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Graphical abstract

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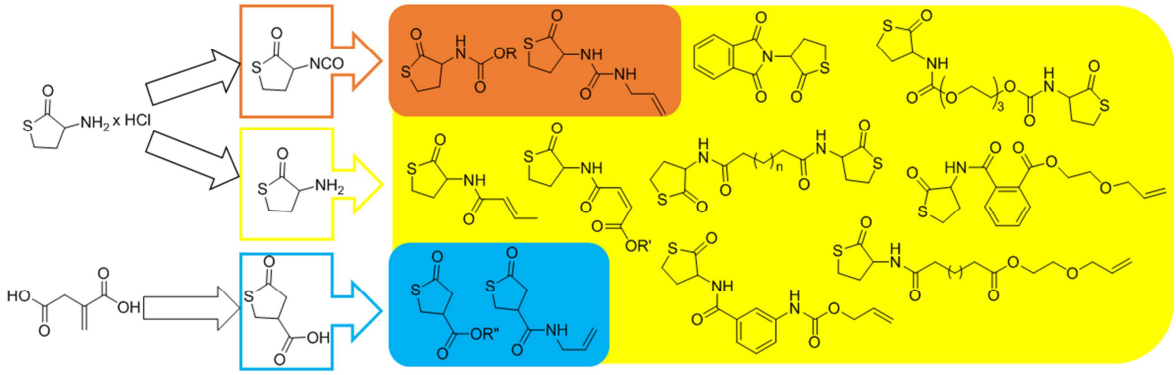

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Synthesis of thiolactone building blocks as potential precursors for sustainable functional materials

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ABSTRACT

A library of multifunctional monomers from homocysteine thiolactone and thioparaconic acid were synthesized using straightforward chemistry routes. A generic protocol was developed, leading to multi-gram amounts of the targeted compounds and enabling up-scaling experiments for promising compounds in the area of functional coatings. Aspects considered during selection of targets and synthesis pathways included functional diversity, expected physical properties, sustainability and commercial availability of reagents, as well as feasibility to achieve an industrially relevant process. Trends were observed in yield, physical properties and chemical behavior.

1. Introduction

Thiolactones are an interesting class of heterocycles that gained much attention within the last few years in several research fields.[1,2] Especially homocysteine thiolactone **1**, i.e. 2-aminodihydrothiophen-2(3*H*)-one, which is available on large scale and originating from a renewable source, plays an important role in polymer chemistry.[3-8] Originally used in biochemistry and medicine, its derivatives find application in bioconjugation or as drugs for treatment of liver diseases.[9,10] Recent progress in polymer science demonstrates the versatility of these compounds in polymeric materials, such as hydrogels[11] and functionalized hybrid materials.[12]

Moreover, this class of cyclic thiol derivatives can be used for creating functional polyurethanes.[3] The use of thiol-ene chemistry as alternative synthetic step-growth technique for polymers has several advantages over common free radical bulk polymerizations, such as high conversion and lack of inhibition by oxygen.[13] Also, it shows much potential over the commonly used isocyanate strategy in the widely applied class of polyurethanes, such as late gelation time, low shrinkage, functional group tolerance and the use of less harmful compounds.[14] On the other hand, thiol compounds have certain disadvantages, such as oxygen sensitivity and, thus, limited shelf life and commercial availability. All those restrictions can be overcome by in-situ generation of the thiol functionality. In this context, the use of monomers with a protected thiol, masked in a γ-butyrothiolactone structure, offers a sustainable and improved method for the synthesis of multifunctional polymers with the advantages of *in situ* activation and polymerization by one-pot, rapid and orthogonal amine-thiol-ene conjugation (Scheme 1).[3,1] Indeed, the use of functional amines to open the thiolactone ring allows for the introduction of additional features into the polymer chains [15,16] and offers a platform for (multi-)functional materials, such as hydrogels[11] and polymers with defined architectures.[17-20]

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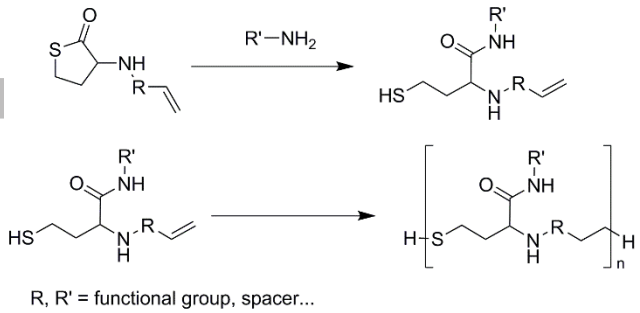
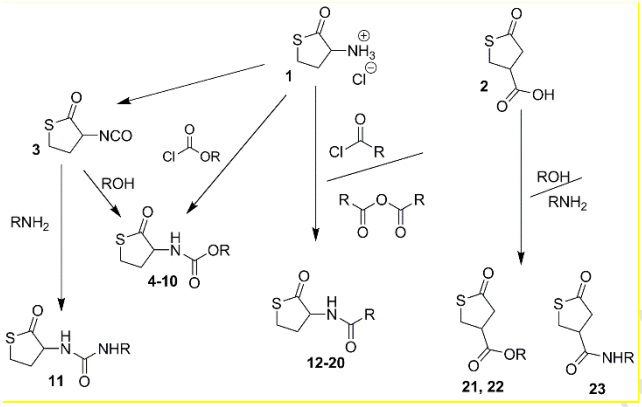


Scheme 1. Scheme for two-step amine-thiol-ene polyaddition of thiolactones.

A new field of application for the conjugated amine-thiol-ene polyaddition covers the area of functional coatings.[21] Products from sustainable sources and high solids coatings are, besides the "smart" functionality, desired features. In this context, a monomer platform with a wide range of physical and chemical properties is needed. Here, the syntheses and qualitative considerations of the properties of a large set of thiolactone derived structures, derived from **1** or **2** (thioparaconic acid) and summarized in Scheme 2, will be discussed.



Scheme 2. Overview of the chemical syntheses of thiolactone-derived structures.

The potential polymers derived from such thiolactone compounds are either polyurethanes, if derived from **6**-**10,** polyamides, if derived from **12**-**20** and **23**, or polyesters (from **21**, **22**). While both polyurethanes and polyamides show an excellent resistance to abrasion, polyamides typically provide better heat and chemical resistance in addition to better crack resistance. Polyesters, on the other hand, would show a rather hydrophobic behavior. The physical properties of the resulting polymers are influenced by the amine used for the thiolactone aminolysis, but also largely depend on the 'R'-segment of the thiolactone building blocks. For example, spacer segments with low polar functional groups, e.g. in **8**, **9**, **15**, **16**, **21** and **22**, decrease interaction and glass transition temperature, while aromatic segments, present in **12** and **14**, enhance rigidity and impact resistance. Additional reactive functional groups, such as a triple bond in **7** or additional double bonds in **18**, allows for the formation of hyperbranched structures and cross-linking, or post-modification in case of coatings.

2. Results and discussion

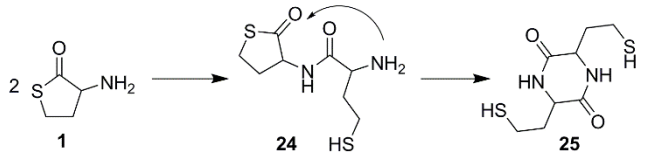
2.1. Precursors and general procedures

Generalized procedure for acid chloride coupling with D,L-homocysteine thiolactone (hydrochloride)

The reaction of acids with amines is an established synthetic method, offering multiple effective pathways. The reaction of homocysteine thiolactone **1** with acid derivatives has previously been reported as well.[3,22,16] The synthetic pathway, using a two-phase system of water and 1,4-dioxane and five equivalents of sodium bicarbonate for deprotection of the hydrochloride salt, subsequently reacted with activated carbonyl compounds at low temperatures over a long time, seems effective and – sometimes – high yielding, but also bears some limitations. Due to the low concentration of the starting compounds, large amounts of solvents need to be used to obtain large amounts (> 30g) of the desired products. The extraction using large amounts of organic solvents lowers the life cycle assessment of the procedure. By comparing different organic solvents. i.e. acetone, tetrahydrofuran, hexane and ethyl acetate, and taking into account their boiling point, miscibility with water, toxicity and hazardousness, ethyl acetate turned out to be the solvent of choice. By lowering the ratios of the reactants and screening of the reaction conditions, a generalized and upscalable procedure was obtained (General procedure A, Experimental Section), resulting in products of high purity and in high yields of up to 99% (molecules **4**-**20**, see Scheme 2).

