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Synthesis of New Diketopiperazines, Thiolation to Thiodiketopiperazines, and Examination of Their ROS-Generating Properties

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A variety of new symmetrical and unsymmetrical diketopiperazines have been prepared from free amino acids by using a previously developed microwave-assisted protocol. This included the successful incorporation of L-pyroglutamic acid as an unusual building block. The diketopiperazines were then thiolated electrophilically to the corresponding bis(methylthio)- and epidithiodiketopiperazines. Initial experiments showed a promising activity towards the generation of reactive oxygen species in HeLa cells.

Introduction

Thiodiketopiperazines are a class of fungal secondary metabolites (mycotoxins).[1] They all share a mutual structural motif: A cyclic dipeptide (diketopiperazine) bearing sulfur units at the α positions of the peptide bonds. Thiodiketopiperazine natural products generally differ by type and connectivity of the sulfur units as well as by annulation (*cis*/*trans*) of the peripheral rings (Figure 1). Most commonly, a disulfide bridge can be found in the central ring [e.g., in the antiviral gliotoxin (**1**)[2] or the antibacterial epicorazin A (**2**)[3]]. Furthermore, there are bis(methylthio)-diketopiperazines bearing two methyl thioether moieties [e.g., in the HIV-1 replication-inhibiting epicoccin G (**3**)[4]]. Sulfides containing one, three, or four sulfur atoms are also known. The sulfur groups can furthermore be bound in different rings of the system as a bridging function [e.g., in the antimicrobial, unsymmetrical epicoccin A (**4**)[5]].

Natural products with thiodiketopiperazine units possess toxic properties towards a variety of organisms, including fungi, bacteria, and viruses. The mode of action of this class of mycotoxins is presumably based on the conjugation with proteins through thiol groups and the generation of reactive oxygen species (ROSs), which can lead to programed cell death (apoptosis).[1,6]

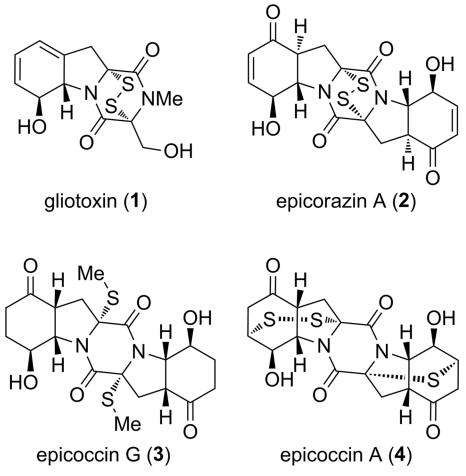

Figure 1. Examples of thiodiketopiperazines with different types and connectivity of their sulfur units.

Thiolation at the α positions of the peptide bonds plays a crucial role in the total synthesis of thiodiketopiperazine natural products. The introduction of sulfur units at a late stage of the synthesis is reasonable due to their sensitivity towards redox reactions. In principle, there are two different approaches to the thiolation of diketopiperazines: The treatment of α,α′-diacylimmonium ions with nucleophilic sulfur reagents(biomimetic approach), for example, hydrogen sulfide,[7] trithiocarbonate,[7] and thioacetate,[8] or the treatment of α,α′-dicarbanions with electrophilic sulfur reagents, for example, elementary sulfur,[9] diphenyl disulfide,[10] and disulfur dichloride.[11] In 2012, Nicolaou et al. published a general and easily reproducible method for the generation of bis(methylthio)- and epidithiodiketopiperazines with elemental sulfur and NaHMDS (sodium hexamethyldisilazane) as base.[12] We were able to transfer this

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protocol to the synthesis of a selection of symmetrical and unsymmetrical, mostly functionalized compounds.[9a] Herein we wish to report the synthesis of additional and, furthermore, unusual diketopiperazines from unprotected amino acids and their thiolation under Nicolaou's conditions.

Results and Discussion

First, we synthesized various diketopiperazines starting from the commercially available, enantiomerically pure amino acids **5a**–**5i** (Figure 2) by using a previously reported one-pot protocol.[13]

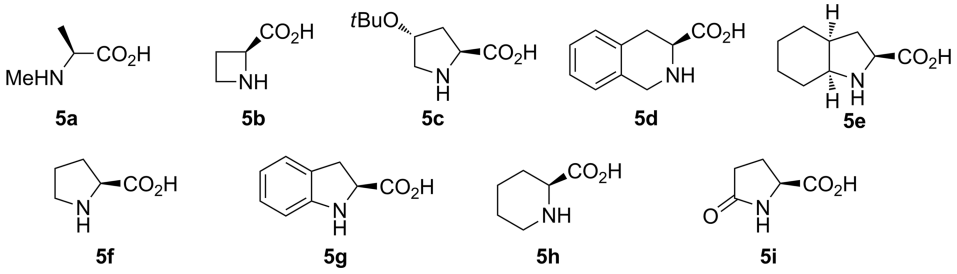
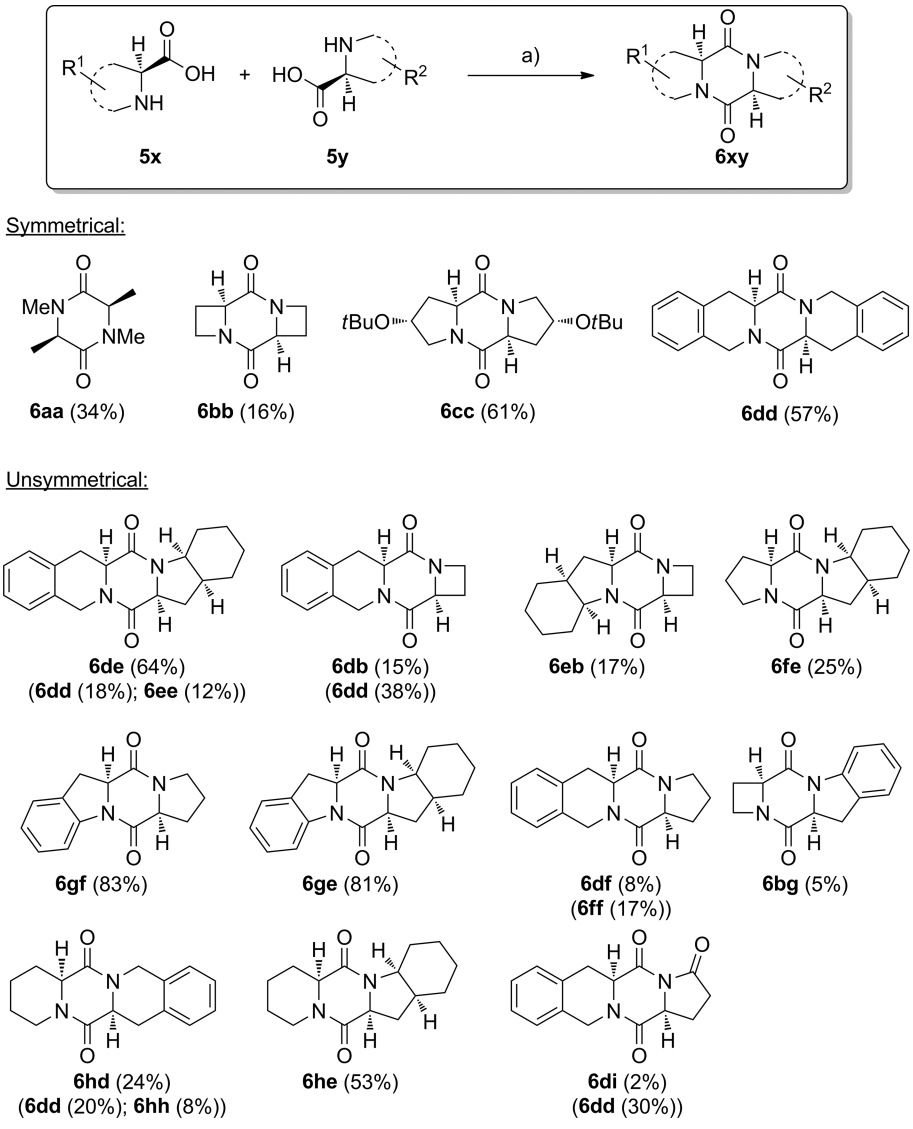


Figure 2. Overview of the amino acid starting materials **5a**–**5i** employed for the preparation of diketopiperazines.



Scheme 1. Synthesis of diketopiperazines **6** with yields (including yields of isolated homodimers). Reagents and conditions: a) $MeOPCl_2$, NEt_3, dimethylimidazolium dimethyl phosphate, toluene, 35 °C, 2 h–overnight; then **5y** (for unsymmetrical products); then microwave irradiation, 145 °C, 1 h, or reflux, 4–6.5 h.

In a typical procedure (Scheme 1), the first amino acid **5x** was treated with the coupling reagent methyl dichlorophosphite at a slightly elevated temperature (35 °C) to generate an activated oxazaphospholidinone.[14] To enhance the solubility of very polar amino acids, some ionic liquid (dimethylimidazolium dimethyl phosphate) can be added. In

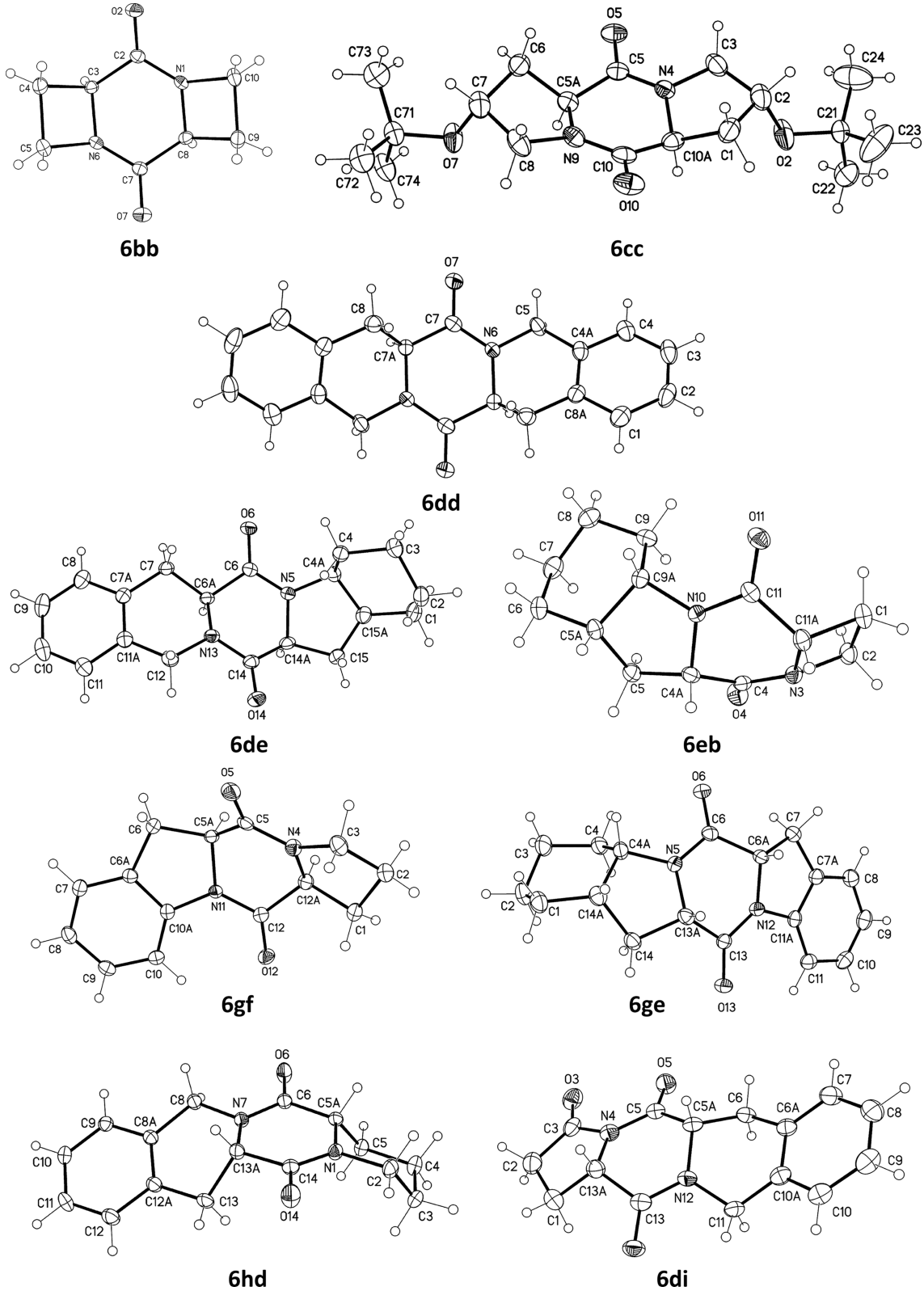


Figure 3. Molecular structures (from top left to bottom right) of **6bb**, **6cc** (one of the two crystallographic independent molecules is shown), **6dd**, **6de**, **6eb**, **6gf**, **6ge**, **6hd**, and **6di**; displacement parameters are drawn at the 50% probability level.

the case of unsymmetrical diketopiperazines, the second amino acid **5y** was then added (this step was omitted for symmetrical products). Then the mixture was heated in a closed Pyrex vial in a microwave at 145 °C (up to ca. 500 mg scale) or at reflux (for a larger scale), to give the desired diketopiperazine **6xy** (of course, **6xy** is chemically identical to **6yx**, however, in this manuscript the order of addition reflects the nomenclature).

