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Macrocycle Synthesis

# Molecular Design and Synthesis of a Planar Telomestatin Analogue

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**Abstract:** Hypothetical macrocycles containing eight fused oxazole units would be logical planar analogues of telomestatin, but DFT calculations suggest the presence of excessive macrocyclic ring strain in such molecules that could complicate their synthesis and/or stability. We therefore designed a planar, $C_4$-symmetric macrocycle composed of four oxazole and four thiazole units containing little or no ring strain. Cyclo(-ox-thia)$_4$ (**1**) was successfully prepared from serine and cysteine in 19 steps to furnish the first example of an octa-azole macrocycle containing eight fused azole units.

## Introduction

Telomestatin is a natural product isolated from *Streptomyces anulatus* 3533-SV4 containing a fascinating macrocyclic scaffold composed of seven fused oxazoles and a thiazoline unit (Figure 1).[1] The evolutionary pressures associated with its biosynthetic production remain unclear,[2] but telomestatin has molecular dimensions similar to the G-tetrad units of G-quadruplex structures (Figure 1).[3] Accordingly, telomestatin can bind various G-quadruplexes with good affinity ($K_d$ = 10–100 nM)[4] and it exhibits lower affinity for duplex DNA ($K_d \approx 1$ μM).[5] Telomestatin is an inhibitor of telomerase,[6] but it also inhibits the PCR polymerases used for assaying telomerase inhibition.[7] Telomestatin induces the shortening of telomere in treated cells more rapidly than what is expected for a single mechanism involving telomerase inhibition,[8] and it induces senescence and apoptosis in a variety of tumor cell types while exhibiting less toxicity towards normal progenitor cells.[9] The progression of telomestatin as a drug candidate has been hindered by its limited solubility and chemical stability properties that restrict its synthetic scalability and handling.[10]

Driven by potential biological applications, the total synthesis of telomestatin,[10a] its enantiomer,[10c] and a variety of related analogues have been reported.[11] Based upon a recent high-resolution solution structure of a telomestatin analogue bound to a human telomeric G-quadruplex,[12] the relative planarity of such macrocycles is important for mediating stacking interactions with the planar array of guanine residues of the terminal G-tetrads of G-quadruplex structures. Telomestatin itself is not fully planar due to the presence of a thiazoline unit (Figure 2, a,b). To facilitate stacking interactions with G-tetrads, a fully planar telomestatin analogue is therefore a high-value synthetic target. The synthetic pathways towards such molecules, however, are highly challenging,[13,14] and a fully planar telomestatin analogue has not yet been reported. One conceptually simple approach would be the replacement of the thiazoline unit in telomestatin with an oxazole unit. Indeed, the synthesis of macrocyclic octa-oxazoles containing eight oxazole units has been proposed for over a decade,[14] but no such examples have been confirmed to exist. Herein we report that macrocyclic ring strain disfavors the formation of macrocyclic octa-oxazoles. By replacing four oxazoles with thiazole units, ring strain can be minimized, thereby facilitating the synthesis of planar macrocyclic octa-azoles such as cyclo(-ox-thia)$_4$ (**1**; Figure 1). This compound represents, to the best of our knowl-

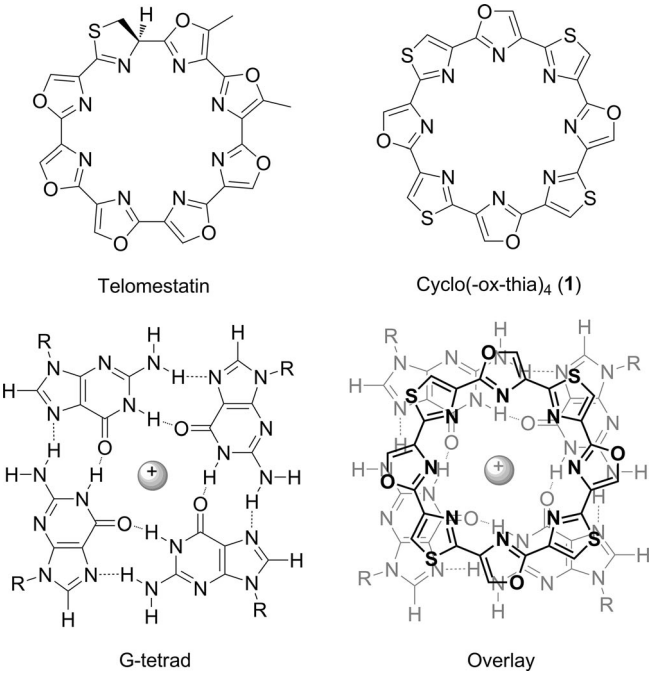


Figure 1. Structures of telomestatin, the planar telomestatin analogue cyclo(-ox-thia)$_4$ (**1**), a G-tetrad, and the overlay of cyclo(-ox-thia)$_4$ and a G-tetrad.

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edge, the first confirmed example of a macrocycle containing eight fused azole units.

