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Synthesis and structure–activity relationships of 2-alkylidenethiazolidine-4,5-diones as antibiotic agents

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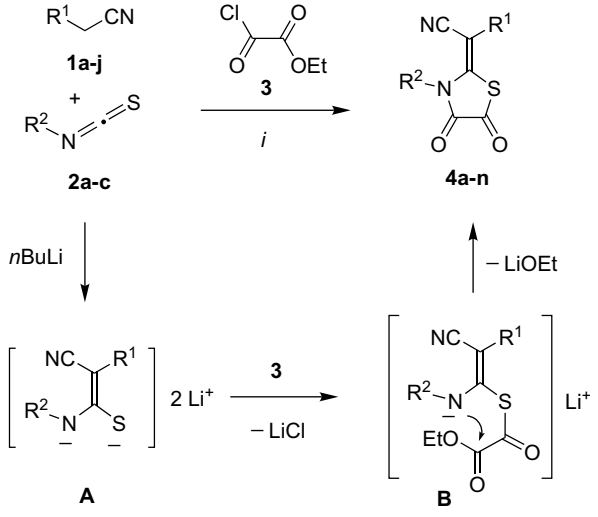
Abstract—2-Alkylidenethiazolidine-4,5-diones were prepared by novel one-pot cyclizations of arylacetonitriles with isothiocyanates and ethyl 2-chloro-2-oxoacetate. The products show antibiotic activity against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*.

1. Introduction

The formation of resistant strains of bacterial pathogens represents an increasing problem. For example, infections caused by *Staphylococcus aureus* are common during prolonged hospitalization.[1e,f] Therefore, the development of new antimicrobial agents is of considerable importance in medicinal chemistry. Oxazolidines and thiazolidines represent pharmacologically relevant heterocyclic systems, which have also been used as synthetic building blocks.[1–5] We have recently reported a new and efficient synthesis of novel *N*-aryl-2-alkylidenethiazolidine-4,5-diones based on one-pot cyclizations of nitriles with *N*-aryl-*iso*-thiocyanates and oxalic acid dielectrophiles.[6] Herein, we wish to report full details of our methodology. With regard to our preliminary communication, we have extended the preparative scope of our methodology to the use of alkyl-substituted isothiocyanates, which allows the synthesis of alkyl-substituted thiazolidine-4,5-diones. In addition, we report for the first time that the novel thiazolidine-4,5-diones prepared exhibit antibiotic activity against the Gram-positive bacteria *Bacillus subtilis* and *S. aureus*. These bacteria are often a source for severe infections in immunosuppressed persons or in patients during their stay in hospitals.

2. Chemistry

The reaction of dilithiated benzylcyanide (**1a**)[7] with *N*-phenyl-*iso*-thiocyanate (**2a**) and ethyl 2-chloro-2-oxoacetate (**3**) afforded the thiazolidine-4,5-dione **4a** in 83% yield (Scheme 1). The use of **3** proved to be mandatory, since employment of oxalyl chloride or diethyl oxalate resulted in polymerization or low yields, respectively. In addition, the sequential addition of the starting mate-



Scheme 1. Synthesis of 2-alkylidenethiazolidine-4,5-diones **4a–n**. Reagents and conditions: (i) (a) *n*-BuLi (2.2 equiv), 1 h, 0 °C; (b) **2**, 1 h, 0 °C; (c) **3**, 16 h, 0 → 20 °C.

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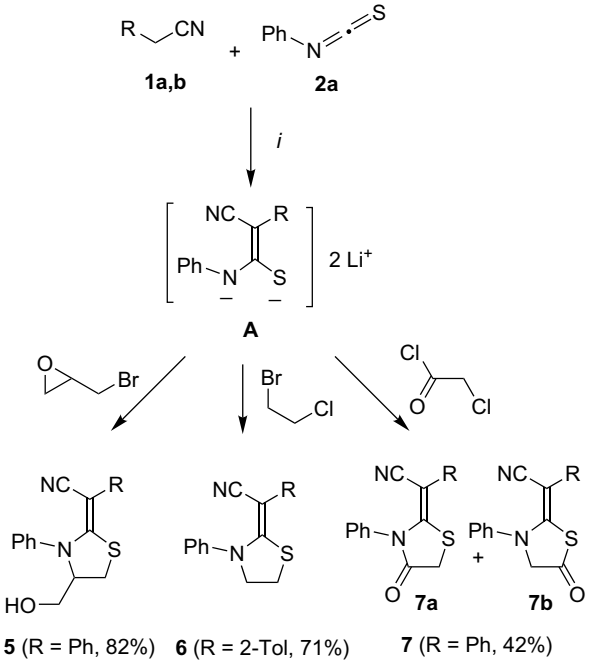
rials, the temperature and the use of NaH/THF proved to be important parameters during the optimization. The reaction proceeded by attack of the dianion onto the central carbon atom of **2a** to give intermediate **A**, attack of the sulfur atom onto **3** (intermediate **B**) and subsequent cyclization via the nitrogen atom. The cyclization proceeded with very good *S*/*N*-regioselectivity and *E*-diastereoselectivity, due to the steric effect of the phenyl group.

