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ORIGINAL ARTICLE

Ensembling three multicomponent reactions for the synthesis of a novel category of pseudo-peptides containing dithiocarbamate and *N,X*-heterocylic groups

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Abstract
Consecutive multicomponent reactions have been applied for the synthesis of novel pseudo-peptides bearing dithiocarbamate and *N,X*-heterocyclic groups (X = S, O) in only one structure. The first multicomponent reaction includes the synthesis of dithiocarbamates using an amine or amino acid, CS_2 and an electrophile. The second MCR is synthesis of Asinger imines using 2-chloroisobutyraldehyde, NaXH (X = S, O), ketone and ammonia. The final MCR is Ugi reaction to afford the corresponding three-dimensional pseudo-peptides. Various Asinger imines, carboxylic acids and isocyanides were applied in this protocol to provide diversities of pseudo-peptides in high to excellent yields.

Keywords Consecutive multicomponent reaction · Pseudo-peptide · Dithiocarbamate · Asinger imine · Ugi reaction

Introduction

Peptides are one of the most interesting classes of bioactive molecules that represent a wide variety of biological activities such as anticancer and antimicrobial characteristics, but they usually cannot be used for synthesizing effective medical drugs because they are rapidly changed or degenerated in the body. To solve this issue, novel, stable and biologically active pseudo-peptides have been synthesized. These new derivatives can be utilized in drug design by offering a wide range of extremely specified and safe drugs (Nielsen 2004).

Multicomponent reactions (MCRs) are among the most precious processes in organic chemistry due to their powerful characteristics such as high atom economy, high efficiency and diversity-oriented synthesis. The Ugi four-component reaction (Ugi-4CR) is undoubtedly one of the most studied and used MCRs (Ugi et al. 1959; Trost 1991; Tietze 1996; Domling 2006; Herrera and Marques-Lopez 2015; Zhu et al. 2015; Rotstein et al. 2014; Estevez et al. 2014; Brauch et al. 2013). This reaction offers a one-pot synthesis of immensely functionalized α-acylaminocarboxamide or pseudo-peptide, a construction found in many biologically active molecules (Keating and Armstrong 1995). In the recent 20 years, the application of consecutive reactions, especially the Ugi reaction, has widely expanded in the drug industry and in research laboratories (Keating and Armstrong 1995; Ugi 1962; Ugi et al. 2003).

The Asinger reaction was investigated for the first time in 1956 by Friedrich Asinger (Asinger et al. 1964; Weber et al. 1992; Asinger and Offermans 1967). The Asinger reaction is a simple four-component reaction with efficient procedure for the synthesis of 3-thiazolines and 3-oxazolines, which are a group of bioactive heterocyclic compounds containing both sulfur (oxygen) and nitrogen in the ring. In recent years, 3-thiazolines and 3-oxazolines have attracted a lot of attention because the imine bond of these compounds can be subjected to nucleophilic attack by various nucleophiles

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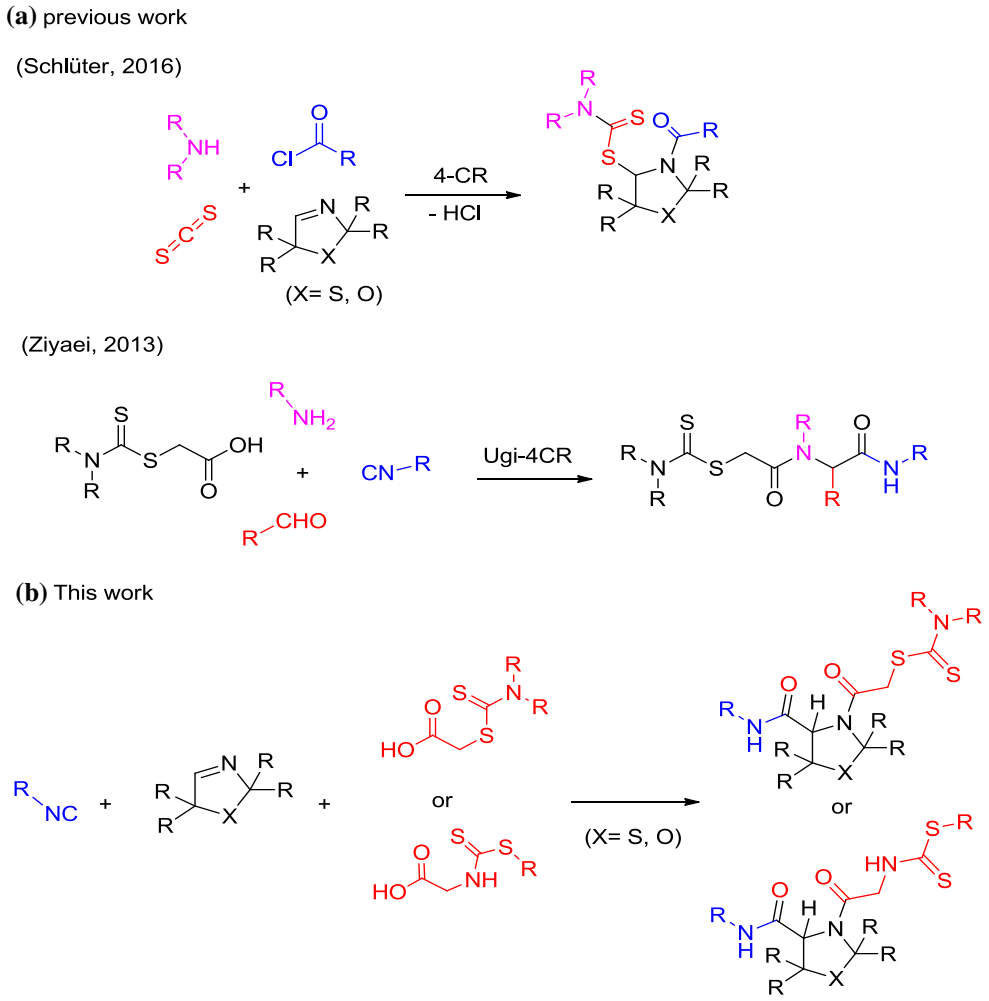
(Martens et al. 1981; Stalling et al. 2013; Kröger et al. 2015a, b; Stalling and Martens 2013; Franz et al. 2017).