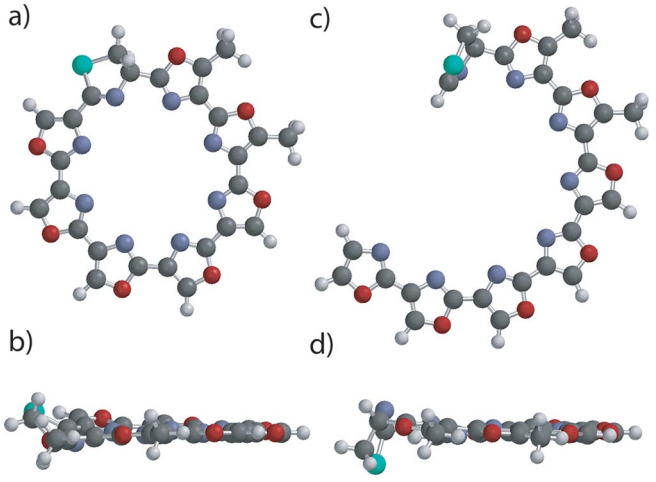



Figure 2. a) Top and b) side views of the DFT-optimized geometry (SVWN/DN**) of telomestatin. c) Top and d) side views of the DFT-optimized geometry (SVWN/DN**) of a hypothetical, linearized telomestatin analogue.[15]

## Results and Discussion

DFT calculations revealed the presence of macrocyclic ring strain in the natural product telomestatin and related macrocycles. Qualitative assessments of the ring strain were conducted by taking a DFT-optimized structure of each macrocycle and "cutting" it in silico across a single σ bond by the addition of $H_2$. The conformation of the linear analogue was then calculated by using the geometry of the optimized macrocycle as a starting point.[15] By comparing the relative geometries of the optimized linear and circular forms, the ring strain present in the parent macrocycle can be assessed. Consistent with a high degree of ring strain, the optimized geometry of linearized telomestatin is splayed open, with the ends of the molecule approximately 10 Å apart (Figure 2, c, d). Similar results were also obtained for the hypothetical octa-oxazole cyclo(-oxa)$_8$, with the ends of the linearized molecule approximately 11 Å apart (see Figure S1 in the Supporting Information). We reasoned that this type of ring strain originates from the relationship between the number of units in the macrocycle and the preferred internal bond angles ($\phi$) of each 2,4-substituted oxazole unit (Figure 3). According to DFT calculations and crystallographic data,[16] 2,4-disubstituted oxazoles prefer an angle $\phi$ of 35°. The same approximate angle was observed between the three terminal oxazole units of the linearized telomestatin analogue (Figure 2, c). In contrast, in a hypothetical macrocycle containing eight 2,4-fused azole units, the angle $\phi$ is constrained to be (360°/8) = 45°. The difference between the preferred $\phi$ of 2,4-disubstituted oxazoles (35°) and the $\phi$ required by the macrocycle (45°) multiplied over eight units explains the presence of excessive macrocyclic ring strain in the hypothetical octa-oxazole cyclo(-oxa)$_8$ (see Figure S1). These results may explain why this target has been pursued for over 10 years with no apparent synthetic success.[14] The single thiazoline unit present in telomestatin will relieve some of this macrocyclic ring strain, perhaps explaining the feasibility of its synthesis.[10a]

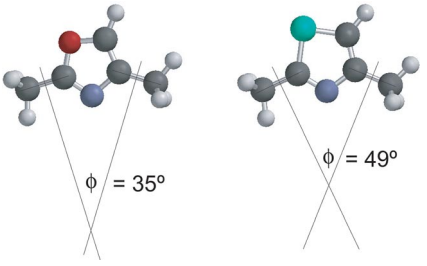



Figure 3. Internal angles ($\phi$) defined by the two exocyclic carbon–carbon bonds of 2,4-dimethyloxazole and 2,4-dimethylthiazole according to DFT-optimized (SVWN/DN**) geometries. These same angles were observed in the crystal structures of 2,4-diphenyloxazole and 2,4-diphenylthiazole derivatives.[16]

According to the results of DFT calculations (Figure 3) and crystallographic data,[16] 2,4-disubstituted thiazoles prefer an angle $\phi$ of 49°. This angle is larger than the internal angles required by macrocycles containing eight 2,4-fused azole units ($\phi$ = 45°). DFT-based geometry optimization of a hypothetical octa-thiazole containing eight identical units, cyclo(-thia)$_8$, revealed a nonplanar, "saddle-shaped" molecule with twisting between the thiazole units that becomes more pronounced upon linearization (Figure 4). These results suggested that the preparation of cyclo(-thia)$_8$ might be synthetically feasible, but that the product would probably not possess the desired planarity of an ideal telomestatin analogue.