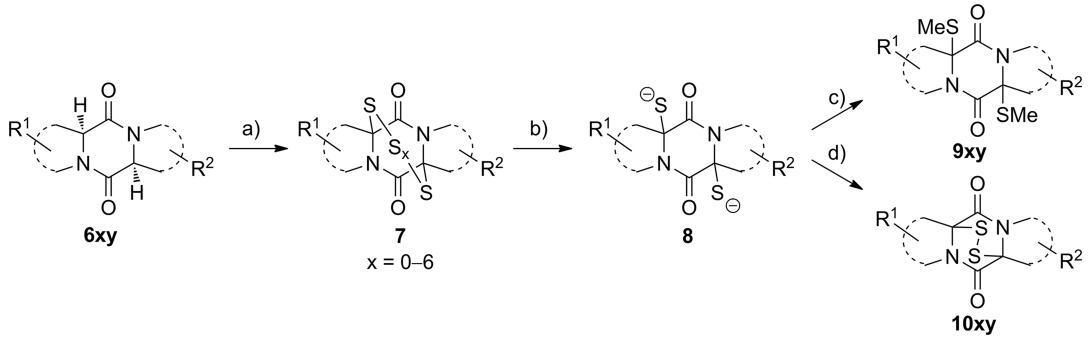
A variety of symmetrical and unsymmetrical diketopiperazines were successfully prepared in up to 83% yield. The low yields of diketopiperazines containing L-azetidine-2-carboxylate (**6bb**,[15] **6db**, **6eb**, **6bg**) are probably due to the low solubility of the starting material in toluene. The use of other solvents to improve solubility and yield may be considered, however, toluene was still our solvent of choice as it has a sufficiently high boiling point to allow the use of high temperatures for the dimerization reaction and is easy to remove from the reaction mixture, thereby facilitating work-up and purification. It should be noted that only a few L-azetidine-2-carboxylate diketopiperazines are known (with annulated four,[15] five (1 example),[16] and six-membered rings[16,17]).

Furthermore, in some cases, the corresponding homodimers were formed in a significant competing reaction (e.g., along with **6db**, **6df**, **6hd**, **6di**); the products could generally be separated by column chromatography. All the other products were isolated in good-to-very-good yields. Many of the dimers were crystalline and were analyzed by X-ray crystallography (Figure 3), along with a diketopiperazine containing pyroglutamate as an unusual building block (**6di**),[18] an interesting and novel structural motif, albeit in only poor yields.[19]

With several diketopiperazines in hand, we went on to synthesize their sulfur-bearing analogues by using NaHMDS and sulfur (Scheme 2). After reduction to the α,α-diketopiperazine-dithiolates **8** with $NaBH_4$, two different work-ups led to either bis(methylthio)diketopiperazines **9** (by treatment with methyl iodide) or epidithiodiketopiperazines **10** (under oxidative conditions with potassium triiodide).

The thiodiketopiperazines successfully prepared from the symmetrical diketopiperazines are shown in Figure 4. Because starting material **6aa** is sterically less hindered, we assume the presence of two enantiomers of the products **9aa** and **10aa**. Only one NMR signal was detected for both the methyl and methylthio groups, which confirms the presence of only one diastereomer.

Because we measured a noticeable optical rotation, one can presume a *cis* geometry of the sulfur functionalities, as the corresponding *trans* isomers would be achiral (*meso* compounds). We obtained an enantiomerically pure crystal of **9aa**, which was analyzed by X-ray crystallography (Figure 5). Diketopiperazine **6bb** could neither be transformed into a bis(methylthio)- nor an epidithiodiketopiperazine un-



Scheme 2. General synthesis of bis(methylthio)diketopiperazines **9** and epidithiodiketopiperazines **10** by the Nicolaou protocol.[12] Reagents and conditions: a) NaHMDS, S_8, THF, room temp.; then **6**; then NaHMDS, room temp., 30 min; b) $NaBH_4$, THF/MeOH (1:1), 0 °C to room temp., 45 min; c) MeI, room temp., overnight; d) KI_3, room temp., 10 min.

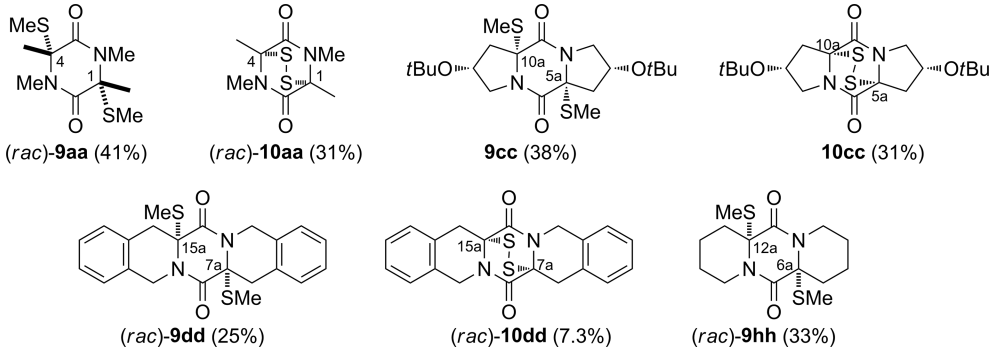


Figure 4. Synthesized symmetrical thiodiketopiperazines with yields.

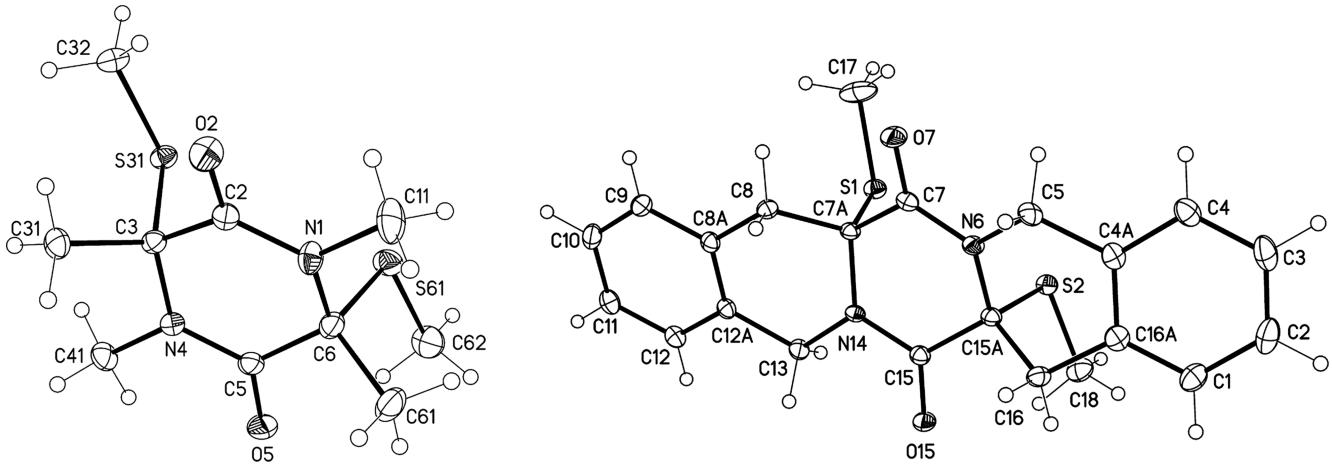


Figure 5. Molecular structures of **9aa** (left) and *rac*-**9dd** (right); displacement parameters are drawn at the 50% probability level.

der the described reaction conditions. A reason for this might be the poor solubility of **6bb** in THF, making it hard to carry out the α deprotonation.

The protected hydroxyproline dimer **6cc** was also subjected to the thiolation conditions. Both sulfur-functionalized compounds **9cc** and **10cc** were obtained as single diastereomers. Derivative **9cc** is *cis*-configured, as only one signal for the methyl groups was observed in the NMR spectra. For epithiodiketopiperazines, such as **10cc**, a *cis* geometry can be corroborated due to the strong steric hindrance of a hypothetical *trans* disulfide. Furthermore, we suppose that the sulfur attack proceeds from the less-hindered convex face of the molecule with retention of configuration to give the (5a*R*,10a*R*) configuration of **9cc/10cc**, as shown. In support of this stereochemistry, we previously reported a very similar derivative, for which the stereochemical outcome was proven by X-ray crystallography.[9a]

(*S*)-Tetrahydroisoquinoline dimer **6dd** was successfully thiolated to **9dd** and **10dd**, albeit in lower yields than those recently reported by Nicolaou et al.[20] The low yield of **10dd** can be explained by product loss during recrystallization. The products were also obtained diastereomerically pure as the *cis* isomers. Derivative **9dd** could be crystallized and was analyzed by X-ray crystallography, which revealed a racemic structure (Figure 5). As both **9dd** and **10dd** exhibit pronounced optical rotations, the presence of a scalemic rather than a racemic mixture, from which a racemate crystallized, can be assumed.

Bis(methylthio)diketopiperazine **9hh** was obtained from the dimer of (*S*)-pipecolic acid (**6ff**), which itself was formed as a side-product during the synthesis of **6df**. A scalemic mixture was also formed in this case as there is no favored side of attack.

Next, we carried out experiments to synthesize novel thiolated compounds from a selection of the unsymmetrical diketopiperazines shown in Scheme 1. The structures of all the successfully synthesized bis(methylthio)- **9** and epidithiodiketopiperazines **10** are depicted in Figure 6.

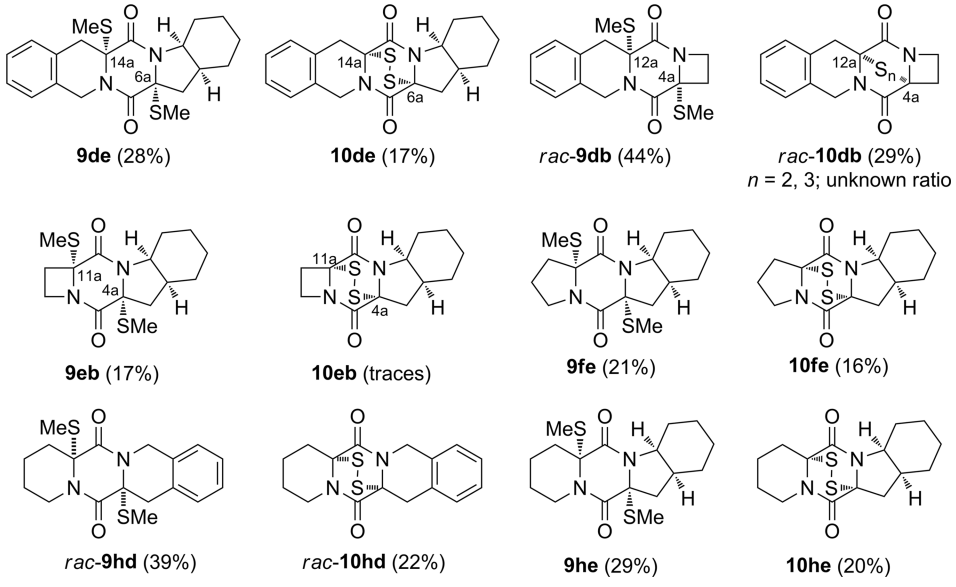


Figure 6. Synthesized unsymmetrical thiodiketopiperazines with yields.

Diketopiperazine **6de** is sterically highly demanding and shows an arched structure due to the octahydroindole moiety. The electrophilic attack of the sulfur unit most likely proceeds from the more accessible convex face. Accordingly, after thiolation, we obtained diastereo- and enantiomerically pure **9de** and **10de** with the (6a*R*,14a*R*) configuration.

When converting unsymmetrical diketopiperazine **6db** into **9db/10db**, there is probably no favored side for the sulfur attack because of its nearly planar structure. In accord with the postulated mechanism for thiolation, which implies the intermediate presence of dianions, we obtained the corresponding thiodiketopiperazines as *cis* isomers. In the case of **10db**, the product was formed as a mixture of epidithio- and epitrithiodiketopiperazine. The latter was only detected by mass spectrometry; the two compounds were not distinguishable in the NMR spectra. This implies that the geometry hardly changes when substituting a disulfide- for a trisulfide bridge.

The synthesis of the unsymmetrical bis(methylthio)diketopiperazine **9eb** was successful as well, however, the yield was relatively low (17%), which may also be due to the low solubility of the starting material **6eb**. The formation of epidithiodiketopiperazine **10eb** was only observed in trace quantities. Both products were probably formed as the (4a*R*,11a*R*) enantiomers with *cis* geometry.

Enantiomerically pure thiodiketopiperazines **9fe**, **10fe**, **9he**, and **10he** were also prepared following the general thiolation protocol, as well as racemic **9hd** and **10hd**. Diketopiperazines **6gf**, **6ge**, **6df**, **6db**, and **6id** were not subjected to the thiolation conditions either because the thiolated species are already known[1,2,21] or because there was insufficient starting material. Furthermore, the nucleophilic thioacetylation of sarcosine anhydride following the pioneering work of Trown[8] led to good results, and a crystal structure of the *cis* isomer could be obtained (see compound **SI-11** in the Supporting Information).

Strong evidence for the formation of enantiomerically pure thiolated products from diketopiperazines with a hydroindole unit was provided by the crystal structure of compound **9fe** (Figure 7). It is a single enantiomer with an absolute configuration of (5*R*,6*S*,10*S*,12*R*) that results from sulfur attack from the less hindered convex face with retention of configuration.

The cytotoxic properties of many thiodiketopiperazine natural products are probably due to the formation of reactive oxygen species through sulfide redox cycling. For the best-investigated representative of this class of mycotoxins, namely gliotoxin (**1**), there already exist detailed studies and hints regarding its mode of action.[2,22] However, to the best of our knowledge, there are no reports of corresponding studies on bis-annulated systems, such as the natural products **2**–**4** or the synthetic derivatives shown in Figure 6. In principle, the thiodiketopiperazines in Figure 5 should also be able to generate ROSs through redox cycling. To better understand this process and to possibly find a connection between structure and activity, we investigated the ability of these compounds to produce ROSs by visualizing this process in a test organism (HeLa cells).

