

# One-pot multicomponent synthesis of two novel thiolactone scaffolds

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**Abstract** We designed two novel thiolactone scaffolds. Both scaffolds can be accessed by a convergent Ugi multicomponent reaction (MCR) and are, thus, amenable to library synthesis. Design, stereoselectivity, structures, full experimental details, and virtual libraries will be reported.

**Keywords** Multicomponent reaction (MCR) · Isocyanide · Thiolactone · Virtual library

## Abbreviations

MCR	Multicomponent reaction
HTMP	Homocysteine thiolactone-induced protein modification
HTL	Homocysteine thiolactone
UDC	Ugi-deprotection-cyclization sequences
IMCR	Isocyanide based MCR
FDA	Food and drug administration

## Introduction

Thiolactones are an interesting class of heterocyclic scaffolds (Fig. 1). They can be found in microbial natural products with

potent antibacterial and antitumor activities such as thiolactomycin **1** [1]. Also of importance is the widespread use of thiolactone cores as synthetic intermediates for the construction of ligands relevant for applications in catalysis and medicinal chemistry. For example, Erdosteine **2** and Prasugrel **3** are recently marketed FDA-approved drugs for the treatment of chronic obstructive lung diseases [2] and platelet aggregation, respectively [3].<sup>1</sup>

Other bioactivities reported for thiolactones include H3 modulatory [4], anticancer and antibacterial [5], anti Alzheimer activity [6]. In addition, 2-keto thiomorpholine derivatives have been described as antibacterial topoisomerase-IV inhibitors [7]. Enantiomerically pure thiolactones have been used in the large-scale manufacture of the clinical candidate farnesyltransferase inhibitor AZD3409 [8]. A final application of thiolactones to be mentioned here is hair regrowth in personal care articles [9]. A general importance of the thioester moiety is also reflected in its use as an activated alkylation/acylation agents in biochemistry. Thus, most anabolic pathways to biochemical building blocks include thioesters at some point such as in fatty acid synthesis [10]. Thus, thiolactone derivatives are of great interest to study the chemical biology of these pathways. Homocysteine thiolactone-induced protein modification (HTPM) is a unique post-translational protein modification that is recognized as an emergent biomarker for cardiovascular disease [11]. HTPM involves the site-specific acylation of proteins at lysine residues by homocysteine thiolactone (HTL) to produce protein homocystamide, which has been found at elevated levels in patients with coronary heart disease. Consequently, thiolactones are an attractive synthetic target for several areas of chemical, biochemical and pharmaceutical research.

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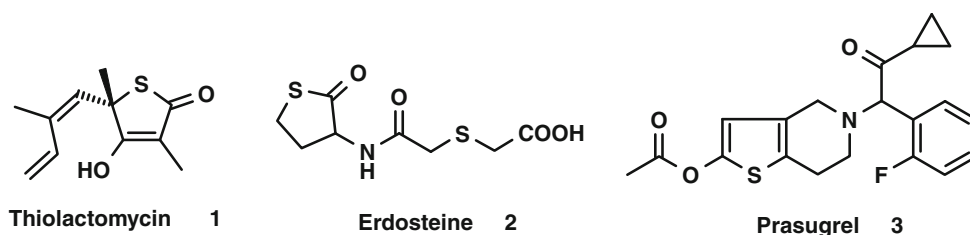
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<sup>1</sup> Chemically the latter comprise of 2-*O*-acetyl thiophene unit which is a prodrug and is hydrolyzed in vivo to the thiolactone.

**Fig. 1** Structures of representative bioactive thiolactones



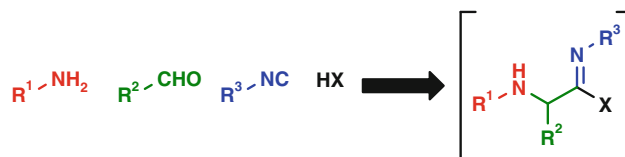
Surprisingly, there are currently only a few synthetic pathways described towards thiolactones apart from simply derivatisation of readily available homocysteine lactone [12]. These include acylation [13], Schiff base formation [14], alkylation and sulfonation [15]. Other methods include sulfur introduction into lactones using potassium thioacetate [16], cycloadditions [14, 17], oxidation of thiophene precursors [18] and cyclisation of open chain precursors [19]. An additional synthetic approach towards the  $\gamma$ -thiolactone moiety includes thiocarbonyl induced heterocumulenic Pauson–Khand reaction [20].

A powerful alternative strategy for the rapid introduction of molecular diversity in the construction of thiolactones involves multicomponent reactions (MCRs). MCRs are reactions consisting of 3 or more starting materials in a one-pot fashion allowing for the rapid and efficient assembly of a great number of scaffolds [21, 22]. We have recently published in preliminary form a new approach to thiolactone scaffolds via an MCR approach. Here we would like to report full details of the design, synthesis, structure, experimental procedures and virtual chemistry space of two new thiolactone syntheses [23].

In order to assess novel scaffolds by MCR a detailed understanding of the functional groups reactivity and the reaction mechanism is necessary. New scaffolds based on isocyanide MCR can be accessed based on two fundamentally different strategies.

The first strategy uses protecting groups for functional groups not compatible with other groups in a specific MCR mechanism. After the initial MCR the protecting group is removed or/and reacted in a subsequent reaction, e.g., cyclization. Examples involve the very useful Ugi–deprotection–cyclization sequences (UDC) and others [24–31]. This strategy involves multiple steps and the potential isolation of the intermediate.

The second strategy uses bifunctional starting materials with unprotected functional groups orthogonal to an initial MCR, which can participate in the later course of the MCR mechanism. Examples include a oxazole ring formation [32] and lactone ring formation [33]. This strategy differs from those that use bifunctional starting materials for the formation of  $\beta$ -lactam ring formation, lactone formation, or iminodicarboxylic acid mono amide [34–36] in that no intermediates are isolated and the final product is obtained in one synthetic step (“one-pot”). In this article, we discuss the use of a



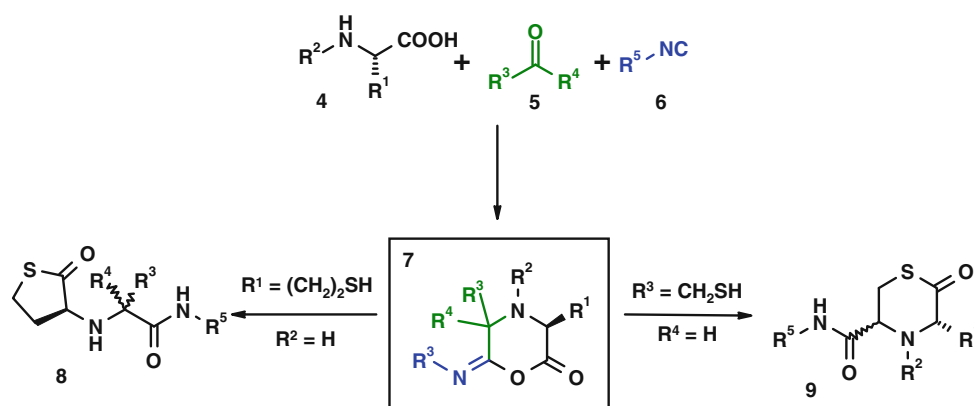
**Scheme 1** Formation of the IMCR hallmark intermediate  $\alpha$ -adduct

bifunctional amino acid for the Ugi 4-component-5-centered reaction. The mechanistic hallmark of Ugi-type IMCRs is the formation of a reactive intermediate  $\alpha$ -adduct (Scheme 1). This common intermediate is the result of the addition of the Schiff base and the acid anion onto the isocyanide carbon via a highly reactive nitrilium ion intermediate. The formation of the  $\alpha$ -adduct is a unique feature of the isocyanide functional group and accounts for the large scaffold diversity of the Ugi reaction in subsequent rearrangement reactions [22].