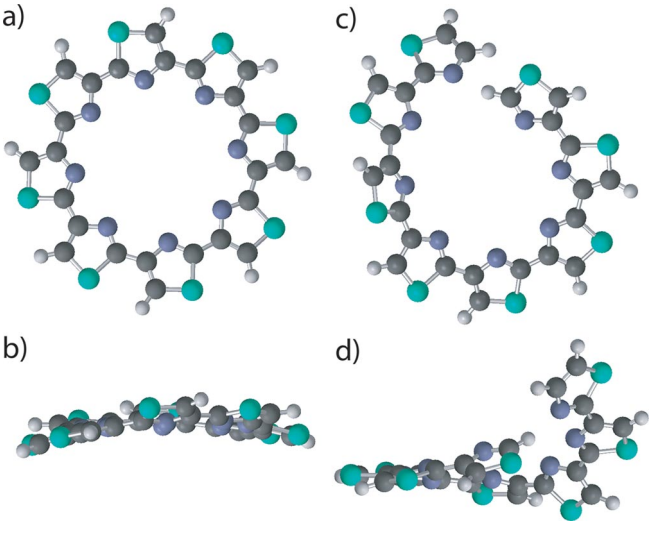



Figure 4. a) Top and b) side views of the DFT-optimized geometry (SVWN/DN**) of the hypothetical macrocycle cyclo(-thia)$_8$. c) Top and d) side views of the DFT-optimized geometry (SVWN/DN**) of a linearized, hypothetical cyclo(-thia)$_8$ analogue.[15]

Because 2,4-disubstituted oxazoles prefer an angle $\phi$ of 35° and 2,4-disubstituted thiazoles prefer an angle $\phi$ of 49° (Figure 3), we speculated that a planar macrocycle with little or no ring strain could be obtained by combining equal numbers of thiazole and oxazole units. To mimic the pseudo $C_4$ symmetry of G-tetrads, we designed cyclo(-ox-thia)$_4$ to contain four alternating 2,4-fused oxazole-thiazole units. DFT-based geometry

optimization of cyclo(-ox-thia)$_4$ revealed a fully planar macrocycle (Figure 5, a, b) with little or no ring strain (Figure 5, c, d). These results suggested that cyclo(-ox-thia)$_4$ (**1**) should be a synthetically feasible target, and that the resulting macrocycle should adopt a planar conformation.

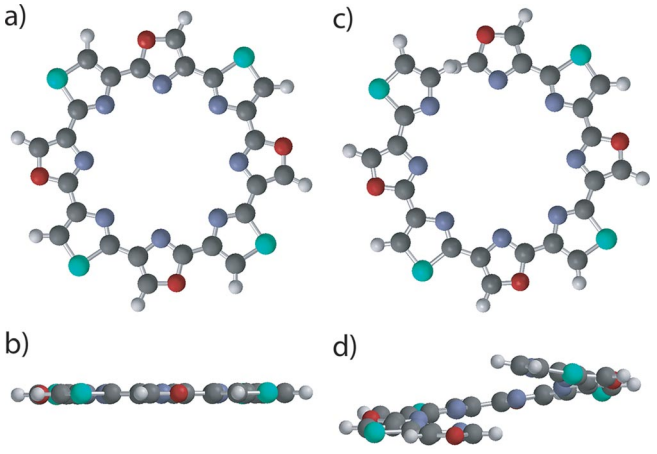
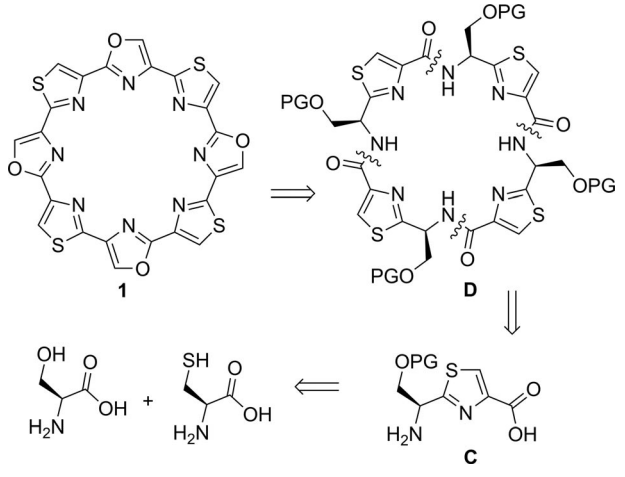


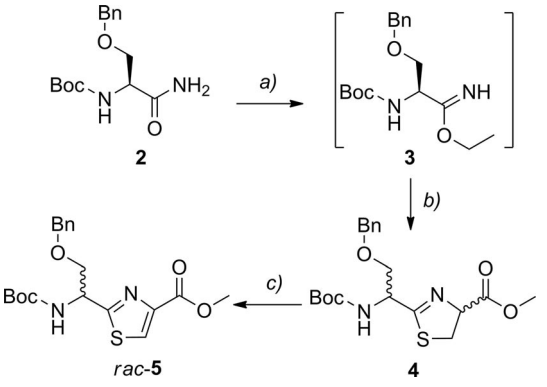

Figure 5. a) Top and b) side views of the DFT-optimized geometry (SVWN/DN**) of cyclo(-ox-thia)$_4$ (**1**). c) Top and d) side views of the DFT-optimized geometry (SVWN/DN**) of a linearized, hypothetical cyclo(-ox-thia)$_4$ analogue.[15]

