 349; HRMS: [M^+]: calcd for $C_{14}H_{24}N_2O_4S_2$: 348.1177; found: 348.1194.

Thioester 16: Thioester **16** was obtained in 77% yield from **14** and **15** according to the general procedure A. $[\alpha]_D^{25} = -20$ ($c = 0.50$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 3379$, 3303, 2978, 2930, 1730, 1715, 1698, 1684, 1616, 1507, 1489, 1456, 1368, 1286, 1248, 1164, 1012 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 6.64$ (br, 1H; NH), 5.88 (br, 1H; NH), 3.85–3.62 (m, 8H; OCH$_3$ and CH$_2$), 3.43 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.20 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.19 (d, $J = 12.0$ Hz, 1H; CH$_2$), 1.81 (s, 3H; CH$_3$), 1.61 (s, 3H; CH$_3$), 1.59 (s, 3H; CH$_3$), 1.50 (s, 3H; CH$_3$), 1.44 ppm (s, 9H; *tert*-butyl); ^{13}C NMR (CDCl$_3$): $\delta = 202.8$, 179.9, 175.7, 173.6, 153.7, 90.7, 83.6, 79.6, 63.0, 58.7, 53.2, 52.8, 42.8, 42.0, 40.8, 35.9, 29.6, 28.3, 25.2, 24.8, 22.9 ppm; MS: [M^++H]: 591; HRMS: [M^++H]: calcd for $C_{23}H_{35}N_4O_6S_4$: 591.1439; found: 591.1423.

2-Oxothiazolidinylterthiazoline methyl ester 17: Methyl ester **17** was obtained in 93% yield from **16** according to the general procedure A. $[\alpha]_D^{25} = -248.4$ ($c = 0.95$ in CHCl$_3$). IR (neat): $\tilde{\nu} = 3294$, 2977, 2929, 2857, 1735, 1701, 1684, 1624, 1437, 1372, 1013 cm^{-1}; ^{1}H NMR (CDCl$_3$): $\delta = 5.76$ (br, 1H; NH), 3.84 (d, $J = 11.2$ Hz, 1H; CH$_2$), 3.80 (s, 3H; OCH$_3$), 3.78

(d, $J=12.0$ Hz, 1H; CH_2), 3.72 (d, $J=11.2$ Hz, 1H; CH_2), 3.70 (d, $J=10.8$ Hz, 1H; CH_2), 3.41 (d, $J=11.6$ Hz, 1H; CH_2), 3.38 (d, $J=11.6$ Hz, 1H; CH_2), 3.28 (d, $J=12.0$ Hz, 1H; CH_2), 3.10 (d, $J=10.8$ Hz, 1H; CH_2), 1.70 (s, 3H; CH_3), 1.64 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.54 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=177.9$, 177.3, 176.2, 173.7, 84.3, 84.0, 83.6, 62.9, 52.7, 44.1, 43.0, 41.1, 40.4, 26.0, 25.8, 25.5, 23.9 ppm; MS: $[M^++H]$: 473; HRMS: $[M^++H]$: calcd for $C_{18}H_{25}N_4O_3S_4$: 473.0809; found: 473.0812.

2-Oxothiazolidinylterthiazolinecarboxylic acid 18: Compound **18** was obtained in 84% yield from **17** according to the general procedure B. $[\alpha]_D^{25}=-210.3$ ($c=0.5$, acetone). IR (neat): $\tilde{\nu}=3203$, 2972, 2929, 2864, 1699, 1675, 1618, 1016 cm^{-1}; ^1H NMR ([D_6]acetone): $\delta=5.86$ (s, 1H; NH), 3.84 (d, $J=12.0$ Hz, 1H; CH_2), 3.77 (d, $J=12.0$ Hz, 1H; CH_2), 3.68 (d, $J=11.0$ Hz, 2H; CH_2), 3.39 (t, $J=12.0$ Hz, 2H; CH_2), 3.26 (d, $J=12.0$ Hz, 1H; CH_2), 3.21 (d, $J=12.0$ Hz, 1H; CH_2), 1.69 (s, 3H; CH_3), 1.63 (s, 3H; CH_3), 1.61 (s, 3H; CH_3), 1.56 ppm (s, 3H; CH_3); ^{13}C NMR ([D_6]acetone): $\delta=178.2$, 177.5, 174.2, 172.7, 85.2, 84.5, 84.4, 44.1, 43.2, 41.6, 41.1, 26.2, 25.69, 25.7, 23.8 ppm; MS: $[M^++2H]$: 460; HRMS: $[M^++2H]$: calcd for $C_{17}H_{24}N_4O_3S_4$: 460.0731; found: 460.0712.