Introduction of dithiocarbamate groups in the structure of various types of organic and inorganic compounds is well established for the synthesis of novel biologically active compounds (Csomos et al. 2006; Cao et al. 2005, 2006; Huang et al. 2009; Bacharaju et al. 2012; Zou et al. 2014; Jiao et al. 2016). Compounds containing the dithiocarbamate functionality have shown various biological activities such as antitumor, anticancer, or antibacterial in medicine (Aboul-Fadl and El-Shorbagi 1996; Cascio et al. 1996; Imamura et al. 2001; Scozzafava et al. 2000; Hou et al. 2006), as pesticides, fungicides, or herbicides in agriculture (Marinovich et al. 2002; Malik and Rao 2000), as radiopharmaceutical agents for biological sensing and imaging (Berry et al. 2012), as mono- and bidentate ligands in coordination chemistry (Macias et al. 2002; Ziyaei Halimehjani et al. 2011), as polymerization agents (Lai and Shea 2006; Bathfield et al. 2006), and as intermediate in synthetic organic chemistry (Maddani and Prabhu 2007; Das et al. 2008; Wong and Dolman 2007; Guillaneuf et al. 2008; Ziyaei Halimehjani et al. 2009, 2016; McMaster et al. 2012; Ziyaei Halimehjani and Airamlounezhad 2014; Ziyaei Halimehjani and Hosseinkhany 2015; Ziyaei Halimehjani and Lotfi Nosood 2017). Due to the extensive application of these compounds in various branches of science, synthesis of novel dithiocarbamates with different substitution pattern is still interesting. Recently, we have developed a one-pot four-component reaction for the synthesis of dithiocarbamates using carbon disulfide, cyclic imines, acid chlorides, and commercially available primary or secondary amines (Scheme 1a) (Schlüter et al. 2016). In addition, novel categories of pseudo-peptides containing dithiocarbamate motif were synthesized in our group via classical Ugi-4CRs (Scheme 1a) (Ziyaei Halimehjani et al. 2013). In continuation of these works, here we wished to combine our previous finding in CS_2-MCRs with our expertise using heterocyclic imines (3-thiazolines and 3-oxazolines) in



Scheme 1 Published and proposed MCRs for the synthesis of dithiocarbamates

consecutive MCRs for the synthesis of a new category of pseudo-peptides containing dithiocarbamate and *N,X*-heterocyclic groups (X = S, O) in a single structure (Scheme 1b, c).

Results and discussion

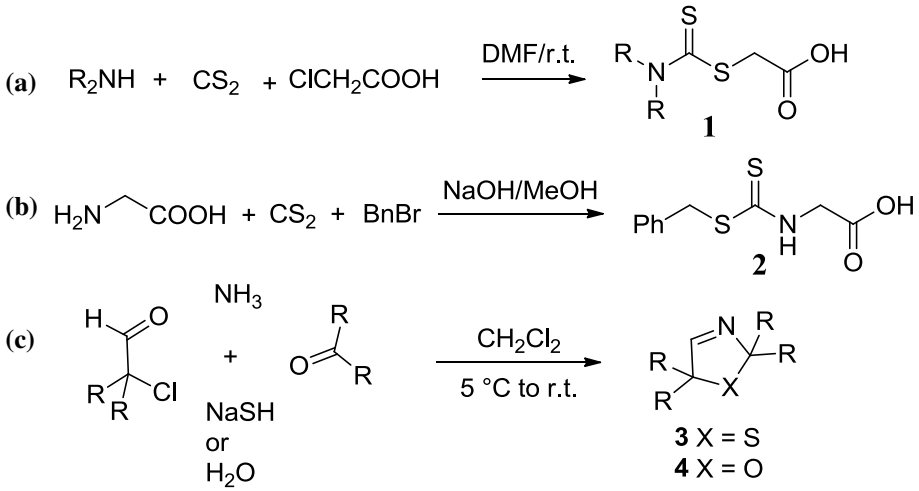
To expand our research work in multicomponent reactions, here we report the use of the Ugi reaction for the synthesis of new pseudo-peptides containing dithiocarbamate and *N,X*-heterocyclic groups in a single structure. First of all, multicomponent reactions were used for the synthesis of two categories of acid derivatives **1** and **2** bearing a dithiocarbamate motif. The first category **1** was produced via the one-pot three-component reaction of a secondary amine, carbon disulfide and chloroacetic acid (Scheme 2a). The second category of acid derivatives **2** was prepared via the one-pot three-component reaction of glycine, carbon disulfide and benzyl bromide in the presence of sodium hydroxide (Scheme 2b). Then, two different types of cyclic imines (3-thiazolines and 3-oxazolines) were synthesized as precursors for the further reaction steps. As example, the five-membered 2,5-dihydro-1,3-thiazoles **3** and 2,5-dihydro-1,3-oxazole **4** were prepared by modified Asinger reaction via reaction of an α-chloro aldehyde with a second variable carbonyl compound, NH_3, and NaSH or H_2O in CH_2Cl_2.