The retrosynthetic analysis of cyclo(-ox-thia)$_4$ (**1**) was simplified by its $C_4$ symmetry. By cyclodehydrating a protected $C_4$-symmetric tetra-alcohol derivative **D**, four oxazolines can be generated in a single step[17] and subsequent oxidation should furnish to the target macrocycle **1**.[18] The key precursor **D** can be derived from four identical thiazole-containing amino acid building blocks of type **C** (Scheme 1), which can be assembled from Ser and Cys amino acids.



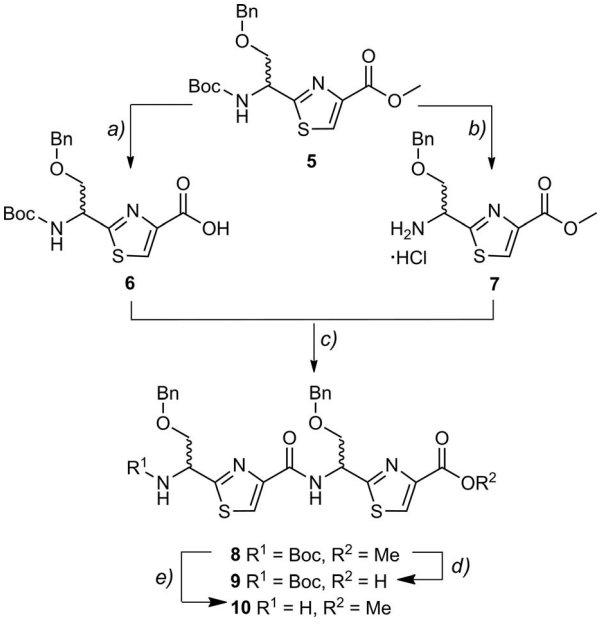

Scheme 1. Retrosynthetic analysis of cyclo(-ox-thia)$_4$ (**1**). PG = protecting group.

The synthesis of cyclo(-ox-thia)$_4$ (**1**) commenced with the preparation of a 2,4-disubstituted thiazole amino acid **C** (Scheme 1). Commercially available Boc-Ser(OBn)-OH was treated with Boc anhydride and ammonium hydrocarbonate[19] to furnish Boc-Ser(OBn)-NH$_2$ (**2**). Compound **2** was *O*-ethylated to give imidate **3**,[20] which, without isolation, was treated with H-Cys-OMe•HCl to give thiazoline **4** in 65 % yield (Scheme 2). Thiazoline **4** was oxidized by using DBU (1,8-diazabicyclo-[5.4.0]undec-1-ene) and BrCCl$_3$[21] to give the racemic thiazole **5** in 98 %.



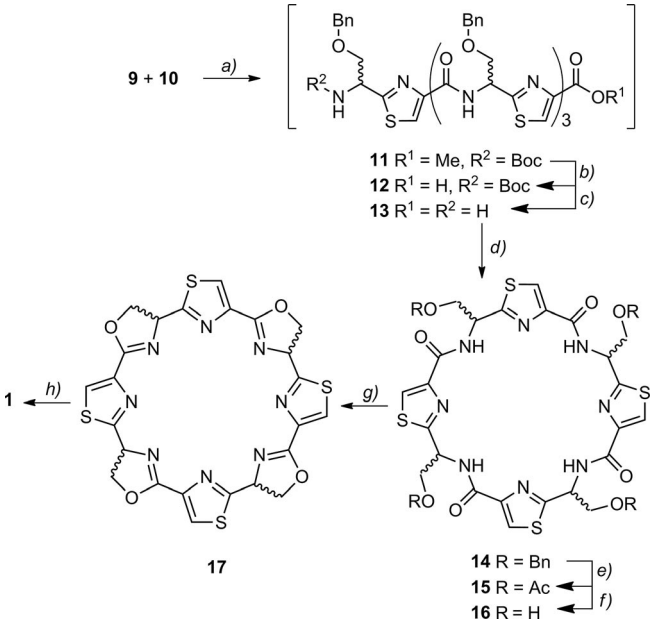

Scheme 2. Synthesis of racemic thiazole **5**. Reagents and conditions: a) 1.1 equiv. $Et_3O{\cdot}BF_4$, 3 equiv. $CaCO_3$, $CH_2Cl_2$, room temp., Ar, 9 h; b) 1.1 equiv. H-Cys-OMe•HCl, 1 equiv. $Et_3N$, $CH_2Cl_2$, room temp., $N_2$, 16 h, 65 %; c) 2 equiv. DBU, 1.05 equiv. $BrCCl_3$, $CH_2Cl_2$, 0 °C to room temp., 1.5 h, 98 %.

