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 Mehtaa

*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 (received 08 Jul 04; accepted 11 Jan 05; published on the web 19 Jan 05)

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 biosisosteric 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

\[
\text{DuP-721} \quad 1
\]

\[
\text{Linezolid} \quad 2
\]
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.\(^6\) 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](image)

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 thirane 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 µg/mL).

![Scheme 1](image)
A general strategy for the synthesis of thiazolidine rings was required that could lead to this new class of compounds. There is a report\textsuperscript{11} on the iodo-cyclisation of $N$-allyl- and $S$-allyl-thioureas for the synthesis of dihydrothiazoles (Scheme 2, Eq. 1 and 2); the synthesis of achiral oxazolidinones utilizes an iodo-cyclocarbamation reaction.\textsuperscript{12} By the latter reaction an $N$-allyl-carbamate \textsuperscript{6} is cyclized using iodine through the intermediacy of an iodonium species \textsuperscript{7} leading to oxazolidinones \textsuperscript{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

Retroynthetic 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-$(N$-acetylaminomethyl)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.

\[
\begin{align*}
\text{Scheme 3. Retrosynthesis of thiazolidine-2-thiones and thiazolidin-2-ones.}
\end{align*}
\]

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 H₂, Pd/C, PPh₃/H₂O; P(OEt)₃/H₂O, NaBH₄) or into an acetamide group (with CH₃COSH) failed. Treating azide 14a with propane-1,3-dithiol and triethylamine 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. 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) 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) CS$_2$, Et$_3$N, r.t.; (b) PhCH$_2$Br, CH$_3$CN, r.t.; (c) NaH, allyl bromide, $n$-Bu$_4$NI, 0 °C; (d) I$_2$, CH$_3$CN, r.t.; (e) NaN$_3$ or LiN$_3$, DMF; (f) HS(CH$_2$)$_3$SH, Et$_3$N, MeOH; (g) Ac$_2$O, Et$_3$N, CH$_2$Cl$_2$, 0 °C → r.t.; (h) propylene oxide, TFA, CH$_2$Cl$_2$.

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)\textsuperscript{16} and antifungal MIC was performed by NCCLS microbroth dilution method [M 27 (A)\textsuperscript{17} and M 38 (P)\textsuperscript{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 19\textsuperscript{a} showed mild antifungal activity (Table 1).

Table 1. Activity of thiazolidines (RS)-3 and 19\textsuperscript{a} against fungi

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)</th>
<th>Flucanazole</th>
<th>Linezolid (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida parapsilosis 22019 (QC)\textsuperscript{a}</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Candida krusei 6258 (QC)\textsuperscript{a}</td>
<td>8</td>
<td>&gt;16</td>
<td>32</td>
</tr>
<tr>
<td>Paecilomyces variotti 22319 (QC)\textsuperscript{b}</td>
<td>-</td>
<td>≥16</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Candida albicans A-26\textsuperscript{a}</td>
<td>16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Candida albicans Y-01-19\textsuperscript{a}</td>
<td>16</td>
<td>&gt;16</td>
<td>16</td>
</tr>
<tr>
<td>Candida tropicalis 750\textsuperscript{a}</td>
<td>16</td>
<td>≥16</td>
<td>0.25</td>
</tr>
<tr>
<td>Candida krusei 766.1\textsuperscript{a}</td>
<td>16</td>
<td>&gt;16</td>
<td>≥64</td>
</tr>
<tr>
<td>Candida glabrata 90030\textsuperscript{a}</td>
<td>16</td>
<td>&gt;16</td>
<td>32</td>
</tr>
<tr>
<td>Histoplasma capsulatum\textsuperscript{a}</td>
<td>16</td>
<td>&gt;16</td>
<td>4</td>
</tr>
<tr>
<td>Cryptococcus neoformans \textsuperscript{1}\textsuperscript{a}</td>
<td>2</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>Cryptococcus neoformans M 106\textsuperscript{a}</td>
<td>2</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Aspergillus fumigatus 1008\textsuperscript{b}</td>
<td>16</td>
<td>&gt;16</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Aspergillus fumigatus Si-1\textsuperscript{b}</td>
<td>8</td>
<td>&gt;16</td>
<td>&gt;64</td>
</tr>
</tbody>
</table>