The prepared acid derivatives **1–2** and Asinger imines **3–4** were applied in the next multicomponent reaction (Schemes 3, 4). For this purpose, an equivalent of an acid, an Asinger imine and an isocyanide were reacted in MeOH at room temperature to afford the corresponding Ugi adducts **6**.

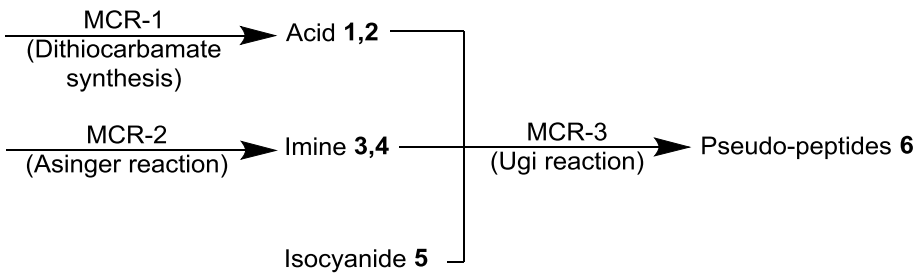
Under Ugi-3CRs, various bis-amides were obtained easily with high yields. Carboxylic acids **1–2** derived from glycine or secondary amines were applied successfully in this protocol. Also, the diversities of isocyanides **5** including cyclohexyl isocyanide, butyl isocyanide, benzyl isocyanide, 4-chlorophenyl isocyanide, *p*-toluenesulfonylmethyl isocyanide and methyl isocyanoacetate were used to give the diversities of Ugi adducts **6** with a high degree of functionalization in high yields (Fig. 1).

In addition, with this protocol, both thiazolidine and oxazolidine heterocycles can be simply introduced in the skeleton of Ugi adducts to provide a novel category of three-dimensional pseudo-peptides **6**.

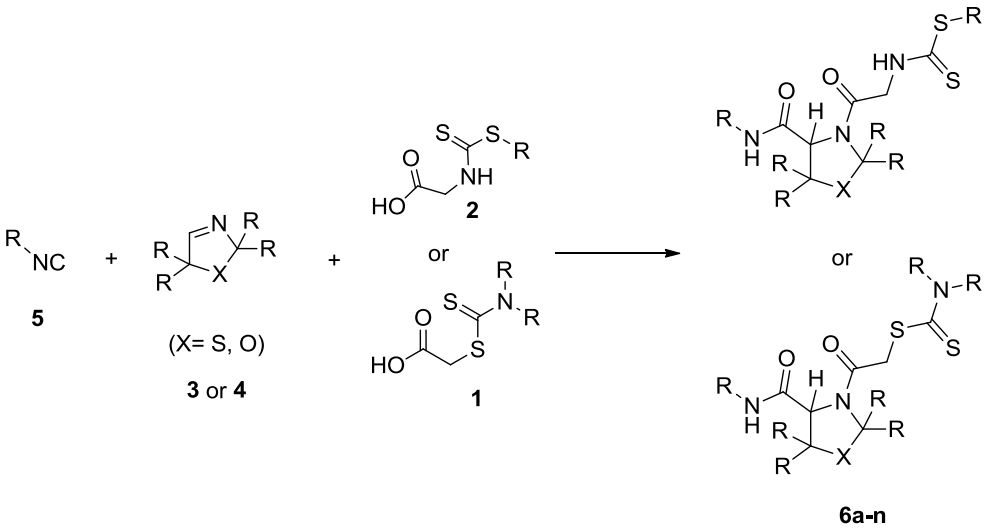
The structures of products **6a–n** were confirmed by IR, ^{1}H and ^{13}C NMR and HRMS analysis. The IR spectra of the products show characteristic absorbance bands at 3200–3500 cm^{-1} for the N–H bond stretching vibration and at 1650–1750 cm^{-1} for the carbonyls of the amide groups. The ^{1}H NMR spectra of the products show a characteristic peak at 6–7 ppm for the amide hydrogen and a singlet peak at 4.4–5.0 ppm for the CH group in the thiazolidine and oxazolidine ring. ^{13}C peaks of



Scheme 2 **a** One-pot three-component route for synthesis of dithiocarbamates **1** containing a carboxylic acid group. **b** Synthesis of dithiocarbamate **2** from glycine. **c** Modified Asinger reaction for the synthesis of 3-thiazolines **3** and 3-oxazolines **4**



Scheme 3 Synthetic strategy ensembling three MCRs



Scheme 4 U-3CRs for the synthesis of novel pseudo-peptides **6**

the carbons in amide moieties were observed around 166 and 169 ppm in ^{13}C NMR spectra. Also, the peaks at 192–198 ppm were assigned to the carbon of the dithiocarbamate group. In addition, the structure of compound **6f** was confirmed by single crystal X-ray diffraction and ORTEP representations are shown in Fig. 2 (CCDC 1824814); for details of the crystal structure data and refinement of **6f** see the Supporting Information). X-ray analysis shows planar geometry for the dithiocarbamoyl moiety.