With a suitable amino acid of type **C** in hand, the construction of a macrocyclic lactam of type **D** was commenced (Scheme 1). Accordingly, amino acid **5** was deprotected by parallel treatment with LiOH in MeOH/$H_2O$ or with TFA in $CH_2Cl_2$. Upon work-up, these reactions furnished the free acid **6** and the ammonium chloride salt **7**, respectively. Compounds **6** and **7** were coupled together by using 1 equiv. of TBTU (*N*,*N*,*N*′,*N*′-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate) and excess NMM (*N*-methylmorpholine) to give dipeptide **8** in 70 % yield over three steps (Scheme 3). Dimerization of **8** via




Scheme 3. Synthesis of dipeptides **8**–**10**. Reagents and conditions: a) 6 equiv. LiOH, MeOH/$H_2O$ (1:2), room temp., $N_2$; $NaHSO_4$; b) TFA/$CH_2Cl_2$, (1:3), room temp., $N_2$; Amberlyst ($Cl^-$); c) 1 equiv. TBTU, 5 equiv. NMM, room temp., $N_2$, 16 h, 70 % (3 steps); d) 6 equiv. LiOH, MeOH/$H_2O$ (1:2), room temp., $N_2$; citric acid; e) TFA/$CH_2Cl_2$ (1:3), room temp., $N_2$; Amberlyst ($Cl^-$).

intermediates **9** and **10** to the tetrapeptide **11** was conducted in an analogous fashion by using 1.5 equiv. of PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate) as coupling reagent; tetrapeptide **11** was obtained in an overall yield of 70 % (Schemes 3 and 4). Compound **11** is sparingly soluble in $CDCl_3$, showing line broadening and splitting in its $^1H$ NMR spectrum consistent with the formation of aggregates.




Scheme 4. Reagents and conditions: a) 1.5 equiv. PyBOP, 6 equiv. NMM, dry DMF, room temp., $N_2$, 16 h, 70 %; b) 5 equiv. LiOH, MeOH/$H_2O$ (1:3), room temp., $N_2$; $NaHSO_4$; c) TFA/$CH_2Cl_2$ (1:1), room temp., $N_2$; Amberlyst ($Cl^-$); d) 5 equiv. PyBOP, 10 equiv. NMM, dry DMF, 30 h, 54 %; e) 40 equiv. $BF_3$•$Et_2O$, $CH_2Cl_2$/$Ac_2O$ (1:1), room temp., $N_2$, 16 h, 72 %; f) 10 equiv. LiOH, MeCN/MeOH/$H_2O$ (1:1:1), 45 °C, 8 min, 89 %; g) 12 equiv. DAST, dry $CH_2Cl_2$, room temp., $N_2$, 24 h, 46 %; h) 12 equiv. $BrCCl_3$, 46 equiv. DBU, DMF, 0 °C to room temp., $N_2$, 16 h, 43 %.

The limited solubility of **11** necessitated the use of HPLC to monitor the progress of the deprotection reactions for its conversion into **12** and **13** (Scheme 4). For the macrolactamization of **13**, a dilute solution in DMF (1.5 mM) was treated with 5 equiv. of PyBOP and excess NMM for 30 h to give **14** in an isolated yield of 54 %. Removal of the benzyl protecting groups from **14** proved to be challenging. Catalytic hydrogenation using 10 % Pd on activated charcoal in MeOH or AcOEt was not successful. Transhydrogenation with cyclohexene and $Pd(OH)_2$ in EtOH[22] also did not work. The deprotection of macrocycle **14** using anisole and $AlCl_3$ in $CH_2Cl_2$ resulted in partial conversion, with one or two of the benzyl groups being converted into alcohol groups. A two-step approach to deprotection was therefore conducted. Macrocycle **14** in a mixture of $Ac_2O$ and $CH_2Cl_2$ was treated with $BF_3$•$Et_2O$[23] to give the tetra-acetate **15** (Scheme 4) in an isolated yield of 72 %. Tetra-acetate **15** was then treated with LiOH in a mixture of MeCN/MeOH/$H_2O$ to give the corresponding tetra-alcohol **16** in an isolated yield of 89 %.

Tetra-cyclodehydration of **16** was conducted by using 12 equiv. of DAST (diethylaminosulfur trifluoride) in $CH_2Cl_2$ at room temperature[18] to give a 46 % yield of the macrocycle **17** as a mixture of diastereoisomers (Scheme 4). The oxidation of **17** to the target molecule **1** was performed with a mixture of $BrCCl_3$ and DBU overnight at room temperature.[21] The desired product cyclo(-ox-thia)$_4$ (**1**) was isolated as a white solid by centrifugation and was thoroughly washed with $CHCl_3$, EtOAc, and MeOH. Cyclo(-ox-thia)$_4$ (**1**) is sparingly soluble in DMSO and insoluble in $H_2O$. The $^1H$ NMR spectroscopic data collected in [$D_6$]DMSO are consistent with a single, planar molecule with $C_4$ symmetry (part a of Figure 6 and Figure S4 in the Supporting Information) and the HR-ESI-MS data are consistent with the expected elemental composition of cyclo(-ox-thia)$_4$ (**1**; part b of Figure 6 and Figure S5).[24]

