

Synthesis and antimicrobial activity of novel thiazolidinones

Viswajanani J. Sattigeri,*^a Ajay Soni,^a Smita Singhal,^b Seema Khan,^b Manisha Pandya,^b Pragya Bhateja,^b Tarun Mathur,^b Ashok Rattan,^b Jag Mohan Khanna,^a and Anita Mehta^a

^a Department of Medicinal Chemistry, ^b Department of Microbiology,
New Drug Discovery Research, Ranbaxy Research Laboratories, R&D-II, Plot 20, Sector-18,
Udyog Vihar Industrial Area, Gurgaon, Haryana, 122001 India
E-mail: viswajanani.sattigeri@ranbaxy.com

Dedicated to Dr. Nitya Anand on the occasion of his 80th birthday

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Abstract

A novel synthesis of thiazolidine-2-thione and thiazolidin-2-one derivatives is described with the iodo-cyclothiocarbamation reaction as the key step for the heterocyclic ring formation. This new method has been applied to the synthesis of thiazolidinones as bioisosteric analogs of Linezolid 2. Antimicrobial properties of two new thiazole derivatives are reported.

Keywords: Thiazolidin-2-one, thiazolidine-2-thione, iodo-cyclothiocarbamation, antimicrobial activity

Introduction

Oxazolidinones have attracted attention as a new class of orally active synthetic antibiotics with a unique mechanism of bacterial protein synthesis inhibition.¹⁻⁴ One of the early oxazolidinones studied in detail was DuP-721 (**1**)⁵ (Figure 1) exhibiting a broad spectrum of antibacterial activity including activity against drug-resistant Gram positive bacteria as well as several anaerobes and *Mycobacterium tuberculosis*. However, further development of DuP-721 (**1**) was discontinued because of safety concerns in animal models.

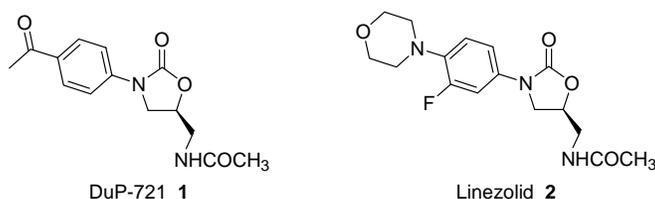


Figure 1

Continued efforts led to the identification of Linezolid (**2**)^{4,6} (Figure 1) with excellent activity against ever increasing *Methicillin Resistant Staphylococcus aureus* (MRSA) and with a better safety profile; Linezolid was approved for clinical use in 2001. However, adverse effects are its potential for inhibition of monoamine oxidase and myelosuppression. Practically all oxazolidinones studied so far have shown the potential for myelosuppression.^{6b} Therefore, it has been an objective to identify a molecule with not only a wider spectrum of antibacterial activities but also providing a better safety profile. So far, most synthetic efforts have been directed at modifying substituents in the aromatic ring of **1** and **2**.⁷ Recently, changes at the 5-methylene group have also been reported.⁸ However, these efforts have not led to a 'better Linezolid'.

We attempted subtle and bioisosteric changes in the pharmacophore oxazolidinone in order to study the impact of these changes on desirable antibacterial activity and also adverse toxicities. Therefore, we considered the modification of the oxazolidinone ring by replacing the ring oxygen by the bulkier sulfur atom leading to thiazolidines;⁹ thiazolidinethione **3** and thiazolidinone **4** (Figure 2) were chosen as targets.

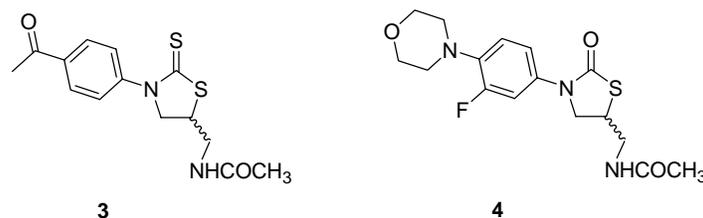
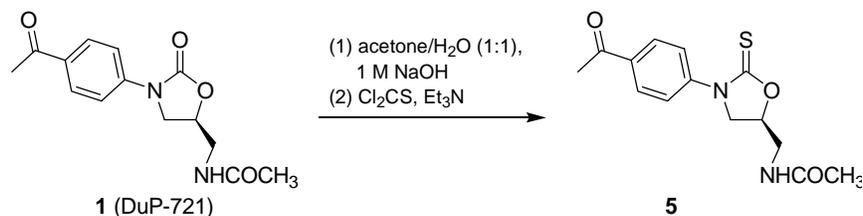


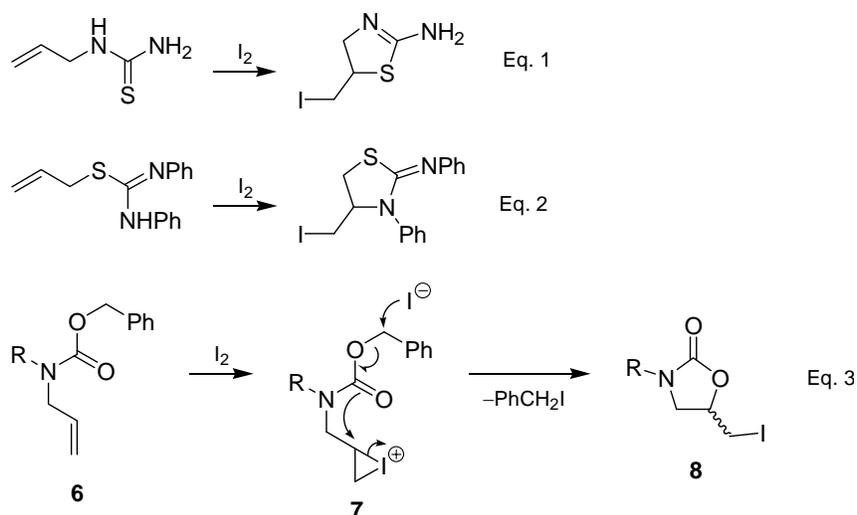
Figure 2

Seneci *et al.*¹⁰ have reported the synthesis of ring-modified oxazolidinone analogs of **1** by introducing as nitrogen, sulfur and phosphorus atoms. Introduction of sulfur was expected to bring in a bulky polarisable atom, thus altering geometry, polarisability, stability, lipophilicity and steric and electronic characteristics of the molecule. It was anticipated that the thiazolidine ring improves the activity of the lead molecules. However, the strategy for the preparation of the corresponding thiazolidine-2-ones, based on thiirane ring opening by a carbamate, proved unsuccessful.¹⁰ Seneci *et al.* succeeded in synthesizing oxazolidine-2-thione **5** by the hydrolysis of the oxazolidinone ring of **1** followed by ring closure with thiophosgene (Scheme 1). Compound **5** exhibited reduced antibacterial activity (MIC against MRSA was 64–128 $\mu\text{g/mL}$).