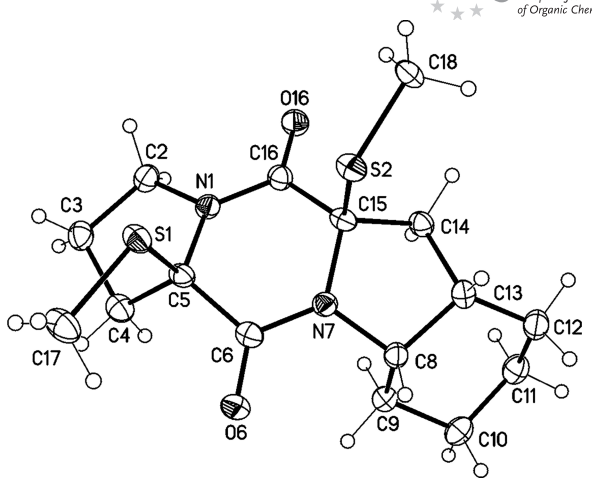


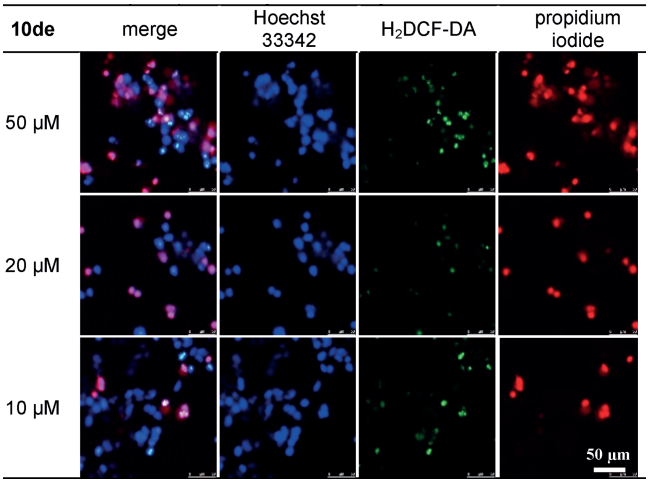
Figure 7. Molecular structure of **9fe**, displacement parameters are drawn at the 50% probability level.

For the cell tests, HeLa cells were incubated with thiodiketopiperazines at different concentrations for 23 h at 37 °C and afterwards visualized with the aid of several fluorescence markers [Hoechst 33342 for staining of nuclei, propidium iodide for staining apoptotic cells,[22] and 2′,7′-dichlorodihydrofluorescein (H_2DCF-DA) for detection of oxidatively stressed cells].[23] We discovered that two of the compounds, **10de** and **10db**, showed distinct tendencies with regard to ROS generation.

Table 1 shows the confocal fluorescence microscope images of HeLa cells incubated with different concentrations (50, 20, and 10 μM) of thiodiketopiperazine **10de**. The staining of the cells with propidium iodide reveals a large number of apoptotic cells (red) with a final concentration of **10de** of 50 μM. Furthermore, treatment with H_2DCF-DA shows a significant amount of cells exhibiting oxidative stress (green), which is not congruent with the apoptotic cells. This is due to the fact that apoptosis leads to perforation of the cell wall, which allows the fluorescein derivative to leave the cell through its porous membrane. This facilitates the differentiation of living oxidatively stressed cells from those that have already suffered apoptosis, which indicates that apoptosis results from a supercritical ROS concentration in the cells. With a lower final concentration of **10de**, smaller amounts of apoptotic/oxidatively stressed cells are visible. In agreement with this tendency, there are only a few dead or ROS-containing cells with a lower substance concentration of 10 μM. Therefore thiodiketopiperazine **10de** indeed seems to enhance intracellular ROS production.

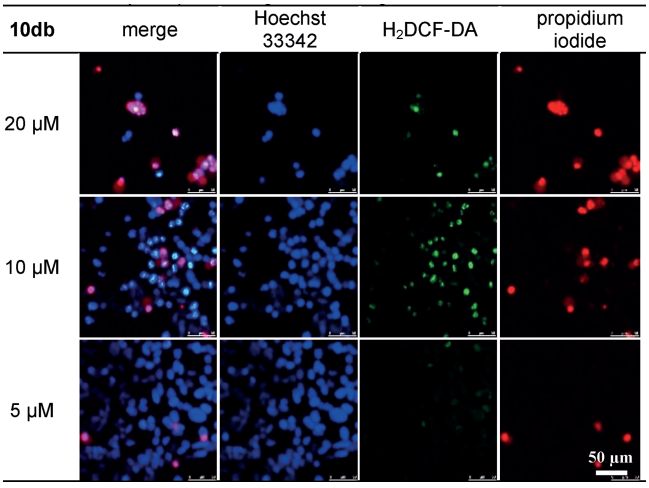
Accordingly, compound **10db** (a mixture of epidithio- and epitrithiodiketopiperazine) was also used for cell tests at concentrations of 20, 10, and 5 μM (Table 2). A clear tendency was again observed; with an increasing thiodiketopiperazine concentration, a higher amount of oxidative stress and apoptosis occurs. Using a concentration of 20 μM **10db**, nearly all the cells are apoptotic. Furthermore, only a few cells per surface unit can be seen; dead cells are no longer able to hold on to the surface. They are presumably

Table 1. ROS generation and apoptosis induced by thiodiketopiperazine **10de** after incubation with HeLa cells at 37 °C for 23 h under a 5% CO_2 atmosphere. Confocal microscopic images after incubation with Hoechst 33342 (blue, 1 μM, 15 min incubation at 37 °C under a 5% CO_2 atmosphere), H_2DCF-DA (green, 1 μM, 15 min incubation at 37 °C under a 5% CO_2 atmosphere), propidium iodide (red, 1 μM, 15 min incubation at 37 °C under a 5% CO_2 atmosphere), and merging of the images.



removed from the well during the first washing step after incubation with the fluorescence markers. When the cells were treated with 10 μM of **10db**, few dead cells but a significant number of ROS-producing cells are observed. In contrast, the sample incubated with a lower concentration of **10db** (5 μM) shows almost exclusively healthy cells.

Table 2. ROS generation and apoptosis induced by thiodiketopiperazine **10db** after incubation with HeLa cells at 37 °C for 23 h under a 5% CO_2 atmosphere. Confocal microscopic images after incubation with Hoechst 33342 (blue, 1 μM, 15 min incubation at 37 °C under a 5% CO_2 atmosphere), H_2DCF-DA (green, 1 μM, 15 min incubation at 37 °C under a 5% CO_2 atmosphere), propidium iodide (red, 1 μM, 15 min incubation at 37 °C under a 5% CO_2 atmosphere), and merging of the images.



It can be stated that, qualitatively, **10db** is more active than **10de** in ROS production. Potentially, the trithiodiketopiperazine contained in **10db** leads to stronger ROS generation than its disulfide analogues. Furthermore, the lower steric hindrance and the fact that it is a mixture of enantiomers probably facilitates a stronger, but also less selective interaction with potential reaction partners within the cells. The exemplary treatment of HeLa cells with thiodiketopiperazines **10de** and **10db** and analysis with confocal microscopy (live cell imaging) has allowed a primary qualitative evaluation of ROS generation by the test substances. The results are in accordance with a redox cycling mechanism, as postulated for gliotoxin (**1**).[2] The incubation tests with the other thiodiketopiperazines did not show any reliable tendencies in terms of their activity and are not described. After optimization of the cell tests, for example, by quantification of the biological effects or by development of automated microscopic methods for detection of highly active thiodiketopiperazine derivatives, an important contribution could be made to the understanding of modes of action of naturally occurring toxic sulfur-containing compounds.

Conclusions

We have prepared a number of novel, including unsymmetrical, diketopiperazines by dimerization of unprotected amino acids. These compounds were functionalized with sulfur moieties to the corresponding bis(methylthio)- and epidithiodiketopiperazines to give a library of new sulfur compounds. The stereochemical outcomes of these reactions have been discussed based on individual structures and X-ray crystallographic analyses. Furthermore, the compounds were analyzed with regard to their activity towards ROS generation by live cell imaging using HeLa cells as the model organism and confocal fluorescence microscopy. Two of the tested compounds showed pronounced qualitative tendencies towards ROS generation. The experimental and biological results presented herein could make an important contribution to the understanding of the cytotoxicity of naturally occurring thiodiketopiperazines.

Experimental Section

General: NMR spectra were recorded with a Bruker Avance 300, 400, or 600 spectrometer as solutions at room temperature. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (TMS) and referenced to residual solvent peaks. All the coupling constants are absolute values and expressed in Hz. The spectra were analyzed according to first order and the signals are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, and m = multiplet. Diastereotopic methylene protons are labeled as H_A and H_B. The ^{13}C NMR signal patterns were analyzed by DEPT and are described as follows: + for primary or tertiary C atom (positive signal), – for secondary C atom (negative signal), and C_q = quaternary C atom (no signal). EI-MS and FAB-MS were performed by using a Finnigan MAT 90 spectrometer (70 eV). ESI-MS spectra were recorded with an Agilent 6230 TOF LC/MS spectrometer. The molecular fragments are quoted as the relation between mass and charge (m/z) and the intensities as a percentage value relative to the intensity of the base

signal (100%). The abbreviation $[M]^+$ refers to the molecule ion and $[M + H]^+$ refers to the protonated molecule ion. IR spectra were recorded with an FTIR Bruker IFS88 spectrometer and the data are reported as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, vw = very weak, and br. = broad). Optical rotations were determined with a Perkin–Elmer 241 polarimeter at 20 °C with a glass cuvette and the D line of sodium. Reactions were monitored by using silica gel coated aluminium plates (Merck, silica gel 60, F_{254}) with detection by examination under UV light (254 nm) and by staining with molybdatophosphate (5% phosphor molybdic acid in ethanol) or potassium permanganate (0.75% $KMnO_4$ in H_2O). Solvents, reagents, and other chemicals were purchased from Sigma–Aldrich, ABCR, and Fisher Scientific. THF and toluene were distilled from sodium prior to use. EtOH was purchased from Acros as absolute solvent. All reactions involving moisture-sensitive reactants were executed under argon in oven-dried glassware. All other solvents, reagents, and chemicals were used as purchased unless stated otherwise. Microwave-assisted reactions were carried out in 10 mL Pyrex vials in a CEM DISCOVER microwave reactor. The temperature was controlled by using an IR sensor.

General Procedure 1 (GP1) – Dimerization of Amino Acids to Diketopiperazines 6xy

Dimerization to Symmetrical Diketopiperazines (5x = 5y): Amino acid **5** (1.00 equiv.) was suspended in absolute toluene. Absolute NEt_3 (4.00 equiv.) and methyl dichlorophosphite (0.50 equiv.) were then added and the mixture was stirred at 35 °C overnight. After irradiation under closed-vessel microwave conditions at 145 °C for 1 h or heating at reflux for 4–6.5 h, the solution was filtered and the precipitate was washed with hot toluene. The filtrate was evaporated under reduced pressure and the resulting crude product was purified by column chromatography.

Dimerization to Unsymmetrical Diketopiperazines (5x ≠ 5y): The first amino acid **5x** (1.00 equiv.) was suspended in absolute toluene. Absolute NEt_3 (4.00 equiv.), methyl dichlorophosphite (1.00 equiv.), and dimethylimidazolium dimethyl phosphate (3–5 drops) were added and the mixture was stirred at 35 °C overnight. Then the second amino acid **5y** (1.20–1.50 equiv.) was added to the mixture. After irradiation under closed-vessel microwave conditions at 145 °C for 1 h or heating at reflux for 4–6 h, the solution was filtered and the precipitate was washed with hot toluene. The filtrate was evaporated under reduced pressure and the resulting crude product was purified by column chromatography.

General Procedure 2 (GP2) – Synthesis of Bis(methylthio)diketopiperazines 9xy: NaHMDS (1.0 m in THF, 3.00 equiv.) was added to a solution of sulfur (8.00 equiv.) in dry THF at room temperature. Then diketopiperazine **6xy** (1.00 equiv.) in dry THF and more NaHMDS (1.0 m in THF, 3.00 equiv.) were added and the mixture was stirred for 0.5 h at room temp. A saturated solution of NH_4Cl was added, the resulting mixture was extracted with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was dissolved in degassed THF/EtOH (1:1) and $NaBH_4$ (25.0 equiv.) was added and the mixture was stirred for 45 min at room temp. Then MeI (50.0 equiv.) was added and again the mixture was stirred overnight. It was then quenched with a saturated solution of NH_4Cl and then extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification by column chromatography afforded the title compounds.

General Procedure 3 (GP3) – Synthesis of Epidithiodiketopiperazines 10xy: NaHMDS (1.0 M in THF, 3.00 equiv.) was added to a solution of sulfur (8.00 equiv.) in dry THF at room temperature. Then diketopiperazine **6xy** (1.00 equiv.) in dry THF and more NaHMDS (1.0 m in THF, 3.00 equiv.) were added and the mixture was stirred for 30 min at room temp. A saturated solution of NH_4Cl was added and the resulting mixture was extracted with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was dissolved in degassed THF/EtOH (1:1) and $NaBH_4$ (25.0 equiv.) was added. The mixture was stirred for 45 min at room temp. Then the mixture was cooled to 0 °C, quenched by the addition of a saturated solution of NH_4Cl, and extracted with EtOAc. The combined organic extracts were stirred with a solution of KI_3 for 10 min, a solution of $Na_2S_2O_3$ was added, and the mixture was stirred until the dark color disappeared. The resulting mixture was extracted with EtOAc. The combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification by column chromatography afforded the title compounds.

(3*S*,8*S*)-1,6-Diazatricyclo[6.2.0.0^{3,6}]decane-2,7-dione (6bb): This compound was synthesized following GP1 from L-azetidine-2-carboxylic acid (**5b**, 1.00 g, 9.09 mmol, 1.00 equiv.) in toluene (68 mL) at reflux for 6.5 h. The resulting crude product was purified by column chromatography (EtOAc). The title compound was obtained as a colorless solid (133 mg, 0.800 mmol, 16%). R_f (EtOAc) = 0.04, m.p. 191–196 °C (decomp.). $[\alpha]_D^{20}$ = +9.1 (*c* = 0.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52–2.61, 2.75–2.84 (2 m, 4 H, NCH_2CH_2), 4.01–4.09, 4.11–4.17 (2 m, 4 H, NCH_2), 4.98 (t, ^3J = 7.7 Hz, 2 H, 2 *C*H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5 (–, 2 NCH_2CH_2), 48.3 (–, 2 NCH_2), 63.4 (+, 2 *C*H), 168.7 (C_q, 2 *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2933 (vw), 2896 (vw), 1650 (m), 1447 (w), 1416 (m), 1286 (w), 1229 (w), 1114 (w), 1057 (w), 1044 (w), 972 (vw), 924 (w), 806 (vw), 767 (vw), 742 (w), 678 (w), 617 (vw), 519 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 166 (70) $[M]^+$, 110 (42), 56 (100). HRMS (EI): calcd. for $C_8H_{10}N_2O_2$ 166.0742; found 166.0741.