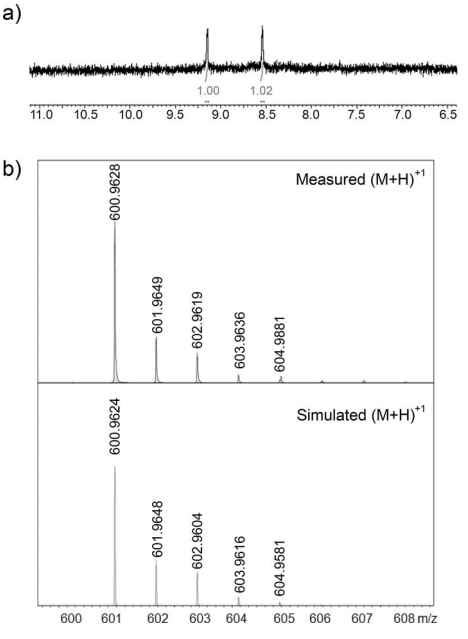



Figure 6. a) Expanded $^1H$ NMR spectrum (300 MHz, [$D_6$]DMSO) of **1**. b) Recorded and simulated HR-ESI-MS of **1** in the *m/z* region of $[M + H]^+$. For the full spectra, see Figures S4 and S5.

## Conclusions

Given their high potential for biological and medicinal applications, telomestatin analogues containing four,[11a,11b] five,[11c,11l] six,[11d–11g,11m,13d] and seven[11f,11h–11k] oxazole units have been previously synthesized. Like telomestatin itself, these analogues are all nonplanar molecules. Planar telomestatin analogues containing eight oxazole units have been proposed for over a decade,[14] but no example of a macrocyclic octa-oxazole has been confirmed to exist, despite extensive synthetic efforts towards this goal.[14] Our computational results suggest that excessive ring strain in octa-oxazole macrocycles poses a barrier to their preparation. We therefore incorporated four thiazole units into our design of cyclo(-ox-thia)$_4$ (**1**) to eliminate macrocyclic ring strain. Accordingly, **1** could be prepared by using standard synthetic transformations. To the best of our knowledge, cyclo(-ox-thia)$_4$ represents the first fully planar telomestatin analogue, and it is the first example of an octa-azole macrocycle contain-

ing eight fused azole units. Our approach to the molecular design of unstrained macrocycles will facilitate the synthesis of water-soluble octa-azole macrocycles with interesting biological properties.

## Experimental Section

### Materials and Methods

**General Synthetic Methods and Reagents:** Unless otherwise noted, all reactions were performed under nitrogen. Distilled solvents were used for all reactions, work-up procedures, TLC, and preparative column chromatography. All additional chemicals were purchased from Bachem, Fluka, Sigma–Aldrich, Merck, and Novabiochem in purum or puriss. grades. For all aq. solutions, $H_2O$ was purified on a Purelab Ultra MK2 apparatus from ELGA Labwater. Melting points were determined by using an Olympus microscope with a TECON-Controller Series 150. TLC was performed on alumina plates layered with 0.2 mm silica 60 $F_{254}$ from Merck and were developed in a solvent-saturated chamber. Preparative column chromatography was performed by using silica 60 (particle size 43–63 μm) from Merck. Analytical HPLC was performed with a Varian ProStar instrument with two solvent delivery Modules Model 210 and a Varian ProStar UV/Vis Detector Model 335 on a reversed-phase MODULO-CART QS UPTISPHERE 300 10ODB column from INTERCHROM (250 × 4.6 mm, N° Serie 329548b). Solvent mixtures of MeCN and water containing 0.03 % TFA were used as eluent for all substances. Gradients were varied according to the polarity of the substances. For semi-preparative HPLC a YMCbasic BA99S11-1510WT B-22-10P instrument from YMC Europe GmbH [S-10Pμm, 150 × 10 mm, No. 101504729 (W)] was used. For preparative HPLC a Varian ProStar instrument with two solvent delivery Modules Model 218, a Varian ProStar UV/Vis Detector Model 325, and a reversed-phase C18 5 μm OBD column from Waters XBridge (19 × 50 mm, Part. No. 186002977 154138338112 04) were used. Optical rotations ($[\alpha]_D^{20}$) were measured with a Perkin–Elmer 241MC Polarimeter. IR spectra were recorded with a Perkin–Elmer-Spectrum ONE FT-IR spectrometer. NMR spectra were recorded with a Bruker AV-300 or AV2-400 spectrometer. ESI mass spectra were recorded with a triple stage quadrupole instrument (Finnigan TSQ 700, San Jose, CA) equipped with a combined Finnigan atmospheric pressure ion (API) source. The solutions (ca. 0.1–1 μmol $mL^{-1}$) were continuously introduced through the electrospray interface with a syringe infusion pump (Harvard Instruments, Southnatick, MA) at a flow rate of 3 μL $min^{-1}$. The spray voltage was held at 4.5 kV, the source analyzer transfer capillary was kept at 200 °C, and the sheath gas used was $N_2$ with an inlet pressure of 30 psi. The resolution was adjusted at a peak width of 0.7 to 0.8 u at half peak height for both scanning quadrupoles. Representative mass spectra were obtained with an average of 20 scans. EI mass spectra were recorded with a sector field mass analyzer (Finnigan MAT95, San Jose, CA). The ionization energy was 70 eV for EI and 150 eV for CI with $NH_3$ as reactant gas.