***N*-Boc-amino-thiol–terthiazoline 19**: Compound **19** was obtained in 75% yield from **17** according to the procedure for the preparation of **15**. $[\alpha]_D^{25}=-121.2$ ($c=0.50$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3390$, 2978, 2932, 1739, 1720, 1614, 1490, 1456, 1368, 1281, 1245, 1166, 1125, 1064, 1012 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=5.66$ (br, 1H; NH), 3.79–3.76 (m, 5H; OCH_3 and CH_2), 3.72 (d, $J=10.8$ Hz, 1H; CH_2), 3.70 (d, $J=12.0$ Hz, 1H; CH_2), 3.36 (d, $J=11.6$ Hz, 1H; CH_2), 3.28 (d, $J=10.8$ Hz, 1H; CH_2), 3.18–3.10 (m, 2H; CH_2), 1.62 (s, 3H; CH_3), 1.61 (s, 3H; CH_3), 1.59 (s, 3H; CH_3), 1.54 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=178.1$, 177.5, 173.7, 153.9, 84.0, 83.6, 83.5, 80.1, 59.3, 52.8, 43.3, 43.0, 41.1, 28.3, 26.0, 25.4, 23.9 ppm; MS: $[M^++H]$: 547; HRMS: $[M^++H]$: calcd for $C_{22}H_{35}N_4O_4S_4$: 547.1541; found: 547.1438.

2-Oxothiazolidinylseptithiazoline methyl ester 20: Methyl ester **20** was obtained in 64% yield from **18** and **19** according to the general procedure A. $[\alpha]_D^{25}=-322.2$ ($c=0.50$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3294$, 2977, 2929, 2857, 1735, 1701, 1684, 1624, 1437, 1372, 1013 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=5.70$ (s, 1H; NH), 3.85 (d, $J=11.0$ Hz, 1H; CH_2), 3.78–3.68 (m, 6H; CH_2), 3.43–3.36 (m, 4H; CH_2), 3.28–3.22 (m, 4H; CH_2), 3.09 (d, $J=11.0$ Hz, 1H; CH_2), 1.69 (s, 3H; CH_3), 1.64 (s, 3H; CH_3), 1.63 (s, 3H; CH_3), 1.62 (s, 3H; CH_3), 1.59 (s, 3H; CH_3),1.56 (s, 6H; CH_3), 1.53 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=178.6$, 178.1, 178.0, 177.4, 175.9, 173.7, 173.4, 84.3, 84.0, 83.7 (2C), 83.6, 44.1, 43.1, 42.8, 42.7, 41.1, 40.3, 26.3, 26.2, 25.8, 25.6, 23.9 ppm; MS: $[M^++H]$: 869; HRMS: $[M^++H]$: calcd for $C_{34}H_{45}N_8O_3S_8$: 869.1380; found: 869.1377.

Quaterthiazoline methyl ester 21a: Methyl ester **21a** was obtained in 88% yield from **10b** and **15** according to the general procedure A. $[\alpha]_D^{25}=-388.2$ ($c=0.46$ in $CHCl_3$). IR (neat): $\tilde{\nu}=2977$, 2945, 2862, 1737, 1618, 1577, 1448, 1367, 1284, 1234, 1122, 1013, 958, 767 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=7.88$ (d, $J=6.8$ Hz, 2H; phenyl), 7.49–7.40 (m, 3H; phenyl), 3.92 (d, $J=12.0$ Hz, 1H; CH_2), 3.80 (s, 3H; OCH_3), 3.73–3.69 (m, 3H; CH_2), 3.46 (d, $J=11.2$ Hz, 1H; CH_2), 3.36 (d, $J=11.2$ Hz, 1H; CH_2), 3.26 (d, $J=11.2$ Hz, 1H; CH_2), 3.10 (d, $J=12.0$ Hz, 1H; CH_2), 1.74 (s, 3H; CH_3), 1.63 (s, 3H; CH_3), 1.62 (s, 3H; CH_3), 1.54 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=178.5$, 178.2 (2C), 173.7, 168.5, 132.8, 131.5, 128.5 (2C), 128.4 (2C), 84.0 (2C), 83.6 (2C), 52.8, 43.2, 43.0, 42.9, 41.0, 226.0, 25.8 (2C), 23.8 ppm; MS: $[M^+]$: 532; HRMS: $[M^++H]$: calcd for $C_{24}H_{29}N_4O_2S_4$: 533.1173; found: 533.1192; elemental analysis calcd (%) for $C_{24}H_{28}N_4O_2S_4$: C 54.11, H 5.30, N 10.52; found: C 53.89, H 5.34; 10.35.

Quaterthiazolinecarboxylic acid 21b: Carboxylic acid **21b** was obtained in 99% yield from **21a**. $[\alpha]_D^{25}=-376.2$ ($c=0.5$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3360$, 2978, 2930, 2863, 1733, 1719, 1616, 1575, 1447, 1371, 1254, 1177, 1016, 958, 767 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.87$ (d, $J=8.4$ Hz, 2H; phenyl), 7.49–7.40 (m, 3H; phenyl), 3.91 (d, $J=11.6$ Hz, 1H; CH_2), 3.69–3.66 (m, 3H; CH_2), 3.46 (d, $J=11.2$ Hz, 1H; CH_2), 3.28–3.21 (m, 3H; CH_2), 1.74 (s, 3H; CH_3), 1.63 (s, 6H; CH_3), 1.56 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=180.5$, 179.1, 178.9, 175.4, 168.7, 132.8, 131.6, 128.6, 128.5, 84.0, 83.8, 83.6, 83.5, 43.3, 43.0, 42.8, 40.7, 26.0, 25.8 (2C), 24.1 ppm; MS: $[M^+]$: 518; HRMS: $[M+1]^+$: calcd for $C_{23}H_{27}N_4O_2S_4$: 519.1017; found: 519.1003; elemental analysis calcd (%) for $C_{23}H_{26}N_4O_2S_4 \cdot 0.5H_2O$: C 52.43, H 5.22, N 10.97; found: C 52.37, H 5.15, N, 10.62.