(7a*S*,15a*S*)-8,13,15a,16-Tetrahydropyrazino[1,2-*b*:4,5-*b*′]diisoquinoline-7,15(5*H*,7a*H*)-dione (6dd): This compound was synthesized following GP1 from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5d**, 1.00 g, 5.64 mmol, 1.00 equiv.) in toluene (40 mL) at reflux for 4 h. The resulting crude product was purified by column chromatography (*c*Hex/EtOAc, 1:1). The title compound was obtained as a colorless solid (516 mg, 1.62 mmol, 57%). R_f (*c*Hex/EtOAc, 1:1) = 0.28, m.p. 215–222 °C (decomp.). $[\alpha]_D^{20}$ = –422.3 (*c* = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.02 (dd, ^2J = 15.9, ^3J = 12.1 Hz, 2 H, 2 NCHC*H*H), 3.46 (dd, ^2J = 15.9, ^3J = 3.7 Hz, 2 H, 2 NCHCH*H*), 4.29 (dd, ^3J = 12.0, ^3J = 3.7 Hz, 2 H, 2 NC*H*), 4.35 (d, ^2J = 17.0 Hz, 2 H, 2 NC*H*H), 5.40 (d, ^2J = 17.0 Hz, 2 H, 2 NCH*H*), 7.18–7.28 (m, 8 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.2 (–, 2 $NCHCH_2$), 44.0 (–, 2 NCH_2), 55.7 (+, 2 NCH), 126.3 (+, 2 CH_{Ar}), 127.07 (+, 2 CH_{Ar}), 127.09 (+, 2 CH_{Ar}), 128.8 (+, 2 CH_{Ar}), 131.4 (C_q, 2 C_{Ar}), 132.3 (C_q, 2 C_{Ar}), 164.1 (C_q, 2 *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 3007 (vw), 2956 (vw), 2858 (vw), 1647 (m), 1586 (w), 1492 (vw), 1446 (w), 1347 (w), 1328 (w), 1293 (w), 1250 (w), 1221 (w), 1103 (w), 989 (w), 966 (vw), 773 (w), 760 (w), 750 (w), 711 (w), 689 (w), 604 (vw), 510 (vw), 476 (w), 441 (w), 428 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 318 (22) $[M]^+$, 86 (64), 84 (100). HRMS (EI): calcd. for $C_{20}H_{18}N_2O_2$ 318.1368; found 318.1365.

(4a*S*,6a*S*,14a*S*,15a*S*)-1,2,3,4,4a,7,12,14a,15,15a-Decahydro-14*H*-indolo[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-6,14(6a*H*)-dione (6de): This compound was synthesized following GP1 from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5d**, 151 mg, 0.853 mmol,

1.00 equiv.), with stirring with $MeOPCl_2$ at 35 °C for 2.5 h instead of overnight, and L-octahydroindole-2-carboxylic acid (**5e**, 173 mg, 1.02 mmol, 1.20 equiv.) in toluene (4.0 mL) under closed-vessel microwave conditions with dimethylimidazolium dimethyl phosphate (4 drops). The resulting crude product was purified by column chromatography (*c*Hex/EtOAc, 2:1→EtOAc). The title compound was obtained as a colorless solid (169 mg, 0.546 mmol, 64%). Furthermore, homodimers **6dd** [R_f (EtOAc) = 0.76, 27.2 mg, 76.8 μmol, 18%] and **6ee** [R_f (EtOAc) = 0.27, 37.0 mg, 51.2 μmol, 12%] were obtained as colorless solids. R_f (EtOAc) = 0.65, m.p. 152–155 °C. $[a]_D^{20}$ = –61.0 (*c* = 0.91, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02–1.12 (m, 1 H, CH_2), 1.19 (qt, ^3J = 12.9, ^4J = 2.7 Hz, 1 H, CH_2), 1.34 (qt, ^3J = 12.8, ^4J = 3.6 Hz, 1 H, CH_2), 1.49–1.58 (m, 1 H, CH_2), 1.61–1.69 (m, 1 H, CH_2), 1.73 (dt, ^2J = 13.1, ^3J = 4.7 Hz, 1 H, CH_2), 1.80–1.86 (m, 1 H, CH_2), 2.08–2.16 (m, 1 H, CH_2), 2.30–2.46 (m, 3 H, CH_2CHCH_2, 2 CH_2), 3.09 (dd, ^2J = 15.5, ^3J = 11.2 Hz, 1 H, CH_2), 3.36 (dd, ^2J = 15.5, ^3J = 4.4 Hz, 1 H, CH_2), 3.97 (ddd, ^3J = 11.4, ^3J = 4.5, ^4J = 1.0 Hz, 1 H, NC*H*), 4.02–4.07 (m, 1 H, NC*H*), 4.09–4.16 (m, 1 H, NC*H*), 4.29 (d, ^2J = 15.7 Hz, 1 H, CH_2), 5.03 (d, ^2J = 15.7 Hz, 1 H, CH_2), 7.20–7.32 (m, 4 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (–, *C*H_2), 23.3 (–, *C*H_2), 25.7 (–, *C*H_2), 27.4 (–, *C*H_2), 29.1 (–, *C*H_2), 30.2 (–, *C*H_2), 35.8 (+, CH_2CHCH_2), 43.9 (–, N*C*H_2), 55.9 (+, *C*H), 56.3 (+, *C*H), 59.2 (+, *C*H), 126.2 (+, *C*H_{Ar}), 127.1 (+, *C*H_{Ar}), 127.5 (+, *C*H_{Ar}), 127.7 (+, *C*H_{Ar}), 133.1 (C_q, *C*$_{Ar}$), 134.6 (C_q, *C*$_{Ar}$), 165.6 (C_q, *C*=O), 168.6 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2926 (vw), 2858 (vw), 1655 (w), 1496 (vw), 1448 (w), 1404 (w), 1360 (w), 1234 (w), 1188 (w), 1154 (vw), 1106 (vw), 1001 (vw), 930 (vw), 766 (vw), 743 (w), 662 (vw), 648 (vw), 604 (w), 562 (vw), 520 (vw), 505 (vw), 485 (w), 443 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 310 (100) [M]$^+$, 153 (27), 132 (50). HRMS (EI): calcd. for $C_{19}H_{22}N_2O_2$ 310.1681; found 310.1683.

(4a*S*,12a*S*)-1,5,10,12a-Tetrahydroazeto[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-4,12(2*H*,4a*H*)-dione (6db): This compound was synthesized following GP1 from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5d**, 150 mg, 0.849 mmol, 1.00 equiv.), with stirring with $MeOPCl_2$ at 35 °C for 2.5 h instead of overnight, and L-azetidine-2-carboxylic acid (**5b**, 103 mg, 1.02 mmol, 1.20 equiv.) in toluene (4.0 mL) under closed-vessel microwave conditions with dimethylimidazolium dimethyl phosphate (4 drops). The resulting crude product was purified by column chromatography (*c*Hex/EtOAc, 1:1). The title compound was obtained as a colorless solid (31.2 mg, 0.129 mmol, 15%). Furthermore, the homodimer **6dd** (51.6 mg, 0.162 mmol, 38%) was obtained as a colorless solid. R_f (EtOAc) = 0.19, m.p. 158–160 °C. $[a]_D^{20}$ = –8.6 (*c* = 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (dt, ^3J = 7.6, ^3J = 7.6 Hz, 2 H, NCHCH_2), 3.04–3.17 (m, 2 H, NCHCH_2), 3.92 (dd, ^2J = 10.4, ^3J = 5.1 Hz, 1 H, NCH_2), 3.97–4.07 (m, 2 H, NCH_2, NC*H*), 4.25 (d, ^2J = 15.8 Hz, 1 H, NCH_2), 4.78 (t, ^3J = 7.7 Hz, 1 H, NC*H*), 4.93 (d, ^2J = 15.8 Hz, 1 H, NCH_2), 7.15–7.27 (m, 4 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 (–, NCH*C*H_2), 29.5 (–, NCH*C*H_2), 43.9 (–, N*C*H_2), 47.9 (–, N*C*H_2), 54.4 (+, N*C*H), 61.5 (+, N*C*H), 126.2 (+, *C*H_{Ar}), 127.2 (+, *C*H_{Ar}), 127.5 (+, *C*H_{Ar}), 127.8 (+, *C*H_{Ar}), 132.93 (C_q, *C*$_{Ar}$), 134.3 (C_q, *C*$_{Ar}$), 168.2 (C_q, *C*=O), 168.6 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2952 (vw), 1650 (m), 1492 (w), 1438 (w), 1407 (w), 1367 (w), 1311 (w), 1231 (w), 1153 (w), 1128 (w), 1062 (w), 932 (w), 765 (w), 755 (w), 740 (w), 716 (w), 665 (w), 627 (vw), 607 (w), 577 (vw), 527 (vw), 507 (w), 492 (w), 472 (w), 442 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 242 (100) [M]$^+$, 214 (45), 132 (39), 104 (52). HRMS (EI): calcd. for $C_{14}H_{14}N_2O_2$ 242.1055; found 242.1052.

(4a*S*,5a*S*,9a*S*,11a*S*)-Decahydro-4*H*-azeto[1′,2′:4,5]pyrazino[1,2-*a*]indole-4,11(2*H*)-dione (6eb): This compound was synthesized following GP1 from L-octahydroindole-2-carboxylic acid (**5e**, 627 mg, 3.70 mmol, 1.00 equiv.), with stirring with $MeOPCl_2$ at 35 °C for 2 h instead of overnight, and L-azetidine-2-carboxylic acid (**5b**, 449 mg, 4.44 mmol, 1.20 equiv.) in toluene (17 mL) at reflux for 6 h with dimethylimidazolium dimethyl phosphate (4 drops). The resulting crude product was purified by column chromatography (EtOAc→CH_2Cl_2/MeOH, 98:2). The title compound was obtained as a colorless solid (151 mg, 0.643 mmol, 17%). R_f (EtOAc) = 0.18, m.p. 162–164 °C. $[a]_D^{20}$ = –1.2 (*c* = 0.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99–1.09 (m, 1 H, CH_2), 1.17 (qt, ^3J = 12.9, ^4J = 2.9 Hz, 1 H, CH_2), 1.32 (qt, ^3J = 12.9, ^4J = 3.5 Hz, 1 H, CH_2), 1.47–1.55 (m, 1 H, CH_2), 1.60–1.73 (m, 2 H, CH_2), 1.77–1.85 (m, 1 H, CH_2), 1.90–1.95 (m, 1 H, CH_2), 2.28–2.37 (m, 3 H, CH_2CHCH_2, 2 CH_2), 2.61–2.67 (m, 2 H, CH_2), 3.96–4.19 (m, 4 H, 2 NC*H*, 2 CH_2), 4.83 (t, ^3J = 7.7 Hz, 1 H, NC*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (–, *C*H_2), 22.6 (–, *C*H_2), 23.5 (–, *C*H_2), 25.8 (–, *C*H_2), 27.8 (–, *C*H_2), 27.9 (–, *C*H_2), 35.9 (+, CH_2CHCH_2), 47.5 (–, NCH_2), 56.3 (+, *C*H), 59.2 (+, *C*H), 63.1 (+, *C*H), 167.6 (C_q, *C*=O), 169.8 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2925 (w), 2857 (w), 1661 (m), 1399 (m), 1347 (w), 1279 (w), 1263 (w), 1233 (w), 1176 (w), 1149 (w), 1115 (w), 1057 (w), 953 (vw), 890 (w), 821 (vw), 772 (w), 741 (vw), 689 (w), 640 (w), 612 (w), 533 (vw), 509 (vw), 444 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 234 (51), 178 (69), 124 (100). HRMS (EI): calcd. for $C_{13}H_{18}N_2O_2$ 234.1368; found 234.1369.

(5a*S*,13a*S*)-1,2,3,6,11,13a-Hexahydro-13*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-5,13(5a*H*)-dione (6df): This compound was synthesized following GP1 from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5d**, 100 mg, 0.565 mmol, 1.00 equiv.) and L-proline (**5f**, 97.5 mg, 0.847 mmol, 1.50 equiv.) in toluene (5.0 mL) under closed-vessel microwave conditions with addition of dimethylimidazolium dimethyl phosphate. The resulting crude product was purified by column chromatography (EtOAc). The title compound was obtained as a colorless solid (12.2 mg, 47.6 μmol, 8%). Furthermore, homodimer **6ff** was obtained (25.3 mg, 0.130 mmol, 17%). R_f (EtOAc) = 0.22. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81–2.05 (m, 2 H, CH_2), 2.09–2.24 (m, 1 H, CH_2), 2.33 (dtd, ^2J = 13.6, ^3J = 7.0, ^4J = 3.3 Hz, 1 H, CH_2), 3.03 (dd, ^2J = 15.5, ^3J = 11.1 Hz, 1 H, CH_2), 3.34 (dd, ^2J = 15.6, ^3J = 4.3 Hz, 1 H, CH_2), 3.46–3.62 (m, 2 H, CH_2), 3.97–4.11 (m, 2 H, NC*H*), 4.37 (d, ^2J = 16.0 Hz, 1 H, CH_2), 4.86 (d, ^2J = 16.1 Hz, 1 H, CH_2), 7.09–7.36 (m, 4 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0 (–, *C*H_2), 28.4 (–, *C*H_2), 30.8 (–, *C*H_2), 44.4 (–, N*C*H_2), 45.4 (–, N*C*H_2), 56.0 (+, N*C*H), 59.1 (+, N*C*H), 126.3 (+, *C*H_{Ar}), 127.2 (+, *C*H_{Ar}), 127.7 (+, *C*H_{Ar}), 127.8 (+, *C*H_{Ar}), 132.9 (C_q, *C*$_{Ar}$), 134.4 (C_q, *C*$_{Ar}$), 165.3 (C_q, *C*=O), 167.8 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2976 (vw), 2862 (vw), 1671 (w), 1646 (m), 1417 (w), 1365 (w), 1346 (w), 1303 (w), 1272 (w), 1227 (w), 1211 (w), 1156 (w), 1110 (w), 1029 (w), 962 (w), 922 (w), 870 (vw), 747 (m), 650 (w), 627 (w), 603 (w), 568 (w), 508 (w), 494 (w), 459 (w), 441 (w), 425 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 256 (100) [M]$^+$, 257 (31). HRMS (EI): calcd. for $C_{15}H_{16}N_2O_2$ 256.1206; found 256.1207.