Scheme 1

A general strategy for the synthesis of thiazolidine rings was required that could lead to this new class of compounds. There is a report¹¹ on the iodo-cyclisation of *N*-allyl- and *S*-allylthioureas for the synthesis of dihydrothiazoles (Scheme 2, Eq. 1 and 2); the synthesis of achiral oxazolidinones utilizes an iodo-cyclocarbamation reaction.¹² By the latter reaction an *N*-allyl-carbamate **6** is cyclized using iodine through the intermediacy of an iodonium species **7** leading to oxazolidinones **8** (Scheme 2, Eq. 3). Our strategy to synthesize the thiazolidinones was to employ a hitherto unknown iodo-cyclothiocarbamation reaction as the key step involving a dithiocarbamate in place of a carbamate for the iodo-cyclisation reaction. The use of this method would lead to the synthesis of racemic thiazolidinones. Only the *S* enantiomer of the antibacterial oxazolidin-2-ones is active, the *R* enantiomer is completely inactive, and we expected that the biological activity of the thiazolidinone racemate would be reduced by 50%.



Scheme 2

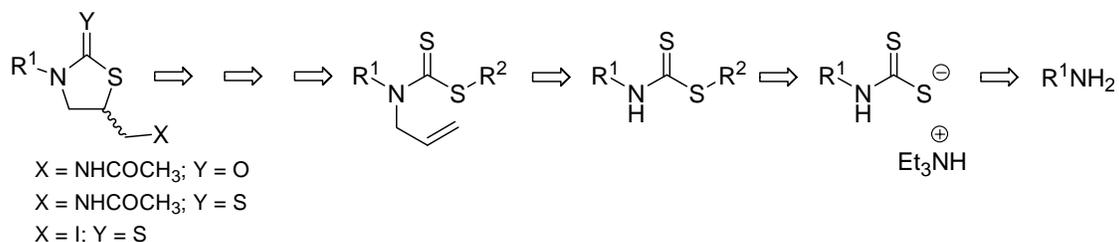
Results and Discussion

Synthesis

Retrosynthetic analysis (Scheme 3) identifies 2-iodomethylthiazolidine-2-thione as key intermediate, which can conceivably be obtained by an iodo-cyclisation reaction of an *N*-allyldithiocarbamate. This dithiocarbamate could be synthesized by *N*-allylation of the corresponding thiourethane that is available by the *S*-alkylation of the triethylammonium dithiocarbamate derived from a primary amine. The thiazolidine-2-thione could then be converted into the desired 5-(acetaminomethyl)thiazolidine-2-thiones and thiazolidin-2-ones.

Condensation of aniline (**9a**) with carbon disulfide in the presence of triethylamine gave the corresponding dithiocarbamate salt **10a**; subsequent alkylation with benzyl bromide furnished the corresponding *S*-benzyl derivative **11a** (Scheme 3); *N*-allylation of **11a** using sodium hydride

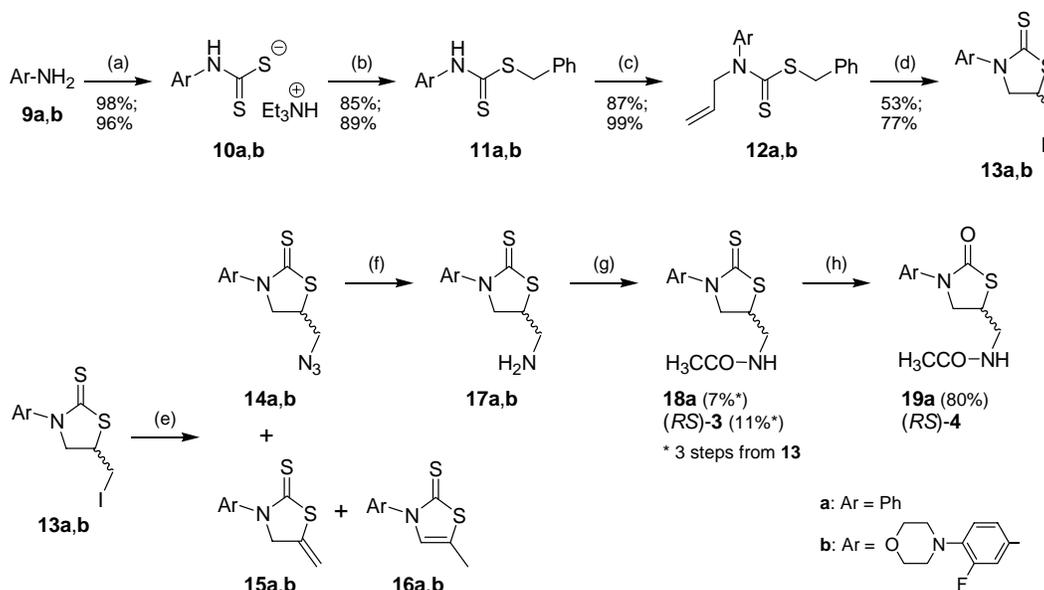
and allyl bromide in the presence of tetrabutylammonium iodide gave the N-allyl derivative **12a**. The key reaction of iodo-cyclothiocarbamation went smoothly and was carried out successfully using iodine in acetonitrile to give the thiazolidin-2-thione **13a**.



Scheme 3. Retrosynthesis of thiazolidine-2-thiones and thiazolidin-2-ones.