Sexithiazoline methyl ester 22a: Methyl ester **22a** was obtained in 85% yield from **11b** and the thiol derived from **24** according to the general procedure A. $[\alpha]_D^{25}=-399.4$ ($c=0.5$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3406$, 2976, 2924, 2866, 1673, 1624, 1602, 1528, 1444, 1434, 1363, 1011 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.87$ (d, $J=7.2$ Hz, 2H; phenyl), 7.48–7.42 (m, 3H; phenyl), 3.92 (d, $J=11.2$ Hz, 1H; CH_2), 3.80 (s, 3H; OCH_3), 3.72–3.68 (m, 5H; CH_2), 3.46 (d, $J=11.2$ Hz, 1H; CH_2), 3.29–3.24 (m, 4H; CH_2), 3.09 (d, $J=11.2$ Hz, 1H; CH_2), 1.74 (s, 3H; CH_3), 1.64 (s, 3H; CH_3), 1.63 (s, 3H; CH_3), 1.62 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.53 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=178.5$, 178.4, 178.3, 178.2 (2C), 173.8, 168.5, 132.8, 131.6, 128.6, 128.5, 84.0, 83.7, 83.6 (2C), 52.8, 43.3, 43.1, 43.0, 42.9, 41.1, 26.0, 25.9, 25.8 (2C), 23.9 ppm; MS: $[M^++H]$: 732; elemental analysis calcd (%) for $C_{32}H_{38}N_6O_2S_6 \cdot H_2O$: C 51.31, H 5.38, N 11.22; found: C 51.21, H 5.21, N 10.88.

Sexithiazolinecarboxylic acid 22b: Carboxylic acid **22b** was obtained in 94% yield from **22a** according to the general procedure B. $[\alpha]_D^{25}=-419.6$ ($c=0.24$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3200$, 2970, 2926, 2849, 1731, 1624, 1602, 1452, 1432, 1362, 1253, 1181, 1011, 957 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.87$ (d, $J=7.2$ Hz, 2H; phenyl), 7.49–7.40 (m, 3H; phenyl), 3.92 (d, $J=10.8$ Hz, 1H; CH_2), 3.73–3.65 (m, 5H; CH_2), 3.46 (d, $J=11.2$ Hz, 1H; CH_2), 3.29–3.21 (m, 5H; CH_2), 1.74 (s, 3H; CH_3), 1.63 (s, 6H; CH_3), 1.62 (s, 3H; CH_3), 1.61 (s, 3H; CH_3), 1.55 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=180.4$, 179.0, 178.7, 178.6, 178.5, 175.3, 168.7, 132.8, 131.6, 128.6, 128.5, 84.0, 83.8, 83.6 (2C), 83.5, 43.3, 43.1, 43.0, 42.9, 42.8, 40.7, 26.0, 25.9 (2C), 25.8, 24.1 ppm; MS: $[M^+-H]$: 715; HRMS: $[M^+-H]$: calcd for $C_{31}H_{35}N_6O_2S_6$: 715.1146; found: 715.1123; elemental analysis calcd (%) for $C_{31}H_{36}N_6O_2S_6 \cdot 0.75H_2O$: C 51.04, H 5.18, N 11.52; found: C 51.23, H 5.21, N 11.88.

Octithiazoline methyl ester 23a: Methyl ester **23a** was obtained in 83% yield from **21b** and **19** according to the general procedure A. $[\alpha]_D^{25}=-402.4$ ($c=0.25$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3405$, 2978, 2924, 2868, 1674, 1625, 1604, 1528, 1445, 1435, 1363, 1012 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.87$ (d, $J=7.2$ Hz, 2H; phenyl), 7.49–7.42 (m, 3H; phenyl), 3.92 (d, $J=11.2$ Hz, 1H; CH_2), 3.80 (s, 3H; OCH_3), 3.72–3.68 (m, 7H; CH_2), 3.46 (d, $J=12.0$ Hz, 1H; CH_2), 3.28–3.24 (m, 6H; CH_2), 3.09 (d, $J=12.0$ Hz, 1H; CH_2), 1.74 (s, 3H; CH_3), 1.63 (S, 3H; CH_3), 1.62 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.57 (s, 9H; CH_3), 1.53 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=178.5$, 178.4, 178.3, 178.2, 173.8, 168.5, 132.8, 131.6, 128.6, 128.5, 84.0, 83.7, 83.6, 52.8, 43.3, 43.1, 43.0, 42.9, 41.1, 26.0, 25.9, 25.8, 23.9 ppm; MS: $[M^++H]$: 929; elemental analysis calcd (%) for $C_{40}H_{48}N_8O_2S_8$: C 51.69, H 5.21, N 12.06; found: C 51.45, H 5.31, N 11.99.