**Supporting Information** (see footnote on the first page of this article): Further details of the synthesis and characterization of cyclo(-ox-thia)$_4$ (**1**).

## *Acknowledgments*

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**Keywords:** Synthesis design · Density functional calculations · Natural products · Macrocycles · Nitrogen heterocycles

[1] K. Shin-ya, K. Wierzba, K. Matsuo, T. Ohtani, Y. Yamada, K. Furihata, Y. Hayakawa, H. Seto, *J. Am. Chem. Soc.* **2001**, *6*, 1262.
[2] X. H. Jian, H. X. Pan, T. T. Ning, Y. Y. Shi, Y. S. Chen, Y. Li, X. W. Zeng, J. Xu, G. L. *Tang*, *ACS Chem. Biol.* **2012**, *7*, 646.
[3] a) K. Mu-Yong, H. Vankayalapati, K. Shin-Ya, K. Wierzba, L. H. Hurley, *J. Am. Chem. Soc.* **2002**, *124*, 2098; b) T. T. Charvat, D. J. Lee, W. E. Robinson, A. R. Chamberlin, *Bioorg. Med. Chem.* **2006**, *14*, 4552; c) S. Agrawal, R. P. Ojha, S. Maiti, *J. Phys. Chem. B* **2008**, *112*, 6828; d) A. K. Chaubey, K. D. Dubey, R. P. Ojha, *J. Comput.-Aided Mol. Des.* **2012**, *26*, 289; e) M. Toro, P. Bucek, A. Avino, J. Jaumot, C. Gonzalez, R. Eritja, R. Gargallo, *Biochimie* **2009**, *91*, 894–902.
[4] a) M. Kim, M. Gleason-Guzman, E. Izbicka, D. Nishioka, L. H. Hurley, *Cancer Res.* **2003**, *63*, 3247; b) M. Kim, H. Vankayalapati, K. Shin-ya, K. Wierzba, L. H. Hurley, *J. Am. Chem. Soc.* **2002**, *124*, 2098; c) E. M. Rezler, J. Seenisamy, S. Bashyam, M. Y. Kim, E. White, W. D. Wilson, L. H. Hurley, *J. Am. Chem. Soc.* **2005**, *127*, 9439.
[5] a) J. Seenisamy, S. Bashyam, V. Gokhale, H. Vankayalapati, D. Sun, A. Siddiqui-Jain, N. Streiner, K. Shin-Ya, E. White, W. D. Wilson, L. H. Hurley, *J. Am. Chem. Soc.* **2005**, *127*, 2944; b) D. Monchaud, M.-P. Teulade-Fichou, *Org. Biomol. Chem.* **2008**, *6*, 627.
[6] K. Shin-ya, *Nihon Rinsho* **2004**, *62*, 1277.
[7] A. De Cian, G. Cristofari, P. Reichenbach, E. De Lemos, D. Monchaud, M. P. Teulade-Fichou, K. Shin-Ya, L. Lacroix, J. Lingner, J. L. Mergny, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 17347.
[8] a) T. Tauchi, K. Shin-Ya, G. Sashida, M. Sumi, A. Nakajima, T. Shimamoto, J. H. Ohyashiki, K. Ohyashiki, *Oncogene* **2003**, *22*, 5338; b) D. Gomez, N. Aouali, A. Renaud, C. Douarre, K. Shin-Ya, J. Tazi, S. Martinez, C. Trentesaux, H. Morjani, J. F. Riou, *Cancer Res.* **2003**, *63*, 6149.
[9] M. A. Shammas, R. J. Shmookler Reis, C. Li, H. Koley, L. H. Hurley, K. C. Anderson, N. C. Munshi, *Clin. Cancer Res.* **2004**, *10*, 770.
[10] a) T. Doi, M. Yoshida, K. Shin-ya, T. Takahashi, *Org. Lett.* **2006**, *8*, 4165; b) D. Monchaud, A. Granzhan, N. Saettel, A. Guedin, J. L. Mergny, M. P. Teulade-Fichou, *J. Nucleic Acids* **2010**, 1; c) T. Doi, K. Shibata, M. Yoshida, M. Takagi, M. Tera, K. Nagasawa, K. Shin-ya, T. Takahashi, *Org. Biomol. Chem.* **2011**, *9*, 387.
[11] a) Z. Zhang, G. Yuan, *ARKIVOC* **2011**, 360; b) X. Liu, H. T. Ngo, Z. Ge, S. J. Butler, K. A. Jolliffe, *Chem. Sci.* **2013**, *4*, 1680; c) S. K. Chattopadhyay, S. Biswas, S. K. Ghosh, *Synthesis* **2008**, *7*, 1029; d) J. Linder, T. P. Garner, H. E. Williams, M. S. Searle, C. J. Moody, *J. Am. Chem. Soc.* **2011**, *133*, 1044; e) K. Iida, M. Tera, T. Hirokawa, K. Shin-Ya, K. Nagasawa, *J. Nucleic Acids* **2010**, 1; f) G. S. Minhas, D. S. Pilch, J. E. Kerrigan, E. J. LaVoie, J. E. Rice, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3891; g) S. G. Rzuczek, D. S. Pilch, E. J. LaVoie, J. E. Rice, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 913; h) M. Tera, K. Iida, H. Ishizuka, M. Takagi, M. Suganuma, T. Doi, K. Shin-ya, K. Nagasawa, *ChemBioChem* **2009**, *10*, 431; i) M. Tera, K. Iida, K. Shin-ya, K. Nagasawa, *Nucleic Acids Symp. Ser.* **2009**, 231; j) K. Shibata, M. Yoshida, T. Takahashi, M. Takagi, K. Shin-ya, T. Doi, *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1453; k) M. Satyanarayana, S. G. Rzuczek, E. J. Lavoie, D. S. Pilch, A. Liu, L. F. Liu, J. E. Rice, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3802; l) D. Hernándeza, E. Riegoa, A. Franceschb, C. Cuevasb, F. Albericioa, M. Álvareza, *Tetrahedron* **2007**, *63*, 9862; m) S. K. Chattopadhyay, S. Biswas, *Tetrahedron Lett.* **2006**, *47*, 7897.
[12] W. J. Chung, B. Heddi, M. Tera, K. Iida, K. Nagasawa, A. T. Phan, *J. Am. Chem. Soc.* **2013**, *135*, 13495.
[13] a) J. Deeley, A. Bertram, G. Pattenden, *Org. Biomol. Chem.* **2008**, *6*, 1994; b) D. S. Pilch, C. M. Barbieri, S. G. Rzuczek, E. J. Lavoie, J. E. Rice, *Biochimie* **2008**, *90*, 1233; c) A. Bertram, N. Maulucci, O. M. New, S. M. Mohd Nor, G. Pattenden, *Org. Biomol. Chem.* **2007**, *5*, 1541; d) M. Satyanarayana, S. G. Rzuczek, E. J. Lavoie, D. S. Pilch, A. Liu, L. F. Liu, J. E. Rice, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3802.
[14] a) C. M. Marson, M. Saadi, *Org. Biomol. Chem.* **2006**, *4*, 3892; b) E. J. Lavoie, J. E. Rice, L. F. Liu, US Pat. 8093235 B2, **2012**, accession number: BCI: BCI201200113908, ISSN: 0098-1133.
[15] The reported conformations of the linearized molecules represent local, not global, energetic minima.