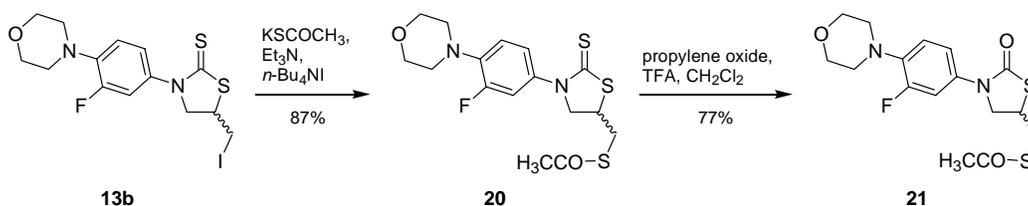
To obtain the desired acetamidomethyl derivative **19a**, 5-(iodomethyl)-1,3-thiazolidine-2-thione **13a** was reacted with sodium azide in DMF to give the azide **14a**, which proved very unstable to handle; in addition, variable amounts of elimination products **15a** and **16a** were formed. Therefore, the iodide displacement was attempted with other nitrogen nucleophiles such as benzylamine, benzhydrylamine, phthalimide etc. However, either unreacted starting material **13a** was recovered or only elimination products **15a** and/or **16a** were obtained. Attempts to convert the azide group of **14a** into an amine (with H_2 , Pd/C, $\text{PPh}_3/\text{H}_2\text{O}$; $\text{P}(\text{OEt})_3/\text{H}_2\text{O}$, NaBH_4) or into an acetamide group (with CH_3COSH) failed. Treating azide **14a** with propane-1,3-dithiol and triethylamine¹³ furnished a very low yield of amine **17a**, which was acetylated with acetic anhydride forming the 5-(acetamidomethyl)thiazolidinethione **18a** in about 7% overall yield of three steps. The final conversion of thiazolidine-2-thione **18a** into thiazolidine-2-one **19a** was achieved using propylene oxide and trifluoroacetic acid.¹⁴

This synthetic strategy was applied to the synthesis of Linezolid analogs **3** and **4** as racemates. The reaction sequence used for the conversion of aniline (**9a**) into **13a** transformed 3-fluoro-4-(morpholin-4-yl)aniline (**9b**)¹⁵ into the 5-(iodomethyl)-1,3-thiazolidine-2-thione **13b**, with the iodo-cyclothiocarbamation reaction as last step (Scheme 4). Subsequently, reaction of **13b** with lithium azide at room temperature furnished azide **14b** as minor product, while the major products were the elimination products **15b** and **16b**. Following the protocol used for the preparation of **18a**, azide **14b** was transformed into 5-(acetamidomethyl)thiazolidine-2-thione (*RS*)-**3** in 11% overall yield over the last three steps. Finally, thiazolidine-2-thione (*RS*)-**3** upon reaction with propylene oxide was converted into thiazolidin-2-one (*RS*)-**4** in 63% yield.



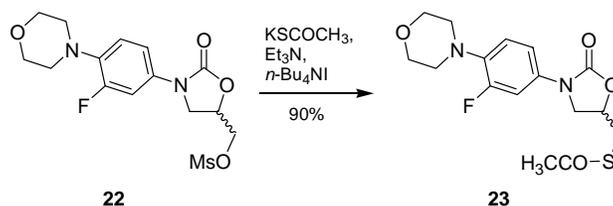
Scheme 4. Reagents and conditions: (a) CS₂, Et₃N, r.t.; (b) PhCH₂Br, CH₃CN, r.t.; (c) NaH, allyl bromide, *n*-Bu₄NI, 0 °C; (d) I₂, CH₃CN, r.t.; (e) NaN₃ or LiN₃, DMF; (f) HS(CH₂)₃SH, Et₃N, MeOH; (g) Ac₂O, Et₃N, CH₂Cl₂, 0 °C → r.t.; (h) propylene oxide, TFA, CH₂Cl₂.

Due to the inherent basicity of nitrogen nucleophiles the reaction with the iodomethyl intermediates **13a,b** provided mainly elimination products **15a,b** and **16a,b**. The reaction of **13b** with the more nucleophilic potassium thioacetate efficiently furnished thioacetate **20** (Scheme 5). Thiazolidinethione **20** was converted into thiazolidinone **21** upon reaction with propylene oxide.



Scheme 5

The thioacetate analog **23** of Linezolid **2** was synthesized from mesylate **22**¹⁵ and potassium thioacetate (Scheme 6).



Scheme 6

Biological activity

Thiazolidines (*RS*)-**3**, (*RS*)-**4**, **13–21**, and oxazole **23** were tested for antimicrobial activities. For antibacterial primary screening were used *S. aureus* ATCC 25923, MRSA 15187, *S. epidermidis* 32965, *Enterococcus faecalis* ATCC 29212, VRE 6A, *Streptococcus pneumoniae* 6303, *S. pneumoniae* AB34, *S. pyogenes* 19615. For antifungal primary screening were used *Candida albicans* A26, *Candida albicans* Y-01-19, *C. krusei* 766-1, *Candida glabrata* 90030, *Candida tropicalis* ATCC 750, *Cryptococcus neoformans* I, *Aspergillus fumigatus* 1008. Antibacterial and antifungal primary screening was performed using agar diffusion assay. Antibacterial MIC was performed by NCCLS agar dilution method (NCCLS M7 A5)¹⁶ and antifungal MIC was performed by NCCLS microbroth dilution method [M 27 (A)¹⁷ and M 38 (P)¹⁸].

The activity profiles of the thiazolidines (*RS*)-**3**, (*RS*)-**4**, **13–20** and oxazole **23** against the bacterial strains tested were found to be inferior compared to the oxazolidinones **1** and **2**. We observed that there is almost complete loss of antibacterial activity of the thio compounds when compared to the oxygen analogs. Compounds which were inactive in primary screening showed MIC of >16 µg/mL against the bacteria tested. However, the activity profile against the fungi used for screening was found to be a little encouraging. The thiazolidinones (*RS*)-**3** and **19a** showed mild antifungal activity (Table 1).