Octithiazolinecarboxylic acid 23b: Carboxylic acid **23b** was obtained in 95% yield from **23a** according to the general procedure B. $[\alpha]_D^{25}=-422.1$ ($c=0.15$ in $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta=7.88$ (d, $J=6.4$ Hz, 1H; phenyl), 7.49–7.40 (m, 3H; phenyl), 3.92 (d, $J=12.0$ Hz, 1H; CH_2), 3.74–3.64 (m, 7H; CH_2), 3.46 (d, $J=12.0$ Hz, 1H; CH_2), 3.29–3.20 (m, 7H; CH_2), 1.74 (s, 3H; CH_3), 1.66 (s, 3H; CH_3), 1.64 (s, 6H; CH_3), 1.63 (s, 3H; CH_3), 1.62 (s, 3H; CH_3), 1.61 (s, 3H; CH_3), 1.55 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=180.4$, 179.0, 178.7, 178.6, 178.5, 175.3, 168.7, 132.8, 131.6, 128.6, 128.5, 84.0, 83.8, 83.6 (2C), 83.5, 43.3, 43.1, 43.0, 42.9, 42.8, 40.7, 26.0, 25.9 (2C), 25.8, 24.1 ppm; MS: $[M^++H]$: 915; elemental analysis calcd (%) for $C_{39}H_{46}N_8O_2S_8 \cdot 0.75H_2O$: C 50.43, H 5.15, N 12.06; found: C 50.63, H 5.10, N 12.31.

2-Oxothiazolidinylbithiazoline 24: Compound **24** was obtained in 72% yield over two steps from **14** and **8** according to the general procedure A. $[\alpha]_D^{25}=-203.3$ ($c=0.50$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3340$, 2983, 2940, 1734, 1698, 1681, 1656, 1618, 1558, 1541, 1507, 1284, 1223, 1125, 1017, 772 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=5.98$ (br, 1H; NH), 3.85 (d, $J=12.0$ Hz, 1H; CH_2), 3.81 (s, 3H; OCH_3), 3.77 (d, $J=11.2$ Hz, 1H; CH_2), 3.71 (d, $J=11.2$ Hz, 1H; CH_2), 3.43 (d, $J=12.0$ Hz, 1H; CH_2), 3.38 (d, $J=11.2$ Hz, 1H; CH_2), 3.11 (d, $J=12.0$ Hz, 1H; CH_2), 1.69 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.54 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=177.4$, 176.2, 174.2, 173.6, 84.2, 83.9, 63.0, 52.8, 43.9, 41.1, 40.4, 25.7, 25.6, 23.1 ppm; MS: $[M^++H]$: 374; HRMS: $[M^++H]$: calcd for $C_{14}H_{20}N_3O_3S_3$: 374.0667; found: 374.0669.

General procedure for the preparation of difunctional thiol–carboxylic acids 25, 27, and 32: A 10 % aq. NaOH (2.2 equiv) solution was added to a THF/MeOH (8:1, v/v) solution of *N*-Boc-thiazolidinone at 0 °C. The solution was then stirred at room temperature for 15 min and acidified with 1 N $KHSO_4$ to pH 4–5 after being diluted with EtOAc. The aqueous phase was extracted with EtOAc (10 mL) three times and the combined organic extracts were dried with $MgSO_4$, filtered, concentrated, and purified by column chromatography on acidic silica gel (hexane/EtOAc, 1:2) to afford the desired thiol–carboxylic acid.

Thiol–septithiazolinecarboxylic acid 25: Compound **25** was obtained in 81 % yield from **20**. $[\alpha]_D^{25}=-283.4$ ($c=0.40$ in $CHCl_3$). IR (neat): $\tilde{\nu}=$ 3335, 2980, 2932, 2860, 1717, 1164, 1011 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.77$ (d, $J=11.0$ Hz, 1H; CH_2), 3.70–3.63 (m, 6H; CH_2), 3.53 (d, $J=12.0$ Hz, 1H; CH_2), 3.45 (d, $J=12.0$ Hz, 1H; CH_2), 3.29–3.20 (m, 6H; CH_2), 3.08 (d, $J=12.0$ Hz, 1H; CH_2), 1.93 (s, 3H; CH_3), 1.69 (s, 3H; CH_3),1.64 (s, 3H; CH_3), 1.60 (s, 9H; CH_3), 1.54 (s, 3H; CH_3), 1.53 (s, 3H; CH_3), 1.51 ppm (s, 9H; *tert*-butyl); ^{13}C NMR ($CDCl_3$): $\delta=180.3$, 179.4, 178.5, 177.8, 175.1, 173.6, 169.7, 148.6, 84.4, 83.9, 83.8, 83.7, 83.5, 83.4, 67.4, 43.7, 43.1, 42.7, 42.6, 40.7, 37.1, 29.7, 28.0, 26.2, 26.1, 25.6, 25.1, 24.1, 23.4 ppm; MS: $[M^++H]$: 929; HRMS: $[M^++H]$: calcd for $C_{37}H_{53}N_8O_4S_8$: 929.1955; found: 929.1964.