(4a*S*,11a*S*)-1,4a,5,11a-Tetrahydro-4*H*-azeto[1′,2′:4,5]pyrazino-[1,2-*a*]indole-4,11(2*H*)-dione (6bg): This compound was synthesized following GP1 from L-azetidine-2-carboxylic acid (**5b**, 50.0 mg, 0.495 mmol, 1.00 equiv.) and (*S*)-indoline-2-carboxylic acid (**5g**, 121 mg, 0.742 mmol, 1.50 equiv.) in toluene (5.0 mL) under closed-vessel microwave conditions with addition of dimethylimidazolium dimethyl phosphate. The resulting crude product was purified by column chromatography (*c*Hex/EtOAc, 1:1). The title compound was obtained as a colorless solid (5.9 mg, 25.8 μmol, 5%). R_f (*c*Hex/EtOAc, 1:1) = 0.10. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67–2.74 (m, 2 H, CH_2), 3.21 (dd, ^2J = 16.7, ^3J = 10.5 Hz, 1 H, CH_2),

3.69 (dd, ^2J = 16.7, ^3J = 9.0 Hz, 1 H, CH_2), 4.01–4.10 (m, 2 H, CH_2), 4.70 (t, ^3J = 9.7 Hz, 1 H, NC*H*), 4.99 (t, ^3J = 7.8 Hz, 1 H, NC*H*), 7.00–7.11 (m, 1 H, CH_{Ar}), 7.14–7.23 (m, 2 H, CH_{Ar}), 8.06 (d, ^3J = 7.8 Hz, 1 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8 (–, *C*H$_2$), 29.3 (–, *C*H$_2$), 47.9 (–, N*C*H$_2$), 60.0 (+, N*C*H), 62.9 (+, N*C*H), 115.9 (+, *C*H$_{Ar}$), 125.0 (+, *C*H$_{Ar}$), 125.1 (+, *C*H$_{Ar}$), 127.9 (+, *C*H$_{Ar}$), 130.9 (C$_q$, *C*$_{Ar}$), 140.6 (C$_q$, *C*$_{Ar}$), 167.8 (C$_q$, *C*=O), 167.9 (C$_q$, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2920 (w), 2853 (w), 1666 (m), 1598 (w), 1481 (w), 1460 (w), 1405 (m), 1325 (w), 1283 (w), 1245 (w), 1207 (w), 1112 (w), 1056 (w), 1023 (w), 964 (vw), 920 (vw), 871 (vw), 751 (m), 712 (w), 666 (vw), 636 (vw), 550 (w), 489 (w), 449 (w), 426 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 228 (100) [M]$^+$, 167 (40), 149 (100), 117 (55), 69 (51). HRMS (EI): calcd. for $C_{13}H_{12}N_2O_2$ 228.0893; found 228.0891.

(6a*S*,14a*S*)-1,3,4,7,12,14a-Hexahydropyrido[1′,2′:4,5]pyrazino-[1,2-*b*]isoquinoline-6,14(2*H*,6a*H*)-dione (6hd): This compound was synthesized following GP1 from L-pipecolic acid (**5h**, 500 mg, 3.87 mmol, 1.00 equiv.) and (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5d**, 823 mg, 4.65 mmol, 1.20 equiv.) in toluene (40 mL) at reflux for 4 h with the addition of dimethylimidazolium dimethyl phosphate. The resulting crude product was purified by column chromatography (*c*Hex/EtOAc, 3:1 → 2:1 → EtOAc). The title compound was obtained as an off-white solid (287 mg, 1.12 mmol, 24%). Furthermore, homodimers **6hh** (95.4 mg, 0.353 mmol, 8%) and **6dd** (236 mg, 0.874 mmol, 20%) were obtained both as colorless solids. R_f (EtOAc) = 0.22. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.68 (m, 3 H, CH_2), 1.77 (d, ^2J = 13.2 Hz, 1 H, CH_2), 2.00 (d, ^2J = 13.9 Hz, 1 H, CH_2), 2.39 (dd, ^2J = 13.1, ^3J = 2.3 Hz, 1 H, CH_2), 2.55 (td, ^2J = 12.9, ^3J = 2.9 Hz, 1 H, NCH_2), 2.97 (dd, ^2J = 15.8, ^3J = 12.6 Hz, 1 H, NCH_2), 3.47 (dd, ^2J = 16.1, ^3J = 3.6 Hz, 1 H, CH_2), 3.92 (dd, ^2J = 12.1, ^3J = 2.6 Hz, 1 H, CH_2), 4.15–4.25 (m, 2 H, 2 NC*H*), 4.69–4.77 (m, 1 H, NCH_2), 5.48 (d, ^2J = 17.3 Hz, 1 H, NCH_2), 7.11–7.25 (m, 4 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (–, *C*H$_2$), 24.8 (–, *C*H$_2$), 32.1 (–, *C*H$_2$), 34.9 (–, *C*H$_2$), 42.6 (–, N*C*H$_2$), 43.9 (–, N*C*H$_2$), 55.6 (+, N*C*H), 59.4 (+, N*C*H), 126.3 (+, *C*H$_{Ar}$), 126.9 (+, *C*H$_{Ar}$), 127.0 (+, *C*H$_{Ar}$), 129.0 (+, *C*H$_{Ar}$), 131.3 (C$_q$, *C*$_{Ar}$), 132.2 (C$_q$, *C*$_{Ar}$), 163.4 (C$_q$, *C*=O), 164.4 (C$_q$, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2929 (vw), 2849 (vw), 1649 (w), 1437 (w), 1346 (vw), 1320 (w), 1296 (w), 1233 (w), 1143 (vw), 1100 (vw), 1019 (vw), 978 (vw), 891 (vw), 850 (vw), 760 (w), 648 (vw), 601 (vw), 512 (vw), 487 (vw), 473 (vw), 433 (vw), 418 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 270 (100) [M]$^+$, 130 (25), 104 (33), 84 (33). HRMS (EI): calcd. for $C_{16}H_{18}N_2O_2$ 270.1363; found 270.1364.

(4a*S*,6a*S*,12a*S*,13a*S*)-Dodecahydro-12*H*-pyrido[1′,2′:4,5]pyrazino-[1,2-*a*]indole-6,12(6a*H*)-dione (6he): This compound was synthesized following GP1 from L-pipecolic acid (**5h**, 250 mg, 1.94 mmol, 1.00 equiv.) and L-octahydroindole-2-carboxylic acid (**5e**, 393 mg, 2.32 mmol, 1.20 equiv.) in toluene (20 mL) at reflux for 4 h with the addition of dimethylimidazolium dimethyl phosphate. The resulting crude product was purified by column chromatography (*c*Hex/EtOAc, 3:1 → 2:1 → 1:1). The title compound was obtained as an off-white solid (273 mg, 1.04 mmol, 53%). R_f (EtOAc) = 0.21. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.03–1.36 (m, 6 H, CH_2), 1.39–1.58 (m, 5 H, CH_2), 2.34–2.00 (m, 5 H, 4 CH_2,1 CH$_2$C*H*CH$_2$), 2.67 (td, ^3J = 12.9, ^4J = 3.5 Hz, 1 H, CH_2), 3.68–3.78 (m, 1 H, NCH_2), 4.02–4.10 (m, 2 H, 2 NC*H*), 4.10–4.16 (m, 1 H, NC*H*), 4.43 (d, ^2J = 13.7 Hz, 1 H, NCH_2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.7 (–, *C*H$_2$), 21.0 (–, *C*H$_2$), 22.7 (–, *C*H$_2$), 23.2 (–, *C*H$_2$), 23.4 (–, *C*H$_2$), 25.9 (–, *C*H$_2$), 28.5 (–, *C*H$_2$), 30.3 (–, *C*H$_2$), 35.4 (+, CH$_2$*C*HCH$_2$), 42.3 (–, N*C*H$_2$), 56.6 (+, *C*H), 57.5 (+, *C*H), 60.6 (+, *C*H), 165.6 (C$_q$, *C*=O), 169.3 (C$_q$, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2923 (w), 2854 (w), 1652 (m), 1448 (w), 1409 (m), 1370 (w), 1334 (w), 1288 (w), 1258 (w), 1202 (w), 1202 (w), 1135 (w), 1113 (w), 1005 (vw), 889 (vw), 865 (vw), 820 (vw), 660 (w), 633 (w), 609 (w), 556 (vw), 466 (vw), 442 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 262 (100) [M]$^+$, 84 (20). HRMS (EI): calcd. for $C_{15}H_{22}N_2O_2$ 262.1676; found 262.1678.

(5a*S*,13a*S*)-1,6,11,13a-Tetrahydro-3*H*-pyrrolo[1′,2′:4,5]pyrazino-[1,2-*b*]isoquinoline-3,5,13(2*H*,5a*H*)-trione (6di): This compound was synthesized following GP1 from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5d**, 550 mg, 3.11 mmol, 1.00 equiv.) and L-pyroglutamic acid (**5i**, 481 mg, 3.72 mmol, 1.20 equiv.) in toluene (40 mL) at reflux for 4 h with the addition of dimethylimidazolium dimethyl phosphate. The resulting crude product was purified by column chromatography (*c*Hex/EtOAc, 2:1). The title compound was obtained as an off-white solid (15.6 mg, 57.7 µmol, 2%). Furthermore, homodimer **6dd** was obtained as a colorless solid (256 mg, 0.805 mmol, 30%). R_f (EtOAc) = 0.24. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (dt, ^2J = 8.6, ^3J = 5.3 Hz, 2 H, CH_2), 2.62 (m, 2 H, CH_2), 3.21 (dd, ^2J = 15.5, ^3J = 9.9 Hz, 1 H, CH_2), 3.37 (dd, ^3J = 15.5, ^4J = 4.9 Hz, 1 H, CH_2), 4.17 (dd, ^2J = 9.8, ^3J = 4.9 Hz, 1 H, NC*H*), 4.42 (d, ^2J = 15.6 Hz, 1 H, NCH_2), 4.49 (t, ^3J = 8.5 Hz, 1 H, NC*H*), 4.96 (d, ^2J = 15.6 Hz, 1 H, NCH_2), 7.21–7.34 (m, 4 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (–, *C*H$_2$), 29.4 (–, *C*H$_2$), 31.6 (–, *C*H$_2$), 43.9 (–, N*C*H$_2$), 55.7 (+, N*C*H), 57.0 (+, N*C*H), 126.3 (+, *C*H$_{Ar}$), 127.6 (+, *C*H$_{Ar}$), 127.9 (+, *C*H$_{Ar}$), 128.0 (+, *C*H$_{Ar}$), 133.0 (C$_q$, *C*$_{Ar}$), 133.6 (C$_q$, *C*$_{Ar}$), 165.2 (C$_q$, *C*=O), 166.7 (C$_q$, *C*=O), 172.8 (C$_q$, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 3115 (w), 2923 (w), 1768 (vw), 1649 (vw), 1442 (vw), 1392 (w), 1112 (w), 763 (vw), 609 (vw), 493 (vw), 405 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 270 (100) [M]$^+$, 158 (22), 130 (39), 104 (21). HRMS (EI): calcd. for $C_{15}H_{14}N_2O_3$ 270.0999; found 270.0999.

(2*R*,5a*R*,7*R*,10a*R*)-2,7-Di-*tert*-butoxy-5a,10a-bis(methylthio)octahydro-5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (9cc): Prepared according to GP2, starting from diketopiperazine **6cc** (102 mg, 0.300 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 5:1) afforded the title compound (49.2 mg, 0.114 mmol, 38%) as a colorless solid. R_f (*c*Hex/EtOAc, 5:1) = 0.17, m.p. 142–148 °C. $[\alpha]_D^{20}$ = –28.6 (*c* = 1.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 [s, 18 H, 2 C(CH_3)$_3$], 2.28 (s, 6 H, 2 SCH_3), 2.48 (dd, ^2J = 14.7, ^3J = 3.5 Hz, 2 H, 2 C*H*HCSMe), 2.66 (dd, ^2J = 14.7, ^3J = 3.5 Hz, 2 H, 2 CH*H*CSMe), 3.36 (dd, ^2J = 12.4, ^3J = 5.6 Hz, 2 H, 2 NC*H*H), 4.13–4.19 (m, 2 H, 2 C*H*O*t*Bu), 4.29 (dd, ^2J = 12.4, ^3J = 7.6 Hz, 2 H, 2 NCH*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (+, 2 S*C*H$_3$), 28.2 [+, 2 C(*C*H$_3$)$_3$], 43.9 (–, 2 *C*H$_2$), 52.3 (–, 2 *C*H$_2$), 66.8 (+, 2 *C*HO*t*Bu), 69.1 (C$_q$, 2 *C*SCH$_3$), 74.2 [C$_q$, 2 *C*(CH$_3$)$_3$], 164.4 (C$_q$, 2 *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2968 (vw), 2921 (vw), 1658 (w), 1404 (w), 1389 (w), 1363 (w), 1233 (vw), 1189 (w), 1131 (vw), 1092 (w), 1015 (w), 901 (vw), 884 (vw), 770 (vw), 716 (vw), 688 (vw), 672 (vw), 660 (vw), 611 (vw), 484 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 430 (2) [M]$^+$, 381 (44), 336 (100) [M – 2SMe]$^+$, 280 (58), 225 (88). HRMS (EI): calcd. for $C_{20}H_{34}S_2N_2O_4$ 430.1960; found. 430.1957.