Table 1. Activity of thiazolidines (*RS*)-**3** and **19a** against fungi

Organism	MIC (µg/mL)			
	3	19a	Flucanazole	Linezolid (2)
<i>Candida parapsilosis</i> 22019 (QC) ^a	2	8	2	>16
<i>Candida krusei</i> 6258 (QC) ^a	8	>16	32	>16
<i>Paecilomyces variotti</i> 22319 (QC) ^b	-	≥16	>64	>16
<i>Candida albicans</i> A-26 ^a	16	-	-	-
<i>Candida albicans</i> Y-01-19 ^a	16	>16	16	>16
<i>Candida tropicalis</i> 750 ^a	16	≥16	0.25	>16
<i>Candida krusei</i> 766.1 ^a	16	>16	≥64	>16
<i>Candida glabrata</i> 90030 ^a	16	>16	32	>16
<i>Histoplasma capsulatum</i> ^a	16	>16	4	>16
<i>Cryptococcus neoformans</i> I ^a	2	2	0.125	>16
<i>Cryptococcus neoformans</i> M 106 ^a	2	2	0.5	>16
<i>Aspergillus fumigatus</i> 1008 ^b	16	>16	>64	>16
<i>Aspergillus fumigatus</i> Si-I ^b	8	>16	>64	>16

^a MIC indicates 80% growth inhibition. ^b MIC indicates 50% growth inhibition.

Summary

We have shown that the cyclothiocarbamation reaction can be used to synthesize thiazolidinones. Contrary to our expectations, the thiazolidinone analogues were found to be inactive as anti-bacterials. The present study adds to the importance of the oxazolidinone as the pharmacophore as changes in the ring renders the compounds inactive. Given the precedence that thiazolidinone compounds have hitherto been tested for antifungal activity,⁹ future modifications of compounds **3** and **19a** may lead to a new generation of inhibitors.

Experimental Section

General Procedures. All reagents were obtained from commercial sources. Solvents were either commercially obtained as analytical grade or freshly distilled prior to use. According to literature protocols¹⁵ were prepared: 3-fluoro-4-morpholin-4-ylaniline (**9b**) and [3-(3-fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl methanesulfonate (**22**). Analytical thin layer chromatography was carried out on precoated silica gel 60F₂₅₄ plates using either UV absorption or iodine staining for visualization. Column chromatography was carried out using 100–200 mesh silica gel. HPLC analysis were carried out using Waters 2695 Separations Module HPLC system with Waters 2996 photodiode array (PDA) detector using a Kromasil C-18 (250 × 4.6 mm) column; mobile phase: sodium acetate buffer (pH 5.5)/acetonitrile (80–20:20–80); flow rate 1 mL/min, run time 55 minutes. ¹H NMR spectra were recorded on a Bruker DRX 300 MHz instrument (300 MHz); chemical shift values are reported relative to tetramethylsilane as internal standard. IR spectra were recorded on a Paragon 1000pc FT-IR spectrophotometer. LCMS spectra were obtained from a PE-SCIEX AP₁ 3000 LC/MS/MS system using electron spray ionization at 80–250 °C using 6 mM ammonium acetate buffer of pH 6.7.

Triethylammonium phenyldithiocarbamate (10a). A mixture of aniline **9a** (9.31 g, 0.1 mol), carbon disulfide (9.14 g, 0.12 mol) and triethylamine (30.36 g, 0.3 mol) was stirred at room temperature for 16 h. The precipitated salt was filtered off, thoroughly washed with ether and dried in vacuo to furnish the dithiocarbamic acid salt **10a** (26.5 g, 98%) as a pale yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 9.26 (1H, br s, NH), 7.65 (2H, d, 7.5 Hz, H_{Ph}), 7.32 (2H, m, H_{Ph}), 7.12 (1H, t, *J* = 7.2 Hz, H_{Ph}), 3.27 (6H, q, *J* = 7.2 Hz, CH₂N), 1.40 (9H, t, *J* = 7.2 Hz, CH₃). IR (KBr): $\tilde{\nu}$ 3137.6, 2976.6, 1586.4, 1511.9, 1298.3, 986.4, 697.4 cm⁻¹.

Benzyl phenyldithiocarbamate (11a). To the dithiocarbamic acid salt **10a** (5.40 g, 20 mmol) in acetonitrile (20 mL) was added benzyl bromide (3.76 g, 22 mmol), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, the residue was diluted with ethyl acetate (50 mL) and washed with water (20 mL). The organic layer was separated, washed with brine and dried (Na₂SO₄). Evaporation of the solvent followed by purification of the residue over a silica gel column using ethyl acetate/hexane (20:80) as eluent

furnished **11a** (4.4 g, 85%) as a sticky yellow solid. $R_f = 0.7$ (ethyl acetate/hexane 20:80). ^1H NMR (300 MHz, CDCl_3): δ 8.78 (1H, br s, NH), 6.85–7.50 (10H, m, H_{Ph}), 4.56 (2H, s, CH_2). IR (CH_2Cl_2): $\tilde{\nu}$ 1570.3, 1494.8, 1326.1, 1025.2, 694.5 cm^{-1} .

Benzyl N-allyl-N-phenyldithiocarbamate (12a). To a solution of the dithiocarbamate **11a** (3 g, 11.6 mmol) in dry tetrahydrofuran (50 mL), cooled to 0 °C, was added sodium hydride (50% dispersion in oil, 668 mg, 13.9 mmol), and the mixture was stirred for 30 min. Then, allyl bromide (1.68 g, 13.9 mmol) and tetrabutylammonium iodide (428 mg, 1.16 mmol) were added, and the reaction mixture was gradually warmed to room temperature and stirred overnight. The reaction mixture was concentrated to one-third of its volume, diluted with ethyl acetate (50 mL) and washed with water. The aqueous layer was extracted with ethyl acetate (2 × 10 mL) and the combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was chromatographed over a silica gel column using ethyl acetate/hexane (10–90:15–85) as eluent to furnish **12a** (3 g, 87%) as an oil. $R_f = 0.72$ (ethyl acetate/hexane 20:80). ^1H NMR (300 MHz, CDCl_3): δ 7.20–7.32 (7H, m, H_{Ph}), 7.06 (1H, t, $J = 7.5$ Hz, H_{Ph}), 6.84 (2H, d, $J = 7.5$ Hz, H_{Ph}), 5.80 (1H, br s, =CH), 5.23 (1H, d, $J = 16.8$ Hz, $\text{H}_{\text{A}=\text{C}}$), 5.10 (1H, d, $J = 9.9$ Hz, $\text{H}_{\text{B}=\text{C}}$), 4.29 (2H, s, CH_2S) and 3.64 (2H, br s, CH_2N). IR (CH_2Cl_2): $\tilde{\nu}$ 1636.4, 1570.0, 1484.4, 1208.2, 952.0 cm^{-1} . LCMS: m/z (%) 300.1 (100) [M+1].