\textsuperscript{a} MIC indicates 80% growth inhibition. \textsuperscript{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 antibacterials. 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, 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 protocols 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 ºC 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, HPh), 7.32 (2H, m, HPh), 7.12 (1H, t, J = 7.2 Hz, HPh), 3.27 (6H, q, J = 7.2 Hz, CH2N), 1.40 (9H, t, J = 7.2 Hz, CH3). IR (KBr): ν 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. 

\[ R_f = 0.7 \text{ (ethyl acetate/hexane 20:80).} \]

\[ \text{1H NMR (300 MHz, CDCl}_3\): } \delta 8.78 (1H, br s, NH), 6.85–7.50 (10H, m, H\text{Ph}), 4.56 (2H, s, CH}_2. \]

IR (CH\text{2Cl}_2): \nu \text{ 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\text{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. 

\[ R_f = 0.72 \text{ (ethyl acetate/hexane 20:80).} \]

\[ \text{1H NMR (300 MHz, CDCl}_3\): } \delta 7.20–7.32 (7H, m, H\text{Ph}), 7.06 (1H, t, \text{J} = 7.5 \text{ Hz, H\text{Ph}}), 6.84 (2H, d, \text{J} = 7.5 \text{ Hz, H\text{Ph}}), 5.80 (1H, br s, =\text{CH}), 5.23 (1H, d, \text{J} = 16.8 \text{ Hz, H\text{AC}}), 5.10 (1H, d, \text{J} = 9.9 \text{ Hz, H\text{BC}}), 4.29 (2H, s, CH\text{2S}) \text{ and 3.64 (2H, br s, CH}_2\text{N). IR (CH}_2\text{Cl}_2\): } \nu \text{ 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\text{2SO}_4). Evaporation of the solvent followed by purification of the residue over a silica gel column using ethyl acetate/hexane (10:90–85:15) as eluent furnished the thiazolidine-thiazolidine-2-thione 13a (880 mg, 53%) as a light yellow solid. (99.35% purity by HPLC; (t \text{R} = 22.509 min; PDA 265 nm). mp 166 °C. 

\[ R_f = 0.2 \text{ (ethyl acetate/hexane 20:80).} \]

\[ \text{1H NMR (300 MHz, CDCl}_3\): } \delta 7.26–7.52(5H, m, H\text{Ph}), 4.67 (1H, m, H\text{CS}), 3.78 (1H, dd, \text{J} = 11.3, 3.27 \text{ Hz, H\text{ACN}}), 3.28–3.49 (3H, m, CH\text{2I, H\text{BCN)}}. \]

IR (KBr): \nu 1636.4, 1570.0, 1484.4, 1208.2, 952.0 cm\text{^{-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\text{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\text{2Cl}_2): \nu 3454.5, 2928.9, 2864.6, 2105.9 (N\text{3}), 1667.3, 1593.6, 1493.4, 1439.1, 1358.7, 1290.9, 1096.8, 1064.6 cm\text{^{-1.}
(5RS)-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 (Na₂SO₄) 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 (Na₂SO₄). 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, CDCl₃): δ 7.46–7.57 (3H, m, HPh), 7.20–7.26 (2H, m, HPh), 4.49 (1H, s, H AC=), 4.09 (1H, s, H BC=), 4.30 (2H, s, CH₂N). IR (KBr): ν ~ 1636, 1491, 1368, 1293, 1281, 1059, 833 cm⁻¹.

5-Methyl-3-phenyl-1,3-thiazole-2(3H)-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, CDCl₃): δ 7.51–7.60 (3H, m, H Ph) and 7.24–7.26 (2H, m, HPh), 6.34 (1H, s, =CHN), 1.96 (3H, s, CH₃). IR (KBr): ν ~ 1558, 1489, 1432, 1341, 1288, 1234, 1063, 959, 836 cm⁻¹.