(2*R*,5a*R*,7*R*,10a*R*)-2,7-Di-*tert*-butoxytetrahydro-1*H*,5*H*,6*H*,10*H*-5a,10a-epidithiodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (10cc): Prepared according to GP3, starting from diketopiperazine **6cc** (109 mg, 0.323 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 5:1 → 3:1) afforded the title compound (40.4 mg, 0.101 mmol, 31%) as a colorless solid. R_f (*c*Hex/EtOAc, 5:1) = 0.53, m.p. 174–179 °C. $[\alpha]_D^{20}$ = –195.8 (*c* = 1.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 [s, 18 H, 2 C(CH_3)$_3$], 2.18 (dd, ^2J = 14.4, ^3J = 6.1 Hz, 2 H, 2 C*H*HCSMe), 3.31 (dd, ^2J = 14.4, ^3J = 7.3 Hz, 2 H, 2 CH*H*CSMe), 3.52 (dd, ^2J = 11.7, ^3J = 6.7 Hz, 2 H, 2 NC*H*H), 3.89 (dd, ^2J = 11.7, ^3J = 6.6 Hz, 2 H, 2 NCH*H*), 4.33

(quint., ^3J = 6.6 Hz, 2 H, 2 C*H*O*t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [+, 2 C(*C*H$_3$)$_3$], 39.7 (–, 2 *C*H$_2$), 51.4 (–, 2 *C*H$_2$), 68.6 (+, 2 *C*HO*t*Bu), 74.3, 74.7 [2 C$_q$, *C*S*S*C, 2 *C*(CH$_3$)$_3$], 163.5 (C$_q$, 2 *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 3370 (vw), 2923 (w), 2852 (w), 1692 (m), 1463 (w), 1435 (w), 1388 (w), 1364 (w), 1302 (vw), 1257 (w), 1213 (w), 1192 (w), 1158 (w), 1105 (w), 1090 (w), 1044 (w), 961 (vw), 937 (vw), 890 (w), 850 (vw), 685 (vw), 638 (w), 547 (vw), 504 (vw), 486 (w), 428 (vw), 402 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 400 (4) [M]$^+$, 385 (8), 336 (100) [M – S$_2$]$^+$, 280 (88), 224 (85), 206 (40), 57 (49). HRMS (EI): calcd. for $C_{18}H_{28}S_2N_2O_4$ 400.1491; found 400.1493.

6a,12a-Bis(methylthio)octahydrodipyrido[1,2-a:1′,2′-*d*]pyrazine-6,12(2*H*,6a*H*)-dione (9hh): Prepared according to GP2, starting from diketopiperazine **6hh** (43.3 mg, 0.195 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 3:1 → EtOAc) afforded the title compound (22.1 mg, 63.9 µmol, 33%, scalemic mixture) as a colorless solid. R_f (*c*Hex/EtOAc, 3:1) = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.49 (m, 2 H, C*H*$_2$), 1.59–1.69 (m, 2 H, C*H*$_2$), 1.72–1.84 (m, 4 H, C*H*$_2$), 1.91 (tt, ^3J = 13.4, ^4J = 3.5 Hz, 2 H, CH$_3$SC$_q$C*H*$_2$), 2.18 (s, 6 H, 2 SC*H*$_3$), 2.49 (ddd, ^2J = 14.6, ^3J = 4.9, ^4J = 3.1 Hz, 2 H, CH$_3$SC$_q$C*H*$_2$), 3.16 (td, ^3J = 15.6, ^4J = 3.1 Hz, 2 H, NC*H*$_2$), 4.48–4.55 (m, 2 H, NC*H*$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, 2 S*C*H$_3$), 19.7 (–, 2 *C*H$_2$), 24.2 (–, 2 *C*H$_2$), 32.6 (–, 2 *C*H$_2$), 38.4 (–, 2 *C*H$_2$), 66.2 (C$_q$, 2 *C*SCH$_3$), 165.5 (C$_q$, 2 *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2937 (m), 2857 (w), 1645 (s), 1434 (m), 1386 (s), 1278 (s), 1264 (m), 1246 (m), 1189 (m), 1154 (m), 1138 (m), 1107 (m), 1070 (m), 991 (w), 962 (m), 928 (m), 860 (w), 833 (m), 780 (w), 752 (w), 721 (w), 669 (m), 526 (w), 488 (w), 406 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 314 (1) [M]$^+$, 267 (100) [M – SCH$_3$]$^+$, 220 (85), 192 (33). HRMS (EI): calcd. for $C_{14}H_{22}N_2O_2S_2$ 314.1117; found 314.1116.

(4a*S*,6a*R*,14a*R*,15a*S*)-6a,14a-Bis(methylthio)-1,2,3,4,4a,7,12,14a,15,15a-decahydro-14*H*-indolo[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-6,14(6a*H*)-dione (9de): Prepared according to GP2, starting from diketopiperazine **6de** (35.8 mg, 0.115 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 10:1) afforded the title compound (13.0 mg, 32.3 µmol, 28%) as a yellow oil. R_f (*c*Hex/EtOAc, 10:1) = 0.23. $[\alpha]_D^{20}$ = –26.5 (*c* = 0.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–0.96 (m, 1 H, C*H*$_2$), 1.11–1.28 (m, 2 H, C*H*$_2$), 1.46–1.54 (m, 1 H, C*H*$_2$), 1.57–1.63 (m, 1 H, C*H*$_2$), 1.69–1.76 (m, 2 H, C*H*$_2$), 2.04 (s, 3 H, SC*H*$_3$), 2.16 (s, 3 H, SC*H*$_3$), 2.19–2.24 (m, 1 H, C*H*$_2$), 2.28–2.36 (m, 1 H, C*H*$_2$), 2.49–2.58 (m, 1 H, C*H*$_2$), 2.91–2.98 (m, 1 H, CH$_2$C*H*CH$_2$), 3.01 (d, ^2J = 16.7 Hz, 1 H, C*H*$_2$), 3.58 (d, ^2J = 16.7 Hz, 1 H, C*H*$_2$), 4.11–4.17 (m, 1 H, NC*H*), 4.50 (d, ^2J = 17.7 Hz, 1 H, C*H*$_2$), 4.97 (d, ^2J = 17.7 Hz, 1 H, C*H*$_2$), 7.12–7.25 (m, 4 H, C*H*$_{Ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (+, S*C*H$_3$), 15.3 (+, S*C*H$_3$), 21.2 (–, *C*H$_2$), 22.9 (–, *C*H$_2$), 25.3 (–, *C*H$_2$), 27.0 (–, *C*H$_2$), 31.8 (+, CH$_2$*C*HCH$_2$), 35.9 (–, *C*H$_2$), 37.5 (–, *C*H$_2$), 44.5 (–, *C*H$_2$), 58.2 (+, N*C*H), 64.8 (C$_q$, *C*SCH$_3$), 69.6 (C$_q$, *C*SCH$_3$), 125.7 (+, *C*H$_{Ar}$), 127.0 (+, *C*H$_{Ar}$), 127.3 (+, *C*H$_{Ar}$), 128.5 (+, *C*H$_{Ar}$), 130.4 (C$_q$, *C*$_{Ar}$), 131.3 (C$_q$, *C*$_{Ar}$), 165.4 (C$_q$, *C*=O), 165.8 (C$_q$, *C*=O) ppm.

(4a*S*,6a*R*,14a*R*,15a*S*)-2,3,4,4a,7,12,15,15a-Octahydro-1*H*,6*H*,14*H*-6a,14a-epidithioindolo[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-6,14-dione (10de): Prepared according to GP2, starting from diketopiperazine **6de** (44.4 mg, 0.143 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 5:1) afforded the title compound (9.0 mg, 24 µmol, 17%) as a yellow solid. R_f (*c*Hex/EtOAc, 5:1) = 0.20, m.p. 171–172 °C. $[\alpha]_D^{20}$ = –88.1 (*c* = 0.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.43 (m, 3 H, C*H*$_2$), 1.54–1.62 (m, 1 H, C*H*$_2$), 1.63–1.69 (m, 1 H, C*H*$_2$), 1.72–1.80 (m, 1 H, C*H*$_2$), 1.81–1.89 (m, 1 H, C*H*$_2$), 2.12–2.23 (m, 2 H, C*H*$_2$), 2.86–2.94 (m, 1 H, C*H*$_2$), 3.05–3.12 (m, 1 H, CH$_2$C*H*CH$_2$), 3.37 (d, ^2J = 16.4 Hz, 1 H, C*H*$_2$), 3.85 (d, ^2J = 16.4 Hz, 1 H, C*H*$_2$), 4.18–4.26 (m, 1 H, NC*H*), 4.45 (d, ^2J = 15.6 Hz, 1 H, C*H*$_2$), 4.92 (d, ^2J = 15.6 Hz, 1 H, C*H*$_2$), 7.27–7.35 (m, 4 H, C*H*$_{Ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (–, *C*H$_2$), 22.8 (–, *C*H$_2$), 25.1 (–, *C*H$_2$), 27.8 (–, *C*H$_2$), 33.5 (–, *C*H$_2$), 34.9 (–, *C*H$_2$), 35.3 (+, CH$_2$*C*HCH$_2$), 43.2 (–, *C*H$_2$), 58.2 (+, N*C*H), 73.1, 75.3 (2 C$_q$, *C*S*S*C), 126.3 (+, *C*H$_{Ar}$), 127.8 (+, *C*H$_{Ar}$), 128.1 (+, *C*H$_{Ar}$), 128.2 (+, *C*H$_{Ar}$), 131.9 (C$_q$, *C*$_{Ar}$), 132.0 (C$_q$, *C*$_{Ar}$), 162.4 (C$_q$, *C*=O), 165.1 (C$_q$, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2928 (m), 2860 (w), 1670 (s), 1461 (w), 1367 (m), 1298 (m), 1242 (m), 1199 (m), 1181 (m), 1093 (m), 1027 (w), 966 (w), 881 (w), 838 (w), 816 (w), 747 (m), 723 (w), 697 (w), 665 (w), 631 (w), 613 (w), 582 (w), 543 (m), 520 (w), 508 (w), 497 (w), 456 (w), 413 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 308 (77) [M – S$_2$]$^+$, 279 (22), 149 (57), 85 (59), 43 (100). HRMS (EI): calcd. for $C_{19}H_{20}N_2O_2$ [M – S$_2$]$^+$ 308.1525; found 308.1523.

4a,12a-Bis(methylthio)-1,5,10,12a-tetrahydroazeto[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-4,12(2*H*,4a*H*)-dione (9db): Prepared according to GP2, starting from diketopiperazine **6db** (20.3 mg, 83.8 µmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 3:1) afforded the title compound (12.3 mg, 36.8 µmol, 44%, scalemic mixture) as a yellow solid. R_f (*c*Hex/EtOAc, 3:1) = 0.15, m.p. 136–140 °C. $[\alpha]_D^{20}$ = –2.7 (*c* = 0.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, SC*H*$_3$), 2.37 (s, 3 H, SC*H*$_3$), 2.72 (ddd, ^2J = 11.9, ^3J = 7.8, ^3J = 4.0 Hz, 1 H, C*H*$_2$), 3.09–3.16 (m, 1 H, C*H*$_2$), 3.28 (d, ^2J = 16.2 Hz, 1 H, C*H*$_2$), 3.49 (d, ^2J = 16.2 Hz, 1 H, C*H*$_2$), 4.10–4.15 (m, 1 H, C*H*$_2$), 4.21–4.28 (m, 1 H, C*H*$_2$), 4.68 (s, 2 H, C*H*$_2$), 7.23–7.32 (m, 4 H, C*H*$_{Ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (+, S*C*H$_3$), 13.9 (+, S*C*H$_3$), 32.0 (–, *C*H$_2$), 35.9 (–, *C*H$_2$), 45.4 (–, *C*H$_2$), 47.3 (–, *C*H$_2$), 65.5 (C$_q$, *C*SCH$_3$), 72.3 (C$_q$, *C*SCH$_3$), 126.1 (+, *C*H$_{Ar}$), 127.4 (+, *C*H$_{Ar}$), 127.6 (+, *C*H$_{Ar}$), 128.2 (+, *C*H$_{Ar}$), 131.7 (C$_q$, *C*$_{Ar}$), 131.8 (C$_q$, *C*$_{Ar}$), 167.0 (C$_q$, *C*=O), 167.7 (C$_q$, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2919 (w), 2853 (vw), 1671 (w), 1650 (m), 1499 (vw), 1455 (vw), 1379 (m), 1282 (w), 1219 (w), 1184 (w), 1152 (w), 1112 (w), 1094 (w), 1019 (w), 991 (w), 951 (w), 917 (vw), 825 (vw), 800 (vw), 768 (w), 747 (w), 725 (w), 685 (w), 644 (vw), 603 (w), 562 (w), 507 (w), 407 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 334 (3) [M]$^+$, 300 (8), 287 (100) [M – SCH$_3$]$^+$, 279 (39), 259 (31), 239 (30), 167 (33), 149 (84), 130 (32). HRMS (EI): calcd. for $C_{16}H_{18}S_2N_2O_2$ 334.0810; found 334.0808.

1,2,5,10-Tetrahydro-4*H*,12*H*-4a,12a-epidithioazeto[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-4,12-dione and 1,2,5,10-Tetrahydro-4*H*,12*H*-4a,12a-epitrithioazeto[1′,2′:4,5]pyrazino[1,2-*b*]isoquinoline-4,12-dione (10db): Prepared according to GP3, starting from diketopiperazine **6db** (28.6 mg, 0.118 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 2:1) afforded the title compound as an inseparable mixture (10.5 mg, 34.5 µmol, 29%, scalemic mixture) as a colorless solid. R_f (*c*Hex/EtOAc, 2:1) = 0.36, m.p. 193–195 °C (decomp.). $[\alpha]_D^{20}$ = –236.2 (*c* = 0.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (ddd, ^2J = 13.4, ^3J = 8.5, ^3J = 5.2 Hz, 1 H, C*H*$_2$), 3.27 (d, ^2J = 16.7 Hz, 1 H, C*H*$_2$), 3.27–3.34 (m, 1 H, C*H*$_2$), 3.61 (d, ^2J = 16.7 Hz, 1 H, C*H*$_2$), 4.03 (td, ^2J = 9.3, ^3J = 5.2 Hz, 1 H, C*H*$_2$), 4.14 (td, ^2J = 8.8, ^3J = 7.1 Hz, 1 H, C*H*$_2$), 4.64 (d, ^2J = 16.2 Hz, 1 H, C*H*$_2$), 5.26 (d, ^2J = 16.2 Hz, 1 H, C*H*$_2$), 7.21–7.31 (m, 4 H, C*H*$_{Ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (–, *C*H$_2$), 35.3 (–, *C*H$_2$), 45.3 (–, *C*H$_2$), 46.1 (–, *C*H$_2$), 71.7 (C$_q$, *C*S), 80.0 (C$_q$, *C*S), 126.1 (+, *C*H$_{Ar}$), 127.8 (+, *C*H$_{Ar}$), 128.1 (+, *C*H$_{Ar}$), 128.4 (+, *C*H$_{Ar}$), 130.8 (C$_q$, *C*$_{Ar}$), 130.9 (C$_q$, *C*$_{Ar}$), 167.6 (C$_q$, *C*=O), 167.7 (C$_q$, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2919 (vw), 1685 (vw), 1451 (vw), 1411 (vw), 1356 (vw), 1274 (vw), 1230 (vw), 1194 (vw), 1160 (vw), 1101 (vw), 1005 (vw), 969 (vw), 761 (vw), 722 (vw), 674 (vw), 624 (vw), 542 (vw), 500 (vw) cm^{-1}. MS (EI, 70 eV):

m/*z* (%) = 336 (0.6) $[M]^+$ (trithio), 304 (0.4) $[M]^+$ (dithio), 272 (1) $[M - S_2]^+$ (trithio), $[M - S]^+$ (dithio), 240 (100) $[M - S_3]^+$ (trithio), $[M - S_2]^+$ (dithio). HRMS [EI]: calcd. for , $C_{14}H_{12}S_2N_2O_2$ (dithio) 304.0340; found 304.0338.