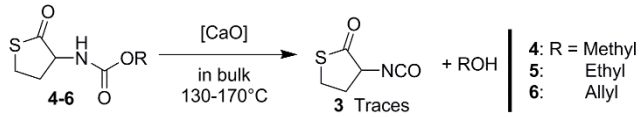
Synthesis of thiolactone isocyanate

Old reports describe the synthesis of thiolactone isocyanate **3** in a way that is suitable for lab scale.[23] Starting from homocysteine thiolactone, the isocyanate is formed within hours under the influence of gaseous phosgene. Experiments to use organic carbonates as a potential phosgene replacement for carbamate synthesis failed.[24-26] Reasons for this are the conditions needed for the reaction of amines with the carbonates, the less reactive amine on a secondary position of the thiolactone moiety as well as the tendency for ring condensation, forming a stable diketopiperazine **25** (Scheme 3).[27]



Scheme 3. Self-condensation of homocysteine thiolactone, resulting in a diketopiperazine.[27]

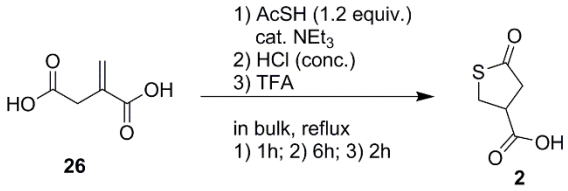
Taking these facts into account, thiolactone isocyanate was prepared starting from a recent protocol reported by our group [28], using triphosgene in solution at low temperatures. Despite an aqueous workup, the average yield is as high as 85%, resulting in approximately 65g of product with the experimental conditions used. A phosgene-free synthesis of isocyanate **3** that involves the elimination of an alcohol was attempted, starting from existing thiolactone carbamates making use of a catalyst [29] at elevated temperatures (Scheme 4). For this pyrolysis, different carbamates were used (vide infra, **4**-**6**). Even though traces of the corresponding alcohols could be identified, none of the performed experiments gave the desired result. A procedure, using a Lewis acid and a base [30], was tested for **4** and only resulted in low yields, also making meticulous working under dry inert gas atmosphere inevitable. The isolation of the pure product was not possible due to limited purification methods, considering the reactive nature of compound **3**.



Scheme 4. Adapted synthesis of thiolactone isocyanate from a carbamate.[29] Only traces of the products could be identified.

Synthesis of thioparaconic acid

Unlike the compounds mentioned above, thiolactone acid is not derived from homocysteine thiolactone **1**, but from the renewable compound itaconic acid (**26**), which can be transformed into thioparaconic acid **2** in an effective three step synthesis (Scheme 5).[31,20] The first step of the synthesis was slightly modified, using lower amounts of thioacetic acid and catalytic amounts of triethylamine, resulting in identical yields after only one hour reaction time. For esterification reactions, the crude acid could be used, while recrystallization from chloroform prior to use was necessary for more complex procedures.



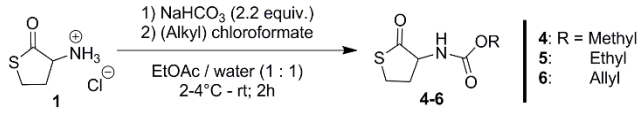
Scheme 5. Synthesis of thioparaconic acid **2** from itaconic acid **26**.

2.2. Carbamates

Different ways for the preparation of homocysteine thiolactone carbamates are possible (Scheme 2, **4**-**10**). The two different approaches used in this article are highly effective, but also suffer from several disadvantages. Both protocols are discussed in the following paragraphs. All synthesized carbamates show good solubility in common organic solvents and excellent thermostability.

Carbamates from chloroformates

The synthesis, starting from homocysteine thiolactone hydrochloride and chloroformates, is more convenient than the synthetic pathway via the thiolactone isocyanate, providing carbamates in high yields in a one-step procedure (Scheme 6). During our research, compounds **4**-**6** were synthesized accordingly. The products were purified by simple filtration over silica gel. However, this process is restricted to the commercial availability of the chloroformate compounds, which is rather limited. Additionally, the toxicity of chloroformates is evident, even though they are easier to handle than phosgene. During the optimization, different amounts of chloroformates were used. In Table 1, only the number of equivalents resulting in the highest yields are displayed.



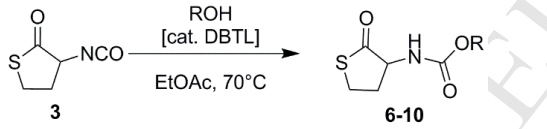
Scheme 6. Synthesis of thiolactone carbamates from commercial chloroformates.

Table 1. Overview of thiolactone carbamates from commercial chloroformates.

Product	Alkyl chloroformate (equiv.)	Yield (%)
4	Methyl chloroformate (1.25 equiv.)	93
5	Ethyl chloroformate (1.15 equiv.)	99
6	Allyl chloroformate (1.10 equiv.)	97

Carbamates from D,L-homocysteine thiolactone isocyanate

Numerous procedures describe the urethane formation from isocyanates and alcohols.[32] The reactions were carried out in dry ethyl acetate, with dibutyltin dilaurate (DBTL) catalysis (general procedure B, in Experimental Section; Scheme 7). The yields were excellent to quantitative (Table 2), resulting in easy product purification, such as recrystallization or extraction. Nevertheless, the precedent synthesis of the thiolactone isocyanate needs to be taken into account, including triphosgene, pyridine and careful compliance of the synthetic procedure.[28]



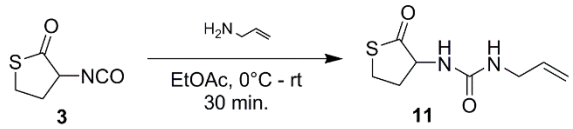
Scheme 7. Synthesis of thiolactone carbamates from thiolactone isocyanate and alcohols.

Table 2. Overview of different thiolactone carbamates, synthesized using general procedure B.

Product	Alcohol	Yield (%)
6	Allyl alcohol (1.1 equiv.)	96
7	Propargyl alcohol (1.1 equiv.)	Quant.
8	2-Allyloxyethanol (1.0 equiv.)	98
9	Undec-10-ene-1-ol (1.0 equiv.)	87
10	Triethylene glycol	Quant.

Substituted urea from D,L-homocysteine thiolactone isocyanate

To introduce another functional group to the monomer portfolio, a urea was synthesized based on thiolactone isocyanate **3** (Scheme 8). Possible side reactions like aminolysis could be suppressed by performing the reaction at low temperatures and use of the less reactive allylamine.[5] The resulting product **11** was obtained in good yields (85%) and shows moderate solubility in most solvents.