The preparative scope of our methodology was studied (Scheme 1, Table 1). The reaction of arylmethylnitriles **1b–h** with phenyl-*iso*-thiocyanate (**2a**) and **3** afforded the thiazolidine-4,5-diones **4b–h**. Starting with 2-thienylacetonitrile **2i**, the thiazolidine-4,5-dione **4i** was prepared. The reaction of ethyl-*iso*-thiocyanate (**2b**) with **1a**,**e** and **1i** gave the corresponding thiazolidine-4,5-diones **4j–l**. The one-pot cyclization of **1a** with allyl-*iso*-thiocyanate (**2c**) and **3a** afforded the allyl-substituted thiazolidine-4,5-dione **4m**. All products were formed with very good regio- and good to very good *E*/*Z*-diastereoselectivity.

Table 1. Products and yields

4	R^1	R^2	4[a] (%)	*E*:*Z*
a	C_6H_6	C_6H_5	83	>98:2
b	2-MeC_6H_5	C_6H_5	48	>98:2
c	4-MeC_6H_5	C_6H_5	61	>98:2
d	2-(MeO)C_6H_5	C_6H_5	46	>98:2
e	4-(MeO)C_6H_5	C_6H_5	53	>98:2
f	3-BrC_6H_5	C_6H_5	15	7:1
g	4-BrC_6H_5	C_6H_5	12	7:1
h	2-Naphthyl	C_6H_5	16	7:1
i	Thiophenyl	C_6H_5	88	1:10
j	C_6H_5	Et	47	>98:2
k	4-(MeO)C_6H_5	Et	42	5:1
l	Thiophenyl	Et	63	10:1
m	C_6H_5	Allyl	49	>98:2

[a] Yields of isolated products.



Scheme 2. Products and yields: Reagents and conditions: (i) (a) *n*-BuLi (2.2 equiv), 1 h, 0 °C; (b) **2a**, 1 h, 0 °C; (c) dielectrophile, 16 h, 0 → 20 °C.

For studies related to the structure–activity relationship, we also prepared related thiazolidines (Scheme 2). We recently reported the one-pot reaction of arylmethylnitriles with isothiocyanates and epibromohydrin to give 2-alkylidene-(4-hydroxymethyl)thiazolidines, such as **5**.[8] Based on a recently reported methodology,[9] we prepared the thiazolidine **6** by cyclization of (4-methylphenyl)acetonitrile with phenyl-*iso*-thiocyanate and 1-bromo-2-chloroethane. The latter gave, in our hands, better results than 1,2-dibromoethane, which was used in the original publication.[9] The cyclization of phenylacetonitrile with phenyl-*iso*-thiocyanate and chloroacetic chloride afforded, following a known procedure,[10] the thiazolidinone **7** as a 1:1 mixture of regioisomers **7a** and **7b**.

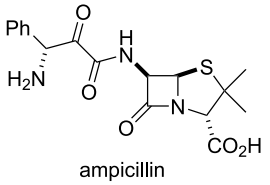
3. Biological tests

The 2-alkylidenethiazolidine-4,5-diones and other thiazolidine derivatives prepared were tested for their antibiotic properties. Some of the tested compounds showed antibiotic activity against the Gram-positive bacteria *B. subtilis* and *S. aureus*. No growth inhibition for the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* or the yeast *Candida maltosa* was observed. The results of the screening are summarized in Table 2.

Table 2. Antibacterial properties of selected compounds

4	Inhibition zone diameter[a]	
	Bacillus subtilis ATCC 6051	*Staphylococcus aureus* ATCC 6538
4a	12	13
4b	Inactive	8
4c	9	Inactive
4d	Inactive	Inactive
4e	10	8
4f	9	12
4g	7	14
4h	9	13
4i	9	14
4j	10	12
4k	Inactive	Inactive
4l	Inactive	12
4m	10	10
7[b]	Inactive	Inactive
8	Inactive	Inactive
Ampicillin	15	16

[a] Diameter is given in centimetres excluding the diameter of the paper disc of 6 mm.
[b] 1:1 Mixture of **7a** and **7b**.



ampicillin

The results show that 2-alkylidenethiazolidine-4,5-diones are interesting inhibitors of the growth of Gram-positive bacteria. Especially the 3- and 4-brominated derivatives **4f** and **4g**, and derivatives **4a**,**h** and **4j** show antibacterial effects comparable to the common antibiotic ampicillin. The aryl substitution at the ring nitrogen is not necessary as the allyl derivative **4m** also shows antimicrobial effects on *S. aureus*. Mandatory for the antibacterial effects is the presence of the thiazolidine-4,5-dione moiety. The thiazolidin-4-one **7** and the thiazolidines **5** and **6** are not active against any of the tested bacterial strains. Compared to **4a**, halogenation of the phenyl moiety in entry **4f** and **4g** shows an increase of the activity against *S. aureus*. In contrast, the antibiotic activity is decreased for the methyl and methoxy derivatives **4b**–**d**.