Conclusion

In conclusion, Ugi reaction was applied for the synthesis of a novel category of pseudo-peptides containing glycine, dithiocarbamate, and *N,X*-heterocycles via consecutive multicomponent reactions. This protocol provides a novel category of three-dimensional pseudo-peptides as potential biologically active compounds. The presence of various functional groups such as amide, dithiocarbamate and *N,X*-heterocycle together in a single structure may have synergic effects to provide a new family of compounds with interesting biological activities in the pharmaceutical industry. The dithiocarbamates were applied extensively for the protection of the amino groups in amino acids for peptide synthesis. So, by simple deprotection, the amino group can be furnished in the structure of Ugi adducts for further applications.

Experimental

Materials and methods

Column chromatographic purification was carried out using SiO_2 (0.040–0.060 mm, type KG 60). TLC was performed on Macherey–Nagel SiO_2 F254 plates on aluminum sheets. Melting points were obtained on a melting apparatus of Laboratory Devices and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "Golden Gate" diamond-ATR (attenuated total reflection) unit. ^{1}H and ^{13}C NMR spectra of isolated products were recorded on a Bruker AMX R500 (measuring frequency: ^{1}H NMR = 500.1 MHz, ^{13}C NMR = 125.8 MHz) or a Bruker Avance III 500 (measuring frequency: ^{1}H NMR = 499.9 MHz, ^{13}C NMR = 125.7 MHz) in $CDCl_3$ solution. Mass spectra were obtained on a Waters Q-TOF Premier (ESI) spectrometer. Asinger or modified Asinger reaction was applied for the synthesis of *N,X*-cyclic imines according to previous reports (Asinger et al. 1964; Weber et al. 1992; Asinger and Offermans 1967).

General procedure for the synthesis of acid derivatives bearing the dithiocarbamate group

(a) Using amino acid for the synthesis of acid derivatives

In a 25 mL round bottom flask equipped with a magnetic stir bar in an ice bath, sodium hydroxide (10 mmol), glycine (5 mmol) and MeOH (8 mL) were added. The mixture was stirred for 0.5 h. Then, carbon disulfide (6 mmol) was added and the mixture was stirred for 1 h. Then, benzyl chloride (4.5 mmol) was added to the reaction mixture at room temperature and the mixture was stirred for 24 h. Finally, water (15–20 mL) was added to the reaction mixture and the pH of the reaction was adjusted to 5 by adding hydrogen chloride to the reaction. The reaction mixture was filtered and the precipitate was washed with water and petroleum ether.