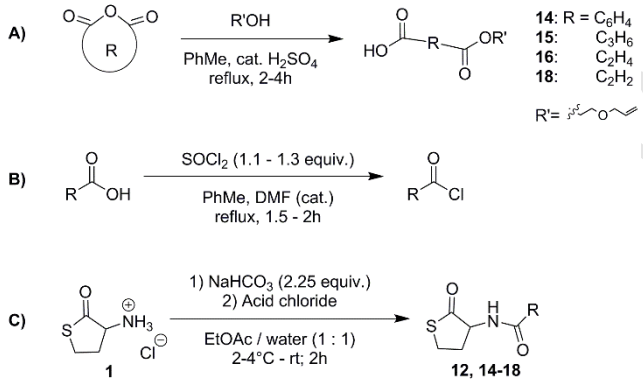
Scheme 8. Synthesis of N-Allyl-N'-(γ-butyrothiolacton-2-yl) urea.

2.3. Amides

Monothiolactone amides

The synthesis of thiolactone amides proved most effective when starting from homocysteine thiolactone **1** and acid chlorides (Scheme 9C). If monomers derived from diacids, the reaction of the corresponding anhydrides with alcohols (Scheme 9A) to a monoacid monoester and subsequent transformation into the acid chlorides (Scheme 9B) was found to be the best pathway. It should be mentioned that - in case of ester containing aliphatic acids - a coloring appears during the chlorination, which could not be completely removed with the purification methods used. The reaction of the anhydride with homocysteine thiolactone and subsequent acid chlorination is also possible, but the losses during the reaction are significant. A summary of the obtained mono-thiolactone amides is displayed in Table 3.

The monomer properties vary according to the starting compounds, ranging from liquid compounds (**15**, **16**) to barely soluble solids (**12**, **14**). When using phthalic anhydride and allyl alcohol, the degradation of the allyl ester was observed during the chlorination step. In a side reaction, thiolactone phthalimide (**14**) was formed, which was isolated during purification.



Scheme 9. A) Alcoholysis of a cyclic anhydride to obtain a monoacid monoester. B) Acid chlorination using thionyl chloride. C) Amidation reaction starting from thiolactone **1**.

Table 3. Overview of amides derived from homocysteine thiolactone **1** and acid chlorides, derived from the corresponding acids or cyclic anhydrides.

Product	Acid / anhydride	Alcohol	Yield (%)	State and solubility in common organic solvents
12	*N*-Alloc anthranilic acid	-	74	Solid, barely soluble
(-)	Phthalic anhydride*	Allyl alcohol	-	-
14		2-Allyloxyethanol	17	Solid, barely soluble
15	Glutaric anhydride	2-Allyloxyethanol	40	Red oil, soluble
16	Succinic anhydride	2-Allyloxyethanol	40	Brown oil, soluble
17	Crotonic acid	-	62	Solid, soluble
18	Maleic anhydride	2-Allyloxyethanol	70	Solid, barely soluble

Byproduct homocysteine thiolactone phthalimide: **13**

Bisthiolactones

The bisthiolactones (**19** & **20**) synthesized in this study were derived from the corresponding difunctional acid chlorides. The products were obtained in yields of around 40% (see Table 4); the premature precipitation of the product effectively seems to inhibit the completion of the reaction. In case of phthaloyl chloride, the product could not be isolated in a pure state; its existence could only be verified by LC-MS (see supporting information). The products show - as a result of their symmetry - low solubility in all kinds of organic solvents, hence a purification was not possible.

Table 4. Overview of bisthiolactones from acid chlorides.

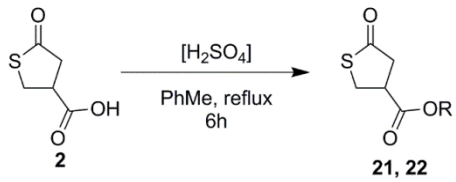
Product	Acid chloride	Yield (%)
-	Phthaloyl chloride	-
19	Glutaryl chloride	43
20	Adipoyl chloride	45

2.4. Thioparaconic acid esters and amides

A difference in reactivity between 3-substituted γ–thiolactones and 2-(*N*-)substituted derivatives has been observed in literature. Keul et al. demonstrated, using an asymmetrical bisthiolactone, that the susceptibility of 2- substituted γ-thiolactone rings towards amines is roughly 2.5 times higher than starting from the corresponding 3-substituted heterocycle.[20] This was not further investigated by them, but a possible answer can be found in a publication from Reyniers et al.[33] As a result of interactions with substituents in the 2-position, a stable intermediate is hypothesized. The lack of stabilization during the ring-opening could explain the lower reactivity of thioparaconic acid derivatives.

Thioparaconic acid esters

As known in literature, esterifications of thioparaconic acid[34] can be performed under acid catalysis (Scheme 10)[35], using a Dean Stark apparatus.[36] This procedure allows ester synthesis in only one step with a relatively low risk of side reactions, in contrast to making intermediate acid chlorides. The ease of workup, the simple reaction setup, use of less reactants and fewer purification steps, prior to the esterification, were considered more important than the resulting yield of around 65% (see Table 5).



Scheme 10. Synthesis of thioparaconic acid esters **21** & **22**.

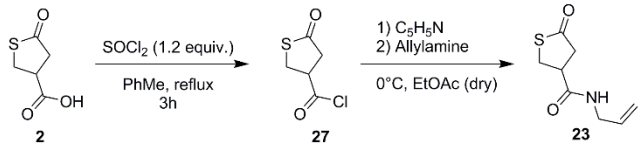
Table 5. Overview of yields of the thioparaconic acid esters obtained.

Product	Alcohol	Yield (%)
21	Allyl alcohol (3.0 equiv.)	63
22	2-Allyloxyethanol (2.0 equiv.)	64
(-)	Propargyl alcohol (1.7 equiv.)	-

The products were obtained in moderate yields, except for propargyl alcohol. A possible explanation is the low reactivity due to the electron withdrawing effect of the alkyne bond, a too strong dilution in the reaction mixture or formation of azeotropes with the toluene. All esters are liquid with low viscosity, offering the opportunity to perform aminolysis and thiol-ene reactions in bulk, which is ideal for planned use in coating formulations.

Thioparaconic acid allylamide

To overcome the stability limitations earlier mentioned, thioparaconic acid allylamide **23** was synthesized, following a known procedure,[20] without purification of the intermediate **27**. The resulting allylamide was obtained in low yield as a white solid, which also showed limited solubility in most solvents.



Scheme 11. Synthesis of thioparaconic allylamide, following a procedure via the thioparaconic acid chloride.[20]

3. Conclusions and outlook

A library of monomers with different chemical structures and functionalities was synthesized, applying reliable chemical methods. Thiolactone carbamates from commercial (alkyl) chloroformates (**4** – **6**) have been made in high yields, involving straightforward purification. Also thiolactone carbamates, originating from thiolactone isocyanate (**3**) and alcohols (**6 – 10**), have been prepared in high yields and is most effective under DBTL catalysis. Thiolactone urea **11** could be obtained in good yields from thiolactone isocyanate (**3**) and allylamine at low temperatures. Thiolactone amides (**12, 14 – 18**) are most conveniently synthesized from **1** and acid chlorides. Depending on the synthesis of the precursors, the products are colored and a purification is inevitable. Bisthiolactone amides (**19, 20**) were obtained in low yields; the solids show low solubility in most organic solvents. Thioparaconic acid esters (**21, 22**) are synthesized from the corresponding acid and alcohols under acid catalysis with yields depending on the reactivity of the alcohol. Finally, thioparaconic acid amide **23** was obtained as a solid in low yields. The synthetic processes used for the monomers were optimized to enable scale-up and safe processing of diverse starting compounds, typically with amounts higher than 50 grams.

4. Experimental

4.1. Materials and instruments

D,L-Homocysteine thiolactone hydrochloride and allyl chloroformate were commissioned from Haihang Industry Co., Ltd. 2-Allyloxyethanol and DBTL were ordered from TCI. All other compounds were purchased from Sigma Aldrich.

Ethyl acetate and pyridine were dried over calcium hydride prior to use, alcohols were dried over molecular sieves. Toluene was dried using sodium.