Infections caused by *S. aureus* are common during prolonged hospitalization and present a severe problem in public health organizations (vide supra). Therefore, the inhibition of the growth of *S. aureus* by 2-alkylidenethiazolidine-4,5-diones **4** makes them excellent candidates for the development of antibiotics.

4. Experimental

4.1. General procedure for the preparation of 2-alkylidenethiazolidin-4,5-diones

To a THF-solution (10 mL) of the arylacetonitrile (2.0 mmol) was added *n*-butyllithium (1.6 M, 4.4 mmol) at 0 °C. After stirring for 1 h, isothiocyanate (2.0 mmol) was added and the solution was stirred for 1 h at 0 °C, followed by addition of ethyl 2-chloro-2-oxoacetate (2.0 mmol). After warming to 20 °C 16 h, an aqueous solution of HCl (30 mL, 1 M) was added. The organic and the aqueous layers were separated and the aqueous layer was extracted three times with ethylacetate (30 mL). The combined organic layers were extracted with brine (30 mL), dried over Na_2SO_4, filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, hexane–ethylacetate = 5:1) to give the thiazolidine-4,5-dione **4**.

4.2. 2-(1-Cyano-1-phenyl)methylidene-3-phenylthiazolidine-4,5-dione (4a)

Starting with phenylacetonitrile (0.586 g, 5.0 mmol), *n*-butyllithium (6.9 mL, 11 mmol, 1.6 M), phenyl-*iso*-thiocyanate (0.768 g, 5.7 mmol) and ethyl 2-chloro-2-oxoacetate (0.888 g, 6.5 mmol) in 25 mL of THF, **4a** was obtained as a yellow solid (1.268 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.41 (m, 3H, CH), 7.43–7.51 (m, 4H, CH), 7.63–7.69 (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 90.66, 114.12 (C), 119.48, 127.71, 128.99, 129.41, 129.59, 129.61 (CH), 132.22, 134.16, 146.32, 157.34, 179.45 (C). MS (EI, 70 eV): *m*/*z* (%) = 306 (M^+, 27), 218 (33), 190 (2), 159 (100), 114 (25). IR (KBr): ν = 2193 (w), 1739 (s), 1591 (s), 1492 (s), 1444 (w). UV–vis (MeCN): λ_{max} (lg ε) = 340.34 (4.02). Anal. Calcd for $C_{17}H_{10}N_2O_2S$: C, 66.65; H, 3.29; N, 9.14. Found: C, 66.41; H, 3.39; N, 8.89.

4.3. 2-(1-Cyano-1-(2-tolyl))methylidene-3-phenylthiazolidine-4,5-dione (4b)

Starting with 2-tolylacetonitrile (0.262 g, 2 mmol), *n*-butyllithium (0.24 mL, 2 mmol, 1.5 M), phenyl-*iso*-thiocyanate (0.270 g, 2 mmol) and ethyl 2-chloro-2-oxoacetate (0.241 g, 2 mmol) in 10 mL of THF, **4b** was obtained as a yellow solid (0.308 g, 48%). T_m = 169 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 7.20–7.29 (m, 1H, CH), 7.28–7.30 (m, 1H, CH), 7.37 (dt, ^4J = 1 Hz, ^3J = 7 Hz, 1H, 7.45–7.49 (m, 2H, CH), 7.66 (dd, ^4J = 2 Hz, ^3J = 6 Hz, 4H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): 19.42 (CH_3), 93.45, 112.67 (C), 126.81, 128.40 (CH), 130.14 (C), 130.27, 130.59, 130.74, 131.18, 131.63 (CH), 132.93, 133.14, 137.87, 159.23, 170.12 (C). MS (EI, 70 eV): *m*/*z* = 320 (M^+, 43), 232 (100), 173 (94), 150 (65), 129 (55). IR (KBr): ν = 2982 (w), 2936 (w), 2199 (w), 1740 (s), 1697 (m), 1598 (m), 1580 (m), 1492 (m), 1457 (w). Anal. Calcd for $C_{18}H_{12}N_2O_2S$: C, 67.48; H, 3.78; N, 8.74. Found: C, 67.21; H, 3.49; N, 8.49.

4.4. 2-(1-Cyano-1-(4-tolyl))methylidene-3-phenylthiazolidine-4,5-dione (4c)

Starting with 4-methylphenylacetonitrile (0.656 g, 5.0 mmol), *n*-butyllithium (6.9 mL, 11 mmol, 1.6 M), phenyl-*iso*-thiocyanate (0.768 g, 5.7 mmol) and ethyl 2-chloro-2-oxoacetate (0.888 g, 6.5 mmol) in 25 mL of THF, **4c** was obtained as a yellow solid (0.663 g, 61%). T_m = 180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.39 (s, 3H, CH_3), 7.24–7.28 (m, 5H, CH), 7.45–7.48 (m, 2H, CH), 7.63–7.68 (m, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.20 (CH_3), 94.42, 113.50, 126.65 (C) 128.38, 129.37, 129.88, 130.01, 131.37 (CH), 133.30, 140.42, 143.23, 156.40, 178.50 (C). MS (EI, 70 eV): *m*/*z* = 320 (M^+, 71), 232 (28), 173 (100), 129 (16), 102 (7); the exact molecular mass for $C_{18}H_{12}N_2O_2S$ *m*/*z* = 320.0620 ± 2 ppm [M^+] was confirmed by HRMS (EI, 70 eV). IR (KBr): ν = 3431 (s), 3061 (w), 2197 (w), 1742 (s), 1589 (s), 1493 (m). UV–vis (MeCN): λ_{max} (lg ε) = 247.92 (4.03).