Thiol–terthiazolinecarboxylic acid 27: Compound **27** was obtained in 72 % yield from **17**. $[\alpha]_D^{25}=-202.2$ ($c=0.50$ in $CHCl_3$). IR (neat): $\tilde{\nu}=$ 3336, 2981, 2932, 2861, 1717, 1163, 1011 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=3.76$ (d, $J=12.0$ Hz, 1H; CH_2), 3.69 (d, $J=12.0$ Hz, 1H; CH_2), 3.67 (d, $J=12.0$ Hz, 1H; CH_2), 3.52 (d, $J=12.0$ Hz, 1H; CH_2), 3.44 (d, $J=11.6$ Hz, 1H; CH_2), 3.26 (d, $J=12.0$ Hz, 1H; CH_2), 3.21 (d, $J=12.0$ Hz, 1H; CH_2), 3.09 (d, J = 11.6 Hz, 1H; CH_2), 1.94 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.56 (s, 6H; CH_3), 1.51 ppm (s, 9H; *tert*-butyl); ^{13}C NMR ($CDCl_3$): $\delta=179.7$, 178.3, 175.8, 173.7, 169.7, 148.6, 84.3, 83.8, 83.7, 83.3, 67.3, 43.6, 42.9, 40.8, 37.0, 27.9, 25.7, 24.9, 23.8, 23.3 ppm; MS: $[M^+]$: 532; HRMS: $[M^+]$: calcd for $C_{21}H_{32}N_4O_4S_4$: 532.1306; found: 532.1322.

Thiol–bithiazolinecarboxylic acid (32): Compound **32** was obtained in 75 % yield from **24**. $[\alpha]_D^{25}=-131.9$ ($c=0.50$ in $CHCl_3$). IR (neat): $\tilde{\nu}=$ 3337, 2982, 2932, 2862, 1719, 1163, 1011 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=5.55$ (br, 1H; NH), 3.74 (d, $J=10.8$ Hz, 1H; CH_2), 3.69 (d, $J=12.0$ Hz, 1H; CH_2), 3.34 (d, $J=12.0$ Hz, 1H; CH_2), 3.22 (d, $J=11.6$ Hz, 1H; CH_2), 3.21–3.10 (m, 2H; CH_2), 1.62 (s, 3H; CH_3), 1.61 (s, 3H; CH_3), 1.55 (s, 3H; CH_3), 1.51 ppm (s, 9H; *tert*-butyl); ^{13}C NMR ($CDCl_3$): $\delta=179.3$, 176.3, 83.7, 59.3, 43.2, 40.9, 29.8, 28.1, 25.6, 23.9 ppm; MS: $[M^++H]$: 434; HRMS: $[M^++H]$: calcd for $C_{17}H_{28}N_3O_4S_3$: 434.1242; found: 434.1245.

General procedure for the synthesis of cyclo-oligothiazolines: BOP-Cl (2.0 equiv) and Et_3N (4.0 equiv) were added to a solution of thiol–carboxylic acid in CH_2Cl_2 (4 mmolL^{-1}) and the mixture was stirred at room temperature for 18–20 h. The solution was then washed with 5 % aq. $NaHCO_3$ and brine. The organic layer was separated and dried with $MgSO_4$, filtered, concentrated, and purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1) to give a mixture of products generated by cyclo-oligomerization (**27** provided a mixture of dimer and trimer, and **32** provided a mixture of trimer and tetramer, respectively). The mixture was then treated with neat TFA at room temperature for 20 min and evaporated to dryness. The residue was dissolved in benzene and refluxed for 4 h, then evaporated to leave the crude products. The crude products were purified by PTLC (hexane/EtOAc, 1:3) to give pure cyclo-oligothiazolines (**27** provided **30** and **31**, and **32** provided **33** and **31**, respectively).

Cyclic octithiazoline (30): $[\alpha]_D^{25}=-220$ ($c=0.50$ in $CHCl_3$). IR (neat): $\tilde{\nu}=$ 2974, 2927, 2861, 1621, 1432, 1365, 1268, 1178, 1009, 908 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.70$ (d, $J=10.8$ Hz, 8H; CH_2), 3.19 (d, $J=10.8$ Hz, 8H; CH_2), 1.63 ppm (s, 24H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=175.7$, 83.1, 43.6, 25.2 ppm; MS: $[M^++H]$: 793; HRMS: $[M^++H]$: calcd for $C_{32}H_{41}N_8S_8$: 793.1220; found: 793.1205.

Cyclic dodecithiazoline (31): $[\alpha]_D^{25}=-283$ ($c=0.22$ in $CHCl_3$). IR (neat): $\tilde{\nu}=2975$, 2927, 2860, 1624, 1432, 1366, 1247, 1178, 1010, 907 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.76$ (d, $J=10.8$ Hz, 12H; CH_2), 3.21 (d, $J=10.8$ Hz, 12H; CH_2), 1.76 ppm (s, 36H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=176.6$, 83.4, 43.0, 25.9 ppm; MS: $[M^+]$: 1188; HRMS: $[M^+]$: calcd for $C_{48}H_{60}N_{12}S_{12}$: 1188.1712; found: 1188.1730.

Cyclic novithiazoline (33): $[\alpha]_D^{25}=-223$ ($c=0.50$ in $CHCl_3$). IR (neat): $\tilde{\nu}=$ 2975, 2927, 2861, 1622, 1431, 1366, 1264, 1179, 1009, 907 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.75$ (d, $J=11.2$ Hz, 9H; CH_2), 3.22 (d, $J=11.2$ Hz, 9H; CH_2), 1.62 ppm (s, 27H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=175.7$, 83.5, 43.3, 25.7 ppm; MS: $[M^++H]$: 892; HRMS: $[M^++H]$: calcd for $C_{36}H_{46}N_9S_9$: 892.1362; found: 892.1318.