Compounds were weighed using a Kern EG620-3NM balance.

^{1}H-NMR experiments were performed with a Bruker Avance (Ultrashield) 300 (300MHz) or a Bruker Avance 400 (400MHz), ^{13}C-NMR spectra were recorded using a Bruker DRX500 (500 MHz) spectrometer.

LC-MS and HRMS analyses were performed on an Agilent Technologies 1100 series LC/MSD system with a diode array detector (DAD) and single quad MS. The exact mass of the target molecules was calculated using a chemical structure analysis program (ChemBioDraw Ultra 14.0).

4.2. General procedures

General procedure A - Reaction of acid chlorides or cyclic anhydrides with homocysteine thiolactone: If not mentioned otherwise, homocysteine thiolactone hydrochloride (1.0 equiv.) is dissolved in a 1:1 mixture of water and ethyl acetate (concentration 1.5 mol/l) and cooled down with an ice bath for at least 15 minutes. Sodium bicarbonate (2.1 or 2.25 equiv., adapted to the product formed) is added in a few portions. An addition funnel is mounted, equipped with the acid chloride / anhydride (1.1 equiv.) mixed with half of its volume of ethyl acetate or another appropriate solvent. The resulting solution is added to the reaction mixture within 15 minutes. Solid acid chlorides / anhydrides are either dissolved in ethyl acetate or directly added portion wise. After the addition is completed, the ice bath is removed and the mixture is stirred for several hours, the progress of the reaction is monitored with TLC. The reaction mixture is acidified to pH < 5.5 using 6N hydrochloric acid. Solid products are filtered off with a glass filter and rinsed with demineralized water. Liquid phases are separated, the aqueous phase is extracted with ethyl acetate, the organic phases are combined and dried with anhydrous magnesium sulfate. The crude solution is filtered twice over silica gel and solvent is evaporated under reduced pressure. Follow-up actions are mentioned in the specific procedures.

General procedure B - Reaction of homocysteine thiolactone isocyanate with alcohols: A Schlenk flask, equipped with a stir bar and septum is dried with a heat gun under vacuum and flushed with argon. Dry ethyl acetate, thiolactone isocyanate, alcohol and catalytic amounts of dibutyltin dilaurate (DBTL; usually 2 – 3 drops with a glass pipette per 50mL solution) are subsequently added to the flask. The reaction mixture is stirred for four hours at 65 °C. The solvent and excessive alcohol, if possible, is removed using a rotary evaporator. Follow-up actions are mentioned in the specific procedures.

4.3. **Thioparaconic acid** (**2**) was synthesized according to literature [31] with a slightly modified procedure: itaconic acid was treated with 1.2 equiv. thioacetic acid and 3 drops of triethylamine. The acidic treatments were performed using concentrated (12N) hydrochloric acid and 50 % less trifluoroacetic acid, resulting in brown crystals. Yield: 90 %. Recrystallization was performed according to literature using chloroform.[20]

4.4. **Homocysteine thiolactone isocyanate** (**3**) was synthesized according to literature.[28] Analytical data is accordingly.

4.5. **Methyl (homocysteine thiolactone) carbamate** (**4**) was synthesized according to general procedure A, using 61.2 g (0.4 mol, 1.0 equiv.) homocysteine thiolactone hydrochloride, 38.6 mL (0.5 mol, 1.25 equiv.) methyl chloroformate and 75.6 g (0.9 mol, 2.25 equiv.) sodium bicarbonate. The organic solvent was directly removed after acidification, and the product was filtered off as white, crystalline solid. The solid was washed with water and the aqueous phases were combined and extracted with 100 mL ethyl acetate. The organic phase was separated, dried and the solvent was removed under reduced pressure. The total amount of product was 65.17 g (93 %). ^{1}H-NMR (300 MHz, CDCl3): δ (ppm) = 5.13 (s, 1H, N<u>H</u>), 4.26 (m, 1H, NC<u>H</u>), 3.64 (s, 3H, CH_3), 3.33-3.12 (m, 2H, C<u>H</u>$_2$S), 2.80 (m, 1H, CHC<u>H</u>$_2$), 1.93 (m, 1H, CHC<u>H</u>$_2$); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.4 (C), 156.9 (C), 60.0 (CH), 51.8 (CH_3), 31.3 (CH_2), 27.1 (CH_2); M (calc.): 175.03031; M (found): 176.0371; Δ = 2.8 ppm

4.6. **Ethyl (homocysteine thiolactone) carbamate** (**5**) was synthesized according to general procedure A, using 61.2 g (0.4 mol, 1.0 equiv.) homocysteine thiolactone hydrochloride, 22 mL (0.23 mol, 25 g, 1.15 equiv.) ethyl chloroformate and 37.8 g (0.45 mol, 2.25 equiv.) sodium bicarbonate. The layers were separated, the aqueous phase was extracted with 50 mL ethyl acetate and the combined organic layers were dried over magnesium sulfate and subsequently filtered over silica gel. After removal of the solvent, a viscous oil (37.3 g, 98.6 %) was obtained which crystallized over time. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.10 (s, 1H, CNH), 4.26 (dt, 1H, CHN, 12.9, 6.6 Hz), 4.07 (q, 2H, OC<u>H</u>$_2$CH$_3$, 7.1 Hz), 3.27 (ddd, 1H, SCH_2, 12.1, 11.4, 5.1 Hz), 3.17 (ddd, 1H, 11.3, 7.1, 1.5 Hz), 2.80 (dt, 1H, SCH$_2$C<u>H</u>$_2$, 11.7, 5.7 Hz), 2.04 – 1.83 (m, 1H, SCH$_2$C<u>H</u>$_2$), 1.19 (t, 3H, OCH$_2$C<u>H</u>$_3$, 7.1 Hz); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.3 (C), 156.5 (C), 61.3 (CH_2), 60.5 (CH), 31.4 (CH_2), 27.1 (CH_2), 14.5 (CH_3); M (calc.): 189.04596; M+H (found): 190.0531; Δ = 0.7 ppm

4.7. ***N*-Allyl (homocysteine thiolactone) carbamate** (**6**) was synthesized according to general procedure A. The use of 0.5 mol (76.83 g, 1.0 equiv.) homocysteine thiolactone hydrochloride, 1.1 mol (92.5 g, 2.1 equiv.) and 0.475 mol (57.25 g, 50 mL, 0.95 equiv.) resulted in 92.37 g pure, white, crystalline product (96.7 %). Following general procedure B, 5.7 g (0.04 mol, 1.0 equiv.) homocysteine thiolactone isocyanate, 2.32 g (2.7 mL, 0.04 mol, 1.0 equiv.) allyl alcohol, 5 mL dry ethyl acetate and one drop of DBTL were reacted for two hours at 70 °C. The solvent was evaporated, giving 8.0 g (99.8 %) liquid product, which hardened over time. Analytical data are according to literature.[3]

4.8. ***N*-Propargyl (homocysteine thiolactone) carbamate** (**7**) was synthesized according to general procedure B, using 13.3 g (0.095 mol, 1.0 equiv.) homocysteine thiolactone isocyanate, 6 g propargyl alcohol (0.1 mol, 6 mL, 1.1 equiv.) in 25 mL ethyl acetate. Analytical data is according to literature.[37] Quantitative yield of a light brown oil. Note: The product slowly darkened over an extended period of time, even under exclusion of light, but no changes in chemical composition could be detected by NMR.