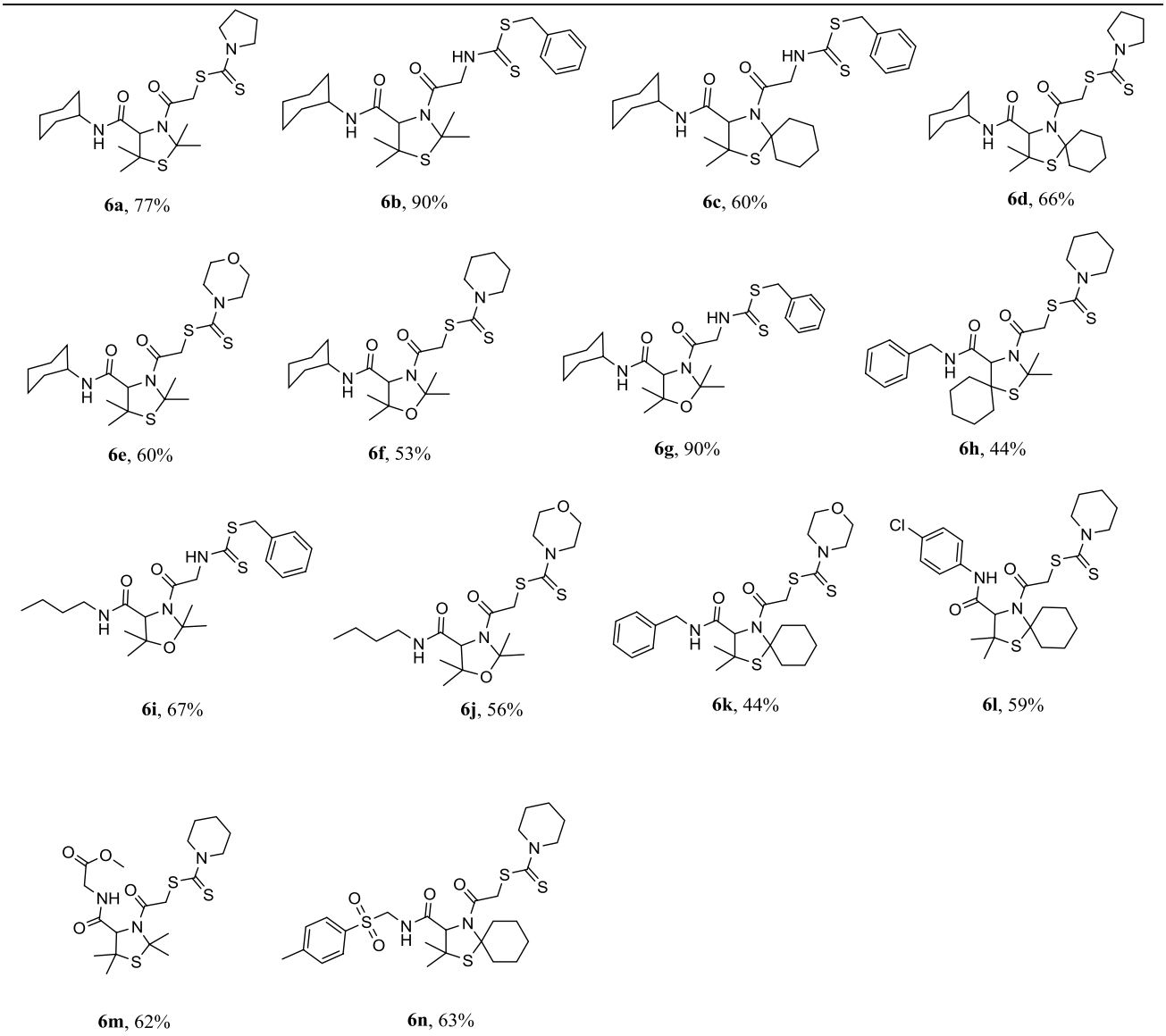


Fig. 1 Diversity in the synthesis of pseudo-peptides. **a** Isolated yield

(b) Using chloroacetic acid for the synthesis of acid derivatives

In a 25 mL round bottom flask equipped with a magnetic stir bar in an ice bath, a secondary amine (5 mmol), DMF (5 mL) and carbon disulfide (6 mmol) were added. The mixture was stirred for 1 h. Then chloroacetic acid (5 mmol) was added to reaction mixture at room temperature and the mixture was stirred for 12 h. Finally, water (15–20 mL) was added to the reaction mixture and the precipitate was collected and washed with petroleum ether for more purification. All acids were characterized based on their IR, ^{1}H NMR and ^{13}C NMR techniques.

General procedure for the synthesis of Ugi adducts

A solution of an acid derivative (1 mmol) and an *N,X*-heterocyclic imine (1 mmol) in MeOH (5 mL) was stirred for 0.5 h at room temperature. Then, isocyanide (1 mmol) was added to the reaction mixture at the same temperature. The reaction progress was monitored by TLC. After 24 h, the precipitate was filtered and purified by column chromatography using petroleum ether and ethyl acetate mixture as eluent (SiO_2, PE/EtOAc; 3:1 V/V). All compounds were characterized using IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

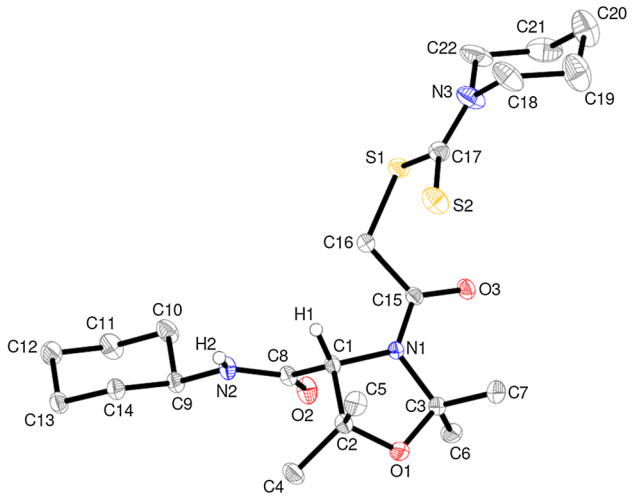


Fig. 2 ORTEP representations of compound **6f** with thermal ellipsoids at 50% probability. Hydrogen atoms (exception: hydrogen atoms at stereogenic center and amide group) and opposite enantiomer are omitted for clarity. The atom numbering does not follow IUPAC nomenclature

2-[4-(Cyclohexylcarbamoyl)-2,2,5,5-tetramethylthiazolidin-3-yl]-2-oxoethyl pyrrolidine-1-carbodithioate (6a):

White crystalline solid (yield, 352 mg, 77%); mp: 77–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (d, J = 8.1 Hz, 1H), 4.84 (s, 1H), 4.40 (d, J = 16.0 Hz, 1H), 3.92–3.64 (m, 6H), 2.13–2.09 (m, 2H), 2.03 (s, 3H), 2.03–1.93 (m, 7H), 1.78 (s, 3H), 1.74–1.68 (m, 2H), 1.44 (s, 3H), 1.43–1.22 (m, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.3, 168.6, 166.3, 77.9, 74.2, 55.2, 50.8, 50.2, 48.4, 41.7, 33.8, 32.8, 31.3, 29.6, 26.1, 25.4, 24.7, 24.5, 24.3 ppm; IR (ATR): ν 3308, 2928, 2855, 2196, 2184, 2161, 1651, 1538, 1434, 1367, 1249, 1220, 1161, 1133, 1009, 956, 891, 874, 846, 808, 766, 691, 655, 634, 613, 601 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{35}N_3O_2S_3$ $[M+Na]^+$ 480.1789; found: 480.1798.

Benzyl {2-[4-(cyclohexylcarbamoyl)-2,2,5,5-tetramethylthiazolidin-3-yl]-2-oxoethyl} carbamodithioate (6b)

Brown powder (yield, 444 mg, 90%); mp 159–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (t, J = 3.9 Hz, 1H), 7.39–7.27 (m, 5H), 6.51 (d, J = 8.2 Hz, 1H), 4.56–4.48 (m, 3H), 4.36–4.27 (m, 2H), 3.83 (m, 1H), 2.04 (s, 3H), 2.00 (s, 3H), 1.97–1.91 (m, 2H), 1.76–1.58 (m, 5H), 1.46 (s, 3H), 1.44–1.19 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 167.5, 165.7, 136.2, 129.0, 128.5, 127.4, 76.3, 74.5, 50.5, 48.6, 39.9, 33.8, 33.0, 32.9, 31.6, 28.9, 25.4, 24.7, 24.6 ppm; IR (ATR) ν 3261, 3161, 2987, 2926, 2854, 1673, 1540, 1495, 1449, 1395, 1366, 1297, 1263, 1251, 1230, 1164, 1134, 1104, 1029, 990, 953, 891, 798, 771, 712, 694, 665, 645, 617, 598 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{35}N_3O_2S_3$ $[M+Na]^+$ 516.1789; found: 516.1776.