(5RS)-5-(Iodomethyl)-3-phenyl-1,3-thiazolidine-2-thione (13a). To a solution of the allyl compound **12a** (1.5 g, 5 mmol) in acetonitrile (20 mL) was added iodine (2.53 g, 10 mmol), and the reaction mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with chloroform (50 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL) followed by sodium thiosulphate (10 mL) solution. The organic layer was further washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by purification of the residue over a silica gel column using ethyl acetate/hexane (20:80) as eluent furnished the thiazolidine-thiazolidine-2-thione **13a** (880 mg, 53%) as a light yellow solid. (99.35% purity by HPLC; ($t_R = 22.509$ min; PDA 265 nm). mp 166 °C. $R_f = 0.2$ (ethyl acetate/hexane 20:80). ^1H NMR (300 MHz, CDCl_3): δ 7.26–7.52 (5H, m, H_{Ph}), 4.67 (1H, m, HCS), 3.78 (1H, dd, $J = 11.3, 3.27$ Hz, $\text{H}_{\text{A}=\text{C}}$), 3.28–3.49 (3H, m, CH_2I , $\text{H}_{\text{B}=\text{C}}$). IR (KBr): $\tilde{\nu}$ 1490, 1407, 1388, 1263, 1235, 1051, 692 cm^{-1} . LCMS: m/z (%) 335.8 (100) [M+1].

(5RS)-5-(Azidomethyl)-3-phenyl-1,3-thiazolidine-2-thione (14a). To a solution of the iodomethyl compound **13a** (500 mg, 1.5 mmol) in dimethylformamide (2.5 mL) was added sodium azide (390 mg, 6 mmol), and the reaction mixture was heated at 80 °C for 3 h. After cooling ethyl acetate (25 mL) was added; the solution was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent furnished the crude azide **14a** as dark oil (430 mg) which contained also the thiazoles **15a** and **16a**. (Due to its instability the azide **14a** was used as such and the thiazoles **15a** and **16a** were obtained upon column chromatography after the acetylation step, *vide infra*). The IR spectra of the crude mixture confirmed the presence of the azide. IR (CH_2Cl_2): $\tilde{\nu}$ 3454.5, 2928.9, 2864.6, 2105.9 (N_3), 1667.3, 1593.6, 1493.4, 1439.1, 1358.7, 1290.9, 1096.8, 1064.6 cm^{-1} .

(5*RS*)-5-(Aminomethyl)-3-phenyl-1,3-thiazolidine-2-thione (17a). To a solution of the crude azide **14a** (425 mg, 2.6 mmol) in methanol (10 mL) under a nitrogen atmosphere was added triethylamine (1.3 g, 12.9 mmol) and propane-1,3-dithiol (1.39 g, 12.9 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (20 mL) and washed with water and brine. The organic extract was dried (Na_2SO_4) and concentrated to give the crude amine **17a**. (1.2 g, contaminated with propanedithiol).

5-Methylene-3-phenyl-1,3-thiazolidine-2-thione (15a). The amine **17a** (1.2 g crude, contaminated with propane-1,3-dithiol) obtained from above was dissolved in dichloromethane (15 mL) and cooled to 0 °C. To this solution was added acetic anhydride (0.79 g, 7.74 mmol) and triethylamine (0.78 g, 7.74 mmol). The reaction mixture was gradually warmed to room temperature and stirred for 8 h. The reaction mixture was diluted with more dichloromethane (10 mL), washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent followed by chromatographic purification of the residue on a silica gel column (200–400 mesh) using ethyl acetate/hexane (10:90) as eluent furnished the thiazole **15a** (150 mg, 57%) as a light yellow solid, mp 106–107 °C ^1H NMR (300 MHz, CDCl_3): δ 7.46–7.57 (3H, m, H_{Ph}), 7.20–7.26 (2H, m, H_{Ph}), 4.49 (1H, s, $\text{H}_{\text{A}=\text{C}}$), 4.09 (1H, s, $\text{H}_{\text{B}=\text{C}}$), 4.30 (2H, s, CH_2N). IR (KBr): $\tilde{\nu}$ 1636, 1491, 1368, 1293, 1281, 1059, 833 cm^{-1} .

5-Methyl-3-phenyl-1,3-thiazole-2(3*H*)-thione (16a). Using ethyl acetate/hexane (20:80) as eluent, furnished the thiazoline **16a** (40 mg, 15%) as a light yellow solid; mp 149 °C. ^1H NMR (300 MHz, CDCl_3): δ 7.51–7.60 (3H, m, H_{Ph}) and 7.24–7.26 (2H, m, H_{Ph}), 6.34 (1H, s, =CHN), 1.96 (3H, s, CH_3). IR (KBr): $\tilde{\nu}$ 1558, 1489, 1432, 1341, 1288, 1234, 1063, 959, 836 cm^{-1} .