4.9. **2-Allyloxyethyl (homocysteine thiolactone) carbamate** (**8**) was synthesized according to general procedure B, using 15 g (0.104 mol, 1.0 equiv.) homocysteine thiolactone isocyanate, 11.2 mL (0.11 mol, 1.05 equiv.) 2-allyloxyethanol and catalytic DBTL. The mixture was allowed to cool down after the reaction and solvent was removed. Afterwards, oily residue was properly stirred with hexane and the top layer was decanted. The residual oil was dried under vacuum to give 24 g (98 %) of a golden yellow, viscous liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.84 (ddt, 1H, C<u>H</u>CH$_2$, 17.3, 10.4, 5.7 Hz), 5.34 (d, 1H, $NHCO_2$, 6.6 Hz), 5.22 (dq, 1H, CHC<u>H</u>$_2$, 17.3, 1.6 Hz), 4.32 – 4.20 (m, 1H, C<u>H</u>NH), 4.21 – 4.14 (m, 2H, CO_2CH_2), 3.95 (dt, 2H, C<u>H</u>$_2$CHCH$_2$, 5.7, 1.4 Hz), 3.62 – 3.52 (m, 2H, CO_2CH_2C<u>H</u>$_2$), 3.33 – 3.12 (m, 2H, SCH_2), .82 – 2.71 (m, 1H, SCH$_2$C<u>H</u>$_2$), 2.04 – 1.87 (m, 1H, SCH$_2$C<u>H</u>$_2$); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.1 (C), 156.2 (C), 134.4 (CH), 17.4 (CH_2), 72.0 (CH_2), 68.1 (CH_2), 64.5 (CH_2), 60.6 (CH), 31.3 (CH_2), 27.1 (CH_2); M (calc.): 245.07218; M+H (found): 246.093; Δ = 5.2 ppm

4.10. **Undec-10-en-yl (homocysteine thiolactone) carbamate** (**9**) was synthesized according to general procedure B, using 5.7 g (0.04 mol, 1.0 equiv.) homocysteine thiolactone isocyanate, 8 mL (0.04 mol, 1.0 equiv.) undec-10-ene-1-ol and catalytic DBTL. After the reaction, the mixture was allowed to cool down and added to cold hexane (200 mL). The precipitate was filtered off and dried under vacuum to give 10.9 g (87 %) of a greyish, amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.74 (ddt, 1H, CH_2C<u>H</u>, 16.9, 10.1, 6.7 Hz), 5.03 (bs, 1H, NH), 4.90 (m, 2H, C<u>H</u>$_2$CH), 4.25 (dt, 1H, CHN, 12.9, 6.4 Hz), 4.00 (t, 2H, CO_2CH_2, 6.7 Hz), 3.35 – 3.11 (m, 2H, SCH_2), 2.82 (dt, 1H, NCHC<u>H</u>$_2$12.3, 5.7 Hz), 2.04 – 1.81 (m, 2H alkyl), 1.60 – 1.43 (m, 3H, alkyl), 1.36 – 1.15 (m, 12H, alkyl); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.1 (C), 156.6 (C), 139.1 (CH), 114.1 (CH_2), 65.5 (CH_2), 60.0 (CH), 33.7 (CH_2),

31.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 25.8 (CH_2); M (calc.): 313.17116; M+H (found): 314.1789; Δ = 1.5 ppm

4.11. **Triethyleneglycol bis (homocysteine thiolactone) carbamate** (**10**) was synthesized according to general procedure B, using 7.3 g (0.051 mol, 1.0 equiv.) homocysteine thiolactone isocyanate, 3.75 g (0.025 mol, 3.75 mL, 0.50 equiv.) and catalytic DBTL. The reaction mixture was washed with 2N hydrochloric acid and dried. After removal of the organic solvent, the product was obtained as highly viscous oil which crystallized over time. Yield: 10.9 g (100 %). ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 7.64 (d, 2H, $NHCO_2$, 8.7 Hz), 4.35 (ddd, 2H, CHN, 12.8, 8.8, 7.0 Hz), 4.13 – 4.05 (m, 4H, CO2CH_2), 3.63 – 3.55 (m, 4H, $CO_2CH_2CH_2$), 3.54 (s, 4H, OC_2H_4O), 3.46 – 3.32 (m, 2H, SCH_2), 3.31 – 3.18 (m, 2H, SCH_2), 2.49 – 2.34 (m, 2H, SCH_2CH_2), 2.20 – 2.00 (m, 2H, SCH_2CH_2); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 205.2 (C), 156.4 (C), 70.6 (CH_2), 69.4 (CH_2), 64.6 (CH_2), 60.6 (CH), 31.3 (CH_2), 27.1 (CH_2); M (calc.): 436.09741; M+NH_4 (found): 454.1315; Δ = 0.6 ppm

4.12. **N-Allyl-N'-(γ-butyrothiolacton-2-yl) urea** (**11**) was synthesized according to general procedure B, using 5.3 g (0.037 mol, 4 mL, 1.0 equiv.) homocysteine thiolactone isocyanate, and 2.7 mL (0.036 mol, 0.98 equiv.) allylamine. No catalyst was used. The isocyanate was dissolved in 20 mL ethyl acetate and cooled down to 0 °C. Allylamine was dissolved in 10 mL ethyl acetate and added dropwise to the isocyanate solution under vigorous stirring. The system was slowly warmed up to room temperature and allowed to stir for additional 30 minutes. Subsequently most of the ethyl acetate was removed under reduced pressure and the precipitate was washed with hexane, to result in 6.3 g (85 %) crystalline white solid. ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 6.30 (d, 1H, CHN<u>H</u>, 8.1 Hz), 6.20 (t, 1H, CH_2N<u>H</u>, 5.8 Hz), 5.80 (ddt, 1H, C<u>H</u>CH_2, 17.2, 10.3, 5.1 Hz), 5.12 (dq, 1H, CHC<u>H</u>$_2$, 17.2, 1.8 Hz), 5.03 (dq, 1H, CHC<u>H</u>$_2$, 10.2, 1.7 Hz), 4.42 (ddd, 1H, CHN, 12.6, 8.1, 6.9 Hz), 3.63 (tt, 2H, 5.4, 1.7 Hz), 3.36 (ddd, 1H, SCH_2, 11.9, 11.1, 5.3 Hz), 3.23 (ddd, 1H, SCH_2, 11.1, 7.0, 1.6 Hz), 2.51 (m, 1H, SCH_2C<u>H</u>$_2$), 2.11 – 1.93 (m, 1H, SCH_2CH_2); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 207.0 (C), 157.7 (C), 136.9 (CH), 114.9 (CH_2), 59.8 (CH), 42.2 (CH_2), 31.5 (CH_2), 27.0 (CH_2); M (calc.): 200.06195; M+H (found): 201.0695; Δ = 1,4 ppm