N-[(5RS)-3-Phenyl-2-thioxo-1,3-thiazolidin-5-yl]methylacetamide (18a). Using ethyl acetate/hexane (40:60) as eluent furnished the thiazolidinethione 18a (50 mg) as a yellow solid (96.4% purity by HPLC; tᵣ = 19.206 min; PDA 237 nm). mp 111–112 °C. Rᵣ = 0.8 (ethyl acetate/hexane 50:50). 1H NMR (300MHz, CDCl₃): 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, HₐCN), 3.48 (1H, dd, J = 7.1, 2.42 Hz, HₐCN), 3.27 (1H, dd, J = 14.0, 3.1 Hz, HₐCₐNH), 2.93 (1H, dd, J = 14.0, 7.6Hz, HₐCNH), 2.37 (3H, s, CH₃). IR (CHCl₃): ν ~ 3377, 2927, 1693, 1595, 1498, 1243, 1131, 958, 761 cm⁻¹. LCMS: m/z (%) 267 (100) [M+1].

N-[(5RS)-2-Oxo-3-phenyl-1,3-thiazolidin-5-yl]methylacetamide (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; tᵣ = 18.181 min; PDA 245 nm). Rᵣ = 0.75 (ethyl acetate/hexane 50:50). 1H NMR (300MHz, CDCl₃): δ 7.41–7.59 (2H, m, HPh), 7.36–7.40 (2H, m, HPh), 7.13(1H, m, HPh), 4.97 (1H, br s, NH), 4.53 (1H, m, 5-H), 3.67 (1H, t, J = 8.79 Hz, 4-Hₐ), 3.28 (1H, m, 4-Hₐ), 3.43 (1H, dd, J = 13.87 Hz, CHₐNH), 2.84 (1H, dd, J =
13.86, 9.15 Hz, CH$_3$NH), 2.37 (3H, s, CH$_3$). 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\(^\text{15}\) (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. \(^1\)H NMR (300 MHz, CDCl$_3$): $\delta$ 9.15 (1H, br s, NH), 7.62 (1H, dd, $J$ = 14.1, 2.1 Hz, Har), 7.20 (1H, d, $J$ = 8.1 Hz, Har), 6.87 (1H, t, $J$ = 9 Hz, Hz), 3.85 (4H, t, $J$ = 4.5 Hz, CH$_2$OCH$_2$), 3.25 (6H, q, $J$ = 7.27 Hz, 3 x CH$_2$N), 3.05 (4H, t, $J$ = 4.5 Hz, CH$_2$NCH$_2$), 1.39 (9H, t, $J$ = 7.28 Hz, 3 x CH$_3$); 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). \(^1\)H NMR (300 MHz, CDCl$_3$): $\delta$ 7.30 (5H, m, Har), 6.89 (1H, t, $J$ = 8.7 Hz, Hz), 6.62 (2H, m, Hz), 5.85 (1H, br s, =CH), 5.25 (1H, d, $J$ = 19.5 Hz, HAC=), 5.13 (2H, d, $J$ = 9.9 Hz, HBC=), 4.30 (2H, s, CH$_2$S), 3.87 (4H, s, CH$_2$OCH$_2$), 3.69 (2H, br s, CH$_2$N) and 3.06 (4H, s, CH$_2$NCH$_2$). IR (CH$_2$Cl$_2$): $\tilde{\nu}$ 1567.8, 1513, 1451, 1258.6, 1119.2, 968.9, 701.2 cm$^{-1}$. LCMS: $m/z$ (%) 402.8 (80) [M+1], 234.6 (100) [M – C(S)SCH$_2$Ph+2].

**(5RS)-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 (40–60:40–60) 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). \(^1\)H NMR (300 MHz, CDCl$_3$): $\delta$ 6.95–7.08 (3H, m, Har), 4.60 (1H, s, HCS), 3.87 (4H, t, $J$ = 4.59 Hz, CH$_2$OCH$_2$), 3.75 (1H, dd, $J$ = 8.79, 4.2 Hz, HACN), 3.32–3.46 (3H, m, Har), 3.15 (4H, t, $J$ = 4.41 Hz, CH$_2$NCH$_2$). IR (CH$_2$Cl$_2$): $\tilde{\nu}$ 1672, 1513, 1451, 1401, 1251, 1119, 1046, 957, 921, 734 cm$^{-1}$. LCMS: $m/z$ (%) 438.7 (100) [M+1].