***N*-[[*(5RS)*-3-Phenyl-2-thioxo-1,3-thiazolidin-5-yl]methyl]acetamide (18a).** Using ethyl acetate/hexane (40:60) as eluent furnished the thiazolidinethione **18a** (50 mg) as a yellow solid (96.4% purity by HPLC; $t_{\text{R}} = 19.206$ min; PDA 237 nm). mp 111–112 °C. $R_{\text{f}} = 0.8$ (ethyl acetate/hexane 50:50). ^1H NMR (300MHz, CDCl_3): δ 7.33–7.73 (5H, m, H_{Ph}), 6.13 (1H, br s, NH), 4.66 (1H, q, $J = 7.2$ Hz, HCS), 3.89 (1H, t, $J = 9.74$ Hz, $\text{H}_{\text{A}=\text{CN}}$), 3.48 (1H, dd, $J = 7.1, 2.42$ Hz, $\text{H}_{\text{B}=\text{CN}}$), 3.27 (1H, dd, $J = 14.0, 3.1$ Hz, $\text{H}_{\text{A}=\text{CNH}}$), 2.93 (1H, dd, $J = 14.0, 7.6$ Hz, $\text{H}_{\text{B}=\text{CNH}}$), 2.37 (3H, s, CH_3). IR (CHCl_3): $\tilde{\nu}$ 3377, 2927, 1693, 1595, 1498, 1243, 1131, 958, 761 cm^{-1} . LCMS: m/z (%) 267 (100) $[\text{M}+1]$.

***N*-[[*(5RS)*-2-Oxo-3-phenyl-1,3-thiazolidin-5-yl]methyl]acetamide (19a).** To a solution of thiazolidine-2-thione **18a** (40 mg, 0.15 mmol) in dry dichloromethane (0.5 mL) at 0 °C was added propylene oxide (8.7 mg, 0.15 mmol) and trifluoroacetic acid (17.2 mg, 0.15 mmol), and the reaction mixture was stirred for 1h. Solvent and excess of reagents were evaporated; the residue was chromatographed on a silica gel column using ethyl acetate/hexane (40:60) as eluent to furnish **19a** (30 mg, 80%) as an oil (98.13% purity by HPLC; $t_{\text{R}} = 18.181$ min; PDA 245 nm). $R_{\text{f}} = 0.75$ (ethyl acetate/hexane 50:50). ^1H NMR (300MHz, CDCl_3): δ 7.41–7.59 (2H, m, H_{Ph}), 7.36–7.40 (2H, m, H_{Ph}), 7.13(1H, m, H_{Ph}), 4.97 (1H, br s, NH), 4.53 (1H, m, 5-H), 3.67 (1H, t, $J = 8.79$ Hz, 4- H_{A}), 3.28 (1H, m, 4- H_{B}), 3.43 (1H, dd, $J = 13.87$ Hz, $\text{CH}_{\text{A}}\text{NH}$), 2.84 (1H, dd, $J =$

13.86, 9.15 Hz, CH_BNH), 2.37 (3H, s, CH₃). LCMS: *m/z* (%) 273 (17) [M+Na], 251 (100) [M+1].

Triethylammonium 3-fluoro-4-morpholin-4-ylphenyldithiocarbamate (10b). Following the protocol for the preparation of **11a**, the reaction of the aniline **9b**¹⁵ (5 g, 25.5 mmol), carbon disulfide (2.3 g, 30.6 mmol) and triethylamine (7.75 g, 76.5 mmol) furnished the corresponding thiocarbamic acid salt **10b** (9.1 g, 96%) as a yellow solid; mp 100–101 °C. ¹H NMR (300 MHz, CDCl₃): δ 9.15 (1H, br s, NH), 7.62 (1H, dd, *J* = 14.1, 2.1 Hz, H_{ar}), 7.20 (1H, d, *J* = 8.1 Hz, H_{ar}), 6.87 (1H, t, *J* = 9 Hz, H_{ar}), 3.85 (4H, t, *J* = 4.5 Hz, CH₂OCH₂), 3.25 (6H, q, *J* = 7.27 Hz, 3 x CH₂N), 3.05 (4H, t, *J* = 4.5 Hz, CH₂NCH₂), 1.39 (9H, t, *J* = 7.28 Hz, 3 x CH₃); IR (KBr): $\tilde{\nu}$ 3165.8, 2959.1, 1578.7, 1508.0, 1307.1, 1236.7, 1114.5, 993.1, 683.4 cm⁻¹. LCMS: *m/z* (%) 197.1 (100), 102.1 (80).

Benzyl (3-fluoro-4-morpholin-4-ylphenyl)dithiocarbamate (11b). The solution of the dithiocarbamic acid salt **10b** (3.54 g, 10 mmol) in acetonitrile (40 mL) reacted with benzyl bromide (1.88 g, 11 mmol) at room temperature for 3 h to furnish, after purification on a silica gel column with methanol/dichloromethane (2.5:97.5) as eluent, **11b** (3.2 g, 89%) as a yellow solid; mp 115–117 °C. *R_f* = 0.7 (ethyl acetate/hexane 50:50).

Benzyl *N*-allyl-*N*-(3-fluoro-4-morpholin-4-ylphenyl)dithiocarbamate (12b). As described for compound **12a** the *N*-allylation of the dithiocarbamate ester **11b** (3.2 g, 8.8 mmol) in dry tetrahydrofuran (50 mL) using sodium hydride (50% dispersion in oil, 0.5 g, 10.4 mmol), allyl bromide (1.28 g, 10.6 mmol) and tetrabutylammonium iodide (0.33 g, 0.88 mmol) furnished, after a silica gel column purification with ethyl acetate/hexane (40:60) as eluent, **12b** (3.5 g, 99%) as an oil. *R_f* = 0.7 (ethyl acetate/hexane 60:40). ¹H NMR (300 MHz, CDCl₃): δ 7.30 (5H, m, H_{ar}), 6.89 (1H, t, *J* = 8.7 Hz, H_{ar}), 6.62 (2H, m, H_{ar}), 5.85 (1H, br s, =CH), 5.25 (1H, d, *J* = 19.5 Hz, H_AC=), 5.13 (2H, d, *J* = 9.9 Hz, H_BC=), 4.30 (2H, s, CH₂S), 3.87 (4H, s, CH₂OCH₂), 3.69 (2H, br s, CH₂N) and 3.06 (4H, s, CH₂NCH₂). IR (CH₂Cl₂): $\tilde{\nu}$ 1567.8, 1502.6, 1451.4, 1258.6, 1119.2, 968.9, 701.2 cm⁻¹. LCMS: *m/z* (%) 402.8 (80) [M+1], 234.6 (100) [M – C(S)SCH₂Ph+2].