4.13. **Synthesis of *N*-Alloc-anthranilic acid homocysteine thiolactone amide** (**12**) 13.7 g (0.1 mol, 1.0 equiv.) anthranilic acid and 21 g (0.25 mol, 2.5 equiv.) sodium bicarbonate were dissolved in a 1:1 mixture of ethyl acetate and water (100 mL) and cooled down with an ice bath. Allyl chloroformate (0.15 mol, 1.5 equiv.) was subsequently added and the mixture was allowed to warm up to room temperature. The biphasic system was acidified with 6N hydrochloric acid and the layers were separated. The aqueous phase was extracted with 100 mL ethyl acetate and the combined organic phases were dried over magnesium sulfate to give 22.1 g (100 %) white solid.
The *N*-Alloc-anthranilic acid was suspended in 100 mL dry toluene and 14.9 g (9.14 mL, 0.125 mol, 1.25 equiv.) thionyl chloride and catalytic amounts of DMF was added. The reaction mixture was refluxed for 2 hours with subsequent removal of excess thionyl chloride under vacuum at ambient temperatures. The crude acid chloride was processed according to general procedure A, using 15.3 g (0.1 mol, 1.0 equiv.). The crude product was purified using column chromatography (hexane / ethyl acetate 1:1.5). Yield: 23.5 g (73.5 % overall yield). ^{1}H-NMR (300 MHz, d_6-DMSO): 9.88 (s, 1H, $NHCO_2$), 8.71 (d, 1H, CONH, 8.4 Hz), 7.98 (t, 1H, COCC<u>H</u>CNH, 1.9 Hz), 7.64 – 7.57 (m, 1H, CH_{Ar}), 7.49 – 7.34 (m, 2H, CH_{Ar}), 5.99 (ddt, 1H, C<u>H</u>CH_2, 17.2, 10.6, 5.4 Hz), 5.36 (dq, 1H, 17.2, 1.7 Hz), 5.24 (dq, 1H, 10.4, 1.4 Hz), 4.83 (ddd, 1H, CHN, 12.8, 8.4, 7.1 Hz), 4.62 (dt, 2H, 5.4, 1.5 Hz), 3.52 – 3.39 (m, 1H, SCH_2), 3.37 – 3.27 (m, 1H; SCH_2), 2.53 – 2.41 (m, 1H, SCH_2C<u>H</u>$_2$), 2.38 – 2.21 (m, 1H, SCH_2C<u>H</u>$_2$); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 205.8 (C), 166.8 (C), 153.7 (C), 139.8 (C), 135.1 (C), 133.7 (CH), 129.2 (CH), 121.5 (CH), 118.1 (CH_2), 65.2 (CH), 59.2 (CH_2), 30.3 (CH_2), 27.2 (CH_2); M (calc.): 320.08308; M+H (found): 321.0914; Δ = 3.3 ppm

Homocysteine thiolactone phthalimide (13) was identified as side product: ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 7.98 – 7.94 (m, 4H, H_{Ar}), 5.21 (dd, 1H, NCH, J = Hz), 3.63 – 3.41 (m, 2H, SCH_2), 2.77 – 2.51 (m, 2H, SCH_2CH_2); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.3 (C), 156.93 (C), 60.5 (CH), 52.4 (CH), 31.3 (CH_2), 27.1 (CH_2); M (calc.): 247.03031; M+H (found): 248.0373; Δ = 1.2 ppm

4.14. **Synthesis of phthalic acid –(2-allyloxy)ethyl ester - homocysteine thiolactone amide** (**14**): 29.6 g (0.2 mol, 1.0 equiv.), 30 mL (0.28 mol, 1.4 equiv.), 17 mL (17 g, 0.21 mol, 1.05 equiv.) pyridine, 0.2 g DMAP and 15 mL toluene were mixed in a 100 mL round bottom flask and stirred under reflux for 3 hours. The resulting mixture was stirred with water and brought to pH 10-12. The organic phase was removed and the aqueous phase was acidified using concentrated hydrochloric acid. Subsequent extraction with 200 mL ethyl acetate and filtration of the organic phase over silica gave 49 g (98 %) phthalic acid mono(2-allyloxyethyl)ester as colorless liquid. Slight turbidity resulted from residual phthalic anhydride. The monoester was dried in a Schlenk flask under high vacuum and 75 mL dry toluene was added, followed by 16 mL (0.22 mol, 1.1 equiv.) thionyl chloride. The reaction mixture was refluxed for 1.5 hours under inert gas atmosphere. Excessive thionyl chloride was removed under reduced pressure and the product was taken up in 30 mL ethyl acetate, proceeding with general procedure A using 0.15 mol (23 g) homocysteine thiolactone hydrochloride. The crude product was purified using column chromatography (hexane / ethyl acetate = 1:1). Yield: 11.68 g (16.7 %) white solid. ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 8.77 (d, 1H, CONH, 8.3 Hz), 7.77 – 7.48 (m, 4H, CH_{Ar}), 5.89 (ddt, 1H, C<u>H</u>CH_2, 17.3, 10.6, 5.4 Hz), 5.26 (dq, 1H, CHC<u>H</u>$_2$, 17.3, 1.7 Hz), 5.15 (dq, 1H, CHC<u>H</u>$_2$, 10.4, 1.3 Hz), 4.77 (ddd, 1H, NCH, 12.4, 8.4, 7.0 Hz), 4.36 – 4.26 (m, 2H, CO_2CH_2), 3.99 (dt, 2H, 5.3, 1.5 Hz), 3.70 – 3.63 (m, 2H, C<u>H</u>$_2$$OCH_2CH$), 3.51 – 3.40 (m, 1H, SCH_2), 3.38 (m, 1H, SCH_2), 2.56 - .245 (m, 1H, SCH_2C<u>H</u>$_2$), 2.28 – 2.12 (m, 1H, SCH_2C<u>H</u>$_2$); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 25.6 (C), 168.3 (C), 167.3 (C), 137.5 (C), 135.5 (CH), 132.0 (CH), 130.8 (C), 130.4 (CH), 129.5 (CH), 128.2 (CH), 117.0 (CH_2), 71.5 (CH_2), 67.7 (CH_2), 64.7 (CH_2), 59.0 (CH), 30.5 (CH_2), 27.3 (CH_2); M (calc.): 349.09839; M+H (found): 350.1061; Δ = 1.2 ppm

4.15. **Synthesis of glutaric acid –(2-allyloxy)ethyl ester - homocysteine thiolactone amide** (**15**): 22.8 g (0.2 mol, 1.0 equiv.) glutaric anhydride, 30 g (0.23 mol, 1.5 equiv.), 0.2 g DMAP and 5 mL pyridine were added to a 100 mL round bottom flask and stirred for four hours under reflux. The reaction mixture was cooled down and 30 mL water and excess sodium bicarbonate was added while stirring. The aqueous phase was separated, acidified using concentrated hydrochloric acid and extracted with 100 mL ethyl acetate. The organic phase was dried, filtered over silica using ethyl acetate as eluent and the solvent was removed under reduced pressure, giving 28 g (64.7 %) oily, colorless product.
The formed monoester (0.129 mol, 1.0 equiv.) was mixed with 120 mL dry toluene, 19.9 g (12.2 mL, 0.17 mol, 1.3 equiv.) thionyl chloride and 2 drops DMF and was refluxed for 1.5 hours under inert gas atmosphere. Excessive thionyl chloride was removed under vacuum. The black crude product was processed without purification, following general procedure **A** using 18.3 g (0.12 mol, 0.93 equiv.) homocysteine thiolactone hydrochloride and 0.24 mol (20 g, 1.86 equiv.) sodium bicarbonate. Column chromatography using ethyl acetate / hexane (2:1) gave 25 g (0.08 mol, 40 % overall yield) a cherry red, viscous oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.18(s, 1H, NH), 5.83 (ddt, 1H; C<u>H</u>CH_2, 17.4, 10.2, 5.7 Hz), 5.29 – 5.09 (m, 2H, CHC<u>H_2</u>), 4.49 (dt, 1H, NCH, 13.1, 6.7 Hz), 4.23 – 4.11 (m, 2H, CO_2CH_2), 3.96 (dt, 2H, $OCH_2CHC\underline{H_2}$, 5.7, 1.4 Hz), 3.66 – 3.48 (m, 2H, SCH_2), 2.81 (dddt, 12.1, 6.6, 5.1, 1.4 Hz), 2.36 (dt, 2H, CH_2CO_2, 2.1 Hz), 2.25 (dt, 2H, $NCOCH_2$, 1.8 Hz), 1.93 (m, 1H, $SCH_2C\underline{H_2}$), 1.89 (dq, 2H, 1.3 Hz); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.3 (C), 173.1 (C), 173.0 (C), 134.2 (CH), 117.4 (CH_2), 71.9 (CH_2), 67.7 (CH_2), 63.4 (CH_2), 58.9 (CH), 34.8 (CH_2), 33.0 (CH_2), 31.0 (CH_2), 27.3 (CH_2), 20.8 (CH_2); M (calc.): 230,06128; M (calc.): 315.11404; M+H (found): 316.1217; Δ = 1.2 ppm