Monothiazoline methyl ester (6b): MeI (85.0 µL, 1.36 mmol) and K_2CO_3 (312 mg, 2.26 mmol) were added to a DMF (5 mL) solution of **6a** (100 mg, 0.45 mmol) at 0 °C and the resulting mixture was stirred for 1 h. The reaction mixture was washed with H_2O (15 mL) four times after being diluted with EtOAc. The combined organic extracts were dried with $MgSO_4$, filtered, concentrated, and purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to give **6b** as a colorless oil (108 mg, quantitative yield). $[\alpha]_D^{25}=-39.6$ ($c=0.5$ in $CHCl_3$). IR (neat): $\tilde{\nu}=2992$, 2929, 2845, 1735, 1602, 1447, 1233, 1119, 956 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.86$ (d, $J=7.6$ Hz, 2H; phenyl), 7.48–7.39 (m, 3H; phenyl), 3.91 (d, $J=12.0$ Hz, 1H; CH_2), 3.82 (s, 3H; OCH_3), 3.30 (d, $J=10.8$ Hz, 1H; CH_2), 1.66 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=173.7$, 168.2, 132.7, 131.4, 128.4, 128.3, 84.4, 52.8, 41.5, 23.8 ppm; MS: $[M^++H]$: 236; HRMS: $[M^++H]$: calcd for $C_{12}H_{14}NO_2S$: 236.0745; found: 236.0734.

General procedure for the preparation of oligothiazoline carboxamides: procedure C: $MeNH_2$ (20 equiv, 2.0 M in THF) was added to a THF solution (THF/MeOH 2:1 was used in the case of hexi- and octithiazolines) of oligothiazoline methyl ester. The resulting solution was stirred at room temperature for 20–36 h. After removal of the solvent, the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1) to give the corresponding oligothiazoline carboxamide.

Monothiazolinecarboxamide 6c: Compound **6c** was obtained in 100 % yield from **6b**. $[\alpha]_D^{25}=-162.2$ ($c=0.44$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3407$, 3354, 2977, 2928, 2864, 1667, 1524, 1447, 1256, 959, 768 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.86$ (d, $J=8.4$ Hz, 2H; phenyl), 7.53–7.42 (m, 3H; phenyl), 6.93 (br, 1H; *NH*), 3.77 (d, $J=12.0$ Hz, 1H; CH_2), 3.40 (d, $J=12.0$ Hz, 1H; CH_2), 2.87 (d, $J=4.8$ Hz, 3H; $NHCH_3$), 1.58 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta=175.3$, 168.8, 132.7, 131.8, 128.5, 128.3, 84.9, 41.5, 26.1, 24.7 ppm; MS: $[M^++H]$: 235; HRMS: $[M^++H]$: calcd For $C_{12}H_{15}N_2OS$: 235.0905; found: 235.0904.

Bithiazolinecarboxamide 10c: Compound **10c** was obtained in quantitative yield from **10a**. $[\alpha]_D^{25}=-221.8$ ($c=0.5$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3410$, 3347, 2975, 2928, 2865, 1670, 1615, 1525, 1447, 1252, 1175, 1016, 957 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.87$ (d, $J=7.6$ Hz, 2H; phenyl), 7.50–7.41 (m, 3H; phenyl), 6.76 (br, 1H; *NH*), 3.88 (d, $J=10.8$ Hz, 1H; CH_2), 3.59 (d, $J=11.6$ Hz, 1H; CH_2), 3.42 (d, $J=12.0$ Hz, 1H; CH_2), 3.23 (d, $J=12.0$ Hz, 1H; CH_2), 2.88 (s, 1.5H; $NHCH_3$), 2.87 (s, 1.5H; $NHCH_3$), 1.72 (s, 3H; CH_3), 1.45 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=178.2$, 175.3, 168.6, 132.7, 131.7, 128.5 (2C), 84.4, 83.9, 43.2, 41.3, 26.1, 25.9, 24.6 ppm; MS: $[M^++H]$: 334; HRMS: $[M^++H]$: calcd for $C_{16}H_{20}N_3OS_2$: 334.1048; found: 334.1046.