(5*RS*)-3-(3-Fluoro-4-morpholin-4-ylphenyl)-5-(iodomethyl)-1,3-thiazolidine-2-thione (13b). Following the procedure as described for **13a**, the reaction of *N*-allyldithiocarbamate **12b** (3.9 g, 9.7 mmol) in acetonitrile (30 mL) with iodine (2.46 g, 19.4 mmol) and subsequent purification over a silica gel column with ethyl acetate/hexane (40–60:60–40) as eluent furnished **13b** (3.3 g) as a light yellow oil. (89.39% purity by HPLC; *t_R* = 20.467 min; PDA 260 nm). *R_f* = 0.5 (ethyl acetate/hexane 50:50). ¹H NMR (300 MHz, CDCl₃): δ 6.95–7.08 (3H, m, H_{ar}), 4.60 (1H, s, HCS), 3.87 (4H, t, *J* = 4.59 Hz, CH₂OCH₂), 3.75 (1H, dd, *J* = 8.79, 4.2 Hz, H_ACN), 3.32–3.46 (3H, m, CH₂I, H_BCN), 3.15 (4H, t, *J* = 4.41 Hz, CH₂NCH₂). IR (CH₂Cl₂): $\tilde{\nu}$ 1672, 1513, 1451, 1401, 1251, 1119, 1046, 957, 921, 734 cm⁻¹. LCMS: *m/z* (%) 438.7 (100) [M+1].

(5*RS*)-5-(Azidomethyl)-3-(3-fluoro-4-morpholin-4-ylphenyl)-1,3-thiazolidine-2-thione (14b). As described for **14a**, the reaction of **13b** (500 mg, 1.14 mmol) dissolved in dimethylformamide (5 mL) with lithium azide (100 mg, 2.24 mmol) dissolved in water (0.5 mL) [commercially obtained as 20% (w/v) solution in water] at room temperature for 4 h furnished the crude azide

14b (400 mg) as an oil, which was contaminated with thiazoles **15b** and **16b**. (Due to its instability azide **14b** was used as such and the thiazoles **15b** and **16b** were obtained upon column chromatography after the acetylation step, *vide infra*). The IR spectra of the crude mixture confirmed the presence of the azide. IR (CHCl₃): $\tilde{\nu}$ 2857, 2107 (N₃), 1673, 1512, 1387, 1293, 1249, 1119, 948, 919 cm⁻¹.

3-(3-Fluoro-4-morpholin-4-ylphenyl)-5-methylene-1,3-thiazolidine-2-thione (15b). The crude azide **14b** (400mg, <1.13 mmol) dissolved in methanol (3 mL) reacted with propane-1,3-dithiol (536 mg, 4.95 mmol) and triethylamine (500 mg, 4.95 mmol) at room temperature for 14 h to furnish the crude amine **17b** which, in turn, reacted with acetic anhydride (500 mg, 4.95 mmol) and triethylamine (500 mg, 4.95 mmol). After work-up as described for **15a**, the residue was chromatographed over silica gel (200–400 mesh) with ethyl acetate/hexane (30:70) as eluent furnishing thiazole **15b** (100 mg, 28%) as a white solid; mp 188–189 °C. ¹H NMR (300 MHz, CDCl₃): δ 6.91–7.06 (3H, m, H_{ar}), 4.49 (1H, s, H_AC=), 4.14 (1H, s, H_BC=), 4.27 (2H, s, CH₂N), 3.88 (4H, br s, CH₂OCH₂), 3.16 (4H, br s, CH₂NCH₂). IR (KBr): $\tilde{\nu}$ 1638, 1510, 1372, 1294, 1246, 1118, 1069, 949 cm⁻¹. LCMS: *m/z* (%) 311 (100) [M+1].

3-(3-Fluoro-4-morpholin-4-ylphenyl)-5-methyl-1,3-thiazole-2(3H)-thione (16b). Using ethyl acetate/hexane (40:60) as eluent furnished thiazole **16b** (80 mg, 22%) as a thick oil. ¹H NMR (300 MHz, CDCl₃): δ 6.94–7.08 (3H, m, H_{ar}), 6.31 (1H, bs, =CHN), 3.88 (4H, t, *J* = 4.67 Hz, CH₂OCH₂), 3.15–3.24 (4H, m, CH₂NCH₂), 1.97 (3H, s, CH₃); IR (DCM): $\tilde{\nu}$ 1513, 1450, 1291, 1260, 1119, 1069, 975, 939 cm⁻¹. LCMS: *m/z* (%) 311 (100) [M+1].

N-[(5RS)-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-thioxo-1,3-thiazolidin-5-yl]methyl]acetamide [(RS)-3]. Methanol/dichloromethane (4:96) as eluent furnished thiazolidine-2-thione (*RS*)-**3** (46 mg) as a light brown oil. (88.3% purity by HPLC; *t_R* = 19.154 min; PDA 250 nm). *R_f* = 0.45 (ethyl acetate/hexane 50:50). ¹H NMR (300 MHz, CDCl₃): δ 7.19–7.31 (2H, m, H_{ar}), 7.02 (1H, t, *J* = 9 Hz, H_{ar}), 6.12 (1H, br s, NH), 4.60 (1H, m, HCS), 3.92 (4H, br s, CH₂OCH₂), 3.70–3.86 (1H, m, H_ACN), 3.28–3.33 (1H, m, H_BCN), 3.47–3.52 (1H, m, CH_ANH), 2.99–3.10 (1H, m, CH_BNH), 3.17 (4H, br s, CH₂NCH₂), 2.91 (3H, s, CH₃). IR (CHCl₃): $\tilde{\nu}$ 1693, 1515, 1449, 1250, 1118, 1033, 937 cm⁻¹. LCMS: *m/z* (%) 370 (100) [M+1], 354 (25) [M – CH₃].