(4a*R*,5a*S*,9a*S*,11a*R*)-4a,11a-Bis(methylthio)decahydro-4*H*-azeto-[1′,2′:4,5]pyrazino[1,2-*a*]indole-4,11(2*H*)-dione (9eb): Prepared according to GP2, starting from diketopiperazine **6eb** (21.2 mg, 90.5 μmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 1:1) afforded the title compound (4.9 mg, 15 μmol, 17%) as a yellow oil. R_f (*c*Hex/EtOAc, 1:1) = 0.28. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–0.99 (m, 1 H, CH_2), 1.11–1.22 (m, 1 H, CH_2), 1.24–1.34 (m, 1 H, CH_2), 1.52–1.86 (m, 4 H, CH_2), 2.04 (dd, ^2J = 13.1 Hz, 1 H, CH_2), 2.12 (s, 3 H, SCH_3), 2.35 (s, 3 H, SCH_3), 2.48–2.57 (m, 2 H), 2.68 (ddd, ^2J = 12.1, ^3J = 7.8, ^3J = 4.2 Hz, 1 H, CH_2), 2.85–3.03 (m, 2 H), 4.00–4.07 (m, 2 H), 4.11–4.17 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (+, S*C*H$_3$), 14.7 (+, S*C*H$_3$), 21.1 (–, *C*H$_2$), 23.3 (–, *C*H$_2$), 25.3 (–, *C*H$_2$), 27.1 (–, *C*H$_2$), 31.9 (–, *C*H$_2$), 32.2 (+, CH$_2$*C*HCH$_2$), 35.5 (–, *C*H$_2$), 46.4 (–, *C*H$_2$), 58.1 (+, N*C*H), 71.4 (C_q, *C*SCH$_3$), 74.2 (C_q, *C*SCH$_3$), 167.2 (C_q, *C*=O), 169.8 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2921 (vw), 2854 (vw), 1664 (vw), 1383 (vw), 1168 (vw), 1102 (vw), 956 (vw), 841 (vw), 819 (vw), 793 (vw), 727 (vw), 621 (vw), 464 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 326 (0.3) $[M]^+$, 279 (3) $[M - SCH_3]^+$, 232 (0.6) $[M - 2SCH_3]^+$, 86 (61), 84 (100). HRMS (EI): calcd. for $C_{15}H_{22}S_2N_2O_2$ 326.1123; found 326.1121.

6a,14a-Bis(methylthio)-1,3,4,7,12,14a-hexahydropyrido[1′,2′:4,5]-pyrazino[1,2-*b*]isoquinoline-6,14(2*H*,6a*H*)-dione (9hd): Prepared according to GP2, starting from diketopiperazine **6hd** (52.8 mg, 0.195 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 10:1) afforded the title compound (27.1 mg, 75.1 μmol, 39%, scalemic mixture) as a colorless solid. R_f (*c*Hex/EtOAc, 5:1) = 0.24. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (m, 2 H, CH_2), 1.68 (ddd, ^2J = 14.6, ^3J = 13.4, ^3J = 3.7 Hz, 1 H, CH_2), 1.82 (dd, ^2J = 18.6, ^3J = 16.4 Hz, 2 H, CH_2), 1.90–2.01 (m, 1 H, NCH_2), 2.13 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 2.50–2.59 (m, 1 H, NCH_2), 3.18–3.29 (m, 2 H, CH_2), 3.63 (d, ^2J = 16.9 Hz, 1 H, CH_2), 4.52–4.62 (m, 1 H, NCH_2), 5.16 (d, ^2J = 17.8 Hz, 1 H, NCH_2), 7.16–7.31 (m, 4 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, *C*H$_3$), 14.8 (+, *C*H$_3$), 19.5 (–, *C*H$_2$), 24.2 (–, *C*H$_2$), 32.5 (–, *C*H$_2$), 37.5 (–, *C*H$_2$), 38.6 (–, N*C*H$_2$), 43.9 (–, N*C*H$_2$), 68.0 (C_q, C_qS*C*H$_3$), 64.3 (C_q, C_qS*C*H$_3$), 125.8 (+, *C*H$_{Ar}$), 126.9 (+, *C*H$_{Ar}$), 127.3 (+, *C*H$_{Ar}$), 128.6 (+, *C*H$_{Ar}$), 130.0 (C_q, C_{Ar}), 131.0 (C_q, C_{Ar}), 165.2 (C_q, *C*=O), 165.7 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2918 (w), 1652 (m), 1499 (vw), 1383 (m), 1281 (w), 1243 (w), 1179 (w), 1141 (w), 1113 (w), 1071 (w), 980 (w), 858 (w), 749 (m), 731 (w), 707 (w), 680 (w), 603 (vw), 555 (w), 530 (vw), 508 (w), 430 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 362 (1) $[M]^+$, 315 (68) $[M - SCH_3]^+$, 268 (100) $[M - 2SCH_3]^+$, 240 (95), 130 (42), 103 (20). HRMS (EI): calcd. for $C_{18}H_{22}N_2O_2S_2$ 362.1117; found 362.1119.

1,2,3,4,7,12-Hexahydro-6*H*,14*H*-6a,14a-epidithiopyrido[1′,2′:4,5]-pyrazino[1,2-*b*]isoquinoline-6,14-dione (10hd): Prepared according to GP3, starting from diketopiperazine **6hd** (52.8 mg, 0.195 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 5:1) afforded the title compound (12.5 mg, 37.6 μmol, 22%, scalemic mixture) as a colorless solid. R_f (*c*Hex/EtOAc, 5:1) = 0.27. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.58 (m, 2 H, CH_2), 1.71 (m, 1 H, CH_2), 1.82–1.95 (m, 2 H, CH_2), 2.43 (ddd, ^2J = 15.8, ^3J = 13.2, ^3J = 4.1 Hz, 1 H, CH_2), 2.92 (td, ^3J = 13.2, ^3J = 3.9 Hz, 1 H, NCH_2), 3.33 (d, ^2J = 16.4 Hz, 1 H, NCH_2), 3.82 (d, ^2J = 16.4 Hz, 1 H, CH_2), 4.06 (ddt, ^2J = 15.6, ^3J = 4.9, ^3J = 2.1 Hz, 1 H, CH_2), 4.47 (d, ^2J = 15.5 Hz, 1 H, NCH_2), 4.85 (d, ^2J = 15.6 Hz, 1 H, NCH_2), 7.18–7.32 (m, 4 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5 (–, *C*H$_2$), 22.3 (–, *C*H$_2$), 29.1 (–, *C*H$_2$), 33.4 (–, *C*H$_2$), 40.8 (–, N*C*H$_2$), 43.2 (–, N*C*H$_2$), 69.8 (C_q, C_qS$_2$), 71.9 (C_q. C_qS$_2$), 126.3 (+, *C*H$_{Ar}$), 127.9 (+, *C*H$_{Ar}$), 128.2 (+, *C*H$_{Ar}$), 128.3 (+, *C*H$_{Ar}$), 130.7 (C_q, C_{Ar}), 131.0 (C_q, C_{Ar}), 162.9 (C_q, *C*=O), 165.1 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2925 (vw), 2849 (vw), 1673 (w), 1494 (vw), 1444 (vw), 1354 (vw), 1255 (vw), 1238 (vw), 1168 (vw), 1146 (vw), 1115 (vw), 1050 (vw), 962 (vw), 896 (vw), 853 (vw), 749 (vw), 712 (vw), 660 (vw), 645 (vw), 619 (vw), 548 (vw), 525 (vw), 490 (vw), 435 (vw) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 332 (1) $[M]^+$, 270 (100) $[M - S_2]^+$. HRMS (EI): calcd. for $C_{16}H_{16}N_2O_2S_2$ 332.0648; found 332.0649.

(4a*S*,6a*R*,12a*R*,13a*S*)-6a,12a-Bis(methylthio)dodecahydro-12*H*-pyrido[1′,2′:4,5]pyrazino[1,2-*a*]indole-6,12(6a*H*)-dione (9he): Prepared according to GP2, starting from diketopiperazine **6he** (43.5 mg, 0.166 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 10:1→5:1) afforded the title compound (17.0 mg, 75.1 μmol, 29%) as an off-white solid. R_f (*c*Hex/EtOAc, 5:1) = 0.27. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (ddd, ^2J = 14.0, ^3J = 10.5, ^4J = 3.7 Hz, 1 H, CH_2), 1.14–1.31 (m, 3 H, CH_2), 1.49–1.58 (m, 2 H, CH_2), 1.62 (dd, ^2J = 13.1, ^3J = 3.3 Hz, 1 H, CH_2), 1.70–1.83 (m, 4 H, CH_2), 1.91 (tt, ^2J = 13.4, ^3J = 3.3 Hz, 1 H, CH_2), 2.16 (s, 3 H, SCH_3), 2.18–2.26 (m, 4 H, SCH_3, CH$_2$C*H*CH$_2$), 2.32 (t, ^3J = 13.1 Hz, 1 H, CH_2), 2.45–2.59 (m, 2 H, CH_2), 2.97 (ddd, ^2J = 18.6, ^3J = 10.4, ^4J = 5.4 Hz, 1 H, CH_2), 3.08 (td, ^2J = 13.4, ^3J = 3.1 Hz, 1 H, NCH_2), 4.10–4.20 (m, 1 H, NCH_2), 4.45–5.56 (m, 1 H, NC*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (+, *C*H$_3$), 15.4 (+, *C*H$_3$), 19.5 (–, *C*H$_2$), 21.2 (–, *C*H$_2$), 23.0 (–, *C*H$_2$), 24.3 (–, *C*H$_2$), 25.3 (–, *C*H$_2$), 26.9 (–, *C*H$_2$), 31.6 (+, CH$_2$*C*HCH$_2$), 32.5 (–, *C*H$_2$), 36.1 (–, *C*H$_2$), 38.4 (–, N*C*H$_2$), 58.1 (+, *C*H), 65.4 (C_q, C_qSCH$_3$), 68.4 (C_q, C_qSCH$_3$), 164.4 (C_q, *C*=O), 164.8 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2920 (m), 2854 (w), 1726 (w), 1650 (s), 1386 (s), 1287 (m), 1263 (m), 1199 (m), 1158 (m), 1135 (m), 1103 (w), 1070 (w), 1024 (w), 939 (w), 891 (w), 834 (w), 813 (w), 780 (w), 747 (w), 702 (w), 670 (m), 605 (w), 585 (w), 517 (w), 451 (w), 435 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 354 (2) $[M]^+$, 307 (100) $[M - SCH_3]^+$, 260 (87) $[M - (SCH_3)_2]^+$, 232 (22), 179 (17). HRMS (EI): calcd. for $C_{17}H_{26}N_2O_2S_2$ 354.1430; found 354.1432.

(4a*S*,6a*R*,12a*R*,13a*S*)-Decahydro-1*H*,6*H*,12*H*-6a,12a-epidithio-pyrido[1′,2′:4,5]pyrazino[1,2-*a*]indole-6,12-dione (10he): Prepared according to GP3, starting from diketopiperazine **6he** (43.2 mg, 0.165 mmol, 1.00 equiv.). Column chromatography (*c*Hex/EtOAc, 10:1→5:1) afforded the title compound (10.7 mg, 33.0 μmol, 20%) as an off-white solid. R_f (*c*Hex/EtOAc, 5:1) = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (dd, ^2J = 8.4, ^3J = 5.8 Hz, 4 H, CH_2), 1.69–1.96 (m, 6 H, CH_2), 2.11–2.25 (m, 3 H, CH_2), 2.44 (ddd, ^2J = 15.9, ^3J = 13.2, ^3J = 4.1 Hz, 1 H, CH_2), 2.87 (ddd, ^2J = 13.1, ^3J = 6.4, ^3J = 2.5 Hz, 1 H, CH$_2$C*H*CH$_2$), 2.96 (td, ^2J = 13.2, ^3J = 3.8 Hz, 1 H, CH_2), 3.01–3.09 (m, 1 H, NC*H*), 4.12 (q, ^3J = 7.1 Hz, 2 H, 1 CH_2, 1 NCH_2), 4.23 (dt, ^2J = 12.8, ^3J = 6.4 Hz, 1 H, NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4 (–, *C*H$_2$), 20.8 (–, *C*H$_2$), 22.3 (–, *C*H$_2$), 22.8 (–, *C*H$_2$), 25.1 (–, *C*H$_2$), 27.8 (–, *C*H$_2$), 28.6 (–, *C*H$_2$), 34.6 (–, *C*H$_2$), 35.0 (+, CH$_2$*C*HCH$_2$) 41.0 (–, N*C*H$_2$), 58.3 (+, *C*H), 71.3 (+, C_qS$_2$), 71.4 (+, C_qS$_2$), 160.0 (C_q, *C*=O), 165.0 (C_q, *C*=O) ppm. IR (ATR): $\tilde{\nu}$ = 2923 (w), 2854 (w), 1684 (m), 1446 (w), 1358 (w), 1263 (w), 1205 (w), 1166 (w), 1147 (w), 1107 (w), 1058 (w), 845 (w), 739 (vw), 687 (vw), 654 (w), 599 (vw), 504 (w), 454 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 324 (1) $[M]^+$, 260 (100) $[M - S_2]^+$, 179 (19). HRMS (EI): calcd. for $C_{15}H_{20}N_2O_2S_2$ 324.0961; found 324.0962.