Terthiazolinecarboxamide 11c: Compound **11c** was obtained in quantitative yield from **11a**. $[\alpha]_D^{25}=-382.4$ ($c=0.22$ in $CHCl_3$). IR (neat): $\tilde{\nu}=$ 3409, 3369, 2975, 2928, 2860, 1670, 1654, 1617, 1540, 1522, 1508, 1447, 1363, 1254, 1175, 1013, 958, 939, 769 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.87$ (d, $J=8.0$ Hz, 2H; phenyl), 7.48–7.41 (m, 3H; phenyl), 6.55 (br, 1H; NH), 3.91 (d, $J=11.2$ Hz, 1H; CH_2), 3.68 (d, $J=11.2$ Hz, 1H; CH_2), 3.59 (d, $J=10.8$ Hz, 1H; CH_2), 3.46 (d, $J=10.8$ Hz, 1H; CH_2), 3.23 (d, $J=11.6$ Hz, 1H; CH_2), 3.22 (d, $J=11.2$ Hz, 1H; CH_2), 2.86 (s, 1.5H; $NHCH_3$), 2.85 (s, 1.5H; $NHCH_3$), 1.74 (s, 3H; CH_3), 1.62 (s, 3H; CH_3), 1.49 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta=178.7$, 178.0, 175.2, 168.6, 132.8, 131.6, 128.6, 128.5, 84.5, 84.0, 83.5, 43.2, 43.0, 41.2, 26.1, 25.9 (2C), 24.7 ppm; MS: $[M^++H]$: 433; HRMS: $[M^++H]$: calcd for $C_{20}H_{25}N_4OS_3$: 433.1190; found: 433.1199; elemental analysis calcd (%) for $C_{20}H_{24}N_4OS_3 \cdot 0.25H_2O$: C 54.98, H 5.65, N 12.82; found: C 55.06, H 5.77, N, 12.50.

Quaterthiazolinecarboxamide 21c: Compound **21c** was obtained in quantitative yield from **21a** according to the general procedure C. $[\alpha]_D^{25}=-364.2$ ($c=0.48$ in $CHCl_3$). IR (neat): $\tilde{\nu}=3410$, 3369, 2978, 2930, 2861, 1669, 1654, 1617, 1541, 1523, 1510, 1447, 1362, 1254, 1174, 1013, 959, 938, 769 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.88$ (d, $J=6.8$ Hz, 2H; phenyl), 7.49–7.42 (m, 3H; phenyl), 6.73 (br, 1H; *NH*), 3.91 (d, $J=12.0$ Hz, 1H; CH_2), 3.71 (d, $J=12.0$ Hz, 1H; $\mathrm{CH_2}$), 3.67 (d, $J=11.6$ Hz, 1H; $\mathrm{CH_2}$), 3.57 (d, $J=12.0$ Hz, 1H; $\mathrm{CH_2}$), 3.46 (d, $J=12.0$ Hz, 1H; $\mathrm{CH_2}$), 3.28–3.21 (m, 3H; $\mathrm{CH_2}$), 2.86 (s, 1.5H; $\mathrm{NHCH_3}$), 2.85 (s, 1.5H; $\mathrm{NHCH_3}$), 1.74 (s, 3H; $\mathrm{CH_3}$), 1.63 (s, 3H; $\mathrm{CH_3}$), 1.57 (s, 3H; $\mathrm{CH_3}$), 1.45 ppm (s, 3H; $\mathrm{CH_3}$); ^{13}C NMR ($\mathrm{CDCl_3}$): $\delta=178.6$, 178.1, 175.2, 168.6, 132.8, 131.6, 128.6, 128.5, 84.5, 84.0, 83.6 (2C), 43.3, 43.1, 42.9, 41.2, 26.1, 25.9 (2C), 25.8, 24.6 ppm; MS: [M^+]: 531; HRMS: [M^++H]: calcd for $\mathrm{C_{24}H_{30}N_5OS_4}$: 532.1333; found: 532.1357; elemental analysis calcd (%) for $\mathrm{C_{24}H_{29}N_5OS_4{\cdot}0.75H_2O}$: C 51.91, H 5.21, N 10.52; found: C 52.43, H 5.22, N 10.27.

Hexithiazolinecarboxamide 22c: Compound **22c** was obtained in quantitative yield from **22a** according to the general procedure C. $[\alpha]_D^{25}=-370.0$ ($c=0.28$ in $\mathrm{CHCl_3}$). IR (neat): $\tilde{\nu}=3406$, 2976, 2924, 2866, 1673, 1624, 1602, 1528, 1444, 1434, 1363, 1011 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$): $\delta=7.87$ (d, $J=7.2$ Hz, 2H; phenyl), 7.49–7.40 (m, 3H; phenyl), 6.72 (br, 1H; *NH*), 3.92 (d, $J=12.0$ Hz, 1H; $\mathrm{CH_2}$), 3.73–3.62 (m, 5H; $\mathrm{CH_2}$), 3.57 (d, $J=11.6$ Hz, 1H; $\mathrm{CH_2}$), 3.46 (d, $J=11.2$ Hz, 1H; $\mathrm{CH_2}$), 3.29–3.20 (m, 4H; $\mathrm{CH_2}$), 2.86 (s, 1.5H; $\mathrm{NHCH_3}$), 2.85 (s, 1.5H; $\mathrm{NHCH_3}$), 1.74 (s, 3H; $\mathrm{CH_3}$), 1.64 (s, 3H; $\mathrm{CH_3}$), 1.63 (s, 3H; $\mathrm{CH_3}$), 1.62 (s, 3H; $\mathrm{CH_3}$), 1.61 (s, 3H; $\mathrm{CH_3}$), 1.45 ppm (s, 3H; $\mathrm{CH_3}$); ^{13}C NMR ($\mathrm{CDCl_3}$): $\delta=178.6$, 178.5 (2C), 178.1, 175.2, 168.6, 132.9, 131.6, 128.6, 128.5, 84.5, 84.0, 83.7, 83.5, 43.3, 43.1, 43.0 (2C), 42.9, 41.2, 26.1, 25.9 (2C), 24.9, 24.6 ppm; MS: [M^+]: 729; HRMS: [M^++H]: calcd for $\mathrm{C_{32}H_{40}N_7OS_6}$: 730.1618; found: 730.1647; elemental analysis calcd (%) for $\mathrm{C_{32}H_{39}N_7OS_6}$: C 52.57, H 5.51, N 13.41; found: C 52.73, H 5.64, N 13.44.