4.5. 2-(1-Cyano-1-(2-methoxy)phenyl)methylidene-3-phenylthiazolidine-4,5-dione (4d)

Starting with 2-methoxyphenylacetonitrile (0.736 g, 5.0 mmol), *n*-butyllithium (6.9 mL, 11 mmol, 1.6 M), phenyl-*iso*-thiocyanate (0.768 g, 5.7 mmol) and ethyl 2-chloro-2-oxoacetate (0.888 g, 6.5 mmol) in 25 mL of THF, **4d** was obtained as a yellow solid (0.776 g, 2.31 mmol, 46%). T_m = 88 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.86 (s, 3H, CH_3), 6.96–7.08 (m, 4H, CH), 7.23 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 1H, CH), 7.45 (dt, ^3J = 7 Hz, ^4J = 2 Hz, 1H, CH), 7.49–7.53 (m, 1H, CH), 7.61–7.68 (m, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.14, 55.74 (CH_3), 91.04, 91.05 (C), 110.45, 111.74 (CH), 112.96, 119.63 (C), 120.40, 121.02, 128.33, 128.53, 129.45, 130.17, 130.76, 130.90, 131.28, 131.49, 131.67, 132.34 (CH), 144.47, 155.74, 156.82, 157.4, 178.67, 178.68 (C). MS (EI, 70 eV): *m*/*z* = 336 (M^+, 46), 248 (38), 233 (29), 189 (98), 77 (100); the exact molecular mass for $C_{18}H_{12}N_2O_3S$ *m*/*z* = 336.0569 ±

2 ppm [M^+] was confirmed by HRMS (EI, 70 eV). IR (KBr): ν = 3437 (s), 2203 (w), 1741 (s), 1595 (m), 1492 (m), 1461 (w).

4.6. 2-(1-Cyano-1-(4-methoxy)-phenyl)methylidene-3-phenylthiazolidine-4,5-dione (4e)

Starting with 4-methoxyphenylacetonitrile (0.736 g, 5.0 mmol), *n*-butyllithium (6.9 mL, 11 mmol, 1.6 M), phenyl-*iso*-thiocyanate (0.768 g, 5.7 mmol) and ethyl 2-chloro-2-oxoacetate (0.888 g, 6.5 mmol) in 25 mL of THF, **4e** was obtained as a yellow solid (0.890 g, 53%). T_m = 176 °C. ^{1}HNMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3H, CH_3), 6.92 (d, ^3J = 7 Hz, 2H, CH), 7.28 (d, ^3J = 7 Hz, 2H, CH), 7.44–7.46 (m, 2H, CH), 7.62–7.64 (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.41 (CH_3), 94.37 (C), 114.73 (CH), 123.58 (C), 128.94, 130.15, 131.07, 131.51 (CH), 133.39, 142.94, 156.49 (C) 160.90, 178.52 (CO). MS (EI, 70 eV): *m*/*z* = 336 (M^+, 26), 248 (12), 233 (13), 189 (100), 174 (25); the exact molecular mass for $C_{18}H_{12}N_2O_3S$ *m*/*z* = 336.0569 ± 2 ppm [M^+] was confirmed by HRMS (EI, 70 eV). IR (KBr): ν = 3424 (w), 2965 (w), 2937 (w), 2841 (w), 2196 (w), 1743 (s), 1723 (s). 1600 (s), 1510 (s), 1493 (m), 1461 (w). UV–vis (MeCN): λ_{max} (lg ε) = 250.12 (4.06). Anal. Calcd for $C_{13}H_2N_2O_3S$: C, 64.27; H, 3.60; N, 8.33. Found: C, 64.30; H, 3.59; N, 8.45.