Our new MCR scaffold design is based on leveraging the acylation power of the common  $\alpha$ -adduct intermediate and the careful introduction of nucleophilic starting materials with differential reactivity. Compound classes in accordance with this design principle must have a functional group appropriate for the Ugi reaction and a reactive and suitably spaced nucleophilic functional group placed in a position to undergo an intramolecular transacylation. In order to access stereochemically pure reaction products, we chose to start with chiral  $\alpha$ -amino acids. The use of  $\alpha$ -amino acids in the Ugi reaction to output many different scaffolds has been widely described [37–42]. During the IMCRs of  $\alpha$ -amino acids a cyclic six-membered  $\alpha$ -adduct **7** is formed (Scheme 2). The choice of the component and nature of the additional nucleophilic functionality determine the structural fate of the reaction product. Appropriate compounds that we could identify for our thiolactone scaffold design are mercaptoacetaldehyde and homocysteine, both of which incorporate a strongly nucleophilic sulfhydryl side chain in a position to undergo transacylation. Although in a classic Ugi reactions methanol is the solvent of choice, the use of a protic, yet non-nucleophilic solvent (e.g., trifluoroethanol) is crucial here to avoid intermolecular reaction of the  $\alpha$ -adduct with methanol to form the methylester and to favor the intermolecular transacylation to form thiolactones.

The first thiolactone scaffold is generated by the reaction of homocysteine, oxo components, and isocyanides. This

**Scheme 2** New IMCR scaffolds by intramolecular nucleophilic acylations



reaction smoothly affords product class **8** with broad diversity. Herein, the intermediate  $\alpha$ -adduct **7** reacts with the sulfhydryl side chain of the aminoacid probably via a tricyclic acylation transition state attacking the activated cyclic ester.

The second thiomorpholine scaffold, however, is generated by the reaction of isocyanides, mercaptoacetaldehyde, and  $\alpha$ -aminoacids affording product class **9** again with broad diversity. Herein, the intermediate  $\alpha$ -adduct **7** reacts with the sulfhydryl side chain of the mercaptoacetaldehyde probably also via a tricyclic acylation transition state attacking the activated cyclic ester.

## Experimental section

### General experimental methods

Standard syringe techniques were applied for the transfer of air-sensitive reagents. Dry solvents were purchased from Aldrich, Fisher Scientific, Acros Organics or Alfa Aesar and used as received.  $^1\text{H}$ - and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Ultrashield Plus 600 at 600 MHz. Chemical shift values are in ppm relative to TMS. Abbreviations used are s = singlet, brs = broad singlet, d = doublet, brd = broad doublet, m = multiplet; data in parenthesis are given in the following order: multiplicity, number of protons, and coupling constants in Hz. Flash chromatography was performed with the indicated solvent mixture on Silica gel, MP Silitech 32–63 D, 60 Å, Bodman. Chromatotron chromatography was performed on Harrison Research Chromatotron, Ser. no. 65F with the indicated solvent mixture using Silica gel, Merck, TLC grade 7749, with gypsum binder and fluorescent indicator (Sigma Aldrich). Thin layer chromatography was performed using Whatmann flexible-backed TLC plates on aluminum with fluorescence indicator. Compounds on TLC were visualized by UV detection. HPLC-MS measurements were done on a Shimadzu prominence UFLC (HPLC) and an API 2000 LC/MS/MS System, Applied Biosystems MDS SCIEX, (MS) using a Dionex Acclaim 120 column (C18, 3  $\mu\text{m}$ , 120 Å, 2.1  $\times$  150 mm), mobile phase: water with 0.1%

acetic acid and acetonitrile, gradient: 5–90% acetonitrile in 7 min, injection volume: 5  $\mu\text{L}$ , detection wavelength 254 nm. HRMS measurements were performed at the Department of Chemistry, University of Pittsburgh with a Q-ToF spectrometer, ionization mode: ESI. All purchased chemicals were used as received.

### General procedure for preparation of compounds **10–20**

Homocysteine (2 mmol, 270 mg) is solubilized in 10 mL of trifluoroethanol (TFE) and cooled under nitrogen to  $-20^\circ\text{C}$ . Solutions of isocyanide (2 mmol) and aldehyde (2 mmol) in 5 mL of trifluoroethanol are added simultaneously dropwise using a syringe. The reaction mixture is stirred cold for 1 h and allowed to warm to room temperature, and stirred overnight. The solvent is removed under reduced pressure, the residue is dissolved in ethyl acetate, and washed with water, and brine. The organic layer is dried over anhydrous magnesium sulfate and concentrated. In most cases, the product can be crystallized from ethyl acetate to yield the major diastereomer. In other cases, the crude product is purified by column chromatography on silica gel with heptane/ethyl acetate elution gradient from 3/1 to 1/2.

#### *N*-Benzyl-2-cyclopropyl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-acetamide (**10**)

Crystalline solid; yield 470 mg (77%) as a mixture of diastereomers (77:23);  $^1\text{H}$ -NMR of the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 0.38 (m, 1H), 0.56–0.65 (m, 3H), 0.95–0.97 (m, 1H), 1.87 (m, 2H), 2.42–2.45 (m, 1H), 2.52 (d, 1H), 3.16–3.18 (m, 2H), 3.41–3.44 (m, 1H), 4.40–4.49 (m, 2H), 7.26–7.34 (m, 5H), 7.46 (br, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 2.7, 3.1, 14.9, 26.4, 30.2, 32.3, 36.3, 65.3, 126.6, 126.9, 127.8, 137.6, 172.4, 207.0; HPLC-MS (ESI-TOF):  $t_r$  = 7.59 min,  $m/z$  = 305  $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{S}[\text{M}+\text{Na}]^+$  327.1143, found 327.1136. X-ray structure determination:  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ ,  $M_r$  = 304.41, monoclinic, space group  $P2_1/c$ ,  $a$  = 16.534(2),  $b$  = 10.1055(11),  $c$  = 9.4045(4) Å,  $\beta$  = 103.269(7)°,

$V = 1529.4(3) \text{ \AA}^3$ ;  $Z = 4$ ;  $\rho_{\text{calcd}} = 1.322 \text{ g cm}^{-3}$ ,  $F_{000} = 648$ ,  $\mu = 0.218 \text{ mm}^{-1}$ . A suitable single crystal for the X-ray diffraction study was selected, coated with perfluorinated ether, fixed in a capillary, and transferred to the diffractometer. Preliminary examination and data collection were carried out on a  $\kappa$ -CCD device (Xcalibur) at the window of a sealed tube with graphite monochromated Mo- $K_{\alpha}$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Data collection was performed at 153 K within the  $\Theta$ -range of  $3.00^\circ < \Theta < 25.51^\circ$ . A total of 27313 reflections were integrated, and corrected for Lorentz and polarization effects. A correction for absorption effects and/or decay was applied during the scaling procedure. After merging ( $R_{\text{int}} = 0.040$ ), 2830 [1895:  $I_o > 2\sigma(I_o)$ ] independent reflections remained, and all were used to refine 274 parameters. The structure was solved by a combination of direct methods and difference—Fourier syntheses. All hydrogen positions were found and refined with isotropic displacement parameters. Full-matrix least-squares refinement was carried out by minimizing  $\sum w (F_o^2 - F_c^2)^2$ , and converged with  $R1 = 0.0363$  [ $I_o > 2\sigma(I_o)$ ],  $wR2 = 0.0959$  (all data),  $\text{GOF} = 1.022$ , and shift/error  $< 0.001$ . The hydrogen atom bound to N2 appears to be disordered over two positions (2/3:1/3) [43–50].