**(5RS)-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): ν 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 (400 mg, <1.13 mmol) dissolved in methanol (3 mL) reacted with propane-1,3-dithiol (536 mg, 4.95 mmol) and triethyl amine (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): ν ~ 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): ν ~ 1513, 1450, 1291, 1260, 1119, 1069, 975, 939 cm⁻¹. LCMS: m/z (%) 311 (100) [M+1].

N-[[(RS)-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; tR = 19.154 min; PDA 250 nm). Rf = 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), 6.20 (1H, br s, NH), 4.60 (1H, m, HCS), 3.92 (4H, br s, CH₂OCH₂), 3.70–3.86 (1H, m, HₐCN), 3.28–3.33 (1H, m, HₜCN), 3.47–3.52 (1H, m, CH₂NH), 2.99–3.10 (1H, m, CHₐNH), 3.17 (4H, br s, CH₂NCH₂), 2.91 (3H, s, CH₃). LCMS: m/z (%) 370 (100) [M+1], 354 (25) [M –CH₃].

N-[(RS)-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; tR = 20.867 min; PDA 255 nm). Rf = 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-Hₐ), 3.38–3.50 (1H, m, 4-Hₜ), 3.06 (4H, t, J = 4.2 Hz, CH₂NCH₂), 3.26 (1H, dd, J = 5.7, 4.2 Hz, CH₂NH), 2.82 (1H, dd, J = 9.3, 4.8 Hz, CH₂NH), 2.37 (3H, s, CH₃). LCMS: m/z (%): 354.6 (100) [M+1].
S-[(5RS)-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-thioxo-1,3-thiazolidin-5-ylmethyl] 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). \(^1\)H NMR (300 MHz, CDCl₃): \( \delta \) 6.96–7.08 (3H, m, Hₐr), 4.66 (1H, m, HCS), 3.87 (4H, t, \( J = 4.38 \) Hz, CH₂OCH₂), 3.63 (1H, dd, \( J = 11.43, 8.25 \) Hz, HₐCN), 3.05–3.27 (3H, m, H₂BCN, 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-[(5RS)-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-thiazolidin-5-ylmethyl] ethanethioate (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 ºC 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. \(^1\)H NMR (300 MHz, CDCl₃): \( \delta \) 7.11–7.26 (2H, m, Hₐr), 6.96 (1H, t, \( J = 9.09 \) Hz, Hₐr), 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-Hₐ), 3.30 (1H, dd, \( J = 13.8, 3.57 \) Hz, 4-Hₐ), 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-[(5RS)-3-(3-Fluoro-4-morpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-ylmethyl] ethanethioate (23). To a solution of mesylate 22₁₅ (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 (30–40:70–60) 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). \(^1\)H NMR (300 MHz, CDCl₃): \( \delta \) 7.42 (1H, dd, \( J = 14.35, 2.39 \) Hz, Hₐr), 7.10 (1H, dd, \( J = 8.87, 2.25 \) Hz, Hₐr), 6.92 (1H, t, \( J = 9.1 \) Hz, Hₐr), 4.78 (1H, m, 5-H), 4.05 (1H, t, \( J = 8.85 \) Hz, 4-Hₐ), 3.66 (1H, dd, \( J = 8.9, 6.4 \) Hz, 4-Hₐ), 3.86 (4H, t, \( J = 4.4Hz \), CH₂OCH₂), 3.32 (2H, dd, \( J = 5.23, 2.76 \) Hz, CH₂S), 3.06 (4H, t, \( J = 4.6Hz \), CH₂NCH₂), 2.40 (3H, s, CH₃). IR (KBr): \( \tilde{\nu} \) 1752, 1698, 1521, 1425, 1333, 1114, 1039, 935, 868, 808, 748 cm⁻¹. LCMS: \( m/z \) (%) 354.9 (100) [M+1].
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References