4.7. 2-(1-Cyano-1-(3-bromophenyl))methylidene-3-phenylthiazolidine-4,5-dione (4f)

Starting with 3-bromophenylacetonitrile (0.588 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.6 M), phenyl-*iso*-thiocyanate (0.260 g, 3.0 mmol) and ethyl 2-chloro-2-oxoacetate (0.422 g, 3.1 mmol) in 15 mL of THF, **4f** was obtained as a yellow solid (0.167 g, 15%, *E*/*Z* = 7:1). T_m = 138 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.31 (dt, ^3J = 5 Hz, ^4J = 1 Hz, 1H, CH), 7.35–7.38 (m, 1H, CH), 7.42–7.47 (m, 2H, CH), 7.53–7.64 (m, 5H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 92.66 (C, *E*), 94.37 (C, *Z*), 113.06 (C, *E*), 113.44 (C, *Z*), 123.04 (C, *E*), 123.26 (C, *Z*), 126.53 (C, *E*), 126.67 (C, *Z*), 128.26 (CH, *Z*), 128.36 (CH, *E*), 129.08 (CH, *Z*), 129.23 (CH, *E*), 129.53, 130.05 (CH, *Z*), 130.08, 130.73 (CH, *E*), 131.44 (CH, *Z*), 131.55 (CH, *E*), 131.81 (CH, *Z*), 132.41 (CH, *E*), 132.58 (CH, *Z*), 133.17 (CH, *E*), 133.23 (C, *Z*), 133.33 (C, *E*), 143.74 (C, *Z*), 144.77, 156.22 (C, *E*), 156.38 (C, *Z*), 177.69 (C, *E*), 178.34 (C, *Z*). MS (EI, 70 eV): *m*/*z* = 386 (M^+, 2), 237 (3), 159 (3), 131 (3), 28 (100). IR (KBr): ν = 3451 (s), 2203 (w), 1741 (s), 1667 (w), 1580 (m), 1491 (w), 1464 (w), 1450 (w), 1411 (w). UV–vis (MeCN): λ_{max} (lg ε) = 335.00 (4.00).

4.8. 2-(1-Cyano-1-(4-bromophenyl))methylidene-3-phenylthiazolidine-4,5-dione (4g)

Starting with 4-bromophenylacetonitrile (0.351 g, 3.0 mmol), *n*-butyllithium (2.7 mL, 6.6 mmol, 2.5 M), phenyl-*iso*-thiocyanate (0.287 g, 3.3 mmol) and ethyl 2-chloro-2-oxoacetate (0.434 g, 3.6 mmol) in 15 mL of THF, **4g** was obtained as a yellow solid (0.136 g, 12%, *E*/*Z* = 7:1). T_m = 180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.25 (dt, ^3J = 6 Hz, ^4J = 2 Hz, 2H, CH), 7.46 (dd, ^3J = 6 Hz, ^4J = 2 Hz, 2H, CH), 7.59 (dt, ^3J = 6 Hz, ^4J = 2 Hz, 2H, CH), 7.63–7.68 (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 93.21, 112.32, 126.83 (C), 128.44, 129.58, 130.59 (CH), 131.28 (C), 131.75, 132.68 (CH), 133.43, 144.25, 162.78, 177.54 (C). MS (EI, 70 eV): *m*/*z* = 386 (M^+, 4), 237 (11), 113 (5), 77 (10), 32 (100). IR (KBr): ν = 3436 (s), 2203 (w), 1741 (s), 1634 (w), 1584 (s), 1486 (m). UV–vis (MeCN): λ_{max} (lg ε) = 249.79 (4.04), 339.85 (4.07).

4.9. 2-(1-Cyano-1-(2-naphthyl))methylidene-3-phenylthiazolidine-4,5-dione (4h)

Starting with 2-naphthylacetonitrile (0.501 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.6 M), phenyl-*iso*-thiocyanate (0.405 g, 3.0 mmol) and ethyloxalyl chloride (0.422 g, 3.1 mmol) in 15 mL of THF, **4h** was obtained as a yellow solid (0.167 g, 16%, *E*/*Z* = 7:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 (dt, ^3J = 8 Hz, ^4J = 2 Hz, 1H, CH), 7.49–7.54 (m, 1H, CH), 7.60 (dt, ^3J = 7 Hz, ^4J = 2 Hz, 1H, CH), 7.65–7.70 (m, 3H, CH), 7.70–7.93 (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 93.24, 114.11 (C), 126.62, 128.45, 128.57 (CH), 129.07 (C), 129.51, 129.77 (CH), 130.31 (C), 130.41, 130.96 (CH), 131.67 (C), 131.90, 132.70 (CH), 132.05, 132.80 (C), 133.50 (CH), 159.23, 178.07 (C). MS (EI, 70 eV): *m*/*z* = 356 (M^+, 3), 209 (24), 165 (11), 91 (28), 77 (100). IR (KBr): ν = 3061 (w), 2963 (w), 2926 (w), 2203 (w), 1742 (s), 1596 (m), 1494 (w). UV–vis (MeCN): λ_{max} (lg ε) = 223.64 (4.50), 255.04 (4.08).