*1-(2-Oxo-tetrahydro-thiophen-3-ylamino)-cyclohexanecarboxylic acid (2,4,6-trimethyl-phenyl)-amide (11)*

Crystalline solid; yield 236 mg (33%);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 1.34\text{--}1.42$  (m, 2H),  $1.47\text{--}1.65$  (m, 1H),  $1.67\text{--}1.78$  (m, 4H),  $1.87\text{--}1.88$  (m, 1H),  $1.96\text{--}2.16$  (m, 2H),  $2.20\text{--}2.24$  (s, 6H and m, 2H),  $2.27$  (s, 3H),  $2.67\text{--}2.71$  (m, 1H),  $3.16\text{--}3.23$  (m, 2H),  $3.49\text{--}3.52$  (m, 1H),  $6.84$  (s, 2H),  $8.83$  (s, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150 MHz):  $\delta = 18.4$ ,  $20.7$ ,  $21.2$ ,  $21.4$ ,  $22.8$ ,  $24.9$ ,  $26.7$ ,  $30.1$ ,  $32.5$ ,  $32.9$ ,  $34.5$ ,  $61.9$ ,  $63.4$ ,  $128.7$ ,  $128.9$ ,  $131.5$ ,  $134.6$ ,  $136.1$ ,  $175.0$ ,  $209.0$ ; HPLC-MS (ESI-TOF):  $r_t = 11.68 \text{ min}$ ,  $m/z = 361$  [ $\text{M}+\text{H}$ ] $^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$  [ $\text{M}$ ] $^+$  360.1871 found 360.1871. X-ray structure determination:  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$ ,  $M_r = 360.51$ , monoclinic, space group  $P2_1/c$ ,  $a = 9.9108(7)$ ,  $b = 19.9983(12)$ ,  $c = 9.7831(7) \text{ \AA}$ ,  $\beta = 96.917(6)^\circ$ ,  $V = 1924.9(2) \text{ \AA}^3$ ;  $Z = 4$ ;  $\rho_{\text{calcd}} = 1.244 \text{ g cm}^{-3}$ ,  $F_{000} = 776$ ,  $\mu = 0.184 \text{ mm}^{-1}$ . A suitable single crystal for the X-ray diffraction study was selected, coated with perfluorinated ether, fixed in a capillary, and transferred to the diffractometer. Preliminary examination and data collection were carried out on a  $\kappa$ -CCD device (Xcalibur) at the window of a sealed tube with graphite monochromated Mo- $K_{\alpha}$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Data collection was performed at 173 K within the  $\Theta$ -range of  $2.90^\circ < \Theta < 25.39^\circ$ . A total of 36,019 reflections were integrated, and corrected for Lorentz and polarization effects. A correction for absorption effects and/or decay was applied

during the scaling procedure. After merging ( $R_{\text{int}} = 0.042$ ), 3507 [2644:  $I_o > 2\sigma(I_o)$ ], independent reflections remained, and all were used to refine 338 parameters. The structure was solved by a combination of direct methods and difference—Fourier syntheses. All hydrogen positions were found and refined with isotropic displacement parameters. Full-matrix least-squares refinement was carried out by minimizing  $\sum w (F_o^2 - F_c^2)^2$  and converged with  $R1 = 0.0446$  [ $I_o > 2\sigma(I_o)$ ],  $wR2 = 0.1277$  (all data),  $\text{GOF} = 1.065$ , and shift/error  $< 0.001$ .

*(S)-4,8-Dimethyl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-non-7-enoic acid benzhydryl-amide (13)*

Yellow oil; yield 396 mg (43%) as a mixture of diastereomers;  $^1\text{H-NMR}$  of the mixture of diastereomers ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 0.91\text{--}0.96$  (m, 3H),  $1.23\text{--}1.25$  (m, 1H),  $1.37\text{--}1.60$  (m, 2H),  $1.66\text{--}1.74$  (m, 6H),  $1.79$  (s, 3H),  $1.81\text{--}1.92$  (m, 2H),  $1.94\text{--}2.02$  (m, 2H),  $2.36\text{--}2.38$  (m, 1H),  $3.03\text{--}3.06$  (m, 2H),  $3.24\text{--}3.28$  (m, 2H),  $5.05\text{--}5.08$  (m, 1H),  $6.22\text{--}6.26$  (m, 1H),  $7.19\text{--}7.46$  (m, 10H),  $8.11\text{--}8.24$  (m, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150 MHz):  $\delta = 17.71$ ,  $17.74$ ,  $19.0$ ,  $20.1$ ,  $25.2$ ,  $25.4$ ,  $25.76$ ,  $25.77$ ,  $27.0$ ,  $27.1$ ,  $29.2$ ,  $29.4$ ,  $29.5$ ,  $31.2$ ,  $31.3$ ,  $33.2$ ,  $36.4$ ,  $37.5$ ,  $41.0$ ,  $41.9$ ,  $42.2$ ,  $56.2$ ,  $56.39$ ,  $56.43$ ,  $59.3$ ,  $59.4$ ,  $66.56$ ,  $66.61$ ,  $124.5$ ,  $124.6$ ,  $126.9$ ,  $127.2$ ,  $127.3$ ,  $127.4$ ,  $127.5$ ,  $127.6$ ,  $127.8$ ,  $128.58$ ,  $128.61$ ,  $128.65$ ,  $128.8$ ,  $131.4$ ,  $131.5$ ,  $141.7$ ,  $141.92$ ,  $141.96$ ,  $173.6$ ,  $173.9$ ,  $207.73$ ,  $207.77$ ; carbon signals are doubled as a mixture of diastereomers; HPLC-MS (ESI-TOF):  $r_t = 12.73 \text{ min}$ ,  $m/z = 465$  [ $\text{M}+\text{H}$ ] $^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_2\text{S}$  [ $\text{M}+\text{Na}$ ] $^+$  464.6626, found 465.2765.