Benzyl {2-[3-(cyclohexylcarbamoyl)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decan-4-yl)]-2-oxoethyl} carbamodithioate (6c)

White powder (yield, 320 mg, 60%); mp 185–186 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (t, J = 3.8 Hz, 1H), 7.39–7.26 (m, 5H), 6.42 (d, J = 8.2 Hz, 1H), 4.53–4.47 (m, 3H), 4.35–4.30 (m, 2H), 3.83 (m, 1H), 3.07–3.00 (m, 2H), 2.12–1.61 (m, 13H), 1.45 (s, 3H), 1.43–1.18 (m, 8H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 167.5, 165.9, 136.1, 129.0, 128.6, 127.5, 82.3, 76.2, 51.0, 49.6, 48.7, 39.9, 36.9, 36.8, 34.0, 32.9, 25.7, 25.4, 24.9, 24.7, 24.4 ppm; IR (ATR) ν 3325, 3088, 2930, 2849, 1675, 1650, 1604, 1517, 1489, 1454, 1396, 1367, 1336, 1311, 1276, 1243, 1226, 1202, 1164, 1134, 1076, 1043, 983, 965, 936, 902, 865, 831, 810, 779, 766, 721, 702, 674, 651, 630, 589 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{27}H_{39}N_3O_2S_3$ $[M+Na]^+$ 556.2102; found: 556.2108.

2-[3-(Cyclohexylcarbamoyl)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decan-4-yl] -2-oxoethyl pyrrolidine-1-carbodithioate (6d)

White crystalline solid (yield, 328 mg, 66%); mp 86–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, J = 8.2 Hz, 1H), 4.76 (s, 1H), 4.29 (d, J = 16 Hz, 1H), 3.83–3.58 (m, 6H), 3.08 (m, 1H), 2.98 (m, 1H), 2.05–1.08 (m, 28H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.3, 168.6, 166.4, 82.1, 77.8, 55.2, 50.8, 49.4, 48.5, 42.4, 37.5, 36.1, 34.0, 32.8, 32.8, 26.1, 25.9, 25.6, 25.4, 25.4, 25.0, 24.6, 24.5, 24.3 ppm; IR (ATR) ν 3291, 2926, 2853, 2165, 1650, 1534, 1434, 1389, 1352, 1250, 1219, 1184, 1158, 1132, 1042, 1008, 956, 879, 867, 845, 803, 769, 692, 640, 623, 594, 584 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{39}N_3O_2S_3$ $[M+Na]^+$ 520.2102; found: 520.2090.

2-[4-(Cyclohexylcarbamoyl)-2,2,5,5-tetramethylthiazolidin-3-yl]-2-oxoethyl morpholine-4-carbodithioate (6e)

Cream powder (yield, 284 mg, 60%); mp 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (d, J = 8.2 Hz, 1H), 4.73 (s, 1H), 4.28 (d, J = 16.2 Hz, 1H), 4.21–4.17 (brs, 2H), 3.91–3.87 (brs, 2H), 3.80–3.66 (m, 6H), 1.93 (s, 3H), 1.90–1.83 (m, 4H), 1.69 (s, 3H), 1.67–1.51 (m, 3H), 1.37 (s, 3H), 1.35–1.09 (m, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.2, 168.6, 165.9, 78.0, 74.2, 66.1, 65.8, 51.4, 50.6, 50.2, 48.4, 41.9, 33.8, 32.8, 31.2, 29.5, 25.4, 24.7, 24.6, 24.5, 24.5 ppm; IR (ATR) ν 3306, 2929, 2851, 1974, 1651, 1538, 1450, 1420, 1355, 1299, 1268, 1227, 1164, 1112, 1065, 1028, 996, 891, 867, 806, 652, 630, 613, 581 cm^{-1}; HRMS

(ESI-TOF) calcd for $C_{21}H_{35}N_3O_3S_3$ $[M+Na]^+$ 496.1738; found: 496.1737.

2-[4-(Cyclohexylcarbamoyl)-2,2,5,5-tetramethyloxazolidin-3-yl]-2-oxoethyl piperidine-1-carbodithioate (6f)

Cream powder (yield, 241 mg, 53%); mp 203–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (d, J = 8.0 Hz, 1H), 4.58 (s, 1H), 4.30 (m, 1H), 4.17 (d, J = 15.6 Hz, 1H), 4.07–3.89 (m, 2H), 3.82–3.74 (m, 2H), 3.57 (d, J = 15.6 Hz, 1H), 1.91–1.87 (m, 2H), 1.6 z9 (s, 3H), 1.67–1.53 (m, 12H), 1.49 (s, 3H), 1.34–1.28 (m, 5H), 1.20–1.09 (m, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1, 167.9, 165.3, 96.7, 81.1, 70.7, 53.2, 51.8, 48.5, 40.9, 32.9, 30.6, 27.7, 27.3, 25.9, 25.9, 25.3, 25.2, 24.6, 24.0 ppm; IR (ATR) ν 3308, 3073, 2980, 2932, 2857, 2165, 2148, 2035, 1684, 1635, 1546, 1472, 1415, 1230, 1162, 1145, 1114, 1009, 975, 948, 894, 844, 807, 773, 725, 683, 631 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{37}N_3O_3S_2$ $[M+Na]^+$ 478.2174; found: 478.2153.