4.10. 2-(1-Cyano-1-(2-thiophenyl))methylidene-3-phenylthiazolidine-4,5-dione (4i)

Starting with 2-thiophenylacetonitrile (0.369 g, 3.0 mmol), *n*-butyllithium (4.2 mL, 6.6 mmol, 1.5 M), phenyl-*iso*-thiocyanate (0.405 g, 3.0 mmol) and ethyl 2-chloro-2-oxoacetate (0.374 g, 3.1 mmol) in 15 mL of THF, **4i** was obtained as a yellow solid (0.821 g, 88%, *Z*/*E* = 10:1). T_m = 202 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (dd, ^3J = 5 Hz, ^3J = 4 Hz, 1H, CH), 7.22 (dd, ^3J = 4 Hz, ^4J = 1 Hz, 1H, CH), 7.45 (dd, ^3J = 6 Hz, ^4J = 2 Hz, 2H, CH), 7.50 (dd, ^3J = 5 Hz, ^4J = 1 Hz, 1H, CH), 7.63–7.66 (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 88.78 (*Z*), 90.83 (*E*), 112.81 (*Z*), 115.92 (C, *E*), 126.40 (*Z*), 127.15 (*Z*), 127.83 (*E*), 128.52 (*Z*), 128.95 (*E*), 129.20 (*Z*), 129.64 (*E*), 129.75 (*E*), 130.29 (*Z*), 131.25 (*E*), 131.71 (CH, *Z*), 131.76 (*Z*), 132.31 (C, *E*), 132.54 (CH), 133.30 (*Z*), 134.05 (*E*), 135.51 (*Z*), 135.62 (*E*), 156.48 (*E*), 157.78 (*Z*), 177.48 (*E*), 177.81 (C, *Z*). MS (EI, 70 eV): *m*/*z* = 312 (M^+, 45), 224 (9), 165 (100), 147 (4), 121 (30). IR (KBr): ν = 3421 (w), 2201 (w), 1749 (s), 1718 (s), 1594 (s), 1492 (s). UV–vis (MeCN): λ_{max} (lg ε) = 237.26 (4.03). Anal. Calcd for $C_{15}H_8N_2O_2S_2$: C, 57.68; H, 2.58; N, 8.97. Found: C, 57.47; H, 2.62; N, 9.31.

4.11. 2-(1-Cyano-1-phenyl)methylidene-3-ethylthiazolidine-4,5-dione (4j)

Starting with phenylacetonitrile (0.351 g, 3.0 mmol), *n*-butyllithium (2.7 mL, 6.6 mmol, 2.5 M), ethyl-*iso*-thiocyanate (0.287 g, 3.3 mmol) and ethyl 2-chloro-2-oxoacetate (0.434 g, 3.6 mmol) in 15 mL of THF, **4j**

was obtained as a yellow solid (0.361 g, 47%). T_m = 134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.84 (t, ^3J = 7 Hz, 3H, CH_3, *Z*), 1.50 (t, ^3J = 7 Hz, 3H, CH_3, *E*), 3.54 (q, ^3J = 7 Hz, 2H, CH_2, *Z*), 4.47 (q, ^3J = 7 Hz, 2H, CH_2, *E*), 7.36–7.47 (m, 5H, CH, *E*/*Z*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.67 (CH_3, *Z*), 14.07 (CH_3, *E*), 41.33 (CH_2, *E*), 41.92 (CH_2, *Z*), 92.04 (C, *E*), 96.05 (C, *Z*), 116.23 (C, *E*), 116.69 (C, *Z*), 129.32 (CH, *Z*), 129.41 (CH, *E*), 129.79 (CH, *Z*), 129.93 (CH, *E*), 130.30 (CH, *E*), 130.45 (CH, *Z*), 131.28 (C, *Z*), 131.62 (C, *E*), 142.40 (C, *Z*), 144.38 (C, *E*), 157.00 (C, *E*), 158.59 (C, *Z*), 178.60 (C, *Z*), 178.70 (C, *E*). MS (EI, 70 eV): *m*/*z* = 258 (M^+, 33), 159 (100), 142 (19), 114 (22), 88 (9). IR (KBr): ν = 2205 (m), 1733 (s), 1718 (s), 1585 (s), 1448 (w). UV–vis (MeCN): λ_{max} (lg ε) = 334.14 (4.03). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.74; H, 4.17; N, 11.24.

4.12. 2-(1-Cyano-1-(4-methoxyphenyl))methylidene-3-ethylthiazolidine-4,5-dione (4k)