*N-tert-Butyl-3-(5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-propionamide (14)*

Colorless oil; yield 330 mg (45%) as a mixture of diastereomers (81:19);  $^1\text{H-NMR}$  for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 1.34$  (s, 9H),  $1.88$  (s, 3H),  $1.90\text{--}2.03$  (m, 2H),  $2.44\text{--}2.50$  (m, 1H),  $3.21\text{--}3.27$  (m, 2H),  $3.32\text{--}3.34$  (m, 1H),  $3.39\text{--}3.44$  (m, 1H),  $3.96\text{--}4.00$  (m, 1H),  $4.09\text{--}4.12$  (m, 1H),  $7.1$  (s, 1H),  $7.57$  (s, 1H),  $9.73$  (br, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150 MHz):  $\delta = 12.2$ ,  $27.3$ ,  $28.5$ ,  $28.6$ ,  $30.9$ ,  $50.9$ ,  $51.1$ ,  $51.2$ ,  $61.8$ ,  $66.8$ ,  $111.0$ ,  $141.4$ ,  $152.8$ ,  $164.3$ ,  $170.2$ ,  $207.7$ ; HPLC-MS (ESI-TOF):  $r_t = 8.87 \text{ min}$ ,  $m/z = 369$  [ $\text{M}+\text{H}$ ] $^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_4\text{S}$  [ $\text{M}+\text{Na}$ ] $^+$  339.1416, found 391.1397.

*3-Methyl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-N-(2,4,6-trimethyl-phenyl)-butyramide (15)*

Colorless solid; yield 160 mg (25 %) only the major diastereomer was isolated as precipitate;  $^1\text{H-NMR}$  for the



major diastereomer (CDCl<sub>3</sub>, 600 MHz):  $\delta$  = 1.00 (d, 3H), 1.07 (d, 3H), 1.77 (br, 1H), 1.95 (m, 1H), 2.16 (s, 6H), 2.24 (s, 3H), 2.31–2.36 (m, 1H), 2.67–2.70 (m, 1H), 3.20–3.25 (m, 3H), 3.47–3.50 (m, 1H), 6.86 (s, 2H), 8.74 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  = 17.5, 18.7, 19.9, 20.7, 26.9, 31.1, 31.9, 67.1, 67.2, 128.8, 131.3, 134.5, 136.6, 171.5, 207.4; HPLC-MS (ESI-TOF):  $r_t$  = 10.88 min,  $m/z$  = 335 [M+H]<sup>+</sup>; HRMS (ESI-TOF)  $m/z$  calcd for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S [M+Na]<sup>+</sup> 357.1613, found 357.1598.

*N*-Benzyl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-4-phenyl-butyramide (**16**)

Colorless solid; yield 540 mg (73%) only the major diastereomer was isolated as precipitate; <sup>1</sup>H-NMR for the major diastereomer (CDCl<sub>3</sub>, 600 MHz):  $\delta$  = 1.75–1.93 (m, 3H), 2.10–2.13 (m, 1H), 2.40–2.43 (m, 1H), 2.70–2.76 (m, 2H), 3.10–3.15 (m, 2H), 3.22–3.23 (m, 1H), 3.31–3.35 (m, 1H), 4.36–4.48 (m, 2H), 7.16–7.19 (m, 3H), 7.24–7.27 (m, 5H), 7.30–7.33 (m, 2H), 7.53–7.55 (m, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  = 26.3, 30.5, 31.4, 34.5, 42.4, 59.9, 65.6, 125.3, 126.6, 126.9, 127.6, 127.7, 127.8, 137.5, 140.1, 172.9, 207.0; HPLC-MS (ESI-TOF):  $r_t$  = 10.71 min,  $m/z$  = 368 [M+H]<sup>+</sup>; HRMS (ESI-TOF)  $m/z$  calcd for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S [M+Na]<sup>+</sup> 391.1456, found 391.1449.

2-Methyl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-*N*-(2,4,6-trimethyl-phenyl)-propionamide (**17**)

Colorless oil; yield 340 mg (53%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  = 1.47 (d, 6H,  $J$  = 6.60 Hz), 1.97–2.04 (m, 2H), 2.14 (s, 6H), 2.25 (s, 3H), 2.71–2.73 (m, 1H), 3.21–3.27 (m, 2H), 3.54–3.57 (m, 1H), 6.86 (s, 2H), 8.92 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  = 18.5, 20.9, 26.4, 26.7, 26.8, 34.9, 59.8, 63.9, 128.9, 131.4, 134.8, 136.5, 174.9, 208.8; HPLC-MS (ESI-TOF):  $r_t$  = 10.40 min,  $m/z$  = 321 [M+H]<sup>+</sup>; HRMS (ESI-TOF)  $m/z$  calcd for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S [M+H]<sup>+</sup> 321.1637, found 321.1639.

*N*-tert-Butyl-3-methyl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-butyramide (**18**)

Colorless solid; yield 254 mg (47%) as a mixture of diastereomers (88:12); <sup>1</sup>H-NMR for the major diastereomer (CDCl<sub>3</sub>, 600 MHz):  $\delta$  = 0.91 (d, 3H,  $J$  = 6.96 Hz), 1.01 (d, 3H,  $J$  = 6.96 Hz), 1.35 (s, 9H), 1.87–1.94 (m, 1H), 2.11–2.16 (m, 1H), 2.53–2.57 (m, 1H), 2.85 (d, 1H,  $J$  = 4.68 Hz), 3.19–3.32 (m, 3H), 6.98 (s, 1H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  = 17.3, 19.2, 27.4, 28.5, 31.3, 33.3, 50.4, 68.2, 68.6, 172.5, 206.9; HPLC-MS (ESI-TOF):  $r_t$  = 10.05 min,  $m/z$  = 273 [M+H]<sup>+</sup>; HRMS (ESI-TOF)

$m/z$  calcd for C<sub>13</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S [M+Na]<sup>+</sup> 295.1456, found 295.1457.

*N*-tert-Butyl-2-naphthalen-2-yl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-acetamide (**19**)

Colorless solid; yield 380 mg (53%) as a mixture of diastereomers (65:35); <sup>1</sup>H-NMR of the mixture of diastereomers (CDCl<sub>3</sub>, 600 MHz):  $\delta$  = 1.30 (s, 9H), 1.32 (s, 9H from minor isomer), 1.92–2.03 (m, 1H), 2.34–2.38 (m, 1H), 2.60–2.65 (m, 1H from minor isomer), 3.11–3.24 (m, 2H), 3.33–3.36 (m, 1H), 3.41–3.44 (m, 1H from minor isomer), 4.39 (s, 1H from minor isomer), 4.55 (s, 1H), 6.12 (s, 1H), 6.95 (s, 1H from minor isomer), 7.36–7.51 (m, 4H), 7.79–7.85 (m, 3H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  = 27.6, 28.7, 28.8, 32.2, 32.9, 51.1, 51.2, 65.5, 65.7, 66.7, 67.2, 124.7, 125.1, 126.2, 126.3, 126.36, 126.4, 126.5, 127.4, 127.70, 127.72, 128.02, 128.04, 128.92, 128.94, 133.1, 133.2, 133.3, 136.4, 136.6, 170.7, 170.9, 207.1, 208.1; carbon signals are doubled as a mixture of diastereomers; HPLC-MS (ESI-TOF):  $r_t$  = 11.13 min,  $m/z$  = 357 [M+H]<sup>+</sup>; HRMS (ESI-TOF)  $m/z$  calcd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>S [M+Na]<sup>+</sup> 379.1456, found 379.1468.