Benzyl {2-[4-(cyclohexylcarbamoyl)-2,2,5,5-tetramethyloxazolidin-3-yl]-2-oxoethyl)}carbamodithioate (6g)

Cream powder (yield, 429 mg, 90%); mp 181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (brs, 1H), 7.32–7.21 (m, 5H), 5.97 (d, J = 8.2 Hz, 1H), 4.48–4.45 (m, 2H), 4.35 (d, J = 17.7 Hz, 1H), 4.09–4.05 (m, 2H), 3.79 (m, 1H), 1.94–1.86 (m, 2H), 1.74 (s, 3H), 1.70–1.55 (m, 6H), 1.45 (s, 3H), 1.35–1.28 (m, 5H), 1.22–1.08 (m, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2, 166.9, 164.5, 135.9, 129.0, 128.6, 127.5, 97.1, 81.3, 69.3, 49.6, 48.8, 39.9, 33.0, 30.7, 27.6, 26.9, 25.3, 25.0, 24.7 ppm; IR (ATR) ν 3269, 2983, 2935, 2853, 1659, 1645, 1548, 1495, 1444, 1416, 1371, 1320, 1264, 1252, 1197, 1148, 1119, 1093, 1072, 1017, 991, 945, 913, 891, 846, 770, 702, 665, 636, 599, 581 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{35}N_3O_3S_2$ $[M+Na]^+$ 500.2018; found: 500.2035.

2-[4-(Benzylcarbamoyl)-2,2-dimethyl-1-thia-3-azaspiro[4.5]decan-3-yl]-2-oxoethyl piperidine-1-carbodithioate (6h)

Cream powder (yield, 228 mg, 44%); mp: 186–187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (m, 5H), 6.75 (t, J = 5.7 Hz, 1H), 4.97 (s, 1H), 4.53–4.41 (m, 2H), 4.36–4.29 (m, 2H), 4.13–3.75 (m, 3H), 3.62 (d, J = 15.9 Hz, 1H), 2.17 (m, 1H), 1.91 (s, 3H), 1.84–1.74 (m, 6H), 1.69–1.57 (m, 10H), 1.28–1.21 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3, 169.4, 166.4, 137.5, 128.8, 127.8, 127.7, 73.4, 56.8, 53.3, 51.8, 43.8, 42.0, 40.1, 34.4, 31.6, 29.5, 25.9, 25.9, 25.3, 24.5, 24.1, 22.7, 21.7 ppm; IR (ATR) ν 3594, 3248, 3067, 2932, 2856, 1681, 1625, 1550, 1447, 1426, 1400, 1362, 1309, 1284, 1256, 1227, 1170, 1136, 1112, 1069, 1004, 981, 954, 895, 872, 855, 802, 737, 695, 638, 610, 571 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{26}H_{37}N_3O_2S_3$ $[M+Na]^+$ 542.1946; found: 542.2019.

Benzyl {2-[4-(butylcarbamoyl)-2,2,5,5-tetramethyloxazolidin-3-yl]-2-oxoethyl}carbamodithioate (6i)

Cream powder (yield, 300 mg, 66.6%); mp 126–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (t, J = 4.1 Hz, 1H), 7.38–7.26 (m, 5H), 6.24 (t, J = 5.8 Hz, 1H), 4.61–4.40 (m, 3H), 4.22 (s, 1H), 4.10 (dd, J = 17.6 and 3.9 Hz, 1H), 3.38 (m, 1H), 3.27 (m, 1H), 1.79 (s, 3H), 1.75 (s, 3H), 1.57–1.44 (m, 5H), 1.40–1.34 (m, 5H), 0.95 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4, 168.0, 164.6, 135.9, 129.0, 128.6, 127.5, 97.1, 81.4, 69.3, 49.6, 39.9, 39.7, 31.5, 30.7, 27.6, 27.0, 25.2, 20.1, 13.6 ppm; IR (ATR) ν 3282, 2990, 2956, 2868, 1680, 1651, 1560, 1495, 1477, 1445, 1407, 1370, 1343, 1264, 1197, 1154, 1009, 989, 947, 919, 879, 846, 782, 753, 712, 694, 667, 632, 602, 592, 580 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{33}N_3O_3S_2$ $[M+Na]^+$ 474.1861; found: 474.1857.

2-[4-(Butylcarbamoyl)-2,2,5,5-tetramethyloxazolidin-3-yl]-2-oxoethyl morpholine-4-carbodithioate (6j)

Cream powder (yield, 241 mg, 56%); mp 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (t, J = 5.8 Hz, 1H), 4.6 (s, 1H), 4.27–3.80 (m, 5H), 3.72–3.67 (m, 5H), 3.33 (m, 1H), 3.21 (m, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.50–1.44 (m, 5H), 1.33–1.27 (m, 5H), 0.88 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.1, 168.8, 164.9, 96.8, 81.2, 70.8, 66.1, 66.0, 51.5, 50.9, 40.8, 39.4, 31.5, 30.7, 27.8, 27.3, 25.3, 20.1, 13.6 ppm; IR (ATR) ν 3297, 2934, 2850, 1658, 1555, 1464, 1420, 1394, 1379, 1361, 1300, 1285, 1263, 1246, 1225, 1195, 1159, 1110, 1060, 1025, 1007, 992, 910, 878, 864, 842, 801,723, 698, 661, 617, 597, 571 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{33}N_3O_4S_2[M+Na]^+$ 454.1810; found: 454.1807.