Starting with 4-methoxyphenylacetonitrile (0.441 g, 3.0 mmol), *n*-butyllithium (2.7 mL, 6.6 mmol, 2.5 M), ethyl-*iso*-thiocyanate (0.287 g, 3.3 mmol) and ethyl 2-chloro-2-oxoacetate (0.434 g, 3.6 mmol) in 15 mL of THF, **4k** was obtained as a yellow solid (0.364 g, 42%, *E*/*Z* = 5:1). T_m = 120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.92 (t, ^3J = 7 Hz, 3H, CH_3, *Z*), 1.52 (t, ^3J = 7 Hz, 3H, CH_3, *E*), 3.65 (q, ^3J = 7 Hz, 2H, CH_2, *Z*), 3.87 (s, 3H, CH_3), 4.48 (q, ^3J = 7 Hz, 2H, CH_2, *E*), 6.97 (d, ^3J = 6 Hz, 2H, CH, *Z*), 6.99 (d, ^3J = 6 Hz, 2H, CH, *E*), 7.33 (d, ^3J = 6 Hz, 2H, CH, *Z*), 7.34 (d, ^3J = 6 Hz, 2H, CH, *E*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.57 (*Z*), 13.92 (*E*) (CH_3), 41.11 (*E*), 41.73 (*Z*) (CH_2), 55.21 (*Z*), 55.31 (*E*) (CH_3), 91.73 (*E*), 96.00 (*Z*) (C), 114.56 (*Z*), 114.64 (*E*) (CH), 116.21 (*E*), 116.70 (*Z*), 123.40 (*E*), 123.77 (*Z*) (C), 130.98 (*Z*), 131.20 (*E*) (CH), 141.58 (*Z*), 143.57 (*E*), 156.98 (*E*), 158.54 (*Z*), 160.07 (*Z*), 160.81 (*E*), 178.61 (*Z*), 178.78 (*E*) (C). MS (EI, 70 eV): *m*/*z* = 288 (M^+, 36), 189 (100), 171 (7), 146 (10), 102 (4). IR (KBr): ν = 1739 (s), 1718 (m), 1604 (w), 1583 (m), 1511 (m). UV–vis (MeCN): λ_{max} (lg ε) = 231.39 (4.08), 248.33 (4.06), 344.75 (4.00). Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72. Found: C, 58.61; H, 4.48; N, 9.89.

4.13. 2-(1-Cyano-1-(2-thiophenyl))methylidene-3-ethylthiazolidine-4,5-dione (4l)

Starting with 2-thiophenylacetonitrile (0.369 g, 3.0 mmol), *n*-butyllithium (2.7 mL, 6.6 mmol, 2.5 M), ethyl-*iso*-thiocyanate (0.287 g, 3.3 mmol) and ethyloxalyl chloride (0.434 g, 3.6 mmol) in 15 mL of THF, **4l** was obtained as a yellow solid (0.496 g, 63%, *Z*/*E* = 10:1). T_m = 157 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (t, ^3J = 7 Hz, 3H, CH_3, *E*), 1.54 (t, ^3J = 7 Hz, 3H, CH_3, *Z*), 3.73 (q, ^3J = 7 Hz, 2H, CH_2, *E*), 4.52 (q, ^3J = 7 Hz, 2H, CH_2, *Z*), 7.11 (dd, ^3J = 7 Hz, 1H, CH, *Z*), 7.12 (dd, ^3J = 7 Hz, 1H, CH, *E*), 7.21 (dd, ^3J = 4 Hz, ^4J = 1 Hz, 1H, CH, *E*), 7.24 (dd, ^3J = 4 Hz, ^4J = 1 Hz, 1H, CH, *Z*), 7.53 (dd, ^3J = 4 Hz, ^4J = 1 Hz, 1H, CH, *Z*), 7.57 (dd, ^3J = 4 Hz, ^4J = 1 Hz, 1H, CH, *E*). ^{13}C NMR (75 MHz, $CDCl_3$) (*Z*-Isomer): δ = 14.18 (CH_3), 41.56 (CH_2), 85.90, 115.52 (C), 127.80, 129.87, 131.52 (CH), 131.19, 145.36, 157.11, 178.11 (C). MS (EI, 70 eV): *m*/*z* = 264 (M^+, 14), 207 (6), 166 (82), 120 (100), 70 (32); the exact molecular mass for $C_{11}H_9N_2O_2S_2$ *m*/*z* = 265.01054 ± 2 ppm [$(M+1)^+$] was confirmed by HRMS (FT-ICR). IR (KBr): ν = 3118 (w), 2199 (s), 1730 (s), 1723 (s), 1563 (s), 1518 (w), 1451 (w), 1423 (w). UV–vis (MeCN): λ_{max} (lg ε) = 241.43 (4.01).

4.14. 2-(1-Cyano-1-phenyl)methylidene-3-allylthiazolidine-4,5-dione (4m)

Starting with phenylacetonitrile (0.351 g, 3.0 mmol), *n*-butyllithium (2.7 mL, 6.6 mmol, 2.5 M), allyl-*iso*-thiocyanate (0.327 g, 3.3 mmol) and ethyloxalyl chloride (0.490 g, 3.6 mmol) in 10 mL of THF, **4m** was obtained as a yellow solid. (0.395 g, 49%). T_m = 131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.09 (dt, ^3J = 6 Hz, 2H, CH_2), 5.40 (dd, $^2J_{gem}$ = 2 Hz, $^3J_{trans}$ = 17 Hz, 1H, CH), 5.45 (dd, $^2J_{gem}$ = 2 Hz, $^3J_{cis}$ = 10 Hz, 1H, CH), 6.05 (ddt, $^3J_{trans}$ = 17 Hz, $^3J_{cis}$ = 10 Hz, ^3J = 6 Hz, 1H, CH), 7.38–7.51 (m, 5H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.15 (CH_2), 92.95, 116.26 (C), 119.29 (CH_2), 127.78, 129.44, 129.88, 130.38 (CH), 131.48, 143.84, 157.01, 178.46 (C). MS (EI, 70 eV): *m*/*z* = 270 (M^+, 32), 242 (15), 201 (17), 159 (100), 114 (12). IR (KBr): ν = 3299 (s), 2202 (w), 1736 (s), 1546 (w), 1591 (m), 1531 (m), 1494 (w), 1448 (m), 1409 (m).