*N*-Benzhydryl-2-(2-oxo-tetrahydro-thiophen-3-ylamino)-3-phenyl-propionamide (**20**)

Colorless solid; yield 292 mg (34%) as a mixture of diastereomers (72:28); <sup>1</sup>H-NMR of the mixture of diastereomers (CDCl<sub>3</sub>, 600 MHz):  $\delta$  = 1.48–1.54 (m, 1H), 1.62–1.69 (m, 1H), 2.14–2.19 (m, 1H), 2.23–2.27 (m, 1H from minor diastereomer), 2.83–2.86 (m, 1H), 2.98–3.07 (m, 2H), 3.17–3.25 (m, 1H), 3.31–3.34 (m, 1H), 3.48–3.51 (m, 1H), 3.57–3.58 (m, 1H from minor diastereomer), 6.28 (d, 1H,  $J$  = 8.94 Hz), 7.15–7.36 (m, 15H), 8.39 (d, 1H,  $J$  = 8.94 Hz); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  = 26.9, 27.5, 31.1, 33.0, 39.2, 39.3, 56.4, 56.6, 62.3, 63.2, 66.9, 67.1, 127.1, 127.2, 127.3, 127.36, 127.37, 127.39, 127.45, 127.58, 127.61, 128.58, 128.62, 128.64, 128.74, 128.86, 128.88, 129.27, 129.45, 136.5, 137.2, 141.1, 141.7, 141.8, 172.2, 172.3, 206.7, 207.6; carbon signals are doubled as a mixture of diastereomers; HPLC-MS (ESI-TOF):  $r_t$  = 11.53 min,  $m/z$  = 431 [M+H]<sup>+</sup>; HRMS (ESI-TOF)  $m/z$  calcd for C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S [M+Na]<sup>+</sup> 453.1613, found 453.1619.

General procedure for preparation of compounds **21–30**

Amino acid (1 mmol) is dissolved in 10 mL of trifluoroethanol at room temperature. Isocyanide (1 mmol) and 2,5-dihydroxy-1,4-dithiane (0.5 mmol) are added simultaneously. The reaction mixture is stirred overnight at room temperature. The solvent is evaporated, the residue dissolved in ethyl acetate and washed with water and brine. The organic

layer is dried over anh. magnesium sulfate and concentrated. The crude product is purified by column chromatography on silica gel with petroleum ether/ethyl acetate, elution gradient from 2/1 to 1/2.

*5-Benzyl-6-oxo-thiomorpholine-3-carboxylic acid benzylamide (21)*

Crystalline solid; yield: 180 mg (70%) as a mixture of diastereomers;  $^1\text{H-NMR}$  for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 2.31\text{--}2.34$  (m, 1H), 2.42–2.48 (m, 1H), 3.28–3.31 (m, 1H), 3.35–3.36 (m, 1H), 3.38–3.40 (m, 1H), 3.53–3.68 (m, 1H), 3.70–3.75 (m, 2H), 4.17–4.21 (m, 1H), 6.89–7.32 (m, 11H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150 MHz):  $\delta = 30.9$ , 35.2, 42.5, 54.1, 61.6, 126.6, 127.1, 127.3, 128.2, 128.3, 129.1, 137.9, 171.1, 202.3; HPLC-MS (ESI-TOF):  $r_t = 11.61$  min,  $m/z = 341$   $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$  341.1324, found 341.0897. X-ray structure determination:  $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ ,  $M_r = 340.44$ , monoclinic, space group  $\text{C}2/c$ ,  $a = 19.6308(8)$ ,  $b = 13.6382(7)$ ,  $c = 27.5585(10)$  Å,  $\beta = 109.004(3)^\circ$ ,  $V = 6976.1(5)$  Å<sup>3</sup>;  $Z = 16$ ;  $\rho_{\text{calcd}} = 1.297$  g cm<sup>−3</sup>,  $F_{000} = 2880$ ,  $\mu = 0.199$  mm<sup>−1</sup>. A suitable single crystal for the X-ray diffraction study was selected, coated with perfluorinated ether, fixed in a capillary, and transferred to the diffractometer. Preliminary examination and data collection were carried out on a imaging plate device (IPDS 2T) at the window of a rotating anode (Nonius FR591) with graphite monochromated Mo- $\text{K}_\alpha$  radiation ( $\lambda = 0.71073$  Å). Data collection was performed at 173 K within the  $\Theta$ -range of  $3.99^\circ < \Theta < 25.32^\circ$ . A total of 44459 reflections were integrated, and corrected for Lorentz and polarization effects. A correction for absorption effects and/or decay was not applied. After merging ( $R_{\text{int}} = 0.066$ ), 6350 [4480:  $I_0 > 2\sigma(I_0)$ ] independent reflections remained, and all were used to refine 593 parameters. The structure was solved by a combination of direct methods and difference—Fourier syntheses. All hydrogen positions were found and refined with isotropic displacement parameters. Full-matrix least-squares refinement was carried out by minimizing  $\sum w(F_o^2 - F_c^2)^2$  and converged with  $R1 = 0.0332$  [ $I_0 > 2\sigma(I_0)$ ],  $wR2 = 0.0748$  (all data),  $\text{GOF} = 1.057$ , and shift/error  $< 0.001$ . Two crystallographic independent molecules **A** and **B** were found in the asymmetric unit. Both are almost congruent [43–50].

*5-Methyl-6-oxo-thiomorpholine-3-carboxylic acid (2,4,6-trimethyl-phenyl)-amide (22)*

Viscous oil; yield: 105 mg (12%) as a mixture of diastereomers (78:22);  $^1\text{H-NMR}$  for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 1.28$  (s, 3H), 2.10 (s, 6H), 2.20 (s, 3H), 2.39 (brs, 1H), 3.31–3.36 (m, 1H), 3.54–3.59 (m, 2H), 3.85–3.86 (m, 1H), 6.84 (m, 2H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150 MHz):

$\delta = 15.5$  18.1, 20.6, 30.8, 54.8, 55.4, 128.7, 130.3, 134.1, 136.8, 169.6, 202.1; HPLC-MS (ESI-TOF):  $r_t = 10.35$  min,  $m/z = 293$   $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$  292.1324, found 293.1321.

*[(1-Oxo-hexahydro-pyrrolo[2,1-c][1,4]thiazine-4-carbonyl)-amino]-acetic acid methyl ester (23)*

Crystalline solid; yield: 275 mg (34%) as a mixture of diastereomers (76:24);  $^1\text{H-NMR}$  for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 1.86\text{--}1.94$  (m, 2H), 1.95–2.05 (m, 1H), 2.20–2.28 (m, 1H), 2.59–2.64 (m, 1H), 3.30–3.35 (m, 1H), 3.40 (d, 1H,  $J = 12$  Hz), 3.55–3.60 (m, 1H), 3.61–3.67 (m, 1H), 3.69–3.73 (m, 1H), 3.75 (s, 3H), 3.91–3.96 (m, 1H), 4.20–4.27 (m, 1H), 7.69 (brs, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150 MHz):  $\delta = 21.9$ , 24.1, 29.7, 31.2, 40.8, 52.4, 52.7, 61.3, 65.3, 170.0, 171.7, 201.3; HPLC-MS (ESI-TOF):  $r_t = 8.45$  min,  $m/z = 273$   $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$   $[\text{M}+\text{Na}]^+$  295.0728, found : 295.0723.