Octithiazolinecarboxamide 23c: Compound **23c** was obtained in quantitative yield from **23a** according to the general procedure C. $[\alpha]_D^{25}=-390.2$ ($c=0.20$ in $\mathrm{CHCl_3}$). IR (neat): $\tilde{\nu}=3408$, 2976, 2925, 2866, 1673, 1624, 1602, 1527, 1445, 1434, 1364, 1012 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$): $\delta=7.87$ (d, $J=7.2$ Hz, 2H; phenyl), 7.49–7.40 (m, 3H; phenyl), 6.58 (br, 1H; NH), 3.92 (d, $J=12.0$ Hz, 1H; $\mathrm{CH_2}$), 3.73–3.65 (m, 7H; $\mathrm{CH_2}$), 3.57 (d, $J=11.6$ Hz, 1H; $\mathrm{CH_2}$), 3.46 (d, $J=11.2$ Hz, 1H; $\mathrm{CH_2}$), 3.29–3.20 (m, 6H; $\mathrm{CH_2}$), 2.86 (s, 1.5H; $\mathrm{NHCH_3}$), 2.85 (s, 1.5H; $\mathrm{NHCH_3}$), 1.74 (s, 3H; $\mathrm{CH_3}$), 1.64 (s, 6H; $\mathrm{CH_3}$), 1.62 (s, 3H; $\mathrm{CH_3}$), 1.61 (s, 9H; $\mathrm{CH_3}$), 1.45 ppm (s, 3H; $\mathrm{CH_3}$); ^{13}C NMR ($\mathrm{CDCl_3}$): $\delta=178.6$, 178.5 (2C), 178.1, 175.2, 168.6, 132.9, 131.6, 128.6, 128.5, 84.5, 84.0, 83.7, 83.5, 43.3, 43.1, 43.0 (2C), 42.9, 41.2, 26.1, 25.9 (2C), 24.9, 24.6 ppm; MS: [M^++H]: 928; elemental analysis calcd (%) for $\mathrm{C_{40}H_{49}N_9OS_8{\cdot}0.5H_2O}$: C 51.25, H 5.38, N 13.45; found: C 51.47, H 5.48, N 13.33.

Binding studies of 30 by NMR titration using 30 and (*R*)-mandelic acid: A $\mathrm{CDCl_3}$ solutions of **30** (1.5 mM, 0.50 mL) and (*R*)-mandelic acid (18.8 mM, 0.7 mL) were prepared. After recording the NMR spectrum of free **30**, the (*R*)-mandelic acid solution was added to the solution of **30** in portions (10, 10, 10, 10, 20, 20, 20, 20, 40, 40, 40, 80, 80, 80 μL, 10 μL corresponds to 0.25 equiv) and after each addition the NMR spectrum was recorded at room temperature after 30 min of standing at room temperature. All the titrations were duplicated. A plot of the difference in chemical shifts of the thiazoline CH protons versus the ratio of mandelic acid to **30** was curved.

Cytotoxicity: The in vitro cytotoxicity against three cancer cell lines, PC-3, HCT-116, and HPAC, was evaluated by studying the inhibition of cell growth rate using the WST-1 assay protocol. A human pancreatic ductal carcinoma cell line HPAC was obtained from the American Type Culture Collection (Manassas, VA). Human colorectal adenocarcinoma cell line HCT-116 and human prostate adenocarcinoma PC-3 were obtained from Dainippon Sumitomo Pharma Co., Ltd. (Osaka). Cell lines were cultured in a 1:1 mixture of Dulbecco's modified Eagle's medium and Ham's F-12 medium (SIGMA) supplemented with 10% fetal bovine serum (ICN Biomedicals) in a humidified atmosphere of 95% $\mathrm{O_2}$ and 5% $\mathrm{CO_2}$ at 37°C. Cells were seeded at a concentration of 2×10^3 cells per well in the culture medium in 96-well microtiter plates. After incubation for 24 h, treatment of the cells with the test compounds was started. After 72 h, 10 μL WST-1 reagent (Dojindo Laboratories) was added to each well and the plate was incubated at 37°C for 3 h. Absorbance of the culture supernatant at 450 nm was measured using a microplate reader (Molecular Devices). The $\mathrm{IC_{50}}$ values were calculated from the concentration-response curves as the concentration of the test compounds eliciting a decrease in the measured absorbance equivalent to 50% of the vehicle group.

Acknowledgements

We thank Drs. Ryoichi Ando and Yusaku Amno of Mitsubishi Pharma Corporation for cytotoxicity measurements. We thank Dr. Yutaka Matsuo, a group leader of the Nakamura Functional Carbon Cluster Project, ERATO, Japan Science and Technology Agency, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, for the X-ray analysis and the Ministry of Education, Culture, Sports, Science, and Technology, Japan for financial support.

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Received: October 10, 2006