Crystal Structure Determinations of 6bb, 6cc, 6dd, 6de, 6eb, 6gf, 6ge, 6hd, 6di, 9aa, 9dd, 9fe, and SI-11: Single-crystal X-ray diffraction studies were carried out with a Bruker–Nonius Kappa CCD

diffractometer at 123(2) K using Mo-K_α radiation (λ = 0.71073 Å; **6bb**, **6cc**, **6dd**, **6eb**, **6gf**, **6ge**, **9dd**, **SI-11**), a Bruker ApexDuo diffractometer at 120(2) K using Mo-K_α radiation (λ = 0.71073 Å; **6de**), a Bruker–Nonius ApexII diffractometer at 123(2) K using Mo-K_α radiation (λ = 0.71073 Å; **9aa**, **9fe**), and a Bruker D8 Venture diffractometer equipped with a Photon100 detector at 123(2) K using Cu-K_α radiation (λ = 1.54178 Å; **6hd**, **6di**). Direct Methods (SHELXS-97)[24] were used for structure solution and refinement was carried out by using SHELXL97 or SHELXL-2013/2014[24] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined by using a riding model. For **6hd** an extinction correction was applied. Semi-empirical absorption corrections were applied for **6de**, **6eb**, **6hd**, **6di**, and **9dd**. **SI-11** is a non-merohedral twin with three domains.

The absolute configurations of **6bb**, **6cc**, **6dd**, **6de**, **6eb**, **6gf**, and **6ge** were not been established by anomalous dispersion effects in diffraction measurement of the crystals. The enantiomers were assigned by reference to an unchanging stereogenic center in the synthetic procedure. The absolute structures could not be determined reliably by refinement of Flack's x parameter,[25] Parsons' x parameter,[26] or by using Bayesian statistics on Bijvoet differences (Hooft's y parameter[27]).

The absolute configurations of **6hd**, **6di**, **9aa**, and **9fe** were established by anomalous dispersion effects in diffraction measurements of the crystals. In addition, the enantiomers were assigned by reference to an unchanging chiral center in the synthetic procedure for **6hd**, **6di**, and **9fe**.

6bb: Colorless crystals, $C_8H_{10}N_2O_2$, M_r = 166.18, crystal size 0.40 × 0.20 × 0.12 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.5974(2), b = 8.1688(4), c = 14.1310(5) Å, V = 761.56(5) Å^3, Z = 4, ρ = 1.449 Mg m^{-3}, μ(Mo-K_α) = 0.106 mm^{-1}, F(000) = 352, $2\theta_{max}$ = 55°, 7622 reflections, of which 1746 were independent (R_{int} = 0.024), 109 parameters, R_1 = 0.029 [for 1678 $I > 2\sigma(I)$], wR_2 = 0.076 (all data), S = 1.07, largest diff. peak/hole = 0.281/–0.136 e Å^{-3}, Flack's x = 0.2(10), Parsons' x = 0.0(3), Hooft's y = 0.7(4).

6cc: Colorless crystals, $C_{18}H_{30}N_2O_4$, M_r = 338.44, crystal size 0.45 × 0.25 × 0.15 mm, monoclinic, space group $P2_1$ (No. 4), a = 16.036(2), b = 6.047(1), c = 19.709(2) Å, β = 99.60(1)°, V = 1884.4(4) Å^3, Z = 4, ρ = 1.193 Mg m^{-3}, μ(Mo-K_α) = 0.084 mm^{-1}, F(000) = 736, $2\theta_{max}$ = 50°, 25564 reflections, of which 6639 were independent (R_{int} = 0.045), 433 parameters, 1 restraint, R_1 = 0.039 [for 5547 $I > 2\sigma(I)$], wR_2 = 0.079 (all data), S = 1.09, largest diff. peak/hole = 0.134/–0.152 e Å^{-3}, Flack's x = 0.4(7), Parsons' x = 0.6(4), Hooft's y = 0.7(5).

6dd: Colorless crystals, $C_{20}H_{18}N_2O_2$, M_r = 318.36, crystal size 0.20 × 0.12 × 0.04 mm, hexagonal, space group $P6_4$ (No. 172), a = 13.148(2), c = 7.823(1) Å, V = 1171.2(3) Å^3, Z = 3, ρ = 1.354 Mg m^{-3}, μ(Mo-K_α) = 0.088 mm^{-1}, F(000) = 504, $2\theta_{max}$ = 55°, 15941 reflections, of which 1780 were independent (R_{int} = 0.061), 109 parameters, 1 restraint, R_1 = 0.048 [for 1497 $I > 2\sigma(I)$], wR_2 = 0.109 (all data), S = 1.05, largest diff. peak/hole = 0.191/–0.266 e Å^{-3}, Flack's x = 2(2), Parsons' x = 1.8(7), Hooft's y = 0.7(9).

6de: Colorless crystals, $C_{19}H_{22}N_2O_2$, M_r = 310.39, crystal size 0.15 × 0.10 × 0.05 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 10.3629(3), b = 10.5958(4), c = 14.2711(5) Å, V = 1567.01(9) Å^3, Z = 4, ρ = 1.316 Mg m^{-3}, μ(Mo-K_α) = 0.086 mm^{-1}, F(000) = 664, $2\theta_{max}$ = 55°, 19869 reflections, of which 3598 were independent (R_{int} = 0.026), 208 parameters, R_1 = 0.029 [for 3436 $I > 2\sigma(I)$], wR_2 = 0.075 (all data), S = 1.04, largest diff. peak/hole = 0.207/–0.135 e Å^{-3}, Flack's x = 0.0(8), Parsons' x = –0.3(3), Hooft's y = –0.2(3).

6eb: Colorless crystals, $C_{13}H_{18}N_2O_2$, M_r = 234.29, crystal size 0.16 × 0.12 × 0.04 mm, monoclinic, space group $P2_1$ (No. 4), a = 9.128(2), b = 5.978(1), c = 10.924(2) Å, β = 99.15(1)°, V = 588.51(19) Å^3, Z = 2, ρ = 1.322 Mg m^{-3}, μ(Mo-K_α) = 0.090 mm^{-1}, F(000) = 252, $2\theta_{max}$ = 52°, 8164 reflections, of which 2313 were independent (R_{int} = 0.037), 154 parameters, 1 restraint, R_1 = 0.040 [for 1994 $I > 2\sigma(I)$], wR_2 = 0.090 (all data), S = 1.08, largest diff. peak/hole = 0.160/–0.217 e Å^{-3}, Flack's x = –1.0(14), Parsons' x = –1.0(7), Hooft's y = 0.2(9).

6gf: Colorless crystals, $C_{14}H_{14}N_2O_2$, M_r = 242.27, crystal size 0.50 × 0.25 × 0.15 mm, tetragonal, space group $P4_12_12$ (No. 92), a = 8.445(1), c = 32.226(6) Å, V = 2298.3(6) Å^3, Z = 8, ρ = 1.400 Mg m^{-3}, μ(Mo-K_α) = 0.095 mm^{-1}, F(000) = 1024, $2\theta_{max}$ = 55°, 27245 reflections, of which 2570 were independent (R_{int} = 0.033), 163 parameters, R_1 = 0.036 [for 2448 $I > 2\sigma(I)$], wR_2 = 0.081 (all data), S = 1.14, largest diff. peak/hole = 0.233/–0.177 e Å^{-3}, Flack's x = –0.4(12), Parsons' x = –0.1(3), Hooft's y = 0.0(3).

6ge: Colorless crystals, $C_{18}H_{20}N_2O_2$, M_r = 296.36, crystal size 0.40 × 0.12 × 0.08 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 8.3378(6), b = 8.8511(6), c = 19.6570(11) Å, V = 1450.66(16) Å^3, Z = 4, ρ = 1.357 Mg m^{-3}, μ(Mo-K_α) = 0.089 mm^{-1}, F(000) = 632, $2\theta_{max}$ = 55°, 16807 reflections, of which 3323 were independent (R_{int} = 0.034), 199 parameters, R_1 = 0.037 [for 2960 $I > 2\sigma(I)$], wR_2 = 0.087 (all data), S = 1.07, largest diff. peak/hole = 0.226/–0.242 e Å^{-3}, Flack's x = –1.4(11), Parsons' x = –0.5(4), Hooft's y = –0.3(4).

6hd: Colorless crystals, $C_{16}H_{18}N_2O_2$, M_r = 270.32, crystal size 0.36 × 0.18 × 0.04 mm, monoclinic, space group $P2_1$ (No. 4), a = 8.0622(4), b = 10.2212(5), c = 8.2711(4) Å, β = 94.022(1)°, V = 679.90(6) Å^3, Z = 2, ρ = 1.320 Mg m^{-3}, μ(Cu-K_α) = 0.707 mm^{-1}, F(000) = 288, $2\theta_{max}$ = 144.2°, 8180 reflections, of which 2614 were independent (R_{int} = 0.019), 182 parameters, 1 restraint, R_1 = 0.026 [for 2602 $I > 2\sigma(I)$], wR_2 = 0.071 (all data), S = 1.04, largest diff. peak/hole = 0.220/–0.130 e Å^{-3}, Flack's x = 0.00(21), Parsons' x = 0.02(6), Hooft's y = 0.02(4).

6di: Colorless crystals, $C_{15}H_{14}N_2O_3$, M_r = 270.28, crystal size 0.10 × 0.06 × 0.02 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 5.9558(3), b = 9.9182(4), c = 21.0431(9) Å, V = 1243.03(10) Å^3, Z = 4, ρ = 1.444 Mg m^{-3}, μ(Cu-K_α) = 0.842 mm^{-1}, F(000) = 568, $2\theta_{max}$ = 144.8°, 14649 reflections, of which 2443 were independent (R_{int} = 0.047), 181 parameters, R_1 = 0.040 [for 2349 $I > 2\sigma(I)$], wR_2 = 0.102 (all data), S = 1.09, largest diff. peak/hole = 0.220/–0.197 e Å^{-3}, Flack's x = –0.08(35), Parsons' x = –0.03(12), Hooft's y = –0.02(11).

9aa: Colorless crystals, $C_{10}H_{18}N_2O_2S_2$, M_r = 262.38, crystal size 0.24 × 0.12 × 0.06 mm, monoclinic, space group $P2_1$ (No. 4), a = 6.1450(1), b = 6.8961(3), c = 15.1630(6) Å, β = 95.074(2)°, V = 640.04(4) Å^3, Z = 2, ρ = 1.361 Mg m^{-3}, μ(Mo-K_α) = 0.404 mm^{-1}, F(000) = 280, $2\theta_{max}$ = 55°, 7703 reflections, of which 2886 were independent (R_{int} = 0.023), 151 parameters, 1 restraint, R_1 = 0.024 [for 2819 $I > 2\sigma(I)$], wR_2 = 0.058 (all data), S = 1.08, largest diff. peak/hole = 0.222/–0.179 e Å^{-3}, Flack's x = 0.02(5), Parsons' x = 0.03(2), Hooft's y = 0.03(2).

9dd: Colorless crystals, $C_{22}H_{22}N_2O_2S_2$, M_r = 410.54, crystal size 0.50 × 0.15 × 0.10 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 12.8773(13), b = 7.9822(7), c = 19.5887(12) Å, β = 107.621(5)°, V = 1919.0(3) Å^3, Z = 4, ρ = 1.421 Mg m^{-3}, μ(Mo-K_α) = 0.299 mm^{-1}, F(000) = 864, $2\theta_{max}$ = 55°, 34821 reflections, of which 4390 were independent (R_{int} = 0.027), 255 parameters, R_1 = 0.028

[for 4025 $I > 2\sigma(I)$], wR_2 = 0.076 (all data), S = 1.05, largest diff. peak/hole = 0.394/–0.215 e Å^{-3}.

9fe: Colorless crystals, $C_{16}H_{24}N_2O_2S_2$, M_r = 340.49, crystal size 0.28 × 0.20 × 0.04 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 11.0962(9), b = 11.2692(6), c = 13.3747(11) Å, V = 1672.4(2) Å^3, Z = 4, ρ = 1.352 Mg m^{-3}, μ(Mo-K_α) = 0.327 mm^{-1}, F(000) = 728, $2\theta_{max}$ = 55°, 14845 reflections, of which 3813 were independent (R_{int} = 0.065), 201 parameters, R_1 = 0.042 [for 3473 $I > 2\sigma(I)$], wR_2 = 0.090 (all data), S = 1.09, largest diff. peak/hole = 0.294/–0.249 e Å^{-3}, Flack's x = 0.04(8), Parsons' x = 0.01(4), Hooft's y = 0.03(4).

SI-11: Colorless crystals, $C_{10}H_{14}N_2O_4S_2$, M_r = 290.35, crystal size 0.40 × 0.25 × 0.15 mm, triclinic, space group $P\bar{1}$ (No. 2), a = 8.143(1), b = 9.334(1), c = 9.444(1) Å, α = 73.17(1), β = 75.35(1), γ = 75.96(1)°, V = 653.51(13) Å^3, Z = 2, ρ = 1.476 Mg m^{-3}, μ(Mo-K_α) = 0.415 mm^{-1}, F(000) = 304, $2\theta_{max}$ = 55°, 2938 reflections, of which 2938 were independent (R_{int} = 0.000, non-merohedral twin with three domains), 169 parameters, R_1 = 0.110 [for 2413 $I > 2\sigma(I)$], wR_2 = 0.367 (all data), S = 1.19, largest diff. peak/hole = 1.565/–0.885 e Å^{-3}.

CCDC-1407307 (for **6bb**), -1407308 (for **6cc**), -1407309 (for **6dd**), -1407310 (for **6de**), -140731 (for **6eb**), -1407312 (for **6gf**), -1407313 (for **6ge**), -1407314 (for **6hd**), -1407315 (for **6di**), -1407316 (for **9aa**), -1407317 (for **9dd**), -1407318 (for **9ef**), and -1407319 (for **SI-11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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