*5-(2-Methylsulfanyl-ethyl)-6-oxo-thiomorpholine-3-carboxylic acid (1-propyl-butyl)-amide (24)*

Viscous oil; yield: 163 mg (16%) as a diastereomeric mixture (96:4);  $^1\text{H-NMR}$  for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 0.92$  (m, 6H), 1.23–1.43 (m, 6H), 1.45–1.54 (m, 2H), 1.65–1.73 (m, 1H), 2.05–2.22 (m, 4H), 2.29–2.36 (brs, 1H), 2.68–2.73 (m, 2H), 3.24–3.31 (m, 1H), 3.56–3.64 (m, 2H), 3.75–3.81 (m, 1H), 3.86–3.94 (m, 1H), 7.48 (brs, 1H);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  14.0, 15.6, 19.1, 19.4, 28.1, 30.9, 31.3, 37.4, 37.5, 48.8, 54.9, 58.3, 170.9, 202.6; HPLC-MS (ESI-TOF):  $r_t = 11.27$  min,  $m/z = 333$   $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{28}\text{N}_2\text{O}_2\text{S}_2$   $[\text{M}+\text{H}]^+$  333.1670, found 333.1663.

*5-Isopropyl-6-oxo-thiomorpholine-3-carboxylic acid [2-oxo-2-(4-phenyl-piperazin-1-yl)-ethyl]-amide (25)*

Viscous oil; yield: 126 mg (10%) as a mixture of diastereomers (73:27);  $^1\text{H-NMR}$  for the diastereomeric mixture ( $\text{CDCl}_3$ , 600 MHz):  $\delta = 1.04$  (d, 3H,  $J = 7.2$  Hz), 1.08 (d, 1H,  $J = 6.6$  Hz, from minor diast.), 1.12 (d, 1H,  $J = 7.2$  Hz, from minor diast.), 1.19 (d, 3H,  $J = 6.6$  Hz), 1.86–1.91 (m, 0.34H, from minor diast.), 2.18–2.34 (brs, 1H), 2.36–2.41 (m, 1H), 3.17–3.29 (m, 6H), 3.32 (dd, 1H,  $J = 12$  Hz & 14.4 Hz), 3.41 (dd, 0.30H,  $J = 7.8$  Hz & 12.6 Hz, from minor diast.), 3.56–3.62 (m, 4H), 3.72 (t, 0.71H, from minor diast.), 3.79–3.90 (m, 3H), 4.05 (dd, 0.38H,  $J = 3.6$  Hz & 17.4 Hz, from the minor diast.), 4.16 (dd, 1H,  $J = 4.2$  Hz & 10.2 Hz), 4.48 (brd, 0.36H, from minor diast.), 6.93–6.96 (m, 3H & 1H from minor diast.), 7.28–7.32 (m,

2H & 1H from minor diast.), 8.35 (brs, 0.31H, from minor diast.), 8.50 (brs, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 17.1, 20.3, 27.4, 30.9, 41.4, 44.4, 49.4, 49.6, 54.9, 64.4, 116.8, 120.9, 129.3, 166.1, 172.2, 202.0; HPLC-MS (ESI-TOF):  $r_t$  = 10.29 min,  $m/z$  = 405  $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  405.1960, found 405.1995.

**5-Benzyl-6-oxo-thiomorpholine-3-carboxylic acid [(methyl-phenethyl-carbamoyl)-methyl]-amide (26)**

Viscous oil; yield: 298 mg (23%) as a mixture of diastereomers (57:43);  $^1\text{H}$ -NMR for the diastereomeric mixture ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 2.20–2.41 (brs, 1H), 2.79–2.85 (m, 4H), 2.87 (t, 3H,  $J$  = 7.8 Hz), 2.99 (s, 1.7H, from minor diast.), 3.26–3.37 (m, 3H), 3.46–3.69 (m, 8H), 3.76–3.79 (dd, 0.7H,  $J$  = 6 Hz & 11.4 Hz, from minor diast.), 3.80–3.85 (m, 1H), 7.18–7.36 (m, 15H), 7.59 (brs, 0.66H, from the minor diast.), 7.64 (brs, 0.87H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 31.1, 33.8, 34.7, 35.5, 40.2, 40.8, 50.4, 50.7, 54.4, 61.6, 126.5, 126.9, 128.5, 128.6, 128.8, 128.9, 129.9, 137.8, 139.1, 167.4, 172.3, 202.4; HPLC-MS (ESI-TOF):  $r_t$  = 10.58 min,  $m/z$  = 426  $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  426.1851, found 426.1837.

**5-sec-Butyl-6-oxo-thiomorpholine-3-carboxylic acid tert-butylamide (27)**

Viscous oil; yield: 212 mg (34%) as a mixture of diastereomers (73:27);  $^1\text{H}$ -NMR for the diastereomeric mixture ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 0.93 (d, 3H,  $J$  = 5.88 Hz), 0.95–0.98 (m, 3H), 1.09 (d, 1.47H,  $J$  = 6.78 Hz, from minor diast.), 1.38 (s, 9H), 1.40–1.60 (m, 2H), 2.08–2.21 (m, 2H), 3.15 (m, 0.37H, from minor diast.), 3.25–3.31 (m, 2H), 3.54–3.59 (m, 1H), 3.69–3.73 (m, 1H), 7.62 (brs, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 11.9, 14.0, 16.9, 23.9, 27.3, 28.7, 30.9, 33.4, 33.7, 50.8, 54.7, 54.9, 61.9, 64.4, 170.8, 170.9, 202.4, 202.9; HPLC-MS (ESI-TOF):  $r_t$  = 10.92 min  $m/z$  = 273  $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$  273.1637, found 273.1637.

**1-Oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid (2,4,6-trimethyl-phenyl)-amide (28)**

Viscous oil; yield 466 mg (47%) as a mixture of diastereomers (85:15),  $^1\text{H}$ -NMR for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.37 (m, 1H), 1.53–1.66 (m, 1H), 1.70–1.90 (m, 3H), 1.99–2.30 (m, 14H), 2.74–2.85 (m, 1H), 3.01–3.11 (m, 1H), 3.35–3.47 (m, 1H), 3.57–3.78 (m, 3H), 6.90 (s, 2H), 9.00 (brs, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 18.5, 20.9, 26.2, 27.1, 53.6, 64.5, 129.1, 130.9, 134.7, 136.9, 169.0, 200.3;  $^1\text{H}$ -NMR for the minor diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.61–1.65 (m, 3H), 1.74–1.75 (m, 1H), 1.95–2.03 (m, 1H), 2.20 (s, 6H), 2.29 (s, 3H), 2.37

(brd, 1H,  $J$  = 12.6 Hz), 2.85–2.93 (m, 2H), 3.37 (t, 1H,  $J$  = 12 Hz), 3.55 (dd, 1H,  $J$  = 12 Hz & 5.4 Hz), 3.66 (dd, 1H,  $J$  = 14.4 Hz & 5.4 Hz), 3.91 (brs, 1H), 6.93 (s, 2H), 9.22 (s, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 18.4, 19.6, 20.9, 25.2, 26.6, 53.5, 60.0, 65.6, 129.1, 130.7, 134.2, 137.1, 169.0, 201.2; HPLC-MS (ESI-TOF):  $r_t$  = 11.28 min,  $m/z$  = 333  $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$   $[\text{M}+\text{Na}]^+$  355.1456, found 355.1447.