4.16. **Synthesis of succinic acid –(2-allyloxy)ethyl ester - homocysteine thiolactone amid**e (**16**): 20.2 g (0.2 mol, 1.0 equiv.) succinic anhydride, 30 g (0.23 mol, 1.5 equiv.), 0.2 g DMAP and 5 mL pyridine were added to a 100 mL round bottom flask and stirred for four hours under reflux. The reaction mixture was cooled down and 30 mL water and excess sodium bicarbonate was added while stirring. The aqueous phase was separated, acidified using concentrated hydrochloric acid and extracted with 100 mL ethyl acetate. The organic phase was dried, filtered over silica using ethyl acetate as eluent and the solvent was removed under reduced pressure, giving 30.7 g (76 %) oily, colorless product. The formed monoester was mixed with 120 mL dry toluene, 19.9 g (12.2 mL, 0.17 mol, 1.1 equiv.) thionyl chloride and 2 drops DMF and was refluxed for 1.5 hours under inert gas atmosphere. Excessive thionyl chloride was removed under vacuum and the brown crude product was processed following general procedure A. Column chromatography using ethyl acetate gave 24.1 g (40 % overall yield) a brown, viscous oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.25 (d, 1H, CONH, 8.4 Hz), 5.88 (ddt, 1H, C<u>H</u>CH_2, 17.3, 10.5, 5.4 Hz), 5.26 (dq, 1H, CHC<u>H_2</u>, 17.3, 1.8 Hz), 5.15 (dq, 1H, $CHCH_2$, 10.4, 1.5 Hz), 4.59 (ddd, 1H, 12.5, 8.3, 7.0 Hz), 4.19 – 4.09 (m, 2H, CO_2CH_2), 3.97 (dt, 2H, C<u>H_2</u>$CHCH_2$, 5.3, 1.5 Hz), 3.61 – 3.52 (m, 2H, $CO_2CH_cC\underline{H_2}$), 3.47 – 3.21 (m, 2H, SCH_2), 2.60 – 2.35 (m, 5H, $OCOC_2\underline{H_4}CO_2$, $SCH_2C\underline{H_2}$), 2.15 – 1.94 (m, 1H, $SCH_2C\underline{H_2}$); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.3 (C), 172.6 (C), 172.1 (C), 134.3 (CH), 117.2 (CH_2), 71.9 (CH_2), 67.7 (CH_2), 63.8 (CH_2), 59.0 (CH), 31.1 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 27.3 (CH_2); M (calc.): 301.09839; M+H (found): 302.1064; Δ = 2.4 ppm

4.17. **Homocysteine thiolactone but-2-enamide** (**17**) was synthesized according to general procedure **A**, using 30.6 g (0.2 mol, 1.0 equiv.) homocysteine thiolactone hydrochloride, 26.2 g (24 mL, 0.25 mol, 1.25 equiv.) crotonyl chloride and 42 g (0.5 mol, 2.5 equiv.) sodium bicarbonate. Crotonyl chloride was synthesized from crotonic acid (100 g, 1.16 mol, 1.0 equiv.), thionyl chloride (88 mL, 1.2 mol, 1.03 equiv.) and catalytic amounts of DMF, according to literature.[38] A brownish precipitate was formed, filtered off and rinsed with a water-acetone mixture (11: 1). The product was obtained as a white, crystalline powder (23 g, 62%). ^{1}H-NMR (400 MHz, d_6-DMSO): δ (ppm) = 8.23 (d, 1H, NH, 8.4 Hz), 6.66 (dq, 1H, COCH, 15.3, 6.8 Hz), 5.91 (dq, 1H, 15.2, 1.6 Hz), 4.67 (ddd, 1H, CHN, 12.6, 8.4, 7.0 Hz), 3.45 – 3.36 (m, 1H, SCH_2), 3.35 – 3.26 (m, 1H, SCH_2), 2.44 (dddd, 1H, $SCH_2C\underline{H_2}$, 12.3, 7.0, 5.3, 1.6 Hz), 2.09 (qd, 1H, 12.2, 7.0 Hz), 1.81 (dd, 3H, 6.9, 1.7 Hz); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 205.9 (C), 165.4 (C), 139.5 (CH), 125.6 (CH), 58.6 (CH), 30.8 (CH_2), 27.3 (CH_2), 17.8 (CH_3); M (calc.): 185.05105; M+H (found): 186.0586; Δ = 1.5 ppm

4.18. **Synthesis of cis-2-butenedioic acid –(2-allyloxyethyl)ester - homocysteine thiolactone amide** (**18**)**:** Maleic acid (2-allyloxyethyl)ester was synthesized by reacting 19.6 g (0.2 mol, 1.0 equiv.) maleic anhydride, 21.4 g (22.4 mL, 0.21 mol, 1.05 equiv.) 2-allyloxyethanol and 0.2 g DMAP in 15 mL toluene under reflux for 2 hours. 25 mL water and an excess of sodium bicarbonate was added to the reaction mixture at ambient temperature. The organic phase was removed and the aqueous phase was acidified using concentrated hydrochloric acid, followed by extraction using 50 mL ethyl acetate and drying over magnesium sulfate. Yield: 39.3 g (98.5 %) of a colorless liquid.
The maleic acid monoester was dissolved in 100 mL dry ethyl acetate in a Schlenk flask under inert gas atmosphere. 0.3 mol (23 mL, 1.5 equiv.) thionyl chloride and catalytic amounts of DMF were added and the mixture was refluxed for 2 hours. Excessive thionyl chloride was removed under reduced pressure and the crude acid chloride was processed following general procedure A. The solid product formed during the reaction was filtered off and combined with the organic layer of the reaction mixture. 1 mL triethylamine was added to remove left-over acid. The solid was washed with water and dried under reduced pressure, resulting in 39 g (65 %) of an ochery solid. ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 8.93 (d, 1H, CONH, 8.3 Hz), 7.01 (d, 1H, NCOCH, 15.5 Hz), 6.63 (d, 1H, $CHCO_2$, 15.5 Hz), 5.88 (ddt, 1H, $CHCH_2$, 16.8, 10.5, 5.4 Hz), 5.26 (dq, 1H, CHC<u>H_2</u>, 17.3, 1.7 Hz), 5.15 (dq, 1H, $CHCH_2$ 10.5, 1.5 Hz), 4.82 – 4.65 (m, 1H, CHN), 4.32 – 4.26 (m, 2H, CO_2CH_2), 3.98 (dt, 2H, C<u>H_2</u>$CHCH_2$, 5.3, 1.7 Hz), 3.67 – 3.61 (m, 2H, $CO_2CH_2C\underline{H_2}$), 3.51 – 3.27 (m, 2H, SCH_2), 3.02 – 2.76 (m, 1H, CHN), 2.55 – 2.40 (m, 1H, $SCH_2C\underline{H_2}$), 2.19 – 2.03 (m, 1H, $SCH_2C\underline{H_2}$); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 205.3(C), 165.3 (C), 163.4 (C), 137.2 (CH), 135.4 (CH), 129.5 (CH), 117.0 (CH_2), 71.4 (CH_2), 67.8 (CH_2), 64.5 (CH_2), 59.0 (CH), 30.6 (CH_2), 27.4 (CH_2) M (calc.): 299.08274; M+H (found): 300.0903; Δ = 0.9 ppm