4.15. 2-(1-Cyano-1-2-tolyl)methylidene-3-phenylthiazolidin-4-one (7a) and 2-(1-Cyano-1-2-tolyl)methylidene-3-phenylthiazolidin-5-one (7b)

Starting with 2-methylphenylacetonitrile (0.260 g, 2.0 mmol), *n*-butyllithium (2.8 mL, 4.4 mmol, 1.6 M), phenyl-*iso*-thiocyanate (0.234 g, 2.0 mmol) and chloroacetylchloride (0.226 g, 2.0 mmol) in 10 mL of THF, **7** was obtained as a yellow solid in 1:1 mixture of the regioisomers **7a** and **7b** (0.244 g, 0.8 mmol, 42%, *E*/*Z* = 3:1). T_m = 141 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.17 (s, 3H, CH_3, *Z*), 2.20 (s, 3H, CH_3, *E*), 2.33 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.11 (s, 2H, CH_2, *Z*), 4.11 (s, 2H, CH_2, *E*), 6.65–7.02 (m, 5H, CH), 7.23–7.62 (m, 4H, CH). MS (EI, 70 eV): *m*/*z* = 306 (M^+, 21), 259 (9), 210 (13), 74 (14), 28 (100); the exact molecular mass for $C_{18}H_{15}N_2OS$ *m*/*z* = 307.09039 ± 2 ppm [$(M+1)^+$] was confirmed by HRMS (FT-ICR). IR (KBr): ν = 3435 (w), 2192 (m), 1728 (s), 1578 (s), 1492 (w). UV–vis (MeCN): λ_{max} (lg ε) = 230.92 (4.12), 282.49 (4.25).

4.16. 2-(1-Cyano-1-phenyl)methylidene-3-phenylthiazolidine (6)

Starting with phenylacetonitrile (0.234 g, 2.0 mmol), *n*-butyllithium (1.8 mL, 4.4 mmol, 2.5 M), phenyl-*iso*-thiocyanate (0.297 g, 2.2 mmol) and 1-bromo-2-chloroethane (0.312 g, 2.2 mmol) in 10 mL of THF, **6** was obtained as a yellow solid (0.395 g, 1.4 mmol, 71%, *E*/*Z* = 2:1). T_m = 105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.10 (t, ^3J = 7 Hz, 2H, CH_2, *E*), 3.17 (t, ^3J = 7 Hz, 2H, CH_2, *Z*), 4.04 (t, ^3J = 7 Hz, 2H, CH_2, *E*), 4.21

(t, $^3J = 7$ Hz, 2H, CH_2, *Z*), 6.70–6.90 (m, 4H, CH, *E* + *Z*), 7.19–7.47 (m, 5H, CH, *E* + *Z*). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.92$ (*Z*), 28.36 (*E*), 59.04 (*E*), 60.67 (*Z*) (CH_2), 78.06 (*E*), 79.06 (*Z*), 117.71 (*E*), 118.73 (*Z*) (C), 122.63 (*E*), 122.88 (*Z*), 125.31 (*Z*), 125.66 (*E*), 126.77 (*E*), 126.91 (*Z*), 127.36 (*Z*), 127.39 (*E*), 128.22 (*E*), 128.44 (*Z*), 128.68 (*E*), 129.33 (*Z*) (CH), 136.38 (*E*), 138.61 (*Z*), 141.39 (*Z*), 142.34 (*E*), 157.28 (*Z*), 161.19 (*E*) (C). MS (EI, 70 eV): *m*/*z* = 278 (M^+, 53), 218 (7), 136 (17), 117 (30), 28 (100). IR (KBr): $\nu = 2174$ (s), 1595 (w), 1535 (s), 1490 (s), 1463 (w), 1440 (m), 1413 (w). UV–vis (MeCN): λ_{max} (lg ε) = 238.43 (4.03), 254.76 (4.03), 326.97 (4.04).

5. Biological studies

Bacterial cultures were obtained from the ATCC.

Assay for antimicrobial and antifungal activity

A modified disc diffusion method was used to determine the antimicrobial activity of the compounds. Nutrient agar was used for bacteria and malt agar for *Candida maltosa*. A sterile filter disc of 6 mm diameter (B&D research) impregnated with test compound was used for the assay. The paper disc was placed on the agar plate seeded with respective microorganisms. The plates were kept in the refrigerator at 4 °C for 4 h. Then the plates were turned over to incubate overnight at 37 °C in an inverted position. In contrast, *C. maltosa* was incubated at 28 °C for 72 h. At the end of the incubation period the clear zones of inhibition around the paper disc were measured. Negative control experiments were performed by using paper discs loaded with equivalent volume of solvent and positive control experiments were performed by use of an equivalent amount of ampicillin. The amount of substance of the compounds tested during the experiments was 1000 nmol per paper disc.

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