**5-(1-Hydroxy-ethyl)-6-oxo-thiomorpholine-3-carboxylic acid (2-fluoro-phenyl)-amide (29)**

Viscous oil; yield: 107 mg (12%) as a mixture of diastereomers (81:19);  $^1\text{H}$ -NMR for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.46 (d, 3H,  $J$  = 12 Hz), 2.37 (brs, 1H), 2.96 (t, 1H,  $J$  = 12 Hz), 3.31–3.35 (m, 2H), 3.69 (dd, 1H,  $J$  = 18 Hz & 6 Hz), 4.00–4.05 (m, 1H), 4.63–4.67 (m, 1H), 7.06–7.17 (m, 3H), 8.41 (m, 1H), 10.03 (brs, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 18.6, 30.7, 55.6, 63.4, 64.5, 115.9, 120.8, 124.7, 125.8, 169.9, 203.3; HPLC-MS (ESI-TOF):  $r_t$  = 9.42 min,  $m/z$  = 299  $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{15}\text{FN}_2\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  299.0866, found 299.0850.

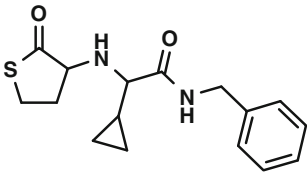
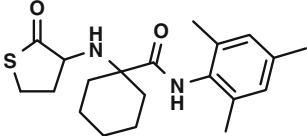
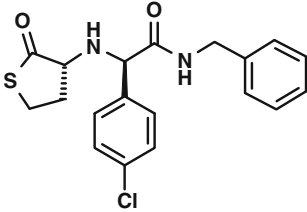
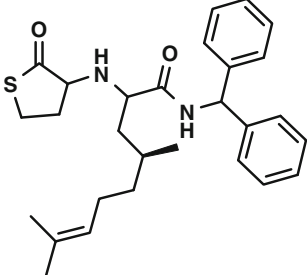
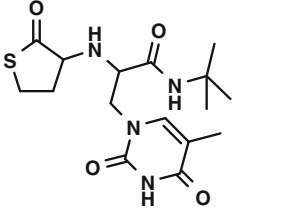
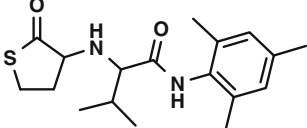
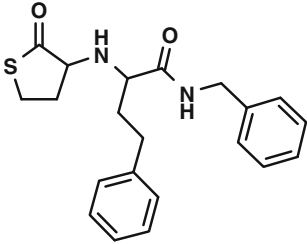
**1-Oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid tert-butylamide (30)**

Viscous oil; yield 254 mg (31%) as a mixture of diastereomers (64:36);  $^1\text{H}$ -NMR for the major diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.39 (s, 9H), 1.50–1.56 (m, 3H), 1.61–1.63 (m, 1H), 1.70 (brd, 1H,  $J$  = 9.6 Hz), 2.33–2.35 (brd, 1H,  $J$  = 2.2 Hz), 2.73–2.80 (m, 2H), 3.24–3.25 (m, 2H), 3.57 (d, 1H,  $J$  = 3 Hz), 3.75 (m, 1H), 7.76 (brs, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 19.2, 25.3, 26.7, 28.7, 30.9, 50.4, 52.9, 59.8, 65.4, 169.7, 201.6;  $^1\text{H}$ -NMR for the minor diastereomer ( $\text{CDCl}_3$ , 600 MHz):  $\delta$  = 1.37 (s, 9H), 1.42–1.40 (m, 1H), 1.57–1.75 (m, 3H), 1.78–1.99 (m, 2H), 2.66 (m, 1H), 2.87–2.90 (m, 1H), 3.41–3.56 (m, 3H), 3.63–3.66 (m, 1H), 7.43 (brs, 1H);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 150 MHz):  $\delta$  = 22.6, 26.0, 27.0, 27.7, 28.6, 50.9, 63.8, 66.4, 169.2, 200.3; HPLC-MS (ESI-TOF):  $r_t$  = 10.69 min,  $m/z$  = 271  $[\text{M}+\text{H}]^+$ ; HRMS (ESI-TOF)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$   $[\text{M}+\text{Na}]^+$  293.1300, found 293.1285.

## Results and discussion

MCR-based homocysteine yields the end-on thio- $\gamma$ -lactone scaffold **8**, which can be broadly varied in the oxo and the isocyanide component (Table 1) with isolated yields ranging from 25 to 77%. The products are formed as separable diastereomeric mixtures with the stereocenter of the  $\alpha$ -amino acid being retained during the reaction. The diastereomeric

**Table 1** End-on thio- $\gamma$ -lactone synthesized via MCR showing compound number, structure, percent yield, and diastereomeric ratio

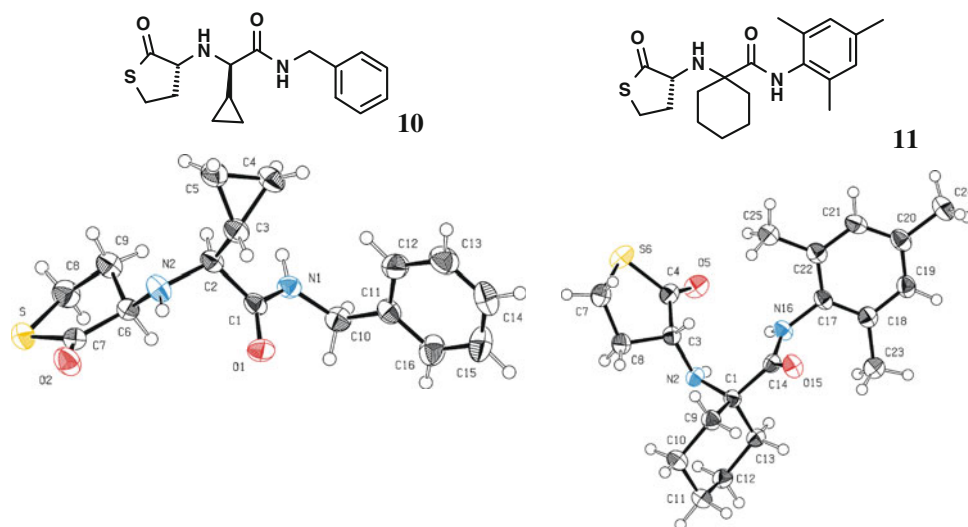
Compound no.	Structure	Yield (%)	Diastereomeric ratio
10		77	77:23
11		33	NA
12		30	85:15
13		43	ND
14		45	81:19
15		25	ND
16		73	ND



**Table 1** continued

Compound no.	Structure	Yield (%)	Diastereomeric ratio
17		53	NA
18		47	88:12
19		53	65:35
20		34	72:28