N-[(5RS)-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-thiazolidin-5-yl]methyl]acetamide [(RS)-4]. Following the protocol for the preparation of **19a**, thiazolidine-2-thione (*RS*)-**3** (100 mg, 0.27 mmol) was reacted with propylene oxide (15 mg, 0.27 mmol) and trifluoroacetic acid (30 mg, 0.27 mmol) in dichloromethane (0.5 mL) at 0 °C for 30 min, and at room temperature for 2 h. Purification over a silica gel column using 50% ethyl acetate-hexane as eluent furnished (*RS*)-**4** (60 mg) as an oil (86% purity by HPLC; *t_R* = 20.867 min; PDA 255 nm). *R_f* = 0.4 (ethyl acetate/hexane 50:50). ¹H NMR (300 MHz, CDCl₃): δ 7.23–7.47 (2H, m, H_{ar}), 6.96 (1H, t, *J* = 9 Hz, H_{ar}), 4.42 (1H, m, 5-H), 3.87 (4H, t, *J* = 4.2 Hz, CH₂OCH₂), 3.60–3.89 (1H, m, 4-H_A), 3.38–3.50 (1H, m, 4-H_B), 3.06 (4H, t, *J* = 4.2 Hz, CH₂NCH₂), 3.26 (1H, dd, *J* = 5.7, 4.2 Hz, CH_ANH), 2.82 (1H, dd, *J* = 9.3, 4.8 Hz, CH_BNH), 2.37 (3H, s, CH₃). LCMS: *m/z* (%): 354.6 (100) [M+1].

S-[[*(5*R,S*)*-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-thioxo-1,3-thiazolidin-5-yl]methyl] ethanethioate (20). To a solution of **13b** (150 mg, 0.34 mmol) in acetonitrile (1 mL) was added potassium thioacetate (78 mg, 0.68 mmol) and tetrabutylammonium iodide (13 mg, 0.034 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water. The aqueous layer was extracted with ethyl acetate (2 × 5 mL), and the combined organic extract was washed with water and brine, and dried (Na₂SO₄). Evaporation of the solvent followed by purification of the residue over a silica gel column using ethyl acetate/hexane (40–60:60–40) as eluent furnished **20** (115 mg) as a sticky semisolid (90.26% purity by HPLC; *t*_R = 21.895 min; PDA 265 nm). *R*_f = 0.4 (ethyl acetate/hexane 40:60). ¹H NMR (300 MHz, CDCl₃): δ 6.96–7.08 (3H, m, H_{ar}), 4.66 (1H, m, HCS), 3.87 (4H, t, *J* = 4.38 Hz, CH₂OCH₂), 3.63 (1H, dd, *J* = 11.43, 8.25 Hz, H_ACN), 3.05–3.27 (3H, m, H_BCN, CH₂S), 3.15 (4H, t, *J* = 4.38 Hz, CH₂NCH₂), 2.36 (3H, s, CH₃). IR (DCM): $\tilde{\nu}$ 1695, 1511, 1380, 1250, 1177, 1119, 1048, 949, 851, 785 cm⁻¹. LCMS: *m/z* (%) 387 (15) [M+1], 345 (100) [M – COCH₃+2].

S-[[*(5*R,S*)*-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-thiazolidin-5-yl]methyl] ethane-thioate (21). Following the protocol for the preparation of **19a** a solution of thiazolidin-2-thione **20** (110 mg, 0.29 mmol) in dichloromethane (2 mL) reacted with propylene oxide (25 mg, 0.43 mmol) and trifluoroacetic acid (49 mg, 0.43 mmol) at 0 °C for 1 h. After purification of the crude residue over a silica gel column using ethyl acetate/hexane (30–40:70–60) as eluent **21** (81 mg) was obtained as a sticky solid (96.25% purity by HPLC; *t*_R = 20.927 min; PDA 262 nm). *R*_f = 0.5 (ethyl acetate/hexane 50:50). TLC: *R*_f 0.5 in 50:50 ethyl acetate-hexane. ¹H NMR (300 MHz, CDCl₃): δ 7.11–7.26 (2H, m, H_{ar}), 6.96 (1H, t, *J* = 9.09 Hz, H_{ar}), 4.40 (1H, m, 5-H), 3.85 (4H, t, *J* = 4.17 Hz, CH₂OCH₂), 3.56 (1H, dd, *J* = 11.25, 3.57 Hz, 4-H_A), 3.30 (1H, dd, *J* = 13.8, 3.57 Hz, 4-H_B), 2.96–3.15 (2H, m, CH₂S), 3.09 (4H, t, *J* = 4.31 Hz, CH₂NCH₂), 2.36 (3H, s, CH₃). IR (DCM): $\tilde{\nu}$ 1693, 1676, 1513, 1450, 1374, 1229, 1119, 953, 921 cm⁻¹. LCMS: *m/z* (%) 370.9 (100) [M+1].

S-[[*(5*R,S*)*-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl] ethane-thioate (23). To a solution of mesylate **22**¹⁵ (150 mg, 0.41 mmol) in acetonitrile (1 mL) was added potassium thioacetate (94 mg, 0.83 mmol) and tetrabutylammonium iodide (15 mg, 0.04 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water. The aqueous layer was extracted with ethyl acetate (2 × 5 mL) and the combined organic extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent followed by purification of the residue over a silica gel column using ethyl acetate/hexane (40:60) as eluent furnished **23** (130 mg) as a semisolid (92.45% purity by HPLC; *t*_R = 20.199 min; PDA 255 nm). *R*_f = 0.2 (ethyl acetate/hexane 50:50). ¹H NMR (300 MHz, CDCl₃): δ 7.42 (1H, dd, *J* = 14.35, 2.39 Hz, H_{ar}), 7.10 (1H, dd, *J* = 8.87, 2.25 Hz, H_{ar}), 6.92 (1H, t, *J* = 9.1 Hz, H_{ar}), 4.78 (1H, m, 5-H), 4.05 (1H, t, *J* = 8.85 Hz, 4-H_A), 3.66 (1H, dd, *J* = 8.9, 6.4 Hz, 4-H_B), 3.86 (4H, t, *J* = 4.4 Hz, CH₂OCH₂), 3.32 (2H, dd, *J* = 5.23, 2.76 Hz, CH₂S), 3.06 (4H, t, *J* = 4.6 Hz, CH₂NCH₂), 2.40 (3H, s, CH₃). IR (KBr): $\tilde{\nu}$ 1752, 1698, 1521, 1425, 1233, 1114, 1039, 935, 868, 808, 748 cm⁻¹. LCMS: *m/z* (%) 354.9 (100) [M+1].

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