[16] a) M. J. Thompson, H. Adams, B. Chen, *J. Org. Chem.* **2009**, *74*, 3856; b) K. S. Nayak, K. N. Venugopala, D. Chopra, T. Govender, G. Kruger, G. E. M. Maguireb, T. N. Guru Rowa, *Acta Crystallogr., Sect. E* **2009**, *65*, 2611.
[17] M. Brandstätter, F. Roth, N. W. Luedtke, *J. Org. Chem.* **2015**, *80*, 40.
[18] A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, D. R. Williams, *Org. Lett.* **2000**, *2*, 1165.
[19] V. F. Pozdnev, *Tetrahedron Lett.* **1995**, *36*, 7115.
[20] B. Wagner, D. Schumann, U. Linne, U. Koert, M. A. Marahiel, *J. Am. Chem. Soc.* **2006**, *128*, 10513.
[21] a) S. L. You, J. W. Kelly, *Org. Lett.* **2004**, *6*, 1681; b) D. R. Williams, S. Patnaik, M. P. Clark, *J. Org. Chem.* **2001**, *66*, 8463.
[22] S. Hanessian, T. J. Liak, B. Vanasse, *Synthesis* **1981**, 396.
[23] C. F. Garbers, J. A. Steenkamp, H. E. Visagie, *Tetrahedron Lett.* **1975**, *16*, 3753.
[24] While attempting to collect $^{13}C$ NMR spectroscopic data, stock solutions of cyclo(-ox-thia)$_4$ prepared in [D$_6$]DMSO degraded over time (see Figure S6 in the Supporting Information). Although the reason for this instability is unknown, similar behavior has been observed for telomestatin and related oligo-oxazoles.[11f]

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