4.19. **Bis(homocysteine thiolactone) glutaramide** (**19**) was synthesized according to general procedure A, using 30.6 g (0.2 mol, 1.0 equiv.) homocysteine thiolactone hydrochloride, 15.84 g (0.093 mol, 12 mL, 0.47 equiv.) glutaryl dichloride and 37.8 g (0.45 mol, 2.25 equiv.) sodium bicarbonate. The brown solid formed was thoroughly washed with water and dried under vacuum. Yield: 14.2 g of a brown solid (43 %). ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 8.17 (d, 2H, NH, 8.4 Hz), 4.59 (ddd, 2H, CHN, 12.6, 8.4, 7.0 Hz), 3.53 – 3.21 (m, 4H SCH_2), 2.41 (dddd, 2H, $CH_2C\underline{H}_2CH_2$, 12.2, 6.9, 5.2, 1.7 Hz), 2.22 – 1.96 (m, 3H, CH_2CO, $CHC\underline{H}_2$) 1.74 (m, 1H, $CHC\underline{H}_2$),); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 206.0 (C), 172.4 (C), 58.6 (CH), 34.9 (CH_2), 30.6 (CH_2), 27.2 (CH_2), 21.7 (CH_2); M (calc.): 330.07080; M+H (found): 331.0795; Δ = 4.3ppm

4.20. **Bis(homocysteine thiolactone) adipamide** (**20**) was synthesized according to general procedure A, using 30.6 g (0.2 mol, 1.0 equiv.) homocysteine thiolactone hydrochloride, 18.3 g (0.1 mol, 14.5 mL, 0.5 equiv.) adipoyl dichloride and 37.8 g (0.45 mol, 2.25 equiv.) sodium bicarbonate. The acid chloride was added within 30 minutes and the resulting slurry was stirred for one hour. The precipitate was filtered off, washed with water and dried under vacuum to give 15.5 g (45.3 %) white solid. ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 8.21 (d, 2H, NH, 8.3 Hz), 4.53 (dt, 2H, CHN, 12.6, 7.6 Hz), 3.43 – 3.18 (m, 4H, SCH_2), 2.40 (dddd, 2H, $CHC\underline{H}_2$, 12.3, 7.1, 5.3, 1.6 Hz), 2.25 – 1.94 (m, 6H, $COCH_2$, $CHC\underline{H}_2$), 1.55 – 1.39 (m, 4H, $COCH_2C\underline{H}_2$); ^{13}C-NMR (500 MHz, d_6-DMSO): δ (ppm) = 206.0 (C), 172.8 (C), 58.6 (CH), 35.5(CH_2), 30.6(CH_2), 27.2(CH_2), 25.2(CH_2); M (calc.): 344.08645; M+1 (found): 345.0941; Δ = 1.1 ppm

4.21. **Synthesis of thioparaconic acid allylester** (**21**): 14.6 g (0.1 mol, 1.0 equiv.) thioparaconic acid, 20 mL (17.8 g, 0.3 mol, 3.0 equiv.) allyl alcohol, 75 mL toluene and two drops of concentrated sulfuric acid were mixed in a round bottom flask, equipped with a Dean Stark apparatus. The mixture was heated up and stirred for 7 hours under reflux. Samples were taken every 2 hours. Upon completion, the reaction mixture was cooled down, washed twice with water and dried over magnesium sulfate. The solvent was removed under reduced pressure. Column chromatography using hexane / ethyl acetate (2 : 1) resulted in 11.7 g (63%) of a light yellow liquid. . ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.85 (ddt, 1H, $C\underline{H}CH_2$, 17.2, 10.4, 5.8 Hz), 5.34 – 5.12 (m, 2H, $CHC\underline{H}_2$), 4.59 (dt, 2H, CH_2CHCH_2, 5.8, 1.4 Hz), 3.65 – 3.46 (m, 2H, SCH_2), 3.45 – 3.28 (m, 1H, $CHCO_2$), 2.86 (dd, 1H, $SCOCH_2$, 17.0, 8.7 Hz), 2.71 (dd, 1H, $SCOCH_2$, 16.9, 7.4 Hz); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 203.5 (C), 169.2 (C), 130.0 (CH), 116.9 (CH_2), 64.3 (CH_2), 41.6 (CH_2), 40.9 (CH), 32.7 (CH_2) M (calc.): 186.03506; M+H (found): 187.0423; Δ = 0.2 ppm

4.22. **Thioparaconic acid 2-allyloxyethylester** (**22**): 14.6g (0.1 mol, 1.0 equiv.) thioparaconic acid, 20 mL (20.4g, 0.2 mol, 2.0 equiv.) 2-allyloxyethanol, 75 mL toluene and 0.2 mL concentrated sulfuric acid were mixed in a round bottom flask, equipped with a Dean Stark apparatus. The mixture was heated up and stirred for 7 hours under reflux. Samples were taken every 2 hours. Upon completion, the reaction mixture was cooled down, washed twice with water and dried over magnesium sulfate. The solvent was removed under vacuum. Yield: 14.8 g (64.4%) of a light yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.92 – 5.72 (m, 1H, $CH_2C\underline{H}$), 5.27 – 5.08 (m, 2H, $C\underline{H}_2CH$), 4.25 (dt, 2H, $CO_2C\underline{H}_2CH_2$, 1.2 Hz), 3.95 (dt, 2H, $OC\underline{H}_2CHCH_2$, 5.7, 1.5 Hz), 3.63 – 3.56 (m, 2H, $C\underline{H}_2OCH_2CH$), 3.56 – 3.47 (m, 2H, SCH_2), 3.43 – 3.31 (m, 1H, $CHCO_2$), 2.91 – 2.79 (m, 1H, $SCOCH_2$), 2.76 – 2.64 (m, 1H, $SCOCH_2$); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 205.0 (C), 171.2 (C), 134.3 (CH), 117.2 (CH_2), 71.9 (CH_2), 67.5 (CH_2), 64.5 (CH_2), 43.3 (CH_2), 42.6 (CH), 34.3 (CH_2); M (calc.): 230.06128; M+H (found): 231.0684; Δ = 0.7 ppm

4.23. **Thioparaconic acid allylamide** (**23**) was synthesized using thioparaconic acid chloride made from 29.2 g, 0.2 mol thioparaconic acid, following known literature.[20] The crude acid chloride was mixed with 20 mL dry toluene in a Schlenk flask and cooled down with an ice bath. A mixture of allylamine (8.6 g, 0.15 mol, 0.85 equiv.), dry pyridine (14.2 g, 14.5 mL, 0.18 mol, 0.9 equiv.) and 20 mL dry toluene was added via cannula. After complete addition, the reaction mixture was allowed to warm up and stirred at room temperature for two more hours. The crude reaction mixture was washed with 80 mL 2N hydrochloric acid. The aqueous phase was extracted with 50 mL ethyl acetate and the combined organic phases were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the crude product was further purified using column chromatography (hexane – ethyl acetate = 1 : 2). A pale yellow oil, which crystallized over time, was obtained (11.3 g, 30.5 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.39 (bs, 1H, CONH) 5.76 (ddt, 1H, $C\underline{H}CH_2$, 17.1, 10.2, 5.6 Hz), 5.24 – 5.02 (m, 2H, $CHC\underline{H}_2$), 3.83 (tt, 2H, 5.7, 1.6 Hz), 3.57 (dd, 1H, SCH_2, 11.2, 9.7 Hz), 3.42 (ddd, 1H, SCH_2, 11.1, 6.6, 0.8 Hz), 3.21 (ddt, 1H, CHCO, 10.8, 9.7, 6.8 Hz), 2.89 (dd, 1H, $SCOCH_2$, 16.8, 10.8 Hz), 2.80 – 2.44 (m, 1H, $SCOCH_2$); ^{13}C-NMR (500 MHz, $CDCl_3$): δ (ppm) = 207.1 (C), 170.7 (C), 135.4 (CH), 115.7 (CH_2), 44.2 (CH_2), 43.7 (CH), 41.5 (CH_2), 35.6 (CH_2); M (calc.): 185.05105; M+H (found): 186.0583; Δ = 0.1 ppm

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Supplementary Material

^{1}H- & ^{13}C-NMR spectra, LC-MS chromatograms and HR-MS spectra of the compounds can be found in the supporting information.

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