NA not applicable, ND not determined

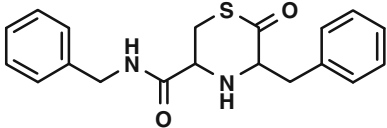
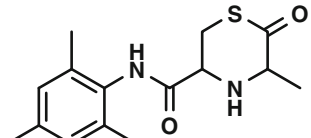
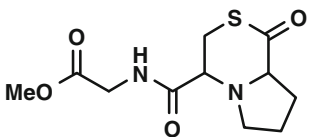
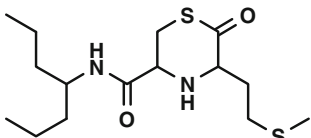
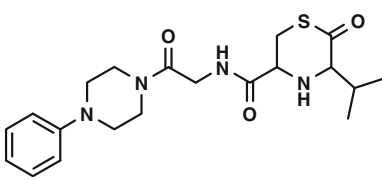
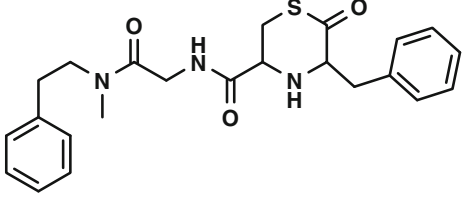
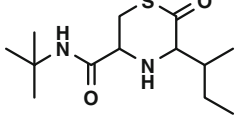
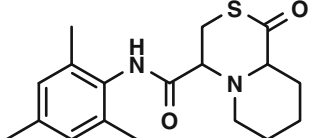
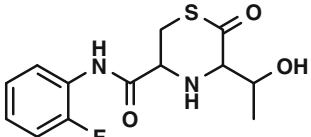
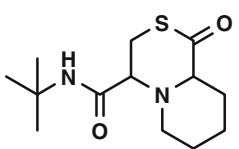
**Fig. 2** 3D structures of the different  $\gamma$ -thiolactones: ORTEP plots of compounds **10** and **11**

ratio varies between 9:1 and 3:2. We were able to determine the stereochemistry of several isolated major diastereomers by X-ray structure analysis (Fig. 2). Thus, in all the determined cases, the major diastereomers have consistently R/R stereo designation [22]. From their analysis, we conclude that

the major diastereomer formed during this reaction has R/R configuration.

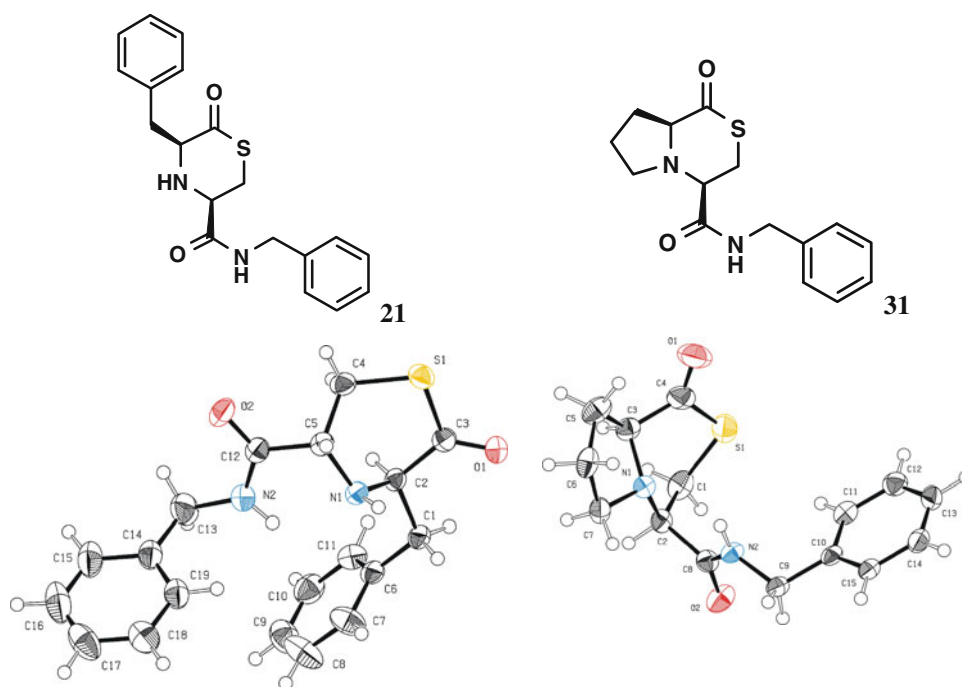
Mercaptoacetaldehyde, however, yields a complementary access to the thiolactone-incorporating scaffold **9** (Table 2). Although the first scaffold bears the reactive thiolactone site

**Table 2** Thiomorpholines synthesized via MCR showing compound number, structure, percent yield, and diastereomeric ratio

Compound no.	Structure	Yield (%)	Diastereomeric ratio
21		70	ND
22		12	78:22
23		34	76:24
24		16	96:4
25		10	73:27
26		23	57:43
27		34	73:27
28		47	85:15
29		17	81:19
30		31	64:36

ND not determined

**Fig. 3** 3D structures of different thiomorpholines: ORTEP plots of thiomorpholine compounds **21** and **31**



end-on, thus being easily accessible for target structures, the thiolactone moiety in the later scaffold is hidden and highly differential acylation of a target structure can be expected. The diversity of the thiomorpholino scaffold space **9** can be accomplished by varying the  $\alpha$ -amino acid and the isocyanide component (Scheme 2). We were able to grow crystals of representatives of both of the scaffolds to prove the structural proposal and stereochemistry and to investigate the 3D structure of the scaffolds (see Supplementary Material) (Fig. 3).

In order to assess the property space of these two scaffolds, we prepared representative virtual libraries for each, and investigated their physicochemical properties using different descriptors (see Supplementary Material). For example, it turned out that, while the majority of the thiomorpholones are “lead like”, according to the Lipinski’s rules, only ~50% of the  $\gamma$ -thiolactones satisfied those rules. (Figs. 1–12 and Table 1 in Supplementary Material). This is due to two factors. First, the average molecular weight of the  $\gamma$ -thiolactones is higher than that of the thiomorpholines due to the constant use of the low molecular weight mercaptoacetaldehyde in the latter scaffold. Second, the average lipophilicity of the  $\gamma$ -thiolactones is much higher than the thiomorpholines due to the constant use of the lipophilic amino acid homo-cysteine. A second fundamental difference between the two backbones relates to the intramolecular position of the thiolactone unit. This might be of importance to consider when designing protein inhibitors. For example, a predicted bioactivity of thiolactones could involve inhibition of proteases via acylation of the active side amino acid. In the case

of the  $\gamma$ -thiolactones, the lactone is at the end of the molecules, whereas in the case of the thiomorpholines, it is in the middle of the backbone. Thus, by means of having two reactive thiolactone backbones, the design opportunities are enhanced.

## Conclusion

Homocysteine and its thiolactone have been described as essential moieties in many bioactive compounds [1–11, 13, 15, 16, 51]. We, therefore, aimed to design novel MCRs which allow us to assemble thiolactone-containing scaffolds and to rapidly synthesize libraries of small molecular weight compounds to investigate their properties. The Ugi reaction of isocyanides, oxocomponents, amines, and acids is perfectly suited for the rapid and effective generation of molecular diversity for the discovery of compounds with novel biological activities. To our knowledge, no other chemical method allows for a comparably easy entry into design/discovery of new matter in terms of breadth of chemical space as well as number of accessible scaffolds. However, up to now, there was no variation of the Ugi–MCRs described leading into thiolactone scaffolds. Several high resolution X-ray structure analyses to prove the stereochemistry and experimental detail of >30 examples of the two thiolactone scaffolds are described. In addition, we are providing virtual libraries of the two MCR scaffolds described here (available in both smiles and sd format) for computational screening exercises in drug discovery (Supplementary Material).

## Supplementary data

CCDC 738597 (10), 738598 (11), 738599 (21) contain the supplementary crystallographic data (excluding structure factors) for the structures reported in this article. These data can be obtained, free of charge, through <http://www.ccdc.cam.ac.uk/cgi-bin/cat/discretionary-req.cgi>, or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K.; fax: (+44)1223-336-033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk).

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