2-[3-(Benzylcarbamoyl)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decan-4-yl]-2-oxoethyl morpholine-4-carbodithioate (6k)

White crystalline solid (yield, 229 mg, 44%); mp 199–200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 6.88 (t, J = 5.7 Hz, 1H), 4.92 (s, 1H), 4.57–4.49 (m, 2H), 4.33 (d, J = 16.2 Hz, 1H), 4.28 (brs, 2H), 3.98 (brs, 2H), 3.83–3.76 (m, 5H), 3.14–3.02 (m, 2H), 1.91–1.78 (m, 4H), 1.74 (s, 3H), 1.67–1.56 (m, 2H), 1.43 (s, 3H), 1.26–1.17 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 169.5, 166.0, 137.5, 128.8, 127.7, 127.7, 82.4, 76.8, 66.3, 66.1, 51.6, 50.8, 49.5, 43.8, 42.7, 37.5, 36.2, 34.0, 25.8, 25.5, 25.1, 24.4 ppm; IR (ATR) ν 3403, 2931, 2902, 2853, 2176, 1696, 1650, 1508, 1451, 1430, 1390, 1358, 1290, 1269, 1227, 1211, 1198, 1186, 1157, 1132, 1117, 1034, 1020, 998, 982,

913, 902, 880, 872, 865, 838, 797, 766, 732, 701, 686, 632, 595, 580 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{35}N_3O_3S_3$ $[M+Na]^+$ 544.1738; found: 544.1737.

2-{3-[(4-Chlorophenyl)carbamoyl]-2,2-dimethyl-1-thia-4-azaspiro[4.5]decan-4-yl}-2-oxoethyl piperidine-1-carbodithioate (6l)

White solid (yield, 318 mg, 59%); mp 139–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 4.97 (s, 1H), 4.38 (d, J = 15.8 Hz, 1H), 4.24 (brs, 1H), 4.12 (brs, 1H), 3.90–3.75 (m, 3H), 3.19 (m, 1H), 3.09 (m, 1H), 2.02 (m, 1H), 1.99–1.83 (m, 3H), 1.75 (s, 3H), 1.73–1.57 (m, 8H), 1.47 (s, 3H), 1.37–1.17 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 168.02, 166.7, 135.8, 129.9, 129.2, 121.2, 82.8, 78.5, 53.5, 51.9, 49.9, 43.1, 37.9, 36.4, 34.1, 26.1, 25.8, 25.5, 25.2, 24.6, 24.2 ppm; IR (ATR) ν 3277, 2934, 2856, 1700, 1625, 1597, 1535, 1491, 1430, 1398, 1352, 1244, 1130, 1009, 978, 829, 751 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{34}N_3O_2S_3Cl$ $[M+Na]^+$ 562.1399; found: 562.1401.

Methyl 2-(2,2,5,5-tetramethyl-3-(2-((piperidine-1-carbonothioyl)thio)acetyl)thiazolidine-4-carboxamido)acetate (6m)

White solid (yield, 286 mg, 62%); mp 136–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (t, J = 5.0 Hz, 1H), 4.94 (s, 1H), 4.34–4.25 (m, 2H), 4.10–4.05 (m, 3H), 3.93 (brs, 1H), 3.85–3.76 (m, 2H), 3.74 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.76 (s, 3H), 1.67 (brs, 6H), 1.43 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5, 170.2, 169.9, 166.4, 77.8, 74.6, 53.4, 52.6, 51.9, 50.3, 42.1, 41.4, 33.9, 31.4, 29.5, 26.1, 25.5, 24.9, 24.2 ppm; IR (ATR) ν 3271, 2984, 2938, 2859, 1744, 1685, 1629, 1545, 1479, 1431, 1360, 1212, 1134, 1006, 979, 872, 752, 655 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{31}N_3O_4S_3$ $[M+Li]^+$ 468.1637; found: 468.1631.

2-{2,2-Dimethyl-3-[(tosylmethyl)carbamoyl]-1-thia-4-azaspiro[4.5]decan-4-yl}-2-oxoethyl piperidine-1-carbodithioate (6n)

White crystalline solid (yield, 376 mg, 63%); mp 200–201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 6.6 Hz, 1H), 4.93–4.88 (m, 2H), 4.65 (dd, J = 14.2 and 6.0 Hz, 1H), 4.31 (brs, 1H), 4.16–4.05 (m, 2H), 3.93 (brs, 1H), 3.83 (brs, 1H), 3.14–3.08 (m, 2H), 3.00 (m, 1H), 2.44 (s, 3H), 1.88–1.53 (m, 15H), 1.29 (s, 3H), 1.25–1.17 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3, 169.6, 166.3, 145.7, 133.9, 130.3, 129.1, 82.8, 77.5, 59.7, 53.4, 51.9, 49.4, 42.7, 37.7, 36.2, 33.9, 26.2, 26.1, 25.7, 25.5, 24.9, 24.6, 24.2, 21.9 ppm; IR (ATR) ν 3310, 2931, 2855, 1700, 1658, 1596, 1519, 1478, 1430, 1390, 1351, 1320, 1284, 1244, 1227, 1137, 1084, 1042, 1002, 978, 925, 875, 852, 813, 742, 700, 670, 624, 609, 578 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{39}N_3O_4S_4$ $[M+Na]^+$ 620.1721; found: 620.1930.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical standard This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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